厚生労働科学研究費補助金

こころの健康科学研究事業

# 基礎研究と臨床研究の融合による、神経疾患によってひきおこされる疼痛に対する新しい治療法の開発に関する研究

平成２０年度　総合研究報告書

主任研究者　柿木　隆介

平成２１（２００９）年　４月

目　　次

厚生労働科学研究費補助金（こころの健康科学研究事業）
（総合）研究報告書

# 基礎研究と臨床研究の融合による、神経疾患によってひきおこされる疼痛に対する新しい治療法の開発に関する研究

（主任）研究者　柿木　隆介　○自然科学研究機構　生理学研究所　教授

研究要旨：基礎研究によって得られたヒトの脳内痛覚認知機構の詳細な知見に基づいて、定位脳手術、脳深部刺激療法による臨床応用をおこない、神経・筋疾患に併発する治療困難な疼痛に対する新たなる治療法の開発をおこなっていく。これまでは経験的に行われてきた視床痛などの治療を、非侵襲的脳機能解析法と神経生理学的知見に基づいた、いわばEvidence-Based Medicineによって行う画期的な試みである。

**分担研究者氏名・所属機関名及び所属機関における職名**
片山容一・日本大学医学部脳神経外科・教授
山本隆充・日本大学医学部先端医学講座応用システム神経科学部門・教授
齋藤洋一・大阪大学医学部脳神経外科・准教授

## A．研究目的

神経・筋疾患による疼痛は、視床痛、幻肢痛を初めとする極めて難治性かつ発症のメカニズムが明らかでは無いものが多い。10年以上前には、ヒトにおける痛覚認知の脳内情報処理機構に関してはほとんど何もわかっておらず、治療も従来からの経験に基づくものが中心であった。しかし、この5年程の間に脳波、脳磁図とfMRIなどの各種非侵襲的脳機能計測法の技術革新に伴い、痛覚認知の脳内情報処理機構がかなり明らかになってきた（研究代表者が主として担当）。また臨床面では、さまざまな外科的手法による除痛効果が報告されてきた。特に定位脳手術の手技を用いた脳深部刺激療法の著明な効果と運動皮質刺激療法が近年の大きな話題となっている（研究分担者が主として担当）。種々の非侵襲的計測法を用いてヒトの脳内痛覚認知機構を明らかにすること、及び、基礎的研究によって得られた知見を元にして除痛治療を行う事、すなわち神経・筋疾患による疼痛治療 におけるEvidence-Based Medicineの施行が主要研究目的である。すなわち、ようやく「科学的に」疼痛のメカニズムと除痛効果についての総合的な研究が可能となってきたと考えている。

疼痛治療のためには、痛覚刺激に対する脳内情報処理過程の解明が必須であり最も基本的な事項である。逆に、基礎的結果に基づく疼痛治療の臨床応用の結果により、さらに基礎的研究を新たに展開できる。本研究によって得られた成果は、今後、神経・筋疾患による疼痛の治療のみならず、がん痛などによる全身疾患の疼痛治療にも応用が可能であり、国民の医療に対する貢献は極めて大きいと考えられる。

## B．研究方法

### 1．研究目標

神経・筋疾患によってひきおこされる難治性疼痛の新しい（画期的な）治療法の開発を最終的な研究目標とする。

### 2．研究仮説、およびその解明方法

神経・筋疾患によってひきおこされる難治性疼痛は、その発症メカニズムと責任部位が明らかにされていないため、治療が困難である。そのためには、先ず、健常人における脳内の痛覚認知機構を最新の非侵襲的脳機能計測法を用いて詳細に明らかにする。その結果に基づき、痛覚認知に重要な役割を果たして

いる部位を脳外科的に刺激、凝固あるいは摘出することにより、除痛治療を行う。また、極めて特殊な痛みを訴える患者さんに対しては、各患者さん各々に非侵襲的脳機能計測を行い、その結果に基づいて治療を行っていく。

**3．研究計画の要約（研究責任者）**

基礎的研究（生理学研究所）では、脳波、脳磁図、fMRI、TMSを併用してAδ線維とC線維を上行する信号の脳内情報処理過程を詳細に検索していく。現在までの研究で、痛覚認知の初期過程には、先ず刺激対側の第1次感覚野（SI）、第2次感覚野（SII）と島が平行して活動し、その後おそらく脳梁を経由して刺激同側のSII、島、帯状回、扁桃体が活動する事が明らかになってきた。したがって是非とも行なわなければならない事は、上記の部位の時間的、空間的な活動の詳細な分析である。

また、痛覚認知は情動と深い関連がある。情動に関係深い辺縁系、特に帯状回と島の役割を明らかにする必要がある。

**4．研究分担者の協力体制**

臨床研究（日本大学医学部、大阪大学医学部）では、視床痛、幻肢痛といった慢性疼痛を呈する患者に対して脊髄刺激、脳深部刺激、大脳皮質運動領刺激などの様々な除痛方法を加え、その効果を検討することにより、病態機序の解明を行っていく。視床痛は難治例が多いが、大脳皮質運動領刺激に有効例が多い。幻肢痛などの末梢性求心路遮断痛に対しては、定位脳手術の手技を用いた脳深部刺激療法（視床知覚中継核刺激）が特に有効である。また、刺激の継続によって疼痛自体が消失する症例も存在することから、視床ならびに大脳皮質での神経機構の再構成についても検討を行う。さらに、研究代表者（柿木）のグループが痛覚認知に関して重要な部位であることを確認している第2次感覚野、島と帯状回の刺激療法についても具体的に見当を開始している。

（倫理面への配慮）

健常被験者を対象とする実験の場合にも患者さんを対象とする治療時にも、実験あるいは治療の意義と内容を良く説明してインフォームドコンセントを取ったあとに実施している。生理学研究所、日本大学医学部および大阪大学医学部で定めた倫理規定を遵守し、倫理委員会の承認を受けている。

**C．研究結果、D．考察**

研究代表者は本年度は４編の英文原著論文を発表した（印刷中を含む）。主要な２論文について内容を紹介する。

動脈の圧受容器が痛覚認知に影響するか否かを痛覚関連誘発脳波を用いて解析した。収縮期には脳波の振幅は拡張期よりも有意に低下している事がわかり、動脈の圧受容器が痛覚認知に影響を及ぼすことが立証された。これは英国バーミンガム大学との共同研究である(Edwards et al., Pain, 2008)。

痛覚認知におけるposterior parietal cortex (PPC)の役割について、第１次体性感覚野と第２次体性感覚野の活動との関連を含めて詳細に解析した。PPCの活動はおそらく第１次体性感覚野の活動に引き続いて現れ、PPCの中でもinferior parietal lobule (BA 40)が痛覚認知に重要であることを発見した。本論文は日本大学、大阪大学との共同研究によってなされた (Nakata et al., Neuroimage, 2008)。

研究分担者（日本大学）は、本年は、low-dose ketamine点滴療法とDual-lead spinal cord stimulation (Dual-lead SCS) の併用療法が神経障害性疼痛に有効であることを明らかにした。

ドラッグチャレンジテストでketamine-sensitiveな症例に対して、100mlの生食に２０mgのケタラール® (0.33mg/Kg) を加え、約１時間かけて点滴するlow-dose ketamine点滴療法を開発した。この方法では、２週間ごとに外来でlow-dose ketamineの点滴を施行し、塩酸マプロチニン(Ludiomil®) 30mg/day、ブロマゼパム（Lexotan®）6mg/day、ガバペンチン(GABAPEN®)600～1200 mg/dayを併用する。また、新しく使用可能となったメドトロニック社製のシナジー脊髄刺激装置では、２本の電極の合計８箇所の刺激点を自由に選択可能であり、陽極と陰極を選択すれば２本の電極間での刺激も可能となり、これまでと違った脊髄刺激を行うこ

とができる。

ケタミン点滴後に明らかに疼痛が抑制される持続時間は１時間から６時間以内が最も多く、２４時間以内が77%であったが、24時間以上持続するものも23%存在した。長期投与によるケタミン耐性の有無についての検討では、モルヒネのような耐性は認めなかった。ケタミンの点滴によって情動面の変化を呈する症例が存在したが、投与量ならびに投与時間の調整によってコントロールが可能であった。Low-dose ketamine点滴療法では、効果の持続時間が短い症例でも一度疼痛を軽減することが疼痛の管理には重要であり、これによって精神的な安定を得られるという症例が多い。また、central sensitizationの解除にも有効であると考えられている。併用薬として、本邦でも使用可能となったガバペンチンには、神経終末からの興奮性アミノ酸の遊離を抑制する作用が報告されており、ケタミンとの相乗効果も期待される。

これまで疼痛に対する脊髄刺激療法の有効例はfailed-back painやCRPSに限られることが多かったが、ketamine-sensitiveなpost-stroke pain症例に対しては、Dual-lead SCSとlow-dose ketamine点滴療法の併用療法が有効であることを明らかにすることができた。

大阪大学（研究分担者）では、脊髄硬膜外刺激が無効であった中枢性疼痛患者の中心溝内に電極を埋め込み、より直接的な一次運動野刺激を試みたところ、中心溝内からの刺激の有効性が、中心前回脳表の刺激と比較すると相対的に優れていることを明らかにした(Hosomi, Saitoh et al: Clin Neurophysiol 2008)。中心溝を術中に展開して、電極を留置することで一時的に中枢性疼痛が顕著に軽減することを明らかにした。また中心溝内で捕らえられる脳表脳波に運動麻痺の上肢の運動関連電位がもっとも顕著に捕らえられることも分かってきた(Yanagisawa, Saitoh et al: Pain Res 2008)。この事象を応用してBrain Machine Interfaceの研究にも取り組んでいる(Yanagisawa et al: NeuroImage, in press)。これらの研究は代表者との共同研究である。最近、MRIのDiffusion tensor image技術が進歩してきたので、これを応用し、脳卒中後疼痛の患者において、運動線維、感覚線維の描出率と疼痛との関連を、主任研究者とともに研究し、両者の描出率がよい患者で、経頭蓋磁気刺激療法による一次運動野刺激の効果が優れていることをつきとめ、より感覚線維の描出率と相関することを報告した(Goto, Saitoh et al: Pain 2008)。２年間で5例の患者に大脳一次運動野刺激療法を施行した。

臨床研究としておこなっている経頭蓋磁気刺激療法はすでに、のべ100例近くになっている。それらの患者において、臨床データを詳細に検討したところ、クロスオーバー試験を行った患者では、シャム刺激に比して有意な除痛効果を認め、若年者、脳に原因を有さない難治性疼痛患者において、有効性が高い結果を得ている(臨床神経生理学会2008，神戸)。

## E．結論

痛覚認知に関与する脳部位が次第に明らかになりつつある。また、これまで経験的に行われてきた外科的除痛療法の作用機序を、基礎的知見に基づいて解釈できるようになってきた。同様に、大脳に情報を送りあるいは情報が送られてくる脊髄の機能も明らかになってきた。

今後は、末梢神経、脊髄、脳幹、大脳を総合的に解析してくる必要があることがあらためて認識された。

## F．健康危険情報

特記すべき事はない。

## G．研究発表

1.　論文発表

**研究代表者**


1. Edwards L, Inui K, Ring C, Wang X, Kakigi R (2008) Pain-related evoked potentials are modulated across the cardiac cycle. Pain, 137(3): 488-494
2. Mochizuki H, Inui K, Yamashiro K, Ootsuru N, Kakigi R (2008) Itching-related somatosensory evoked potentials. Pain, 138(3): 598-603

3. Nakata H, Tamura Y, Sakamoto K, Akatsuka K, Hirai M, Inui K, Hoshiyama M, Saitoh Y, Yamamoto T, Katayama Y & Kakigi R (2008) Evoked magnetic fields following noxious laser stimulation of the thigh in humans. Neuroimage, 42(2): 858-868
4. Nakata H, Sakamoto K, Honda Y, Mochizuki H, Hoshiyama M & Kakigi R (2008) Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement. Neuroimage (in press)
5. 望月秀紀、乾幸二、柿木隆介 (2008) 痛みと痒みの神経機構、Annual Review 神経 2008、 編集（柳澤信夫、篠原幸人、岩田誠、清水輝夫、寺元明)、中外医学社、東京 pp1-10
6. 住谷昌彦、宮内哲、山田芳嗣、柿木隆介（2008）計測と制御 サイボーグ医療第 6 回ファントムペインの解明と回復 社団法人計測自動制御学会誌 47（9）775-779
7. 荻野祐一、 根本英徳、齋藤繁、後藤文夫、乾幸二、柿木隆介(2008) 情動変化が痛覚認知に与える影響、日本ペインクリニック学会誌、15(1):1-6
8. 柿木隆介、乾幸二、宮崎貴浩(2008) 痛み刺激は脳内でどのように情報処理されるか、神経内科 67 397-403

**研究分担者（日本大学医学部脳神経外科）**

1. 山本隆充、深谷親、片山容一 (2009) 脳深部刺激装置、ペインクリニック 30: 167-174
2. 山本隆充、大渕敏樹、加納利和、小林一太、大島秀規、深谷親、片山容一 (2009) 神経障害性疼痛に対するDual-lead を用いた脊髄刺激療法とlow-dose ketamine 点滴療法の併用効果、Pain Research 24: 9-15
3. Kano T, Katayama Y, Kobayashi K, Kasai M, Oshima H, Fukaya C, Yamamoto T (2008) Multiple-cell spike density and neural noise level analysis by semimicroelectrode recording for identification of the subthalamic nucleus during surgery for Parkinson's disease. Neuromodulation 11: 1-7
4. Oshima H, Katayama Y, Fukaya C, Kano T, Kobayashi K, Yamamoto T, Suzuki Y (2008) Direct inhibition of levodopa-induced beginning-of-dose motor deterioration by subthalamic nucleus stimulation in a patient with Parkinson disease. J Neurosurg 108: 160-163
5. Morisita T, Katayama Y, Kano T, Kobayashi K, Fukaya C, Yamamoto T (2008) Effect of subthalamic nucleus stimulation on severe striatal hand deformity in Parkinson's disease. Neuromodulation: Technology at the Neural Interface 11: 124-127
6. 山本隆充、片山容一、深谷 親（2008）神経因性疼痛に対するDBS治療、臨床脳波 50: 209- 215
7. Shijo K, Katayama Y, Yaashita A, Kobayshi K, Oshima H, Fukaya C, Yamamoto T (2008) c-Fos expression after chronic electrical stimulation of sensorimotor cortex in rats. Neuromodulation 11: 187-195
8. Obuchi T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Yamamoto T (2008) Direction and predictive factors for the shift of brain structure during deep brain stimulation electrode implantation for advanced Parkinson's disease. Neuromodulation 11, 302-310
9. 山本隆充、深谷親、片山容一（2008）脳深部刺激療法、治療、90 (7): 2106- 2109
10. 深谷 親、山本隆充、片山容一 (2008) 脳深部刺激療法—その歴史・現状・未来、臨床評価 36: 7-16
11. 山本隆充、大渕敏樹、小林一太、大島秀規、深谷親、片山容一 (2008) Post-stroke painの特徴と治療（山本隆充編 求心路遮断痛の診断と治療）真興交易医書出版部pp119-126
12. 山本隆充、大渕敏樹、小林一太、大島秀規、深谷親、片山容一 (2008) ケタミン点滴療法（山本隆充編 求心路遮断痛の診断と治療）真興交易医書出版部 pp263-272
13. 深谷親、山本隆充、片山容一 (2008) 脳深部刺激療法 （山本隆充編 求心路遮断痛の診断と治療）真興交易医書出版部 pp191-208
14. 山本隆充、片山容一 (2008) 脳深部刺激（森本昌宏編 脊髄電気刺激療法）克誠堂出版 pp243-249
15. 山本隆充、片山容一 (2008) 神経刺激療法（宮崎東洋、北出利勝編 慢性疼痛の

理解と医療連携）真興交易医書出版部 pp210-219

16. 山本隆充、片山容一 (2008) 中枢性疼痛、視床痛、痛みの概念が変わった、新キーワード１００＋アルファー（小川節郎編）真興交易医書出版部 pp. 60-61
17. 山本隆充、片山容一 (2008) 求心路遮断性疼痛、痛みの概念が変わった、新キーワード１００＋アルファー（小川節郎編）真興交易医書出版部 pp. 62-63
18. 山本隆充、片山容一 (2008) 脊髄硬膜外電気刺激療法、痛みの概念が変わった、新キーワード１００＋アルファー（小川節郎　編）真興交易医書出版部 pp. 226-227
19. 山本隆充、片山容一 (2008) 脳深部刺激療法、痛みの概念が変わった、新キーワード１００＋アルファー（小川節郎編）真興交易医書出版部 pp. 228-229
20. 山本隆充、片山容一 (2008) DREZ-lesion、痛みの概念が変わった、新キーワード100＋アルファー（小川節郎　編）真興交易医書出版部 pp. 230-231
21. 大島秀規、片山容一 (2008) 求心路遮断痛の神経学的特徴. ペインクリニック 29:31-35

研究分担者（大阪大学医学部脳神経外科）

1. 齋藤洋一 (2009) 脳神経外科手術のスタンダード　難治性疼痛　脳神経外科速報 19:134-139
2. 齋藤洋一 (2009) 反復的経頭蓋磁気刺激特集痛み診療に用いる治療機器 I ペインクリニック 30:175-184
3. Hosomi K, Saitoh Y, Kishima H, Oshino S, Hirata M, Tani N, Shimokawa T, Yoshimine T (2008) Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. Clin Neurophysiol 119:993-1001
4. Kato H, Shimosegawa E, Oku, N, Kitagawa K, Kishima H, Saitoh Y, Kato A, Yoshimine T (2008) MRI-based correction for partial-volume effect improves detectability of intractable epileptogenic foci on I-123 iomazenil brain SPECT images. J NuclMed 49:383-389
5. Yanagisawa T, Saitoh y, Hirata M, Yamashita O, Kamitani Y, Oshino S, Kishima H,Tani N, Hosomi K, Goto T, Satou M, Kakigi R, Yoshimine T (2008) Mechanistic analysis of motor cortex stimulation for phantom limb pain. Pain Res 23:27-34
6. Sumitani M, Miyauchi S, McCabe CS, Shibata M, Maeda L, Saitoh Y, Tashiro T, Mashimo T (2008) Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. Rheumatology 47:1038-1043
7. Goto T, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, Naoki Tani, Hosomi K, Kakigi R, Yoshimine T (2008) Diffusion tensor fiber tracking in patients with central post-stroke pain; Correlation with efficacy of repetitive transcranial magnetic stimulation. Pain 140:509-518
8. Saitoh Y, Hosomi K: Capter 2. From localization to surgical implantation. In Textbook of therapeutic cortical stimulation Ed: Sergio Canavero, Nova Science Publishers,Inc. Hauppauge NY, 2009 (in press)
9. Oshino S, Kato A, Hirata M, Kishima H,Saitoh Y, Fujinaka T, Yoshimine T (2008) Ipsilateral motor-related hyperactivity inpatients with cerebral occlusive vascular disease. Stroke 39:2769-2775
10. 齋藤洋一 (2008) 脊髄・末梢性難治性疼痛の治療　脳神経外科ジャーナル 17:222-227
11. 齋藤洋一 (2008) 大脳皮質運動野刺激 克誠堂出版　森本昌宏編　脊髄電気刺激療法　pp. 238-242
12. 齋藤洋一 (2008) 求心路遮断痛に対する各種の治療法　２．刺激療法　４）大脳皮質電気刺激療法　ペインクリニック 29S:200-205
13. 貴島晴彦、齋藤洋一、吉峰俊樹 (2008) B. 求心路遮断痛の診断法と臨床的評価　5. PET による求心路遮断痛の脳機能解析 ペインクリニック　29S: 57-63
14. 齋藤洋一 (2008) 大脳皮質電気・磁気刺激による疼痛治療　総合リハビリテーション　36:941-944
15. 細見晃一、齋藤洋一、貴島晴彦、谷直樹、平山東、下川敏雄、押野悟、平田雅之、吉峰俊樹 (2008)神経因性疼痛に対する反

復的経頭蓋磁気刺激療法　機能的脳神経外科　47:135-140

2. 学会発表

研究代表者

1. 柿木隆介（2008.11.14-16）痛み脳：脳波はどのようにして痛みを感じるか？　サテライトシンポジウム　“歯科領域で扱う難治性神経疾患の克服に向けた研究”　第21回日本歯科医学会総会　（横浜）
2. 大鶴直史、乾幸二、山代幸哉、宮崎貴浩、竹島康行、柿木隆介（2008.11.12-14）表皮内電気刺激による細径神経線維機能評価法　第38回日本臨床神経生理学会（神戸）
3. 宮崎貴浩、柿木隆介 (2008.11.12-14) 喫煙がレーザー痛覚刺激による誘発電位に与える影響に関する研究　第38回日本臨床神経生理学会　(神戸)
4. 中田大貴、田村洋平、坂本貴和子、赤塚康介、平井真洋、乾幸二、宝珠山稔、柿木隆介（2008.11.12-14）大腿部を刺激した際の痛覚関連誘発脳磁場　第38回日本臨床神経生理学会（神戸）
5. 望月秀紀、乾幸二、柿木隆介（2008.11.12-14）かゆみの知覚に関する中枢処理機構　第38回日本臨床神経生理学会（神戸）
6. Kakigi R (2008.10.24-26) Electrophysiological studies on human pain perception. The 1st Beijing International Symposium on Clinical Neuro-technology and Neuroscience (BIS-CNN). Beijing, China.
7. Kakigi R (2008.9.21-23) Emotion and pain. The 14th ASEAN Association of Radiology Meeting, Hanoi, Vietnam.
8. Kakigi R (2008.9.21-23) Brain processing of the signals ascending through C and A-delta fibers: fMRI study. The 14th ASEAN Association of Radiology Meeting, Hanoi, Vietnam.
9. Nakata H, Tamura Y, Sakamoto K, Hirai M, Inui K, Hoshiyama M, Kakigi R (2008.8.25-29) Laser-evoked magnetic fields following noxious stimulation of the thigh. The 16th International Conference on Biomagnetism (BIOMAG2008)　Sapporo, Japan.
10. 柿木隆介（2008.8.2）　痛覚の脳内認知機構、　第51回神経内科懇話会　（東京）
11. Kakigi R（2008.7.18-20）Brain processing of the signals ascending through unmyelinated C fibers in humans: an event-related functional magnetic imaging study. The 3rd Asian Pain Symposium, Fukuoka, Japan.
12. 柿木隆介、乾幸二（2008.7.18-20）痒み関連誘発脳波　Itch-related evoked potentials. 第30回日本疼痛学会（福岡）
13. 柿木隆介、乾幸二（2008.7.18-20）喫煙が脳内痛覚認知に与える影響：誘発脳波を用いた研究　第30回日本疼痛学会（福岡）
14. 乾幸二（2008.6.12-14）表皮内電気刺激法を用いた選択的侵害刺激の試み　日本麻酔科学会第55回学術集会（第3回麻酔深度研究会）（横浜市）

研究分担者（日本大学医学部脳神経外科）

1. 山本隆充 (2008.12.6)各分野からの慢性痛治療へのアプローチ 脳外科の観点から、第１回運動器疼痛研究会 (東京)
2. Yamamoto T (2008.10.23-35) Cerebrospinal stimulation therapy for the treatment of intractable pain. 1st Educational Conference of WFNS Neurorehabilitation (Jakarta)
3. Yamamoto T(2008.10.23-35) Motor cortex stimulation for the treatment of intractable pain and movement disorders: How to place the stimulating electrode. 1st Educational Conference of WFNS Neurorehabilitation (Jakarta)
4. 大島秀規 (2008.10.1-3) 神経刺激療法から見た幻肢痛のメカニズム. 第67回日本脳神経外科学会総会 (盛岡)
5. 大島秀規 (2008.7.18-19) パーキンソン病に伴う痛みに対する視床下核刺激療法の効果. 第37回日本慢性疼痛学会 (福岡)
6. 山本隆充 (2008.5.30-31)脳脊髄刺激によるニューロモデユレーション、第１７回日本定位放射線治療学会 (奈良)
7. 山本隆充(2008.1.25-26) 中枢性疼痛の治療：脳脊髄刺激療法とケタミン点滴療法の併用効果、第４７回日本定位・機能神経外科学会 (東京)
8. 山本隆充(2009. 1.23-24)難治性疼痛の長期成績）神経障害性疼痛に対するDual-lead

SCSとlow-dose ketamine 点滴療法の併用効果、第４８回日本定位・機能神経外科学会（東京）

9. 山本隆充(2009. 1.23-24) 大脳皮質運動野慢性刺激による運動機能回復についての検討、第４８回日本定位・機能神経外科学会 (東京)
10. Yamamoto T (2009. 1.7-1) Dual-lead SCS combined with low-dose ketamine drip infusin therapy for the treatment of neuropathic pain. 7th Congress of Asian Australesian Stereotactic and Functional Neurosurgery (Hong-Kong)

研究分担者（大阪大学医学部脳神経外科）

1. Yanagisawa T, Hirata M, Saitoh Y, Kato A, Shibuya D, Fukuma R, Yokoi H, Kamitani Y, Yoshimine T (2008.11.15-19) Neural decoding using gyral and intrasulcal electrocorticograms. Society for neurosciencemeeting 2008 Washington, D.C., USA
2. 細見晃一、齋藤洋一、貴島晴彦、平山東、谷直樹、平田雅之、押野悟、後藤哲、柳澤琢史、Ali Mohamed、下川敏雄、吉峰俊樹 (2008.11.12-14) シンポジウム 難治性神経因性疼痛に対する反復経頭蓋磁気刺激療法 第38回日本臨床神経生理学会(神戸)
3. 平田雅之、後藤哲、谷直樹、甲津綾子、元木優、齋藤洋一、橋本直哉、柳澤琢史、細見晃一、依藤史郎、吉峰俊樹 (2008.11.12-14) シンポジウム 脳磁図、皮質電位、ファイバートラッキング、経頭蓋磁気刺激を用いた術前術中視覚機能評価 第38回日本臨床神経生理学会(神戸)
4. Hosomi K, Kishima H, Saitoh Y, Hirata M, Oshino S, Goto T, Yanagisawa T, Mohamed A, Shimono K, Okinaga T, Shimosegawa E, Hatazawa J, Kato A, YoshimineT (2008.10.25) Comparison between preoperative I-123 iomazenil SPECT and FDG-PET in epilepsy surgery. The 2nd Asian Epilepsy Surgery Congress, Shijiazhuang, China
5. Kishima H, Kato A, Oshino S, Hirata M, Hosomi K, Goto T, Yanagisawa T, Saitoh Y, Yoshimine T (2008.10.25) Surgical treatmentfor intractable epilepsy with cortical dysplasia. 2nd ASIAN EPILEPSY SURGERY CONGRESS, Shijiazhuang, China
6. 平田雅之、後藤哲、柳澤琢史、貴島晴彦、齋藤洋一、押野悟、細見晃一、沖永剛志、下野九理子、加藤天美、吉峰俊樹 (2008.10.19) シンポジウム てんかん外科のための皮質電気刺激と皮質脳波律動変化を併用した脳機能マッピング第４２回日本てんかん学会 (東京)
7. 齋藤洋一、細見晃一、貴島晴彦、柳澤琢史、押野悟、平田雅之、後藤哲、吉峰俊樹(2008.10.1-3)シンポジウム 機能的脳疾患に対する中枢神経刺激療法 現状と展望 第67回日本脳神経外科学会(盛岡)
8. 平田雅之、柳澤琢史、後藤哲、齋藤洋一、福間良平、貴島晴彦、押野悟、細見晃一、加藤天美、横井浩史、鈴木隆文、佐倉 統、神谷之康、吉峰俊樹 (2008.10.1-3)シンポジウム 皮質脳波を用いたBrain machine interfaceによるリアルタイムロボット制御：現状と今後の展望 第67回日本脳神経外科学会(盛岡)
9. 平田雅之、柳澤琢史、後藤哲、齋藤洋一、福間良平、横井浩史、神谷之康、吉峰俊樹 (2008.9.28) シンポジウム 脳表脳波計測に基づく運動制御の実時間復号化 第23回生体・生理工学シンポジウム(名古屋)
10. 柳澤琢史、平田雅之、齋藤洋一、福間良平、後藤哲、加藤天美、横井浩史、神谷之康、吉峰俊樹 (2008.9.24-26)シンポジウム 中心溝内皮質脳波を用いたBrain machine interfaceによる運動機能再建 第18回日本神経回路学会(つくば市)
11. Oshino S, Kato A, Hirata M, Kishima H,Saitoh Y, Fujinaka T, Yoshimine T (2008.8.25-29) Ipsilateral motor-related hyperactivity in patients with cerebral occlusive vascular disease. 16th International Conference on Biomagnetism(Biomag), Sapporo, Japan
12. Yanagisawa T, Saitoh Y, Hosomi K, Hirata M, Kishima H, Oshino S, Goto T, Yoshimine T (2008.8.25-29) Functional mapping by transcranial magnetic stimulation (TMS) on motor cortex of the patients with

deafferentation pain. 16th International Conference on Biomagnetism(Biomag) Sapporo, Japan

13. Sumitani M, Misaki M, Shibata M, SaitohY, Yanagisawa M, Mashimo T, Yamada Y, Miyauchi S (2008.8.19) Dissociation inaccessing external and internal space representations in patients with CRPS and deafferentation pain. 12th World Congress of Pain, Glasgo, UK
14. Mohamed A, Saitoh Y, Hosomi K, Oshino S, Kishima H, Yoshimine T (2008.6.22)Eficacy of spinal cord stimulation in post-stroke pain. 7th Asian Congress of Neurological Surgeons, Beijin, China
15. 平田雅之、後藤 哲、柳澤琢史、齋藤洋一、貴島晴彦、押野 悟、細見晃一、依藤史郎、吉峰俊樹 (2008.6.13) 臨床神経生理学分野における医工連携の重要性 第２３回日本生体磁気学会 (東京)
16. 齋藤洋一、細見晃一、押野悟、貴島晴彦、平田雅之、住谷昌彦、柴田政彦、吉峰俊樹 (2008.5.17) シンポジウム 脊髄刺激療法の適応について 脳神経外科の立場から 第22回日本ニューロモデュレーション学会 (東京)
17. Saitoh Y (2008.4.5) Repetitive transcranialmagnetic stimulation therapy for intractable neuropathic pain and movement disorder. Kor ean Neuromodulation Society Meeting, Seoul, South Korea
18. Saitoh Y (2008.4.4) Electrical stimulation of primary motor cortex within the centralsulcus for intractable neuropathic pain. Seoul, South Korea
19. 齋藤洋一、吉峰俊樹(2008.2.29-3.1) シンポジウム 経鼻孔的下垂体腫瘍摘出術における手術道具の工夫 第18回日本間脳下垂体腫瘍学会(福井)
20. 泉本修一、齋藤洋一、吉峰俊樹 (2008.2.29-3.1) シンポジウム ラトケのう胞の長期治療成績と長期自然経過 第18回日本間脳下垂体腫瘍学会 (福井)
21. 齋藤洋一、細見晃一、貴島晴彦、柳澤琢史、押野悟、平田雅之、谷直樹、吉峰俊樹 (2008.1.25-26) シンポジウム 中枢性疼痛に対する反復的経頭蓋磁気刺激療法第47回日本定位・機能神経外科学会(浜松)
22. 貴島晴彦、齋藤洋一、細見晃一、谷直樹、押野悟、平田雅之、後藤哲、柳澤琢史、吉峰俊樹 (2008.1.25-26) シンポジウム 運動異常症に対する大脳皮質刺激療法の可能性 第47回日本定位・機能神経外科学会(浜松)
23. 細見晃一、齋藤洋一、貴島晴彦、平田雅之、押野悟、谷直樹、後藤哲、柳澤琢史、Ali Mohamed、吉峰俊樹 (2008.1.25-26) シンポジウム 中枢性疼痛に対する硬膜下一次運動野刺激療法第47回日本定位・機能神経外科学会 (浜松)
24. 平田雅之、後藤 哲、貴島晴彦、齋藤洋一、橋本直哉、柳澤琢史、谷 直樹、押野 悟、細見晃一、加藤天美、依藤史郎、吉峰俊樹 (2008.1.24) シンポジウム 開口合成脳磁図を用いた言語優位半球、言語機能局在の術前評価：侵襲的検査法との比較検証 第３１回日本てんかん外科学会(浜松)
25. 貴島晴彦、加藤天美、齋藤洋一、平田雅之、押野悟、谷直樹、細見晃一、後藤哲、柳澤琢史、沖永剛志、下野九理子、吉峰俊樹 (2008.1.24)シンポジウム 側頭葉てんかんに対する手術前後の社会生活状況の変化 第３１回日本てんかん外科学会(浜松)
26. Saitoh Y (2008.1.23) Stimulation of primary motor cortex for intractable neuropathic pain 浜松医科大学COE国際シンポジウム Hamamatsu, Japan

## H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

特に無い

2. 実用新案登録

特に無い

3. その他

特に無い

-00-

別紙４

研究成果の刊行に関する一覧表

書籍

| 著者氏名 | 論文タイトル名 | 書籍全体の編集者名 | 書 籍 名 | 出版社名 | 出版地 | 出版年 | ページ |
|---|---|---|---|---|---|---|---|
| 望月秀紀、乾幸二、柿木隆介 | 痛みと痒みの神経機構 | 柳澤信夫、篠原幸人、岩田誠、清水輝夫、寺元明 | Annual Review 神経2008 | 中外医学社 | 東京 | 2008 | 1-10 |
| 山本隆充、大渕敏樹、小林一太、大島秀規、深谷親、片山容一 | Post-stroke painの特徴と治療 | 山本隆充 | 求心路遮断痛の診断と治療 | 真興交易医書 | 東京 | 2008 | 119-126 |
| 山本隆充、大渕敏樹、小林一太、大島秀規、深谷親、片山容一 | ケタミン点滴療法 | 山本隆充 | 求心路遮断痛の診断と治療 | 真興交易医書 | 東京 | 2008 | 263-272 |
| 深谷親、山本隆充、片山容一 | 脳深部刺激療法 | 山本隆充 | 求心路遮断痛の診断と治療 | 真興交易医書 | 東京 | 2008 | 191-208 |
| 山本隆充、片山容一 | 脳深部刺激 | 森本昌宏 | 脊髄電気刺激療法 | 克誠堂 | 東京 | 2008 | 243-249 |
| 山本隆充、片山容一 | 神経刺激療法 | 宮崎東洋、北出利勝 | 慢性疼痛の理解と医療連携 | 真興交易医書 | 東京 | 2008 | 210-219 |
| 山本隆充、片山容一 | 痛みの概念が変わった、新キーワード１００＋アルファー | 小川節郎 | 中枢性疼痛、視床痛 | 真興交易医書 | 東京 | 2008 | 60-61 |
| 山本隆充、片山容一 | 痛みの概念が変わった、新キーワード１００＋アルファー | 小川節郎 | 求心路遮断性疼痛、 | 真興交易医書 | 東京 | 2008 | 62-63 |
| 山本隆充、片山容一 | 痛みの概念が変わった、新キーワード１００＋アルファー | 小川節郎 | 脊髄硬膜外電気刺激療法 | 真興交易医書 | 東京 | 2008 | 226-227 |
| 山本隆充、片山容一 | 痛みの概念が変わった、新キーワード１００＋アルファー | 小川節郎 | 脳深部刺激療法 | 真興交易医書 | 東京 | 2008 | 228-229 |
| 山本隆充、片山容一 | 痛みの概念が変わった、新キーワード100＋アルファー | 小川節郎 | DREZ-lesion | 真興交易医書 | 東京 | 2008 | 230-231 |
| Saitoh Y, Hosomi K | Nova Science | Sergio Canavero | In Textbook of therapeutic cortical stimulation Capter 2. From localization to surgical implantation | Inc. Hauppauge NY, | New York | 2009 (in press) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 齋藤洋一 | 脊髄電気刺激療法 | 森本昌宏 | 大脳皮質運動野刺激 | 克誠堂 | 東京 | 2008 | 238-242 |

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Nakata H, Sakamoto K,Honda Y, Mochizuki H,Hoshiyama M, Kakigi R | Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement. | Neuroimage | | | 2009 (in press) |
| Mochizuki H, Inui K, Yamashiro K, Ootsuru N Kakigi R | Itching-related somatosensory evoked potentials. | Pain | 138 | 598-603 | 2008 |
| Nakata H, Tamura Y, Sakamoto K, Akatsuka K, Hirai M, Inui K, Hoshiyama M, Saitoh Y, Yamamoto T, Katayama Y Kakigi R | Evoked magnetic fields following noxious laser stimulation of the thigh in humans. | Neuroimage, | 42 | 858-868 | 2008 |
| Edwards L, Inui K, Ring C, Wang X, Kakigi R | Pain-related evoked potentials are modulated across the cardiac cycle. | Pain | 137 | 488-494 | 2008 |
| 住谷昌彦、宮内哲、山田芳嗣、柿木隆介 | 計測と制御 サイボーグ医療 第6回 ファントムペインの解明と回復 | 社団法人計測自動制御学会誌 | 47 | 775-779 | 2008 |
| 荻野祐一、根本英徳、齋藤繁、後藤文夫、乾幸二、柿木隆介 | 情動変化が痛覚認知に与える影響、 | 日本ペインクリニック学会誌、 | 15 | 1-6 | 2008 |
| 柿木隆介、乾幸二、宮崎貴浩 | 痛み刺激は脳内でどのように情報処理されるか、 | 神経内科 | 67 | 397-403 | 2008 |
| 山本隆充、深谷親、片山容一 | 脳深部刺激装置 | ペインクリニック | 30 | 167-174 | 2009 |
| 山本隆充、大渕敏樹、加納利和、小林一太、大島秀規、深谷親、片山容一 | 神経障害性疼痛に対するDual- lead を用いた脊髄刺激療法とlow- dose ketamine 点滴療法の併用効果 | Pain Research | 24 | 9-15 | 2009 |
| 山本隆充、四条克倫、加納利和、永岡右章、小林一太、深谷 親、片山容一 | 運動野・錐体路におけるMEP モニタリングの実際 | 脳神経外科ジャーナル | 17 | 13-20 | 2008 |
| Kano T, Katayama Y, Kobayashi K, Kasai M, Oshima H, Fukaya C, Yamamoto T | Multiple-cell spike density and neural noise level analysis by semimicroelectrode recording for identification of the subthalamic nucleus during surgery for Parkinson's disease. | Neuromodulation | 11 | 1-7 | 2008 |

| | | | | | |
|---|---|---|---|---|---|
| Oshima H, Katayama Y, Fukaya C, Kano T, Kobayashi K, Yamamoto T, Suzuki Y | Direct inhibition of levodopa-induced beginning-of-dose motor deterioration by subthalamic nucleus stimulation in a patient with Parkinson disease. | Neurosurg | 108 | 160-163 | 2008 |
| Morisita T, Katayama Y, Kano T, Kobayashi K, Fukaya C, Yamamoto T | Effect of subthalamic nucleus stimulation on severe striatal hand deformity in Parkinson's disease. | Neuromodulation Technology at the Neural Interface | 11 | 124-127 | 2008 |
| 山本隆充、片山容一、深谷 親 | 神経因性疼痛に対するDBS治療 | 臨床脳波 | 50 | 209- 215 | 2008 |
| Shijo K, Katayama Y, Yaashita A, Kobayshi K, Oshima H, Fukaya C, Yamamoto T | c-Fos expression after chronic electrical stimulation of sensorimotor cortex in rats. | Neuromodulation | 11 | 187-195 | 2008 |
| Obuchi T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Yamamoto T | Direction and predictive factors for the shift of brain structure during deep brain stimulation electrode implantation for advanced Parkinson's disease. | Neuromodulation | 11 | 302-310 | 2008 |
| 山本隆充、深谷親、片山容一 | 脳深部刺激療法 | 治療 | 90 | 2106-2109 | 2008 |
| 深谷 親、山本隆充、片山容一 | 脳深部刺激療法—その歴史・現状・未来 | 臨床評価 | 36 | 7-16 | 2008 |
| 大島秀規、片山容一 | 求心路遮断痛の神経学的特徴. | ペインクリニック | 29 | 31-35 | 2008 |
| 齋藤洋一 | 脳神経外科手術のスタンダード 難治性疼痛 | 脳神経外科速報 | 19 | 134-139 | 2009 |
| 齋藤洋一 | 反復的経頭蓋磁気刺激特集痛み診療に用いる治療機器 I | ペインクリニック | 30 | 175-184. | 2009 |
| Hosomi K, Saitoh Y, Kishima H, Oshino S, Hirata M, Tani N, Shimokawa T, Yoshimine T | Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. | Clin Neurophysiol | 119 | 993-1001 | 2008 |
| Kato H, Shimosegawa E, Oku, N, Kitagawa K, Kishima H, Saitoh Y, Kato A, Yoshimine T | MRI-based correction for partial-volume effect improves detectability of intractable epileptogenic foci on I-123 iomazenil brain SPECT images. | J Nucl Med | 49 | 383-389 | 2008 |
| Yanagisawa T, Saitoh y, Hirata M, Yamashita O, Kamitani Y, Oshino S, Kishima H,Tani N, Hosomi K, Goto T, Satou M, Kakigi R, Yoshimine T | Mechanistic analysis of motor cortex stimulation for phantom limb pain. | Pain Res | 23 | 27-34. | 2008 |
| Sumitani M, Miyauchi S, McCabe CS, Shibata M, Maeda L, Saitoh Y, Tashiro T, Mashimo T | Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. | Rheumatology | 47 | 1038-1043 | 2008 |

| | | | | | |
|---|---|---|---|---|---|
| Goto T, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, Naoki Tani, Hosomi K, Kakigi R, Yoshimine T | Diffusion tensor fiber tracking in patients with central post-stroke pain; Correlation with efficacy of repetitive transcranial magnetic stimulation. | Pain | 140 | 509-518 | 2008 |
| Oshino S, Kato A, Hirata M, Kishima H,Saitoh Y, Fujinaka T, Yoshimine T | Ipsilateral motor-related hyperactivity inpatients with cerebral occlusive vascular disease. | Stroke | 39 | 2769-2775 | 2008 |
| 齋藤洋一 | 脊髄・末梢性難治性疼痛の治療 | 脳神経外科ジャーナル | 17 | 222-227. | 2008 |
| 齋藤洋一 | 求心路遮断痛に対する各種の治療法　2．刺激療法　4）大脳皮質電気刺激療法 | ペインクリニック | 29S | 200-205. | 2008 |
| 貴島晴彦、齋藤洋一、吉峰俊樹 | B. 求心路遮断痛の診断法と臨床的評価　5. PETによる求心路遮断痛の脳機能解析 | ペインクリニック | 29S | 57-63 | 2008 |
| 齋藤洋一 | 大脳皮質電気・磁気刺激による疼痛治療 | 総合リハビリテーション | 36 | 941-944 | 2008 |
| 細見晃一、齋藤洋一、貴島晴彦、谷直樹、平山東、下川敏雄、押野悟、平田雅之、吉峰俊樹 | 神経因性疼痛に対する反復的経頭蓋磁気刺激療法 | 機能的脳神経外科 | 47 | 135-140 | 2008 |

NeuroImage xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

# Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement

Hiroki Nakata [a,b,c,*], Kiwako Sakamoto [a,d], Yukiko Honda [a], Hideki Mochizuki [a], Minoru Hoshiyama [a,b], Ryusuke Kakigi [a,d]

[a] Department of Integrative Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki, 444-8585, Japan
[b] School of Health Sciences, Nagoya University, Nagoya, Japan
[c] Japan Society for the Promotion of Science, Tokyo, Japan
[d] Department of Physiological Sciences, School of Life Sciences, The Graduate University for Advanced Studies, Hayama, Kanagawa, Japan

ARTICLE INFO

*Article history:*
Received 28 May 2008
Revised 23 August 2008
Accepted 7 November 2008
Available online xxxx

*Keywords:*
Laser evoked magnetic fields (LEFs)
Laser evoked potentials (LEPs)
Magnetoencephalography (MEG)
Gating
Somatosensory

ABSTRACT

In the present study, we investigate the top-down centrifugal modulation of neural responses to a task-relevant noxious stimulation triggering voluntary movement by recording magnetoencephalography (MEG) and electroencephalography (EEG) simultaneously. An auditory warning signal was followed 2–3 s later by a noxious YAG laser stimulation as an imperative signal delivered to the left hand dorsum. Ten normal subjects performed three different conditions, Control, Movement, and Count. In Control, the subjects were asked to relax and rest quietly with no task. In Movement, the subjects extended the left index finger after imperative stimuli. In Count, the subjects counted the number of imperative stimuli silently. The amplitude of the N2 component recorded by EEG, which peaked about 220 ms after noxious stimulation, was significantly attenuated in Movement, but not in Count, compared to Control. The root-mean-square (RMS) from both hemispheres, and areal mean signal (AMS) amplitudes and the equivalent current dipole (ECD) strengths from SI/PPC and bilateral SII recorded at around 170 ms by MEG were not significantly different among the three conditions. In contrast, ECD strengths and AMS amplitudes from the anterior cingulate cortex (ACC), which showed a similar peak to the N2 component, were smaller in Movement than Control and Count. We therefore suspect that neural activities related to generator mechanisms of N2, especially including ACC, are inhibited by movement-related neural activities during the preparatory period. The present findings indicate a characteristic of pain–motor integration in a movement preparatory period.



## Introduction

Many studies have investigated somatosensory–motor integration by recording somatosensory evoked potentials (SEPs) during voluntary movement. Characteristically, the amplitudes of short-latency components are attenuated, while those of long-latency are enhanced (Giblin, 1964; Kakigi, 1986; Hoshiyama and Sheean, 1998; Rossini et al., 1999; Valeriani et al., 2001; Nakata et al., 2003), and this phenomenon is termed 'gating'. The modulation of neural responses during movement is mainly the result of two major mechanisms (Jones et al., 1989; Wasaka et al., 2005a; Kida et al., 2006a). The first mechanism is centrifugal, whereby signals from neurons involved in producing movement modulate ascending somatosensory signals at cortical or subcortical levels. The second mechanism is centripetal, whereby ascending somatosensory signals generated by voluntary movement modulate ascending signals eliciting the SEPs. In addition, since such modulation also has been found in the preparatory period of voluntary movement (Starr and Cohen, 1985; Staines et al., 1997; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Kida et al., 2004, 2006a,b; Wasaka et al., 2005a,b, 2006), the centrifugal mechanism is closely related to the gating effects (Nakata et al., 2003).

This gating effect has been also researched by recording somatosensory evoked magnetic fields (SEFs) using magnetoencephalography (MEG), and similar results were found regarding the cortical responses. That is, the early responses generated from primary somatosensory cortex (SI) were attenuated during voluntary movement, whereas the late responses in the secondary somatosensory cortex (SII) were strengthened (Rossini et al., 1989; Kakigi et al., 1995a, 1997; Huttunen et al., 1996; Forss and Jousmäki, 1998; Lin et al., 2000). Such modulation also occurred before voluntary movement (Wasaka et al., 2003, 2005c; Kida et al., 2006c).

Studies using SEPs and SEFs have focused on the somatosensory–motor integration following the tactile stimulation of ascending Aβ fibers during voluntary movement. However, there are some studies investigating the pain–motor integration following the noxious

* Corresponding author. Fax: +81 564 52 7913.
*E-mail address:* nakata@nips.ac.jp (H. Nakata).

1053-8119/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2008.11.026

stimulation of ascending Aδ fibers. Kakigi and colleagues reported that the amplitudes of laser-evoked potentials (LEPs) elicited by noxious $CO_2$ laser stimulation were attenuated during voluntary movement at vertex electrodes, indicating the opposite results to the modulation of late-components of SEPs (Kakigi and Shibasaki, 1992; Kakigi et al., 1993). In addition, our previous study using laser-evoked magnetic fields (LEFs) showed that voluntary movement attenuated neural activities of SI and SII evoked by noxious stimulation (Nakata et al., 2004), which was also the opposite to the above-mentioned studies. These results indicate that the characteristic of pain–motor integration ascending Aδ fibers is different from that of somatosensory–motor integration ascending Aβ fibers. However, the mechanisms for pain–motor integration are still unknown because of the small number of studies, compared to those on somatosensory–motor integration. In a recent study, Le Pera et al. in Italy reported that the amplitudes of LEPs elicited by $CO_2$ laser stimulation at vertex electrodes were attenuated in the time interval between a visual warning stimulus followed after 1 s by an imperative stimulus (S1–S2 paradigms) (Le Pera et al., 2007). In their experiment, the attenuation was found even if the subjects counted the number of imperative stimuli in the paradigm instead of motor tasks, and a noxious stimulus to evoke the LEPs was irrelevant to the subject's movement task. Thus, their data might include not only movement-related activity but also effects of cognition and attention, on the attenuation of LEPs.

In the current study, to clarify the centrifugal mechanisms of pain–motor integration before voluntary movement, we recorded the MEG and EEG responses simultaneously to noxious stimulation used as a task-relevant imperative signal to trigger voluntary movement in a forewarned reaction time paradigm. Several studies have attempted to clarify the centrifugal modulation of task-relevant tactile inputs, utilizing a forewarned reaction time paradigm where the tactile stimulation used to elicit the SEPs/SEFs was also used as an imperative signal (Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Kida et al., 2004, 2006a,b,c). The application of this paradigm allows one to examine how neural activities just before the task-relevant signal modulate neural responses to that signal. We hypothesized that the neural responses on LEPs and/or LEFs are modulated when noxious stimulation triggers a voluntary movement in a forewarned reaction time paradigm.

## Materials and methods

### *Participants*

Ten normal right-handed males (mean age 31.7 years, range 25–44 years) participated in this study. The subjects did not have a history of any neurological or psychiatric disorders. Informed consent was obtained from all participants. The study was approved by the Ethical Committee of the National Institute for Physiological Sciences, Okazaki, Japan.

### *Experimental paradigm*

The subjects performed a warning stimulus (S1)–imperative stimulus (S2) paradigm. A pair of S1 and S2 stimuli was given to the subjects at an interval of 2–3 s The S1–S1 interval was 10 s to avoid habituation of evoked pain-related cortical responses (Raij et al., 2003). S1 was an auditory pure tone (60 dB SPL, 50 ms duration), presented through a speaker. For S2, a thulium:YAG laser beam (Neurolaser, BAASEL Lasertech, Germany) was applied to the dorsum of the left hand as noxious stimulation. The wavelength was 2000 nm, pulse duration was 1 ms, and spot diameter was 6 mm. To determine the intensity of painful stimulation, we used a visual analogue scale (VAS), in which 0 represented 'not painful' and 10 represented 'an intensity which subjects could not tolerate'. Subjects were asked to rate the intensity of the perceived pain, and a stimulus intensity of VAS 8 was used in each subject for the recording. In addition, subjects were requested to orally provide one adjective from a list of seven descriptors: 'not perceived', 'light touch', 'touch', 'tingling', 'warm', 'pricking', and 'burning'. All subjects reported 'pricking' for the intensity of VAS 8. This method for assessing quality of perception followed some previous studies (Opsommer et al., 2001; Mouraux and Plaghki, 2007). There were two reasons why we selected an intensity of VAS 8. First, because a strong stimulus would evoke clear and large cortical responses (Timmermann et al., 2001), we wanted to select the strongest intensity for each subject. Second, if the stimulus intensity was more than VAS 8, it was expected that subjects could not tolerate all painful stimuli during recordings. The mean intensity across all subjects was 194 mJ. Since the laser stimulator caused large magnetic artifacts, it was set outside of the shielded room, and the laser beam was conducted through optical fibers, approximately 6.5 m in length, into the shielded room. In order to maintain the distance between the laser outlet and the skin surface, a cable of optical fiber was attached to the MEG device, but the irradiated points were slightly moved by the experimenter for each stimulus to avoid tissue damage and habituation of the receptors (Kakigi et al., 1995b). During the recordings, the subjects were instructed to keep their eyes open and look at a small fixation point positioned in front of them at a distance of approximately 1.5 m. The subjects were wearing earplugs to avoid hearing sounds from the stimulator, and non-magnetic goggles for safety.

The recordings were conducted in three conditions. Condition 1 was the resting control (Control). The subjects were asked to relax and rest quietly with no task. In condition 2 (Movement), the subjects extended the left index finger as quickly as possible, when the S2 noxious stimuli were presented. In condition 3 (Count), the subjects were asked to count the number of S2 stimuli silently. To avoid the effect of habituation, only 5 stimuli were applied in one session. Each session consisted of one of three conditions, and the order of these three conditions was random. Ten sessions were conducted for each condition, and consequently 50 stimuli in total for each condition were applied.

### *EEG recordings and analysis*

EEGs were recorded with Ag/AgCl disk electrodes placed on the scalp at Fz, Cz, Pz, C3, and C4, according to the International 10–20 System (Jasper, 1958). Each scalp electrode was referenced to linked earlobes. To eliminate eye movements or blinks exceeding 150 μV, an electrooculogram (EOG) was recorded bipolarly with a pair of electrodes placed 2 cm lateral to the lateral canthus of the left eye and 2 cm above the upper edge of the left orbit. The impedance was maintained at less than 5 k ohm. All of the EEG signals were collected in a signal processor (Neurofax EEG1100, Nihon-Kohden, Tokyo, Japan). The analysis epoch for ERPs was 800 ms including a prestimulus baseline period of 100 ms. The bandpass filter was set at 0.1–100 Hz and the sampling rate was 995 Hz. The peak amplitudes and latencies of N2 and P2 were measured at 170–250 ms, 280–380 ms, respectively. The amplitudes were measured baseline-to-peak. In addition, to clarify the difference in amplitude between N2 and P2, we calculated the N2–P2 component with a peak-to-peak measurement. No digital filter was applied off-line, and all ERP analyses were based on unfiltered data.

For the analysis of each component, the data on peak amplitude and latency was submitted to analyses of variance (ANOVAs) with repeated measures using as within-subject factors, Condition (Control, Movement, and Count), and Electrode (Fz, Cz, Pz, C3 and C4). For all repeated measures factors with more than two levels, it was tested whether Mauchly's sphericity assumption was violated. If the result of Mauchly's test was significant and the assumption of sphericity was violated, the Greenhouse–Geisser adjustment was used to correct for the sphericity altering the degrees of freedom using a correction

Please cite this article as: Nakata, H., et al., Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement, NeuroImage (2009), doi:10.1016/j.neuroimage.2008.11.026

coefficient epsilon. Normalization to assess topographical differences was not applied (Urbach and Kutas, 2002). When significant effects were identified, the Tukey HSD post hoc multiple-comparison was adjusted to identify the specific differences among conditions. Statistical significance was set at $p<0.05$.

*MEG recordings and analysis*

LEFs were recorded with a helmet-shaped 306-channel detector array (Vectorview; ELEKTA Neuromag Oy, Helsinki, Finland), which comprises 102 identical triple sensor elements, in a magnetically shielded room. Each sensor element consists of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID (Superconducting Quantum Interference Device) and thus provides three independent measurements of the magnetic fields. In the present study, we analyzed MEG signals from 204-channel planar-type gradiometers, because the data on magnetometers were usually susceptive to global magnetic noises such as changes in geomagnetic field (Hämäläinen et al., 1993) (these noises can be successfully cancelled out in recording with planar sensors). These planar-type sensors can detect the signals just above local cerebral sources (Nishitani and Hari, 2002, Noguchi and Kakigi, 2005). The signals were recorded with a bandpass of 0.1–200 Hz and digitized at 995 Hz, rejecting noise, blinks, and eye movements from the analysis automatically. The analysis period of 800 ms included a prestimulus baseline of 100 ms. The signals recorded from the 204 gradiometers were used for source localization. Before the recordings, four head position indicator (HPI) coils were attached to specific sites on the subject's head, and then electric current was fed to the HPI coils to determine the exact location of the head with respect to the MEG sensors. The locations of HPI coils with respect to the three anatomical landmarks (nasion and bilateral PA) were also measured using a three-dimensional digitizer to allow alignment of the MEG and magnetic resonance (MR) images obtained with a 3 T MRI system (Allegra scanner, Siemens, Erlangen, Germany). A three-dimensional structural brain image of each subject was obtained using an MP-RAGE sequence with the following parameters: TR=2500 ms, TE=4.38 ms, FA=8°, FOV=230 mm, matrix size=256×256 mm, voxel dimension=0.9×0.9×1.0 mm. The *x*-axis was fixed with the preauricular points, pointing to the right, the positive *y*-axis traversing the nasion, and the positive *z*-axis pointing up. We adopted the head-based coordinate system used in our previous studies (Nakata et al., 2004; Noguchi et al., 2004).

We first calculated vector sums from the longitudinal and latitudinal derivatives of the response recorded on the planar-type gradiometers at each of the 102 sensors' location. This was achieved by squaring MEG signals of gradiometer pairs, summing these signals together, and then recalculating the square root of this sum, following our previous studies (Kida et al., 2006c, 2007; Nakata et al., 2008). The calculation was carried out for all 102 sensors' locations to make an isocontour map of amplitude. Then, we calculated root-mean-square (RMS), in the set of sensors in each hemisphere (96 sensors) to compare the global field power among the three conditions (Hoshiyama et al., 2007). In addition, we analyzed the areal mean signals (AMS) of four gradiometer pairs that showed the largest response to measure amplitude and latency in the regions of interest. Finally, we calculated group averages across subjects. This method of data analysis followed previous studies using the same MEG system as the present study (Tarkiainen et al., 2003; Nakata et al., 2005, 2008; Bonte et al., 2006; Akatsuka et al., 2007a,b).

To identify the sources of the evoked activities, the equivalent current dipole (ECD), which best explains the measured data, was computed by using a least-squares search. Before estimating the ECDs, we examined the magnetic field pattern in 2-ms steps visually to identify all local and stable dipole field patterns. This procedure provided an initial estimate of the number of sources activated during the analysis period (Forss et al., 1999; Avikainen et al., 2002). Then, to select the ECD source, we first identified 3–4 channels, which detected large responses around the central sulcus and the Sylvian fissure (Nguyen et al., 2004; Nakata et al., 2005; Wasaka et al., 2005c, 2007; Kida et al., 2006c, 2007), and selected 16–18 channels around those channels with the large responses. A subset was employed for the estimation of ECDs. This number of channels has been used to cover around the signal maxima channels over somatosensory cortices, following previous studies using the same Neuromag system (Forss et al., 1996, 1999; Lin et al., 2000; Avikainen et al., 2002; Raij et al., 2003; Nguyen et al., 2004; Mõttönen et al., 2005; Nakata et al., 2005, 2008; Wasaka et al., 2005c, 2007; Nevalainen et al., 2006; Sakamoto et al., 2008a,b). These calculations gave the three-dimensional location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MRI to show the source location. The goodness-of-fit (GOF) value of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field variance. Only ECDs explaining more than 85% of the field variance at selected periods of time were used for further analysis. The analysis period was extended to the entire time period and all channels were taken into account in computing a time-varying multi-dipole model. The strengths of the previously found ECDs were allowed to change while their locations and orientations were kept fixed. If signals from any brain regions were insufficiently explained by the model, we re-analyzed the data to estimate more precise regions. The data acquisition and analysis followed Hämäläinen et al. (1993). In addition, the source location was transformed into the Talairach standard brain source (Talairach and Tournoux, 1988), following previous studies (Nishitani et al., 1999; Ploner et al., 2000; Nakata et al., 2005).

For the analysis of RMS from both hemispheres, the data on peak amplitude and latency was submitted to analyses of variance (ANOVAs) with repeated measures using as within-subject factors, Condition (Control, Movement, and Count), and Hemisphere (Left and Right). Data for the peak amplitude and latency of AMS were also submitted to two-way repeated measure ANOVA with Condition and Area. In addition, after confirmation of the dipole moments among the three different conditions, the dipole strengths and peak latencies were submitted to a two-way repeated measure ANOVA with Condition and Source of the dipole. For all repeated measures factors with more than two levels, it was tested whether Mauchly's sphericity assumption was violated. If the result of Mauchly's test was significant and the assumption of sphericity was violated, the Greenhouse–Geisser adjustment was used to correct for the sphericity altering the degrees of freedom using a correction coefficient epsilon. In addition, Tukey HSD post hoc multiple-comparison tests were adjusted for differences of the dipole strengths and peak latencies. Statistical significance was set at $p<0.05$.

*Supplementary experiment*

To clarify the effect of centrifugal modulation in detail, we performed a supplementary study. We recorded LEPs from eight subjects following noxious stimulation of the left hand dorsum, and three conditions were used. Condition 1 was Control. In condition 2 (Right Hand), the subjects extended the right index finger as quickly as possible after the S2 noxious stimuli. In condition 3 (Left Foot), the subjects were asked to perform ankle dorsiflexion of the left foot. Six sessions were conducted for each condition, and consequently 30 stimuli for each condition were applied. EEGs were recorded at Fz, Cz, Pz, C3, and C4, and all EEG signals were collected on a signal processor (Neuropack MEB-2200 system, Nihon-Kohden, Tokyo, Japan). The analysis epoch was 1000 ms, including a prestimulus baseline period of 100 ms, the bandpass filter was set at 0.1–50 Hz, and the sampling rate was 1000 Hz. To judge whether subjects responded to noxious S2

Please cite this article as: Nakata, H., et al., Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement. NeuroImage (2009), doi:10.1016/j.neuroimage.2008.11.026

stimuli precisely, an electromyogram (EMG) was also recorded from a pair of electrodes about 3 cm apart on the skin overlying the contraction muscle in the right forearm (Condition 2) and left anterior tibial muscle (Condition 3). The procedure for data analysis was the same as the main experiment.

## Results

### *Behavioral and EEG data*

The mean reaction time (RT) in Movement was 472 ms (standard error: SE 39 ms).

Fig. 1 displays the grand-averaged LEP waveforms in each condition across all subjects. Clear N2 and P2 components were recorded in all conditions after noxious stimulation. Judging from the morphology, the peak amplitude of N2 was smaller in Movement than Control and Count. This notion was supported by results of ANOVAs.

The ANOVAs for the amplitude of N2 revealed a significant main effect of Condition ($F(2, 18)=6.092$, $p<0.01$). The Tukey HSD post hoc test indicated that the amplitudes were significantly smaller in Movement than Control at Cz, Pz, C3 and C4 ($p<0.05$, $p<0.01$, $p<0.01$, and $p<0.01$, respectively) (Fig. 2A). These results suggest that voluntary movement in a preparatory period reduces the peak amplitude of the N2 component. There was also a significant main effect of Electrode ($F(4, 36)=9.030$, $p<0.01$, $\varepsilon=0.542$), and post hoc testing with collapsing Condition revealed that the amplitude of Cz was significantly larger than that of Fz, Pz, C3, and C4 ($p<0.05$, $p<0.001$, $p<0.01$, and $p<0.01$, respectively).

With regard to the peak amplitude of P2, there was a significant effect of Condition–Electrode interaction ($F(8, 72)=4.056$, $p<0.05$, $\varepsilon=0.410$), and a main effect of Electrode ($F(4, 36)=17.271$, $p<0.001$, $\varepsilon=0.483$). A post hoc test with collapsing Condition indicated that the amplitude of Cz was significantly larger than that of Fz, C3, and C4 ($p<0.001$, respectively), and the amplitude of Pz was also significantly larger than that of Fz, C3, and C4 ($p<0.001$, $p<0.01$, and $p<0.01$, respectively). In Fig. 2B, the post hoc test did not reach the significant level for differences between conditions per electrode, although the average value was smaller in Movement than Control at Cz ($p>0.05$).

The ANOVAs for the peak-to-peak amplitude of N2–P2 confirmed a significant effect of Condition–Electrode interaction ($F(8, 72)=3.704$, $p<0.05$, $\varepsilon=0.574$), and main effects of Condition ($F(2, 18)=3.818$,

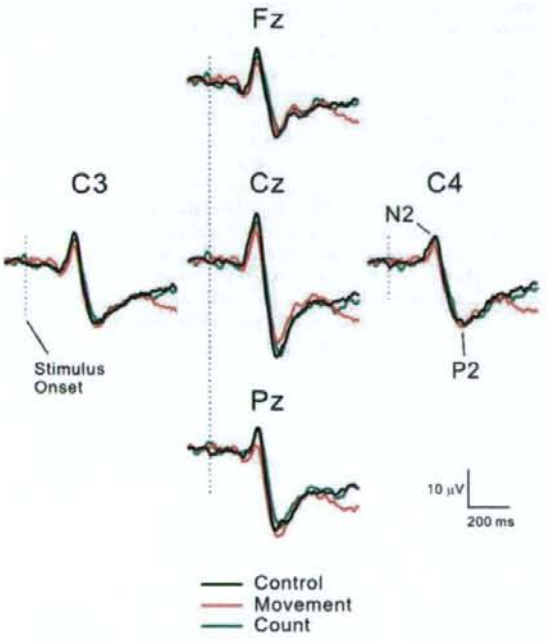


**Fig. 1.** Grand-averaged laser-evoked potentials (LEPs) in each condition following noxious YAG laser stimulation applied to the dorsum of the left hand. Clear N2 and P2 components were recorded in all conditions. Black, red, and green lines indicate waveforms of Control, Movement, and Count, respectively. The vertical line indicates the stimulus onset.

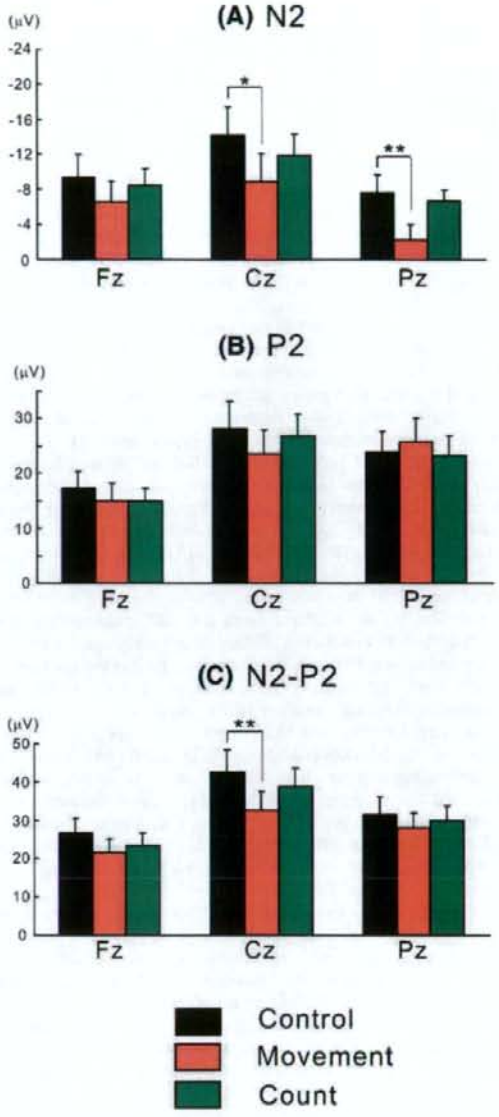


**Fig. 2.** Mean values of N2, P2, and N2–P2 amplitudes at the midline electrode, Fz, Cz, and Pz. A post hoc test indicated that the N2 amplitude at Cz and Pz was significantly smaller in Movement than Control ($p<0.05$, and $p<0.01$, respectively). The peak-to-peak amplitude of N2–P2 at Cz was significantly smaller in Movement than Control ($p<0.01$). Vertical lines indicate standard errors (S.E.). *$p<0.05$, **$p<0.01$.

Please cite this article as: Nakata, H., et al., Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement, NeuroImage (2009), doi:10.1016/j.neuroimage.2008.11.026

**Table 1**
Mean peak latency of N2 and P2 components for each condition with S.E.

| | Fz | Cz | Pz | C3 | C4 |
|---|---|---|---|---|---|
| N2 | | | | | |
| Control | 222.7 (4.9) | 211.9 (6.0) | 217.7 (7.3) | 220.6 (3.9) | 211.6 (6.8) |
| Movement | 229.2 (4.9) | 218.1 (6.0) | 216.4 (7.3) | 220.0 (3.9) | 212.3 (6.8) |
| Count | 230.9 (6.2) | 220.4 (4.1) | 224.1 (4.4) | 227.3 (4.0) | 222.9 (4.5) |
| P2 | | | | | |
| Control | 313.4 (6.3) | 312.1 (5.4) | 312.6 (6.3) | 311.2 (7.4) | 326.9 (9.2) |
| Movement | 313.6 (7.5) | 313.5 (4.1) | 314.2 (6.3) | 313.9 (5.6) | 322.2 (9.9) |
| Count | 323.1 (5.9) | 316.5 (6.6) | 321.4 (6.9) | 319.2 (7.7) | 333.2 (12.0) |

$p<0.05$) and Electrode ($F(4, 36)=18.138$, $p<0.001$). Post hoc testing showed that the amplitude was significantly smaller in Movement than Control at Cz, and C3 ($p<0.01$, $p<0.05$, respectively) (Fig. 2C). A post hoc test with collapsing Condition indicated that the amplitude of Cz was significantly larger than that of Fz, Pz, C3, and C4 ($p<0.001$, $p<0.01$, $p<0.001$, and $p<0.001$, respectively), and the amplitude of Pz was also significantly larger than that of Fz ($p<0.05$).

ANOVAs for the peak latency of N2 indicated a significant effect of Electrode ($F(4, 36)=7.189$, $p<0.001$), and post hoc testing with collapsing Condition demonstrated that the N2 latency was significantly later at Fz than Cz, Pz, and C4 ($p<0.01$, $p<0.05$, and $p<0.001$, respectively). There were no significant main effect and interaction for the P2 latency. Group averages of peak latencies across all subjects are listed in Table 1, and mean and earliest RTs for individual subjects are shown in Table 2.

*MEG data*

Fig. 3A shows the group averages of LEFs across all subjects in the Control condition. A clear and consistent component was recorded in three cortical areas, A, B and C. Fig. 3B shows the isocontour maps in this period in three representative subjects. Just like the grand-averaged LEFs, these isocontour maps revealed distinct neural responses in regions A, B, and C. By ECD analysis, A was estimated to lie between the posterior wall of the central sulcus and superior end of the postcentral fissure contralateral to the stimulation, corresponding to SI or posterior parietal cortex (PPC), and B and C were estimated to be located in the upper bank of the Sylvian fissure, corresponding to SII, in the right and left hemisphere, respectively (Fig. 4). Therefore, we termed them, SI/PPC, cSII (contralateral SII) and iSII (ipsilateral SII). In the Control and Count conditions, these three dipoles were estimated in all subjects, but in Movement, a dipole from SI/PPC could not be estimated in one subject. Their $x$, $y$ and $z$ coordinates and peak latencies are shown in Tables 3 and 4.

Fig. 5A shows the sensor layout of the MEG to calculate the RMS from the left and right hemispheres. The mean values of RMS peak latency from both hemispheres were recorded between 160–190 ms

**Table 2**
Mean and earliest reaction times, and peak latencies of N2 and P2 at Cz in the Movement condition for individual subjects (ms)

| Subject | Mean RT | Earliest RT | N2 peak latency | P2 peak latency |
|---|---|---|---|---|
| A | 663 | 317 | 223.4 | 304.0 |
| B | 390 | 238 | 227.2 | 312.7 |
| C | 486 | 354 | 217.3 | 338.1 |
| D | 351 | 233 | 242.2 | 309.2 |
| E | 617 | 286 | 219.1 | 318.5 |
| F | 496 | 313 | 203.8 | 312.8 |
| G | 505 | 264 | 233.1 | 300.0 |
| H | 555 | 333 | 209.0 | 293.6 |
| I | 269 | 231 | 206.7 | 322.5 |
| J | 383 | 229 | 199.6 | 323.7 |
| Mean | 472 | 280 | 218.1 | 313.5 |
| SE | 39 | 15 | 4.3 | 4.1 |

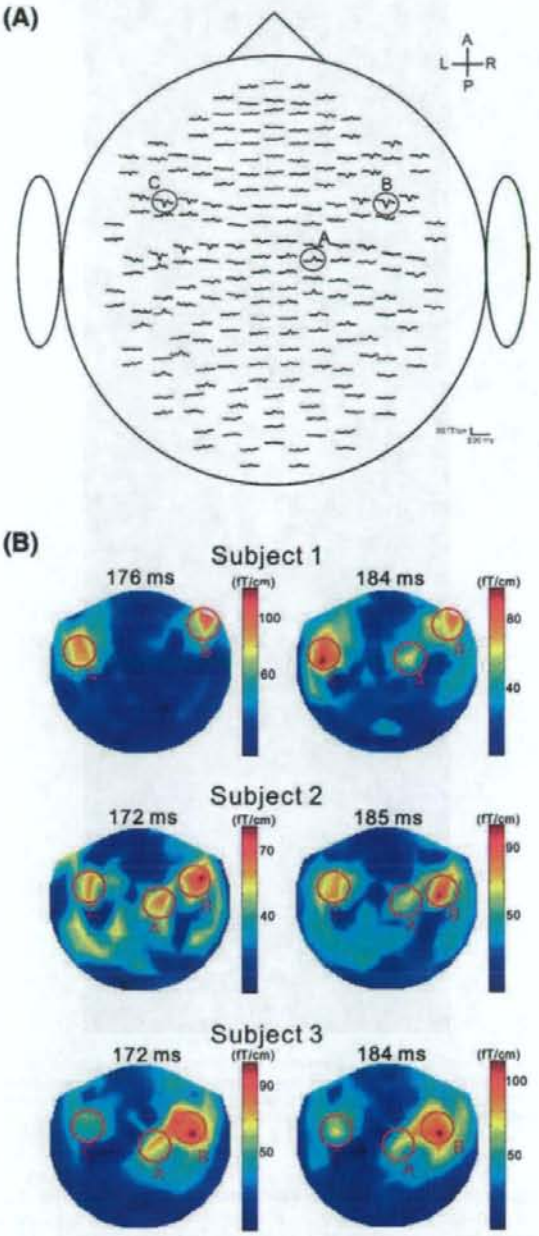


**Fig. 3.** (A) Grand-averaged laser-evoked magnetic fields (LEFs) over 204 planar coils in Control. The head is viewed from the top, and in each response pair, the upper trace illustrates the field derivate along the latitude and the lower trace that along the longitude. All data were digitally filtered (0.1–40 Hz bandpass) for display purposes. (B) The isocontour maps for Control at several time points in three representative subjects.

in each condition, which were clearly earlier than those of N2 component from Cz on EEG (Fig. 5B and Table 1). This result indicated that the MEG and EEG recorded different neural activities at different time period. ANOVA for RMS peak amplitude revealed no significant main effect of Condition and interaction, showing that there were no

Please cite this article as: Nakata, H., et al., Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement, NeuroImage (2009), doi:10.1016/j.neuroimage.2008.11.026

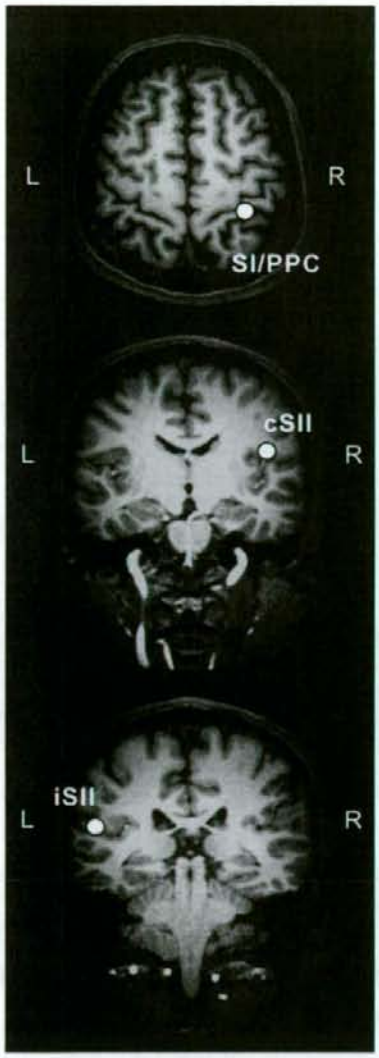


**Fig. 4.** Location of ECDs superimposed on a 2D MRI scan in a representative subject. L = left, R = right, SI = primary somatosensory cortex, PPC = posterior parietal cortex, cSII = secondary somatosensory cortex contralateral to the stimulation, iSII = secondary somatosensory cortex ipsilateral to the stimulation.

significant differences of amplitudes among the three conditions (Fig. 5B and Table 5). ANOVA for RMS peak latency demonstrated a significant main effect of Hemisphere ($F(1, 9) = 13.848$, $p < 0.01$), indicating that the peak latency was earlier in the right hemisphere than the left hemisphere. There were no effect of Condition and interaction for the latency.

Then, we calculated AMS in the regions of interest for all conditions (Fig. 6A). ANOVA for the peak amplitude of AMS revealed a significant main effect of Area ($F(2, 18) = 8.959$, $p < 0.01$), but there were no significant main effects of Condition and interaction (Fig. 6B and Table 5). Post hoc testing with collapsing Condition revealed that SI/PPC was significantly smaller than cSII and iSII ($p < 0.01$, respectively), but there was no significant difference between cSII and iSII. As for peak latency, there was a significant main effect of Area ($F(2, 18) = 7.740$, $p < 0.01$), and post hoc analysis showed that cSII was significantly earlier than SI/PPC ($p < 0.05$).

**Table 3**
Mean Talairach coordinates of the sources with S.E. for each condition

| | | x (mm) | y (mm) | z (mm) |
|---|---|---|---|---|
| Control | SI/PPC | 22.1 (4.4) | −35.9 (1.9) | 53.2 (1.7) |
| | cSII | 47.8 (1.1) | −8.4 (1.1) | 15.8 (1.1) |
| | iSII | −48.7 (0.9) | −14.3 (2.0) | 17.8 (1.3) |
| Movement | SI/PPC | 21.8 (3.3) | −36.2 (2.8) | 56.8 (1.0) |
| | cSII | 49.0 (1.2) | −8.4 (1.2) | 16.0 (1.0) |
| | iSII | −48.9 (1.0) | −13.1 (2.7) | 14.8 (1.1) |
| Count | SI/PPC | 22.4 (2.5) | −35.5 (1.9) | 55.3 (1.8) |
| | cSII | 48.6 (0.9) | −8.9 (2.6) | 16.5 (1.4) |
| | iSII | −50.6 (1.3) | −12.7 (2.1) | 15.7 (1.3) |

There were no significant differences among the conditions. Data are expressed as the mean (S.E.). SI = primary somatosensory cortex, PPC = posterior parietal cortex, cSII = secondary somatosensory cortex contralateral to the stimulation, iSII = secondary somatosensory cortex ipsilateral to the stimulation.

With two-way ANOVAs concerning Condition (Control, Movement, Count) and Source (SI/PPC, cSII, iSII), a significant main effect of Source was found for dipole strength ($F(2, 16) = 15.401$, $p < 0.001$). There was no significant main effect of Condition and Condition–Source interaction, suggesting that ECD strengths were not changed among conditions. This notion was supported by Fig. 7, showing similar ECDs of SI/PPC, cSII and iSII activities. Post hoc testing with collapsing Condition revealed that SI/PPC was significantly smaller than cSII and iSII ($p < 0.001$, respectively), but there was no significant difference between cSII and iSII. In addition, there was a significant main effect of Source on the peak latency of ECD ($F(2, 16) = 9.078$, $p < 0.05$, $\varepsilon = 0.552$). Post hoc analysis demonstrated that cSII was significantly earlier than SI/PPC and iSII ($p < 0.001$, and $p < 0.05$, respectively) (Table 4).

A one-way ANOVA revealed no significant effects on the *x*, *y* and *z* coordinates of ECDs. That is, the source locations of ECDs in SI/PPC, cSII, and iSII did not differ significantly among the conditions (Table 3).

The results of ANOVAs for the peak amplitudes of N2 and P2, RMS, AMS, and ECD strengths are listed in Table 5.

Based on N2 component data, we re-analyzed the ECD around 170–250 ms after noxious stimulation using all 306 channels of MEG to investigate which brain regions were responsible for generator mechanisms of N2. First, we calculated the AMS of five gradiometer pairs (Fig. 8A), showing that peaks were found around 160–230 ms (Fig. 8B). The morphology of the waveforms was clearly different from the results of other areas, which are shown in Fig. 6. Then, we determined the peak amplitude and latency in each condition, and performed one-way ANOVA to investigate differences among the three conditions. ANOVA for the amplitude demonstrated a significant main effect ($F(2, 18) = 3.557$, $p < 0.05$), and post hoc testing revealed that the amplitude was significantly smaller in Movement than Control (Fig. 8C). There was no significant difference in peak latency among conditions. The mean values of the peak latency were 197.4 ms (SE ± 4.8), 198.6 ms (±6.5), and 207.9 ms (±4.4) in the Control, Movement, and Count conditions, respectively.

The ECD for this area was estimated to be located on the anterior cingulate cortex (ACC) from the six, five, and five subjects in the

**Table 4**
Mean peak latencies of the sources with S.E. for each condition

| | SI/PPC | cSII | iSII |
|---|---|---|---|
| Control | 185.0 (5.3) | 169.5 (5.0) | 179.7 (4.3) |
| Movement | 181.8 (5.1) | 164.7 (4.9) | 175.5 (4.0) |
| Count | 185.0 (4.7) | 162.4 (3.3) | 176.2 (4.3) |

There was a significant main effect of Source ($F(2, 16) = 9.078$, $p < 0.05$, $\varepsilon = 0.552$), and post hoc analysis demonstrated that cSII occurred significantly earlier than SI/PPC and iSII ($p < 0.001$, and $p < 0.05$, respectively).

Please cite this article as: Nakata, H., et al., Centrifugal modulation of human LEP components to a task-relevant noxious stimulation triggering voluntary movement, NeuroImage (2009), doi:10.1016/j.neuroimage.2008.11.026