Aus der Neurologischen Klinik des Universitätsklinikums Düsseldorf
Direktor: Prof. Dr. H.-P. Hartung

# Neurophysiologische Untersuchungen zur kortikalen Repräsentation von Schmerz

Habilitationsschrift
zur Erlangung der venia legendi für das Fach Neurologie an der Hohen Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

Vorgelegt von
Dr. med. Markus Ploner
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Dr. med. Markus Ploner
Düsseldorf, 1.6.2006

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## Einleitung

Schmerz ist eine alltägliche und jedem vertraute, unangenehme und doch notwendige Erfahrung. Die Wahrnehmung von Schmerz wird entscheidend von der jeweiligen Situation und von vorangegangenen Erfahrungen geprägt und bedingt in aller Regel ein Verlangen nach Beendigung und künftiger Meidung der auslösenden Reize. Dieses Zusammenspiel aus Sensation, Kognition und Affekt (Melzack und Casey, 1968) macht Schmerz zu einem höchst subjektiven Phänomen.

In seiner physiologischen Funktion ist Schmerz unverzichtbar für den Erhalt der physischen Unversehrtheit. So hat das Fehlen der Fähigkeit, Schmerz zu empfinden unweigerlich schwere gesundheitliche Beeinträchtigungen und eine Verkürzung der Lebenserwartung zur Folge (Nagasako et al., 2003). Andererseits kann Schmerz dauerhaft und von seiner physiologischen Funktion gelöst auftreten. In dieser Form des chronischen Schmerzes hat Schmerz häufig verheerende Auswirkungen auf die Lebensqualität und stellt ein in seiner Bedeutung kaum zu überschätzendes medizinisches Problem dar. In einer durchschnittlichen Erwachsenenpopulation klagt jeder dritte bis vierte über chronische regionale Schmerzsyndrome wie Rücken- oder Kopfschmerzen und jeder zehnte über generalisierte chronische Schmerzsyndrome (Macfarlane et al., 2006). Trotz erheblicher Fortschritte sind die therapeutischen Erfolge beim chronischen Schmerz häufig unbefriedigend. Dies mag auch auf dem in vielerlei Hinsicht unvollständigen Wissen über die anatomischen und physiologischen Grundlagen der Entstehung von Schmerz beruhen.

Nachdem Schmerz lange als eine Variante der Wahrnehmung anderer Modalitäten wie Berührung oder Temperatur verstanden wurde, ist diese Sichtweise inzwischen weitgehend verlassen worden. Stattdessen wird Schmerz zunehmend als eigene Sinnesmodalität aufgefaßt, die von einem eigens auf die Verarbeitung von Schmerz spezialisierten Teil des Nervensystems verarbeitet wird. Über die letzten Jahrzehnte gelangen entscheidende Einblicke in die Mechanismen der Schmerzverarbeitung innerhalb dieses funktionellen Systems. Viele Aspekte, insbesondere jene der zentralen Verarbeitung von Schmerz, sind jedoch weiterhin unbekannt und bedürfen weiterer Klärung. In der vorliegenden Arbeit soll zunächst der gegenwärtige Stand des Wissens über die zentralen Mechanismen der Schmerzverarbeitung zusammengefaßt werden. Anschließend sollen die eigenen Beiträge der letzten Jahre zu diesem Thema geschildert und diskutiert werden. Abschließen soll die Arbeit mit einer Zusammenfassung und einem Ausblick auf offene Fragen und Wege zu weiteren Antworten.

*Das nozizeptive System*

Vom peripheren Rezeptor bis zum zerebralen Kortex wird Schmerz von einem als nozizeptives System bezeichneten spezialisierten Teil des Nervensystems verarbeitet (Craig, 2003; Willis und Westlund, 2004). In der Peripherie aktivieren schmerzhafte Reize spezifische Rezeptoren dünn myelinisierter Aδ- und unmyelinisierter C-Fasern mit unterschiedlichen Leitungsgeschwindigkeiten (Meyer et al., 2006). Diese als Nozizeptoren bezeichneten ersten Neurone des nozizeptiven Systems enden im Hinterhorn des Rückenmarkes. Dort finden sich in oberflächlichen (Lamina I) wie tieferen Schichten des Hinterhorns (Laminae IV-V) die zweiten Neurone des nozizeptiven Systems, deren Axone binnen eines oder weniger Rückenmarkssegmente die Mittellinie kreuzen und überwiegend im Tractus spinothalamicus zu lateralen wie medialen Thalamuskernen aufsteigen (Dostrovsky und Craig, 2006). Von dort projizieren die dritten Neurone des nozizeptiven Systems zu verschiedenen Arealen des zerebralen Kortex (Bushnell und Apkarian, 2006) (Abb. 1). Auf allen Ebenen dieser aufsteigenden Pfade des nozizeptiven Systems kann die Verarbeitung von Schmerz durch absteigende Projektionen moduliert werden (Fields et al., 2006; Woolf und Salter, 2006).

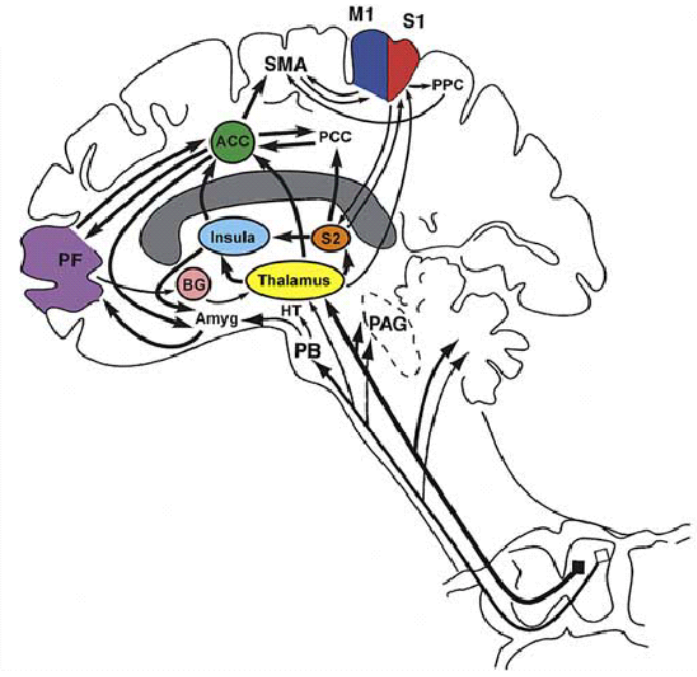


Abb 1. Zentrale Anteile des nozizeptiven Sytems.

S1, primärer somatosensorischer Kortex; S2, sekundärer somatosensorischer Kortex, ACC, anteriorer zingulärer Kortex; PF, präfrontaler Kortex; M1, primärer motorischer Kortex; SMA, supplementär motorisches Areal; PPC, posterior parietaler Kortex; PCC, posteriorer zingulärer Kortex; BG, Basalganglien; HT, Hypothalamus; AMYG, Amygdala; PB, parabrachiale Nuclei; PAG, periaquäduktales Grau. Aus (Apkarian et al., 2005).

*Die Beteiligung des zerebralen Kortex an der Verarbeitung von Schmerz*

Eine Beteiligung des zerebralen Kortex an der Verarbeitung von Schmerz war lange angezweifelt worden. So beobachtete Henry Head, daß rein kortikale Läsionen keinen Einfluß auf die Wahrnehmung schmerzhafter Reize haben (Head und Holmes, 1911). Entsprechend rief die elektrische Reizung des Kortex nur vereinzelt schmerzhafte Empfindungen hervor (Penfield und Boldrey, 1937). Später wurden einige Läsionsstudien publiziert, die diesen Befunden widersprachen, in den beobachteten klinischen Defiziten jedoch höchst uneinheitlich waren (Sweet, 1982; Kenshalo und Willis, 1991). Erste eindeutigere Belege für eine Beteiligung des zerebralen Kortex an der Schmerzverarbeitung ergaben sich aus tierexperimentellen Studien. Schließlich kamen neuere Läsionsstudien an Patienten unter Verwendung hochauflösender strukturell bildgebender Verfahren und Studien der funktionellen Bildgebung mittels Photonen- und Positronenemissionstomographie (SPECT, PET) und der funktionellen Kernspintomographie (fMRI) hinzu. Diese Studien belegten erstmals auf nichtinvasivem Wege die Beteiligung eines ausgedehnten Netzwerkes kortikaler Areale an der Schmerzverarbeitung. Diese räumlichen Aspekte der Schmerzverarbeitung wurden durch die Ergebnisse neurophysiologischer Studien mittels Magnet- und Elektroenzephalographie (MEG, EEG) um die zeitlichen Aspekte ergänzt. Überdies wurden die experimentellen Paradigmen und die psychophysische Erfassung von Schmerz verfeinert, so daß die Betrachtung einzelner Teilaspekte der Wahrnehmung von Schmerz möglich wurde. Techniken wie die kutane Laserstimulation erlauben darüber hinaus die selektive Untersuchung des nozizeptiven Systems ohne die gleichzeitige Reizung von Berührungsafferenzen.

Aufgrund der mittels dieser technischen und methodischen Neuerungen gewonnenen Ergebnisse besteht inzwischen weitestgehende Übereinstimmung hinsichtlich der essentiellen Bedeutung der primären (S1) und sekundären somatosensorischen Kortizes (S2), des insulären Kortex und des vorderen zingulären Kortex (ACC) für die Schmerzwahrnehmung (Bushnell und Apkarian, 2006). Die wesentlichen Befunde hierzu sollen in den folgenden Abschnitten zusammengefaßt werden.

*Der primäre somatosensorische Kortex (S1)*

Der S1-Kortex besteht aus vier streifenförmigen zytoarchitektonischen Arealen entlang des Gyrus postcentralis, den Brodmann-Arealen 3a, 3b, 1 und 2 (Kaas, 2004b). Die Beteiligung des S1-Kortex an der Verarbeitung von Schmerz war besonders umstritten. Nachdem Beobachtungen von Läsions- und Stimulationseffekten beim Menschen keine wesentliche

Beteiligung von S1 an der Schmerzverarbeitung vermuten ließen (Sweet, 1982; Kenshalo und Willis, 1991), wurden in den achtziger Jahren des letzten Jahrhunderts erste tierexperimentelle Belege für eine solche Beteiligung publiziert. Anatomische Studien zeigten nozizeptive Projektionen von lateralen thalamischen Kernen, insbesondere vom Nucleus ventralis posterolateralis (VPL) zum S1-Kortex (Kenshalo et al., 1980; Gingold et al., 1991). Einzelzellableitungen bei der Ratte (Lamour et al., 1983) und bei anästhesierten (Kenshalo und Isensee, 1983; Chudler et al., 1990) und wachen (Kenshalo et al., 1988; Kenshalo et al., 2000) Affen bestätigten die Existenz von auf Schmerzreize respondierenden S1-Neuronen. Diese Neurone sind überwiegend in der zytoarchitektonischen Area 1 bzw. an deren Grenzen gefunden worden. Die Charakteristika der Neurone prädestinieren sie für diskriminative Leistungen. Sie sind überwiegend somatotopisch angeordnet und haben kleine rezeptive Felder. Ihre Aktivität korreliert mit der Dauer und Intensität des Reizes ebenso wie mit der Intensität der Schmerzwahrnehmung. Vergleichende psychophysische Studien legen nahe, daß diese Befunde auf den Menschen zu übertragen sind (Chudler et al., 1990).

Im Gegensatz zu diesen Studien, jedoch entsprechend der Uneinheitlichkeit der Läsionsstudien beim Menschen erbrachten Anfang der neunziger Jahre erste Studien der funktionellen Bildgebung höchst unterschiedliche Ergebnisse. So zeigten sich schmerzassoziiert teils Zunahmen (Talbot et al., 1991), teils Abnahmen (Apkarian et al., 1992) und teils ein unveränderter (Jones et al., 1991) regionaler Blutfluß in S1. Neuere Studien der funktionellen Bildgebung (Andersson et al., 1997; Porro et al., 1998; Coghill et al., 1999; Casey et al., 2001; Hofbauer et al., 2001; Bornhovd et al., 2002; Chen et al., 2002; Petrovic et al., 2002b; Bingel et al., 2004; Moulton et al., 2005) und neurophysiologische Untersuchungen (Tarkka und Treede, 1993; Ploner et al., 1999b; Kanda et al., 2000; Ploner et al., 2000; Timmermann et al., 2001; Ploner et al., 2002a; Inui et al., 2003; Schlereth et al., 2003; Ohara et al., 2004b; Valeriani et al., 2004) stimmen jedoch weitgehend in einer Beteiligung von S1 an der menschlichen Schmerzverarbeitung überein. Darüber hinaus finden sich weitere Belege für eine besondere Bedeutung des S1-Kortex für sensorisch-diskriminative Funktionen der Schmerzwahrnehmung. So sind schmerzevozierte S1-Aktivierungen somatotopisch angeordnet (Tarkka und Treede, 1993; Andersson et al., 1997; Bingel et al., 2004) und können durch ein Fokussieren der Aufmerksamkeit auf die Lokalisation von Schmerz beeinflußt werden (Kulkarni et al., 2005). Zudem bestehen enge Assoziationen zwischen schmerzevozierten S1-Aktivierungen und der Intensität (Porro et al., 1998; Coghill et al., 1999; Hofbauer et al., 2001; Bornhovd et al., 2002; Moulton et al., 2005) und dem Zeitverlauf (Porro et al., 1998; Chen et al., 2002) des wahrgenommenen Schmerzes.

Trotz dieser zunehmend klaren und konsistenten Befunde bleibt die Uneinheitlichkeit der Ergebnisse früherer Läsions- und Bildgebungsstudien bezüglich der Rolle von S1 in der Schmerzwahrnehmung bemerkenswert. Dies mag neben methodischen Gründen zum Teil auf ein modulierende kognitive Einflüsse widerspiegelndes Nebeneinander von schmerzevozierter Exzitation und Inhibition innerhalb von S1 zurückzuführen sein (Bushnell et al., 1999).

*Der sekundäre somatosensorische Kortex (S2)*

Der S2-Kortex befindet sich im parietalen Operculum in der oberen Lippe der Fissura Sylvii beider Hemisphären. Die Beschreibung dieses Areals geht ursprünglich auf die Beobachtung somatosensorischer Effekte intraoperativer kortikaler Stimulationen zurück (Penfield und Rasmussen, 1950; Woolsey et al., 1979). Inzwischen muß jedoch davon ausgegangen werden, daß es sich bei diesem Areal nicht um ein, sondern um bis zu fünf in ihrer Architektur und Konnektivität verschiedene Areale handelt (Whitsel et al., 1969; Burton et al., 1995; Krubitzer et al., 1995; Disbrow et al., 2000; Fitzgerald et al., 2004; Eickhoff et al., 2006a). Methodisch erfordert die Berücksichtigung der komplexen Parzellation der S2-Region eine über übliche Grenzen nichtinvasiver Verfahren hinausgehende räumliche Auflösung. In den meisten Studien zur kortikalen Repräsentation von Schmerz konnte dieser Parzellation daher noch nicht ausreichend Rechnung getragen werden. Im Folgenden wird daher vereinfachend der Terminus S2 verwendet, so daß die Zuordnung der bisherigen Befunde zu den Arealen der S2-Region eine wesentliche Aufgabe künftiger Arbeiten sein wird (Eickhoff et al., 2006b).

Grundsätzlich ist die Beteiligung des S2-Areals an der Verarbeitung von Schmerz weitestgehend unstrittig. So gehören schmerzevozierte Aktivierungen des S2-Kortex beider Hemisphären zu den konsistentesten Befunden bei extra- (Ploner et al., 1999b; Ploner et al., 2000; Ploner et al., 2002a; Timmermann et al., 2001; Schlereth et al., 2003; Tarkka et al., 1993) und intrakraniellen Ableitungen (Lenz et al., 1998a; Frot und Mauguière, 2003; Vogel et al., 2003) und Stimulationen (Mazzola et al., 2005) sowie funktionell bildgebenden Untersuchungen (Coghill et al., 1999; Casey et al., 2001; Hofbauer et al., 2001; Bornhovd et al., 2002; Chen et al., 2002; Bingel et al., 2003; Bingel et al., 2004). Teils wurden hierbei mehrere, funktionell verschiedene schmerzevozierte S2-Aktivierungen gezeigt, was möglicherweise die Parzellierung der S2-Region widerspiegelt (Bingel et al., 2003).

Anatomische Studien zeigen, daß schmerzbezogene Information den S2-Kortex überwiegend über den Nucleus ventralis posterior inferior des Thalamus erreicht (Stevens et al., 1993; Disbrow et al., 2002). Da nozizeptive thalamische Projektionen den S1-Kortex überwiegend

über einen anderen lateralen Thalamuskern, den Nucleus ventralis posterolateralis erreichen (Gingold et al., 1991; Kenshalo und Willis, 1991) und sich die spinalen Afferenzen und Antwortcharakteristika beider Thalamuskerne unterscheiden (Apkarian und Shi, 1994), liegt es nahe, die Existenz anatomisch und funktionell verschiedener, paralleler nozizeptiver Pfade vom Rückenmark zu S1 und zu S2 anzunehmen.

Die funktionelle Bedeutung der S2-Region für die Schmerzverarbeitung ist weniger klar als die des S1-Kortex. Die Antwortcharakteristika nozizeptiver S2-Neurone mit großen, bilateralen rezeptiven Feldern, die Stimulusintensität nicht kodierenden Feuerraten und teils multimodalen Eigenschaften (Whitsel et al., 1969; Robinson und Burton, 1980; Dong et al., 1994) lassen das S2-Areal weniger prädestiniert für sensorisch-diskriminative Leistungen erscheinen. Stattdessen existieren Hinweise auf eine Bedeutung des S2-Areals für kognitive Aspekte der Schmerzwahrnehmung. Läsionen der S2-Region führen bei Affen (Ridley und Ettlinger, 1976, 1978; Murray und Mishkin, 1984) und Menschen (Caselli, 1993) zu Defiziten in taktilen Diskriminations- und Gedächtnisaufgaben. Entsprechend finden sich Projektionen von S2 über den insulären Kortex zu den gedächtnisrelevanten Arealen des medialen Temporallappens (Friedman et al., 1986; Shi und Cassell, 1998). Hierauf basierend wurde ein über S2 führender kortikolimbischer Pfad taktiler Gedächtnisfunktionen postuliert (Friedman et al., 1986). Entsprechend wird S2 eine Schlüsselrolle auch bei schmerzbezogenen Lern- und Gedächtnisvorgängen zugeschrieben (Dong et al., 1989; Lenz et al., 1997). Zusätzlich legen anatomische Arbeiten (Krubitzer und Kaas, 1990; Disbrow et al., 2003) sowie neurophysiologische (Huttunen et al., 1996; Forss und Jousmaki, 1998) und funktionell bildgebende Studien (Ledberg et al., 1995; Binkofski et al., 1999) eine Bedeutung der S2-Region für sensomotorische Transformation und Integration nahe.

Diese Hinweise auf die Funktion von S2 in der Schmerzverarbeitung bedürfen jedoch weiterer experimenteller Bestätigung und Präzisierung. Auch erscheinen Unterschiede in der funktionellen Bedeutung der S2-Region für die Verarbeitung von Berührung und Schmerz möglich. Einige Studien zeigen, daß mit beiden Modalitäten assoziierte Aktivierungen sich zwar überlappen, aber nicht vollständig entsprechen (Coghill et al., 1994; Gelnar et al., 1999; Chen et al., 2002; Ferretti et al., 2003; Vogel et al., 2003; Torquati et al., 2005), wobei schmerzevozierte Aktivierungen tendentiell weiter posterior als taktil-assoziierte Aktivierungen zu liegen scheinen (Eickhoff et al., 2006b). Es bleibt zu klären, wie diese bisher erhobenen Befunde der oben genannten Parzellation des S2-Areals zuzuordnen sind.

*Der insuläre Kortex*

Der architektonisch heterogene insuläre Kortex liegt verborgen von den frontalen und parietalen Opercula und dem Temporallappen in der Tiefe der Fissura Sylvii (Mesulam und Mufson, 1985). Er grenzt unmittelbar an die S2-Region in der oberen Lippe der Fissura Sylvii.

Bis vor einigen Jahren waren Belege für eine Beteiligung des insulären Kortex an der Schmerzverarbeitung rar. Dies hat sich während des letzten Jahrzehnts entscheidend verändert. Studien der funktionellen Bildgebung (Craig et al., 1996; Sawamoto et al., 2000; Casey et al., 2001; Bornhovd et al., 2002; Brooks et al., 2002; Brooks et al., 2005; Schreckenberger et al., 2005) und intrakranielle Ableitungen und Stimulationen (Ostrowsky et al., 2002; Frot und Mauguière, 2003) zeigten übereinstimmend schmerzassoziierte Aktivierungen der Insel. Auch tierexperimentelle Studien bestätigten die Existenz nozizeptiver insulärer Neurone mit großen rezeptiven Feldern und multimodalen, teils auch auf viszerale Reize reagierenden Antworteigenschaften (Hanamori et al., 1998; Ito, 1998; Zhang et al., 1999). Eine Beteiligung der Insel an der Verarbeitung von Schmerz ist somit nicht mehr anzuzweifeln.

Überlegungen zur funktionellen Bedeutung der Insel bei der Schmerzverarbeitung stützen sich bisher vorwiegend auf indirekte Hinweise. Anatomisch und funktionell ist die Insel ein heterogenes Areal (Mesulam und Mufson, 1985; Augustine, 1996). In einer etwas vereinfachten Sichtweise legen Konnektivität und Antworteigenschaften insulärer Neurone nahe, daß in den hinteren Anteilen der Insel überwiegend extrapersonale (auditorische, visuelle und somatosensorische) Information verarbeitet wird, wohingegen die vorderen Anteile vorwiegend mit der Verarbeitung intrapersonaler (limbischer, viszeroautonomer) Information befaßt sind (Mesulam und Mufson, 1985; Augustine, 1996). Schmerzbezogene Aktivierungen in Studien der funktionellen Bildgebung sind dabei sowohl in den vorderen als auch in den hinteren Anteilen der Insel zu finden (Craig et al., 1996; Sawamoto et al., 2000; Casey et al., 2001; Bornhovd et al., 2002; Brooks et al., 2002; Brooks et al., 2005; Schreckenberger et al., 2005). In den hinteren Anteilen konnte dabei eine somatotopische Anordnung schmerzbezogener Aktivierungen gezeigt werden (Brooks et al., 2005). Dies mag die Eigenheit der Sensation Schmerz widerspiegeln, gleichzeitig exterozeptive Information, d.h. Information über einen die physische Unversehrtheit bedrohenden Reiz der Außenwelt und interozeptive Information über den Zustand des Organismus selber zu vermitteln. Diese Auffassung von Schmerz als Phänomen der Interozeption, d.h. der Wahrnehmung des physiologischen Gesamtzustandes des Körpers steht im Mittelpunkt eines in den letzten

Jahren beschriebenen Modells der anatomischen und physiologischen Repräsentation der Interozeption, wozu auch Temperatur, Hunger und Durst gezählt werden (Craig, 2003). In diesem Modell wird die Existenz eines von der Peripherie über die Lamina I des Hinterhorns, den posterioren Anteil des ventromedialen Thalamuskerns (VMpo) bis hin zum insulären Kortex reichenden, eigens der Interozeption gewidmeten neuralen System postuliert. Die rechte anteriore Insel wird hierbei als Substrat einer sinnesübergreifenden Metarepräsentation der Selbstwahrnehmung aufgefaßt (Craig, 2003; Critchley et al., 2004). Eine zunehmende Zahl verschiedenster Befunde stützt dieses Modell der Interozeption als eigene Sinnesmodalität. Die zentrale Bedeutung, die hierbei dem insulären Kortex beigemessen wird erscheint durchaus plausibel, bedarf jedoch sicher weiterer experimenteller Bestätigung.
Festzuhalten bleibt, daß die weit verteilten Konnektionen der Insel zu mit verschiedenen sensorischen Modalitäten und autonomen und limbischen Funktionen befaßten Regionen eine supramodale, integrative Funktion der Insel nahe legen. Die Insel mag somit schmerzbezogene exterozeptive Information, u.a. aus S2 und Thalamus mit interozeptiver Information integrieren. Diese integrierte Information könnte der Steuerung autonomer Funktionen, über die Projektionen zu den limbischen Strukturen des Temporallappens dem schmerzbezogenen Lernen und der Gedächtnisbildung sowie einer einheitlichen Selbstwahrnehmung des Körpers in der rechten vorderen Insel dienen (Craig, 2003).

*Der vordere zinguläre Kortex (ACC)*

Der Gyrus cinguli erstreckt sich entlang des Corpus callosum über weite Teile der medialen Oberfläche beider Hemisphären und läßt sich in vier architektonisch und funktionell verschiedene Unterareale unterteilen (Vogt, 2005).
Die Beteiligung insbesondere der anterioren und mittleren Abschnitte des Gyrus cinguli an der Schmerzwahrnehmung wird durch eine Vielzahl von Studien belegt. In Einzelzellableitungen und Mikrostimulationen beim Menschen (Hutchison et al., 1999) konnte in Übereinstimmung mit tierexperimentellen Daten (Sikes und Vogt, 1992; Yamamura et al., 1996; Koyama et al., 1998; Iwata et al., 2005; Kuo und Yen, 2005) direkt die Existenz über mediale Thalamuskerne versorgter nozizeptiver Neurone mit großen und bilateralen rezeptiven Feldern nachgewiesen werden. Entsprechend konnten in bildgebenden Studien (Craig et al., 1996; Vogt et al., 1996; Davis et al., 1997; Rainville et al., 1997; Derbyshire et al., 1998; Tolle et al., 1999; Kwan et al., 2000; Casey et al., 2001; Buchel et al., 2002) und extra- (Schlereth et al., 2003) und intrakraniellen (Lenz et al., 1998b) neurophysiologischen Ableitungen konsistent schmerzevozierte ACC-Aktivierungen gezeigt werden.

Erste Hinweise auf die funktionelle Bedeutung des ACC gaben Läsionsstudien. So wurde bei Patienten nach chirurgischer Läsion des zingulären Kortex eine Verminderung insbesondere der affektiven Komponente von Schmerz beobachtet (Foltz und White, 1962; Hurt und Ballantine, 1974), ein Effekt, der tierexperimentell bestätigt werden konnte (Vaccarino und Melzack, 1989; Johansen et al., 2001). In den letzten Jahren gelangen dann auch beim Menschen überzeugende experimentelle Belege für eine Kodierung des Schmerzaffektes im ACC. Mittels Hypnose (Rainville et al., 1997) und auf Schmerzaffekt fokussierter Aufmerksamkeit (Kulkarni et al., 2005) gelang eine selektive Modulation des Affektes ohne Veränderung der Intensität der Schmerzsensation. Diese selektive Modulation des Schmerzaffektes korrelierte in PET-Messungen direkt mit Blutflußänderungen im ACC (Rainville et al., 1997; Kulkarni et al., 2005). Umgekehrt geht eine voluntarische biofeedbackartige Modulation der im real-time fMRI bestimmten Funktion des ACC mit einer Änderung insbesondere des Schmerzaffektes einher (deCharms et al., 2005). Zudem weist der ACC eine hohe Dichte an Opioidrezeptoren auf (Vogt et al., 1995), deren Belegung selektiv mit Änderungen des Schmerzaffektes korreliert (Zubieta et al., 2001).

Die Beteiligung des ACC an der Verarbeitung und Wahrnehmung von Schmerz geht jedoch über diese affektiven Aspekte hinaus. So ist der ACC auch an der Placebo-induzierten, endogenen Modulation von Schmerz (Petrovic et al., 2002a; Wager et al., 2004; Bingel et al., 2006) und an verschiedensten, nicht-schmerzbezogenen kognitiven, aufmerksamkeitsbezogenen und motorischen Leistungen beteiligt (Bush et al., 2000; Paus, 2001; Vogt, 2005). Es ist daher wahrscheinlich, daß schmerzevozierte Aktivierungen des ACC neben schmerzspezifischen auch schmerzmodulatorische und unspezifische, mit Aufmerksamkeit und motorischen Leistungen assoziierte Effekte widerspiegeln. Entsprechend konnte eine teilweise Überlappung, jedoch keine vollständige Übereinstimmung motorischer, aufmerksamkeits- und schmerzbezogener ACC-Aktivierungen gezeigt werden (Davis et al., 1997; Derbyshire et al., 1998; Kwan et al., 2000). Darüber hinaus scheint Schmerz mehrere Foci innerhalb des ACC zu aktivieren, deren unterschiedliche Charakteristika das Nebeneinander verschiedener Partialfunktionen des ACC nahelegen (Vogt et al., 1996; Derbyshire et al., 1998; Tolle et al., 1999; Buchel et al., 2002). Unter den vielfältigen Funktionen des ACC mag die räumliche Nähe der nozizeptiven, motorischen und kognitiven Regionen des ACC die direkte Umsetzung von durch Schmerzaffekt motivierten, kognitiv modulierten motorischen Reaktionen erlauben (Vogt, 2005).

*Erster und Zweiter Schmerz*

Erster und Zweiter Schmerz sind das einzigartige perzeptuelle Phänomen, daß einzelne schmerzhafte Reize zwei zeitlich aufeinanderfolgende, qualitativ unterschiedliche Sensationen hervorrufen (Gad und Goldscheider, 1892; Lewis und Pochin, 1937; Bishop und Landau, 1958; Price et al., 1977). Der Erste Schmerz ist kurz, stechend und kann gut lokalisiert werden, während der Zweite Schmerz länger anhaltend, brennend und von eher diffuser Lokalisation ist. Die periphere neurale Grundlage dieses Phänomens ist die gleichzeitige Aktivierung von nozizeptiven Aδ- und C-Fasern mit unterschiedlichen Leitungsgeschwindigkeiten. Die biologischen Funktionen und die unterschiedlichen kortikalen Korrelate beider Sensationen sind bisher kaum bekannt.

Der überwiegende Teil klinischer und experimenteller Studien läßt eine Differenzierung beider Sensationen nicht zu oder bezieht sich lediglich auf die Korrelate Ersten Schmerzes. In einigen EEG- und MEG-Arbeiten gelang es, C-Faser-vermittelte zentrale Korrelate Zweiten Schmerzes zu zeigen (Bromm und Treede, 1987; Arendt-Nielsen, 1990; Bragard et al., 1996; Towell et al., 1996; Magerl et al., 1999; Opsommer et al., 2001; Tran et al., 2002; Qiu et al., 2004; Forss et al., 2005). Mit Zweitem Schmerz assoziierte Aktivierungen waren dabei überwiegend in S2 und dem ACC lokalisiert (Opsommer et al., 2001; Tran et al., 2002; Qiu et al., 2004; Forss et al., 2005). Entsprechend zeigten Einzelzellableitungen bei der Ratte späte, wahrscheinlich C-Faser-vermittelte Antworten auf Schmerzreize im ACC (Kuo und Yen, 2005).

Mit funktionell bildgebenden Verfahren ist eine direkte Darstellung der Korrelate Ersten und Zweiten Schmerzes aufgrund der limitierten zeitlichen Auflösung nicht möglich. Einige Studien zeigten bei Applikation tonischer C-Faser-Reize Aktivierungen der wesentlichen mit Schmerz assoziierten Areale S1, S2, Insel und ACC (Di Piero et al., 1994; Andersson et al., 1997; Iadarola et al., 1998; Petrovic et al., 2000). Eine direkte Gegenüberstellung von Aδ-Faser- und C-Faser-vermittelten Aktivierungen gelang in bisher einer aktuellen fMRI-Studie. Die Ergebnisse zeigten, daß Aktivierungen des ACC und der vorderen Insel insbesondere bei C-Faser-Reizung zu finden sind (Qiu et al., 2005).

Zusammenfassend finden sich somit Hinweise auf eine besondere Assoziation zwischen Zweitem Schmerz und der Funktion des ACC. Eine direkte Darstellung der Sequenz von mit Erstem und Zweiten Schmerz assoziierten zerebralen Aktivierungen gelang jedoch bis auf eine Ausnahme (Ploner et al., 2002a) nicht. Die differentiellen kortikalen Repräsentationen und biologischen Funktionen Ersten und Zweiten Schmerzes sind somit weitgehend unbekannt.

*Schmerz und Aufmerksamkeit*

Die alltägliche wie klinische Erfahrung lehrt, daß Schmerz durch das Fokussieren von Aufmerksamkeit auf oder die Distraktion von Schmerz erheblich moduliert werden kann. Entsprechend belegen psychophysische Studien, daß Aufmerksamkeit erheblichen Einfluß auf die sensorischen wie affektiven Aspekte von Schmerz ausübt (Levine et al., 1982; Miron et al., 1989; Spence et al., 2002). Diese attentionale Modulation der Wahrnehmung von Schmerz geht mit Modulationen neuronaler Aktivität auf allen Ebenen des nozizeptiven Systems einher (Petrovic und Ingvar, 2002; Bushnell et al., 2004). Auf kortikaler Ebene konnte gezeigt werden, daß Aufmerksamkeit schmerzevozierte Aktivität in allen wesentlich an der Schmerzverarbeitung beteiligten kortikalen Arealen, namentlich in S1, S2, dem insulären Kortex und dem ACC, modulieren kann (Bushnell et al., 1999; Peyron et al., 1999; Petrovic et al., 2000). Die neuralen Mechanismen dieser aufmerksamkeitsinduzierten Modulationen der Schmerzwahrnehmung und -verarbeitung sind nur unvollständig bekannt. Funktionell bildgebende Arbeiten verweisen auf eine besondere Bedeutung des ACC und des orbitofrontalen Kortex sowie des periaquäduktalen Grau für dieses Phänomen (Petrovic et al., 2000; Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004). Aktivierungen dieser Areale gehen sowohl mit Reduktionen schmerzassoziierter kortikaler Aktivierungen als auch mit Reduktionen der Schmerzwahrnehmung einher. Möglicherweise steht die Aktivität dieser kortikalen schmerzmodulierenden Areale mit der Aktivität eines auf Hirnstamm- und Rückenmarksebene gut charakterisierten Systems der deszendierenden Schmerzmodulation in Verbindung (Fields et al., 2006). Dieses opioid-sensitive System umfaßt insbesondere die Amygdala und verschiedene Regionen des Hirnstamms, unter anderem das periaquäduktale Grau. Es erscheint plausibel, daß dieses System bei der Vermittlung aufmerksamkeitsinduzierter Modulationen von Schmerz unter Kontrolle des ACC und des orbitofrontalen Kortex steht (Fields et al., 2006).

Neben diesen Effekten der Aufmerksamkeit auf Schmerz hat Schmerz umgekehrt auch entscheidenden Einfluß auf Aufmerksamkeit. Schmerz zieht unwillkürlich Aufmerksamkeit auf sich und interferiert mit anderen behavioralen und kognitiven Abläufen (Eccleston und Crombez, 1999; Grisart und Plaghki, 1999). Da Schmerz unter physiologischen Bedingungen eine Bedrohung der physischen Unversehrtheit signalisiert, erscheint diese unwillkürlich durch Schmerz erregte Aufmerksamkeit erforderlich und sinnvoll. Unter pathologischen Bedingungen kann diese schmerzbedingte Aufmerksamkeit jedoch abnorme Steigerungen erfahren und scheint dann wesentlich zur Chronifizierung von Schmerz beizutragen (Crombez

et al., 2005). Die neuralen Mechanismen dieser Form der Interaktion zwischen Schmerz und Aufmerksamkeit sind bisher unbekannt.

Zusammenfassend konnten in den letzten Jahren entscheidende Fortschritte in der Beschreibung der anatomischen und physiologischen Grundlagen des komplexen Zusammenspiels zwischen Aufmerksamkeit und Schmerz erreicht werden. Jedoch erscheint das Wissen bezüglich dieser zentralen Mechanismen der endogenen Modulation von Schmerz insgesamt lückenhaft und bedarf weiterer Aufklärung, dies insbesondere, da solche Erkenntnisse entscheidende Einblicke in therapeutisch verwertbare Abläufe versprechen.

*Zusammenfassung*

Die vorangegangenen Ausführungen lassen wesentliche Fortschritte in der Beschreibung der zentralen Mechanismen der Schmerzverarbeitung erkennen. Ein kortikales Netzwerk der Schmerzverarbeitung ist beschrieben und die Funktion einzelner Areale ist zu erkennen. Zukünftige Arbeiten versprechen eine weitere Präzisierung der Zuordnung zwischen kortikaler Funktion und Wahrnehmung. Zudem bleiben auf physiologischer Ebene die Interaktionen zwischen den beteiligten kortikalen Arealen und auf perzeptueller Ebene die Interaktionen zwischen verschiedenen Aspekten von Schmerz zu klären. Das Studium dieser neuronalen und perzeptuellen Interaktionen verspricht dabei grundlegende Einblicke in das Zusammenwirken neuronaler Funktion bei der Generierung eines individuellen Perzepts. Darüber hinaus könnte ein verbessertes Verständnis der Effekte endogener und exogener Modulation auf neuronale Aktivität und Schmerzwahrnehmung therapeutisch verwertbare Information liefern.

**Eigene Arbeiten**

Die vorliegenden Arbeiten beschäftigen sich mit grundlegenden Fragen der Verarbeitung von Schmerz im menschlichen Gehirn. Insbesondere wurden die Zeitverläufe und funktionellen Charakteristika schmerzbezogener Aktivierungen einzelner Hirnareale näher untersucht. Ziel der Arbeiten war, zur Klärung der hierarchischen Organisation und funktionellen Bedeutung einzelner Hirnareale bei der Verarbeitung und Wahrnehmung von Schmerz beizutragen. Zudem sollten Einblicke in die zentralen Mechanismen der Modulation von Schmerz gewonnen werden. Die Ergebnisse und Interpretationen der Studien sollen im Folgenden ihrem inneren Zusammenhang nach zusammenfassend dargelegt werden. Vorangehen werden kurze Einführungen in die Verfahren der Magnetenzephalographie und der kutanen Laserstimulation.

*Magnetenzephalographie*

Die vorliegenden Arbeiten wurden unter Verwendung der Magnetenzephalographie durchgeführt und um klinische Beobachtungen ergänzt. Die Magnetenzephalographie (MEG) ist ein der Elektroenzephalographie verwandtes nichtinvasives neurophysiologisches Verfahren. Es erlaubt die zeitlich und räumlich hochaufgelöste Registrierung neuronaler Aktivität. Prinzip der MEG ist die Messung von auf neuronaler Aktivität basierenden Magnetfeldern. Diese Magnetfelder entstehen überwiegend durch mit Ionenströmen einhergehende postsynaptische Potentiale. Die durch Aufsummierung der Aktivität von Tausenden von Nervenzellen detektierbaren Magnetfelder sind äußerst schwach und um sechs bis acht Größenordnungen kleiner als das umgebende, vom Erdmagnetfeld und Störquellen bestimmte Magnetfeld. Zur Messung der Signale werden daher hochempfindliche SQUID-Sensoren verwendet. Moderne MEG-Systeme bestehen aus 100 bis 300 solcher Sensoren, die in einer helmartigen Anordnung den Kopf umschließen. Zur Verminderung externer Störsignale befindet sich das MEG-System in einer gesonderten Abschirmkammer. Mit diesen Systemen ist grundsätzlich die Detektion neuronaler Aktivität aus dem gesamten Gehirn möglich, wobei die Sensitivität für oberflächliche, kortikale Aktivität besonders hoch ist. Da die in der MEG gemessenen Signale durch Liquor, Hirnhäute, Knochen und Kopfhaut kaum verzerrt werden, geht die MEG mit einer hohen räumlichen Auflösung einher.

Die MEG ist somit besonders zur räumlichen und zeitlichen Analyse neuronaler Aktivität geeignet und ergänzt auf indirekten Parametern neuronaler Aktivität beruhende Verfahren der funktionellen Bildgebung wie die Positronenemissionstomographie (PET) und die funktionelle Magnetresonanztomographie (fMRI), die eine besonders hohe räumliche

Auflösung bei im Vergleich zur MEG niedrigerer zeitlicher Auflösung aufweisen. Für weitergehende Grundlagen sei auf entsprechende Übersichtsarbeiten verwiesen (Hämäläinen et al., 1993; Hari, 2005).

*Kutane Laserstimulation*

Die bei den Arbeiten verwendeten Schmerzreize wurden mittels der kutanen Laserstimulation appliziert. Die kutane Laserstimulation ist ein experimentell (Kakigi et al., 2005) und klinisch (Treede, 2003) genutztes Verfahren zur selektiven Untersuchung des nozizeptiven Systems. Die kurzen, bis zu wenigen Millisekunden dauernden Laserreize bewirken einen steilen intradermalen Temperaturanstieg, was zu einer selektiven Aktivierung nozizeptiver Aδ- und C-Fasern ohne begleitende Aktivierung nicht-nozizeptiver Afferenzen führt. Die kurze Reizdauer und der steile Temperaturanstieg führen zu einer hoch synchronen Aktivierung der nozizeptiven Afferenzen, was ein zeitlich gut aufgelöstes Studium der Abläufe im nozizeptiven System erlaubt. Durch das Lasergerät hervorgerufene Artefakte bei MEG-Messungen erfordern eine Positionierung des Lasergerätes außerhalb der abgeschirmten Aufnahmekammer. Der Laserstrahl wird durch eine Glasfaser vom Lasergerät in die Aufnahmekammer zum Probanden oder Patienten geleitet. Aufgrund der simultanen Aktivierung der Aδ- und C-Fasern und deren unterschiedlichen Leitungsgeschwindigkeiten ist die durch den Laserreiz hervorgerufene Sensation eine doppelte. Zuerst verspürt der Proband einen kurzen, gut lokalisierten, nadelstichartigen Schmerz dem ein länger andauernder, diffus lokalisierter brennender Schmerz folgt. Beide Sensationen entsprechen den oben geschilderten Sensationen des Ersten und Zweiten Schmerzes.

*Die parallele Organisation der Schmerzverarbeitung*

In der Einleitung wurde die Beteiligung eines ausgedehnten kortikalen Netzwerks an der Verarbeitung verschiedener Aspekte von Schmerz dargelegt. Die hierarchische Organisation der beteiligten kortikalen Areale und der verschiedenen perzeptuellen Aspekte von Schmerz ist jedoch weitgehend unklar. Auf physiologischer wie perzeptueller Ebene erscheint einerseits eine parallele, weitgehend unabhängige Organisation verschiedener Aspekte von Schmerzverarbeitung und -wahrnehmung möglich. Andererseits ist eine eher hierarchische, interdependente Organisation einzelner kortikaler Areale und verschiedener Aspekte von Schmerz denkbar.

Auf physiologischer Ebene wurde dieser Frage in einer ersten MEG-Studie nachgegangen (Ploner et al., 1999b). In dieser Studie wurden die Lokalisationen und Zeitverläufe

schmerzevozierter Aktivierungen in den primären (S1) und sekundären (S2) somatosensorischen Kortizes analysiert. Hierzu wurden bei gesunden Probanden leicht bis mäßig schmerzhafte kutane Laserreize auf den rechten Handrücken appliziert. Die Analyse der schmerzevozierten neuromagnetischen Antworten zeigt Aktivierungen im kontralateralen Gyrus postcentralis und im parietalen Operculum beider Hemisphären (Abb. 2, links), entsprechend dem kontralateralen S1-Kortex und den bilateralen S2-Arealen. Das entscheidende Ergebnis zeigen die Zeitverläufe der Aktivierungen (Abb. 2, rechts). Diese lassen erkennen, daß die selektiv nozizeptiven Schmerzreize zu einer simultanen Aktivierung dieser Areale führen.

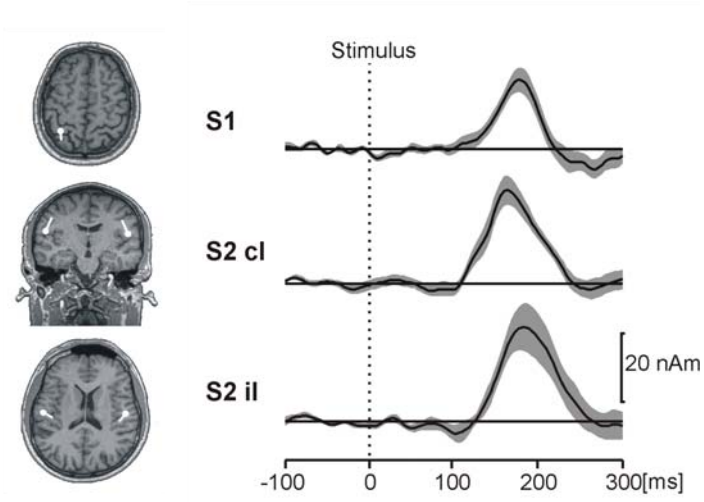


Abb. 2. Lokalisationen und Zeitverläufe schmerzevozierter Aktivierungen in S1 und S2 (Ploner et al., 1999b)

Dies steht im Gegensatz zu der gut bekannten sequentiellen Aktivierung dieser Areale bei der Verarbeitung von Berührung. Intrakranielle Ableitungen (Allison et al., 1989b; Allison et al., 1989a) und MEG-Studien (Hari et al., 1993; Mauguiere et al., 1997; Ploner et al., 2000) zeigen, daß Berührungsreize zunächst zu einer Aktivierung von S1 und erst nach einer Verzögerung von ungefähr 50 ms zu einer Aktivierung von S2 führen. Diese sequentielle Aktivierung von S1 und S2 spiegelt eine serielle Organisation dieser Areale bei der Verarbeitung von Berührung wider (Pons et al., 1987; Garraghty et al., 1990). Eine solche serielle Organisation von S1 und S2 findet sich jedoch nur bei höheren Primaten inklusive des Menschen. Bei niederen Primaten und Nicht-Primaten (Garraghty et al., 1991; Turman et al., 1992) herrscht auch bei bei der Berührungsverarbeitung eine parallele Organisation der somatosensorischen Kortizes vor. Auf diesem Unterschied basierend wurde die Hypothese eines evolutionären shifts von einer basalen, parallelen Organisationsform zu einer mehr

elaborierten, seriellen Organisation somatosensorischer Kortizes formuliert (Garraghty et al., 1991; Kaas, 2004a) (Abb. 3).

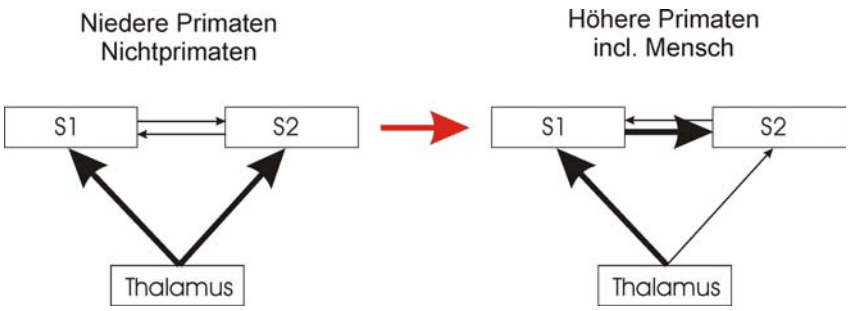


Abb. 3. Evolutionärer shift von paralleler zu serieller Organisation der somatosensorischen Kortizes (nach (Garraghty et al., 1991))

Vor diesem Hintergrund legt der Befund einer simultanen schmerzevozierten Aktivierung von S1 und S2 nahe, eine parallele Organisation von S1 und S2 in der menschlichen Schmerzverarbeitung anzunehmen. Ein hiermit implizierter direkter Zugang schmerzbezogener Information zu S2 findet mit dem Nachweis direkter nozizeptiver Projektionen vom Nucleus ventralis posterior inferior des Thalamus zur S2-Region tierexperimentelle Bestätigung (Stevens et al., 1993; Disbrow et al., 2002). Im Kontext des obengenannten evolutionären shifts könnte die parallele Organisation von Schmerz als ein evolutionärer Erhalt dieser basalen Organisationsform interpretiert werden. Funktionell mag dies die Tatsache widerspiegeln, daß verfeinerte sensorische Fähigkeiten in der Wahrnehmung von Schmerz weniger entscheidend sind als in der Wahrnehmung von Berührung. Stattdessen mag die parallele Organisation der Schmerzverarbeitung eine höhere Robustheit, schnellere Verarbeitungsabläufe und einen direkteren Zugang zu gedächtnisrelevanten und motorischen Arealen ermöglichen.
Zusammenfassend legen die Ergebnisse dieser Studie eine parallele Organisation der Schmerzverarbeitung in den somatosensorischen Kortizes des Menschen nahe. Diese basale parallele Organisationsform unterscheidet die Verarbeitung von Schmerz grundlegend von der seriellen Organisation taktiler Verarbeitung.

*Die parallele Organisation der Wahrnehmung von Schmerz*

Der Befund einer parallelen Organisation der Verarbeitung von Schmerz wird auf Verhaltensebene durch eine klinische Beobachtung ergänzt (Ploner et al., 1999a). Ein

57jähriger Patient mit einer selektiven ischämischen Läsion der rechtshemisphärischen Postzentralregion zeigte ein ungewöhnliches und aufschlußreiches Muster sensorischer Defizite. Die Läsion des Patienten umfaßte mit dem Handareal des Gyrus postcentralis und dem parietalen Operculum die S1- und S2-Areale (Abb. 4)

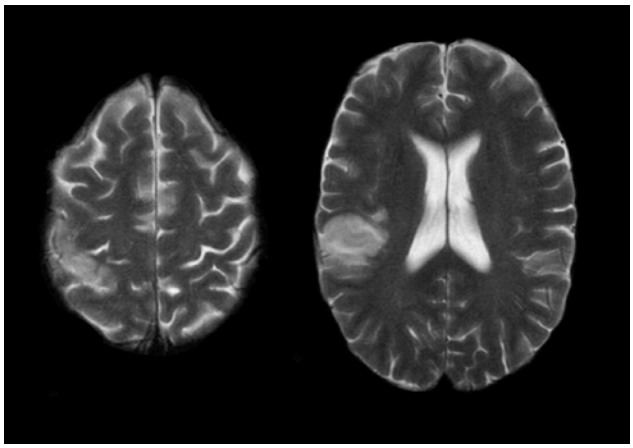

Abb. 4. MRT-Aufnahmen mit ischämischer Läsion der rechtshemisphärischen Postzentralregion (Ploner et al., 1999a)

Berührungen des linken Armes wurden von dem Patienten nicht wahrgenommen. Wurden jedoch üblicherweise schmerzhafte kutane Laserreize auf die linke Hand appliziert, so berichtete der Patient über ein von „irgendwo zwischen Schulter und Fingerspitzen“ herrührendes, deutlich unangenehmes Gefühl, das er zu meiden wünschte. Ansonsten war der kognitiv unbeeinträchtigte Patient nicht in der Lage, die Qualität, Intensität oder Lokalisation der Sensation näher zu beschreiben. Auch die vorgegebene Beschreibung „Schmerz“ wurde vom Patienten nicht bestätigt.

Dieser Patient litt offensichtlich unter einem vollständigen Verlust der Berührungswahrnehmung, während die Wahrnehmung von Schmerz zwar beeinträchtigt, aber nicht aufgehoben war. Zum einen wird somit deutlich, daß das nozizeptive System weniger vulnerabel zu sein scheint als das taktile System. Zum anderen zeigt sich, daß verschiedene perzeptuelle Aspekte von Schmerz voneinander dissoziierbar sind. Die Läsion der Postzentralregion hat bei diesem Patienten zu einer schweren Beeinträchtigung sensorischer und kognitiver Aspekte der Schmerzwahrnehmung bei erhaltenem Schmerzaffekt geführt. Diese läsionsbedingte Dissoziation verschiedener Aspekte von Schmerz zeigt, daß diese zumindest teilweise unabhängig voneinander repräsentiert sein müssen. Auf der Verhaltensebene ergänzt diese klinische Beobachtung somit den experimentellen Befund

einer parallelen Organisation der Schmerzverarbeitung. Im Grundsatz dieser Beobachtung entsprechend gelangen in den letzten Jahren auch experimentelle Dissoziationen der Schmerzwahrnehmung (Rainville et al., 1997; Hofbauer et al., 2001). Diese Hypnose-induzierten selektiven Modulationen sensorischer und affektiver Komponenten von Schmerz verweisen ebenfalls auf eine zumindest teilweise unabhängige Repräsentation dieser Aspekte. Zusammenfassend belegt die aktuelle klinische Beobachtung, daß verschiedene Aspekte von Schmerz voneinander dissoziierbar sind. Dies legt eine unabhängige und somit parallele Organisation und Repräsentation dieser Teilaspekte von Schmerz nahe.

*Die Organisation der Schmerzverarbeitung innerhalb des S1-Kortex*

Der primäre somatosensorische Kortex ist kein einheitliches Areal, sondern besteht aus vier in anterior-posteriorer Ausrichtung aufeinanderfolgenden streifenförmigen zytoarchitektonischen Unterarealen entlang des Gyrus postcentralis, den Areae 3a, 3b, 1 und 2 (Kaas, 2004b). Die Organisation der Schmerzverarbeitung innerhalb dieser Unterareale wurde in einer MEG-Studie näher untersucht und mit der Organisation der Berührungsverarbeitung verglichen (Ploner et al., 2000). Nozizeptive Afferenzen wurden mittels kutaner Laserreizung und taktile Afferenzen mittels nichtschmerzhafter elektrischer Reizung aktiviert. Beide Reize wurden auf die rechte Hand appliziert. Der direkte Vergleich der kortikalen Antworten auf beide Reize deckte grundlegende Unterschiede der Organisation beider Modalitäten innerhalb von S1 auf (Abb. 5).

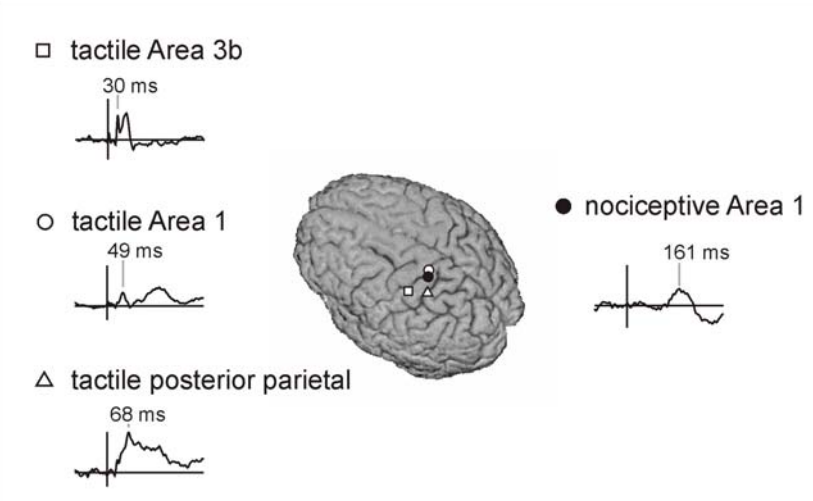


Abb. 5. Vergleich der Lokalisationen und Zeitverläufe berührungs- und schmerzevozierter Aktivierungen (Ploner et al., 2000)

Die taktile Reizung führte zu einer sequentiellen Aktivierung zweier Quellen neuromagnetischer Aktivität innerhalb von S1. Die Schmerzreize hingegen aktivierten nur eine einzige Quelle innerhalb von S1. Die schmerzevozierte Aktivierung war im Mittel 10 mm weiter medial lokalisiert als die frühe berührungsevozierte Aktivierung und entsprach der Lokalisation der späten berührungsevozierten Quelle.

Intra- und extrakranielle Ableitungen beim Affen (McCarthy et al., 1991) und Menschen (Wood et al., 1985; Allison et al., 1989b) zeigen, daß die ersten Komponenten somatosensorisch evozierter Potentiale mit Latenzen um 20 und 30 ms in der Area 3b von S1 generiert werden. Somit ist anzunehmen, daß auch die in der vorliegenden Studie registrierten frühen taktilen Antworten mit Latenzen um 30 ms aus der Area 3b rühren. Die mehr mediale Lokalisation der späteren taktilen S1-Antworten und der schmerzevozierten S1-Antworten deutet hingegen auf Generatoren in der Area 1 hin. Ein mittlerer mediolateraler Lokalisationsunterschied von 10 mm entspricht gut einem mediolateralen Unterschied in der Lokalisation der Handareale der Areae 3b und 1 wie er in intrakraniellen Ableitungen (Wood et al., 1988; Allison et al., 1989b; McCarthy et al., 1991) und anatomischen (Jones et al., 1982) und funktionell bildgebenden Studien (Juliano und Whitsel, 1985; Burton et al., 1997) gezeigt wurde.

Der Befund einer Generierung schmerzevozierter S1-Antworten in der Area 1 wird von tierexperimentellen Studien gestützt. Einzelzellableitungen bei Affen zeigten, daß die meisten nozizeptiven S1-Neurone in der Area 1 lokalisiert sind (Kenshalo und Isensee, 1983; Chudler et al., 1990; Kenshalo et al., 2000). Auch einige funktionell bildgebende Studien zeigten im direkten Vergleich, daß schmerzevozierte S1-Antworten weiter medial als berührungsevozierte S1-Antworten lokalisiert sind (Coghill et al., 1994; Iadarola et al., 1998). Eine folgende MEG-Arbeit einer anderen Gruppe bestätigte direkt den vorliegenden Befund einer Lokalisation schmerzbedingter Antworten in der Area 1 (Inui et al., 2003).

Das Ergebnis einer sequentiellen Aktivierung taktiler S1-Quellen spiegelt eine zumindest partiell seriell organisierte Verarbeitung von Berührung innerhalb des S1-Kortex wider (Kaas, 2004b). Die ausschließliche Generierung nozizeptiver Antworten in der Area 1 zeigt hingegen, daß auch innerhalb von S1 grundlegende Unterschiede zwischen taktiler und nozizeptiver Verarbeitung bestehen. Die Verarbeitung von Schmerz teilt offensichtlich nicht die komplexe und hierarchische Organisation der Berührungsverarbeitung, die sich evolutionär mit einer Verfeinerung sensorischer Fähigkeiten entwickelte (Kaas, 2004a). Stattdessen mag die einfachere Organisation der Schmerzverarbeitung eine rasche Integration schmerzbezogener Information in motorische und kognitive Abläufe ermöglichen.

Teleologisch erscheint dies durchaus sinnvoll, da bei der Wahrnehmung von Schmerz schnelle und effektive Reaktionen auf und die künftige Meidung von schmerzhaften Ereignissen von entscheidenderer Bedeutung sind als elaborierte Objektdiskriminationen und -manipulationen.

*Die Funktion der somatosensorischen Kortizes in der Wahrnehmung von Schmerz*

Zur Frage der funktionellen Bedeutung der somatosensorischen Kortizes in der Verarbeitung und Wahrnehmung von Schmerz wurde in einer weiteren MEG-Studie der Effekt der Reizintensität auf Schmerzwahrnehmung und -verarbeitung untersucht (Timmermann et al., 2001). Bei gesunden Probanden wurden randomisiert Reize in vier unterschiedlichen Reizstärken auf den Handrücken appliziert. Die Probanden wurden gebeten, die Intensität der Wahrnehmung eines jeden Reizes auf einer Skala zwischen 0 (kein Schmerz) und 100 (schlimmster vorstellbarer Schmerz) einzuschätzen. Gleichzeitig wurden die neuromagnetischen Antworten auf die Reize registriert und die Amplituden der S1- und S2-Antworten auf jede der vier Reizstärken bestimmt. Abbildung 6 zeigt das wesentliche Ergebnis dieser Studie.

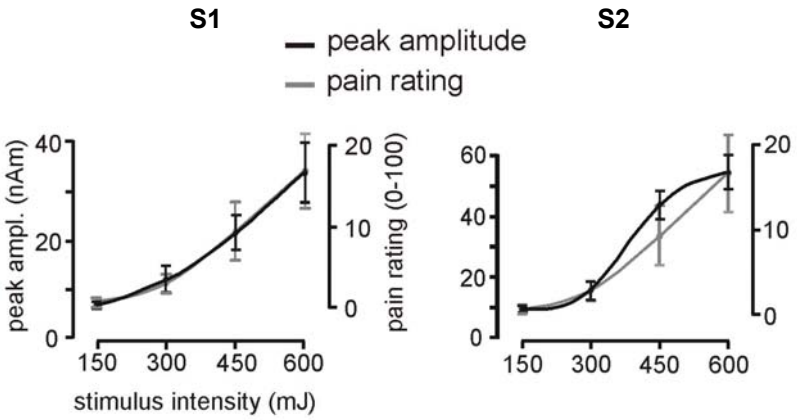


Abb. 6. Effekt der Reizintensität auf Schmerzintensität und Amplituden von S1- und S2-Antworten (Timmermann et al., 2001)

Die Ergebnisse zeigen, daß es mit steigender Reizintensität zu Anstiegen von Schmerzintensität und Antwortamplituden in S1 und S2 kommt. Die Abhängigkeit der Antwortamplituden von der Reizintensität unterschied sich jedoch zwischen S1 und S2. Das Verhältnis zwischen S1-Aktivität und Reizintensität zeigte eine Exponentialfunktion, wobei sich Anstiege von S1-Amplituden und Schmerzintensität glichen. Für das S2-Areal zeigte sich hingegen eine S-förmige Kurve mit einem steilen Anstieg der Amplitude nach Überschreiten

der Schmerzschwelle. Der Anstieg der S2-Amplitude zeigte eine weniger getreue Abbildung der Schmerzintensität. Die enge Entsprechung zwischen Anstieg der S1-Amplitude und Anstieg der Schmerzintensität läßt S1 als prädestiniert für sensorisch-diskriminative Leistungen in der Schmerzwahrnehmung erscheinen. Hingegen verweist das Alles-oder-nichts-Muster der schmerzevozierten S2-Aktivierung eher auf eine nicht-diskriminative Funktion des S2-Areals.

Unterstützung findet die Assoziation zwischen sensorischen Aspekten von Schmerz und der Funktion von S1 durch den zuvor beschriebenen Fallbericht (Ploner et al., 1999a). Bei dem geschilderten Patienten kam es durch eine Läsion, die im wesentlichen die S1- und S2-Areale umfaßte, zu einem Verlust sensorischer Fähigkeiten der Schmerzwahrnehmung. Weitere Unterstützung findet diese Assoziation zwischen sensorischer Schmerzkomponente und der Funktion von S1 durch tierexperimentelle Studien, die eine somatotope Anordnung von nozizeptiven S1-Neuronen, kleine rezeptive Felder und eine gute Kodierung von Intensität und Dauer von Schmerzreizen zeigten (Kenshalo und Isensee, 1983; Lamour et al., 1983; Kenshalo et al., 1988; Chudler et al., 1990; Kenshalo et al., 2000). Auch Studien der funktionellen Bildgebung verweisen auf eine solche Assoziation (Porro et al., 1998; Hofbauer et al., 2001; Bornhovd et al., 2002; Bingel et al., 2004; Moulton et al., 2005).

Bezüglich der Funktion von S2 läßt das oben geschilderte Aktivierungsmuster eher nicht-diskriminative Funktionen vermuten. Welche dies sind, ist bis heute vergleichsweise wenig bekannt. Bezüglich der Verarbeitung von Berührung wurde eine Beteiligung von S2 an kognitiven Funktionen postuliert (Friedman et al., 1986). Dies beruhte auf Beobachtungen von Läsionseffekten in S2 (Ridley und Ettlinger, 1976, 1978; Murray und Mishkin, 1984; Caselli, 1993) und auf anatomischen Studien, die Projektionen von S2 über den insulären Kortex zu den gedächtnisrelevanten Arealen des medialen Temporallappens zeigten (Friedman et al., 1986; Shi und Cassell, 1998). Analog zu dieser Einbindung von S2 in taktile Gedächtnisfunktionen wurde eine Bedeutung von S2 für schmerzbezogene Gedächtnis- und Lernfunktionen vorgeschlagen (Dong et al., 1989; Lenz et al., 1997). Eine solche Assoziation zwischen der Funktion von S2 und kognitiven Aspekten von Schmerz wäre gut mit dem gegenwärtigen Befund des Antwortmusters von S2 auf Schmerzreize hin und der Beeinträchtigung der Erkennung von Schmerz bei dem geschilderten Fallbericht vereinbar.

Zusammenfassend belegen die erhobenen Befunde somit eine Beteiligung des S1-Kortex an sensorischen Aspekten von Schmerz und lassen eine Assoziation zwischen S2 und kognitiven Aspekten von Schmerz plausibel erscheinen.

*Die kortikale Repräsentation von Schmerz unterschiedlicher Körpergewebe*

Schmerz kann oberflächlich oder tief in Muskeln, Gelenken, Eingeweiden oder Gefäßen wahrgenommen werden. In einer eigenen Studie wurde der Frage nachgegangen, ob sich die kortikale Verarbeitung von Schmerz unterschiedlicher Gewebetypen unterscheidet. Hierfür wurden bei gesunden Probanden Laserreize auf die Haut und in Blutgefäße des Handrückens appliziert. Die intravenöse Applikation gelang mittels Einführung einer sterilen Glasfaser durch einen Venenverweilkatheter, womit der Laserreiz durch die Glasfaser auf die Venenwand appliziert werden konnte. Kortikale Antworten auf beide Reize wurden magnetenzephalographisch registriert und miteinander verglichen.

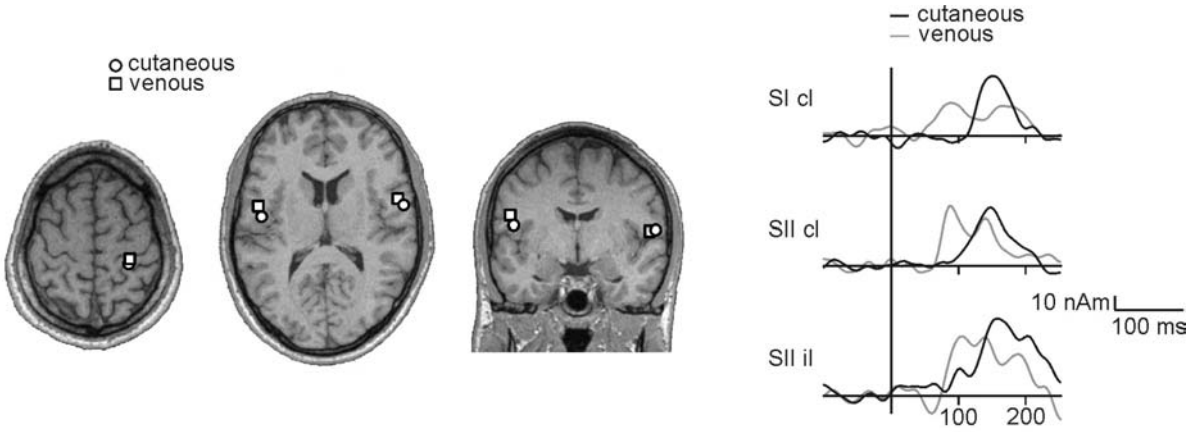


Abb. 7. Lokalisationen und Zeitverläufe schmerzevozierter Aktivierungen aus venösem und kutanem Gewebe (Ploner et al., 2002b)

Abbildung 7 zeigt, daß beide Reiztypen das kontralaterale S1-Areal und die bilateralen S2-Areale aktivieren. Es zeigte sich kein Unterschied der Antwortlokalisationen auf beide Reize. Auch das Aktivierungsmuster stimmte zwischen beiden Konditionen überein, beide Reize aktivierten nahezu simultan die S1- und S2-Areale. Jedoch führte die intravenöse Stimulation in allen Arealen im Mittel zu 50 ms früheren Aktivierungen als die kutane Stimulation. Diese Ergebnisse zeigen, daß auf Ebene der somatosensorischen Kortizes kein grundsätzlicher Unterschied zwischen der kortikalen Verarbeitung von kutanem Schmerz und von Schmerz aus der Gefäßwand besteht. Der generelle Latenzunterschied zwischen beiden Konditionen verweist jedoch auf Unterschiede in der peripheren Verarbeitung beider Reize. Mögliche systematische Unterschiede der Lokalisation beider Reize oder der Latenz der Rezeptoraktivierung können rechnerisch kaum eine Latenzdifferenz von 50 ms erklären, so daß der Latenzunterschied am ehesten auf Unterschiede der Leitungsgeschwindigkeiten zwischen kutanen und venösen nozizeptiven Afferenzen zurückzuführen ist. Möglicherweise

spiegelt der Latenzunterschied somit die Aktivierung unterschiedlicher Populationen nozizeptiver Aδ-Fasern wider, wie sie vom Affen bekannt sind (Treede et al., 1995; Treede et al., 1998).

Zieht man die mesodermale Herkunft der Venen in Betracht, so liegt es nahe, die vorliegenden Befunde mit Arbeiten zur kortikalen Schmerzverarbeitung anderer Gewebe mesodermalen Ursprungs, wie z.B. des Muskels zu vergleichen. Diese Studien zeigten keinen grundlegenden Unterschied zwischen kutanem und muskulärem Schmerz (Svensson et al., 1997; Niddam et al., 2002; Chang et al., 2004). Die in den eigenen Arbeiten erhobenen Befunde zur Verarbeitung kutanen Schmerzes erscheinen somit übertragbar auf Schmerz mesodermalen Gewebes.

*Die kortikale Repräsentation Ersten und Zweiten Schmerzes*

Es ist ein einzigartiges perzeptuelles Phänomen, daß einzelne Schmerzreize zwei aufeinanderfolgende und qualitativ unterschiedliche Sensationen hervorrufen. Diese Sensationen werden als Erster Schmerz und Zweiter Schmerz bezeichnet. Die periphere Grundlage dieses Phänomens ist die gleichzeitige Aktivierung zweier Typen nozizeptiver Fasern mit unterschiedlichen Leitungsgeschwindigkeiten (Aδ- und C-Fasern, ~10 m/s und ~1 m/s). Die zentralen Korrelate und die biologische Funktion beider Sensationen sind bisher weitgehend unbekannt. In einer eigenen Studie wurden die zentralen Korrelate Ersten und Zweiten Schmerzes daher näher untersucht (Ploner et al., 2002a).

In einem ersten Schritt wurden gesunde Probanden gebeten, den Zeitverlauf der Wahrnehmung der schmerzhaften Laserreize mit der Fingerspanne von Daumen und Zeigefinger der linken Hand widerzugeben. Die Schmerzreize wurden auf den rechten Handrücken appliziert. Der Zeitverlauf dieser Ratingprozedur wurde mittels eines ultraschallbasierten Bewegungsmeßsystems aufgezeichnet. Die Ergebnisse zeigen, daß der äußerst kurze Reiz von 1 ms Dauer ein langanhaltendes Perzept von 2 bis 3 sec Dauer hervorruft (Abb. 8, links). Entsprechend zeigt der Zeitverlauf der globalen schmerzevozierten neuromagnetischen Aktivität, daß der kurze Laserreiz zu einer langanhaltenden kortikalen Aktivierung von 2 bis 3 sec Dauer führt (Abb. 8, rechts). Wahrnehmung wie assoziierte kortikale Aktivität zeigen initial einen steilen Anstieg, einen ersten Gipfel und nachfolgend einen steilen Abfall, was der Wahrnehmung Ersten Schmerzes entspricht. Anschließend findet sich eine langanhaltende, langsam abebbende Sensation und kortikale Aktivität entsprechend der Wahrnehmung Zweiten Schmerzes.

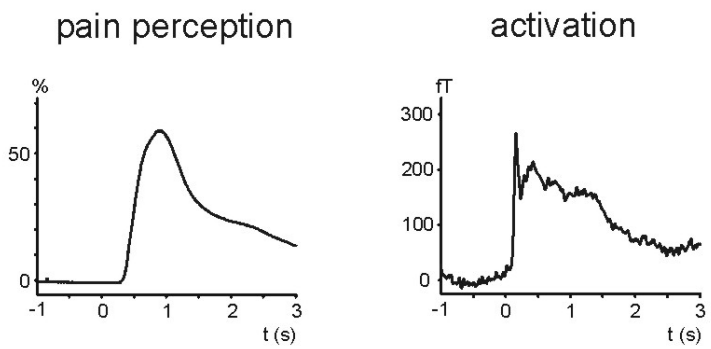


Abb 8. Zeitverläufe von Schmerzwahrnehmung und globaler schmerzevozierter kortikaler Aktivität auf kurzdauernde Laserreize von 1 ms Dauer (Ploner et al., 2002a)

Im nächsten Schritt wurden die Lokalisationen und Zeitverläufe schmerzevozierter kortikaler Aktivität bestimmt. Im Vergleich zu den vorangegangenen Studien wurde hierzu das Zeitfenster von 300 ms auf 3000 ms verlängert. Abbildung 9 zeigt auf der linken Seite die Lokalisationen schmerzevozierter Aktivierungen.

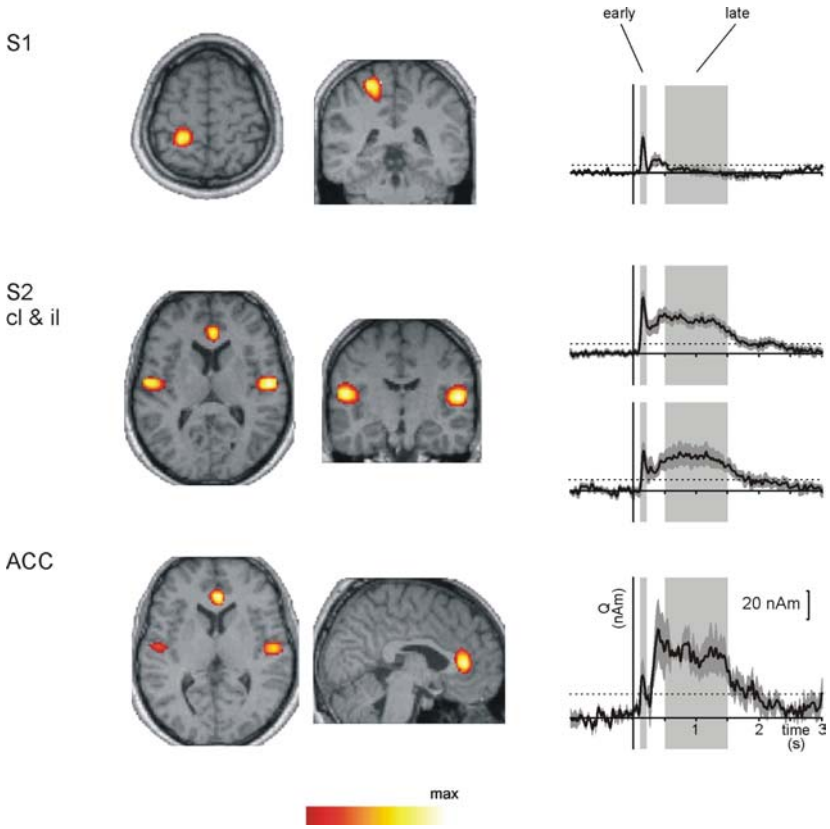


Abb. 9. Lokalisationen und Zeitverläufe schmerzevozierter kortikaler Aktivität. Die grau hinterlegten Abschnitte geben Zeiträume Aδ-Faser-vermittelter, mit Erstem Schmerz assoziierter und C-Faser vermittelter, mit Zweitem Schmerz assoziierter Aktivität wider. (Ploner et al., 2002a)

Es finden sich die bekannten schmerzevozierten Aktivierungen in S1 und S2. Zusätzlich zeigt sich eine Aktivierung im vorderen zingulären Kortex (ACC). Die rechte Seite der Abbildung zeigt die Zeitverläufe der Aktivierungen in diesen Arealen. Mit grauen Hinterlegungen wurden Latenzbereiche mit Aδ-Faser-vermittelter, mit Erstem Schmerz assoziierter und C-Faser-vermittelter, mit Zweitem Schmerz assoziierter Aktivität markiert. Die Zeitverläufe lassen grundlegende Unterschiede zwischen den Arealen erkennen. S1 wird nur im frühen Zeitfenster signifikant aktiviert, im späten Zeitfenster findet sich hier keine signifikante Aktivität. Der ACC zeigt ein umgekehrtes Aktivierungsmuster. Es findet sich eine starke Aktivierung im späten Zeitfenster und eine vergleichsweise schwache, aber signifikante Aktivierung im frühen Zeitfenster. Die Amplituden der S2-Aktivierungen erscheinen ausgeglichen zwischen den Zeitfenstern. Diese Befunde zeigen, daß Erster Schmerz insbesondere mit der Aktivierung des S1-Areals einhergeht, während Zweiter Schmerz eng mit der Aktivierung des ACC assoziiert ist. Beide Sensationen sind mit bilateraler Aktivierung des S2-Areals verbunden.

Die vorliegenden Ergebnisse zeigen erstmals direkt die kortikalen Korrelate der zeitlichen Sequenz Ersten und Zweiten Schmerzes. Während die Korrelate Ersten Schmerzes in den vorangegangenen eigenen und anderen Arbeiten ausgiebig analysiert werden konnten (Kakigi et al., 2005), haben zentrale Korrelate Zweiten Schmerzes in nur vergleichsweise wenigen neurophysiologischen Studien gezeigt werden können (Bromm und Treede, 1987; Arendt-Nielsen, 1990; Bragard et al., 1996; Towell et al., 1996; Magerl et al., 1999; Opsommer et al., 2001; Tran et al., 2002; Qiu et al., 2004; Forss et al., 2005). Die Lokalisierung gelang in nur wenigen Studien (Opsommer et al., 2001; Tran et al., 2002; Qiu et al., 2004; Forss et al., 2005). Überwiegend waren mit Zweitem Schmerz assoziierte Aktivierungen dabei in S2 und dem ACC lokalisiert. Auch auf die vorliegende Arbeit folgende Einzelzellableitungen bei der Ratte (Kuo und Yen, 2005) und eine fMRI-Studie (Qiu et al., 2005) stützen eine Assoziation zwischen der Funktion des ACC und C-Faser-Reizung bzw. Zweitem Schmerz.

Funktionell spiegelt der aktuelle Befund einer unterschiedlichen Repräsentation Ersten und Zweiten Schmerzes wahrscheinlich die unterschiedlichen perzeptuellen Charakteristika und biologischen Funktionen beider Sensationen wider. Erster Schmerz signalisiert Bedrohung und versorgt das Individuum mit ausreichend sensorischer Information für eine schnelle und angemessene motorische Antwort, d.h. eine rasche Fluchtreaktion. Erster Schmerz dient damit der umgehenden Beendigung einer Gefahrensituation. Zweiter Schmerz mit seiner starken affektiven Komponente bindet längeranhaltend Aufmerksamkeit und initiiert Verhaltensweisen zur Begrenzung des Schadens und zur Optimierung der Erholung. Zweiter

Schmerz vermittelt somit eine erholungsfördernde und heilende Funktion von Schmerz (Wall, 1979).

*Schmerzinduzierte Modulationen kortikaler Erregbarkeit*

Schmerz und Berührung sind eng miteinander verbundene Modalitäten. Die alltägliche Erfahrung lehrt, daß schmerzhafte Reize und Reaktionen auf diese Reize meist mit Berührungswahrnehmungen einhergehen. Interaktionen zwischen beiden Modalitäten sind auf der Verhaltensebene wiederholt beschrieben worden (Melzack und Wall, 1965; Apkarian et al., 1994; Hollins et al., 1996; Bolanowski et al., 2000) und lassen sich teils therapeutisch nutzen, man bedenke die transkutane elektrische Nervenstimulation (TENS) (Hansson und Lundeberg, 1999). Entsprechend dieser engen Assoziation findet sich eine beträchtliche Überlappung der kortikalen Repräsentationen beider Modalitäten, was insbesondere die somatosensorischen Kortizes betrifft. Interaktionen zwischen beiden Modalitäten auf kortikaler Ebene sind jedoch nur unvollständig bekannt (Tommerdahl et al., 1996; Rossi et al., 1998; Dowman, 1999; Tran et al., 2003). In einer weiteren Studie wurden diese Interaktionen daher näher charakterisiert (Ploner et al., 2004).

Unter Verwendung eines Konditionierungs-Test-Stimulus-Paradigmas wurde der Effekt von Schmerzreizen auf die Verarbeitung von Berührung untersucht (Abb. 10).

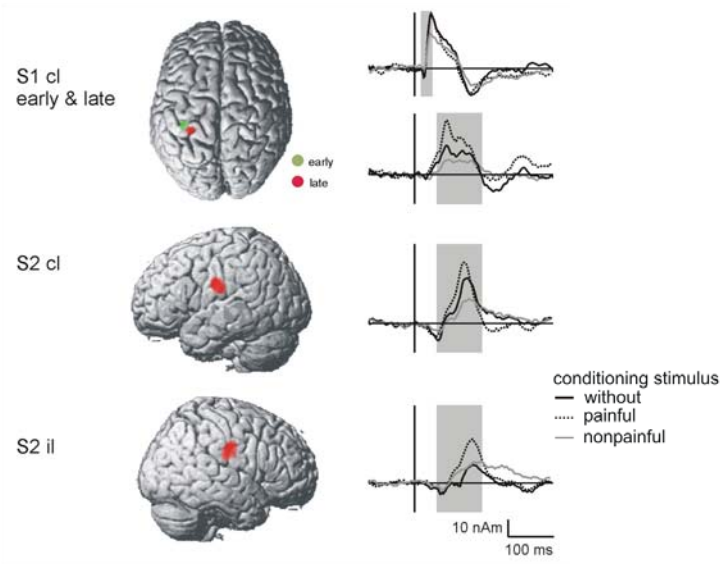


Abb. 10. Lokalisationen und Zeitverläufe berührungsevozierter kortikaler Aktivität. Der Effekt schmerzhafter konditionierender Reize zeigt sich im Vergleich zwischen gepunkteten und durchgezogenen Verläufen. (Ploner et al., 2004)

Konkret wurde hierfür ein schmerzhafter Laserreiz auf den rechten Handrücken gesunder Probanden appliziert. 500 ms nach diesem schmerzhaften Reiz wurde eine nicht-schmerzhafte taktile Reizung appliziert und es wurde der modulierende Effekt des konditionierenden Schmerzreizes auf die Verarbeitung des taktilen Testreizes untersucht.

Es läßt sich erkennen, daß der schmerzhafte konditionierende Reiz keinen wesentlichen Einfluß auf die erste kortikale Verarbeitungsstufe des taktilen Testreizes im S1-Areal hat. In späteren Verarbeitungsstufen innerhalb des S1-Areals und in den beiderseitigen S2-Arealen findet sich jedoch eine schmerzbedingt signifikante Erhöhung der Amplituden auf die taktilen Testreize hin. Ein Kontrollexperiment zeigt, daß diese Fazilitierung nicht räumlich spezifisch ist. Das heißt, daß schmerzhafte konditionierende Reize auf der linken Hand ebenfalls zu einer Fazilitierung der Verarbeitung taktiler Reize an der rechten Hand führen. Kurze schmerzhafte Reize führen somit zu einer räumlich unspezifischen, globalen Fazilitierung taktiler Verarbeitung in den somatosensorischen Kortizes. Dieser fazilitierende Effekt von Schmerz auf die Verarbeitung von Berührung war zuvor nicht bekannt.

Bezüglich der funktionellen Bedeutung dieses fazilitierenden Effekts fällt auf, daß der Effekt phänomenologisch attentionalen Effekten auf die Verarbeitung von Berührung ähnelt. Wiederholt wurde gezeigt, daß Aufmerksamkeit die ersten Komponenten berührungsevozierter Potentiale mit Latenzen unter 40 ms unbeeinflußt läßt, während spätere Verarbeitungsstufen in S1 und S2 mit Latenzen über 40 ms fazilitiert werden (Josiassen et al., 1982; Michie et al., 1987; Desmedt und Tomberg, 1989; Mima et al., 1998; Eimer und Forster, 2003). Jedoch sind diese attentionalen Effekte räumlich spezifisch und entsprechen wahrscheinlich der von Posner beschrieben „orienting“-Funktion der Aufmerksamkeit (Posner und Petersen, 1990). Vor diesem Hintergrund mag der aktuelle Befund einer räumlich unspezifischen Fazilitierung eher die „alerting“-Funktion von Aufmerksamkeit repräsentieren (Posner und Petersen, 1990; Corbetta und Shulman, 2002). Diese folgt unwillkürlich auf relevante und/oder neue Reize und wird wahrscheinlich von einem kortiko-subkortikalen Netzwerk unter Einschluß der rechtsseitigen frontalen, parietalen und zingulären Kortizes vermittelt (Corbetta und Shulman, 2002; Downar et al., 2002; Downar et al., 2003). Die „alerting“-Funktion geht mit einer Änderung des behavioralen Status zur Vorbereitung auf die Verarbeitung besonders relevanter Reize einher (Posner und Petersen, 1990). Dies trifft insbesondere auf den Schmerz zu, der eine existentielle Bedrohung signalisiert und das Individuum zur Meidung weiteren Schadens anhält.

Zusammenfassend konnte in der vorgelegten Studie erstmals eine schmerzbedingte Fazilitierung taktiler Verarbeitung gezeigt werden. Es erscheint plausibel, dies als ein

physiologisches Korrelat unwillkürlicher schmerzbedingter attentionaler Effekte aufzufassen. Da eine pathologisch vermehrte schmerzbedingte Aufmerksamkeit wesentlich für die Chronifizierung von Schmerz zu sein scheint (Crombez et al., 2005), verspricht die nähere Charakterisierung dieses Effektes bei Gesunden und Schmerzkranken Einblicke in die Entstehung chronischen Schmerzes.

*Schmerzinduzierte Modulationen spontaner oszillatorischer Aktivität*

In einer folgenden Arbeit wurde der Effekt von Schmerz auf spontane oszillatorische Aktivität untersucht (Ploner et al., 2006a). Spontane Oszillationen sind ein wesentliches Charakteristikum der neuronalen Aktivität des ruhenden Gehirns (Hari und Salmelin, 1997; Niedermeyer, 2005; Pfurtscheller und Lopes da Silva, 2005). Solche spontanen Oszillationen oder Hirnrhythmen werden vor allem über primär sensorischen und motorischen Kortizes beobachtet und finden sich überwiegend in Frequenzbereichen um 10 Hz ($\alpha$-Band) und 20 Hz ($\beta$-Band). Die regionale Ausprägung der oszillatorischen Aktivität spiegelt den Funktionszustand des jeweiligen sensorischen oder motorischen Systems wider. Eine höhere Amplitude oszillatorischer Aktivität geht mit einem Ruhezustand einher, während niedrigere Amplituden eine exogene oder endogene Aktivierung des Systems signalisieren. Darüber hinaus wird vermutet, daß eine Suppression oszillatorischer Aktivität mit einer vermehrten kortikalen Exzitabilität einhergeht (Steriade und Llinas, 1988).

Einige wenige Studien der letzten Jahre beschäftigen sich mit den Effekten von Schmerz auf spontane oszillatorische Aktivität (Mouraux et al., 2003; Ohara et al., 2004a; Raij et al., 2004). Diese Studien zeigten, daß Schmerz spontane Oszillationen über dem sensomotorischen Kortex der kontralateralen Hemisphäre supprimiert, was im Grunde dem Effekt taktiler Reize entspricht. Zieht man jedoch die breite Interaktion von Schmerz mit sensorischen, motorischen und kognitiven Prozessen in Betracht (Melzack und Casey, 1968; Eccleston und Crombez, 1999), so erscheint eine über das sensomotorische System hinausgehende, globale Modulation kortikaler Systeme möglich. Dieser Frage wurde in der vorliegenden Studie nachgegangen.

Hierzu wurden bei gesunden Probanden schmerzhafte kutane Laserreize auf den rechten Handrücken appliziert und der Effekt dieser Reize auf spontane oszillatorische Aktivität analysiert. Diese schmerzbedingten Effekte wurden mit den Effekten taktiler Reize verglichen. Zunächst wurde eine globale Zeit-Frequenz-Repräsentation (TFR) berechnet. Diese zeigt Veränderungen neuronaler Aktivität in Abhängigkeit von Frequenz und Zeit

relativ zu einer Prästimulus-baseline. Abbildung 11 zeigt eine solche globale TFR gemittelt über alle 122 MEG-Sensoren und über alle Probanden.

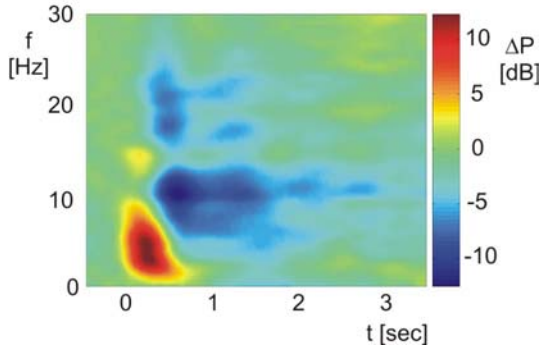


Abb. 11. Globale Zeit-Frequenz-Repräsentation schmerzinduzierter Modulationen spontaner oszillatorischer Aktivität gemittelt über alle Epochen, Sensoren und Probanden.(Ploner et al., 2006a)

Die Abbildung zeigt zunächst eine schmerzbedingte Zunahme (in rot kodiert) neuronaler Aktivität unterhalb von 10 Hz, was den in den vorangegangenen Studien analysierten schmerzevozierten Antworten entspricht. Anschließend findet sich eine langanhaltende, bis mindestens 2 sec dauernde Suppression (in blau kodiert) neuronaler Aktivität im α- und β-Band.

In einem nächsten Analyseschritt wurden die schmerzinduzierten Suppressionen oszillatorischer neuronaler Aktivität lokalisiert (Abb. 12).

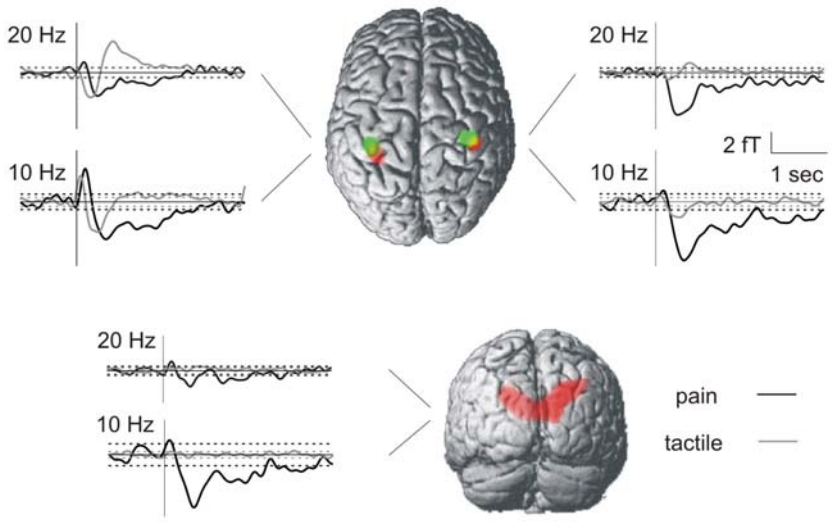


Abb. 12. Lokalisationen und Zeitverläufe schmerzinduzierter Modulationen spontaner oszillatorischer Aktivität. Modulationen im α-Band sind in rot, im β-Band in grün kodiert. (Ploner et al., 2006a)

Lokale Maxima fanden sich in den beiderseitigen primär motorischen und somatosensorischen Arealen und über den visuellen Kortizes. Neben den Lokalisationen zeigt die Abbildung die Zeitverläufe oszillatorischer Aktivität im α- und β-Band in den jeweiligen Arealen. Es läßt sich entnehmen, daß die kurzdauernden Schmerzreize in allen Arealen zu einer langanhaltenden Suppression spontaner oszillatorischer Aktivität führen. Entsprechend der funktionellen Assoziation einer solchen Suppression kann dies als eine schmerzinduziert globale Aktivierung sensorischer und motorischer Systeme interpretiert werden. Zieht man die Ergebnisse der vorangegangenen Studie in Betracht, so zeigt sich hier ein weiteres mögliches Korrelat eines globalen attentionalen Effektes von Schmerz im Sinne eines „alerting"-Effekts.

*Spontane oszillatorische Aktivität und Exzitabilität der somatosensorischen Kortizes*

In den beiden vorangegangenen Studien wurden die schmerzinduzierten Phänomene einer vermehrten Erregbarkeit des somatosensorischen Systems und einer globalen Suppression spontaner oszillatorischer Aktivität beschrieben. Vor dem Hintergrund des Postulates einer Assoziation zwischen kortikaler Exzitabilität und oszillatorischer Aktivität (Steriade und Llinas, 1988) erscheint es möglich, daß beide Phänomene in enger Beziehung zueinander stehen. Dieser Hypothese wurde in einer weiteren Studie nachgegangen (Ploner et al., 2006b).

In dieser Studie wurde das zuvor eingeführte Konitionierungs-Test-Stimulus-Paradigma verwendet (Ploner et al., 2004). Der konditionierende Schmerzreiz sollte oszillatorische Aktivität supprimieren und die kortikale Exzitabilität erhöhen. Die kortikalen Antworten auf den taktilen Testreiz dienten als Maß der Exzitabilität der somatosensorischen Kortizes. Auf der Auswertung einzelner trials basierend wurde die schmerzbedingte Modulation spontaner oszillatorischer Aktivität mit der Modulation der Exzitabilität in Beziehung gesetzt. Abbildung 13 zeigt die Ergebnisse. Es läßt sich eine signifikante negative Korrelation zwischen der Ausprägung oszillatorischer Aktivität, vor allem im α-Band, und kortikaler Exzitabilität erkennen. Die insgesamt vergleichsweise niedrigen Korrelationskoeffizienten resultieren dabei aus der single-trial basierten Analyse. Bei solchen Analysen sind die Meßwerte naturgemäß stark von Störsignalen geprägt. Sie eignen sich daher nicht zur Aufklärung der maximalen Varianz der Meßwerte, sind jedoch besonders sensitiv für das Aufdecken subtiler Zusammenhänge.

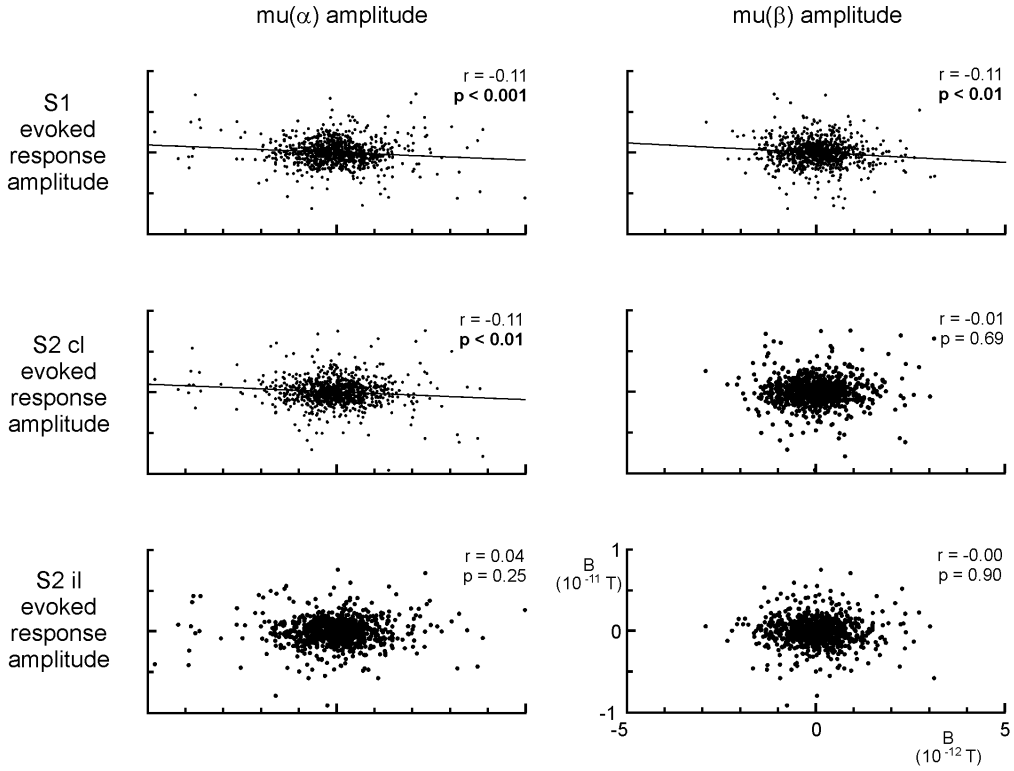


Abb. 13. Korrelation zwischen schmerzbedingten Modulationen oszillatorischer Aktivität (x-Achse) über dem primären sensomotorischen Kortex und schmerzbedingten Modulationen kortikaler Exzitabilität (y-Achse) in S1 und S2. (Ploner et al., 2006b)

Die signifikante negative Korrelation zwischen oszillatorischer Aktivität und Exzitabilität von S1 und S2 legt nahe, daß beide Phänomene tatsächlich in einer engen Beziehung zueinander stehen. Dieser Befund stützt somit das grundlegende Postulat einer Assoziation zwischen oszillatorischer Aktivität und neuronaler Exzitabilität (Steriade und Llinas, 1988). Darüber hinaus weisen die Ergebnisse darauf hin, daß die Phänomene der schmerzinduzierten Fazilitierung sensorischer Verarbeitung und der schmerzinduzierten Suppression spontaner oszillatorischer Aktivität in engem Zusammenhang miteinander stehen. Möglicherweise handelt es sich bei beiden Phänomenen um physiologische Korrelate der „alerting"-Funktion von Schmerz.

Über die beiden Phänomenen zugrundeliegenden neuralen Mechanismen läßt sich aufgrund der vorliegenden Daten nur spekulieren. Plausibel erscheint jedoch das oben bereits angerissene Modell von Corbetta (Corbetta und Shulman, 2002). Diese Modell postuliert eine behavioral relevante Reize detektierende globale „alerting"-Funktion von Aufmerksamkeit, die von einem rechtslateralisierten kortiko-subkortikalen Netzwerk vermittelt wird. Auf kortikaler Ebene sind der zinguläre und der inferior frontale Kortex sowie der temporoparietale Übergang wesentliche Bestandteile dieses Netzwerkes. Auf

Hirnstammebene wurde der Locus coeruleus mit seinen noradrenergen Projektionen als wesentlich für diese Funktion postuliert. Eine solche Assoziation zwischen korrelierten Modulationen oszillatorischer Aktivität und kortikaler Exzitabilität, einer Aktivierung des Locus coeruleus mit seinen noradrenergen Projektionen und einer alerting-Funktion wird durch verschiedene Befunde gestützt. Eine Aktivierung des Locus coeruleus supprimiert oszillatorische Aktivität in Thalamus und Kortex, vermehrt thalamische und kortikale Exzitabilität und ist mit Reizrelevanz und Aufmerksamkeit assoziiert (McCormick et al., 1991; Aston-Jones et al., 2000; Berridge und Waterhouse, 2003; Coull, 2005). Darüber hinaus konnte gezeigt werden, daß Schmerz zum somatosensorischen Thalamus projizierende Neurone des Locus coeruleus aktiviert (Voisin et al., 2005). Möglicherweise sind die in den eigenen Studien beobachteten schmerzinduzierten Phänomene mit diesem rechtslateralisierten kortikosubkortikalen Netzwerk unter Beteiligung des Locus coeruleus und entsprechenden noradrenergen Projektionen assoziiert. Dieses Netzwerk könnte der Optimierung der Funktion sensorischer und motorischer Systeme dienen, um das Individuum auf die Verarbeitung von und Reaktion auf Reize existentieller Relevanz vorzubereiten. Auf Verhaltensebene mag dies mit einer Optimierung sensorischer und motorischer Leistungen einhergehen (Linkenkaer-Hansen et al., 2004; Raij et al., 2004).

**Zusammenfassung und Ausblick**

Schmerz ist eine komplexe sensorische, kognitive und affektive Erfahrung. Schmerz wird entscheidend von vorangegangenen Erfahrungen und der aktuellen Situation geprägt und ist somit stets subjektiv. In seiner physiologischen Funktion ist er unverzichtbar für den Erhalt der physischen Unversehrtheit, von seiner physiologischen Funktion gelöst stellt er als chronischer Schmerz ein entscheidendes medizinisches Problem dar.

In einer Reihe neurophysiologischer Studien unter Verwendung der Magnetenzephalographie und der kutanen Laserstimulation wurden die zentralnervösen Mechanismen der Verarbeitung und Wahrnehmung von Schmerz näher charakterisiert. Insbesondere wurden die Zeitverläufe und funktionellen Charakteristika schmerzbezogener kortikaler Aktivierungen untersucht, um so Einblicke in die hierarchische Organisation und die funktionelle Bedeutung einzelner Hirnareale für die Schmerzwahrnehmung zu erlangen.

Die Arbeiten zeigen, daß die kortikale Verarbeitung von Schmerz sowohl zwischen als auch innerhalb verschiedener kortikaler Areale teilweise parallel organisiert ist. Dies gilt für Schmerz aus oberflächlichen wie tiefen Körpergeweben. Auf Verhaltensebene findet sich dies mit einer Dissoziierbarkeit und somit Unabhängigkeit verschiedener perzeptueller Aspekte von Schmerz wieder. Die parallele Organisation der Schmerzverarbeitung entspricht einer basalen, evolutionär alten Organisationsform und unterscheidet Schmerz von anderen Modalitäten. Funktionell mag die parallele Organisation von Schmerz eine höhere Robustheit, schnellere Verarbeitungsabläufe und einen direkteren Zugang zu motorischen und gedächtnisrelevanten Arealen ermöglichen.

Die vorgelegten Arbeiten legen nahe, daß die einzelnen an der Schmerzverarbeitung beteiligten kortikalen Areale unterschiedliche Teilfunktionen versehen. Der primäre somatosensorische Kortex (S1) ist prädestiniert für sensorische Funktionen. Der sekundäre somatosensorische Kortex (S2) mag mit kognitiven und sensomotorisch integrativen Funktionen befaßt sein, während der vordere zinguläre Kortex (ACC) mit der affektiven Komponente von Schmerz assoziiert ist. Die genannten Areale sind unterschiedlich an der Generierung der Sensationen Ersten und Zweiten Schmerzes beteiligt. Erster Schmerz ist eng mit der Aktivierung von S1 verbunden, während Zweiter Schmerz insbesondere mit einer Aktivierung des ACC einhergeht. Dies mag die unterschiedlichen biologischen Funktionen beider Sensationen widerspiegeln. Erster Schmerz signalisiert Bedrohung, versorgt das Individuum mit ausreichend sensorischer Information für eine schnelle und angemessene motorische Antwort und dient damit der umgehenden Beendigung einer Gefahrensituation. Zweiter Schmerz mit einer starken affektiven Komponente bindet längeranhaltend

Aufmerksamkeit, initiiert Verhaltensweisen zur Schadensbegrenzung und Heilung und vermittelt eine erholungsfördernde und heilende Funktion von Schmerz.

Weitere Studien zeigen, daß die Effekte von Schmerz über die direkte Aktivierung umschriebener Hirnareale hinausgehen. Entsprechend unserer alltäglichen Erfahrung moduliert Schmerz global den Funktionszustand und die Erregbarkeit sensorischer und motorischer Systeme. Dies entspricht wahrscheinlich einem globalen Aufmerksamkeitseffekt im Sinne einer „alerting"-Funktion von Schmerz. Diese „alerting"-Funktion optimiert die Funktion sensorischer und motorischer Systeme, um das Individuum auf die Verarbeitung von und Reaktion auf existentiell relevante Reize vorzubereiten. Eine pathologische Vermehrung einer solchen schmerzbezogenen Aufmerksamkeit scheint wesentlich an der Chronifizierung von Schmerz beteiligt.

Eine auf den eigenen Befunden basierende schematische Übersicht über die Organisation der Schmerzverarbeitung zeigt Abbildung 14. Zusammenfassend konnten die vorgelegten Studien zum Wissen über die physiologischen Grundlagen der zentralen Schmerzverarbeitung beitragen. Es gelangen Einblicke in die hierarchische Organisation des kortikalen Netzwerks der Schmerzverarbeitung sowie Zuordnungen zwischen der Funktion einzelner kortikaler Areale und verschiedenen Aspekten der Schmerzwahrnehmung. Darüber hinaus konnten globale attentionale Effekte von Schmerz beschrieben werden.

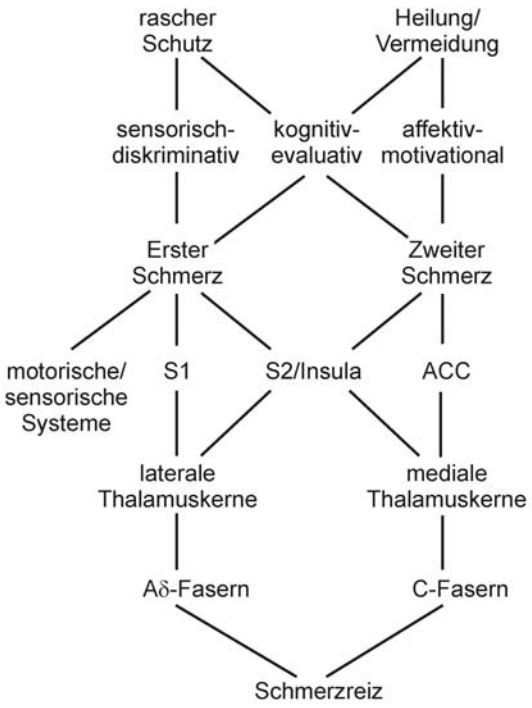


Abb. 14. Die Organisation der Schmerzverarbeitung. S1, primärer somatosensorischer Kortex; S2, sekundärer somatosensorischer Kortex, ACC, vorderer zingulärer Kortex;

Wesentliche Fragen für die weitere Arbeit sind das Zusammenspiel der verschiedenen kortikalen Areale in der Generierung eines individuellen Perzepts. Auch die exogene und endogene z.B. attentionale Modulation der Schmerzwahrnehmung werden aktuell intensiv untersucht, sind aber noch nicht ausreichend verstanden. Ein verbessertes Verständnis dieser Mechanismen verspricht dabei Einblicke in die Entstehung und Linderung von Schmerz. Die Übertragung der experimentellen Paradigmen und beobachteten Phänomene der vorgelegten Arbeiten auf chronisch schmerzkranke Patienten könnte somit therapeutisch verwertbare Einblicke in die Entstehung chronischen Schmerzes liefern.

**Literatur**


Allison T, McCarthy G, Wood CC, Williamson PD, Spencer DD (1989a) Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol 62:711-722.

Allison T, McCarthy G, Wood CC, Darcey TM, Spencer DD, Williamson PD (1989b) Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. J Neurophysiol 62:694-710.

Andersson JL, Lilja A, Hartvig P, Langstrom B, Gordh T, Handwerker H, Torebjork E (1997) Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. Exp Brain Res 117:192-199.

Apkarian AV, Shi T (1994) Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals. J Neurosci 14:6779-6795.

Apkarian AV, Stea RA, Bolanowski SJ (1994) Heat-induced pain diminishes vibrotactile perception: a touch gate. Somatosens Mot Res 11:259-267.

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK (2005) Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9:463-484.

Apkarian AV, Stea RA, Manglos SH, Szeverenyi NM, King RB, Thomas FD (1992) Persistent pain inhibits contralateral somatosensory cortical activity in humans. Neurosci Lett 140:141-147.

Arendt-Nielsen L (1990) Second pain event related potentials to argon laser stimuli: recording and quantification. J Neurol Neurosurg Psychiatry 53:405-410.

Aston-Jones G, Rajkowski J, Cohen J (2000) Locus coeruleus and regulation of behavioral flexibility and attention. Prog Brain Res 126:165-182.

Augustine JR (1996) Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev 22:229-244.

Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I (2002) Imaging how attention modulates pain in humans using functional MRI. Brain 125:310-319.

Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 42:33-84.

Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C (2006) Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120:8-15.

Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C (2003) Single trial fMRI reveals significant contralateral bias in responses to laser pain within thalamus and somatosensory cortices. Neuroimage 18:740-748.

Bingel U, Lorenz J, Glauche V, Knab R, Glascher J, Weiller C, Buchel C (2004) Somatotopic organization of human somatosensory cortices for pain: a single trial fMRI study. Neuroimage 23:224-232.

Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H (1999) A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Eur J Neurosci 11:3276-3286.

Bishop GH, Landau WM (1958) Evidence for a double peripheral pathway for pain. Science 128:712-713.

Bolanowski SJ, Maxfield LM, Gescheider GA, Apkarian AV (2000) The effects of stimulus location on the gating of touch by heat- and cold-induced pain. Somatosens Mot Res 17:195-204.

Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C (2002) Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125:1326-1336.

Bragard D, Chen AC, Plaghki L (1996) Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO2 laser stimulation of tiny cutaneous surface areas in man. Neurosci Lett 209:81-84.

Bromm B, Treede RD (1987) Human cerebral potentials evoked by CO2 laser stimuli causing pain. Exp Brain Res 67:153-162.

Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N (2002) fMRI of thermal pain: effects of stimulus laterality and attention. Neuroimage 15:293-301.

Brooks JC, Zambreanu L, Godinez A, Craig AD, Tracey I (2005) Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. Neuroimage 27:201-209.

Buchel C, Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C (2002) Dissociable Neural Responses Related to Pain Intensity, Stimulus Intensity, and Stimulus Awareness within the Anterior Cingulate Cortex: A Parametric Single-Trial Laser Functional Magnetic Resonance Imaging Study. J Neurosci 22:970-976.

Burton H, Fabri M, Alloway K (1995) Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. J Comp Neurol 355:539-562.

Burton H, MacLeod AM, Videen TO, Raichle ME (1997) Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. Cereb Cortex 7:3-17.

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215-222.

Bushnell MC, Apkarian AV (2006) Representation of pain in the brain. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 107-124. Philadelphia: Elsevier.

Bushnell MC, Villemure C, Duncan GH (2004) Psychophysical and Neurophysiological Studies of Pain Modulation by Attention. In: Psychological Methods of Pain Control: Basic Science and Clinical Perspectives (Price DD, Bushnell MC, eds), pp 99-116. Seattle: IASP Press.

Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen J, Carrier B (1999) Pain perception: is there a role for primary somatosensory cortex? [In Process Citation]. Proc Natl Acad Sci U S A 96:7705-7709.

Caselli RJ (1993) Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans. Neurology 43:762-771.

Casey KL, Morrow TJ, Lorenz J, Minoshima S (2001) Temporal and spatial dynamics of human forebrain activity during heat pain: analysis by positron emission tomography. J Neurophysiol 85:951-959.

Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Chen AC (2004) Comparative EEG activation to skin pain and muscle pain induced by capsaicin injection. Int J Psychophysiol 51:117-126.

Chen JI, Ha B, Bushnell MC, Pike B, Duncan GH (2002) Differentiating noxious- and innocuous-related acivation of human somatosensory cortices using temporal analysis of fMRI. J Neurophysiol 88:464-474.

Chudler EH, Anton F, Dubner R, Kenshalo DR, Jr. (1990) Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. J Neurophysiol 63:559-569.

Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 82:1934-1943.

Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH (1994) Distributed processing of pain and vibration by the human brain. J Neurosci 14:4095-4108.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Coull JT (2005) Psychopharmacology of human attention. In: Neurobiology of attention (Itti L, Rees G, Tsotsos J, eds), pp 50-56. Amsterdam: Elsevier.

Craig AD (2003) Pain mechanisms: Labeled lines versus convergence in central processing. Annu Rev Neurosci 26:1-30.

Craig AD, Reiman EM, Evans A, Bushnell MC (1996) Functional imaging of an illusion of pain [see comments]. Nature 384:258-260.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004) Neural systems supporting interoceptive awareness. Nat Neurosci 7:189-195.

Crombez G, Van Damme S, Eccleston C (2005) Hypervigilance to pain: an experimental and clinical analysis. Pain 116:4-7.

Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997) Functional MRI of pain- and attention-related activations in the human cingulate cortex. J Neurophysiol 77:3370-3380.

deCharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, Gabrieli JD, Mackey SC (2005) Control over brain activation and pain learned by using real-time functional MRI. Proc Natl Acad Sci U S A 102:18626-18631.

Derbyshire SW, Vogt BA, Jones AK (1998) Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex. Exp Brain Res 118:52-60.

Desmedt JE, Tomberg C (1989) Mapping early somatosensory evoked potentials in selective attention: critical evaluation of control conditions used for titrating by difference the cognitive P30, P40, P100 and N140. Electroencephalogr Clin Neurophysiol 74:321-346.

Di Piero V, Ferracuti S, Sabatini U, Pantano P, Cruccu G, Lenzi GL (1994) A cerebral blood flow study on tonic pain activation in man. Pain 56:167-173.

Disbrow E, Roberts T, Krubitzer L (2000) Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. J Comp Neurol 418:1-21.

Disbrow E, Litinas E, Recanzone GH, Slutsky D, Krubitzer L (2002) Thalamocortical connections of the parietal ventral area (PV) and the second somatosensory area (S2) in macaque monkeys. Thalamus & Related Systems 1:289-302.

Disbrow E, Litinas E, Recanzone GH, Padberg J, Krubitzer L (2003) Cortical connections of the second somatosensory area and the parietal ventral area in macaque monkeys. J Comp Neurol 462:382-399.

Dong WK, Chudler EH, Sugiyama K, Roberts VJ, Hayashi T (1994) Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. J Neurophysiol 72:542-564.

Dong WK, Salonen LD, Kawakami Y, Shiwaku T, Kaukoranta EM, Martin RF (1989) Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. Brain Res 484:314-324.

Dostrovsky JO, Craig AD (2006) Ascending projection systems. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 187-203. Philadelphia: Elsevier.

Dowman R (1999) Laser pain fails to inhibit innocuous-related activity in the central somatosensory pathways. Psychphysiology 36:371-378.

Downar J, Mikulis DJ, Davis KD (2003) Neural correlates of the prolonged salience of painful stimulation. Neuroimage 20:1540-1551.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2002) A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. J Neurophysiol 87:615-620.

Eccleston C, Crombez G (1999) Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 125:356-366.

Eickhoff SB, Schleicher A, Zilles K, Amunts K (2006a) The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb Cortex 16:254-267.

Eickhoff SB, Amunts K, Mohlberg H, Zilles K (2006b) The Human Parietal Operculum. II. Stereotaxic Maps and Correlation with Functional Imaging Results. Cereb Cortex 16:268-279.

Eimer M, Forster B (2003) Modulations of early somatosensory ERP components by transient and sustained spatial attention. Exp Brain Res 151:24-31.

Ferretti A, Babiloni C, Gratta CD, Caulo M, Tartaro A, Bonomo L, Rossini PM, Romani GL (2003) Functional topography of the secondary somatosensory cortex for nonpainful and painful stimuli: an fMRI study. Neuroimage 20:1625-1638.

Fields HL, Basbaum AI, Heinricher MM (2006) Central nervous system mechanisms of pain modulation. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 125-142. Philadelphia: Elsevier.

Fitzgerald PJ, Lane JW, Thakur PH, Hsiao SS (2004) Receptive field properties of the macaque second somatosensory cortex: evidence for multiple functional representations. J Neurosci 24:11193-11204.

Foltz EL, White LE (1962) Pain "relief" by frontal cingulumotomy. J Neurosurgery 19:89-100.

Forss N, Jousmaki V (1998) Sensorimotor integration in human primary and secondary somatosensory cortices. Brain Res 781:259-267.

Forss N, Raij TT, Seppa M, Hari R (2005) Common cortical network for first and second pain. Neuroimage 24:132-142.

Friedman DP, Murray EA, O'Neill JB, Mishkin M (1986) Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol 252:323-347.

Frot M, Mauguière F (2003) Dual representation of pain in the operculo-insular cortex in humans. Brain 126:438-450.

Gad J, Goldscheider A (1892) Ueber die Summation von Hautreizen. Z klin Med 20:339-373.

Garraghty PE, Florence SL, Kaas JH (1990) Ablations of areas 3a and 3b of monkey somatosensory cortex abolish cutaneous responsivity in area 1. Brain Res 528:165-169.

Garraghty PE, Florence SL, Tenhula WN, Kaas JH (1991) Parallel thalamic activation of the first and second somatosensory areas in prosimian primates and tree shrews. J Comp Neurol 311:289-299.

Gelnar PA, Krauss BR, Sheehe PR, Szeverenyi NM, Apkarian AV (1999) A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. Neuroimage 10:460-482.

Gingold SI, Greenspan JD, Apkarian AV (1991) Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys. J Comp Neurol 308:467-490.

Grisart JM, Plaghki LH (1999) Impaired selective attention in chronic pain patients. Eur J Pain 3:325-333.

Hämäläinen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys 65:413-497.

Hanamori T, Kunitake T, Kato K, Kannan H (1998) Responses of neurons in the insular cortex to gustatory, visceral, and nociceptive stimuli in rats. J Neurophysiol 79:2535-2545.

Hansson P, Lundeberg T (1999) Transcutaneous electrical nerve stimulation, vibration and acupuncture as pain-relieving measures. In: Textbook of pain (Wall PD, Melzack R, eds), pp 1341-1351. Edinburgh: Churchill Livingstone.

Hari R (2005) Magnetoencephalography in Clinical Neurophysiological Assessment of HUman Cortical Functions. In: Electroencephalography: basic principles, clinical applications, and related fields (Niedermeyer E, Lopes da Silva F, eds), pp 1165-1197. Philadelphia: Lippincott Williams & Wilkins.

Hari R, Salmelin R (1997) Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci 20:44-49.

Hari R, Karhu J, Hamalainen M, Knuutila J, Salonen O, Sams M, Vilkman V (1993) Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. Eur J Neurosci 5:724-734.

Head H, Holmes G (1911) Sensory disturbances from cerebral lesions. Brain 34:102-254.

Hofbauer RK, Rainville P, Duncan GH, Bushnell MC (2001) Cortical representation of the sensory dimension of pain. J Neurophysiol 86:402-411.

Hollins M, Sigurdsson A, Fillingim L, Goble AK (1996) Vibrotactile threshold is elevated in temporomandibular disorders. Pain 67:89-96.

Hurt RW, Ballantine HTJ (1974) Stereotactic anterior cingulate lesions for persistent pain: a report on 68 cases. Clin Neurosurg 21:334-351.

Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO (1999) Pain-related neurons in the human cingulate cortex. Nat Neurosci 2:403-405.

Huttunen J, Wikstrom H, Korvenoja A, Seppalainen AM, Aronen H, Ilmoniemi RJ (1996) Significance of the second somatosensory cortex in sensorimotor integration: enhancement of sensory responses during finger movements. Neuroreport 7:1009-1012.

Iadarola MJ, Berman KF, Zeffiro TA, Byas-Smith MG, Gracely RH, Max MB, Bennett GJ (1998) Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. Brain 121:931-947.

Inui K, Wang X, Qiu Y, Nguyen BT, Ojima S, Tamura Y, Nakata H, Wasaka T, Tran TD, Kakigi R (2003) Pain processing within the primary somatosensory cortex in humans. Eur J Neurosci 18:2859-2866.

Ito SI (1998) Possible representation of somatic pain in the rat insular visceral sensory cortex: a field potential study. Neurosci Lett 241:171-174.

Iwata K, Kamo H, Ogawa A, Tsuboi Y, Noma N, Mitsuhashi Y, Taira M, Koshikawa N, Kitagawa J (2005) Anterior cingulate cortical neuronal activity during perception of noxious thermal stimuli in monkeys. J Neurophysiol 94:1980-1991.

Johansen JP, Fields HL, Manning BH (2001) The affective component of pain in rodents: Direct evidence for a contribution of the anterior cingulate cortex. PNAS 98:8077-8082.

Jones AK, Brown WD, Friston KJ, Qi LY, Frackowiak RS (1991) Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc R Soc Lond B Biol Sci 244:39-44.

Jones EG, Friedman DP, Hendry SH (1982) Thalamic basis of place- and modality-specific columns in monkey somatosensory cortex: a correlative anatomical and physiological study. J Neurophysiol 48:545-568.

Josiassen RC, Shagass C, Roemer RA, Ercegovac DV, Straumanis JJ (1982) Somatosensory evoked potential changes with a selective attention task. Psychophysiology 19:146-159.

Juliano SL, Whitsel BL (1985) Metabolic labeling associated with index finger stimulation in monkey SI: between animal variability. Brain Res 342:242-251.

Kaas JH (2004a) Evolution of somatosensory and motor cortex in primates. Anat Rec A Discov Mol Cell Evol Biol 281:1148-1156.

Kaas JH (2004b) Somatosensory System. In: The Human Nervous System (Paxinos G, Mai JK, eds). Amsterdam: Elsevier.

Kakigi R, Inui K, Tamura Y (2005) Electrophysiological studies on human pain perception. Clin Neurophysiol 116:743-763.

Kanda M, Nagamine T, Ikeda A, Ohara S, Kunieda T, Fujiwara N, Yazawa S, Sawamoto N, Matsumoto R, Taki W, Shibasaki H (2000) Primary somatosensory cortex is actively involved in pain processing in human. Brain Res 853:282-289.

Kenshalo DR, Willis WD (1991) The role of the cerebral cortex in pain sensation. In: Cerebral Cortex (Peters A, Jones EG, eds), pp 153-212. New York: Plenum Press.

Kenshalo DR, Iwata K, Sholas M, Thomas DA (2000) Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. J Neurophysiol 84:719-729.

Kenshalo DR, Jr., Isensee O (1983) Responses of primate SI cortical neurons to noxious stimuli. J Neurophysiol 50:1479-1496.

Kenshalo DR, Jr., Giesler GJ, Jr., Leonard RB, Willis WD (1980) Responses of neurons in primate ventral posterior lateral nucleus to noxious stimuli. J Neurophysiol 43:1594-1614.

Kenshalo DR, Jr., Chudler EH, Anton F, Dubner R (1988) SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. Brain Res 454:378-382.

Koyama T, Tanaka YZ, Mikami A (1998) Nociceptive neurons in the macaque anterior cingulate activate during anticipation of pain. Neuroreport 9:2663-2667.

Krubitzer L, Clarey J, Tweedale R, Elston G, Calford M (1995) A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. J Neurosci 15:3821-3839.

Krubitzer LA, Kaas JH (1990) The organization and connections of somatosensory cortex in marmosets. J Neurosci 10:952-974.

Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, Frackowiak RS, Friston KJ, Jones AK (2005) Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci 21:3133-3142.

Kuo CC, Yen CT (2005) Comparison of anterior cingulate and primary somatosensory neuronal responses to noxious laser-heat stimuli in conscious, behaving rats. J Neurophysiol 94:1825-1836.

Kwan CL, Crawley AP, Mikulis DJ, Davis KD (2000) An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. Pain 85:359-374.

Lamour Y, Willer JC, Guilbaud G (1983) Rat somatosensory (SmI) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation. Exp Brain Res 49:35-45.

Ledberg A, O'Sullivan BT, Kinomura S, Roland PE (1995) Somatosensory activations of the parietal operculum of man. A PET study. Eur J Neurosci 7:1934-1941.

Lenz FA, Gracely RH, Zirh AT, Romanoski AJ, Dougherty PM (1997) The sensory-limbic model of pain memory. Pain Forum 6:22-31.

Lenz FA, Rios M, Chau D, Krauss GL, Zirh TA, Lesser RP (1998a) Painful stimuli evoke potentials recorded from the parasylvian cortex in humans. J Neurophysiol 80:2077-2088.

Lenz FA, Rios M, Zirh A, Chau D, Krauss G, Lesser RP (1998b) Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. J Neurophysiol 79:2231-2234.

Levine JD, Gordon NC, Smith R, Fields HL (1982) Post-operative pain: effect of extent of injury and attention. Brain Res 234:500-504.

Lewis T, Pochin EE (1937) The double pain response of the human skin to a single stimulus. Clinical Science 3:67-76.

Linkenkaer-Hansen K, Nikulin VV, Palva S, Ilmoniemi RJ, Palva JM (2004) Prestimulus oscillations enhance psychophysical performance in humans. J Neurosci 24:10186-10190.

Macfarlane GJ, Jones GT, McBeth J (2006) Epidemiology of pain. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 1199-1214. Philadelphia: Elsevier.

Magerl W, Ali Z, Ellrich J, Meyer RA, Treede RD (1999) C- and A delta-fiber components of heat-evoked cerebral potentials in healthy human subjects. Pain 82:127-137.

Mauguiere F, Merlet I, Forss N, Vanni S, Jousmaki V, Adeleine P, Hari R (1997) Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. Electroencephalogr Clin Neurophysiol 104:281-289.

Mazzola L, Isnard J, Mauguiere F (2005) Somatosensory and Pain Responses to Stimulation of the Second Somatosensory Area (SII) in Humans. A Comparison with SI and Insular Responses. Cereb Cortex.

McCarthy G, Wood CC, Allison T (1991) Cortical somatosensory evoked potentials. I. Recordings in the monkey Macaca fascicularis. J Neurophysiol 66:53-63.

McCormick DA, Pape HC, Williamson A (1991) Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. Prog Brain Res 88:293-305.

Melzack R, Wall PD (1965) Pain mechanisms: a new theory. Science 150:971-979.

Melzack R, Casey KL (1968) Sensory, motivational, and central control determinants of pain: a new conceptual model in pain. In: The skin senses (Kenshalo DRJ, ed). Springfield, IL: Charles C. Thomas.

Mesulam MM, Mufson EJ (1985) The insula of Reil in man and monkey. In: Cerebral Cortex (Peters A, Jones EG, eds), pp 179-226. New York: Plenum Press.

Meyer RA, Ringkamp M, Campbell JN, Raja SN (2006) Peripheral mechanisms of cutaneous nociception. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 3-34. Philadelphia: Elsevier.

Michie PT, Bearpark HM, Crawford JM, Glue LCT (1987) The effects of spatial selective attention on the somatosensory event-related potential. Psychophysiology 24:449-463.

Mima T, Nagamine T, Nakamura K, Shibasaki H (1998) Attention modulates both primary and secondary somatosensory cortical activities in humans: a magnetoencephalographic study. J Neurophysiol 80:2215-2221.

Miron D, Duncan GH, Bushnell MC (1989) Effects of attention on the intensity and unpleasentness of thermal pain. Pain 39:345-352.

Moulton EA, Keaser ML, Gullapalli RP, Greenspan JD (2005) Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. J Neurophysiol 93:2183-2193.

Mouraux A, Guerit JM, Plaghki L (2003) Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between A partial partial differential- and C-fibre afferent volleys. Clin Neurophysiol 114:710-722.

Murray EA, Mishkin M (1984) Relative contributions of SII and area 5 to tactile discrimination in monkeys. Behav Brain Res 11:67-83.

Nagasako EM, Oaklander AL, Dworkin RH (2003) Congenital insensitivity to pain: an update. Pain 101:213-219.

Niddam DM, Yeh TC, Wu YT, Lee PL, Ho LT, Arendt-Nielsen L, Chen AC, Hsieh JC (2002) Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. Neuroimage 17:1437-1450.

Niedermeyer E (2005) The normal EEG of the waking adult. In: Electroencephalography: basic principles, clinical applications, and related fields (Niedermeyer E, Lopes da Silva F, eds), pp 167-192. Philadelphia: Lippincott Williams & Wilkins.

Ohara S, Crone NE, Weiss N, Lenz FA (2004a) Attention to a painful cutaneous laser stimulus modulates electrocorticographic event-related desynchronization in humans. Clin Neurophysiol 115:1641-1652.

Ohara S, Crone NE, Weiss N, Treede RD, Lenz FA (2004b) Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. J Neurophysiol 91:2734-2746.

Opsommer E, Weiss T, Plaghki L, Miltner WH (2001) Dipole analysis of ultralate (C-fibres) evoked potentials after laser stimulation of tiny cutaneous surface areas in humans. Neurosci Lett 298:41-44.

Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F (2002) Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cerebral Cortex 12:376-385.

Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2:417-424.

Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389-443.

Penfield W, Rasmussen T (1950) The Cerebral Cortex of Man. New York: Macmillan.

Petrovic P, Ingvar M (2002) Imaging cognitive modulation of pain processing. Pain 95:1-5.

Petrovic P, Kalso E, Petersson KM, Ingvar M (2002a) Placebo and opioid analgesia-- imaging a shared neuronal network. Science 295:1737-1740.

Petrovic P, Petersson KM, Hansson P, Ingvar M (2002b) A regression analysis study of the primary somatosensory cortex during pain. Neuroimage 16:1142-1150.

Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M (2000) Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85:19-30.

Peyron R, Garcia-Larrea L, Gregoire MC, Costes N, Convers P, Lavenne F, Mauguiere F, Michel D, Laurent B (1999) Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 122 ( Pt 9):1765-1780.

Pfurtscheller G, Lopes da Silva F (2005) EEG event-related desynchronization (ERD) and event-related synchronization. In: Electroencephalography: basic principles, clinical applications, and related fields (Niedermeyer E, Lopes da Silva F, eds), pp 1003-1016. Philadelphia: Lippincott Williams & Wilkins.

Ploner M, Freund HJ, Schnitzler A (1999a) Pain affect without pain sensation in a patient with a postcentral lesion. Pain 81:211-214.

Ploner M, Schmitz F, Freund HJ, Schnitzler A (1999b) Parallel activation of primary and secondary somatosensory cortices in human pain processing. J Neurophysiol 81:3100-3104.

Ploner M, Schmitz F, Freund HJ, Schnitzler A (2000) Differential organization of touch and pain in human primary somatosensory cortex. J Neurophysiol 83:1770-1776.

Ploner M, Gross J, Timmermann L, Schnitzler A (2002a) Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci U S A 99:12444-12448.

Ploner M, Holthusen H, Noetges P, Schnitzler A (2002b) Cortical representation of venous nociception in humans. J Neurophysiol 88:300-305.

Ploner M, Pollok B, Schnitzler A (2004) Pain facilitates tactile processing in human somatosensory cortices. J Neurophysiol 92:1825-1829.

Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A (2006a) Pain suppresses spontaneous brain rhythms. Cereb Cortex 16:537-540.

Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A (2006b) Oscillatory activity reflects the excitability of the human somatosensory system. Neuroimage: in press.

Pons TP, Garraghty PE, Friedman DP, Mishkin M (1987) Physiological evidence for serial processing in somatosensory cortex. Science 237:417-420.

Porro CA, Cettolo V, Francescato MP, Baraldi P (1998) Temporal and intensity coding of pain in human cortex. J Neurophysiol 80:3312-3320.

Posner MI, Petersen SE (1990) The attention system of the human brain. Annu Rev Neurosci 13:25-42.

Price DD, Hu JW, Dubner R, Gracely RH (1977) Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain 3:57-68.

Qiu Y, Inui K, Wang X, Nguyen BT, Tran TD, Kakigi R (2004) Effects of distraction on magnetoencephalographic responses ascending through C-fibers in humans. Clin Neurophysiol 115:636-646.

Qiu Y, Noguchi Y, Honda M, Nakata H, Tamura Y, Tanaka S, Sadato N, Wang X, Inui K, Kakigi R (2005) Brain Processing of the Signals Ascending Through Unmyelinated C Fibers in Humans: An Event-Related Functional Magnetic Resonance Imaging Study. Cereb Cortex.

Raij TT, Forss N, Stancak A, Hari R (2004) Modulation of motor-cortex oscillatory activity by painful Adelta- and C-fiber stimuli. Neuroimage 23:569-573.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277:968-971.

Ridley RM, Ettlinger G (1976) Impaired tactile learning and retention after removals of the second somatic sensory projection cortex (SII) in the monkey. Brain Res 109:656-660.

Ridley RM, Ettlinger G (1978) Further evidence of impaired tactile learning after removals of the second somatic sensory projection cortex (SII) in the monkey. Exp Brain Res 31:475-488.

Robinson CJ, Burton H (1980) Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. J Comp Neurol 192:93-108.

Rossi A, Decchi B, Groccia V, Della Volpe R, Spidalieri R (1998) Interactions between nociceptive and non-nociceptive afferent projections to cerebral cortex in humans. Neuroscience Letters 248:155-158.

Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, Konishi J, Shibasaki H (2000) Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci 20:7438-7445.

Schlereth T, Baumgartner U, Magerl W, Stoeter P, Treede RD (2003) Left-hemisphere dominance in early nociceptive processing in the human parasylvian cortex. Neuroimage 20:441-454.

Schreckenberger M, Siessmeier T, Viertmann A, Landvogt C, Buchholz HG, Rolke R, Treede RD, Bartenstein P, Birklein F (2005) The unpleasantness of tonic pain is encoded by the insular cortex. Neurology 64:1175-1183.

Shi CJ, Cassell MD (1998) Cascade projections from somatosensory cortex to the rat basolateral amygdala via the parietal insular cortex. J Comp Neurol 399:469-491.

Sikes RW, Vogt BA (1992) Nociceptive neurons in area 24 of rabbit cingulate cortex. J Neurophysiol 68:1720-1732.

Spence C, Bentley DE, Phillips N, McGlone FP, Jones AKP (2002) Selective attention to pain: a psychophysical investigation. Experimental Brain Research 145:395-402.

Steriade M, Llinas RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649-742.

Stevens RT, London SM, Apkarian AV (1993) Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. Brain Res 631:241-246.

Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL (1997) Cerebral processing of acute skin and muscle pain in humans. J Neurophysiol 78:450-460.

Sweet WH (1982) Cerebral localization of pain. In: New perspectives in cerebral localization (Thompson RA, Green JR, eds), pp 205-242. New York: Raven.

Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991) Multiple representations of pain in human cerebral cortex [see comments]. Science 251:1355-1358.

Tarkka IM, Treede RD (1993) Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO2 laser. J Clin Neurophysiol 10:513-519.

Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A (2001) Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J Neurophysiol 86:1499-1503.

Tolle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F, Zieglgansberger W, Willoch F, Schwaiger M, Conrad B, Bartenstein P (1999) Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann Neurol 45:40-47.

Tommerdahl M, Delemos KA, Vierck CJ, Jr., Favorov OV, Whitsel BL (1996) Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. J Neurophysiol 75:2662-2670.

Torquati K, Pizzella V, Babiloni C, Del Gratta C, Della Penna S, Ferretti A, Franciotti R, Rossini PM, Romani GL (2005) Nociceptive and non-nociceptive sub-regions in the human secondary somatosensory cortex: an MEG study using fMRI constraints. Neuroimage 26:48-56.

Towell AD, Purves AM, Boyd SG (1996) CO2 laser activation of nociceptive and non-nociceptive thermal afferents from hairy and glabrous skin. Pain 66:79-86.

Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM (2002) Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 22:2748-2752.

Tran TD, Hoshiyama M, Inui K, Kakigi R (2003) Electrical-induced pain diminishes somatosensory evoked magnetic cortical fields. Clin Neurophysiol 114:1704-1714.

Tran TD, Inui K, Hoshiyama M, Lam K, Qiu Y, Kakigi R (2002) Cerebral activation by the signals ascending through unmyelinated C-fibers in humans: a magnetoencephalographic study. Neuroscience 113:375-386.

Treede RD (2003) Neurophysiological studies of pain pathways in peripheral and central nervous system disorders. J Neurol 250:1152-1161.

Treede RD, Meyer RA, Campbell JN (1998) Myelinated mechanically insensitive afferents from monkey hairy skin: heat-response properties. J Neurophysiol 80:1082-1093.

Treede RD, Meyer RA, Raja SN, Campbell JN (1995) Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. J Physiol 483:747-758.

Turman AB, Ferrington DG, Ghosh S, Morley JW, Rowe MJ (1992) Parallel processing of tactile information in the cerebral cortex of the cat: effect of reversible inactivation of SI on responsiveness of SII neurons. J Neurophysiol 67:411-429.

Vaccarino AL, Melzack R (1989) Analgesia produced by injection of lidocaine into the anterior cingulum bundle of the rat. Pain 39:213-219.

Valeriani M, Barba C, Le Pera D, Restuccia D, Colicchio G, Tonali P, Gagliardo O, Treede RD (2004) Different neuronal contribution to N20 somatosensory evoked potential and to CO2 laser evoked potentials: an intracerebral recording study. Clin Neurophysiol 115:211-216.

Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR (2004) Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain 109:399-408.

Vogel H, Port JD, Lenz FA, Solaiyappan M, Krauss G, Treede RD (2003) Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. J Neurophysiol 89:3051-3060.

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533-544.

Vogt BA, Derbyshire S, Jones AK (1996) Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. Eur J Neurosci 8:1461-1473.

Vogt BA, Watanabe H, Grootoonk S, Jones AKP (1995) Topography of diprenorphine binding in human cingulate gyrus and adjacent cortex derived from coregistered PET and MR images. Human Brain Mapping 3:1-12.

Voisin DL, Guy N, Chalus M, Dallel R (2005) Nociceptive stimulation activates locus coeruleus neurones projecting to the somatosensory thalamus in the rat. J Physiol 566:929-937.

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303:1162-1167.

Wall PD (1979) On the relation of injury to pain. The John J. Bonica lecture. Pain 6:253-264.

Whitsel BL, Petrucelli LM, Werner G (1969) Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. J Neurophysiol 32:170-183.

Willis WD, Westlund KN (2004) Pain System. In: The Human Nervous System (Paxinos G, Mai JK, eds), pp 1125-1170. Amsterdam: Elsevier.

Wood CC, Cohen D, Cuffin BN, Yarita M, Allison T (1985) Electrical sources in human somatosensory cortex: identification by combined magnetic and potential recordings. Science 227:1051-1053.

Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR (1988) Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 68:99-111.

Woolf CJ, Salter MW (2006) Plasticity and pain: role of the dorsal horn. In: Wall and Melzack's Textbook of Pain (McMahon SB, Koltzenburg M, eds), pp 91-105. Philadelphia: Elsevier.

Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51:476-506.

Yamamura H, Iwata K, Tsuboi Y, Toda K, Kitajima K, Shimizu N, Nomura H, Hibiya J, Fujita S, Sumino R (1996) Morphological and electrophysiological properties of ACCx nociceptive neurons in rats. Brain Res 735:83-92.

Zhang ZH, Dougherty PM, Oppenheimer SM (1999) Monkey insular cortex neurons respond to baroreceptive and somatosensory convergent inputs. Neuroscience 94:351-360.

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS (2001) Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293:311-315.

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Ploner M, Freund HJ, Schnitzler A (1999a) Pain affect without pain sensation in a patient with a postcentral lesion. Pain 81:211-214.

Ploner M, Schmitz F, Freund HJ, Schnitzler A (2000) Differential organization of touch and pain in human primary somatosensory cortex. J Neurophysiol 83:1770-1776.

Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A (2001) Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J Neurophysiol 86:1499-1503.

Ploner M, Holthusen H, Noetges P, Schnitzler A (2002b) Cortical representation of venous nociception in humans. J Neurophysiol 88:300-305.

Ploner M, Gross J, Timmermann L, Schnitzler A (2002a) Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci U S A 99:12444-12448.

Ploner M, Pollok B, Schnitzler A (2004) Pain facilitates tactile processing in human somatosensory cortices. J Neurophysiol 92:1825-1829.

Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A (2006a) Pain suppresses spontaneous brain rhythms. Cereb Cortex 16:537-540.

Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A (2006b) Oscillatory activity reflects the excitability of the human somatosensory system. Neuroimage: in press.

# Parallel Activation of Primary and Secondary Somatosensory Cortices in Human Pain Processing

MARKUS PLONER, FRANK SCHMITZ, HANS-JOACHIM FREUND, AND ALFONS SCHNITZLER
*Department of Neurology, Heinrich-Heine University, D-40225 Dusseldorf, Germany*

**Ploner, Markus, Frank Schmitz, Hans-Joachim Freund, and Alfons Schnitzler.** Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J. Neurophysiol.* 81: 3100–3104, 1999. Cerebral processing of pain has been shown to involve primary (SI) and secondary (SII) somatosensory cortices. However, the temporal activation pattern of these cortices in nociceptive processing has not been demonstrated so far. We therefore used whole-head magnetoencephalography to record cortical responses to cutaneous laser stimuli in six healthy human subjects. By using selective nociceptive stimuli our results confirm involvement of contralateral SI and bilateral SII in human pain processing. Beyond they show for the first time simultaneous activation onset of contralateral SI and SII after ~130 ms, indicating parallel thalamocortical distribution of nociceptive information. This contrasts to the serial cortical organization of tactile processing in higher primates and instead corresponds to the parallel cortical organization in lower primates and nonprimates. Thus our finding suggests preservation of the basic mammalian parallel organizational scheme in human pain processing, whereas in the tactile modality parallel organization appears to be abandoned in favor of a serial processing scheme. Functionally, preservation of direct access to SII underscores the relevance of this area in human pain processing, probably reflecting an important role of SII in nociceptive learning and memory.

## INTRODUCTION

From Head's statement that "pure cortical lesions cause no increase or decrease of sensibility to measured painful stimuli" (Head and Holmes 1911) it was inferred for decades that the cerebral cortex is not involved in human pain processing. Converging clinical and experimental evidence has substantially modified this view over the past years. In particular, participation of primary (SI) and secondary (SII) somatosensory cortices has been confirmed by data from experimental animal, human lesion (for reviews see Kenshalo and Willis 1991; Sweet 1982), and functional imaging studies (Casey et al. 1996; Coghill et al. 1994; Craig et al. 1996; Talbot et al. 1991). However, the temporal characteristics of nociceptive processing in these cortices have remained largely unknown. Especially it is unknown whether SI and SII are activated in a serial or a parallel mode. Serial processing of tactile information in higher primates (Garraghty et al. 1990; Pons et al. 1987, 1992), including humans (Allison et al. 1989a,b; Hari et al. 1993; Mima et al. 1998), may suggest a corresponding sequential activation of SI and SII to nociceptive stimuli, although no direct evidence for this has been presented so far.

We therefore used whole-head magnetoencephalography (MEG) to investigate the time course of cortical responses in SI and SII to selective nociceptive cutaneous laser stimuli.

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## METHODS

Six healthy right-handed male volunteers aged 28–38 yr (mean 33 yr) paricipated in the study. All subjects gave informed consent before the experiment. The procedure was approved by the local ethical committee.

### *Stimulation procedure*

In 2 subsequent runs, 40 selective nociceptive cutaneous laser stimuli (Bromm and Treede 1984) were applied to the dorsum of each hand with a Tm:YAG laser (Baasel Lasertech) with a wavelength of 2,000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Interstimulus intervals were randomly varied between 10 and 14 s, and stimulation site was slightly changed within an area of $4 \times 3$ cm after each stimulus. Before the recordings individual pain thresholds were determined with increasing and decreasing stimulus intensities at 50-mJ steps. Threshold was defined as intensity that elicited painful sensations in at least three of five applications. Stimulation intensity was adjusted to twofold pain threshold intensity, i.e., between 600- and 700-mJ pulse energy. After the recordings, subjects were asked to rate mean stimulus intensity on a category scale, including "mild," "mild to moderate," "moderate," "moderate to severe," and "severe" pain. No tactile sensation was evoked at any intensity.

### *Data acquisition and analysis*

Cortical responses were recorded with a Neuromag-122 whole-head neuromagnetometer (Ahonen et al. 1993) in a magnetically shielded room. The laser beam was led through an optical fiber from outside into the recording room. Signals were digitized at 483 Hz, band-pass filtered between 0.03 and 40 Hz, and averaged with respect to laser stimuli. Simultaneous recordings of vertical and horizontal electrooculogram were used to reject epochs contaminated by blink artifacts and eye movements. Analysis was focused on an epoch comprising 100 ms prestimulus baseline and 300 ms after stimulation. Sources of evoked responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for >85% of the local field variance (goodness of fit) were accepted. Dipole location, orientation, and strength were estimated within a spherical conductor model of each subject's head determined from the individual magnetic resonance images (MRI) acquired on a 1.5 T Siemens-Magnetom. The final spatiotemporal source model consisted of two or three dipoles with fixed locations and orientations. Dipole strength was allowed to vary over time to provide the best fit for the recorded data (for further details concerning data acquisition and analysis see Hämäläinen et al. 1993). The resulting source strength waveforms as a function of time were used for determination of peak and onset latencies. On the basis of fiducial point markers MRI and MEG coordinate systems were aligned, and source locations

 

were superposed on the individual MRI scans. To quantify location of sources MRI scans were adjusted to the Talairach coordinate system (Talairach and Tournoux 1988). In each individual, distances of SII sources were determined along the medial–lateral *x*-axis to the circular insular sulcus and along the anterior–posterior *y*-axis to the verticofrontal plane passing through the anterior commissure (VCA). Source locations were also calculated in standardized Talairach coordinates.

## RESULTS

In all subjects, stimuli elicited at least moderately painful, "pinprick-like" sensations. Field patterns of pain-evoked neuromagnetic responses indicated temporally overlapping activity of two almost orthogonally oriented cortical sources in the contralateral and one source in the ipsilateral hemisphere (Fig. 1a). Precise determination of activation sites and subsequent superposition on individual MRI scans revealed a contralateral source with an anterior–posterior current direction in the postcentral hand area and bilateral sources with inferior–superior orientations in the upper banks of the Sylvian fissures thus corresponding to contralateral SI and bilateral SII cortices, respectively (Fig. 1*b*); 95% confidence limits for localization of SI sources in each direction were 4 ± 2 mm (mean ± SD) in both hemispheres and of SII sources 5 ± 2 mm in the left and 5 ± 3 mm in the right hemisphere. Absolute medial–lateral distances between SII sources and circular insular sulcus were 13 ± 5 mm in the left hemisphere and 14 ± 4 mm in the right hemisphere. Distances of SII sources to the VCA were −15 ± 8 mm and −6 ± 3 mm, respectively. Mean standardized Talaraich coordinates (*x*, *y*, *z*) were −21, −33, 59 (left SI); 24, −30, 58 (right SI); −51, −15, 18 (left SII); 52, −6, 17 (right SII). Figure 1*c* shows the time course of source activations in a single subject, and Fig. 2 illustrates the group mean (±SE) activities across left- and right-hand stimulations of all subjects. Onset latencies of contralateral SI (131 ± 7 ms) and contralateral SII (126 ± 4 ms) were not statistically different (two-tailed Wilcoxon signed rank test, $P = 0.33$). Slightly steeper slopes most likely reflecting a higher degree of neuronal synchronization caused shorter peak latencies in contralateral SII (163 ± 4 ms) than in SI (174 ± 3 ms) ($P = 0.013$). Onsets and peaks of contralateral SII preceded ipsilateral SII by 12 ms ($P = 0.008$) and 18 ms ($P = 0.005$), respectively. Table 1 gives individual and mean onset and peak latencies of all stimulation conditions.

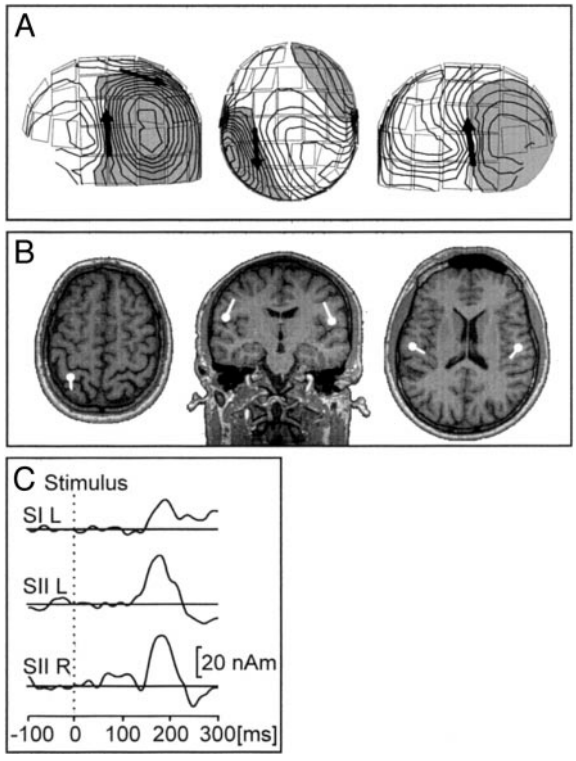


FIG. 1. Cortical responses to cutaneous laser stimuli applied to right hand in a representative subject. *A*: magnetic field patterns at 176 ms after stimulus application displayed over the helmet-shaped sensor array viewed from the left, top, and the right. Squares show locations of 61 sensor pairs. Shaded areas indicate fields directed into the head; isocontours are seperated by 45 fT. Arrows represent location and direction of cortical sources. *B*: location of cortical sources superposed on magnetic resonance imaging scans. *Left*: axial slice through SI hand area; *middle* and *right*: coronal and axial slice through SII. *C*: source strengths as a function of time. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; L, left; R, right.

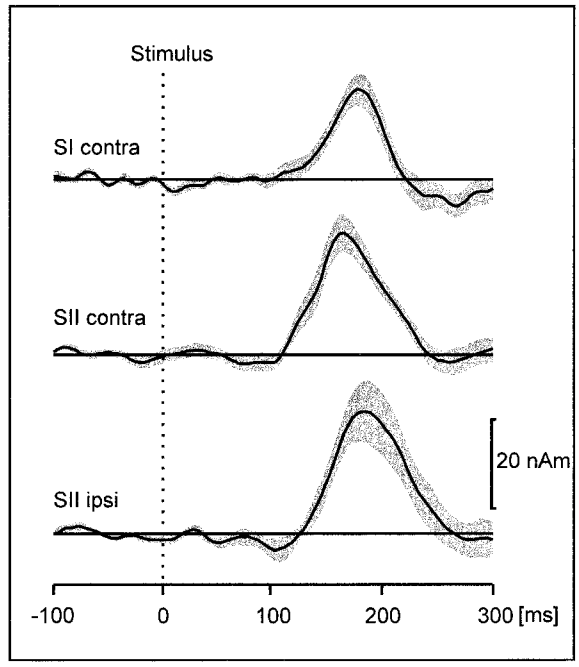


FIG. 2. Mean source strengths as a function of time across left and right hand stimulation of all subjects. Shaded areas depict ±SE. contra, contralateral; ipsi, ipsilateral.

## DISCUSSION

By using selective nociceptive stimuli our results confirm previous observations of SI and SII involvement in human pain processing (Casey et al. 1996; Coghill et al. 1994; Craig et al. 1996; Greenspan and Winfield 1992; Kenshalo and Willis 1991; Lenz et al. 1998; Sweet 1982; Talbot et al. 1991). In addition, we show for the first time the temporal aspects of nociceptive processing in human somatosensory cortices.

Previous neurophysiological recordings of cortical responses to selective nociceptive stimuli either could not demonstrate SI activation (Bromm and Chen 1995; Hari et al. 1983, 1997; Huttunen et al. 1986; Kakigi et al. 1995; Valeriani et al. 1996; Watanabe et al. 1998) or did not provide sufficient spatial resolution to localize sources (Spiegel et al. 1996;

TABLE 1. *Latencies of cortical responses to cutaneous laser stimuli*

| | | SI Contralateral | | SII Contralateral | | SII Ipsilateral | |
|---|---|---|---|---|---|---|---|
| Subject | Hand | Onset (131 ± 7) | Peak (174 ± 3) | Onset (126 ± 4) | Peak (163 ± 4) | Onset (138 ± 4) | Peak (181 ± 4) |
| 1 | r | 126 | 175 | 140 | 174 | — | — |
| | l | 150 | 186 | 148 | 183 | 153 | 195 |
| 2 | r | 126 | 168 | 121 | 158 | 116 | 160 |
| | l | — | — | 120 | 162 | 155 | 183 |
| 3 | r | 145 | 187 | 133 | 176 | 144 | 180 |
| | l | 152 | 178 | 134 | 175 | 140 | 175 |
| 4 | r | 96 | 160 | 104 | 156 | 120 | 167 |
| | l | 84 | 172 | 106 | 138 | 126 | 188 |
| 5 | r | 120 | 168 | 121 | 173 | 135 | 174 |
| | l | 153 | 184 | 138 | 163 | 143 | 195 |
| 6 | r | 142 | 173 | 132 | 157 | 134 | 165 |
| | l | 143 | 168 | 113 | 138 | 151 | 206 |

Values in parentheses represent mean ± SE. Latencies are given in ms. No ipsilateral SII source could be identified to right hand stimuli in subject 1 and no contralateral SI source could be identified to left hand stimuli in subject 2. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; r, right hand; l, left hand.

Tarkka and Treede 1993). The failure to detect SI activation in some studies might have been due to the paucity of nociceptive neurons in SI as revealed in experimental animal studies (Kenshalo and Willis 1991) and to different stimulus characteristics possibly activating different fiber populations. In our study, very short laser pulses of relatively high energies probably yielded a higher degree of neuronal synchronization and therefore could well account for larger responses. The latency of the SI response is inconsistent with conduction via A-$\beta$ fibers but agrees well with activation of A-$\delta$ fibers. Selectivity of cutaneous laser stimulation is further corroborated by the absence of any tactile sensations in our study and by results of microneurographic recordings (Bromm and Treede 1984).

The locations and orientations of our SII sources are in accordance with previous MEG and functional imaging studies on tactile (Coghill et al. 1994; Hari et al. 1993; Ledberg et al. 1995; Mima et al. 1998; Schnitzler et al. 1999) and nociceptive (Casey et al.1996; Coghill et al. 1994; Craig et al. 1996; Hari et al. 1983, 1997; Kakigi et al. 1995; Talbot et al. 1991; Watanabe et al. 1998) processing. The inferior–superior current flow and the distances of SII sources to the insula and the VCA rule out a significant contribution of insular activity to the identified sources. Failure to detect activation of insular cortex, which was also shown to participate in nociceptive processing (Casey et al. 1996; Coghill et al. 1994; Craig et al. 1996), may be due to possible cancellation of currents in the opposite walls of the insula and to mainly radially oriented insular source currents not detected by MEG.

Our finding of simultaneous activation of SI and SII to selective nociceptive stimuli contrasts to the temporal activation pattern of tactile processing. Intracranial and magnetoencephalographic recordings in humans revealed sequential activation of SI peaking at 20–50 ms and SII peaking at ~100–130 ms (Allison et al. 1989a,b; Hari et al. 1993; Mima et al. 1998; Schnitzler et al. 1999). Accordingly, ablation experiments in higher primates showed a dependence of SII responses on the integrity of SI, indicating serial processing of tactile information (Garraghty et al. 1990; Pons et al. 1987, 1992). Results of a single study (Zhang et al. 1996) with cortical cooling of SI were interpreted as indication for a possible parallel activation of tactile pathways to SI and SII in higher primates. However, incomplete deactivation of SI cannot be ruled out in this study, and virtually all of the anatomic and electrophysiological work in macaques clearly supports a predominantly serial relay of tactile information from SI to SII (Pons 1996). By contrast, ablation experiments in lower primates and nonprimates revealed independent activation of SI and SII via parallel thalamocortical pathways (Garraghty et al. 1991; Turman et al. 1992). Thus for tactile processing in higher primates an evolutionary shift from the basic mammalian parallel cortical organization to serial organization of somatosensory cortices has been proposed. Our results strongly suggest that the parallel mode of cortical organization also applies to human pain processing, whereas in the tactile modality parallel organization appears to be abandoned in favor of a serial processing scheme. Anatomically, parallel nociceptive processing is likely to be subserved by distinct spinothalamocortical pathways via the ventroposterior inferior thalamic nucleus (VPI) to SII (Friedman and Murray 1986; Stevens et al. 1993) and via the ventroposterior lateral thalamic nucleus (VPL) to SI (Gingold et al. 1991). Differences in spinal input, response properties, and receptive field sizes of nociceptive neurons along VPL-SI and VPI-SII projections (Apkarian and Hodge 1989; Apkarian and Shi 1994; Dong et al. 1989; Kenshalo and Willis 1991) indicate an anatomic and functional segregation of both pathways from the spinal cord to cortex.

Functionally, serial processing implies greater synaptic distance between SII and the periphery and some loss of processing speed in exchange for preferential use of SI (Garraghty et al. 1991). Given restricted receptive field sizes, somatotopical arrangement, and accuracy of intensity coding of both SI and VPL neurons (Apkarian and Shi 1994; Kenshalo and Willis 1991), we conclude that discriminative capabilities mediated by SI are less important in pain than in tactile perception. Instead preserved direct access of nociceptive information to SII indicates crucial importance of this area in human pain processing. Direct corticolimbic projections from SII to the temporal lobe limbic structures have been proposed to subserve tactile learning and memory (Friedman et al. 1986; Mishkin 1979). Similarly, SII may play a key role in relaying nociceptive information to the temporal lobe limbic structures (Dong et al. 1989; Lenz et al. 1997). Thus direct thalamocortical projection to SII provides fast and effective access of nociceptive signals to the anatomic substrates of pain-related learning and

memory. For obvious reasons, physical integrity and survival of the individual are heavily dependent on efficient and successful reaction to and avoidance of harmful events. Therefore we hypothesize that the fundamental relevance of pain-associated learning and memory accounts for the evolutionary preservation of the direct thalamic input to SII. Conversely, the involvement of learning and memory mechanisms in chronification of pain (Fordyce 1986) opens novel approaches for exploring the role of SII in chronic pain syndromes.

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Address for reprint requests: A. Schnitzler, Dept. of Neurology, Heinrich-Heine University, Moorenstr. 5, D-40225 Dusseldorf, Germany.

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## REFERENCES

AHONEN, A. I., HÄMÄLÄINEN, M. S., KAJOLA, M. J., KNUUTILA, J.E.T., LAINE, P. P., LOUNASMAA, O. V., PARKKONEN, L. T., SIMOLA, J. T., AND TESCHE, C. D. 122-channel SQUID instrument for investigating the magnetic signals from the human brain. *Phys. Scripta* T49: 198–205, 1993.

ALLISON, T., MCCARTHY, G., WOOD, C. C., DARCEY, T. M., SPENCER, D. D., AND WILLIAMSON, P. D. Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. *J. Neurophysiol.* 62: 694–710, 1989a.

ALLISON, T., MCCARTHY, G., WOOD, C. C., WILLIAMSON, P. D., AND SPENCER, D. D. Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. *J. Neurophysiol.* 62: 711–722, 1989b.

APKARIAN, A. V. AND HODGE, C. J. Primate spinothalamic pathways. II. The cells of origin of the dorsolateral and ventral spinothalamic pathways. *J. Comp. Neurol.* 288: 474–492, 1989.

APKARIAN, A. V. AND SHI, T. Squirrel monkey lateral thalamus. I. Somatic nocicresponsive neurons and their relation to spinothalamic terminals. *J. Neurosci.* 14: 6779–6795, 1994.

BROMM, B. AND CHEN, A.C.N. Brain electrical source analysis of laser evoked potentials in response to painful trigeminal nerve stimulation. *Electroencephalogr. Clin. Neurophysiol.* 95: 14–26, 1995.

BROMM, B. AND TREEDE, R. D. Nerve fiber discharges, cerebral potentials and sensations induced by $CO_2$ laser stimulation. *Hum. Neurobiol.* 3: 33–40, 1984.

CASEY, K. L., MINOSHIMA, S., MORROW, T. J., AND KOEPPE, R. A. Comparison of human cerebral activation patterns during cutaneous warmth, heat pain, and deep cold pain. *J. Neurophysiol.* 76: 571–581, 1996.

COGHILL, R. C., TALBOT, J. D., EVANS, A. C., MEYER, E., GJEDDE, A., BUSHNELL, M. C., AND DUNCAN, G. H. Distributed processing of pain and vibration by the human brain. *J. Neurosci.* 14: 4095–4108, 1994.

CRAIG, A. D., REIMAN, E. M., EVANS, A., AND BUSHNELL, M. C. Functional imaging of an illusion of pain. *Nature* 384: 258–260, 1996.

DONG, W. K., SALONEN, L. D., KAWAKAMI, Y., SHIWAKU, T., KAUKORANTA, E. M., AND MARTIN, R. F. Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. *Brain Res.* 484: 314–324, 1989.

FORDYCE, W. E. Learning processes in pain. In: *The Psychology of Pain* (2nd ed.), edited by R. A. Steinbach. New York: Raven, 1986, p. 49–65.

FRIEDMAN, D. P. AND MURRAY, E. A. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *J. Comp. Neurol.* 252: 348–373, 1986.

FRIEDMAN, D. P., MURRAY, E. A., O'NEILL, J. B., AND MISHKIN, M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. *J. Comp. Neurol.* 252: 323–347, 1986.

GARRAGHTY, P. E., FLORENCE, S. L., TENHULA, W. N., AND KAAS, J. H. Parallel thalamic activation of the first and second somatosensory areas in prosimian primates and tree shrews. *J. Comp. Neurol.* 311: 289–299, 1991.

GARRAGHTY, P. E., PONS, T. P., AND KAAS, J. H. Ablations of areas 3b (SI proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas. *Somatosens. Mot. Res.* 7: 125–135, 1990.

GINGOLD, S. I., GREENSPAN, J. D., AND APKARIAN, A. V. Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys. *J. Comp. Neurol.* 308: 467–490, 1991.

GREENSPAN, J. D. AND WINFIELD, J. A. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 58: 29–39, 1992.

HÄMÄLÄINEN, M., HARI, R., ILMONIEMI, R. J., KNUUTILA, J., AND LOUNASMAA, O. V. Magnetoencephalography—theory, instrumentation, and application to noninvasive studies of the working human brain. *Rev. Mod. Phys.* 65: 413–497, 1993.

HARI, R., HÄMÄLÄINEN, M., KNUUTILA, J., SALONEN, O., SAMS, M., AND VILKMAN, V. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. *Eur. J. Neurosci.* 5: 724–734, 1993.

HARI, R., KAUKORANTA, E., REINIKAINEN, K., HUOPANIEMIE, T., AND MAUNO, J. Neuromagnetic localization of cortical activity evoked by painful dental stimulation in man. *Neurosci. Lett.* 42: 77–82, 1983.

HARI, R., PORTIN, K., KETTENMANN, B., JOUSMÄKI, V., AND KOBAL, G. Right-hemisphere preponderance of responses to painful $CO_2$ stimulation of the human nasal mucosa. *Pain* 72: 145–151, 1997.

HEAD, H. AND HOLMES, G. Sensory disturbances from cerebral lesions. *Brain* 34: 102–254, 1911.

HUTTUNEN, J., KOBAL, G., KAUKORANTA, E., AND HARI, R. Cortical responses to painful $CO_2$ stimulation of nasal mucosa; a magnetoencephalographic study in man. *Electroencephalogr. Clin. Neurophysiol.* 64: 347–349, 1986.

KAKIGI, R., KOYAMA, S., HOSHIYAMA, M., KITAMURA, Y., SHIMOJO, M., AND WATANABE, S. Pain-related magnetic fields following painful $CO_2$ laser stimulation in man. *Neurosci. Lett.* 192: 45–48, 1995.

KENSHALO, D. R. AND WILLIS, W. D. The role of the cerebral cortex in pain sensation. In: *Cerebral Cortex, Normal and Altered States of Function*, edited by E. G. Jones and A. Peters. New York: Plenum, 1991, vol. 9, p. 153–212.

LEDBERG, A., O'SULLIVAN, B. T., KINOMURA, S., AND ROLAND, P. E. Somatosensory activations of the parietal operculum of man. A PET study. *Eur. J. Neurosci.* 7: 1934–1941, 1995.

LENZ, F. A., GRACELY, R. H., ZIRH, A. T., ROMANOSKI, A. J., AND DOUGHERTY, P. M. The sensory-limbic model of pain memory. *Pain Forum* 6: 22–31, 1997.

LENZ, F. A., RIOS, M., CHAU, D., KRAUSS, G. L., ZIRH, T. A., AND LESSER, R. P. Painful stimuli evoke potentials recorded from the parasylvian cortex in humans. *J. Neurophysiol.* 80: 2077–2088, 1998.

MIMA, T., NAGAMINE, T., NAKAMURA, K., AND SHIBASAKI, S. Attention modulates both primary and secondary somatosensory cortical activities in humans: a magnetoencephalographic study. *J. Neurophysiol.* 80: 2215–2221, 1998.

MISHKIN, M. Analogous neural models for tactual and visual learning. *Neuropsychologia* 17: 139–151, 1979.

PONS, T. P. Serial processing in the somatosensory system of macaques. In: *Somesthesis and the Neurobiology of the Somatosensory Cortex*, edited by O. Franzén, R. Johansson, and L. Terenius. Basel: Birkhäuser, 1996, p. 187–195.

PONS, T. P., GARRAGHTY, P. E., FRIEDMAN, D. P., AND MISHKIN, M. Physiological evidence for serial processing in somatosensory cortex. *Science* 237: 417–420, 1987.

PONS, T. P., GARRAGHTY, P. E., AND MISHKIN, M. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *J. Neurophysiol.* 68: 518–527, 1992.

SCHNITZLER, A., VOLKMANN, J., ENCK, P., FRIELING, T., WITTE, O. W., AND FREUND, H. J. Different cortical organisation of visceral and somatic sensation in humans. *Eur. J. Neurosci.* 11: 305–315, 1999.

SPIEGEL, J., HANSEN, C., AND TREEDE, R. D. Laser-evoked potentials after painful hand and foot stimulation in humans: evidence for generation of the middle-latency component in the secondary somatosensory cortex. *Neurosci. Lett.* 216: 179–182, 1996.

STEVENS, R. T., LONDON, S. M., AND APKARIAN, A. V. Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. *Brain Res.* 631: 241–246, 1993.

SWEET, W. H. Cerebral localization of pain. In: *New Perspectives in Cerebral Localization*, edited by R. A. Thompson and J. R. Green. New York: Raven, 1982, p. 205–242.

TALAIRACH, J. AND TOURNOUX, P. *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme, 1988.

TALBOT, J. D., MARRETT, S., EVANS, A. C., MEYER, E., BUSHNELL, M. C., AND DUNCAN, G. H. Multiple representations of pain in human cerebral cortex. *Science* 251: 1355–1358, 1991.

TARKKA, I. M. AND TREEDE, R. D. Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a $CO_2$ laser. *J. Clin. Neurophysiol.* 10: 513–519, 1993.

TURMAN, A. B., FERRINGTON, D. G., GHOSH, S., MORLEY, J. W., AND ROWE, M. J. Parallel processing of tactile information in the cerebral cortex of the cat: effect of reversible inactivation of SI on responsiveness of SII neurons. *J. Neurophysiol.* 67: 411–429, 1992.

VALERIANI, M., RAMBAUD, L., AND MAUGIERE, F. Scalp topography and dipolar source modelling of potentials evoked by $CO_2$ laser stimulation of the hand. *Electroencephalogr. Clin. Neurophysiol.* 100: 343–353, 1996.

WATANABE, S., KAKIGI, R., KOYAMA, S., HOSHIYAMA, M., AND KANEOKE, Y. Pain processing traced by magnetoencephalography in the human brain. *Brain Topogr.* 10: 255–264, 1998.

ZHANG, H. Q., MURRAY, G. M., TURMAN, A. B., MACKIE, P. D., COLEMAN, G. T., AND ROWE, M. J. Parallel processing in cerebral cortex of the marmoset monkey: effect of reversible SI inactivation on tactile responses in SII. *J. Neurophysiol.* 76: 3633–3655, 1996.

PAIN

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Clinical Note

# Pain affect without pain sensation in a patient with a postcentral lesion

M. Ploner, H.-J. Freund, A. Schnitzler*

*Department of Neurology, University of Duesseldorf, Moorenstrasse 5, 40225 Duesseldorf, Germany*

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**Abstract**

We report findings from clinical examination and cutaneous laser stimulation in a 57-year-old male, who suffered from a right-sided postcentral stroke. In this patient, we were able to demonstrate (i) a dissociation of discriminative and affective components of pain perception and, for the first time in humans, (ii) the dependence of sensory-discriminative pain component and first pain sensation on the integrity of the lateral pain system. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

*Keywords:* Pain perception; Somatosensory cortex

## 1. Introduction

Cerebral structures involved in pain processing are commonly divided into a lateral and a medial pain system (Albe-Fessard et al., 1985). These two systems diverge at the thalamic level. The main constituents of the lateral pain system are the lateral thalamic nuclei and the primary (SI) and secondary (SII) somatosensory cortices (Kenshalo and Willis, 1991). The medial pain system essentially consists of the medial thalamic nuclei and the anterior cingulate cortex (Vogt et al., 1993).

These anatomically segregated systems are supposed to subserve functionally different components of pain perception. Experimental and lesion data in humans indicate a close association between motivational-affective aspects of pain and the medial pain system (Vogt et al., 1993; Craig et al., 1996; Rainville et al., 1997). However, an association between the sensory-discriminative component of pain perception and the lateral pain system, as deduced from neurophysiological experiments in monkeys (Kenshalo and Willis, 1991), has not yet unequivocally been proven in humans.

A further characteristic of pain perception is the appearance of two subsequent and qualitatively distinct sensations following single painful stimuli. Peripherally, the neural basis of this phenomenon is a dual pathway for pain with A$\delta$-fibers mediating pricking first pain and C-fibers mediating dull second pain (Bishop and Landau, 1958). Centrally, a representation of first pain in the lateral pain system has been suggested (Hassler, 1976), but no direct evidence for this has been presented so far.

Here, we report findings from clinical examination, cutaneous laser stimulation and magnetic resonance imaging (MRI) of a patient with a selective ischemic lesion of the right SI and SII cortices. This patient offered the unique possibility to study possible dissociations between sensory-discriminative and motivational-affective components of pain perception and between first and second pain. Our results demonstrate, for the first time in humans, a loss of pain sensation with preserved pain affect, and provide clear evidence for the crucial role of the lateral pain system in the sensory-discriminative pain component and in first pain sensation.

## 2. Case report

### 2.1. Case history

A 57-year-old male with no history of previous neurological diseases suffered from a cardioembolic stroke in the

* Corresponding author. Tel.: +49-211-811-7893; fax: +49-211-811-9033; e-mail: schnitz@neurologie.uni-duesseldorf.de

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territory of the right middle cerebral artery. While initial left hemiparesis resolved within the first few hours left-sided sensory deficits persisted. MRI performed 3 days after stroke showed a lesion confined to the right postcentral gyrus and the parietal operculum extending from 12 mm to 54 mm above the anterior commissure-posterior commissure-line, thus comprising the hand area of SI and SII (Fig. 1). No other lesions were visible on the scans studied. Preserved median nerve somatosensory evoked short-latency potentials and diminished long latency potentials suggested integrity of peripheral somatosensory pathways and partial lesion of SI.

### 2.2. Clinical examination

Evaluation of the patient's deficits 5 and 12 days after stroke was based on extensive clinical examination including light touch, static tactile thresholds with von Frey-hair stimuli, two-point and sharp-dull discrimination, sense of movement, graphaesthesia, stereognosia thermaesthesia (test tubes filled with hot and cold water), pallaesthesia and motor testing.

While sensory examination of the patient's right side was within normal limits, left-sided examination revealed hypaesthesia of foot, leg and face and anaesthesia of hand and arm, in all the above mentioned tests except for nearly normal pallaesthesia (Table 1). In particular, thermal stimuli did not evoke any sensation. Motor testing showed only marginal left-sided pronation when maintenance of arms against gravity was examined without any further motor deficit. These deficits remained stable and unchanged across the two examinations.

### 2.3. Cutaneous laser stimulation

Controlled, selective thermonociceptive stimuli were applied by means of cutaneous laser stimulation (Bromm and Treede, 1991) using a Tm:YAG-Laser (Baasel Lasertech) with a wavelength of 2000 nm, a pulse duration of 1 ms and a spotdiameter of 6 mm. Twelve days after stroke, pain thresholds on the dorsum of feet and hands were determined with increasing and decreasing stimulus intensities at 50 mJ steps (actual output intensity can vary up to 5% from demanded intensity). The threshold was defined as intensity that elicited painful sensations in at least three of five applications. Reaction times to 20 painful laser stimuli (stimulus intensity 450 mJ) applied to the dorsum of each hand were measured in two subsequent runs. Stimulation site was slightly changed between successive stimuli, interstimulus intervals varied randomly between 10 and 14 s. The patient was instructed to lift the index finger contralateral to stimulation as soon as any sensation was perceived. Finger lift was detected by a photoelectric barrier. Due to the failure to correctly place the index finger of the proprioceptively impaired left hand into the photoelectric barrier motor reactions of the sensory impaired left hand could not be recorded

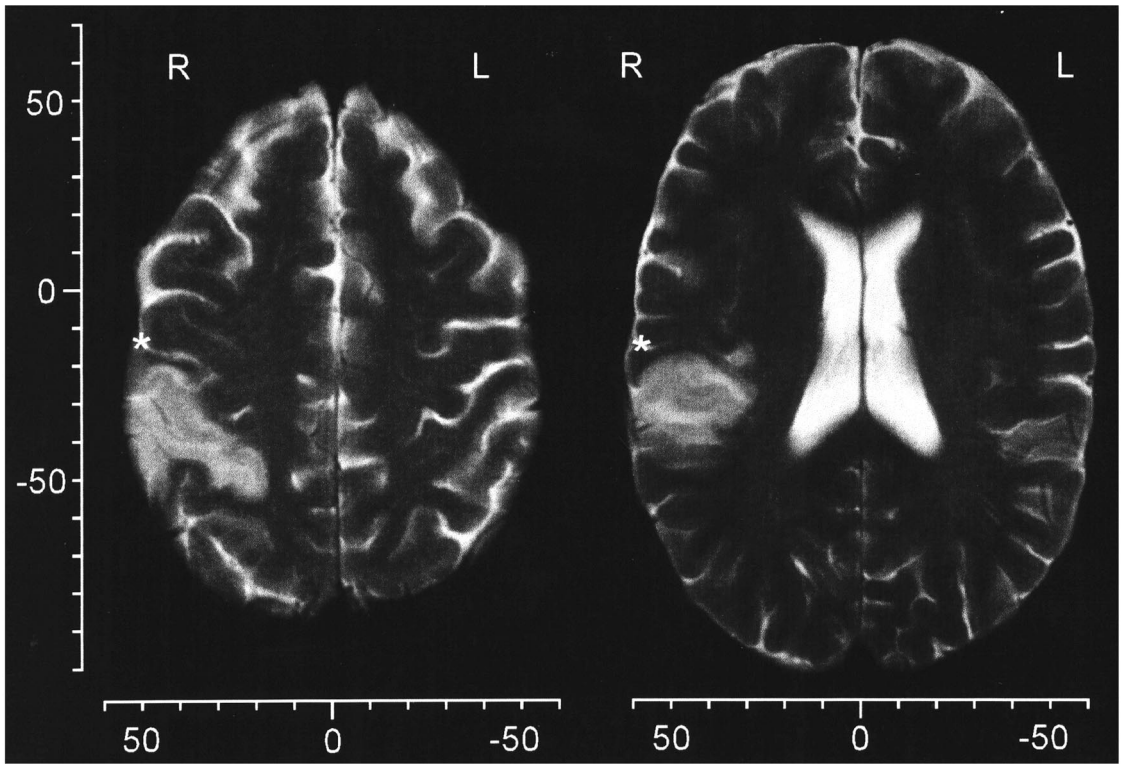


Fig. 1. Transaxial MRI-slices at 42 mm (left) and 18 mm (right) parallel above the anterior commissure-posterior commissure-line. Scales give coordinates in mm according to the Talairach frame of reference (Talairach and Tournoux, 1988). Markers (*) indicate the central sulcus.

Table 1
Sensory testing

| | Right hand | Left hand |
|---|---|---|
| von Frey-hair stimuli (mN) | 2.83 | >6.65 |
| Two-point-discrimination (mm) | 12 | – |
| Sharp-dull-discrimination[a] | 5/5 | 0/5 |
| Sense of mcp joint movement[a] | 5/5 | 0/5 |
| Graphaesthesia[a] | 5/5 | 0/5 |
| Stereognosia[a] | 5/5 | 0/5 |
| Pallaesthesia (tuning fork) | 100% | 75% |
| Pain threshold (mJ) | 200 | –[b] |

[a]Number of correct trials.
[b]At 350 mJ and more the patient described a 'clearly unpleasant' feeling. mcp, metacarpophalangeal; –, no sensation.

and thus reaction times could not be determined for six stimuli to the normal right hand. In two prior control runs mean reaction times to binaural acoustic stimuli had been 300 ms (SD = 67 ms) for right index finger lift and 246 ms (SD = 64 ms) for left index finger lift, so that prolonged reaction times due to accompanying left-sided motor deficits could reliably be excluded.

Pain thresholds were 200 mJ for right hand and both feet. Evoked pain sensations were characterized as 'pinprick-like' and were well localized within 2–3 cm. For left hand, up to an intensity of 600 mJ, no pain sensation could be elicited. However, at intensities of 350 mJ and more, the patient spontaneously described a 'clearly unpleasant' intensity dependent feeling emerging from an ill-localized and extended area 'somewhere between fingertips and shoulder', that he wanted to avoid. The fully cooperative and eloquent patient was completely unable to further describe quality, localization and intensity of the perceived stimulus. Suggestions from a given word list containing 'warm', 'hot', 'cold', 'touch', 'burning', 'pinprick-like', 'slight pain', 'moderate pain' and 'intense pain' were denied nor did the patient report any kind of paraesthesias (all descriptions translated from German). Reaction times to laser stimuli on the right hand showed a bimodal distribution with medians at 400 ms and 1000 ms. By contrast, stimulation of the left hand yielded exclusive long-latency responses with a median at 1426 ms (Fig. 2).

## 3. Discussion

In the patient reported here, clinical examination and cutaneous laser stimulation revealed prolonged reaction times to painful laser stimuli, an elevated pain threshold, loss of sensory-discriminative pain component and preserved motivational-affective dimension of pain. This clear perceptual dissociation was paralleled by an anatomical dissociation between affected lateral pain system and spared medial pain system. This pattern of impairment shows the essential role of SI and/or SII for the sensory-discriminative aspects of pain perception in humans. By contrast, detection of and reaction to painful stimuli as well as pain affect do obviously not require integrity of SI and SII. Nevertheless, damage to SI and SII produced hypalgesia in our patient, suggesting interaction between medial and lateral pain system in normal pain experience.

Most previous lesion studies in humans agreed on the crucial importance of the postcentral gyrus and/or the parietal operculum in pain perception (Sweet, 1982; Boivie et al., 1989; Greenspan and Winfield, 1992). Although these studies are clinically well documented, the partial lack of information about lesion extent, presence of additional lesions and manifold, and ambiguous clinical presentations interfered with a consistent concept of these structures in human pain perception. Moreover, clinical examination of pain perception was carried out with non-selective pain-evoking stimuli. Thus, activation of pain afferents was always contaminated by activation of tactile pathways. Cutaneous laser stimulation, as applied in our study, overcomes this limitation by selective activation of thermonociceptive afferents (Bromm and Treede, 1991). Thus, our findings refer to cutaneous but not necessarily to deep nociception.

More recent evidence for an involvement of SI and SII in pain processing comes from functional imaging studies. Most of them showed pain associated increases of cerebral blood flow in contralateral SI and SII (Talbot et al., 1991; Coghill et al., 1994; Casey et al., 1996; Craig et al., 1996; Andersson et al., 1997; Derbyshire et al., 1997; Rainville et al., 1997). According to the Talairach-coordinates (Talairach and Tournoux, 1988), activation foci were located in regions corresponding to our patient's lesion. But again,

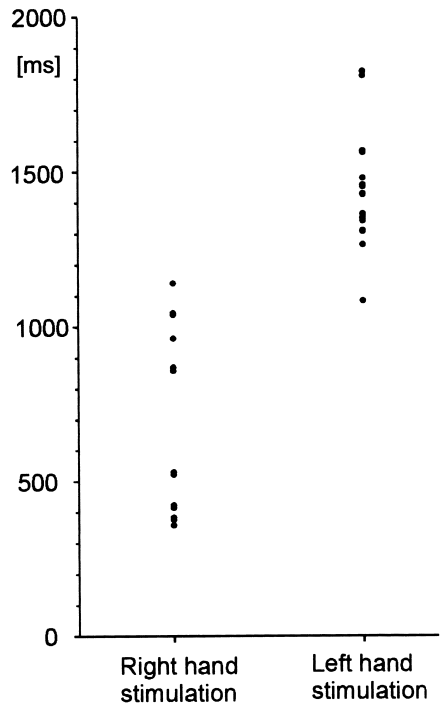


Fig. 2. Reaction times to cutaneous laser stimulation of the normal right ($N$ = 14) and the affected left ($N$ = 20) hand.

only in a few of these studies were selective painful stimuli applied (Andersson et al., 1997; Derbyshire et al., 1997). Additionally, while it has been possible to vary pain affect experimentally without changing physical stimulus parameters (Craig et al., 1996; Rainville et al., 1997), an inverse experiment has not yet been carried out. Thus, selective evaluation of the sensory-discriminative pain component and the subserving cerebral structures is lacking.

Our observation of an association between SI and sensory-discriminative pain component is supported by experimental animal data (Kenshalo and Willis, 1991): nociceptive neurons in SI of monkeys encode stimulus intensity and are somatotopically organized, features that are predestinating for discriminative functions. By contrast, nociceptive neurons in SII seem to reflect learning of, or attention to, pain-evoking stimuli rather than direct involvement in sensory-discriminative aspects of pain perception.

While bimodal distribution of reaction times to laser stimulation of the unaffected right hand is in accordance with previous results in healthy subjects (Campbell and LaMotte, 1983), reaction times to left-sided painful stimuli showed a loss of short-latency responses that are believed to be related to activation of Aδ-fibers and first pain sensation (Campbell and LaMotte, 1983). Thus, loss of short-latency reactions in our patient supports generation of first pain sensation in the lateral pain system (Hassler, 1976). Interestingly, both the patient's description of the perceived stimulus and the prolonged reaction times to laser stimulation of the affected left hand are not fully consistent with properties of second pain (Bishop and Landau, 1958; Campbell and LaMotte, 1983). In agreement with results of human psychophysical (Koltzenburg et al., 1993) and imaging (Andersson et al., 1997) studies using selective C-fiber stimulation, this suggests a contribution of the lateral pain system to second pain sensation.

In conclusion, we were able to demonstrate, for the first time in humans, the representation of sensory-discriminative pain component and first pain sensation in the lateral pain system. In contrast, pain affect and the ability to detect painful stimuli do not, in principle, require integrity of these structures.

## Acknowledgements

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## References

Albe-Fessard, D., Berkley, K.J., Kruger, L., Ralston, H.J. and Willis, W.D., Diencephalic mechanisms of pain sensation, Brain Res., 356 (1985) 217–296.

Andersson, J.L., Lilja, A., Hartvig, P., Langstrom, B., Gordh, T., Handwerker, H. and Torebjork, E., Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography, Exp. Brain Res., 117 (1997) 192–199.

Bishop, G.H. and Landau, W.M., Evidence for a double peripheral pathway for pain, Science, 128 (1958) 712–713.

Boivie, J., Leijon, G. and Johansson, I., Central post-stroke pain-a study of the mechanisms through analyses of the sensory abnormalities, Pain, 37 (1989) 173–185.

Bromm, B. and Treede, R.D., Laser-evoked cerebral potentials in the assessment of cutaneous pain sensitivity in normal subjects and patients, Rev. Neurol. (Paris), 147 (1991) 625–643.

Campbell, J.N. and LaMotte, R.H., Latency to detection of first pain, Brain Res., 266 (1983) 203–208.

Casey, K.L., Minoshima, S., Morrow, T.J. and Koeppe, R.A., Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain, J. Neurophysiol., 76 (1996) 571–581.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C. and Duncan, G.H., Distributed processing of pain and vibration by the human brain, J. Neurosci., 14 (1994) 4095–4108.

Craig, A.D., Reiman, E.M., Evans, A. and Bushnell, M.C., Functional imaging of an illusion of pain, Nature, 384 (1996) 258–260.

Derbyshire, S.W., Jones, A.K., Gyulai, F., Clark, S., Townsend, D. and Firestone, L.L., Pain processing during three levels of noxious stimulation produces differential patterns of central activity, Pain, 73 (1997) 431–445.

Greenspan, J.D. and Winfield, J.A., Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum, Pain, 50 (1992) 29–39.

Hassler, R., Interaction between the systems involved in fast pain perception and in slow, persistent pain, Langenbecks Arch. Chir., 342 (1976) 47–61.

Kenshalo, D.R. and Willis, W.D., The role of the cerebral cortex in pain sensation. In: A. Peters and E.G. Jones (Eds.), Cerebral Cortex, Vol. 9, Plenum Press, New York, 1991, pp. 153–212.

Koltzenburg, M., Handwerker, H.O. and Torebjork, H.E., The ability of humans to localise noxious stimuli, Neurosci. Lett., 150 (1993) 219–222.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B. and Bushnell, M.C., Pain affect encoded in human anterior cingulate but not somatosensory cortex, Science, 277 (1997) 968–971.

Sweet, W.H., Cerebral localization of pain. In: R.A. Thompson and J.R. Greer (Eds.), New Perspectives in Cerebral Localization, Raven Press, New York, 1982, pp. 205–242.

Talairach, J. and Tournoux, P., Co-planar Stereotaxic Atlas of the Human Brain, Thieme, Stuttgart, 1988.

Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C. and Duncan, G.H., Multiple representations of pain in human cerebral cortex, Science, 251 (1991) 1355–1358.

Vogt, B.A., Sikes, R.W. and Vogt, L.J., Anterior cingulate cortex and the medial pain system. In: B.A. Vogt and M. Gabriel (Eds.), Neurobiology of Cingulate Cortex and Limbic Thalamus: a Comprehensive Handbook, Birkhauser, Boston, MA, 1993, pp. 313–344.

# Differential Organization of Touch and Pain in Human Primary Somatosensory Cortex

MARKUS PLONER, FRANK SCHMITZ, HANS-JOACHIM FREUND, AND ALFONS SCHNITZLER
*Department of Neurology, Heinrich-Heine-University, D-40225 Düsseldorf, Germany*

**Ploner, Markus, Frank Schmitz, Hans-Joachim Freund, and Alfons Schnitzler.** Differential organization of touch and pain in human primary somatosensory cortex. *J. Neurophysiol.* 83: 1770–1776, 2000. Processing of tactile stimuli within somatosensory cortices has been shown to be complex and hierarchically organized. However, the precise organization of nociceptive processing within these cortices has remained largely unknown. We used whole-head magnetoencephalography to directly compare cortical responses to stimulation of tactile and nociceptive afferents of the dorsum of the hand in humans. Within the primary somatosensory cortex (SI), nociceptive stimuli activated a single source whereas tactile stimuli activated two sequentially peaking sources. Along the postcentral gyrus, the nociceptive SI source was located 10 mm more medially than the early tactile SI response arising from cytoarchitectonical area 3b and corresponded spatially to the later tactile SI response. Considering a mediolateral location difference between the hand representations of cytoarchitectonical areas 3b and 1, the present results suggest generation of the single nociceptive response in area 1, whereas tactile stimuli activate sequentially peaking sources in areas 3b and 1. Thus nociceptive processing apparently does not share the complex and hierarchical organization of tactile processing subserving elaborated sensory capacities. This difference in the organization of both modalities may reflect that pain perception rather requires reactions to and avoidance of harmful stimuli than sophisticated sensory capacities.

## INTRODUCTION

The primary somatosensory cortex (SI) participates in central processing of both tactile and nociceptive stimuli (for reviews see Kaas 1990; Kenshalo and Willis 1991). However, SI is not a homogeneous area but consists of four cytoarchitectonically distinct fields arranged from rostral to caudal and referred to as areas 3a, 3b, 1, and 2 (Brodmann 1909; Vogt and Vogt 1919). These areas each contain a separate body representation (Kaas et al. 1979) characterized by a distinct connectivity (Burton and Fabri 1995; Felleman and Van Essen 1991; Jones 1984, 1986), submodality distribution (Iwamura et al. 1993; Kaas et al. 1979; Powell and Mountcastle 1959), and receptive field configuration (Hyvärinen and Poranen 1978; Iwamura et al. 1993; Kaas et al. 1979).

Cutaneous information is predominantly processed in areas 3b and 1 whereas areas 3a and 2 mainly receive information from the deep body tissues (Hyvärinen and Poranen 1978; Iwamura et al. 1993; Powell and Mountcastle 1959). The cutaneous fields areas 3b and 1 are connected with area 2, the posterior parietal cortex, and the secondary somatosensory cortex (Burton and Fabri 1995; Burton et al. 1995; Jones et al. 1978). Anatomic (Burton and Fabri 1995; Felleman and Van Essen 1991; Jones 1986) and physiologic studies (Garraghty et al. 1990; Hyvärinen and Poranen 1978; Iwamura et al. 1993; Kaas et al. 1979; Pons et al. 1992) indicate a partially hierarchical organization of these areas with area 3b representing the first cortical stage of tactile processing (for review see Iwamura 1998).

Accordingly, neurophysiological recordings in monkeys and humans have revealed that the earliest cortical components of somatosensory evoked potentials and fields originate from area 3b located in the rostral bank of the postcentral gyrus (Allison et al. 1989a; McCarthy et al. 1991; Wood et al. 1985, 1988). Subsequent responses are generated in the caudally adjoining area 1 and later in the posterior parietal cortex and SII (Allison et al. 1989a,b; Forss et al. 1994; Hari et al. 1993; McCarthy et al. 1991; Wood et al. 1985, 1988).

By contrast, a recent study in humans demonstrated simultaneous activation of SI and SII to nociceptive stimuli suggesting a parallel activation pattern (Ploner et al. 1999). However, within SI, the organization of nociceptive processing has remained largely unknown. Thus it is unclear whether the complex and hierarchical organization of tactile processing subserving elaborated sensory capacities also applies to human pain processing. We therefore used whole-head magnetoencephalography (MEG) to record cortical responses to tactile and nociceptive stimuli in healthy human subjects. By directly comparing cortical responses to both stimuli in the same subjects we investigated whether nociceptive processing shares the organization of tactile processing within SI.

## METHODS

Six healthy male right-handed volunteers with a mean age of 33 yr (range, 28–38 yr) participated in the experiment. All subjects were experienced in pain experiments and gave their informed consent before participation. The study was approved by the local ethics committee.

### *Stimulation*

Tactile and nociceptive afferents of the hands were stimulated by using electrical sensory nerve and cutaneous laser stimulation, respectively. For the nociceptive stimulations data of three subjects from our previous study (Ploner et al. 1999) were included.

In separate runs, ≥40 selective nociceptive cutaneous laser stimuli (Bromm and Treede 1984) were delivered to the dorsum of each hand in the territory of the superficial branch of the radial nerve. Right and

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left hand were stimulated in subsequent runs. The laser device was a Tm:YAG-laser (Baasel Lasertech) with a wavelength of 2000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Interstimulus intervals were randomly varied between 10 and 14 s and stimulation site was slightly changed after each stimulus to avoid tissue damage and sensitization and habituation effects. Stimulation intensity was adjusted to twofold pain threshold intensity, i.e., 600–700 mJ pulse energy. In each individual, laser stimuli elicited clearly painful "pinprick-like" but no tactile sensations.

Tactile afferents were stimulated with 0.3 ms constant voltage pulses delivered to the superficial branch of the radial nerve just proximal to the wrist. At least 150 stimuli each were alternately delivered to both sides at random interstimulus intervals between 2 and 3 s. Stimulus intensity was adjusted to twofold detection threshold intensity, i.e., 40–60 V, thus inducing clear and consistent nonpainful sensations. An electrical stimulus was chosen because its duration closely matches that of the laser stimulus. Moreover, electrical stimuli yield highly synchronized volleys and therefore evoke well-defined and well-studied cortical responses with signal-to-noise ratio superior to natural tactile stimuli. In a control experiment, we verified that locations of reponses to electrical stimuli match those to natural tactile stimuli: In 3 subjects, 150 natural tactile stimuli were delivered to the dorsum of each hand with a pneumatically driven aluminum cylinder of 2 mm diam and a skin contact duration of 600 ms.

### *Data acquisition and analysis*

Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer (Ahonen et al. 1993) in a magnetically shielded room. The helmet-shaped sensor array contains 122 planar SQUID gradiometers which detect the largest signals just above the local cortical current sources. Signals were recorded with a 0.03 Hz high-pass filter and digitally low-pass filtered at 120 Hz. Cortical responses were averaged time-locked to stimulus application. Vertical electrooculogram was used to reject epochs contaminated with blink artifacts. Analysis of evoked responses was focused on an epoch comprising 100 ms prestimulus baseline and 300 ms after stimulation. Sources of responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for more than 85% of the local field variance (goodness of fit) and with 95% confidence limits of source localization $<10$ mm were accepted. Dipole location, orientation, and strength were calculated within a spherical conductor model of each subject's head determined from the individual magnetic resonance images (MRI) acquired on a 1.5 T Siemens-Magnetom. Dipoles were introduced into a spatio-temporal source model where locations and orientations were fixed and source strengths were allowed to vary over time to provide the best fit for the recorded data (for further details concerning data acquisition and analysis see Hämäläinen et al. 1993). Resulting source strengths as a function of time were used for latency determination.

Based on fiducial point markers, MRI and MEG coordinate systems were aligned and sources were superposed on the individual MRI scans. In each individual, distances along the three axes of the Talairach coordinate system (Talairach and Tournoux 1988) were calculated between locations of tactile and nociceptive responses. In addition, source locations were calculated in standardized Talairach coordinates.

## RESULTS

In all subjects, stimulation of tactile afferents elicited clear and consistent nonpainful sensations. Conversely, nociceptive stimulation evoked at least moderately painful but no tactile sensations.

In all subjects, the well-known early 20-ms and 30-ms responses to tactile stimulation were explained by a single dipole, fitted around 30 ms, in the contralateral postcentral gyrus corresponding to the hand area of SI. In 9 of 12 hemispheres (5 left and 4 right), an additional subsequently peaking source in the contralateral SI hand area located more medially was necessary to explain the recorded signals. These early SI responses were followed by activity originating from the contralateral posterior parietal cortex in three recordings, and in all recordings, from the upper banks of the Sylvian fissures, bilaterally, corresponding to SII. By contrast, nociceptive stimuli nearly simultaneously activated a single source in the contralateral postcentral gyrus (SI) and bilateral sources in the upper banks of the Sylvian fissures (SII). No nociceptive responses were recorded from the posterior parietal cortex. Latencies and mean standardized Talairach coordinates of nociceptive and tactile responses are given in Table 1.

Figure 1 compares magnetic field patterns, source locations, and source strength waveforms to both stimuli in a single subject. The figure illustrates that, along the postcentral gyrus, the nociceptive SI source was located more medially than the tactile 30-ms response. However, the location of the nociceptive source corresponded well to the later peaking tactile SI source. In addition, tactile stimuli later elicited a response arising from the posterior parietal cortex, whereas no corresponding activity was recorded to nociceptive stimuli.

Figure 2 shows locations of later peaking tactile SI responses (Fig. 2*A*) and nociceptive sources (Fig. 2*B*) in SI with respect to the tactile 30-ms response (coordinate center) in axial and coronal planes in all subjects. In each individual, both responses were located more medially and caudally than the tactile 30-ms source. In no subject was there any overlap of 95% confidence limits of source localization with the 30-ms response. The insert in the middle row of the figure demonstrates that the mean relative location of the later peaking tactile SI source and the nociceptive SI source were nearly coinciding. The control experiment revealed that locations of early responses to natural tactile stimuli closely match loca-

TABLE 1. *Peak latencies and standardized Talairach coordinates of tactile and nociceptive responses*

| | Tactile | Nociceptive |
|---|---|---|
| | *Latencies, ms* | |
| SI contralateral | 31 ± 1* | 171 ± 4 |
| SI contralateral later | 64 ± 8 | |
| SII contralateral | 105 ± 5 | 160 ± 5 |
| SII ipsilateral | 116 ± 3 | 175 ± 5 |
| | *Locations* | |
| SI | 36, −24, 52* | 26, −30, 59 |
| SI later | 26, −30, 58 | |
| SII right | 47, −11, 16 | 51, −8, 16 |
| SII left | −49, −14, 20 | −51, −15, 19 |

Values are mean latencies ± SE and mean standardized Talairach coordinates. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; *, tactile 30-ms response. Latencies of contralateral SII responses were significantly shorter than latencies of ipsilateral SII responses to tactile (two-tailed Wilcoxon signed rank test, $P < 0.005$) and nociceptive stimuli ($P < 0.05$). Latencies of contralateral SI and contralateral SII responses to nociceptive stimuli were not statistically different ($P = 0.06$). Because SI responses in both hemispheres were symmetrical, coordinates of SI responses are given for right hemispheric responses only.

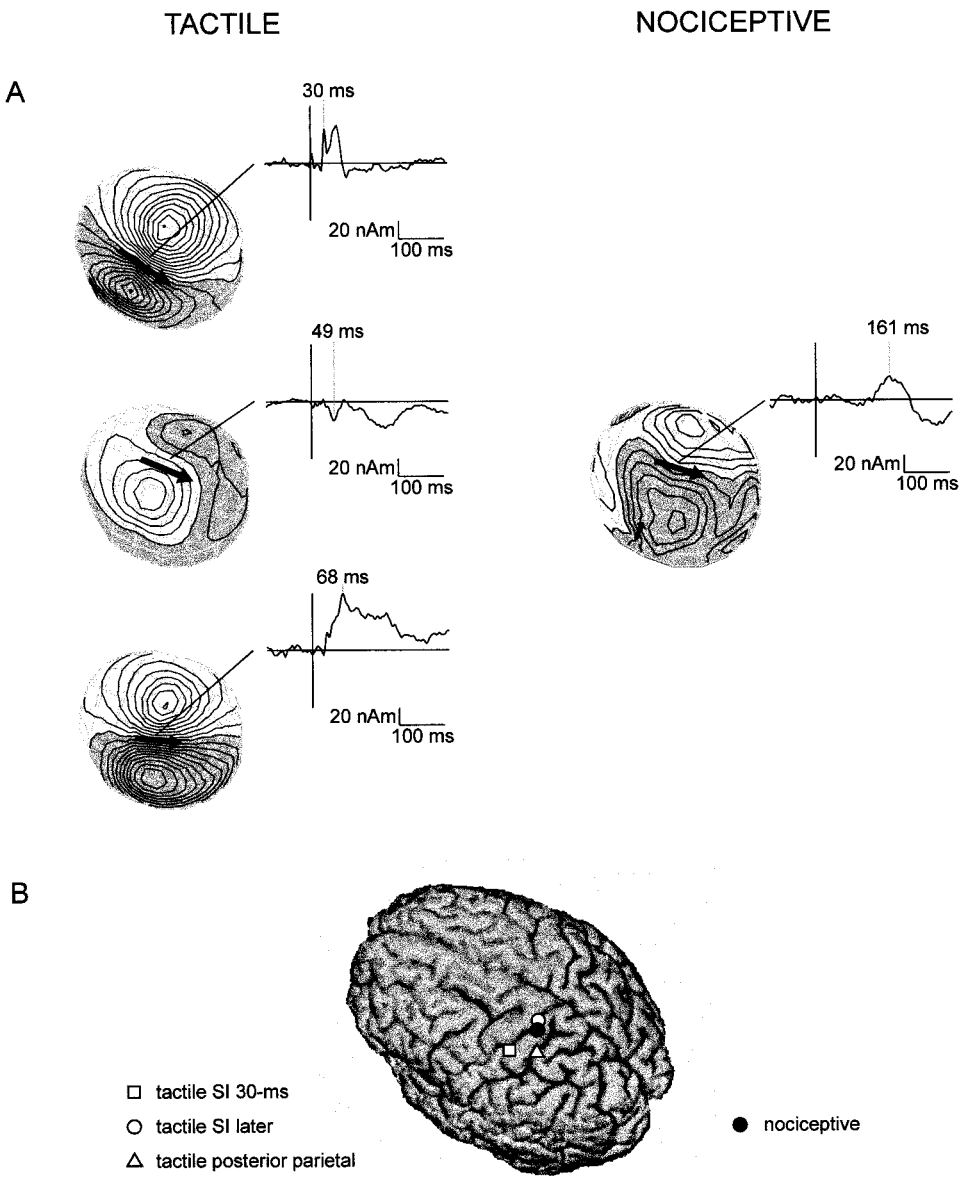


FIG. 1. Comparison of tactile and nociceptive responses in a single subject. *A*: magnetic field patterns at 30, 49, and 68 ms (tactile) and 145 ms (nociceptive) and corresponding dipoles and dipole waveforms. The helmet-shaped sensor array is viewed from the upper left. Shaded areas indicate fields directed into the head, isocontours are separated by 30 fT. Arrows represent location and direction of dipoles, corresponding source strengths as a function of time are shown on the right of the sensor arrays. For the sake of clarity, magnetic field patterns at 49 ms are shown after subtracting activity from other sources using the signal-space projection method (Uusitalo and Ilmoniemi 1997). *B*: location of sources superposed on the subject's brain surface rendering.

tions of 30-ms responses to sensory nerve stimuli (mean location difference along *x*, *y* and *z* axis; 0 mm, 0 mm, and 2 mm).

Figure 3 demonstrates that there was no systematical difference between locations of tactile and nociceptive sources in SII.

## DISCUSSION

In this study, we compared cortical responses to tactile and nociceptive stimuli in human somatosensory cortices. Within SI, our results reveal a fundamental difference in the representation of both modalities: Stimulation of tactile afferents activated two sequentially peaking sources within SI, whereas nociceptive stimuli merely evoked a single SI response. Along the postcentral gyrus, this single nociceptive source was significantly more medially located than the early tactile 30-ms response and corresponded spatially to the later peaking tactile source. These results expand previous findings indicating distinct temporal activation patterns of SI and SII in nociceptive and tactile processing (Ploner et al. 1999).

Intra- and extracranial recordings in monkeys (McCarthy et al. 1991) and humans (Allison et al. 1989a; Wood et al. 1985) revealed generation of the early 20-ms and 30-ms components of somatosensory evoked potentials and fields in cytoarchitectonical area 3b. Accordingly, in this study, 30-ms SI responses

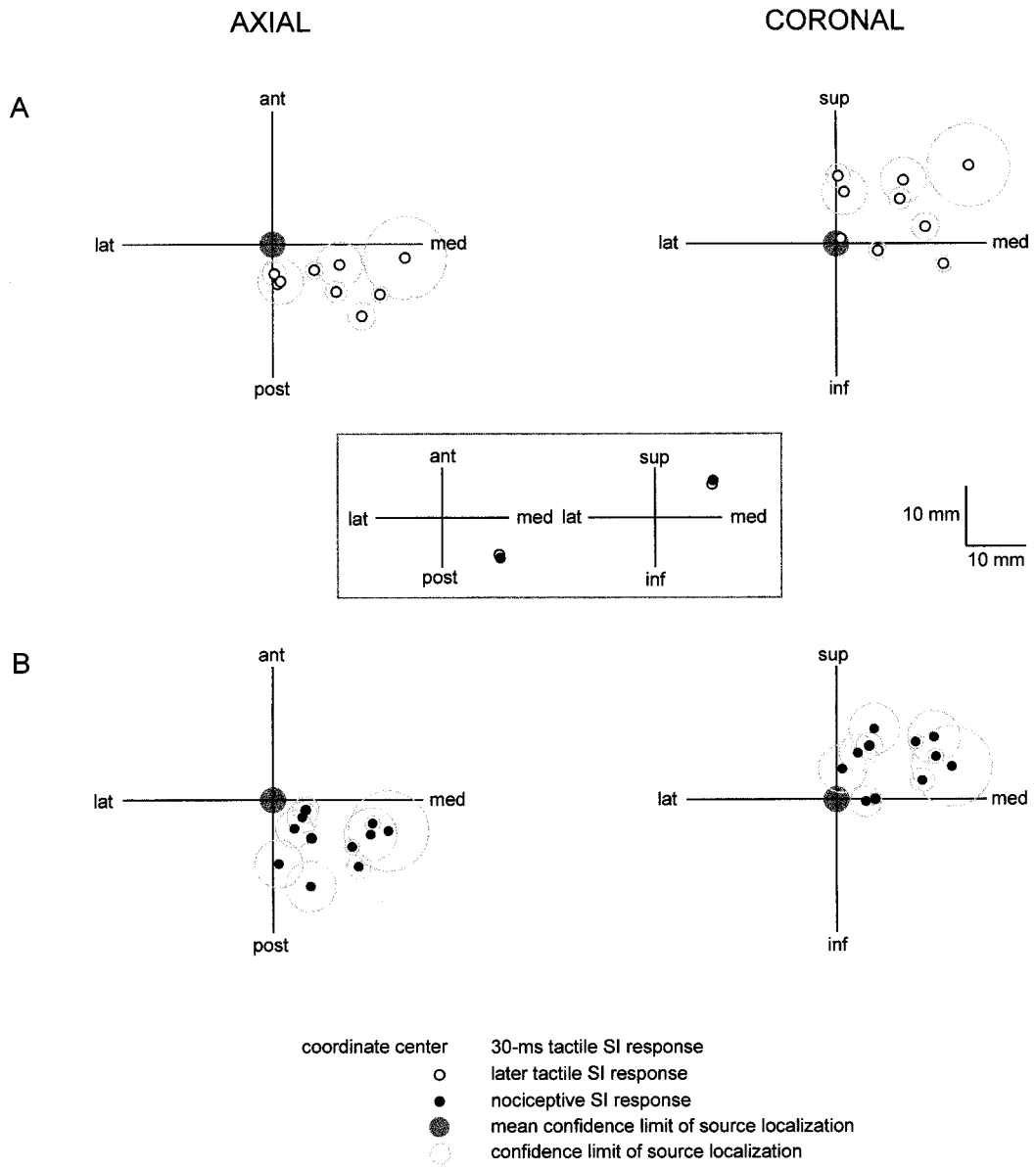


FIG. 2. Comparison of tactile and nociceptive responses in SI, group results. The axes of the diagrams represent the axes of the Talairach coordinate system (Talairach and Tournoux 1988), sizes of shaded circles and areas indicate individual and mean 95% confidence limits of source localization, respectively. *A*: location of later peaking tactile SI sources (black circles) with respect to tactile 30-ms SI sources (coordinate center). *B*: location of nociceptive SI sources (black dots) with respect to tactile 30-ms sources. In one recording, no nociceptive SI response could be identified. In both comparisons, the example from Fig. 1 corresponds to the most medially located responses. *Inset*, mean locations of later tactile peaking SI sources and nociceptive SI sources with respect to tactile 30-ms SI sources. Note that the scaling on the right applies to all diagrams including the insert. ant, anterior; post, posterior; lat, lateral; med, medial; sup; superior; inf, inferior.

to tactile stimuli most likely arise from area 3b in the rostral bank of the postcentral gyrus. By contrast, the more medial location of both the nociceptive and the later peaking tactile source suggests generation of these responses in cytoarchitectonical area 1. A mean mediolateral location difference to the 30-ms response of 10 mm corresponds to a mediolateral location difference between the hand representations of areas 1 and 3b as revealed by intracranial recordings (Allison et al. 1989a; McCarthy et al. 1991; Wood et al. 1988), and anatomic (Jones et al. 1982), metabolic labeling (Juliano and Whitsel 1985), and functional neuroimaging studies (Burton et al. 1997). In humans, this mediolateral distance between responses attributed to areas 1 and 3b amounts to ~10 mm (Allison et al. 1989a; Burton et al. 1997; Wood et al. 1988) and thus agrees well with our findings.

Macrostructurally, in humans, area 1 has been shown to comprise the crown of the postcentral gyrus and the superficial parts of its rostral and caudal banks (Geyer et al. 1997, 1999; White et al. 1997). Consequently, because MEG does not detect radially oriented currents (Hämäläinen et al. 1993), recorded activity might predominantly originate from the fissural parts and less from the convexial parts of area 1. Conversely, a mainly radial orientation of convexial area 1 sources and the predominance of more consistently activated 3b

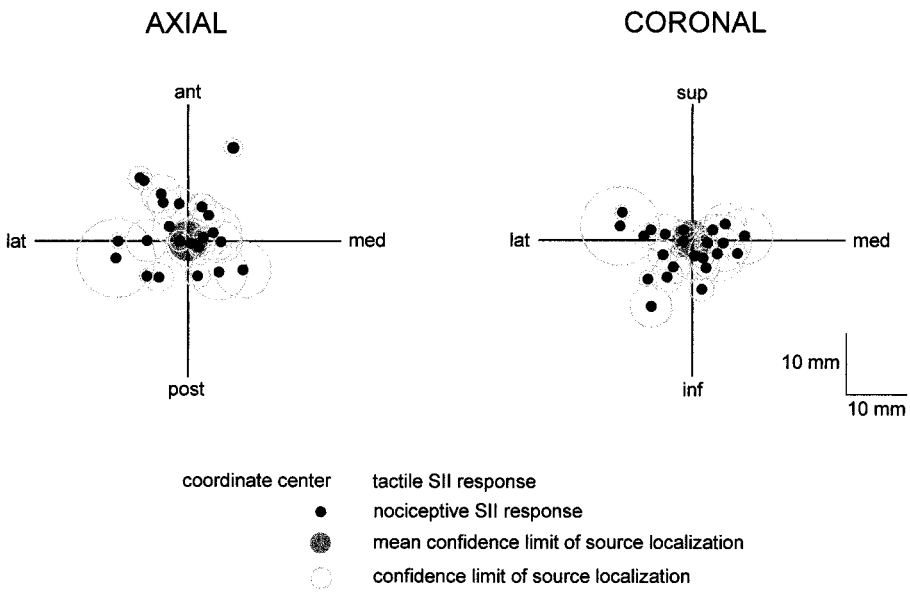


FIG. 3. Comparison of tactile and nociceptive responses in SII, group results. Location of nociceptive SII sources with respect to tactile SII sources and corresponding confidence limits of source localization. In one recording, no contralateral nociceptive SII response could be identified. For further details, see Fig. 2.

sources (Allison et al. 1989a; Wood et al. 1985, 1988) may account for the partial failure to detect area 1 responses in MEG. Furthermore, in previous studies using median nerve stimuli, frequent activation of posterior parietal cortex might have complicated identification of area 1 sources (Forss et al. 1994). However, in the posterior parietal cortex, most somesthetic neurons respond to complex activations of deep receptors related to exploratory movements (for review see Hyvärinen 1982). Consequently, in this study, stimulation of a cutaneous nerve branch supplying the dorsum of the hand might have accounted for less intensive activation of the posterior parietal cortex thus facilitating detection of area 1 sources.

Generation of nociceptive SI responses in cytoarchitectonical area 1 is supported by results from experimental animal studies: Single neuron recordings in monkeys revealed location of most nociceptive SI neurons at the rostral and caudal borders of area 1 (Chudler et al. 1990; Kenshalo and Isensee 1983). In addition, positron emission tomography studies in humans directly comparing locations of SI responses to nociceptive and tactile stimuli (Coghill et al. 1994; Iadarola et al. 1998) showed a corresponding slight but insignificant mediolateral location difference between activation foci. By contrast, using intrinsic optical imaging, a recent study in monkeys showed pain-associated activations in area 3a whereas neuronal activity in areas 1 and 3b was suppressed by painful stimuli (Tommerdahl et al. 1998). However, in this study, temporal dimensions of stimulations and responses were in the range of seconds and thus differ from the brief stimuli and responses recorded in our study which probably reflect distinct neural mechanisms. Furthermore, in this (Tommerdahl et al. 1998) and the aforementioned studies (Coghill et al. 1994; Iadarola et al. 1998), as a result of different stimulus characteristics and recording techniques, responses were most likely mainly mediated by slowly conducting C fibers whereas in the present study exclusively early A-$\delta$ fiber mediated responses were analyzed.

Locations of SII activations to nociceptive and tactile stimuli did not differ systematically. However, considering the small extent of SII and the complex folding of cortex buried in the Sylvian fissure, the possibility remains that spatial resolution of MEG might be insufficient to detect a consistent macrostructurally definable location difference.

In tactile processing, anatomic and physiologic investigations have revealed a partially hierarchical organization of somatosensory cortices with area 3b representing the first cortical stage of a processing cascade comprising area 1, the posterior parietal cortex and SII (for review see Iwamura 1998). Our result of sequentially peaking sources in area 3b, area 1, the posterior parietal cortex, and SII is likely to reflect this organizational mode. By contrast, generation of nociceptive SI responses merely in area 1 is in conflict with this processing hierarchy and thus complements previous findings indicating direct thalamic access of nociceptive information to SII (Ploner et al. 1999).

Taken together, nociceptive processing apparently does not share the elaborated and hierarchical organization of tactile processing which probably evolutionary evolved in parallel with an improvement in sensory capacities. Instead, direct projections from area 1 (Burton et al. 1995; Jones et al. 1978; Stepniewska et al. 1993) and SII to the primary motor cortex (Friedman et al. 1986) and from SII via the insula to the temporal lobe limbic structures (Friedman et al. 1986; Shi and Cassell 1998) would provide an appropriate anatomic substrate for fast and effective integration of nociceptive information into motor and memory processes. Teleologically, this organization appears reasonable as, in pain perception, effective reactions to and future avoidance of harmful stimuli are obviously more important than object identification or manipula-

tion, the more so as almost every painful stimulus is coupled with activation of tactile pathways.

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Address for reprint requests: A. Schnitzler, Dept. of Neurology, Heinrich-Heine-University, Moorenstrasse 5, D-40225 Düsseldorf, Germany.

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## REFERENCES

AHONEN, A. I., HÄMÄLÄINEN, M. S., KAJOLA, M. J., KNUUTILA, J.E.T., LAINE, P. P., LOUNASMAA, O. V., PARKKONEN, L. T., SIMOLA, J. T., AND TESCHE, C. D. 122-channel SQUID instrument for investigating the magnetic signals from the human brain. *Physica Scripta* T49: 198–205, 1993.

ALLISON, T., MCCARTHY, G., WOOD, C. C., DARCEY, T. M., SPENCER, D. D., AND WILLIAMSON, P. D. Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. *J. Neurophysiol.* 62: 694–710, 1989a.

ALLISON, T., MCCARTHY, G., WOOD, C. C., WILLIAMSON, P. D., AND SPENCER, D. D. Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. *J. Neurophysiol.* 62: 711–722, 1989b.

BRODMANN, K. *Vergleichende Lokalisationslehre der Großhirnrinde*. Leipzig: Barth, 1909.

BROMM, B. AND TREEDE, R. D. Nerve fibre discharges, cerebral potentials and sensations induced by CO2 laser stimulation. *Human Neurobiol.* 3: 33–40, 1984.

BURTON, H. AND FABRI, M. Ipsilateral intracortical connections of physiologically defined cutaneous representations in areas 3b and 1 of macaque monkeys: projections in the vicinity of the central sulcus. *J. Comp. Neurol.* 355: 508–538, 1995.

BURTON, H., FABRI, M., AND ALLOWAY, K. Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. *J. Comp. Neurol.* 355: 539–562, 1995.

BURTON, H., MACLEOD, A. M., VIDEEN, T. O., AND RAICHLE, M. E. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. *Cereb. Cortex* 7: 3–17, 1997.

CHUDLER, E. H., ANTON, F., DUBNER, R., AND KENSHALO, D. R., JR. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. *J. Neurophysiol.* 63: 559–569, 1990.

COGHILL, R. C., TALBOT, J. D., EVANS, A. C., MEYER, E., GJEDDE, A., BUSHNELL, M. C., AND DUNCAN, G. H. Distributed processing of pain and vibration by the human brain. *J. Neurosci.* 14: 4095–4108, 1994.

FELLEMAN, D. J. AND VAN ESSEN, D. C. Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1: 1–47, 1991.

FORSS, N., HARI, R., SALMELIN, R., AHONEN, A., HAMALAINEN, M., KAJOLA, M., KNUUTILA, J., AND SIMOLA, J. Activation of the human posterior parietal cortex by median nerve stimulation. *Exp. Brain Res.* 99: 309–315, 1994.

FRIEDMAN, D. P., MURRAY, E. A., O'NEILL, J. B., AND MISHKIN, M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. *J. Comp. Neurol.* 252: 323–347, 1986.

GARRAGHTY, P. E., FLORENCE, S. L., AND KAAS, J. H. Ablations of areas 3a and 3b of monkey somatosensory cortex abolish cutaneous responsivity in area 1. *Brain Res.* 528: 165–169, 1990.

GEYER, S., SCHLEICHER, A., AND ZILLES, K. The somatosensory cortex of human: cytoarchitecture and regional distributions of receptor-binding sites. *Neuroimage* 6: 27–45, 1997.

GEYER, S., SCHLEICHER, A., AND ZILLES, K. Areas 3a, 3b, and 1 of human primary somatosensory cortex. *Neuroimage* 10: 63–83, 1999.

HÄMÄLÄINEN, M., HARI, R., ILMONIEMI, R. J., KNUUTILA, J., AND LOUNASMAA, O. V. Magnetoencephalography—theory, instrumentation, and application to noninvasive studies of the working human brain. *Rev. Mod. Phys.* 65: 413–497, 1993.

HARI, R., KARHU, J., HÄMÄLÄINEN, M., KNUUTILA, J., SALONEN, O., SAMS, M., AND VILKMAN, V. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. *Eur. J. Neurosci.* 5: 724–734, 1993.

HYVÄRINEN, J. Posterior parietal lobe of the primate brain. *Physiol. Rev.* 62: 1060–1129, 1982.

HYVÄRINEN, J. AND PORANEN, A. Receptive field integration and submodality convergence in the hand area of the post-central gyrus of the alert monkey. *J. Physiol. (Lond.)* 283: 539–556, 1978.

IADAROLA, M. J., BERMAN, K. F., ZEFFIRO, T. A., BYAS-SMITH, M. G., GRACELY, R. H., MAX, M. B., AND BENNETT, G. J. Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain* 121: 931–947, 1998.

IWAMURA, Y. Hierarchical somatosensory processing. *Curr. Opin. Neurobiol.* 8: 522–528, 1998.

IWAMURA, Y., TANAKA, M., SAKAMOTO, M., AND HIKOSAKA, O. Rostrocaudal gradients in the neuronal receptive field complexity in the finger region of the alert monkey's postcentral gyrus. *Exp. Brain. Res.* 92: 360–368, 1993.

JONES, E. G. Organization of the thalamocortical complex and its relation to sensory processes. In: *Handbook of Physiology. The Nervous System, Sensory Processes.* Bethesda, MD: Am. Physiol. Soci., 1984, sect. 1, vol. III, p. 149–212.

JONES, E. G. Connectivity of the primate sensory-motor cortex. In: *Cerebral Cortex, Sensory-Motor Areas and Aspects of Cortical Connectivity*, edited by E. G. Jones and A. Peters, New York: Plenum, 1986, vol. 5, p. 113–183.

JONES, E. G., COULTER, J. D., AND HENDRY, S. H. Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *J. Comp. Neurol.* 181: 291–347, 1978.

JONES, E. G., FRIEDMAN, D. P., AND HENDRY, S. H. Thalamic basis of place- and modality-specific columns in monkey somatosensory cortex: a correlative anatomical and physiological study. *J. Neurophysiol.* 48: 545–568, 1982.

JULIANO, S. L. AND WHITSEL, B. L. Metabolic labeling associated with index finger stimulation in monkey SI: between animal variability. *Brain Res.* 342: 242–251, 1985.

KAAS, J. H. Somatosensory System. In: *The Human Nervous System*, edited by G. Paxinos, San Diego: Academic, 1990, p. 813–844.

KAAS, J. H., NELSON, R. J., SUR, M., LIN, C. S., AND MERZENICH, M. M. Multiple representations of the body within the primary somatosensory cortex of primates. *Science* 204: 521–523, 1979.

KENSHALO, D. R. JR. AND ISENSEE, O. Responses of primate SI cortical neurons to noxious stimuli. *J. Neurophysiol.* 50: 1479–1496, 1983.

KENSHALO, D. R. AND WILLIS, W. D. The role of the cerebral cortex in pain sensation. In: *Cerebral Cortex, Normal and Altered States of Function*, edited by E. G. Jones and A. Peters, New York: Plenum, 1991, vol. 9, p. 153–212.

MCCARTHY, G., WOOD, C. C., AND ALLISON, T. Cortical somatosensory evoked potentials. I. Recordings in the monkey *Macaca fascicularis*. *J. Neurophysiol.* 66: 53–63, 1991.

PLONER, M., SCHMITZ, F., FREUND, H. J., AND SCHNITZLER, A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J. Neurophysiol.* 81: 3100–3104, 1999.

PONS, T. P., GARRAGHTY, P. E., AND MISHKIN, M. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *J. Neurophysiol.* 68: 518–527, 1992.

POWELL, T.P.S. AND MOUNTCASTLE, V. B. Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. *Bull. Johns Hopkins Hosp.* 105: 133–162, 1959.

SHI, C. J. AND CASSELL, M. D. Cascade projections from somatosensory cortex to the rat basolateral amygdala via the parietal insular cortex. *J. Comp. Neurol.* 399: 469–491, 1998.

STEPNIEWSKA, I., PREUSS, T. M., AND KAAS, J. H. Architectonics, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *J. Comp. Neurol.* 330: 238–271, 1993.

TALAIRACH, J. AND TOURNOUX, P. *Co-planar Stereotaxic Atlas of the Human Brain.* Stuttgart: Thieme, 1988.

TOMMERDAHL, M., DELEMOS, K. A., FAVOROV, O. V., METZ, C. B., VIERCK, C. J. JR., AND WHITSEL, B. L. Response of anterior parietal cortex to different modes of same-site skin stimulation. *J. Neurophysiol.* 80: 3272–3283, 1998.

UUSITALO, M. A. AND ILMONIEMI, R. J. Signal-space projection method for separating MEG or EEG into components. *Med. Biol. Eng. Comput.* 35: 135–140, 1997.

VOGT, C. AND VOGT, O. Allgemeinere Ergebnisse unserer Hirnforschung. *J. Psychol. Neurol.* 25: 279–461, 1919.

WHITE, L. E., ANDREWS, T. J., HULETTE, C., RICHARDS, A., GROELLE, M., PAYDARFAR, J., AND PURVES, D. Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. *Cereb. Cortex* 7: 18–30, 1997.

WOOD, C. C., COHEN, D., CUFFIN, B. N., YARITA, M., AND ALLISON, T. Electrical sources in human somatosensory cortex: identification by combined magnetic and potential recordings. *Science* 227: 1051–1053, 1985.

WOOD, C. C., SPENCER, D. D., ALLISON, T., MCCARTHY, G., WILLIAMSON, P. D., AND GOFF, W. R. Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. *J. Neurosurg.* 68: 99–111, 1988.

# Differential Coding of Pain Intensity in the Human Primary and Secondary Somatosensory Cortex

LARS TIMMERMANN,[1] MARKUS PLONER,[1] KATRIN HAUCKE,[2] FRANK SCHMITZ,[1] RÜDIGER BALTISSEN,[2] AND ALFONS SCHNITZLER[1]
[1]*Department of Neurology, Heinrich-Heine-University, 40225 Dusseldorf; and* [2]*Department of Psychology, University of Wuppertal, 42119 Wuppertal, Germany*

**Timmermann, Lars, Markus Ploner, Katrin Haucke, Frank Schmitz, Rüdiger Baltissen, and Alfons Schnitzler.** Differential coding of pain intensity in the human primary and secondary somatosensory cortex. *J Neurophysiol* 86: 1499–1503, 2001. The primary (SI) and secondary (SII) somatosensory cortices have been shown to participate in human pain processing. However, in humans it is unclear how SI and SII contribute to the encoding of nociceptive stimulus intensity. Using magnetoencephalography (MEG) we recorded responses in SI and SII in eight healthy humans to four different intensities of selectively nociceptive laser stimuli delivered to the dorsum of the right hand. Subjects' pain ratings correlated highly with the applied stimulus intensity. Activation of contralateral SI and bilateral SII showed a significant positive correlation with stimulus intensity. However, the type of dependence on stimulus intensity was different for SI and SII. The relation between SI activity and stimulus intensity resembled an exponential function and matched closely the subjects' pain ratings. In contrast, SII activity showed an S-shaped function with a sharp increase in amplitude only at a stimulus intensity well above pain threshold. The activation pattern of SI suggests participation of SI in the discriminative perception of pain intensity. In contrast, the all-or-none–like activation pattern of SII points against a significant contribution of SII to the sensory-discriminative aspects of pain perception. Instead, SII may subserve recognition of the noxious nature and attention toward painful stimuli.

## INTRODUCTION

The ability to differentiate intensities of painful stimuli is one of the major properties of the nociceptive system to be classified as a separate sensory modality. In primates, different intensities of nociceptive stimuli are encoded from peripheral nociceptors up to cortical nociceptive neurons (Doubell et al. 1999; Kenshalo and Willis 1991; Raja et al. 1999). In the monkey primary somatosensory cortex (SI) nociceptive neurons respond to both tactile and nociceptive stimuli and faithfully encode the perception of stimulus intensity (Kenshalo et al. 1989, 2000). Therefore SI is attributed to play a role in the sensory-discriminative aspects of pain processing (Kenshalo and Willis 1991; Schnitzler and Ploner 2000). In contrast, in primate area 7b, as a functionally and anatomically related part of the secondary somatosensory cortex (SII) (Whitsel et al. 1969), nociceptive neurons show complex response characteristics (Robinson and Burton 1980). Activity of these neurons reflects poorly if at all the intensity of nociceptive stimuli (Dong et al. 1989, 1994) and points toward an involvement of SII in recognition, learning, and memory of painful events (Dong et al. 1994; Lenz et al. 1997; Schnitzler and Ploner 2000).

In humans, functional brain imaging (Casey et al. 1996; Coghill et al. 1994; Craig et al. 1996; Talbot et al. 1991) and magnetoencephalography (MEG) studies (Kakigi et al. 1999; Ploner et al. 1999b, 2000) demonstrated that peripheral nociceptive stimuli activate SI and SII. Functional imaging studies, focusing on the intensity coding of nociceptive stimuli in humans, found high correlation between pain ratings/stimulus intensity and activity in contralateral SI (Coghill et al. 1999; Derbyshire et al. 1997; Porro et al. 1998) and bilateral SII (Coghill et al. 1999). However, probably due to the indirect measurement of neuronal activation and the limited time resolution of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), these studies did not support the different neurophysiological properties of nociceptive neurons in SI and SII as revealed from nonhuman primates. Thus it remains currently in dispute whether human SI and SII subserve specific and different functions in the processing of nociceptive stimuli.

We therefore used whole-head MEG to record cortical responses within the human SI and SII to different intensities of selectively nociceptive laser stimuli (Bromm and Treede 1984). Our findings provide evidence for a differential coding of nociceptive stimuli in human SI and SII.

## METHODS

Experiments were performed on eight healthy male volunteers (age: mean 28.3 yr, range 26–33 yr) who were experienced in pain experiments. All subjects gave written informed consent prior to the experiments. The study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

### *Stimulation*

One hundred sixty selectively nociceptive laser stimuli (Bromm and Treede 1984) of four different intensities (150, 300, 450, and 600 mJ) were pseudorandomly applied to the dorsum of the right hand using a Thulium:YAG laser (Baasel Lasertech) with a wavelength of 2000 nm. Pulse duration was 1 ms, stimuli were spots of 6-mm diameter, and the

Address for reprint requests: A. Schnitzler, Dept. of Neurology, MEG-Laboratory, Heinrich-Heine-University, Moorenstr. 5, 40225 Dusseldorf, Germany (E-mail: schnitz@neurologie.uni-duesseldorf.de).

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interstimulus interval was randomly varied between 10 and 14 s. After each stimulus the stimulation site was slightly changed within an area of 40 × 40 mm to avoid tissue damage. In all subjects, pain threshold determined by the method of limits ranged between 200 and 300 mJ.

### *Rating*

Before the measurement started a standardized instruction was given for the rating of the applied nociceptive stimuli: the phenomena of first and second pain were described to the subjects. Subjects were instructed to rate the initial, "pin-prick" like, first pain on a rating scale from 0–100. Zero was defined as "no pain" and 100 was defined as the "worst imaginable pain." Subjects were instructed to rate each nociceptive stimulus after a tone signal that followed 3 s after each laser stimulus. To familiarize volunteers with the experimental setup and the rating procedure, a set of 20 stimuli was applied before MEG recordings started.

### *Data acquisition and analysis*

Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer (Ahonen et al. 1993) in a magnetically shielded room. The helmet-shaped sensor array contains 122 planar SQUID gradiometers that detect the largest signals just above the local cortical current sources. The sample rate was 483 Hz, and signals were band-pass filtered between 0.03 and 160 Hz. The vertical electrooculogram was recorded, and epochs contaminated with blink artifacts were excluded. The MEG data were averaged time-locked to the laser stimuli separately for each of the four stimulus intensities. Data analysis focused on a period comprising 100 ms prestimulus baseline and 300 ms after stimulation. During this time period, cortical responses are adequately explained by sources in contralateral SI and bilateral SII (Ploner et al. 1999b, 2000). Sources of responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for more than 85% of the local field variance (goodness-of-fit) and with at least 95% confidence limits of source localization were accepted. Dipole location and orientation were calculated within a spherical conductor model of each subject's head, determined from the individual high-resolution MRIs acquired on a 1.5 T Siemens Magnetom. The MRI and MEG coordinate systems were aligned based on fiducial point markers, and sources were superposed on individual MRI scans.

Dipoles were introduced into a spatiotemporal source model where locations and orientations were fixed and source strengths were allowed to vary over time (for further details see Hämäläinen et al. 1993). The dipole model determined from responses to highest stimulus intensity was applied to evoked responses of all four stimulation intensities. Peak amplitudes of SI and SII sources were determined at all intensities. When no obvious responses were discernible in the low stimulus intensity condition, maximum amplitudes were accepted in a time window of ±60 ms with respect to the peak amplitude of the highest stimulus intensity.

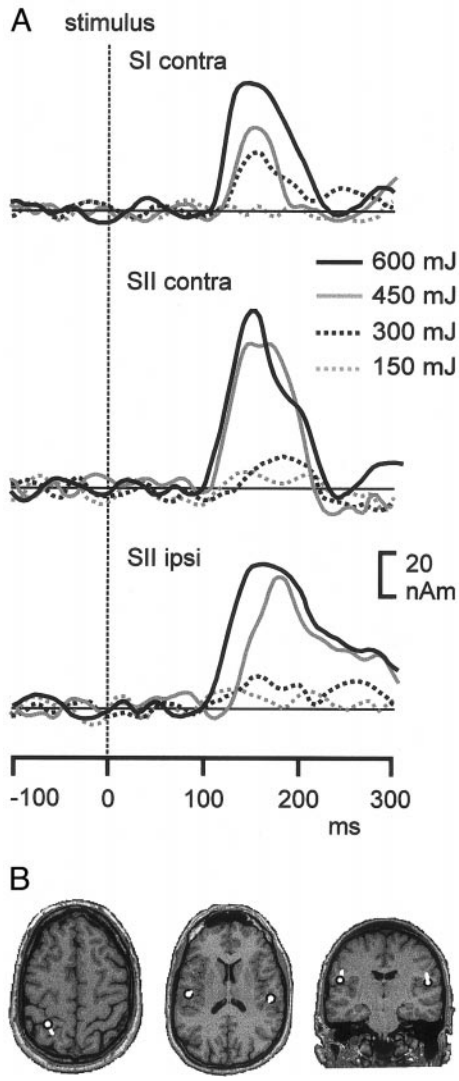


FIG. 1. *A*: source activations in contralateral primary somatosensory cortex (SI) and bilateral secondary somatosensory cortex (SII) at different stimulus intensities in a single subject. Note that SI activity increases monotonically with stimulus intensity. In contrast, subthreshold (150 mJ) and threshold (300 mJ) intensities did not evoke clear contra- or ipsilateral SII activations, whereas stimulation at 450 mJ elicits strong activation that increased very little at 600 mJ (SI contra, contralateral SI; SII contra, contralateral SII; SII ipsi, ipsilateral SII). *B*: localization of the contralateral SI source and bilateral SII sources on high-resolution magnetic resonance imaging (MRI) scans (*left*: axial slice at the level of SI; *middle*: axial slice at the level of SII; *right*: coronal slice at the level of SII).

## RESULTS

Laser stimuli above 250 mJ consistently evoked "pin-prick–like" painful sensations. In all subjects, increased intensities of laser stimulation were rated with higher mean pain scores. This resulted in a significant correlation between stimulus intensity and pain rating ($r = 0.84$, $P < 0.001$, Spearman-rho).

As described previously (Ploner et al. 1999b), nociceptive laser stimuli evoked almost simultaneous activation of contralateral SI and SII (Fig. 1). In general, source strengths in both areas were higher with higher stimulation intensities (Figs. 1 and 2). Consistently, in contralateral SI ($r = 0.76$), contralateral SII ($r = 0.79$), and ipsilateral SII ($r = 0.64$) this resulted in a highly significant correlation between stimulus intensity and source amplitudes ($P < 0.001$). The previously described parallel activation pattern of SI and SII was not grossly altered at lower stimulus intensities.

The relation between stimulus intensity and response amplitude revealed fundamental differences between SI and SII (Figs. 1 and 2). In contralateral SI, increasing stimulus intensities showed continuously increasing source activation closely resembling the exponential stimulus intensity/pain rating function [fit on exponential function $f(x) = b_0 * e^{(b_1 * x)}$: pain ratings: $R^2 = 0.95 \pm 0.02$, mean ± SE; contralateral SI: $R^2 = 0.95 \pm 0.015$]. This exponential function fitted significantly better to the individual stimulus response functions in contralateral SI than to the stimulus response functions in contralateral SII ($R^2$

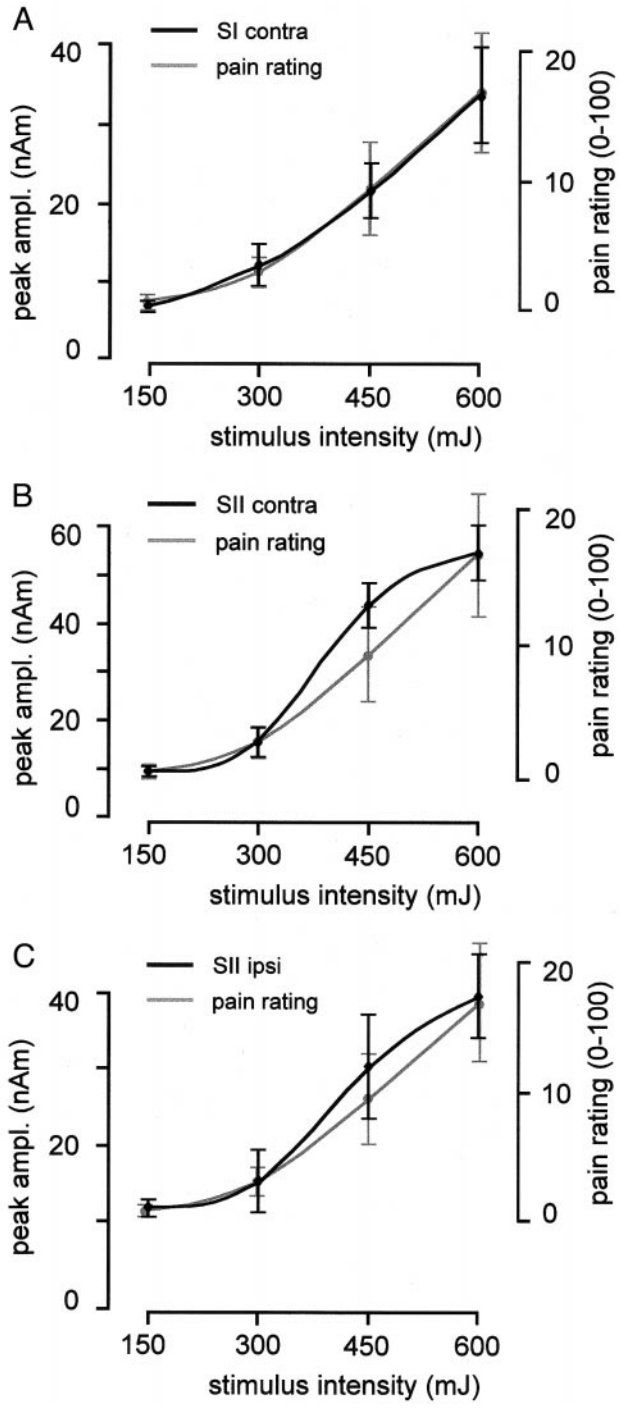


FIG. 2. Source peak amplitudes and pain rating as a function of stimulus intensity. Shown are group means ($n = 8$); error bars indicate standard error (SE). Using the polynomal function $f(x) = b_0 + (b_1 * x) + (b_2 * x^2) + (b_3 * x^3)$ curves were fitted on the stimulus response functions. *A*: amplitudes of contralateral SI activity (black line, left scale) match precisely the subjects' pain ratings (gray line, right scale). Both stimulus response functions are fitted by an exponential curve. *B*: the amplitude of contralateral SII activity (black line, left scale) and pain ratings of the subjects (gray, scale on the *right*) dissociate at 450 mJ: the increase in contralateral SII activity is stronger than the increase in pain ratings, and the curve fitted on the stimulus response function of SII is S-shaped. *C*: amplitudes of ipsilateral SII sources show a similar behavior with a pronounced increase in source activation between 300 and 450 mJ (black line, left scale). Again the increase in source activation is stronger than in pain ratings (gray, scale on the *right*), and the curve fitted on the SII activation is S-shaped.

$= 0.83 \pm 0.056$, $P < 0.05$) and in ipsilateral SII ($R^2 = 0.67 \pm 0.08$, $P < 0.05$, paired *t*-test). In contrast, an S-shaped stimulus-response function was observed in bilateral SII with small activations at the two low-intensity, subthreshold and threshold, stimuli and a sharp increase in source activation at stimuli well above pain threshold. A polynomial function that can either have an S-shaped or exponential appearance [$f(x) = b_0 + (b_1 * x) + (b_2 * x^2) + (b_3 * x^3)$; $x$ corresponds to stimulus intensity] was fitted to the stimulus response functions to describe the differences between SI and SII (Fig. 2). The coefficients determining the increase ($b_1$) and shape ($b_2$ and $b_3$) of the fitted curves were significantly different between the S-shaped functions in contralateral SII and the exponential functions in contralateral SI (contralateral SI: $b_1$, $-0.05 \pm 0.09$; $b_2$, $0.0002 \pm 0.0003$; $b_3$, $-1e-7 \pm 3.1e-7$; contralateral SII: $b_1$, $-0.78 \pm 0.19$; $b_2$, $0.0026 \pm 0.0006$; $b_3$, $-2e-6 \pm 5.4e-7$; ipsilateral SII: $b_1$, $-0.31 \pm 0.098$; $b_2$, $0.0099 \pm 0.0003$, $b_3$, $-7,5e-4 \pm 7e-4$; mean ± SE; paired *t*-tests for $b_1$, $b_2$, and $b_3$ in SI and contralateral SII: $P < 0.02$, Bonferroni corrected). Comparison between bilateral SII and pain ratings revealed clear differences in the step from 300 to 450 mJ in the laser stimuli. The quotient of source activation at 450 and 300 mJ ("activation-ratio") was significantly larger in bilateral SII than in contralateral SI, indicating a significantly steeper increase in source activation between 300 and 450 mJ in SII than in SI ($P < 0.05$, *t*-test, Fig. 3). The absolute amplitudes in contralateral SII compared with contralateral SI and ipsilateral SII were not significantly different.

## DISCUSSION

The present study demonstrates a high correlation of nociceptive stimulus intensity with activity in contralateral SI and bilateral SII. However, the pattern of source activation reveals significant differences between SI and SII. The SI activation closely matches the pain intensity. In contrast, SII activation shows a sharp increase above pain threshold not corresponding to the pain intensity.

In monkeys, the applied physical intensity and perception of painful heat stimuli is highly correlated with the firing rate of wide-dynamic-range (WDR) neurons in SI (Chudler et al. 1990; Kenshalo et al. 1988, 2000). Moreover, after ablation of SI, monkeys show a severe deficit in the detection and discrimination of noxious thermal stimuli (Kenshalo and Willis 1991). These results in nonhuman primates support the view that SI is primarily involved in the encoding of sensory-discriminative aspects of pain (Kenshalo and Willis 1991;

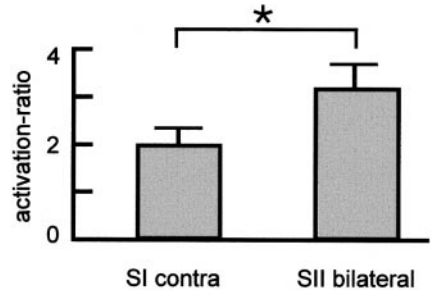


FIG. 3. "Activation-ratio" (quotient of source amplitudes at 450 and 300 mJ) in contralateral SI and bilateral SII. The activation-ratio in bilateral SII is significantly larger than in contralateral SI (* $P < 0.05$, *t*-test; $n = 8$, error bars indicate SE).

Schnitzler and Ploner 2000). Our data demonstrate a high correlation between stimulus intensity, pain ratings, and contralateral SI activation in humans. Thus our results provide evidence that the encoding of stimulus intensity within human SI closely corresponds to the electrophysiological findings in monkeys. This result is corroborated by indirect evidence from clinical lesion studies, suggesting that SI ablation or injury produced impairment of pain sensation (Marshall 1951; Russell 1945). In the light of complementary findings from imaging studies showing spatial discrimination (Andersson et al. 1997; Tarkka and Treede 1993), temporal discrimination (Porro et al. 1998), stimulus size discrimination (Apkarian et al. 2000), and lack of correlation of SI activity with selective modulation of pain unpleasantness (Rainville et al. 1997), SI may serve as a sensory-discriminative evaluator of nociceptive stimuli without necessarily detecting its noxious, "painful" nature.

In nonhuman primates, investigations of the SII territory, including the functionally and anatomically related area 7b (Whitsel et al. 1969), revealed a small population of nociceptive neurons with large receptive fields responding to noxious stimuli (Dong et al. 1989, 1994; Robinson and Burton 1980). These SII neurons receive their major projections from the ventral posterior inferior nucleus (VPI) (Friedman and Murray 1986; Stevens et al. 1993), which consists of a large proportion of nociceptive-specific (NS) neurons poorly encoding the intensity of painful stimuli (Apkarian and Shi 1994). In contrast, nociceptive SI neurons receive primarily projections from thalamic WDR neurons in the ventral posterior lateral nucleus (VPL) (Gingold et al. 1991; Kenshalo et al. 1980), which faithfully represent the stimulus intensity by their firing rate (Apkarian and Shi 1994; Kenshalo et al. 1980). A majority of nociceptive neurons in SII showed complex response characteristics to fearful and threatening visual stimuli but were barely able to encode the intensity of nociceptive stimuli (Dong et al. 1989, 1994) similar to the NS neurons in VPI. These findings indicate a role of SII in spatially directed attention toward and detection/aversion of potentially harmful stimuli (Robinson and Burton 1980), but also in learning and memory of painful stimuli (Dong et al. 1994; Lenz et al. 1997). Our present study shows the capacity of human SII to encode, to a certain extent, the intensity of nociceptive stimuli. Interestingly, mildly painful stimuli around the pain threshold resulted in relatively small SII activations, whereas stronger, clearly painful stimuli were followed by strong activations of SII sources. Within SII, this activation pattern could be well explained by a large proportion of nociceptive neurons lacking the property to faithfully represent the intensity of nociceptive stimuli. It is likely that these neurons subserve, as suggested in monkeys, more complex tasks in pain processing like the detection of, aversion of, and spatially directed attention toward painful stimuli (Robinson and Burton 1980). In summary, the activation of human SII by nociceptive stimuli seems to be similar to the findings in nonhuman primates.

Interestingly, in a number of imaging studies focusing on human cortical pain processing, SII activity dominated over SI activity (Casey et al. 1994; Coghill et al. 1994, 1999; Craig et al. 1996; Davis et al. 1998; Derbyshire et al. 1997; Gelnar et al. 1999; Iadarola et al. 1998; Talbot et al. 1991). The differences in the stimulus-response function of SII and SI in our study could well explain that at moderate pain SII activity exceeds the detection level of PET and fMRI, whereas SI activity barely reaches it.

Recently, a patient with an ischemic lesion including the area of the primary and secondary somatosensory cortex was reported (Ploner et al. 1999a). This patient was able to describe a vague unpleasantness but not the intensity and location of the applied stimulus most probably due to the lesion of SI. Remarkably, he also failed to recognize the noxious nature of the painful stimuli. This deficit in the recognition of the nociceptive character of the stimulus could likely be attributed to the ischemic lesion of SII. Interestingly, these deficits can be differentiated from the "asymbolia for pain" described in patients with insular lesions. These patients demonstrate a lack of withdrawal and show absent or markedly attenuated emotional responses to painful stimuli but recognize well the "painful" nature of the stimulus (Berthier et al. 1988). Taken together, we hypothesize that the insula is involved in *emotional recognition* and motor reaction on noxious stimuli in close connection with the limbic system, in contrast to a possible role of SII in the *cognitive detection* of the noxious, "painful" nature of nociceptive stimuli.

In conclusion, we state that intensity of nociceptive stimuli is differentially represented in the primary and secondary somatosensory cortex. The activation pattern is indicative for a representation of perceived stimulus intensity in contralateral SI and detection and recognition of the noxious nature of painful stimuli in bilateral SII.

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## REFERENCES

AHONEN AI, HÄMÄLÄINEN MS, KAJOLA MJ, KNUUTILA JET, LAINE PP, LOUNASMAA OV, PARKKONEN LT, SIMOLA JT, AND TESCHE CD. 122-channel SQUID instrument for investigating the magnetic signals from the human brain. *Physica Scripta* T49: 198–205, 1993.

ANDERSSON JL, LILJA A, HARTVIG P, LANGSTROM B, GORDH T, HANDWERKER H, AND TOREBJORK E. Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. *Exp Brain Res* 117: 192–199, 1997.

APKARIAN AV, GELNAR PA, KRAUSS BR, AND SZEVERENYI NM. Cortical responses to thermal pain depend on stimulus size: a functional MRI study. *J Neurophysiol* 83: 3113–3122, 2000.

APKARIAN AV AND SHI T. Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals. *J Neurosci* 14: 6779–6795, 1994.

BERTHIER M, STARKSTEIN S, AND LEIGUARDA R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann Neurol* 24: 41–49, 1988.

BROMM B AND TREEDE RD. Nerve fibre discharges, cerebral potentials and sensations induced by $CO_2$ laser stimulation. *Hum Neurobiol* 3: 33–40, 1984.

CASEY KL, MINOSHIMA S, BERGER KL, KOEPPE RA, MORROW TJ, AND FREY KA. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *J Neurophysiol* 71: 802–807, 1994.

CASEY KL, MINOSHIMA S, MORROW TJ, AND KOEPPE RA. Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. *J Neurophysiol* 76: 571–581, 1996.

CHUDLER EH, ANTON F, DUBNER R, AND KENSHALO DR JR. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. *J Neurophysiol* 63: 559–569, 1990.

COGHILL RC, SANG CN, MAISOG JM, AND IADAROLA MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol* 82: 1934–1943, 1999.

COGHILL RC, TALBOT JD, EVANS AC, MEYER E, GJEDDE A, BUSHNELL MC, AND DUNCAN GH. Distributed processing of pain and vibration by the human brain. *J Neurosci* 14: 4095–4108, 1994.

CRAIG AD, REIMAN EM, EVANS A, AND BUSHNELL MC. Functional imaging of an illusion of pain. *Nature* 384: 258–260, 1996.

DAVIS KD, KWAN CL, CRAWLEY AP, AND MIKULIS DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 80: 1533–1546, 1998.

DERBYSHIRE SW, JONES AK, GYULAI F, CLARK S, TOWNSEND D, AND FIRESTONE LL. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 73: 431–445, 1997.

DONG WK, CHUDLER EH, SUGIYAMA K, ROBERTS VJ, AND HAYASHI T. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J Neurophysiol* 72: 542–564, 1994.

DONG WK, SALONEN LD, KAWAKAMI Y, SHIWAKU T, KAUKORANTA EM, AND MARTIN RF. Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. *Brain Res* 484: 314–324, 1989.

DOUBELL TP, MANNION RJ, AND WOOLF C. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: *Textbook of Pain*, edited by Wall PD and Melzack R. London: Churchill Livingstone, 1999, p. 165–182.

FRIEDMAN DP AND MURRAY EA. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *J Comp Neurol* 252: 348–373, 1986.

GELNAR PA, KRAUSS BR, SHEEHE PR, SZEVERENYI NM, AND APKARIAN AV. A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. *Neuroimage* 10: 460–482, 1999.

GINGOLD SI, GREENSPAN JD, AND APKARIAN AV. Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys. *J Comp Neurol* 308: 467–490, 1991.

HÄMÄLÄINEN M, HARI R, ILMONIEMI RJ, KNUUTILA J, AND LOUNASMAA OV. Magnetoencephalography—theory instrumentation and application to noninvasive studies of the working human brain. *Rev Mod Phys* 65: 413–497, 1993.

IADAROLA MJ, BERMAN KF, ZEFFIRO TA, BYAS-SMITH MG, GRACELY RH, MAX MB, AND BENNETT GJ. Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain* 121: 931–947, 1998.

KAKIGI R, WATANABE S, YAMASAKI H, AND MAEDA K. Pain-related brain activities: magnetoencephalographic studies. *Electroencephalogr Clin Neurophysiol Suppl* 49: 245–249, 1999.

KENSHALO DR JR, ANTON F, AND DUBNER R. The detection and perceived intensity of noxious thermal stimuli in monkey and in human. *J Neurophysiol* 62: 429–436, 1989.

KENSHALO DR JR, CHUDLER EH, ANTON F, AND DUBNER R. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res* 454: 378–382, 1988.

KENSHALO DR JR, GIESLER GJ JR, LEONARD RB, AND WILLIS WD. Responses of neurons in primate ventral posterior lateral nucleus to noxious stimuli. *J Neurophysiol* 43: 1594–1614, 1980.

KENSHALO DR, IWATA K, SHOLAS M, AND THOMAS DA. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. *J Neurophysiol* 84: 719–729, 2000.

KENSHALO DR AND WILLIS WD. The role of the cerebral cortex in pain sensation. In: *Cerebral Cortex, Normal and Altered States of Function*, edited by Jones EG and Peters A. New York: Plenum, 1991, vol. 9, p. 153–212.

LENZ FA, GRACELY RH, ZIRH AT, ROMANOSKI AJ, AND DOUGHERTY PM. The sensory-limbic model of pain memory. *Pain Forum* 6: 22–31, 1997.

MARSHALL J. Sensory disturbances in cortical wounds with special reference to pain. *J Neurol Neurosurg Psychiatry* 14: 187–204, 1951.

PLONER M, FREUND HJ, AND SCHNITZLER A. Pain affect without pain sensation in a patient with a postcentral lesion. *Pain* 81: 211–214, 1999a.

PLONER M, SCHMITZ F, FREUND HJ, AND SCHNITZLER A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J Neurophysiol* 81: 3100–3104, 1999b.

PLONER M, SCHMITZ F, FREUND HJ, AND SCHNITZLER A. Differential organization of touch and pain in human primary somatosensory cortex. *J Neurophysiol* 83: 1770–1776, 2000.

PORRO CA, CETTOLO V, FRANCESCATO MP, AND BARALDI P. Temporal and intensity coding of pain in human cortex. *J Neurophysiol* 80: 3312–3320, 1998.

RAINVILLE P, DUNCAN GH, PRICE DD, CARRIER B, AND BUSHNELL MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277: 968–971, 1997.

RAJA SN, MEYER RA, RINGKAMP M, AND CAMPBELL JN. Peripheral neural mechanisms of nociception. In: *Textbook of Pain*, edited by Wall PD and Melzack R. London: Churchill Livingstone, 1999, p. 11–58.

ROBINSON CJ AND BURTON H. Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of *M. fascicularis*. *J Comp Neurol* 192: 93–108, 1980.

RUSSELL WR. Transient disturbances following gunshot wounds of the head. *Brain* 68: 79–97, 1945.

SCHNITZLER A AND PLONER M. Neurophysiology and neuroanatomy of pain perception. *J Clin Neurophysiol* 17: 592–603, 2000.

STEVENS RT, LONDON SM, AND APKARIAN AV. Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. *Brain Res* 631: 241–246, 1993.

TALBOT JD, MARRETT S, EVANS AC, MEYER E, BUSHNELL MC, AND DUNCAN GH. Multiple representations of pain in human cerebral cortex. *Science* 251: 1355–1358, 1991.

TARKKA IM AND TREEDE RD. Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a $CO_2$ laser. *J Clin Neurophysiol* 10: 513–519, 1993.

WHITSEL BL, PETRUCELLI LM, AND WERNER G. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. *J Neurophysiol* 32: 170–183, 1969.

*J Neurophysiol*
88: 300–305, 2002; 10.1152/jn.00782.2001.

# Cortical Representation of Venous Nociception in Humans

MARKUS PLONER,[1] HOLGER HOLTHUSEN,[2] PETER NOETGES,[2] AND ALFONS SCHNITZLER[1]
[1]*Department of Neurology and* [2]*Department of Anesthesiology, Heinrich-Heine-University, 40225 Düsseldorf, Germany*

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**Ploner, Markus, Holger Holthusen, Peter Noetges, and Alfons Schnitzler.** Cortical representation of venous nociception in humans. *J Neurophysiol* 88: 300–305, 2002; 10.1152/jn.00782.2001. Painful sensations can be evoked by application of thermal, mechanical, and chemical stimuli to the blood vessels. The cortical substrates of these sensations are unknown. We therefore used whole-head magnetoencephalography to record cortical responses to painful laser stimuli applied cutaneously and intravenously to the dorsum of the hand in healthy human subjects. Similar to the cutaneous stimuli, venous stimulation nearly simultaneously activated the contralateral primary and the bilateral secondary somatosensory cortices. In the venous stimulation condition, all activation peaks were about 50 ms earlier than in the cutaneous stimulation condition. Locations of responses to both stimuli did not differ. These results show that the afferent volley from the veins reaches the cerebral cortex significantly earlier than that from the skin. This might be due to differences in peripheral conduction velocity. Apart from this, these findings demonstrate that venous nociception shares the cortical representation of cutaneous nociception in human somatosensory cortices. Thus the cortical representation of nociceptive processing from tissues of mesodermal and ectodermal origin appears to be similar.

## INTRODUCTION

In humans, painful sensations can be evoked by application of thermal, mechanical, and chemical stimuli to the veins (Arndt and Klement 1991; Fruhstorfer and Lindblom 1983). These painful sensations have been suggested to be signaled by polymodal nociceptors of the vein wall (Arndt and Klement 1991). Correspondingly, anatomical studies in animals showed a sensory innervation of blood vessels (Hinsey 1928; Lim et al. 1962; Polley 1955; Truex 1936; Woollard 1926) presumably involved in vascular nociception (Bazett and McGlone 1928; Glaser 1926; Moore and Moore 1933; Moore and Singleton 1933; Odermatt 1922). Physiological studies confirmed that thinly myelinated and unmyelinated afferents of the veins respond to thermal (Minut-Sorokhtina and Glebova 1976), mechanical (Davenport and Thompson 1987; Göder et al. 1993; Michaelis et al. 1994), and chemical (Göder et al. 1993; Michaelis et al. 1994) stimuli of high, presumably noxious intensities. Functionally, these afferents may be particularly relevant under pathophysiological conditions (Göder et al. 1993; Michaelis et al. 1994). In cats, stimulation of these afferents elicits responses in the sensory-motor cortex (Thompson et al. 1980). However, in humans the cortical representation of venous nociception is unknown.

Painful stimulation of cutaneous nociceptive afferents has been shown to activate the contralateral primary (SI) and bilateral secondary (SII) somatosensory cortices that are included in a broad network associated with nocieption (for review see Schnitzler and Ploner 2000). Magnetoencephalographic (MEG) investigations revealed nearly simultaneous activation of these cortical areas peaking at 160–180 ms after cutaneous application of selective nociceptive laser stimuli to the hand (Ploner et al. 1999, 2000; Timmermann et al. 2001). This activation pattern suggests parallel thalamocortical distribution of cutaneous nociceptive information to SI and SII.

Here, by using whole-head magnetoencephalography we directly compared cortical responses to cutaneous and intravenous painful laser stimuli applied to the same site on the dorsum of the hand in healthy human subjects. We aimed to investigate whether venous nociception shares the cortical representation of cutaneous nociception in humans.

## METHODS

Six healthy right-handed volunteers aged between 31 and 38 yr (mean 34 yr) participated in the study. None of the subjects had a history of neurological or psychiatric disorders. Informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

### *Stimulation*

Forty painful cutaneous laser stimuli (Bromm et al. 1984) were delivered to the skin of the dorsum of the hand. Depending on the individual anatomy of the veins and its accessability for venous puncture, in four subjects the right hand and in two subjects the left hand was chosen for stimulation. The laser device was a Tm:YAG-laser (Baasel Lasertech) with a wavelength of 2,000 nm and a pulse duration of 1 ms. The optical fiber leading the laser beam into the recording room was connected to a handpiece resulting in a spot diameter of 6 mm. Stimulation site was sligthly changed within an area of 4 × 3 cm after each stimulus. Interstimulus intervals were randomly varied between 10 and 14 s. Applied stimulus intensity was 600 mJ evoking moderately painful sensations.

In a separate run, 40 painful laser stimuli were intravenously applied to the dorsum of the same hand as in the cutaneous stimulation condition. The same laser stimulator with a wavelength of 2,000 nm and a pulse duration of 1 ms was used. In this condition, the bare end of the optical fiber with a diameter of 0.6 mm was led through a cannula of 1.4 mm OD into the veins. A puncture site distal to a vein crossing was chosen so that the tip of the fiber was targeted to the vein wall. The distance between the bare end of the optical fiber in the

Address for reprint requests: A. Schnitzler, Dept. of Neurology, Heinrich-Heine-University, Moorenstrasse 5, D-40225 Düsseldorf, Germany (E-mail: schnitz@neurologie.uni-duesseldorf.de).

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intravenous stimulation condition and the center of the stimulated area in the cutaneous stimulation condition was not allowed to exceed 5 cm in proximal-distal direction. The intravenous position of the optical fiber was continuously controlled and if necessary corrected by one of the investigators who was present in the magnetically shielded room throughout the experiment. Interstimulus intervals were randomly varied between 30 and 60 s. To obtain a maximum signal-to-noise ratio, stimulus intensity was adjusted to evoke moderately to severely painful sensations corresponding to intensities between 6 and 8 on a visual analog scale between 0 (no pain) and 10 (maximally tolerable pain) resulting in stimulus intensities between 500 and 800 mJ.

In both conditions, any stimulus-related noise was masked by white noise applied to subject's ears through plastic tubes.

### *Data acquisition and analysis*

Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer (Ahonen et al. 1993) in a magnetically shielded room. The helmet-shaped sensor array contains 122 planar gradiometers that detect the largest signals just above the local cortical current sources. Signals were recorded with a 0.03-Hz high-pass filter and digitally low-pass filtered at 40 Hz. Cortical responses were averaged time locked to stimulus application. Vertical electrooculogram was used to reject epochs contaminated with blink artifacts. Analysis of evoked responses was focused on an epoch comprising 100-ms prestimulus baseline and 250 ms after stimulation. Sources of evoked responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources with 95% confidence limits of source localization $<$10 mm were accepted. Dipole location, orientation, and strength were calculated within a spherical conductor model of each subject's head determined from the individual magnetic resonance images (MRI) acquired on a 1.5 T Siemens-Magnetom. Dipoles were introduced into a spatiotemporal source model where locations and orientations were fixed and source strengths were allowed to vary over time to provide the best fit for the recorded data (for further details concerning data acquisition and analysis see Hämäläinen et al. 1993). Resulting source strengths as a function of time were used for determination of peak latencies defined as first peak after stimulus delivery of at least 5 nAm.

Based on fiducial point markers, MRI and MEG coordinate systems were aligned, and sources were superposed on the individual MRI scans. Locations of sources were determined in a coordinate system with the *x*-axis passing through the preauricular points, the *y*-axis passing through the nasion normal to the *x*-axis, and the *z*-axis pointing up normal to the *xy*-plane.

## RESULTS

Laser stimuli applied to the skin evoked moderately painful well-localized "pinprick-like" sensations. Likewise, intravenously applied laser stimuli evoked moderately to severely painful well-localized sharp sensations. In both conditions, quality of sensations were stable both within and between subjects. In the intravenous stimulation condition there was a tendency toward habituation that was counterbalanced by changing the position of the optical fiber after 5–15 stimuli. Thus intensity of evoked sensations was slightly more variable in the intravenous laser stimulation condition than in the cutaneous laser stimulation condition.

Figure 1 compares timing and location of cortical responses to cutaneous and intravenous laser stimuli in a representative subject. Cutaneous stimuli evoked responses similar to previous investigations (Ploner et al. 1999, 2000; Timmermann et al. 2001). Field patterns of neuromagnetic responses to cutaneous laser stimuli at 147 ms after stimulus application indicated simultaneous activation of a contralateral parietal source with anterior-posterior current direction and of sources with inferior-superior current directions in the temporoparietal cortex of both hemispheres (Fig. 1*A*). Sensors located above these sources detected maximum signals at 147 and 145 ms in the contralateral and at 161 ms in the ipsilateral hemisphere, respectively (Fig. 1*A*). No earlier responses were detected. Dipole modeling and superposition of dipole location on individual MRI scans showed location of sources in the contralateral postcentral gyrus and bilaterally in the upper banks of the Sylvian fissures, corresponding to contralateral SI and bilateral SII (Fig. 1*B*). Source strengths as a function of time showed activation peaks at 150 ms (contralateral SI), 146 ms (contralateral SII), and 155 ms (ipsilateral SII), respectively (Fig. 1*C*).

Intravenously applied laser stimuli yielded magnetic field patterns similar to cutaneous stimulation suggesting activation of a contralateral SI-source with anterior-posterior current direction and bilateral SII-sources with inferior-superior current directions (Fig. 1*A*). However, in the venous condition this field pattern was observed at 97 ms, i.e., 50 ms earlier than in the cutaneous stimulation condition. Correspondingly, sensors located above the cortical sources detected maximum signals at 87, 89, and 99 ms, respectively (Fig. 1*A*). Source modeling and superposition of source locations on MRI scans confirmed location of sources in the contralateral postcentral gyrus (SI) and in the upper banks of the Sylvian fissures, bilaterally (SII; Fig. 1*B*). Comparison of source strengths as a function of time between both conditions corroborated an earlier activation of sources to intravenously as compared with cutaneously applied stimuli (Fig. 1*C*).

Table 1 shows peak latencies of activations in contralateral SI and bilateral SII to both stimuli for all subjects. Two-way repeated measures ANOVA revealed a significant effect of condition (venous/cutaneous; $P = 0.003$) and of source (SI contralateral/SII contralateral/SII ipsilateral; $P = 0.03$) on the observed latencies. Latencies to venous stimuli were $55 \pm 6$ ms (mean $\pm$ SE) shorter than to cutaneous stimuli. Scheffé's post hoc test showed that latencies of contralateral SII activations were significantly shorter than latencies of ipsilateral SII activations ($P = 0.03$). There was no significant interaction between condition and source ($P = 0.6$). Figure 2 illustrates this latency differences by showing grand averages across source waveforms of contralateral SI and bilateral SII in all subjects. Grand averages of source activations to cutaneous and venous stimuli peaked at 160 and 121 ms (contralateral SI), 151 and 129 ms (contralateral SII), and 167 and 134 ms (ipsilateral SII), respectively.

Peak amplitudes of source activations to cutaneous and venous stimuli were $28 \pm 7$ and $14 \pm 3$ nAm (contralateral SI), $41 \pm 7$ and $43 \pm 10$ nAm (contralateral SII), and $47 \pm 9$ and $29 \pm 9$ nAm (ipsilateral SII), respectively (mean $\pm$ SE). Two-way repeated measures ANOVA revealed a significant effect of condition (venous/cutaneous; $P = 0.03$) but not of source ($P = 0.2$) on the observed amplitudes. There was no significant interaction between condition and source ($P = 0.1$).

Group analysis of source locations did not show a significant effect of condition on source location in *x*-, *y*-, or *z*-direction (repeated measures ANOVA, $P > 0.1$).

## DISCUSSION

In the present study we compared cortical responses to cutaneous and intravenous painful laser stimuli applied to

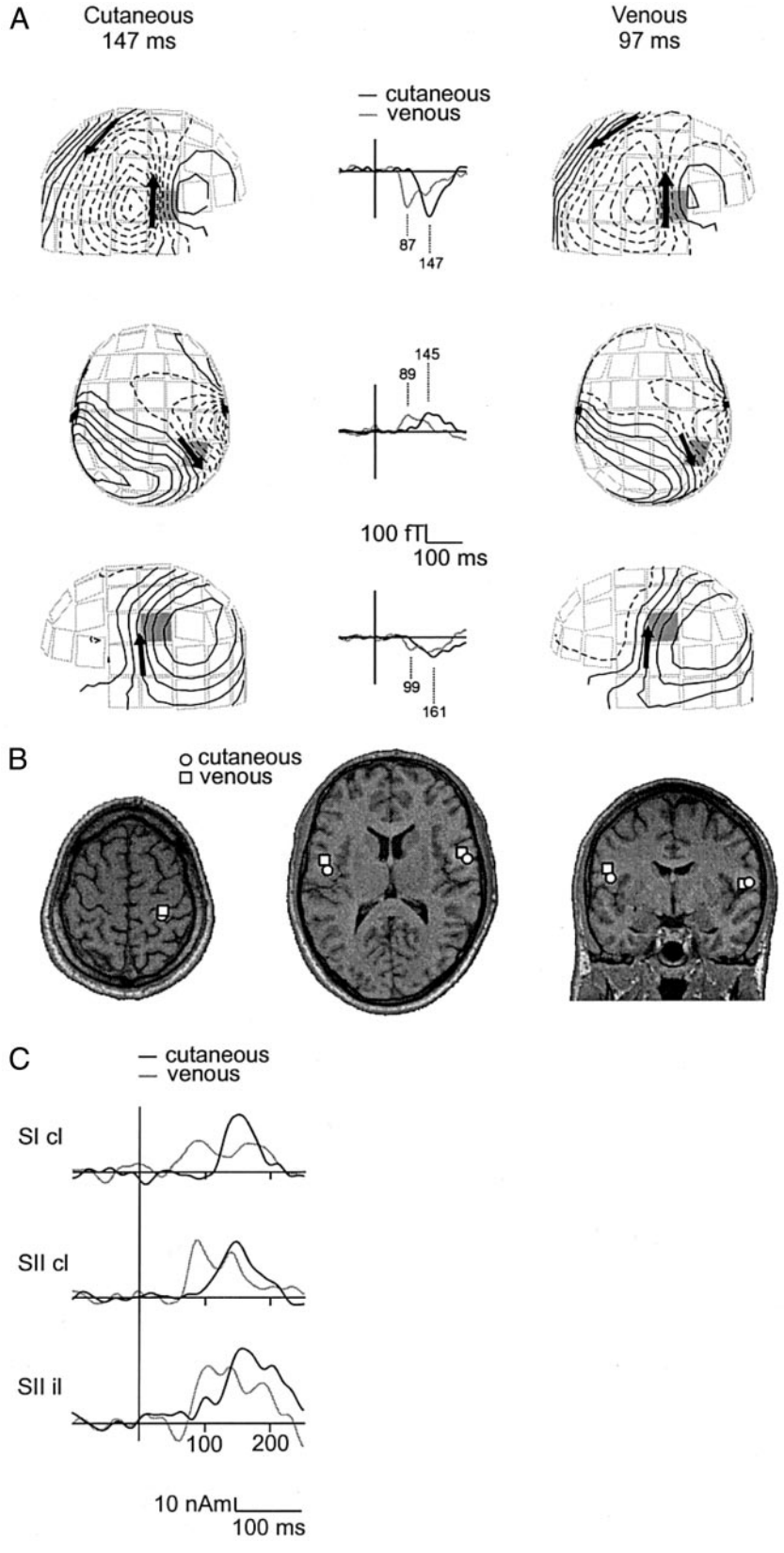


FIG. 1. Exemplary results. Cortical responses to painful cutaneous and venous stimulation of the left hand. *A*: magnetic field patterns at 147 and 97 ms after cutaneous (*left*) and venous (*right*) stimulus application, respectively. The magnetic field patterns are displayed over the helmet-shaped sensor array viewed from the right, top, and the left. Squares show locations of 61 sensor pairs. Isocontour lines are separated by 100 fT. Dashed lines indicate fields directed into the head. Arrows represent location and direction of dipoles. The *middle panel* shows responses to cutaneous and venous stimuli recorded from the same sensors marked by shaded squares on the left and right. *B*: location of sources superposed on axial and coronal magnetic resonance imaging (MRI) scans of the subject's brain, slice thickness 15 mm. *C*: source strengths as a function of time. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; cl, contralateral to stimulus application; il, ipsilateral to stimulus application.

the dorsum of the hand in healthy human subjects. For the first time our results show the cortical representation of venous nociception in humans. Similar to the here and previously (Ploner et al. 1999, 2000; Timmermann et al. 2001) studied responses to cutaneous stimuli venous stimulation evoked nearly simultaneous activation of contralateral SI and bilateral SII. However, comparison of response latencies between stimulations revealed that venous stimuli

TABLE 1. *Group results; latencies of cortical responses to painful cutaneous and venous stimulation in all subjects*

| Subject | Stimulated Hand | SI cl | | SII cl | | SII il | |
|---|---|---|---|---|---|---|---|
| | | Cutaneous | Venous | Cutaneous | Venous | Cutaneous | Venous |
| *mb* | l | 150 | 87 | 146 | 86 | 155 | 103 |
| *rh* | r | 158 | 122 | 152 | 96 | 183 | 100 |
| *hh* | r | 163 | 72 | 175 | 86 | 182 | 92 |
| *rk* | r | | | 148 | 125 | | |
| *pn* | l | 175 | 116 | 152 | 120 | 162 | 125 |
| *rf* | r | 159 | 103 | 134 | 112 | 161 | 126 |
| Mean | | 161 ± 4 | 100 ± 9 | 151 ± 5 | 104 ± 7 | 169 ± 6 | 109 ± 7 |

Values are latencies in ms. Mean values are ± SE. In one subject no responses in SI and ipsilateral SII were observed to both stimuli. Two-way repeated measures analysis of variance shows a significant effect of condition (venous/cutaneous; $P = 0.003$) and of source (SI contralateral/SII contralateral/SII ipsilateral; $P = 0.03$) on the observed latencies. Latencies to venous stimuli were 55 ± 6 ms (mean ± SE) shorter than to cutaneous stimuli. Scheffé's post hoc test showed that latencies of contralateral SII activations were significantly shorter than latencies of ipsilateral SII activations ($P = 0.03$). SI, primary somatosensory cortex; SII, secondary somatosensory cortex; cl, contralateral to stimulus application; il, ipsilateral to stimulus application; l, left; r, right.

activated all three areas about 50 ms earlier than cutaneous stimuli.

These results demonstrate involvement of the somatotopically appropriate region of SI and of SII in processing of nociceptive information from the veins. Locations of SI- and SII-responses did not differ between venous and cutaneous nociceptive stimulations. Previous investigations indicated generation of SI-responses to cutaneous nociceptive stimuli in cytoarchitectonical area 1 of SI (Ploner et al. 2000). Thus venous SI-responses most probably originate from cytoarchitectonical area 1 of SI, too. Locations of SII-responses in the present and previous studies (Ploner et al. 1999, 2000; Timmermann et al. 2001) and inferior-superior source orientations to both stimuli indicate that these responses predominantly originate from SII-cortex in the parietal operculum. However, a contribution of more medially located insular cortex expected to yield mainly radially oriented sources not detected by MEG cannot be ruled out.

Our finding of involvement of SI is in accordance with investigations in the cat showing that stimulation of venous afferents evokes responses in the sensory-motor cortex (Thompson et al. 1980). No further evidence on the cortical representation of vascular nociception has been presented so far, neither in humans nor in animals.

Apart from the general latency difference between cortical responses to cutaneous and venous stimuli, the temporal relationship between activation of sources does not differ between cutaneous and venous stimulation. Thus the organization of

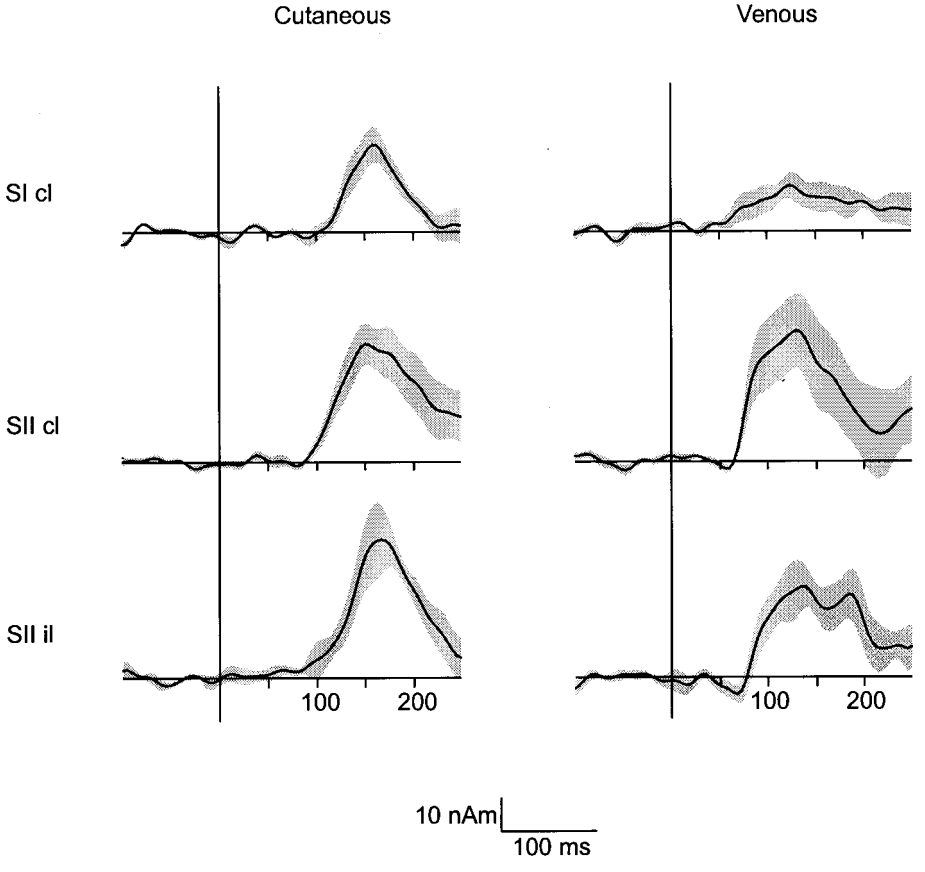


FIG. 2. Group results. Mean source strengths as a function of time across all subjects for painful cutaneous and venous stimulations. Shaded areas depict ±SE. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; cl, contralateral to stimulus application; il, ipsilateral to stimulus application.

nociceptive venous processing appears to share the parallel organization of cutaneous nociceptive processing in human contralateral SI and SII (Ploner et al. 1999, 2000; Timmermann et al. 2001). The significant latency difference between contralateral and ipsilateral SII in both conditions suggests transcallosal transfer of nociceptive information from contralateral to ipsilateral SII. However, there was a significant effect of condition on source amplitudes. Here, differences in stimulus parameters do not allow to distinguish between a physiological and a methodological effect.

Considering the mesodermal origin of the veins, our results might be compared with investigations of the cortical representation of other tissues of mesodermal origin. In a recent functional imaging study, cerebral activations to painful stimulation of the muscle and of the skin were compared (Svensson et al. 1997). In this study, similar cerebral activation patterns including SI and SII were observed in both conditions. This suggests that cortical nociceptive processing from tissues of mesodermal origin, e.g., blood vessels and muscle, is similar to nociceptive processing from tissues of ectodermal origin, e.g., the skin.

Our findings indicate that the afferent volley from the veins reaches the cerebral cortex significantly earlier than that from the skin. It is unlikely that the observed latency difference is due to a difference in stimulation site between venous and cutaneous stimulation. Differences in stimulation site between conditions were kept below 5 cm in distal-proximal direction. Consequently, considering conduction velocities of Aδ-fibers of about 10 m/s (Raja et al. 1999), a systematic difference in conduction distance cannot adequately explain a latency difference of about 50 ms, but at most 5 ms. Likewise, a difference in pain intensity between conditions is unlikely to yield a latency difference of 50 ms since previous evoked potential studies investigating intensity dependence of cortical responses did not show a dependence of latencies on pain intensity (Carmon et al. 1978; Chen et al. 1979; Harkins and Chapman 1978; Spiegel et al. 2000). Nor is the observed latency difference likely to be due to a difference in receptor activation latencies. In comparison to the $CO_2$-laser with a receptor activation time for Aδ-nociceptive afferents of about 40 ms (Bromm and Treede 1984), physical stimulus properties of the Tm:YAG-laser indicate a considerably shorter activation latency (Spiegel et al. 2000). This is confirmed by shorter latencies of cortical responses to Tm:YAG-laser stimuli than to $CO_2$-laser stimuli (Spiegel et al. 2000). Thus most probably, the latency difference between cortical responses to cutaneous and venous stimulation is due to a difference in peripheral or central conduction velocity. Based on the present results we cannot decide between these possibilities. However, except for the latency difference our results reveal a cortical representation of venous nociception similar to cutaneous nociception. Thus a difference in conduction velocity between peripheral venous and cutaneous nociceptive afferents appears most likely to account for the latency difference. However, peripheral conduction velocities of venous and cutaneous afferents have not been compared yet. In monkeys two types of cutaneous nociceptive Aδ-fibers with different response characteristics and a difference in conduction velocity of about 10 m/s, which could well explain a 50-ms latency difference from hand to cerebral cortex have been described (Treede et al. 1995, 1998). It is unclear whether the observed latency difference in our study corresponds to these findings. In addition, a higher intravenous than cutaneous temperature might contribute to faster conduction of venous nociceptive afferents.

In conclusion, the present results show that vascular nociception shares the cortical representation of cutaneous nociception in human somatosensory cortices. However, the afferent volley from the veins reaches the cerebral cortex significantly earlier than from the skin. This might be due to differences in peripheral conduction velocity. Our findings suggest that in human somatosensory cortices nociceptive processing from tissues of mesodermal origin, e.g., the blood vessels, is similar to nociceptive processing from tissues of ectodermal origin, e.g., the skin.

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## REFERENCES

AHONEN AI, HÄMÄLÄINEN MS, KAJOLA MJ, KNUUTILA JET, LAINE PP, LOUNASMAA OV, PARKKONEN LT, SIMOLA JT, AND TESCHE CD. 122-channel SQUID instrument for investigating the magnetic signals from the human brain. *Physica Scripta* T49: 198–205, 1993.

ARNDT JO AND KLEMENT W. Pain evoked by polymodal stimulation of hand veins in humans. *J Physiol (Lond)* 440: 467–478, 1991.

BAZETT HC AND MCGLONE B. Note on pain sensations which accompany deep puncture. *Brain* 51: 18–23, 1928.

BROMM B, JAHNKE MT, AND TREEDE RD. Responses of human cutaneous afferents to CO2 laser stimuli causing pain. *Exp Brain Res* 55: 158–166, 1984.

BROMM B AND TREEDE RD. Nerve fibre discharges, cerebral potentials and sensations induced by $CO_2$ laser stimulation. *Hum Neurobiol* 3: 33–40, 1984.

CARMON A, DOTAN Y, AND SARNE Y. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. *Exp Brain Res* 33: 445–453, 1978.

CHEN AC, CHAPMAN CR, AND HARKINS SW. Brain evoked potentials are functional correlates of induced pain in man. *Pain* 6: 365–374, 1979.

DAVENPORT PW AND THOMPSON FJ. Mechanosensitive afferents of femoral-saphenous vein. *Am J Physiol Regulatory Integrative Comp Physiol* 252: R367–R370, 1987.

FRUHSTORFER H AND LINDBLOM U. Vascular participation in deep cold pain. *Pain* 17: 235–241, 1983.

GLASER W. Die intramurale Innervation der Kranzgefäβe. *Zeitschrift für Anatomie und Entwicklungsgeschichte* 79: 797–804, 1926.

GÖDER R, HÄBLER HJ, JÄNIG W, AND MICHAELIS M. Receptive properties of afferent nerve fibres associated with the rat saphenous vein. *Neurosci Lett* 164: 175–178, 1993.

HÄMÄLÄINEN M, HARI R, ILMONIEMI RJ, KNUUTILA J, AND LOUNASMAA OV. Magnetoencephalography—theory, instrumentation, and application to noninvasive studies of the working human brain. *Rev Mod Phys* 65: 413–497, 1993.

HARKINS SW AND CHAPMAN CR. Cerebral evoked potentials to noxious dental stimulation: relationship to subjective pain report. *Psychophysiology* 15: 248–252, 1978.

HINSEY JC. Observations on the innervation of the blood vessels in skeletal muscle. *J Comp Neurol* 47: 23–60, 1928.

LIM RKS, LIU CN, GUZMAN F, AND BRAUN C. Visceral receptors concerned in visceral pain and the pseudoaffective response to intra-arterial injection of bradykinin and other algesic agents. *J Comp Neurol* 118: 269–293, 1962.

MICHAELIS M, GÖDER R, HÄBLER HJ, AND JÄNIG W. Properties of afferent nerve fibres supplying the saphenous vein in the cat. *J Physiol (Lond)* 474: 233–243, 1994.

MINUT-SOROKHTINA OP AND GLEBOVA NF. On the vascular component of the peripheral cold reception. *Prog Brain Res* 43: 119–127, 1976.

MOORE RM AND MOORE RE. Studies on the pain-sensibility of arteries I. Some observations on the pain-sensibility of arteries. *Am J Physiol* 104: 259–266, 1933.

MOORE RM AND SINGLETON AO. Studies on the pain-sensibility of arteries II. Perpipheral paths of afferent neurones from the arteries of the extremities and of the abdominal viscera. *Am J Physiol* 104: 267–275, 1933.

ODERMATT W. Die Schmerzempfindlichkeit der Blutgefäβe und die Gefäβreflexe. *Bruns' Beiträge zur klinischen Chirurgie* 127: 1–84, 1922.

PLONER M, SCHMITZ F, FREUND HJ, AND SCHNITZLER A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J Neurophysiol* 81: 3100–3104, 1999.

PLONER M, SCHMITZ F, FREUND HJ, AND SCHNITZLER A. Differential organization of touch and pain in human primary somatosensory cortex. *J Neurophysiol* 83: 1770–1776, 2000.

POLLEY EH. The innervation of blood vessels in striated muscle and skin. *J Comp Neurol* 103: 253–267, 1955.

RAJA SN, MEYER RA, RINGKAMP M, AND CAMPBELL JN. Peripheral neural mechanisms of nociception. In: *Textbook of Pain*, edited by Wall PD and Melzack R. Edinburgh, UK: Churchill Livingstone, 1999, p. 11–57.

SCHNITZLER A AND PLONER M. Neurophysiology and functional neuroanatomy of pain perception. *J Clin Neurophysiol* 17: 592–603, 2000.

SPIEGEL J, HANSEN C, AND TREEDE RD. Clinical evaluation criteria for the assessment of impaired pain sensitivity by thulium-laser evoked potentials. *Clin Neurophysiol* 111: 725–735, 2000.

SVENSSON P, MINOSHIMA S, BEYDOUN A, MORROW TJ, AND CASEY KL. Cerebral processing of acute skin and muscle pain in humans. *J Neurophysiol* 78: 450–460, 1997.

THOMPSON FJ, LERNER DN, FIELDS K, AND BLACKWELDER A. Projection of limb venous afferents to the feline motor-sensory cortex. *J Auton Nerv Syst* 2: 39–45, 1980.

TIMMERMANN L, PLONER M, HAUCKE K, SCHMITZ F, BALTISSEN R, AND SCHNITZLER A. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. *J Neurophysiol* 86: 1499–1503, 2001.

TREEDE RD, MEYER RA, AND CAMPBELL JN. Myelinated mechanically insensitive afferents from monkey hairy skin: heat-response properties. *J Neurophysiol* 80: 1082–1093, 1998.

TREEDE RD, MEYER RA, RAJA SN, AND CAMPBELL JN. Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. *J Physiol (Lond)* 483: 747–758, 1995.

TRUEX RC. Sensory nerve terminations associated with peripheral blood vessels. *Proc Soc Exp Biol Med* 34: 699–700, 1936.

WOOLLARD HH. The innervation of blood vessels. *Heart* 13: 319–336, 1926.

# Cortical representation of first and second pain sensation in humans

**Markus Ploner, Joachim Gross, Lars Timmermann, and Alfons Schnitzler***

Department of Neurology, Heinrich Heine University, 40225 Düsseldorf, Germany

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**Single painful stimuli evoke two successive and qualitatively distinct sensations referred to as first and second pain sensation. Peripherally, the neural basis of this phenomenon is a dual pathway for pain with Aδ and C fibers mediating first and second pain, respectively. Yet, the differential cortical correlates of both sensations are largely unknown. We therefore used magnetoencephalography to record and directly compare first and second pain-related cortical responses to cutaneous laser stimuli in humans. Our results show that brief painful stimuli evoke sustained cortical activity corresponding to sustained pain perception comprising early first pain-related and late second pain-related components. Cortical activity was located in primary (S1) and secondary (S2) somatosensory cortices and anterior cingulate cortex. Time courses of activations disclosed that first pain was particularly related to activation of S1 whereas second pain was closely related to anterior cingulate cortex activation. Both sensations were associated with S2 activation. These results correspond to the different perceptual characteristics of both sensations and probably reflect different biological functions of first and second pain. First pain signals threat and provides precise sensory information for an immediate withdrawal, whereas second pain attracts longer-lasting attention and motivates behavioral responses to limit further injury and optimize recovery.**

It is a unique perceptual phenomenon that single painful stimuli yield two successive and qualitatively distinct sensations referred to as first and second pain sensation (1–4). First pain is brief, pricking, and well localized, whereas second pain is longer-lasting, burning, and less well localized. Peripherally, the neural basis of this phenomenon is a dual pathway for pain with Aδ and C fibers mediating first and second pain, respectively (2, 3). Different conduction velocities of both fiber types of about 10–20 and 1 m/s (5, 6) account for the temporal sequence of both sensations with reaction times to first pain of 400–500 ms and to second pain of about 1,000 ms after application of painful stimuli to the hand (1, 2, 4, 7).

The biological functions and the differential cortical correlates of first and second pain are less well known. Anatomical, physiological, and lesion studies in humans and animals have revealed an extensive cortical network associated with sensory, cognitive, and affective aspects of pain (for review, see ref. 8). This network consistently includes primary (S1) and secondary (S2) somatosensory cortices, insular cortex, and anterior cingulate cortex (ACC). However, only a few studies disentangled Aδ and C fiber activations and, thus, first and second pain. Neurophysiological recordings in humans revealed early Aδ fiber-mediated activations in S1, S2, and ACC (for review, see ref. 8), whereas C fiber-mediated cortical responses at latencies of about 1,000 ms have been shown in scalp recordings (9–13) but have not yet been consistently localized. Conversely, functional imaging studies using tonic C fiber stimuli demonstrated activation of S1, S2, Insula, and ACC (14–17) but did not provide temporal information. Thus, the temporal sequence and a differential involvement of Aδ and C fiber-mediated cortical activations related to first and second pain remains to be demonstrated.

Here, we used magnetoencephalography (MEG) to record and compare early Aδ fiber- mediated and late C fiber-mediated cortical responses to single painful cutaneous laser stimuli in healthy human subjects. We directly demonstrate the differential cortical correlates of first and second pain. These findings probably reflect the different perceptual characteristics and biological functions of first and second pain.

## Methods

Ten healthy male subjects with a mean age of 31 years (range, 22–38 years) participated in the study. Informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki. Forty painful cutaneous laser stimuli, which have been shown to activate selectively nociceptive Aδ and C afferents (18), were delivered to the dorsum of the right hand. The laser device was a Tm:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2,000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. The laser beam was led through an optical fiber from outside into the recording room. Stimulation site was slightly changed within an area of $4 \times 3$ cm after each stimulus. Interstimulus intervals were randomly varied between 10 and 14 s. Applied stimulus intensity was 600 mJ evoking moderately painful sensations.

Continuous pain ratings were obtained in four subjects. These measurements were done separately from the MEG recordings to prevent confounding effects of motor- and stimulus-related activation. Subjects were instructed to rate continuously stimulus intensity with the finger span of thumb and index of the left hand while stimuli were applied to the right hand. Minimal finger span was defined as no pain and maximal finger span as worst tolerable pain. Positions of fingertips of thumb and index were tracked by an ultrasound-based motion analysis system (Zebris Medizintechnik, Tübingen, Germany) with a sampling rate of 50 Hz. Euclidean distance of fingertips as a function of time was normalized to individual maximal finger span and averaged with respect to laser stimuli. To familiarize subjects with the rating procedure at least 10 stimuli were applied before the recordings started.

Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer containing 122 planar SQUID gradiometers (19) in a magnetically shielded room. Signals were digitized at 483 Hz, high-pass filtered at 0.03 Hz, and low-pass filtered at 20 Hz. Neuromagnetic activity was averaged time-locked to application of laser stimuli. Vertical and horizontal electrooculograms were used to reject epochs contaminated with blink artifacts and eye movements. An epoch comprising 1,000 ms prestimulus baseline and 3,000 ms after stimulation was analyzed. In each subject, global stimulus-evoked neuromagnetic activity was calculated as mean rectified signal of all 122 sensors. Cortical activity was localized during two time windows reflecting Aδ fiber-mediated first pain-related and C fiber-mediated second pain-related activity, respectively. The early time window

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Abbreviations: ACC, anterior cingulate cortex; MEG, magnetoencephalography.

*To whom reprint requests should be addressed. E-mail: schnitza@uni-duesseldorf.de.



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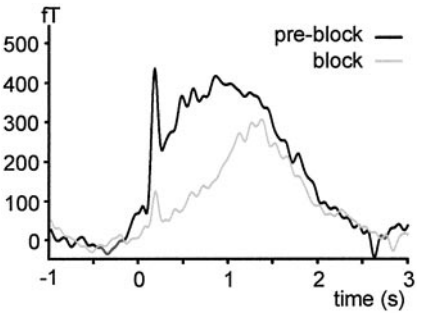


**Fig. 1.** Effect of A fiber pressure block on global stimulus-evoked neuromagnetic activity calculated as mean rectified signal of all sensors corrected to baseline in a single subject.

had a duration of 100 ms and was individually centered around first peak of global stimulus-evoked activity resulting in time windows between 100–200 and 150–250 ms. The late time window had a duration of 1,000 ms and uniformly ranged from 500 to 1,500 ms. For both time windows covariance matrices across all sensors were calculated. From these covariance matrices pain-evoked activity was localized by using a spatial filtering algorithm (20). The spatial filter was used with a realistic head model to estimate power in the whole brain resulting in individual tomographic power maps with voxel sizes of $6 \times 6 \times 6$ mm. This approach is a time-domain variant of the frequency-based dynamic imaging of coherent sources method, which was recently introduced to the investigation of oscillatory activity (21). Further processing of tomographic power maps was performed by using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, www.fil.ion.ucl.ac.uk/spm). Individual maps were spatially normalized to Talairach space by using parameters derived from normalization of individual T1-weighted magnetic resonance images (22). Mean group normalized power maps were calculated for both time windows. From these mean power maps locations of activations defined as local cortical power maxima exceeding 80% of the global maximum were determined. Time courses of activations were individually determined from a spatiotemporal source model with fixed locations and orientations where activation strengths were allowed to vary over time to provide the best fit for the recorded data (23). For source models, locations of activations were individual power maxima within the cortical areas defined previously from the mean group maps. On the basis of resulting activation strengths as a function of time group mean time courses of activations were calculated. For each area 95% confidence intervals of activation were calculated from the 1,000-ms prestimulus baseline. Mean amplitudes of activations were determined in both time windows and an activation ratio early/late was calculated. Friedman's analysis of variance and two-tailed Wilcoxon signed rank tests were used for statistical comparison of activation ratios.

In two subjects, mediation of early and late cortical activity by Aδ and C fibers, respectively, was verified by a selective pressure block of myelinated A fibers. In this procedure compression of the superficial branch of the radial nerve is exerted by a band across the forearm loaded with a weight. By using microneurographic recordings in humans this procedure has been shown to yield a preferential block of myelinated A fibers (24, 25; see ref. 26 for details of the procedure). Conduction block of A fibers was monitored by tactile v.Frey-hair stimuli and nociceptive cutaneous laser stimuli. MEG measurements were started when tactile perception and first pain sensation was abolished but second pain was preserved. This continuation was confirmed by verbal report and an increase in mean reaction time from 378 to 1,148 ms. A fiber block differentially affected early and late activity. Early activity was substantially more attenuated than late activity, as indicated by a decrease in activation ratio early/late from 0.93 to 0.50 (Fig. 1). Thus, Aδ and C fibers most likely mediate early and late activity, respectively.

## Results

Group mean time courses of pain perception (*Left*) and of stimulus-evoked global neuromagnetic activity (*Right*) are shown in Fig. 2. Painful laser stimuli evoked sustained pain perception and sustained neuromagnetic activity. Both parameters show an initial peak within the first 1,000 and 500 ms after stimulus application, respectively, and a longer-lasting later slowly decreasing component. Mean peak intensity of pain was nearly 60% of maximal intensity defined as worst tolerable pain.

Fig. 3 summarizes locations and time courses of pain-evoked cortical activations. Activations were located in the contralateral postcentral gyrus (S1), in the upper banks of the Sylvian fissures bilaterally (S2), and in the ACC. Location of S1 activation was obtained from the early time window, and locations of ACC and bilateral S2 activations from the late time window. Coordinates of activations in Talairach space are given in Table 1. Coordinates of S1 and S2 activations correspond well to results from our previous investigations in early cortical responses to painful laser stimuli (27, 28).

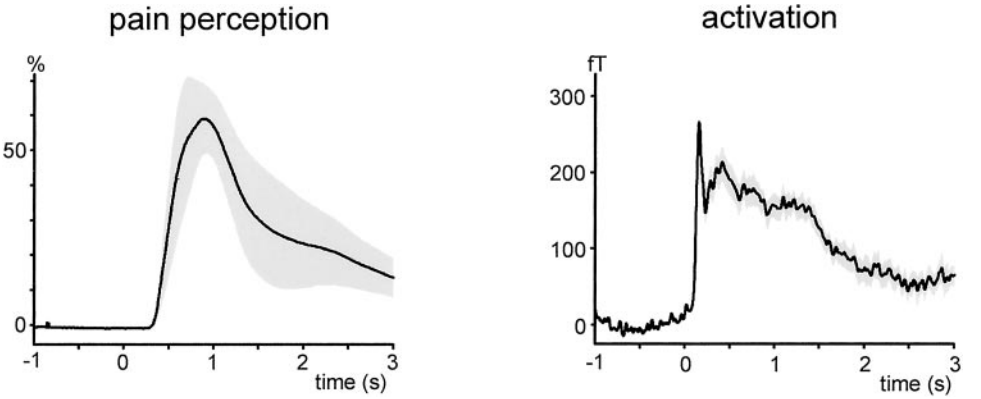


**Fig. 2.** Time courses of stimulus perception and global stimulus-evoked neuromagnetic activity. Time course of stimulus perception was continuously rated by thumb–index finger span of the left hand while the right hand was stimulated. One hundred percent is defined as maximal distance between fingers corresponding to worst tolerable pain. Time course of stimulus-evoked neuromagnetic activity was calculated as mean rectified signal of all sensors corrected to baseline. Rating and MEG signals were recorded separately under the same experimental conditions, except that during the MEG recordings no rating was required. Data were averaged across 4 and 10 subjects, respectively. Shaded areas indicate SEM.

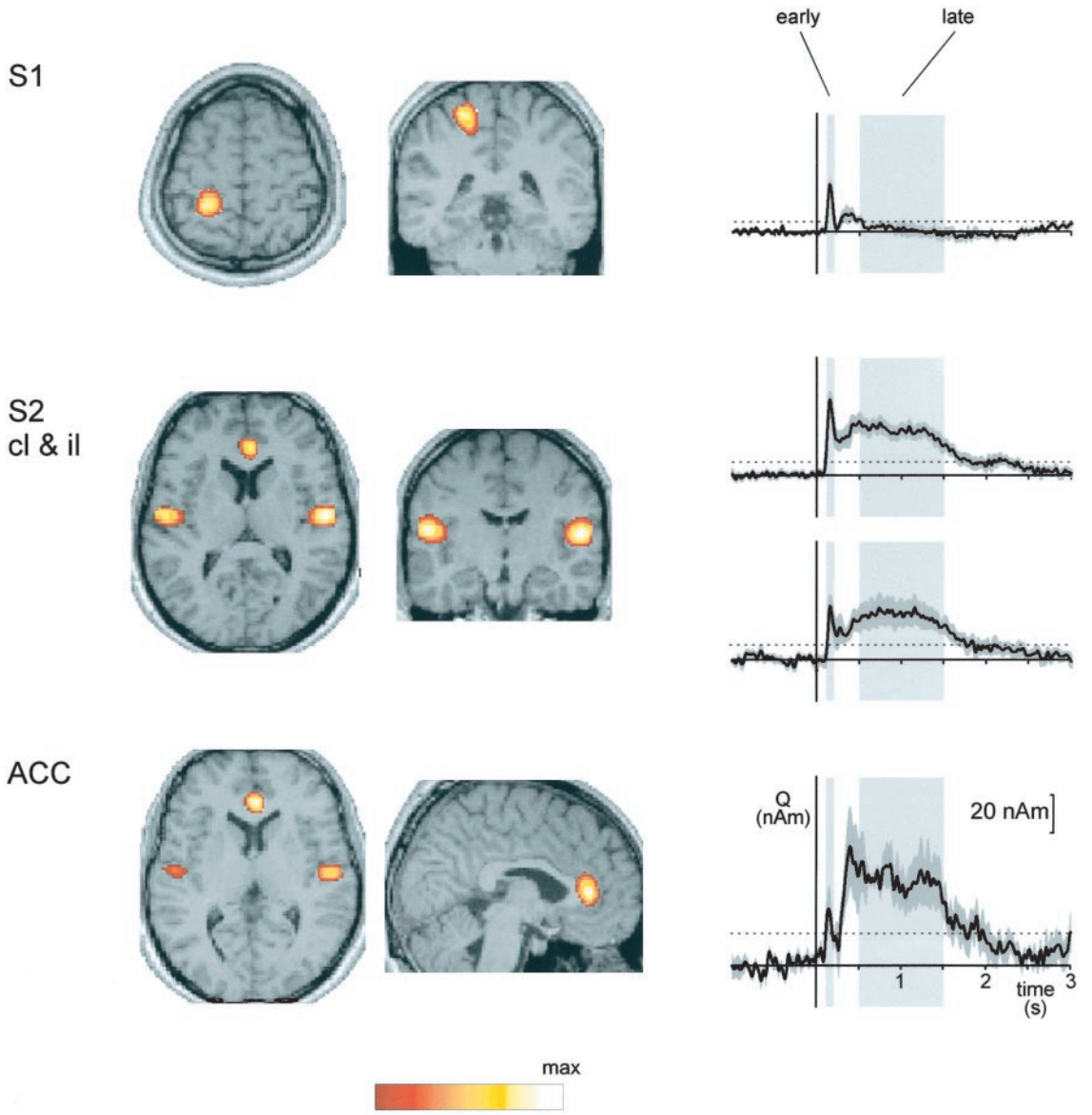


**Fig. 3.** Locations and time courses of pain-evoked activations. Locations of activations are maxima of mean normalized power maps superposed on a normalized structural T1 weighted magnetic resonance image. Power was normalized to the local power maximum coded in white. For the sake of clarity scaling is different for each area. In the time course profiles light-shaded areas depict early and late time windows with predominantly Aδ fiber-mediated first pain-related and predominantly C fiber-mediated second pain-related activity, respectively. Dark-shaded areas indicate SEM. The dotted lines show 95% confidence intervals of activation for each area. In S1, ipsilateral S2, and ACC in one, two, and four subjects, respectively, no individual power maxima corresponding to the mean power maxima were identified. Thus, calculation of group mean activation time courses in S1, ipsilateral S2, and ACC was based on nine, eight, and six subjects, respectively. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex; cl, contralateral; il, ipsilateral.

In the early time window, the time courses of activations show significant activation of S1, bilateral S2, and ACC reflecting Aδ fiber-mediated and first pain-related activation of these areas. In the late time window bilateral S2 and ACC show strong activations, whereas no significant activation is seen in S1 indicating C fiber-mediated and second pain-related activation of bilateral S2 and ACC but not of S1. Fig. 4 summarizes the relationships between early and late activations in S1, S2, and ACC. Activation ratios differ significantly between all areas ($P < 0.05$). S1 shows stronger early than late activation, S2 has a balanced activation pattern, and ACC shows stronger late than early activation. Peak latencies of activations in both time windows are given in Table 1.

## Discussion

In the present study, we investigated the cortical representation of first and second pain sensation to single painful stimuli in humans. By using a continuous pain-rating procedure and magnetoencephalography our results demonstrate that brief painful laser stimuli evoke sustained pain perception and sustained cortical activity comprising Aδ fiber-mediated first pain and C fiber-mediated second pain. Localization of activity revealed activation of contralateral S1, bilateral S2, and ACC. Time courses of activations disclosed differential temporal activation patterns of these areas. S1 showed a strong predominance of first pain-related activation whereas ACC displayed a strong predominance of second pain-related activation. S2 was about

**Table 1. Locations and latencies of cortical activations to painful laser stimulation**

| Region | Location *x*, *y*, *z*, mm | Latency, ms Early | Late |
|---|---|---|---|
| S1 | −24, −40, 62 | 164 ± 8 | |
| S2 cl | −54, −14, 14 | 161 ± 6 | 874 ± 104 |
| S2 il | 54, −14, 10 | 169 ± 4 | 1,057 ± 103 |
| ACC | 4, 34, 16 | 188 ± 20 | 782 ± 156 |

Locations are coordinates in Talairach space. Latencies are mean peak latencies ± SEM. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex; cl, contralateral; il, ipsilateral.

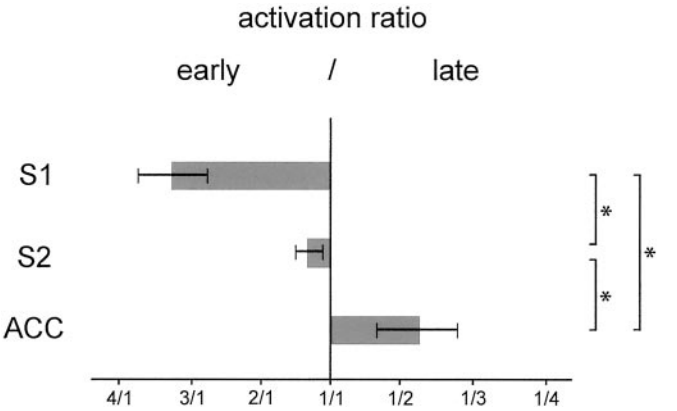


**Fig. 4.** Activation ratio early/late of each area. Ratios were calculated from mean amplitudes in early and late time windows shown in Fig. 3. Error bars represent SEM. Friedman's analysis of variance showed a significant effect of area on activation ratio ($P < 0.05$). Brackets indicate statistical comparisons between activation ratios with two-tailed Wilcoxon signed rank tests. *, $P < 0.05$.

equally activated during first and second pain. These differences in cortical representation probably reflect perceptual and functional differences between first and second pain.

Mediation of early and late pain-evoked activations by Aδ and C fibers is in accordance with conduction velocities of both fiber types of about 10–20 and 1 m/s, respectively (5, 6). In addition, our early and late time windows correspond well to latencies of Aδ and C fiber-mediated cortical responses in previous electroencephalographic studies (9–13) and to reaction times to first and second pain of about 400–500 and 1,000 ms, respectively (1, 2, 4, 7). Taken together, these points strongly suggest that early and late responses reflect perception of first and second pain, respectively. This suggestion is corroborated by the results of the pressure block condition and the correspondence between time courses of pain perception and cortical activation. Thus, a contribution of Aδ fiber-mediated responses to late activations seems very unlikely, although it cannot ultimately be ruled out.

Our finding of participation of S1, bilateral S2, and ACC in human pain processing is in accordance with results from experimental animal studies and neurophysiological, functional imaging and lesion studies in humans (8). However, studies differentially investigating projections of nociceptive Aδ and C fibers are scarce and do not provide consistent evidence on the cortical representation of first and second pain. In humans, neurophysiological recordings revealed Aδ fiber-mediated responses in S1, bilateral S2, and ACC (8), whereas C fiber-mediated responses have not yet been consistently localized. Conversely, neurophysiological investigations in rats revealed C fiber-mediated responses in S1 (29–31), but Aδ fiber-mediated responses in S1 were successfully recorded in only one of these studies (29, 30). So far, the limited temporal resolution of functional imaging does not allow for direct investigation of the temporal sequence of first and second pain-related activations. In a few studies activations to selective C fiber stimulation were investigated. These studies demonstrated activations of S1 and ACC, whereas activation of S2 was inconsistently observed (14–17). However, in these studies tonic painful stimuli were applied which most probably yield activations that reflect a mixture of bottom-up and top-down processes and comprise complex pain-coping strategies and perceptual and physiological phenomena like temporal summation (4) and wind-up (32). Thus, these results probably reflect neural mechanisms distinct from the sequential first and second pain-related activations to single painful stimuli in the present study. Conversely, because cutaneous laser stimulation selectively activates nociceptors responding to heat, the present findings do not necessarily apply to all nociceptive fiber types.

Converging evidence from experimental animal studies and neurophysiological, functional imaging and lesion studies in humans indicate an essential role of S1 in the sensory-discriminative aspects of pain (for reviews, see refs. 8 and 33; for most recent studies, see refs. 34–36). Thus, our finding of strong first pain-related but a virtual lack of second pain-related activation of S1 probably reflects the different perceptual characteristics of first and second pain. First pain is of short duration, sharp and well localized, whereas second pain is longer-lasting, diffuse, and ill localized (1–4). The lack of significant second pain-related activation in S1 in the present study might also contribute to the understanding of divergent results from functional imaging studies concerning participation of S1 in human pain processing (for review, see ref. 37). Partial failure to detect S1 activation was taken as evidence against participation of S1 in pain processing by some investigators and attributed to cognitive modulation of S1 activity and to inhibitory effects within S1 by others (37). The present results add another argument. The strong but short S1 activation is less likely to be detected by single photon emission computed tomography, positron-emission tomography, or functional MRI than the longer-lasting activation of S2 and ACC.

On the basis of response characteristics, anatomical connections, and lesion studies, S2 has been suggested to be involved in cognitive–evaluative components of pain perception like recognition, learning, and memory of painful events (for reviews, see refs. 8 and 38). Our result of about equal first and second pain-related activation of S2 suggests that the recognition of the painful nature of the stimulus and pain-related learning and memory are relevant to both first and second pain. In the present study, as in other MEG studies, activation of insular cortex that has also been shown to participate in pain processing has not been detected most probably because of a mainly radial orientation of insular currents not detected by MEG and a cancellation of currents in the opposite walls of the insula. However, although pain-evoked insular activations have been shown to be located more anteriorly than S2, in principle, a small contribution of insular activation to the S2 signals cannot be ruled out.

A close association between ACC as a part of the limbic system and affective-motivational components of pain perception has been indicated by experimental animal and human lesion, functional imaging, and opioid-binding studies (for reviews, see refs. 8 and 39; for more recent evidence, see refs. 40 and 41). Thus, our finding of particular strong second pain-related activation of ACC supports an association between second pain and pain affect. However, ACC has been shown to participate in a variety of tasks involving cognitive, attention-related, and motor control processes (for reviews, see refs. 42 and 43). Thus, ACC may have a role in interrelating pain affect, attention, and motor responses (44). This role might be reflected by results from functional

imaging studies showing more than one pain-evoked activation focus with different stimulus–response functions within ACC (45–49). These activation foci are located in anterior as well as in posterior regions of the ACC. The location of the ACC focus in the present study corresponds to the most anterior locations.

An association between Aδ fiber-mediated first pain, the sensory component of pain and S1 on the one hand and C fiber-mediated second pain, affective aspects of pain and ACC on the other hand is supported by a recent case report of a patient with a lesion comprising S1 and S2 but sparing of ACC (50). This patient had a selective loss of first pain sensation and sensory aspects of pain, whereas second pain sensation and pain affect were preserved. This possibility to dissociate different perceptual components of pain has recently been experimentally confirmed (51). These findings indicate a parallel mode of pain processing most probably subserved by parallel thalamocortical projections to S1, S2, insula, and ACC (8).

The distinct cortical representations of first and second pain are likely to reflect distinct biological functions of both sensations. First pain signals the noxious nature of a stimulus and provides precise sensory information for an appropriate and rapid motor response, i.e., for an immediate withdrawal. Thus, first pain aims at achieving relative safety from the source of injury. Second pain with its strong affective component attracts longer-lasting attention and initiates behavioral responses to limit further injury and optimize recovery. Thus, second pain may subserve the recuperative healing mechanism of pain (52).

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1. Gad, J. & Goldscheider, A. (1892) *Z. Klin. Med.* **20,** 339–373.
2. Lewis, T. & Pochin, E. E. (1937) *Clin. Sci.* **3,** 67–76.
3. Bishop, G. H. & Landau, W. M. (1958) *Science* **128,** 712–713.
4. Price, D. D., Hu, J. W., Dubner, R. & Gracely, R. H. (1977) *Pain* **3,** 57–68.
5. Adriaensen, H., Gybels, J., Handwerker, H. O. & Van Hees, J. (1983) *J. Neurophysiol.* **49,** 111–122.
6. Van Hees, J. & Gybels, J. (1981) *J. Neurol. Neurosurg. Psychiatry* **44,** 600–607.
7. Campbell, J. N. & LaMotte, R. H. (1983) *Brain Res.* **266,** 203–208.
8. Schnitzler, A. & Ploner, M. (2000) *J. Clin. Neurophysiol.* **17,** 592–603.
9. Bromm, B. & Treede, R. D. (1987) *Exp. Brain Res.* **67,** 153–162.
10. Arendt-Nielsen, L. (1990) *J. Neurol. Neurosurg. Psychiatry* **53,** 405–410.
11. Towell, A. D., Purves, A. M. & Boyd, S. G. (1996) *Pain* **66,** 79–86.
12. Magerl, W., Ali, Z., Ellrich, J., Meyer, R. A. & Treede, R. D. (1999) *Pain* **82,** 127–137.
13. Opsommer, E., Weiss, T., Plaghki, L. & Miltner, W. H. (2001) *Neurosci. Lett.* **298,** 41–44.
14. Di Piero, V., Ferracuti, S., Sabatini, U., Pantano, P., Cruccu, G. & Lenzi, G. L. (1994) *Pain* **56,** 167–173.
15. Andersson, J. L., Lilja, A., Hartvig, P., Langstrom, B., Gordh, T., Handwerker, H. & Torebjork, E. (1997) *Exp. Brain Res.* **117,** 192–199.
16. Iadarola, M. J., Berman, K. F., Zeffiro, T. A., Byas-Smith, M. G., Gracely, R. H., Max, M. B. & Bennett, G. J. (1998) *Brain* **121,** 931–947.
17. Petrovic, P., Petersson, K. M., Ghatan, P. H., Stone-Elander, S. & Ingvar, M. (2000) *Pain* **85,** 19–30.
18. Bromm, B. & Treede, R. D. (1984) *Hum. Neurobiol.* **3,** 33–40.
19. Ahonen, A. I., Hämäläinen, M. S., Kajola, M. J., Knuutila, J. E. T., Laine, P. P., Lounasmaa, O. V., Parkkonen, L. T., Simola, J. T. & Tesche, C. D. (1993) *Physica Scripta* **T49,** 198–205.
20. Van Veen, B. D., van Drongelen, W., Yuchtman, M. & Suzuki, A. (1997) *IEEE Trans. Biomed. Eng.* **44,** 867–880.
21. Gross, J., Kujala, J., Hamalainen, M., Timmermann, L., Schnitzler, A. & Salmelin, R. (2001) *Proc. Natl. Acad. Sci. USA* **98,** 694–699.
22. Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D. & Frackowiak, R. S. J. (1995) *Hum. Brain Mapp.* **2,** 1–25.
23. Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J. & Lounasmaa, O. V. (1993) *Rev. Mod. Phys.* **65,** 413–497.
24. Mackenzie, R. A., Burke, D., Skuse, N. F. & Lethlean, A. K. (1975) *J. Neurol. Neurosurg. Psychiatry* **38,** 865–873.
25. Torebjork, H. E. & Hallin, R. G. (1973) *Exp. Brain Res.* **16,** 321–332.
26. Ziegler, E. A., Magerl, W., Meyer, R. A. & Treede, R. D. (1999) *Brain* **122,** 2245–2257.
27. Ploner, M., Schmitz, F., Freund, H. J. & Schnitzler, A. (1999) *J. Neurophysiol.* **81,** 3100–3104.
28. Ploner, M., Schmitz, F., Freund, H. J. & Schnitzler, A. (2000) *J. Neurophysiol.* **83,** 1770–1776.
29. Schouenborg, J., Kalliomaki, J., Gustavsson, P. & Rosen, I. (1986) *Brain Res.* **397,** 86–92.
30. Kalliomaki, J., Weng, H. R., Nilsson, H. J. & Schouenborg, J. (1993) *Brain Res.* **622,** 262–270.
31. Shaw, F. Z., Chen, R. F., Tsao, H. W. & Yen, C. T. (1999) *Brain Res.* **824,** 183–196.
32. Mendell, L. & Wall, P. (1965) *Nature (London)* **206,** 97–99.
33. Kenshalo, D. R. & Willis, W. D. (1991) in *Cerebral Cortex*, eds. Peters, A. & Jones, E. G. (Plenum, New York), Vol. 9, pp. 153–212.
34. Kenshalo, D. R., Iwata, K., Sholas, M. & Thomas, D. A. (2000) *J. Neurophysiol.* **84,** 719–729.
35. Hofbauer, R. K., Rainville, P., Duncan, G. H. & Bushnell, M. C. (2001) *J. Neurophysiol.* **86,** 402–411.
36. Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R. & Schnitzler, A. (2001) *J. Neurophysiol.* **86,** 1499–1503.
37. Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J. & Carrier, B. (1999) *Proc. Natl. Acad. Sci. USA* **96,** 7705–7709.
38. Lenz, F. A., Gracely, R. H., Zirh, A. T., Romanoski, A. J. & Dougherty, P. M. (1997) *Pain Forum* **6,** 22–31.
39. Vogt, B. A. & Sikes, R. W. (2000) *Prog. Brain Res.* **122,** 223–235.
40. Petrovic, P., Kolso, E., Petersson, K. N. & Ingvar, N. (2002) *Science* **295,** 1737–1740.
41. Johansen, J. P., Fields, H. L. & Manning, B. H. (2001) *Proc. Natl. Acad. Sci. USA* **98,** 8077–8082.
42. Bush, G., Luu, P. & Posner, M. I. (2000) *Trends Cognit. Sci.* **4,** 215–222.
43. Paus, T. (2001) *Nat. Rev. Neurosci.* **2,** 417–424.
44. Devinsky, O., Morrell, M. J. & Vogt, B. A. (1995) *Brain* **118,** 279–306.
45. Tolle, T. R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B. & Bartenstein, P. (1999) *Ann. Neurol.* **45,** 40–47.
46. Vogt, B. A., Derbyshire, S. & Jones, A. K. (1996) *Eur. J. Neurosci.* **8,** 1461–1473.
47. Derbyshire, S. W., Vogt, B. A. & Jones, A. K. (1998) *Exp. Brain Res.* **118,** 52–60.
48. Kwan, C. L., Crawley, A. P., Mikulis, D. J. & Davis, K. D. (2000) *Pain* **85,** 359–374.
49. Buchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B. & Weiller, C. (2002) *J. Neurosci.* **22,** 970–976.
50. Ploner, M., Freund, H. J. & Schnitzler, A. (1999) *Pain* **81,** 211–214.
51. Rainville, P., Carrier, B., Hofbauer, R. K., Bushnell, M. C. & Duncan, G. H. (1999) *Pain* **82,** 159–171.
52. Wall, P. D. (1979) *Pain* **6,** 253–264.

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# Pain Facilitates Tactile Processing in Human Somatosensory Cortices

**Markus Ploner, Bettina Pollok, and Alfons Schnitzler**
*Department of Neurology, Heinrich-Heine-University, 40225 Düsseldorf, Germany*

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**Ploner, Markus, Bettina Pollok, and Alfons Schnitzler.** Pain facilitates tactile processing in human somatosensory cortices. *J Neurophysiol* 92: 1825–1829, 2004. First published April 28, 2004; 10.1152/jn.00260.2004. Touch and pain are intimately related modalities. Despite a substantial overlap in their cortical representations interactions between both modalities are largely unknown at the cortical level. We therefore used magnetoencephalography and selective nociceptive cutaneous laser stimulation to investigate the effects of brief painful stimuli on cortical processing of touch. Using a conditioning test stimulus paradigm, our results show that painful conditioning stimuli facilitate processing of tactile test stimuli applied 500 ms later. This facilitation applies to cortical responses later than 40 ms originating from primary (S1) and secondary (S2) somatosensory cortices but not to earlier S1 responses. By contrast, tactile conditioning stimuli yield a decrease of early as well as late responses to tactile test stimuli. Control experiments show that pain-induced facilitation of tactile processing is not restricted to the site of the painful conditioning stimulus, whereas auditory conditioning does not yield a comparable facilitation. Apart from a lack of spatial specificity, the facilitating effect of pain closely resembles attentional effects on cortical processing of tactile stimuli. Thus these findings may represent a physiological correlate of an alerting function of pain as a change in the internal state to prepare for processing signals of particular relevance.

## INTRODUCTION

Touch and pain are intimately related modalities. According to everyday experience, painful stimuli and appropriate behavioral responses are associated with tactile sensations. This close association of both modalities is paralleled by a substantial overlap between the cortical representation of touch and pain. In particular, the primary (S1) and secondary (S2) somatosensory cortices are involved in processing of both modalities as revealed by functional imaging and neurophysiological studies directly comparing cortical activations to both stimuli (Chen et al. 2002; Coghill et al. 1994; Gelnar et al. 1999; Ploner et al. 2000). Although interactions between both modalities have been characterized on the behavioral level (Apkarian et al. 1994; Bolanowski et al. 2000; Hansson and Lundeberg 1999; Hollins et al. 1996; Melzack and Wall 1965), the modulatory effects of pain on cortical processing of touch and vice versa are largely unknown. A few studies showed that pain inhibits tactile processing in S1 (Rossi et al. 1998; Tommerdahl et al. 1996; Tran et al. 2003), whereas another study did not show this inhibitory effect (Dowman 1999). However, in most of these studies, nonselective nociceptive and tonic painful stimuli were applied (Rossi et al. 1998; Tommerdahl et al. 1996; Tran et al. 2003), which has possibly resulted in confounding of intermodal interaction effects between touch and pain and intramodal tactile interaction effects. In addition, considering the perceptual differences between tonic and phasic pain (Chen and Treede 1985; Rainville et al. 1992), the cortical effects of tonic painful stimulation most probably differ from these of phasic stimuli. Thus results from studies using tonic painful stimuli (Rossi et al. 1998; Tommerdahl et al. 1996) do not necessarily apply to the effects of phasic pain.

Given the strong association between touch and pain in somatosensory cortices, we therefore used magnetoencephalography and selective nociceptive cutaneous laser stimulation to investigate the effect of phasic painful conditioning stimuli on cortical processing of tactile test stimuli applied to the same skin site. Our results show that phasic pain facilitates tactile processing in S1 and S2, which may represent a physiological correlate of the alerting function of pain.

## METHODS

### *Subjects*

Eight healthy male subjects with a mean age of 31 yr (range, 23–45 yr) participated in the experiment. Informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

### *Procedure*

The modulatory effect of phasic pain on tactile processing was studied using a conditioning test stimulus paradigm. Test stimuli were nonpainful electrical pulses activating the tactile afferents of the superficial branch of the radial nerve of the right hand. Conditioning stimuli were either nonpainful electrical stimuli or slightly painful selective nociceptive cutaneous laser stimuli. Conditioning stimuli preceded the test stimuli by 500 ms and were applied to the superficial branch of the right radial nerve or the dorsum of the right hand, respectively. An interval of 500 ms between conditioning and test stimuli were chosen to disentangle early cortical responses evoked by the conditioning stimuli from that evoked by the test stimuli. Prior to the experiment, the paradigm was explained to the subjects so that the subjects knew that only nonpainful test stimuli would occur, while conditioning stimuli would be either painful or nonpainful. Application of painful and nonpainful conditioning stimuli were blocked with the order of blocks counterbalanced between subjects. In each condition, 120 conditioning test stimulus pairs were applied.

### *Stimuli*

Tactile test and conditioning stimuli were 120 constant voltage electrical pulses of 0.3-ms duration delivered to the superficial branch of the radial nerve of the right hand. Intervals between test stimuli were randomly varied between 4 and 6 s. Stimulus intensity was

Address for reprint requests and other correspondence: A. Schnitzler, Dept. of Neurology, Heinrich-Heine-Univ., Moorenstrasse 5, 40225 Düsseldorf, Germany (E-mail: schnitza@uni-duesseldorf.de).

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adjusted to twofold detection threshold intensity, i.e., 40–60 V, thus inducing clear and consistent nonpainful sensations. Characteristics of electrical conditioning and test stimuli were identical. Painful conditioning stimuli were cutaneous laser stimuli, which have been shown to selectively activate nociceptive afferents (Bromm and Treede 1984). Laser stimuli were applied to the dorsum of the right hand in the territory of the superficial branch of the radial nerve. The laser device was a Tm:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2,000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Stimulation site was slightly changed after each stimulus. Stimulus intensity was 100 mJ above individual pain threshold, i.e., 350–400 mJ, thus consistently inducing slightly painful sensations.

### *Data recordings*

Subjects were comfortably seated with eyes closed in a magnetically shielded room. Cortical activity was recorded with a Neuromag-122 whole head neuromagnetometer containing 122 planar SQUID gradiometers. Signals were digitized at 483 Hz, high-pass filtered at 1 Hz, and low-pass filtered at 120 Hz. Neuromagnetic activity was averaged time-locked to application of tactile test stimuli. Vertical electrooculograms were used to reject epochs contaminated with blink artifacts.

### *Data analysis*

An epoch comparing 100 ms prestimulus baseline and 300 ms after stimulation was analyzed. Global stimulus-evoked neuromagnetic activity was calculated as root mean square of the signals of all 122 sensors corrected to baseline. Further analysis of the somatosensory-evoked fields (SEFs) was based on a spatiotemporal source model (Hämäläinen et al. 1993). Sources of evoked responses were modeled as equivalent current dipoles identified during clearly dipolar field patterns. Only sources accounting for >85% of the local field variance were accepted. Source locations, orientations, and strengths were calculated within a realistic head model (boundary-element model) of each subject's head determined from the individual magnetic resonance images acquired on a 1.5-T Siemens-Magnetom. Time courses of activations were obtained from the spatiotemporal source model where locations and orientations of sources were kept fixed and activation strengths were allowed to vary over time to provide the best fit for the recorded data. From the resulting time courses of activations, mean amplitudes of activations were determined in an early (15–40 ms) and a late (50–150 ms) time window, and group mean time courses of activations were calculated. Statistical analysis was done with reference to Siegel and Castellan (1988). Friedman's ANOVA and subsequent post hoc tests were used for comparison of mean amplitudes of activations.

Group mean locations of activations were calculated from covariance matrices across all sensors for the early and the late time window. From these covariance matrices, pain-evoked activity was localized using a spatial filtering algorithm (Van Veen et al. 1997). The spatial filter was employed with a realistic head model to estimate power in the whole brain, resulting in individual tomographic power maps with voxel sizes of $6 \times 6 \times 6$ mm. This approach is a time-domain variant of the frequency-based dynamic imaging of coherent sources (DICS) method, which was recently introduced to the investigation of oscillatory activity (Gross et al. 2001). Further processing of tomographic power maps was carried out using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Individual maps were spatially normalized to Talairach space using parameters derived from normalization of individual T1-weighted MRIs (Friston et al. 1995). Mean group normalized power maps were calculated for both time windows. From these mean power maps, locations of activations, defined as local cortical power maxima exceeding 80% of the global maximum, were determined.

### *Control experiments*

In two subjects, the specificity of the interaction effect was investigated. Spatial specificity was investigated by comparing the effects of painful conditioning stimuli applied to the left and right hand, i.e., contralateral and ipsilateral to the test stimulus that was always applied to the right hand. Modality specificity of the pain-induced modulation of tactile processing was verified by comparing the effects of painful conditioning stimuli with the effects of auditory conditioning stimuli. Auditory stimuli were binaural 1,000-Hz square-wave sounds of 10-ms duration. Stimulus characteristics and procedure were the same as in the other conditions.

## RESULTS

In all subjects, electrical stimulation of tactile afferents elicited clear and consistent nonpainful sensations, while cutaneous laser stimuli consistently evoked slightly painful pinprick-like sensations.

### *SEFs*

Tactile test stimuli evoked the well-known sequence of SEFs, with earliest responses originating from S1 and later responses originating from S1, the posterior parietal cortex and bilateral S2 (Hari and Forss 1999). Exemplary individual and group SEFs are shown in Figs. 1 and 2, respectively. Time courses of global field power (Figs. 1*A* and 2*A*) show a sequence of cortical responses peaking at 35, 59, and 127 ms in the single subject and peaking at 37, 71, and 122 ms for the whole group. Figures 1*B* and 2*B* show the spatial distribution of cortical responses. The earliest responses beginning at ~15 ms and peaking at ~35 ms originate from anterior parts of the postcentral gyrus corresponding to cytoarchitectonical area 3b of S1. The later response peaking at ~70 ms is recorded more posteriorly and medially than the earliest response and is located in the anterior and posterior walls of the postcentral sulcus corresponding to cytoarchitectonical areas 1 and 2 of S1 and to area 5 of the posterior parietal cortex. Subsequent responses are recorded bilaterally over the temporoparietal region and originate from the parietal operculum corresponding to S2. Mean Talairach coordinates of activations are −36, −32, 54 (early S1), −30, −38, 60 (late S1), −54, −14, 24 (contralateral S2), and 46, −16, 28 (ipsilateral S2).

### *Effect of conditioning stimuli*

Individual and group mean time courses of global field power (Figs. 1*A* and 2*A*) show that painful conditioning stimuli yield an enhancement of the later responses to tactile test stimuli peaking at ~70 and 120 ms, whereas early responses peaking at ~35 ms remain unchanged. Locations and time courses of activations (Figs. 1*B* and 2*B*) show that this enhancement applies to the later S1 activation and the bilateral S2 activations but not to the early S1 activation. In contrast, tactile conditioning stimuli result in an attenuation of early, as well as late, activations of S1 and bilateral S2. Figure 3 summarizes these effects of painful and tactile conditioning stimuli. Friedman's ANOVA confirms a significant effect of condition on activation amplitudes ($P < 0.001$). Subsequent post hoc com-

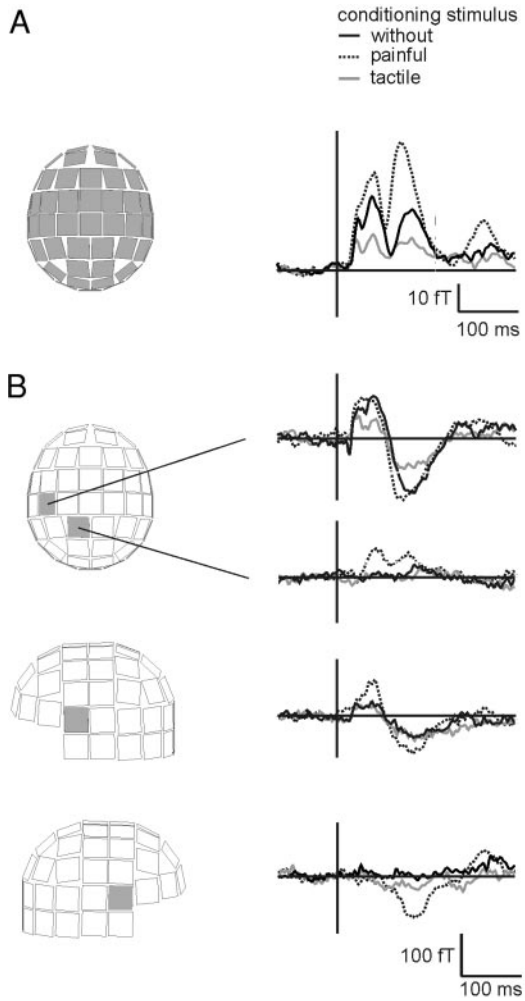


FIG. 1. Effect of conditioning stimuli on cortical responses to tactile test stimuli, exemplary individual results. *A*: time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline. *Left*: helmet-shaped sensor array viewed from the top. *B*: signals of single sensors. Locations of sensors are marked by shaded squares in the *left panels* showing the sensor array from the top, left and right.

parisons of activations show that all later activations are significantly enhanced by painful conditioning stimuli, whereas tactile conditioning stimuli yield a significant decrease of both early and late activations.

### *Control experiments*

Figure 4 compares the effects of painful conditioning stimuli applied to the hand contralateral and ipsilateral to the test stimuli (Fig. 4, *top*) and the effects of auditory and ipsilateral painful conditioning stimuli (Fig. 4, *bottom*). Mean time courses of global field power reveal that painful conditioning stimuli applied to the hand contralateral to the test stimulus yield an enhancement of later responses comparable with the effect of ipsilateral painful conditioning stimuli. In contrast, auditory conditioning stimuli do not yield a comparable enhancement. Thus pain-induced facilitation of tactile processing is not spatially specific and does not occur after auditory conditioning stimuli.

## DISCUSSION

In this study, we investigated the effects of brief painful stimuli on tactile processing in human somatosensory cortices. Using magnetoencephalography and selective nociceptive cutaneous laser stimulation, our results show that phasic painful stimuli facilitate processing of subsequent electrical stimuli applied to tactile afferents innervating the same skin site. Time courses of activations reveal that this facilitation applies to later cortical responses originating from S1 and S2 but not to earliest S1 responses. Control experiments show that pain-induced facilitation of tactile processing is not restricted to the site of the painful conditioning stimulus and does not occur after auditory conditioning stimuli.

Previous studies investigating interactions of touch and pain focused predominantly on the effect of touch on pain. The influential gate control theory (Melzack and Wall 1965) implied that activation of tactile afferents inhibits processing and perception of pain by closing a gate located in the spinal cord dorsal horn. This theory has been extensively studied and has motivated new concepts of pain therapy (Hansson and Lunde-

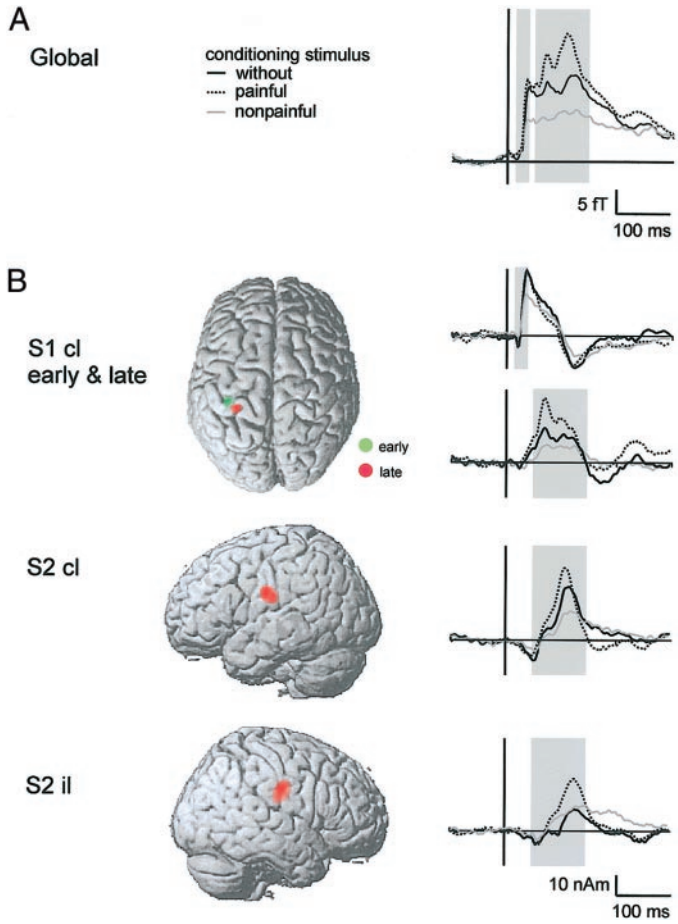


FIG. 2. Effect of conditioning stimuli on cortical responses to tactile test stimuli, group results. *A*: time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline. *B*: locations and time courses of activations. Locations of activations are maxima of mean normalized power maps superposed on a normalized surface rendered structural T1-weighted magnetic resonance image. In the time course panels, shaded areas depict phases of early (15–40 ms) and late (50–150 ms) responses during which mean amplitudes of activations were calculated. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; cl, contralateral; il, ipsilateral.

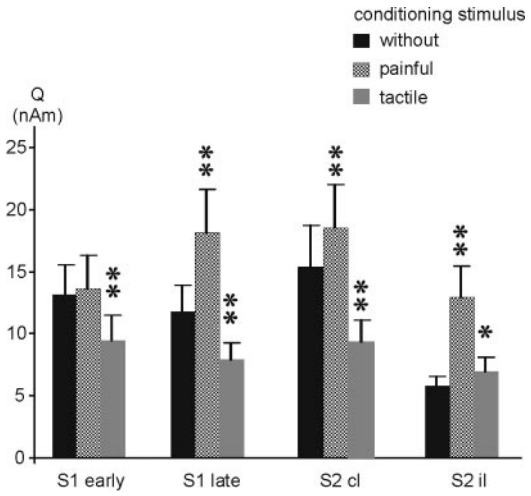


FIG. 3. Effect of conditioning stimuli on mean amplitudes of early (15–40 ms) and late (50–150 ms) activations. Error bars represent SE. Friedman's ANOVA showed a significant effect of conditioning stimuli on mean amplitudes ($P < 0.001$). *$P < 0.05$, **$P < 0.01$ compared with amplitudes of activations without conditioning stimuli.

berg 1999). The reverse effect of pain on touch has been less well studied. At the behavioral level, tonic pain (Apkarian et al. 1994; Bolanowski et al. 2000; Hollins et al. 1996) has been shown to decrease sensitivity to tactile stimuli on the affected limb. Correspondingly, neurophysiological recordings in humans (Rossi et al. 1998) and monkeys (Tommerdahl et al. 1996) showed a pain-evoked decrease of S1 responses to tactile stimulation. However, in these studies the effects of tonic pain were investigated that differ perceptually from that of phasic pain (Chen and Treede 1985; Rainville et al. 1992) and may thus reflect neural mechanisms distinct from the effects of the brief painful stimuli observed in our study. Only a few previous studies investigated the effects of phasic pain on tactile processing. In a recent MEG study, brief painful conditioning stimuli were shown to yield a decrease of S1 responses to tactile test stimuli that already involved very early S1 responses at ~30 ms (Tran et al. 2003). However, in this study, painful conditioning stimuli, as well as nonpainful test stimuli, were electrical stimuli, which activate tactile afferents. Thus intermodal interaction and intramodal stimulus presentation rate effects have most probably been confounded, which may account for the discrepancy between these results and our findings. Another EEG study using selective nociceptive cutaneous laser stimulation did not show a significant effect of pain on cortical processing of tactile test stimuli (Dowman 1999). However, in this study, which did not provide spatial information on cortical activations, a near significant increase of later components of somatosensory-evoked potentials was observed, which, in principle, corresponds to the present results.

Our finding of an attenuation of both early as well as late responses due to nonpainful conditioning stimuli is in good agreement with previous EEG (Allison 1962; Greenwood and Goff 1987; Shagass and Schwartz 1964) and MEG (Mauguiere et al. 1997; Wikström et al. 1996) studies, showing a decrease of the earliest cortical responses with high stimulus presentation rates. This decrease of response amplitudes with high stimulus presentation rates has been proposed to represent an intramodal sensory interaction effect on the level of the somatosensory cortices (Wikström et al. 1996a). The pattern of the pain-evoked modulation of tactile processing observed in this study indicates that this intermodal interaction effect is also located on the cortical level and does not result from interactions on the peripheral, spinal, or subcortical level. Since tactile processing in human somatosensory cortices has a predominantly serial organizational mode (Iwamura 1998), interactions on a level lower than the cortical level should have affected the earliest, as well as later, responses.

The modulatory pattern of pain on tactile processing with a facilitation of later but not the earliest stages of tactile processing closely resembles attentional effects on tactile processing in somatosensory cortices as revealed by EEG (Desmedt and Tomberg 1989; Eimer and Forster 2003; Josiassen et al. 1982; Michie et al. 1987) and MEG (Mima et al. 1998) recordings. These studies showed that focusing attention on a behaviorally relevant tactile stimulus facilitates S1 and S2 responses to tactile stimuli at latencies of 40 ms and later but do not modulate earliest S1 responses with latencies shorter than 40 ms. This attentional facilitation of tactile processing in S1 and S2 has been confirmed by functional imaging studies (Burton et al. 1999; Macaluso et al. 2002; Meyer et al. 1991; Roland 1981) and by neurophysiological studies in monkeys (Hsiao et al. 1993; Hyvarinen et al. 1980; Poranen and Hyvarinen 1982; Steinmetz et al. 2000). However, these attentional effects are spatially specific and are thus likely to reflect the orienting function of attention (Posner and Petersen 1990). In contrast, the control experiments of this study reveal that contralateral painful conditioning stimuli do also facilitate tactile processing, indicating that the present effect is not a spatially specific but a global phenomenon. Moreover, the lack of a comparable facilitation after auditory conditioning stimuli shows that the effect cannot be attributed to the cue function of the painful stimulus. Thus pain-induced facilitation of tactile processing may rather reflect the spatially unspecific alerting function of attention (Corbetta and Shulman 2002; Posner and Petersen 1990), which follows salient stimuli and may be mediated by a right-lateralized fronto-parietal-cingulate network (Corbetta and Shulman 2002; Downar et al. 2002, 2003). This alerting function involves a change in the internal state to prepare for processing signals of high priority (Posner and Petersen 1990), characteristics that particularly apply to the sensation of pain that signals fundamental threat and urges the individual to prevent further harm. Detailed characterization of the facilita-

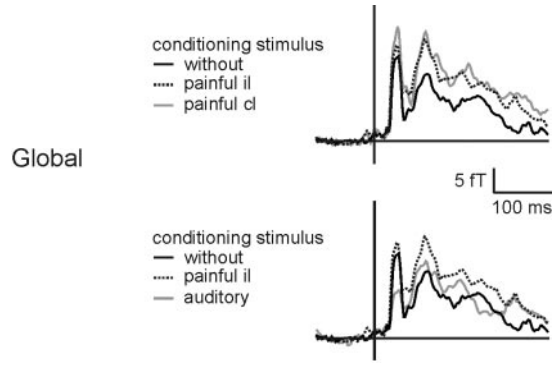


FIG. 4. Effects of contralateral and ipsilateral conditioning stimuli (*top*) and of auditory conditioning stimuli (*bottom*) on cortical responses to tactile test stimuli. Mean time courses of global field power defined as root mean square of the signals of all 122 sensors corrected to baseline averaged for 2 subjects. cl, contralateral; il, ipsilateral.

tion effect in additional, particularly psychophysical, studies will further specify the functional significance of the observed effect.

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REFERENCES

**Allison T.** Recovery functions of somatosensory evoked responses in man. *Electroencephalogr Clin Neurophysiol* 14: 331–343, 1962.

**Apkarian AV, Stea RA**, **and Bolanowski SJ.** Heat-induced pain diminishes vibrotactile perception: a touch gate. *Somatosens Mot Res* 11: 259–267, 1994.

**Bolanowski SJ, Maxfield LM, Gescheider GA**, **and Apkarian AV.** The effects of stimulus location on the gating of touch by heat- and cold-induced pain. *Somatosens Mot Res* 17: 195–204, 2000.

**Burton H, Abend NS, MacLeod AM, Sinclair RJ, Snyder AZ**, **and Raichle ME.** Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study. *Cereb Cortex* 9: 662–674, 1999.

**Chen JI, Ha B, Bushnell MC, Pike B**, **and Duncan GH.** Differentiating noxious- and innocuous-related acivation of human somatosensory cortices using temporal analysis of fMRI. *J Neurophysiol* 88: 464–474, 2002.

**Chen AC and Treede RD.** The McGill Pain Questionnaire in the assessment of phasic and tonic experimental pain: behavioral evaluation of the 'pain inhibiting pain' effect. *Pain* 22: 67–79, 1985.

**Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC**, **and Duncan GH.** Distributed processing of pain and vibration by the human brain. *J Neurosci* 14: 4095–4108, 1994.

**Corbetta M and Shulman GL.** Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3: 201–215, 2002.

**Desmedt JE and Tomberg C.** Mapping early somatosensory evoked potentials in selective attention: critical evaluation of control conditions used for titrating by difference the cognitive P30, P40, P100 and N140. *Electroencephalogr Clin Neurophysiol* 74: 321–346, 1989.

**Dowman R.** Laser pain fails to inhibit innocuous-related activity in the central somatosensory pathways. *Psychophysiology* 36: 371–378, 1999.

**Downar J, Crawley AP, Mikulis DJ, and Davis KD.** A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J Neurophysiol* 87: 615–620, 2002.

**Downar J, Mikulis DJ, and Davis KD.** Neural correlates of the prolonged salience of painful stimulation. *Neuroimage* 20: 1540–1551, 2003.

**Eimer M and Forster B.** Modulations of early somatosensory ERP components by transient and sustained spatial attention. *Exp Brain Res* 151: 24–31, 2003.

**Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD**, **and Frackowiak RSJ.** Spatial registration and normalization of images. *Hum Brain Mapp* 2: 1–25, 1995.

**Gelnar PA, Krauss BR, Sheehe PR, Szeverenyi NM**, **and Apkarian AV.** A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks. *Neuroimage* 10: 460–482, 1999.

**Greenwood PM and Goff WR.** Modification of median nerve somatic evoked potentials by prior median nerve, peroneal nerve and auditory stimulation. *Electroencephalogr Clin Neurophysiol* 68: 295–302, 1987.

**Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A**, **and Salmelin R.** Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proc Natl Acad Sci USA* 98: 694–699, 2001.

**Hämäläinen M, Hari R, Ilmoniemi RJ, Knuutila J, and Lounasmaa OV.** Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Phys* 65: 413–497, 1993.

**Hansson P and Lundeberg T.** Transcutaneous electrical nerve stimulation, vibration and acupuncture as pain-relieving measures. In: *Textbook of Pain*, edited by Wall PD and Melzack R. Edinburgh: Churchill Livingstone, 1999, p. 1341–1351.

**Hari R and Forss N.** Magnetoencephalography in the study of human somatosensory cortical processing. *Phil Trans Roy Soc Lond B* 354: 1145–1154, 1999.

**Hollins M, Sigurdsson A, Fillingim L**, **and Goble AK.** Vibrotactile threshold is elevated in temporomandibular disorders. *Pain* 67: 89–96, 1996.

**Hsiao SS, O'Shaughnessy DM**, **and Johnson KO.** Effects of selective attention on spatial form processing in monkey primary and secondary somatosensory cortex. *J Neurophysiol* 70: 444–447, 1993.

**Hyvarinen J, Poranen A**, **and Jokinen Y.** Influence of attentive behavior on neuronal responses to vibration in primary somatosensory cortex of the monkey. *J Neurophysiol* 43: 870–882, 1980.

**Iwamura Y.** Hierarchical somatosensory processing. *Curr Opin Neurobiol* 8: 522–528, 1998.

**Josiassen RC, Shagass C, Roemer RA, Ercegovac DV**, **and Straumanis JJ.** Somatosensory evoked potential changes with a selective attention task. *Psychophysiology* 19: 146–159, 1982.

**Macaluso E, Frith CD**, **and Driver J.** Directing attention to locations and to sensory modalities: multiple levels of selective processing revealed with PET. *Cereb Cortex* 12: 357–368, 2002.

**Mauguiere F, Merlet I, Forss N, Vanni S, Jousmaki V, Adeleine P, and Hari R.** Activation of a distributed somatosensory cortical network in the human brain: a dipole modelling study of magnetic fields evoked by median nerve stimulation. Part II: Effects of stimulus rate, attention and stimulus detection. *Electroencephalogr Clin Neurophysiol* 104: 290–295, 1997.

**Melzack R and Wall PD.** Pain mechanisms: a new theory. *Science* 150: 971–979, 1965.

**Meyer E, Ferguson SS, Zatorre RJ, Alivisatos B, Marrett S, Evans AC**, **and Hakim AM.** Attention modulates somatosensory cerebral blood flow response to vibrotactile stimulation as measured by positron emission tomography. *Ann Neurol* 29: 440–443, 1991.

**Michie PT, Bearpark HM, Crawford JM**, **and Glue LCT.** The effects of spatial selective attention on the somatosensory event-related potential. *Psychophysiology* 24: 449–463, 1987.

**Mima T, Nagamine T, Nakamura K**, **and Shibasaki H.** Attention modulates both primary and secondary somatosensory cortical activities in humans: a magnetoencephalographic study. *J Neurophysiol* 80: 2215–2221, 1998.

**Ploner M, Schmitz F, Freund HJ**, **and Schnitzler A.** Differential organization of touch and pain in human primary somatosensory cortex. *J Neurophysiol* 83: 1770–1776, 2000.

**Poranen A and Hyvarinen J.** Effects of attention on multiunit responses to vibration in the somatosensory regions of the monkey's brain. *Electroencephalogr Clin Neurophysiol* 53: 525–537, 1982.

**Posner MI and Petersen SE.** The attention system of the human brain. *Annu Rev Neurosci* 13: 25–42, 1990.

**Rainville P, Feine JS, Bushnell MC**, **and Duncan GH.** A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. *Somatosens Mot Res* 9: 265–277, 1992.

**Roland PE.** Somatotopical tuning of postcentral gyrus during focal attention in man. A regional cerebral blood flow study. *J Neurophysiol* 46: 744–754, 1981.

**Rossi A, Decchi B, Groccia V, Della Volpe R**, **and Spidalieri R.** Interactions between nociceptive and non-nociceptive afferent projections to cerebral cortex in humans. *Neurosci Lett* 248: 155–158, 1998.

**Shagass C and Schwartz M.** Recovery functions of somatosensory peripheral nerve and cerebral evoked responses in man. *Electroencephalogr Clin Neurophysiol* 17: 126–135, 1964.

**Siegel S and Castellan NJ.** *Nonparametric Statistics for the Behavioral Sciences.* New York: McGraw-Hill, 1988.

**Steinmetz PN, Roy A, Fitzgerald PJ, Hsiao SS, Johnson KO**, **and Niebur E.** Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature* 404: 187–190, 2000.

**Tommerdahl M, Delemos KA, Vierck CJ Jr, Favorov OV**, **and Whitsel BL.** Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. *J Neurophysiol* 75: 2662–2670, 1996.

**Tran TD, Hoshiyama M, Inui K**, **and Kakigi R.** Electrical-induced pain diminishes somatosensory evoked magnetic cortical fields. *Clin Neurophysiol* 114: 1704–1714, 2003.

**Van Veen BD, van Drongelen W, Yuchtman M**, **and Suzuki A.** Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Trans Biomed Eng* 44: 867–880, 1997.

**Wikström H, Huttunen J, Korvenoja A, Virtanen J, Salonen O, Aronen H**, **and Ilmoniemi RJ.** 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, 1996.

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# Pain Suppresses Spontaneous Brain Rhythms

Markus Ploner, Joachim Gross, Lars Timmermann, Bettina Pollok and Alfons Schnitzler

Department of Neurology, Heinrich-Heine-University, 40225 Düsseldorf, Germany

**The neuronal activity of the resting human brain is dominated by spontaneous oscillatory activity of primary visual, somatosensory and motor areas. These spontaneous brain rhythms are related to the functional state of a system. A higher amplitude of oscillatory activity is thought to reflect an idling state, whereas a lower amplitude is associated with activation and higher excitability of the specific system. Here, we used magnetoencephalography to investigate the effects of pain on spontaneous brain rhythms. Our results show that a focally applied brief painful stimulus globally suppresses spontaneous oscillations in somatosensory, motor and visual areas. This global suppression contrasts with the regionally specific suppressions of other modalities and shows that pain induces a widespread change in cortical function and excitability. This global change in excitability may reflect the alerting function of pain which opens the gates for processing of and reacting to stimuli of existential relevance.**

**Keywords:** cutaneous laser stimulation, human, magnetoencephalography, nociception, oscillations, pain, somatosensory

## Introduction

From the earliest recordings of the human electroencephalogram, spontaneous oscillatory activity at frequencies around 10 Hz (alpha-band) and 20 Hz (beta-band) has been consistently observed over primary visual, somatosensory and motor areas (Berger, 1929; Gastaut, 1952; Hari and Salmelin, 1997; Niedermeyer, 1999). In each of these systems oscillations show a modality-specific reactivity. The occipital alpha-ryhthm is dampened by visual stimuli, whereas alpha- and beta-oscillations over the sensorimotor cortices — termed mu-rhythm — are attenuated by touch and limb movements (Hari and Salmelin, 1997; Pfurtscheller, 1999). This modality specificity is complemented by a spatial specificity with stimulus-induced modulations of oscillations occurring predominantly in the contralateral hemisphere (Hari and Salmelin, 1997; Pfurtscheller, 1999). Spatial distribution and reactivity suggest that oscillatory activity is related to the functional state of a system. A higher amplitude of oscillatory activity is thought to reflect an idling state of a system, whereas a lower amplitude is associated with activation of a system (Hari and Salmelin, 1997; Niedermeyer, 1999; Pfurtscheller, 1999). In addition, suppression of oscillatory activity has been related to a higher degree of excitability in the sense of a thalamocortical gate which can be opened by endogenous or exogenous events (Steriade and Llinas, 1988).

Recently, the effects of pain on spontaneous oscillations have been investigated. Neurophysiological studies revealed that phasic painful stimuli suppress oscillations over the sensorimotor cortex predominantly of the contralateral hemisphere (Mouraux *et al.*, 2003; Ohara *et al.*, 2004; Raij *et al.*, 2004) which, in principle, corresponds to the effect of tactile stimuli. However, pain is a unique experience which disrupts ongoing behavior, demands attention and urges the individual to react (Melzack and Casey, 1968; Eccleston and Crombez, 1999). Thus, pain broadly interferes with sensory, motor and cognitive processes. Correspondingly, pain may not only selectively modulate the function of the sensorimotor system but of cortical systems in general. Therefore, we used the high spatial and temporal resolution of magnetoencephalography to investigate the global effects of pain on spontaneous oscillatory activity.

## Materials and Methods

Twelve healthy right-handed male subjects with a mean age of 33 years (range 22–41 years) participated in the study. Informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

### *Stimulation*

Forty painful cutaneous laser stimuli, which evoke a highly synchronized selective activation of nociceptive afferents without concomitant activation of tactile afferents (Bromm and Treede, 1984) were delivered to the dorsum of the right hand. The laser device was a Tm:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2000 nm, a pulse duration of 1 ms and a spot diameter of 6 mm. The laser beam was led through an optical fiber from outside into the recording room. Stimulation site was slightly changed after each stimulus. Interstimulus intervals were randomly varied between 10 and 14 s. Applied stimulus intensity was 600 mJ, which evoked moderately painful sensations. The subjects passively perceived the stimuli with closed eyes. In four of the subjects, in an additional recording, the left hand was stimulated using the same parameters as in the right-hand stimulation condition.

### *Recordings and Analysis*

During the recordings the subjects were comfortably seated with closed eyes in a magnetically shielded room. Cortical activity was continuously recorded with a Neuromag-122 whole-head neuromagnetometer. Signals were digitized at 483 Hz.

As a first step, time windows and frequency bands of pain-induced changes of cortical activity were identified. To this end, time frequency representations (TFR) were calculated using a Fourier transform approach (Delorme and Makeig, 2004). For each trial the TFR comprised an epoch from 1500 ms before to 3000 ms after stimulus application. A global grand average TFR was obtained by averaging TFRs across trials, sensors and subjects. This global grand average TFR showed prominent pain-induced suppressions of cortical activity in the alpha- (7–15 Hz) and beta- (15–25 Hz) band in a time window between 500 and 1500 ms after stimulus application. Thus, further analysis focused on these frequency bands and on this time window.

In the next step, locations of pain-induced suppressions of cortical activity were calculated. To this end cross-spectral density matrices of power changes in the time window between 500 and 1500 ms as

compared to a baseline period from −1000 to −10 ms were calculated. From these matrices pain-evoked activity was localized using a spatial filtering algorithm (Van Veen *et al.*, 1997; Gross *et al.*, 2001). The spatial filter was employed with a realistic head model to estimate power in the whole brain, and resulted in individual tomographic power maps with voxel sizes of 6 × 6 × 6 mm. Further processing of tomographic power maps was carried out using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK: http://www.fil.ion.ucl.ac.uk/spm). Individual maps were spatially normalized to Talairach space using parameters derived from normalization of individual $T_1$-weighted magnetic resonance images (Friston *et al.*, 1995). Among the five strongest local power maxima individual power maps consistently showed maxima located in the bilateral central region and in the occipital cortex. Mean group normalized power maps were calculated for each of the three regions.

In a third step time courses of pain-induced power changes in the bilateral central region and in the occipital cortex were determined. Using the temporal spectral evolution (TSE) method (Salmelin and Hari, 1994), signals were band-pass filtered from 7 to 15 and from 15 to 25 Hz respectively. Filtered signals were rectified, averaged across trials and across 10 sensors over the bilateral central region and 12 sensors over the occipital cortex. The signals recorded from these sensors showed clear modulation of oscillatory activity. Results did not depend on the number of sensors. From the individual time courses group mean time courses of pain-induced power changes were calculated. For each area and frequency band 95% confidence intervals of power changes were calculated as twice the standard deviation of the 1000 ms prestimulus baseline.

For statistical comparison mean amplitudes of pain-induced power changes during the time window between 500 and 1500 ms were determined for both frequency bands. The lateralization of pain-induced modulations was analyzed by comparing mean amplitudes of right- and left-hemispheric modulations using sequentially Bonferroni-corrected two-tailed Wilcoxon signed-rank tests. Lateralization was visualized by calculating a lateralization ratio (left hemispheric/right hemispheric) of pain-induced modulations to right- and left-sided stimulation.

### *Control Experiment*

In order to compare the effects of pain and touch on cortical activity electrical stimulation of tactile afferents was carried out in 12 healthy right-handed subjects (4 female, 8 male, mean age 32 years, range 24–44 years). Electrical stimuli were applied by using ring electrodes attached to the middle and end phalanx of the index finger of the right hand. Stimuli were rectangular constant voltage pulses of 0.3 ms duration with an interstimulus interval of 3 s. Stimulus intensity was adjusted to 2- to 3-fold detection threshold intensity evoking clear and non-painful sensations. Time courses of tactile-induced power changes in the bilateral central region and in the occipital cortex were determined using the same procedure as for the pain-induced effects. Mean amplitudes of tactile-induced power changes were calculated during a time window between 0 and 1000 ms for both frequency bands. Statistical analysis and visualization was the same as for the painful stimulation condition.

## Results

First, time windows and frequency bands of pain-induced modulations of oscillatory activity were determined. Thus, global grand average time frequency representations (TFR) were calculated. Figure 1 shows that the brief painful stimuli suppress cortical oscillatory activity between 500 and 1500 ms after stimulus application. This suppression occurs in the alpha-band (7–15 Hz) and in the beta-band (15–25 Hz). [Note that the early power increase below the alpha-band reflects evoked responses which have been analyzed previously (Ploner *et al.*, 1999, 2000, 2002; Timmermann *et al.*, 2001).]

Second, we determined locations of pain-induced suppressions of cortical oscillations. Using a time-domain variant of the DICS method (Gross *et al.*, 2001) pain-induced power changes

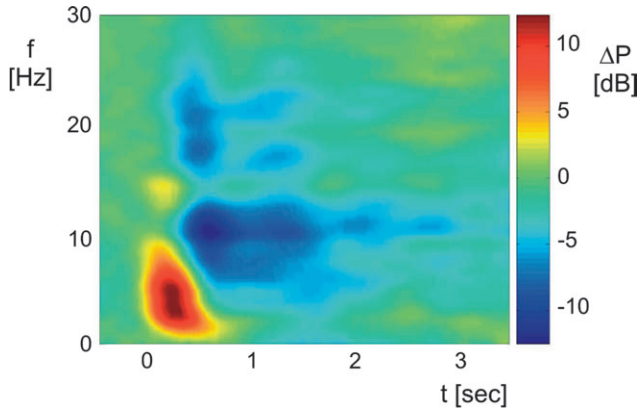


**Figure 1.** Time frequency representation (TFR) of pain-induced modulations of spontaneous neuronal activity averaged across sensors, trials and subjects. Power increases and decreases (ΔP) from baseline are coded in red and blue, respectively.

were localized in the previously identified time window (500–1500 ms) and frequency bands (alpha, beta) relative to a 1000 ms prestimulus baseline. Figure 2 shows the group mean locations of pain-induced power changes. Foci of suppression of spontaneous oscillatory activity were located in the bilateral sensorimotor cortices and in the occipital cortex. Within the bilateral sensorimotor cortices, suppressions in the alpha-band were located slightly more posterior than suppressions in the beta-band corresponding to location in primary somatosensory and motor cortices respectively. Thus, pain suppresses the sensorimotor mu-rhythm bilaterally as well as the occipital alpha-rhythm.

Third, time courses of pain-induced modulations were calculated for each region and frequency band (Fig. 2). Time courses show that the significant pain-induced suppression of about 2000 ms duration applies to the 10 Hz 'sensory' and 20 Hz 'motor' components of the mu-rhythm bilaterally and to the occipital alpha-rhythm. The suppression of the mu-rhythm is stronger in the right, ipsilateral hemisphere than in the left, contralateral hemisphere. This contrasts with the effect of tactile stimuli applied to the right hand. Tactile stimuli induce a short-lasting suppression of the mu-ryhthm mainly in the left, contralateral hemisphere and no comparable suppression of the occipital alpha-rhythm. Figure 3 illustrates the lateralization of suppressions of the mu-rhythm to painful and tactile stimulation by showing a lateralization ratio (left hemispheric/right hemispheric) of suppressions. The figure illustrates the right hemispheric lateralization of suppressions to right-sided painful stimuli and the left hemispheric lateralization of suppressions to right-sided tactile stimulation. To further clarify the lateralization of the pain-induced modulations we applied painful stimuli to the left hand in four of the subjects. The results show that left-sided painful stimuli also yield a right-lateralized suppression of the mu-rhythm. Thus, these findings show that pain-induced modulations of the mu-rhythm are generally lateralized to the right hemisphere and do not reflect an ipsilateral dominance.

## Discussion

The present findings reveal that brief painful stimuli yield a global right-lateralized suppression of spontaneous oscillations in sensory and motor systems.

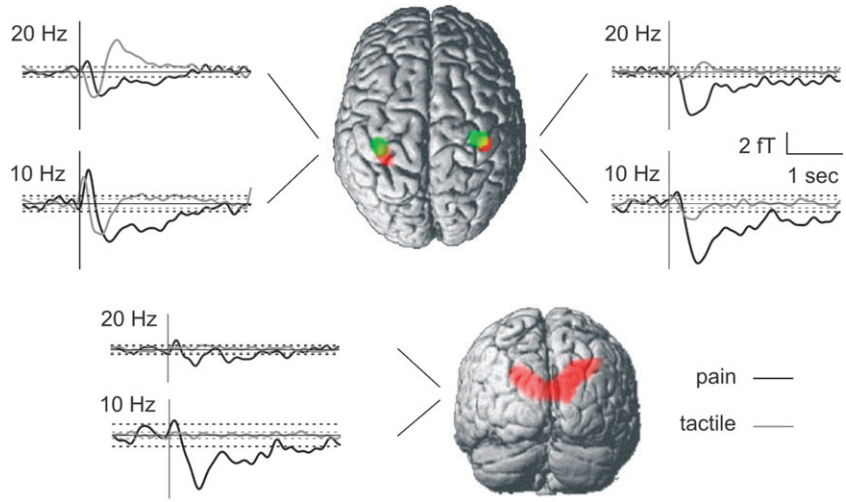


**Figure 2.** Group mean locations and time courses of pain-induced modulations. Locations of 20 Hz and 10 Hz suppressions are coded in green and red respectively. Time courses of pain-induced modulations (black lines) are compared to tactile-induced modulations (grey lines). The dotted lines show 95% confidence intervals of modulation for each modality, area and frequency band.

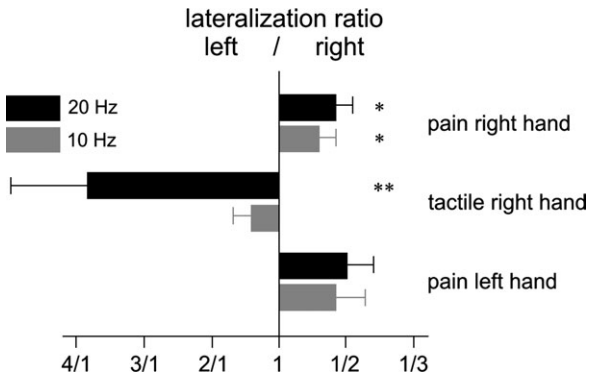


**Figure 3.** Lateralization ratio (left hemispheric/right hemispheric) of suppressions to painful and tactile stimuli. Note that left- and right-lateralized suppressions of the mu-rhythm correspond to bars to the left and the right side, respectively. Error bars represent SEM; $*P \leq 0.05$, $**P \leq 0.01$, sequentially Bonferroni-corrected, two-tailed Wilcoxon signed rank tests.

Our results correspond with recent neurophysiological studies which showed a pain-induced suppression of the mu-rhythm (Mouraux *et al.*, 2003; Ohara *et al.*, 2004) lateralized to the right, contralateral hemisphere (Raij *et al.*, 2004). However, these studies focused on pain-induced effects on the mu-rhythm and did not investigate global effects of pain on spontaneous brain rhythms. Other studies investigating the effects of tonic pain on spontaneous oscillatory activity also revealed pain-induced decreases in alpha-power and mostly an increase in beta-power (Backonja *et al.*, 1991; Veerasarn and Stohler, 1992; Chen and Rappelsberger, 1994; Ferracuti *et al.*, 1994; Chang *et al.*, 2002). However, the effects of tonic pain most probably comprise complex pain-coping strategies and, thus, reflect neural mechanisms distinct from the modulations induced by the brief painful stimuli of the present study.

Further, our results reveal for the first time that the effects of pain outreach the modality and topographically specific effects exerted by other sensory and motor events (Hari and Salmelin, 1997; Pfurtscheller, 1999). Considering that spontaneous oscillations are related to the functional state and the excitability of cortical areas (Pfurtscheller, 1999) our results demonstrate that pain induces a widespread change in cortical function and excitability. This global pain-induced change in cortical function and excitability may be related to the unique biological significance of pain which disrupts ongoing behaviour, demands attention and urges the individual to react (Melzack and Casey, 1968; Eccleston and Crombez, 1999). More specifically, our finding of a global change in excitability may reflect the alerting function of pain, which may be mediated by a right-lateralized cortico-subcortical network dedicated to the detection of salient events (Downar *et al.*, 2000; Corbetta and Shulman, 2002). The right-sided lateralization of this network together with a preponderance of the right hemisphere in the processing of pain (Hari *et al.*, 1997; Coghill *et al.*, 2001) and negative affect (Davidson, 1995) could well account for the right-hemispheric lateralization of the observed effects. The alerting function of pain along with a global suppression of spontaneous brain rhythms may 'open the gates' of sensory and motor systems and prepare the individual for processing of and reacting to stimuli of existential relevance. This pain-induced gating of sensory and motor information may be related to the recently described phenomenon of pain-induced facilitation of sensory (Ploner *et al.*, 2004) and motor processing (Raij *et al.*, 2004).

## Notes

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Address correspondence to Markus Ploner or Alfons Schnitzler, Department of Neurology, Heinrich-Heine-University, Moorenstrasse 5, 40225 Düsseldorf, Germany. Email: ploner@neurologie.uni-duesseldorf.de, schnitza@uni-duesseldorf.de.

## References

Backonja M, Howland EW, Wang J, Smith J, Salinsky M, Cleeland CS (1991) Tonic changes in alpha power during immersion of the hand in cold water. Electroencephalogr Clin Neurophysiol 79:192–203.

Berger H (1929) Über das Elektroenkephalogramm des Menschen. Arch Psychiat Nervenkr 87:527–570.

Bromm B, Treede RD (1984) Nerve fibre discharges, cerebral potentials and sensations induced by $CO_2$ laser stimulation. Hum Neurobiol 3:33–40.
Chang PF, Arendt-Nielsen L, Chen AC (2002) Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. Brain Res Bull 57: 667–675.
Chen AC, Rappelsberger P (1994) Brain and human pain: topographic EEG amplitude and coherence mapping. Brain Topogr 7:129–140.
Coghill RC, Gilron I, Iadarola MJ (2001) Hemispheric lateralization of somatosensory processing. J Neurophysiol 85:2602–2612.
Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.
Davidson RJ (1995) Cerebral asymmetry, emotion, and affective style. In: Brain asymmetry (Davidson RJ, Hugdahl K, eds), pp. 361–387. Cambridge, MA: MIT Press.
Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21.
Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 3:277–283.
Eccleston C, Crombez G (1999) Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 125:356–366.
Ferracuti S, Seri S, Mattia D, Cruccu G (1994) Quantitative EEG modifications during the Cold Water Pressor Test: hemispheric and hand differences. Int J Psychophysiol 17:261–268.
Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ (1995) Spatial registration and normalization of images. Hum Brain Mapp 2:1–25.
Gastaut H (1952) Etude électrocorticographique de la réactivité des rhythmes rolandiques. Rev Neurol 87:176–182.
Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: Studying neural interactions in the human brain. Proc Natl Acad Sci USA 98:694–699.
Hari R, Salmelin R (1997) Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci 20:44–49.
Hari R, Portin K, Kettenmann B, Jousmaki V, Kobal G (1997) Right-hemisphere preponderance of responses to painful $CO_2$ stimulation of the human nasal mucosa. Pain 72:145–151.
Melzack R, Casey KL (1968) Sensory, motivational, and central control determinants of pain: a new conceptual model in pain. In: The skin senses (Kenshalo DRJ, ed.). Springfield, IL: Charles C. Thomas.
Mouraux A, Guerit JM, Plaghki L (2003) Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between A partial differential- and C-fibre afferent volleys. Clin Neurophysiol 114:710–722.
Niedermeyer E (1999) The normal EEG of the waking adult. In: Electroencephalography: basic principles, clinical applications, and related fields (Niedermeyer E, Lopes da Silva F, eds), pp. 149–173. Baltimore, MD: Williams & Wilkins.
Ohara S, Crone NE, Weiss N, Lenz FA (2004) Attention to a painful cutaneous laser stimulus modulates electrocorticographic event-related desynchronization in humans. Clin Neurophysiol 115:1641–1652.
Pfurtscheller G (1999) EEG Event-related desynchronization (ERD) and event-related synchronization (ERS). In: Electroencephalography: basic principles, clinical applications, and related fields (Niedermeyer E, Lopes da Silva F, eds), pp. 958–967. Baltimore, MD: Williams & Wilkins.
Ploner M, Schmitz F, Freund HJ, Schnitzler A (1999) Parallel activation of primary and secondary somatosensory cortices in human pain processing. J Neurophysiol 81: 3100–3104.
Ploner M, Schmitz F, Freund HJ, Schnitzler A (2000) Differential organization of touch and pain in human primary somatosensory cortex. J Neurophysiol 83: 1770–1776.
Ploner M, Gross J, Timmermann L, Schnitzler A (2002) Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci USA 99:12444–12448.
Ploner M, Pollok B, Schnitzler A (2004) Pain facilitates tactile processing in human somatosensory cortices. J Neurophysiol 92:1825–1829.
Raij TT, Forss N, Stancak A, Hari R (2004) Modulation of motor-cortex oscillatory activity by painful Adelta- and C-fiber stimuli. Neuroimage 23:569–573.
Salmelin R, Hari R (1994) Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 60:537–550.
Steriade M, Llinas RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649–742.
Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A (2001) Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J Neurophysiol 86:1499–1503.
Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 44:867–880.
Veerasarn P, Stohler CS (1992) The effect of experimental muscle pain on the background electrical brain activity. Pain 49:349–360.

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# Oscillatory activity reflects the excitability of the human somatosensory system

Markus Ploner,* Joachim Gross, Lars Timmermann, Bettina Pollok, Alfons Schnitzler

*Department of Neurology, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany*

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**The neuronal activity of the resting human brain is dominated by spontaneous oscillations in primary sensory and motor areas. These oscillations are thought to reflect the excitability of sensory and motor systems that can be modulated according to the actual behavioral demands. However, so far, evidence for an association between oscillatory activity and excitability has been inconsistent. Here, we used magnetoencephalography to reinvestigate the relationship between oscillatory activity and excitability in the somatosensory system on a single trial basis. Brief painful stimuli were applied to relate pain-induced suppressions of oscillatory activity to pain-induced increases in excitability. The analysis reveals a significant negative correlation between sensorimotor oscillatory activity, particularly in the α-band, and excitability of somatosensory cortices. Oscillatory activity outside the somatosensory system did not correlate with somatosensory excitability. These findings demonstrate that modulations of sensorimotor oscillatory activity specifically reflect modulations in excitability of the somatosensory system and thus provide direct evidence for the basic tenet of an association between oscillatory activity and cortical excitability.**



## Introduction

Spontaneous oscillatory activity represents a basic feature of the neuronal activity of the human brain. Particularly, spontaneous oscillations in the α-band (8–13 Hz) and β-band (14–30 Hz) are consistently observed in primary visual, somatosensory and motor cortices (Berger, 1929; Gastaut, 1952; Hari and Salmelin, 1997; Niedermeyer, 2005). These oscillations have been related to the functional state of sensory and motor systems (Hari and Salmelin, 1997; Pfurtscheller and Lopes da Silva, 2005). A higher amplitude of oscillatory activity has been associated with an idling state whereas a lower amplitude may signal activation of a system (Steriade and Llinas, 1988; Hari and Salmelin, 1997; Niedermeyer, 2005; Pfurtscheller and Lopes da Silva, 2005). Furthermore, oscillatory activity is thought to reflect the excitability of thalamocortical systems that can be modulated by exogenous or endogenous events (Steriade and Llinas, 1988). However, experimental evidence for this association between oscillatory activity and cortical excitability is sparse and inconsistent. Some studies showed a positive correlation between oscillations and excitability (Brandt et al., 1991; Arieli et al., 1996; Nikouline et al., 2000), whereas others revealed a negative correlation (Brandt and Jansen, 1991; Rossini et al., 1991; Rahn and Basar, 1993a,b; Chen et al., 1999) or did not show any significant relationship (Simoes et al., 2004) between oscillations and excitability.

Therefore, we reinvestigated the relationship between excitability and oscillatory activity – termed mu-rhythm – in the human somatosensory system on a single trial basis. The mu-rhythm comprises two frequency components in the α- and β-band, which can be suppressed by exogenous or endogenous activation of the sensorimotor system. Particularly, painful stimuli have been shown to suppress the mu-rhythm (Mouraux et al., 2003; Ohara et al., 2004; Raij et al., 2004; Ploner et al., 2006) as well as to increase somatosensory excitability (Ploner et al., 2004). Here, we applied brief painful cutaneous laser stimuli in order to relate pain-induced suppressions of the mu-rhythm to pain-induced increases in cortical excitability. Using a conditioning test stimulus paradigm, cortical responses to tactile test stimuli applied 500 ms after the painful conditioning stimuli were used as a measure of somatosensory excitability. Our single trial-based analysis reveals an inverse correlation between oscillatory activity, particularly the α-component of the mu-rhythm, and the excitability of primary (S1) and secondary (S2) somatosensory cortices. Thus, these findings provide direct evidence for the basic tenet of an association between oscillatory activity and cortical excitability in humans.

## Materials and methods

### *Subjects*

Eight healthy male subjects with a mean age of 31 years (range, 23–45 years) participated in the experiment. Informed consent was obtained from all subjects before participation. The study was

* Corresponding author. Fax: +49 211 811 9033.
*E-mail address:* ploner@neurologie.uni-duesseldorf.de.
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approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

*Procedure*

The relationship between oscillatory activity and cortical excitability was studied using a conditioning test stimulus paradigm (Fig. 1A). Conditioning stimuli (CS) were brief painful laser stimuli, which have been shown to suppress oscillatory activity (Ploner et al., 2006) and increase excitability (Ploner et al., 2004) of the human somatosensory cortices. Test stimuli (TS) were non-painful electrical stimuli. Evoked cortical responses to test stimuli were used as a measure of cortical excitability. Conditioning stimuli and test stimuli were both applied to the right hand. The interstimulus interval between conditioning stimuli and test stimuli was 500 ms. At this latency of 500 ms after painful stimuli, both pain-induced suppressions of oscillatory activity (Ploner et al., 2006) and pain-induced increases in excitability (Ploner et al., 2004) have been revealed. In each subject, at least 120 conditioning test stimulus pairs were applied. Intervals between stimulus pairs were randomly varied between 4 and 6 s. Prior to the experiment, the procedure was explained to the subjects so that the subjects knew that only non-painful test stimuli would occur.

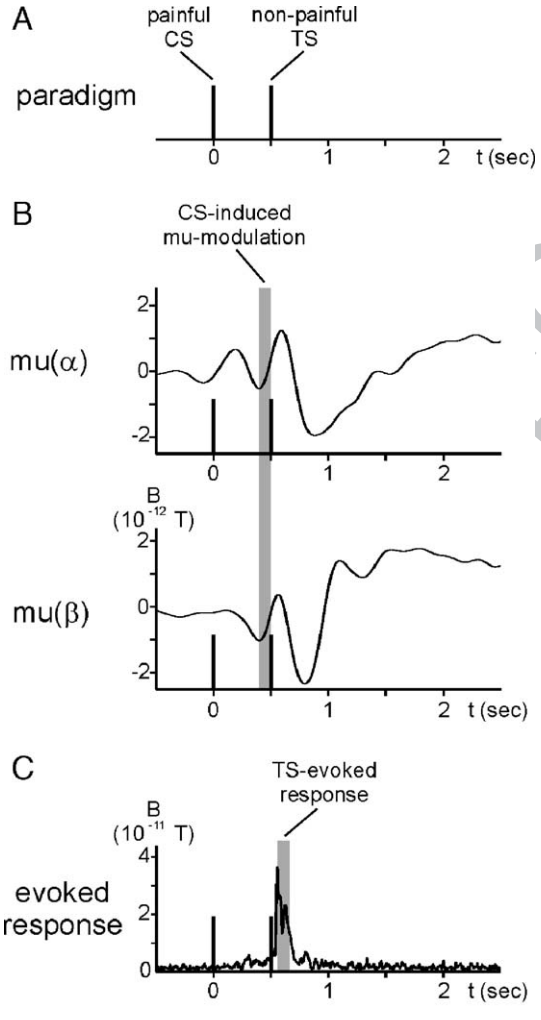


Fig. 1. Paradigm (A) and time courses of stimulus-induced modulations of oscillatory activity (B) and stimulus-evoked responses (C). Induced modulations of oscillatory activity and evoked responses were averaged across trials, subjects, and sensors over the primary sensorimotor cortex and low-pass filtered at 5 Hz. CS, conditioning stimulus; TS, test stimulus; B, magnetic field power.

*Stimuli*

Painful conditioning stimuli were cutaneous laser stimuli, which have been shown to selectively activate nociceptive afferents (Bromm and Treede, 1984). Laser stimuli were applied to the dorsum of the right hand in the territory of the superficial branch of the radial nerve. The laser device was a Tm:YAG-laser (Carl Baasel Lasertechnik, Starnberg, Germany) with a wavelength of 2000 nm, a pulse duration of 1 ms, and a spot diameter of 6 mm. Stimulation site was slightly changed after each stimulus. Stimulus intensity was 100 mJ above individual pain threshold, i.e., 350–400 mJ, thus consistently inducing slightly painful sensations.

Non-painful test stimuli were constant voltage electrical pulses of 0.3 ms duration delivered to the superficial branch of the radial nerve of the right hand. Stimulus intensity was adjusted to two- to threefold detection threshold intensity, i.e., 40–60 V, thus inducing clear and consistent non-painful sensations.

*Data recordings*

Subjects were comfortably seated with eyes closed in a magnetically shielded room. Cortical activity was recorded with a Neuromag-122 whole-head neuromagnetometer containing 122 planar SQUID gradiometers. Signals were digitized at 483 Hz. Neuromagnetic activity was continuously recorded and stored for off-line analysis. Vertical electrooculograms were used to reject epochs contaminated with blink artifacts.

*Data analysis*

Data analysis was based on single trials. Analysis of averaged responses has been reported previously (Ploner et al., 2004). Time courses of modulations of oscillatory activity over the primary sensorimotor cortex induced by the painful conditioning stimuli were analyzed using the TSE method (temporal spectral evolution; Salmelin and Hari, 1994). Because a previous investigation using a time frequency analysis revealed pain-induced suppressions of both components of the mu-rhythm (Ploner et al., 2006), the α- and the β-component of the mu-rhythm were analyzed separately. To this end, using a 4th order butterworth filter data were filtered from 8 to 13 Hz and 15–25 Hz, respectively. Filtered signals of both frequency bands were rectified and averaged across four sensors over the left contralateral hand region of the primary sensorimotor cortex, which mainly generates the mu-rhythm (Salmelin and Hari, 1994; Salmelin et al., 1995; Simoes et al., 2004). Data were detrended by subtracting the best fitting straight line. Mean amplitudes of pain-induced mu-modulations were calculated in a time window from 400 to 500 ms after the painful stimuli. A time window from 400 to 500 ms was chosen because this time window includes pain-induced suppressions of the mu-rhythm (Ploner et al., 2006) but no responses to the test stimuli applied 500 ms after the painful conditioning stimuli. Amplitudes were calculated as relative amplitudes with reference to a 100-ms prestimulus baseline. Single trial amplitudes of mu-modulations were used for correlation analysis. Individual averages were calculated and

significance of pain-induced mu-modulations was tested by comparing mean amplitudes of both frequency bands with baseline amplitudes. Due to the low sample size of 8, the non-parametric two-tailed Wilcoxon signed rank test was used. In addition, grand averages of pain-induced mu-modulations were calculated across trials and subjects for visualization.

Amplitudes of evoked responses to the non-painful test stimuli originating from the primary (S1) and secondary (S2) somatosensory cortices were determined as a measure of the excitability of the somatosensory system. Test stimulus-evoked responses were analyzed on a single trial basis, too. For this purpose, signals were high-pass filtered at 1 Hz and low-pass filtered at 120 Hz and rectified. Evoked responses from S1 were averaged across the same four sensors over the hand region of S1 as the pain-induced mu-modulations. Evoked responses from bilateral S2 were averaged across each four sensors over the parietal operculum of both hemispheres. For each region, mean amplitudes of evoked responses were calculated during a time window from 50 to 150 ms after test stimuli. This time window includes evoked responses to non-painful test stimuli, which originate mainly from contralateral S1 and bilateral S2 and can be modulated by painful conditioning stimuli (Ploner et al., 2004). Data were detrended by subtracting the best fitting straight line. Amplitudes were calculated as relative amplitudes with reference to a 100-ms baseline before application of the conditioning stimuli. Single trial amplitudes of evoked responses were used for correlation analysis. In addition, grand averages of test stimulus-evoked responses were calculated across trials and subjects for visualization.

The relationship between oscillatory activity and cortical excitability was investigated by calculating Pearson's correlation coefficients between pain-induced mu-modulations and evoked responses to the non-painful test stimuli originating from S1 and bilateral S2. This single trial-based correlation analysis takes into account the intertrial variability in amplitude and time course of responses. Thus, single trial-based analyses are well suited for investigating the relationship between oscillations and excitability but, due to the low signal-to-noise ratio, do not explain the maximum variance of the data.

In order to control for the spatial specificity of the observed effects, correlations were calculated between mu-modulations over S1 and evoked responses detected by four sensors outside the somatosensory system over the left temporo-occipital region. The distance from these sensors to the S1 sensors was similar to the distance from the S2 sensors to the S1 sensors. In addition, correlations were calculated between oscillatory activity over occipital sensors and evoked responses from S1.

To verify that the channel groups consisting of four sensors record neural activity from the cortical target areas of interest (S1 and bilateral S2), we computed sensitivity plots. This computation was based on the solution of the forward problem, which allows to compute the signals induced in a sensor generated by a given dipole. For computation of the sensitivity plots, two tangential dipoles were placed in each voxel (size: $6 \times 6 \times 6$ mm) of the brain. For each of these dipoles, the mean squared signal induced in each sensor group (S1 and bilateral S2) was calculated resulting in a tomographic map representing the spatial sensitivity distribution for each sensor group. Group mean sensor sensitivity plots were computed from the normalized individual sensitivity plots.

## Results

In all subjects, conditioning stimuli consistently evoked slightly painful pinprick-like sensations and test stimuli elicited clear and consistent non-painful sensations.

Fig. 1B shows the time courses of the α- and β-components of the mu-rhythm with reference to a prestimulus baseline averaged



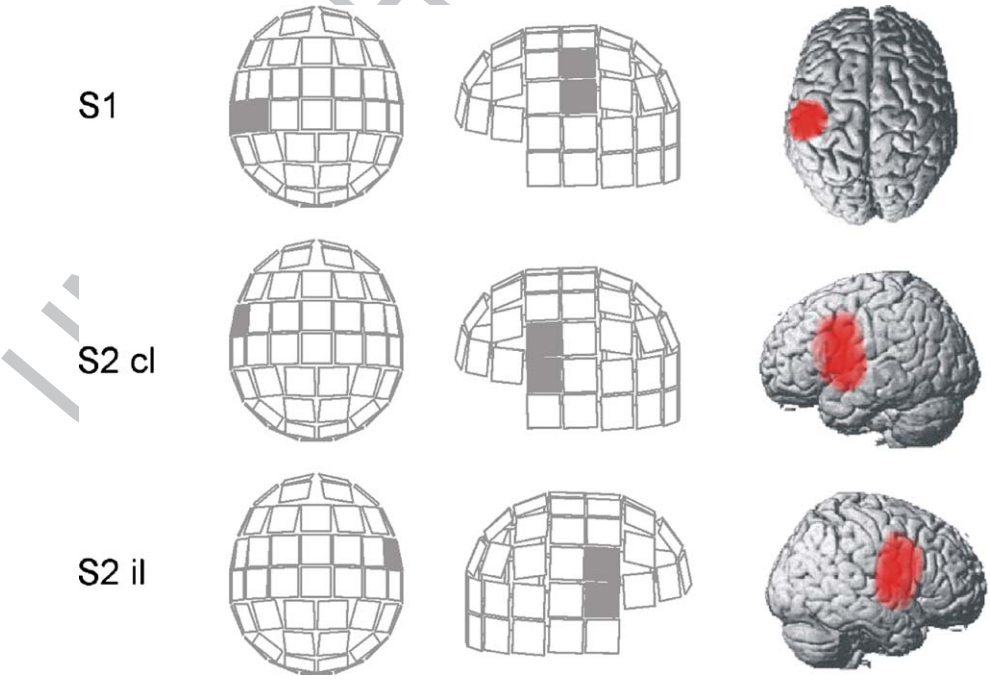


Fig. 2. Left, locations of sensors used for analysis of activity from the left primary somatosensory cortex and the bilateral secondary somatosensory cortices. Right, sensitivity plots of the sensor clusters shown on the left averaged across all subjects.

across all subjects. The figure illustrates that painful conditioning stimuli induce a significant suppression of both components of the mu-rhythm ($p<0.01$ for both components, two-tailed Wilcoxon signed rank tests) with a first peak between 400 and 500 ms after the painful stimuli. Subsequently, the non-painful test stimuli, which are applied 500 ms after the painful conditioning stimuli, yield an interim increase in α- and β-power, which is again followed by a longer-lasting decrease of both components. Fig. 1C shows the evoked responses recorded over S1 averaged across all subjects. The figure demonstrates that non-painful test stimuli evoke responses with a first peak before 50 ms and a later peak between 50 and 150 ms after application of test stimuli. Due to the low stimulus intensity, the slightly painful conditioning stimuli do not yield significant evoked responses (Ploner et al., 2004).

Fig. 2 illustrates the locations of sensors chosen for analysis. The upper row shows the sensors used for analysis of pain-induced mu-modulations as well as for analysis of S1 responses evoked by the non-painful test stimuli. The middle and lower panels show the sensors used for analysis of evoked responses recorded from contralateral and ipsilateral S2, respectively. The sensor sensitivity plots on the right side confirm that these sensor clusters effectively cover the contralateral S1- and bilateral S2-cortices.

Fig. 3 summarizes the relationship between oscillatory activity and cortical excitability. By including each single trial of the experiment the figure shows the correlation analysis between pain-induced amplitude changes of the mu-rhythm and amplitudes of evoked responses to the non-painful test stimuli as a measure of cortical excitability. The figure reveals a significant negative correlation between the α- and β-components of the mu-rhythm and test stimulus-evoked responses from S1 (upper row). In addition, the α- but not the β-component of the mu-rhythm negatively correlates with the test stimulus-evoked response from contralateral S2 (middle row). No significant correlation was observed between both mu-components and responses from ipsilateral S2 (lower row).

The spatial specificity of these correlations is demonstrated by a lack of significant correlation between the mu-rhythm and evoked responses from the temporo-occipital region (mu(α): $r=-0.02$, $p=0.62$; mu(β): $r=0.01$, $p=0.75$). This lack of a significant correlation between temporo-occipital responses and the mu-rhythm contrasts with the significant negative correlation between responses from S2 and the mu-rhythm. Because the distance between the temporo-occipital region and S1 was similar to the distance between S2 and S1, the latter correlation cannot be due to insufficient separation of S1 and S2. In addition, oscillatory activity over occipital areas did not correlate with evoked responses from S1 (occ(α): $r=0.04$, $p=0.22$; occ(β): $r=-0.02$, $p=0.61$). Thus, particularly the α-component of the mu-rhythm but not oscillatory activity outside the somatosensory system selectively correlates with the excitability of somatosensory cortices.

## Discussion

In the present study, we investigated the relationship between oscillatory activity and excitability in the human somatosensory system. By using magnetoencephalography and applying a



Fig. 3. Single trial-based correlations between the α- and β-components of the mu-rhythm and evoked responses from S1 and bilateral S2. The figure includes each single trial from all subjects resulting in at least 960 data points in each panel. Amplitudes of mu-rhythm oscillations and evoked responses are relative amplitudes calculated with reference to baseline period (see Methods for details). S1, primary somatosensory cortex; S2, secondary somatosensory cortex; cl, contralateral; il, ipsilateral; B, magnetic field power.

conditioning test stimulus paradigm, our results reveal an inverse linear correlation between pain-induced modulations of oscillatory activity and pain-induced modulations of cortical excitability in the somatosensory system. This correlation particularly applies to the α-component of the mu-rhythm, indicating that this component is particularly related to the function of the somatosensory system. By demonstrating a significant association between pain-induced suppressions of spontaneous oscillatory activity and pain-induced increases in cortical excitability, the present findings extend our previous observations of both phenomena (Ploner et al., 2004, 2006) and provide direct evidence for the basic tenet of an association between oscillatory activity and cortical excitability in humans.

We applied a single trial-based analysis in order to unravel relationships between oscillations and excitability. This single trial-based analysis may be particularly sensitive for detecting such relationships because it takes into account the intertrial variability in amplitude and time course, which is hidden by response averaging. On the other hand, due to the lower signal-to-noise ratio, the analysis of single trials yields a significantly higher residual variance than the analysis of averaged responses.

Here, we observed a significant correlation between pain-induced suppressions of the mu-rhythm and pain-induced increases in excitability at 400–500 ms and 550–650 ms, respectively. Previous studies on the effects of painful laser stimuli on the mu-rhythm consistently showed a long duration of pain-induced mu-suppressions of at least 1000 ms (Mouraux et al., 2003; Ohara et al., 2004; Raij et al., 2004; Ploner et al., 2006). None of these studies observed a rebound of the mu-rhythm earlier than 1000 ms. Thus, it is unlikely that the present observation reflects a correlation between strengths of pain-induced mu-suppressions and mu-rebounds. Furthermore, we are confident that our finding of a negative correlation between oscillations and excitability is not due to the filtering of the data because smearing of evoked responses into the prestimulus period could result in a false positive but not a false negative correlation.

Previous studies on the relationship between oscillatory activity and excitability in humans yielded inconsistent results. Some studies in the auditory (Rahn and Basar, 1993b), visual (Brandt and Jansen, 1991; Rahn and Basar, 1993a), and motor (Rossini et al., 1991, Chen et al., 1999) system also revealed an inverse correlation between oscillatory activity and excitability that, in principle, corresponds to the present results. However, in these studies spatial information was very limited. Thus, these findings could only be related to a global level of oscillatory activity and excitability but not to the function of a particular system like in the present study. Other studies did not show any (Simoes et al., 2004) or showed a positive (Brandt et al., 1991; Arieli et al., 1996; Nikouline et al., 2000) correlation between oscillatory activity and cortical excitability. However, in most of these studies (Brandt et al., 1991; Arieli et al., 1996; Nikouline et al., 2000), spontaneous fluctuations in oscillatory activity have been investigated. These spontaneous fluctuations are possibly of lower magnitude than fluctuations of pain-induced modulations of the present study and thus might have not allowed to detect a comparable relationship between oscillations and excitability. Furthermore, in the somatosensory system, only the relationship between oscillations and early cortical responses up to 80 ms has been investigated (Nikouline et al., 2000; Simoes et al., 2004). These early responses are known to be less variable and modifiable (Kakigi et al., 2000; Mauguière, 2005) than later responses up to 150 ms, which have been analyzed in the present study. Moreover, in most of these studies the level of prestimulus oscillations has been determined by using a time window of at least several hundred milliseconds (Brandt and Jansen, 1991; Brandt et al., 1991; Rossini et al., 1991; Rahn and Basar, 1993a,b; Nikouline et al., 2000; Simoes et al., 2004). These long time windows may not adequately represent the instantaneous level of oscillatory activity and thus might have obscured a relationship between oscillatory activity and excitability. Lastly, in all of these studies averaged data have been analyzed, which may be less sensitive for detecting a relationship between both phenomena than the present single trial-based analysis.

Our present study reveals a particular association between the α-component of the mu-rhythm and the excitability of the somatosensory system. This is in accordance with previous studies investigating the relationship between α- and β-components of the mu-rhythm and the somatosensory and motor system, respectively. These studies showed that the α-component of the mu-rhythm originates from the postcentral sensory cortex whereas the β-component is generated in the precentral motor cortex (Salmelin and Hari, 1994; Salmelin et al., 1995; Simoes et al., 2004). The present findings complement these observations by providing the first direct functional evidence for an association between the α-component of the mu-rhythm and the functional state of the somatosensory system. Because tactile processing in human somatosensory cortices is mainly serially organized (Kaas, 2004), the correlation between the α-component of the mu-rhythm and the excitability of S2 may reflect the association between oscillatory activity and excitability of S1.

The present findings indicate that the recent observations of pain-induced suppressions of spontaneous oscillatory activity (Ploner et al., 2006) and pain-induced increases in excitability (Ploner et al., 2004) are intimately related. It has been proposed that both phenomena may represent a physiological correlate of the alerting function of pain (Ploner et al., 2004; Ploner et al., 2006). This alerting function of pain may be mediated by a cortical network depending on noradrenergic (NA) modulation from the locus caeruleus (LC), which is dedicated to the detection of behaviorally relevant stimuli (Downar et al., 2000; Corbetta and Shulman, 2002). An association between correlated modulations of oscillatory activity and cortical excitability, activation of the NA-LC system, and an alerting function is supported by several previous studies on the NA-LC system. These studies revealed that activation of the NA-LC system (i) suppresses oscillatory activity in thalamus and cortex, (ii) enhances excitability at the thalamic and cortical level, and (iii) relates to stimulus salience and attention (McCormick et al., 1991; Aston-Jones et al., 2000; Berridge and Waterhouse, 2003; Coull, 2005). In addition, pain has been shown to activate LC neurons projecting to the somatosensory thalamus (Vosin et al., 2005). Thus, we hypothesize that both the pain-induced suppression of oscillatory activity and the pain-induced increase in excitability are associated with a right-lateralized cortical–subcortical network involving the NA-LC system. This network may shape the response properties of sensory and motor systems in order to prepare the individual for processing of and reacting to stimuli of vital relevance. Behaviorally, this may result in an adequate optimization of sensory and motor performance (Linkenkaer-Hansen et al., 2004; Raij et al., 2004).

In conclusion, our results provide direct evidence for the basic principle of an association between oscillatory activity and cortical

excitability. Particularly, the α-component of the sensorimotor mu-rhythm appears to be related to the functional state of the somatosensory system. Modulations of both oscillatory activity and excitability exerted by pain may represent a physiological correlate of an alerting function. Such modulations of oscillatory activity and excitability may be mediated by a cortical–subcortical network depending on noradrenergic modulation from the locus caeruleus.

## Uncited reference

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## References

Arieli, A., Sterkin, A., Grinvald, A., Aertsen, A., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868–1871.

Aston-Jones, G., Rajkowski, J., Cohen, J., 2000. Locus coeruleus and regulation of behavioral flexibility and attention. Prog. Brain Res. 126, 165–182.

Berger, H., 1929. Über das Elektroenkephalogramm des Menschen. Arch. Psychiatr. Nervenkr. 87, 527–570.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Brain Res. Rev. 42, 33–84.

Brandt, M.E., Jansen, B.H., 1991. The relationship between prestimulus-alpha amplitude and visual evoked potential amplitude. Int. J. Neurosci. 61, 261–268.

Brandt, M.E., Jansen, B.H., Carbonari, J.P., 1991. Pre-stimulus spectral EEG patterns and the visual evoked response. Electroencephalogr. Clin. Neurophysiol. 80, 16–20.

Bromm, B., Treede, R.D., 1984. Nerve fibre discharges, cerebral potentials and sensations induced by $CO_2$ laser stimulation. Hum. Neurobiol. 3, 33–40.

Chen, R., Corwell, B., Hallett, M., 1999. Modulation of motor cortex excitability by median nerve and digit stimulation. Exp. Brain Res. 129, 77–86.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev., Neurosci. 3, 201–215.

Coull, J.T., 2005. Psychopharmacology of human attention. In: Itti, L., Rees, G., Tsotsos, J. (Eds.), Neurobiology of Attention. Elsevier, Amsterdam, pp. 50–56.

Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2000. A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. 3, 277–283.

Gastaut, H., 1952. Etude électrocorticographique de la réactivité des rhythmes rolandiques. Rev. Neurol. 87, 176–182.

Hari, R., Salmelin, R., 1997. Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci. 20, 44–49.

Kaas, J.H., 2004. Somatosensory system. In: Paxinos, G., Mai, J.K. (Eds.), The Human Nervous System. Elsevier, Amsterdam, pp. 1059–1092.

Kakigi, R., Hoshiyama, M., Shimojo, M., Naka, D., Yamasaki, H., Watanabe, S., Xiang, J., Maeda, K., Lam, K., Itomi, K., Nakamura, A., 2000. The somatosensory evoked magnetic fields. Prog. Neurobiol. 61, 495–523.

Linkenkaer-Hansen, K., Nikulin, V.V., Palva, S., Ilmoniemi, R.J., Palva, J.M., 2004. Prestimulus oscillations enhance psychophysical performance in humans. J. Neurosci. 24, 10186–10190.

Mauguière, F., 2005. Somatosensory evoked potentials: normal responses, abnormal waveforms, and clinical applications in neurological diseases. In: Niedermeyer, E., Lopes da Silva, F. (Eds.), Electroencephalography: basic principles, clinical applications and related fields. Lippincott Williams and Wilkins, Philadelphia, pp. 1067–1119.

McCormick, D.A., Pape, H.C., Williamson, A., 1991. Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. Prog. Brain Res. 88, 293–305.

Mouraux, A., Guerit, J.M., Plaghki, L., 2003. Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between Aδ- and C-fibre afferent volleys. Clin. Neurophysiol. 114, 710–722.

Niedermeyer, E., 2005. The normal EEG of the waking adult. In: Niedermeyer, E., Lopes da Silva, F. (Eds.), Electroencephalography: Basic Principles, Clinical Applications and Related Fields. Lippincott Williams and Wilkins, Philadelphia, pp. 167–192.

Nikouline, V.V., Wikstrom, H., Linkenkaer-Hansen, K., Kesaniemi, M., Ilmoniemi, R.J., Huttunen, J., 2000. Somatosensory evoked magnetic fields: relation to pre-stimulus mu rhythm. Clin. Neurophysiol. 111, 1227–1233.

Ohara, S., Crone, N.E., Weiss, N., Lenz, F.A., 2004. Attention to a painful cutaneous laser stimulus modulates electrocorticographic event-related desynchronization in humans. Clin. Neurophysiol. 115, 1641–1652.

Pfurtscheller, G., Lopes da Silva, F., 2005. EEG event-related desynchronization (ERD) and event-related synchronization. In: Niedermeyer, E., Lopes da Silva, F. (Eds.), Electroencephalography: Basic Principles, Clinical Applications and Related Fields. Lippincott Williams and Wilkins, Philadelphia, pp. 1003–1016.

Ploner, M., Pollok, B., Schnitzler, A., 2004. Pain facilitates tactile processing in human somatosensory cortices. J. Neurophysiol. 92, 1825–1829.

Ploner, M., Gross, J., Timmermann, L., Pollok, B., Schnitzler, A., 2006. Pain suppresses spontaneous brain rhythms. Cereb. Cortex 16, 537–540.

Rahn, E., Basar, E., 1993a. Enhancement of visual evoked potentials by stimulation during low prestimulus EEG stages. Int. J. Neurosci. 72, 123–136.

Rahn, E., Basar, E., 1993b. Prestimulus EEG-activity strongly influences the auditory evoked vertex response: a new method for selective averaging. Int. J. Neurosci. 69, 207–220.

Raij, T.T., Forss, N., Stancak, A., Hari, R., 2004. Modulation of motor-cortex oscillatory activity by painful Adelta- and C-fiber stimuli. NeuroImage 23, 569–573.

Rossini, P.M., Desiato, M.T., Lavaroni, F., Caramia, M.D., 1991. Brain excitability and electroencephalographic activation: non-invasive evaluation in healthy humans via transcranial magnetic stimulation. Brain Res. 567, 111–119.

Salmelin, R., Hari, R., 1994. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 60, 537–550.

Salmelin, R., Hamalainen, M., Kajola, M., Hari, R., 1995. Functional segregation of movement-related rhythmic activity in the human brain. NeuroImage 2, 237–243.

Simoes, C., Salenius, S., Curio, G., 2004. Short-term (approximately 600 (ms) prediction of perturbation dynamics for 10- and 20-Hz MEG rhythms in human primary sensorimotor hand cortices. NeuroImage 22, 387–393.

Steriade, M., Llinas, R.R., 1988. The functional states of the thalamus and the associated neuronal interplay. Physiol. Rev. 68, 649–742.

Tamura, Y., Hoshiyama, M., Nakata, H., Hiroe, N., Inui, K., Kaneoke, Y., Inoue, K., Kakigi, R., 2005. Functional relationship between human rolandic oscillations and motor cortical excitability: an MEG study. Eur. J. Neurosci. 21, 2555–2562.

Vosin, D.L., Guy, N., Chalus, M., Dallel, R., 2005. Nociceptive stimulation activates locus coeruleus neurones projecting to the somatosensory thalamus in the rat. J. Physiol. 566, 929–937.