Fig.3 Three dimensional high density grid electrodes.
A: high density electrodes (upper) and standard electrodes (lower), B, C: brain surface electrodes conformable to individual brain surface, D, E: intrasulcal electrodes, F: automatic sulcal detection and mold design on 3D CAD.

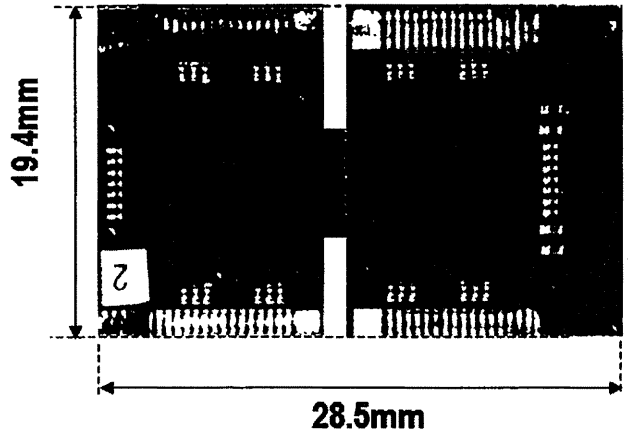

Fig.4 A multichannel amplifier board with 2 sets of a 64 channel amplifier (3×2 cm).

年間にわたり安定して計測できることが示されている[1]。脳溝内に挿入する場合には両面に電極を配置できる（Fig.3）。

マルチチャンネル集積化アンプ

計測した皮質脳波はノイズ混入を防ぐため，すぐに増幅・デジタル化する必要がある。そこで頭部の狭小なスペースに留置できるよう皮質脳波を増幅するアナログアンプを集積化した。1チップあたり64 chを有し，各chは1 kHzでのサンプリングが可能であり，ADコンバーターは12 bit，チップサイズは5×5 mm，消費電力は4.9 mWである[11,12]。東京大学VDECのCMOS 0.18 umプロセスにて製造した。これを2チップ計128 chとして30×20×2.5 mm大の小型基板上に実装する（Fig.4）。この集積化アンプ実装基板は人工骨兼用頭部ケーシングに収納される。

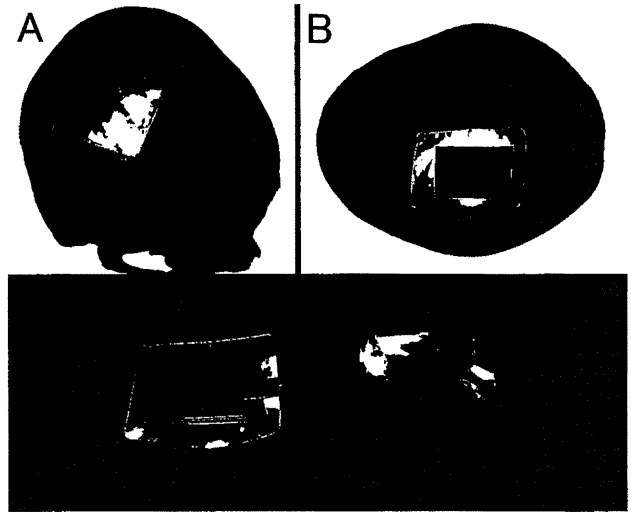

Fig.5 A titanium head casing / artificial skull bone.
A, B: Head casing designed using 3D CAD software. Three dimensional skull bone data were obtained from individual's CT images. A: Outer side view. B: Inner side view. The head casing contains two 64-channel integrated amplifier chips on a small mounting board which are mounted on a folded inner panel as indicated in a gray color. C: A prototype casing. Left: inner side view. Right: outer side view.

人工頭蓋骨兼用頭部ケーシング

頭部ケーシングは，集積化アンプを収容し，開頭部の人工頭蓋骨を兼ねるものを考案した[5,14]。Thin slice bone window CT画像から3次元CAD（3 matic, Materialize Japan, Tokyo）上で，開頭範囲，人工頭蓋

骨の形状，電子回路のレイアウト設計を行い，3次元CAM（Gibbs CAM, Gibbs and Associates, USA）で切削パスを作成し，迅速製造する（Fig.5）。患者CT画像から骨データを抽出して作成し，人工頭蓋骨を兼ねるため埋込による皮膚膨隆がなく，整容学的に優れ，瘻孔形成等のリスクも低い。開頭は頭部ケーシングに合わせて正確に開頭する必要があるため，頭部ケーシングの位置形状データをナビゲーションにあらかじめレジストレーションしておき，ナビゲーションガイド下に開頭を行う。

ワイヤレスデータ通信

体外への皮質脳波の伝送には，Bluetoothプロトコル（Class 2）を用いたワイヤレスデジタル通信を採用し，信頼性を確保している。Bluetooth回路を2ヶ使用することにより400 kbpsのデータ通信速度を確保し，ECoG信号を12 bit×128 chで体外のコンピュータに送信する。しかし，現状では消費電力は300 mWと大きく，埋込装置の消費電力の大半を占める。サイズも現状では60×60×8 mmと大きい。ワイヤレス通信に関しては今後，さらに高速化，小型化，低電力化が必要であり，その解決方法として，ワイヤレスLANやUWBの導入が考えられる。

非接触充電電源

大量の信号計測，データ通信に必要な電力を確保するため本システムでは非接触給電機能を持たせた。体外の送電回路と体内の受電回路からなる。コイル誘導起電方式により，直径40 mmのコイルを用いて，皮下4 cmで4Wと大きな給電能力を持つ。

フッ素ポリマー樹脂腹部ケーシング

ワイヤレス通信回路と非接触充電電源はシリコーンで包埋し，さらにこれをフッ素ポリマー樹脂でパッケージングし，腹部装置を構成する。腹部装置は腹部皮下に留置する。フッ素ポリマー樹脂ケーシングは耐腐食性，生体適合性が高いだけでなく，従来のチタンケーシングに比較してコスト低減も期待できる。

知財戦略とインフラ整備

知財戦略は企業が市場化を行う際に重要であるだけでなく，自らの開発戦略を守りスムーズに進め，さらには日本の科学技術戦略のためにも重要である。そこで我々は開発における発明要素を可能な限り特許出願・取得に結び付けるよう努力しており，これまでにBMI関係の特許出願を国内・国際合わせて6件行い[4,5,7,14,15,16]，うち1件を特許取得した[6]。

また一般的に埋込医療機器開発は欧米に対して大きく遅れており，本邦の研究機関・企業・審査機関は埋込医療機器の臨床応用・実用化に関する経験に乏しい。こうした状況を少しでも改善すべく，厚生労働省の次世代医療機器評価指標作成事業にて神経機能修復装置に関する評価指標を作成した[13]。こうしたガイドラインの整備は，企業の開発目標レベルの設定の明確化や将来の薬事承認審査の迅速化につながるものと期待される。

今後の展望

今後は，本プロトタイプを動物埋込用に改造し，動物実験を開始するとともに，3〜4年後を目処にALS患者等の重症身体障害者に対する臨床試験を目指す。

謝辞

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Development of a fully-implantable wireless device for motor and communication control by electrocorticographic brain-machine interface

Masayuki Hirata[1] / Kojiro Matsushita[1] / Morris Shayne[1] / Tetsu Goto[1] / Takufumi Yanagisawa[1] Takafumi Suzuki[2] / Tsuyoshi Yoshida[3] / Fumihiro Sato[4] / Youichi Saitoh[1] / Haruhiko Kishima[1] Yu Kageyama[1] / Mitsuo Kawato[5] / Toshiki Yoshimine[1]

[1] Department of Neurosurgery, Osaka University Medical School
[2] Graduate School of Information Science and Technology, The University of Tokyo
[3] The Graduate School of Advanced Sciences of Matter, Hiroshima University
[4] Graduate School of Biomedical Engineering, Tohoku University
[5] ATR Computational Neuroscience Laboratories

Abstract: The brain-machine interface (BMI) is a new method for man-machine interface, which enables us to control machines and to communicate with others, without input devices but directly using brain signals. Previously, we successfully developed a real time control system for operating a robot arm using electrocorticographic (ECoG) BMI, with the purpose of restoring motor and communication functions in severely disabled people such as amyotrophic lateral sclerosis patients.

A fully-implantable wireless system is indispensable for the clinical application of invasive BMI in order to reduce the risk of infection. This system includes many new technologies such as two 64-channel integrated analog amplifier chips, a Bluetooth wireless data transfer circuit, a wirelessly rechargeable battery, 3 dimensional tissue-fitting high density electrodes, a titanium head casing, and a fluorine polymer body casing.

Next, we aim a clinical trial of the fully-implantable wireless device after animal experiments.

Keywords: Brain machine interface; Implant; Functional restoration

受付：2011年10月7日

麻痺患者における感覚運動野皮質脳波の変化とBMIへの応用

柳澤 琢史[1,2,4]／平田 雅之[1]／齋藤 洋一[1]／貴島 晴彦[1]／後藤 哲[1]
福間 良平[2]／横井 浩史[3]／神谷 之康[2]／吉峰 俊樹[1]

抄　録：【はじめに】皮質脳波を用いたBMIは麻痺患者や切断肢患者の運動機能再建技術としての応用が示されている。しかし，遠心路遮断後の大脳皮質再構築により麻痺患者の皮質脳波がどのように変化するかは明らかでない。我々は麻痺患者の皮質脳波を用いて，患者の運動もしくは運動意図を推定し，その推定精度を比較することで，大脳皮質再構築後の変化を定量的に検討した。

【方法】感覚運動野に硬膜下電極を留置された難治性疼痛患者7名（脳卒中：4，腕神経叢引き抜き損傷：2，幻視痛：1）およびてんかん患者6名を対象とした。患者が離握手等の運動を施行もしくは想起する際の皮質脳波を計測し時間周波数解析によって運動時の特徴を比較した。また運動に特徴的な周波数帯域のパワーを用いて運動内容の推定を行った。

【結果】麻痺の有無にかかわらず，運動時に特徴的なγ帯域のパワー増加とα・β帯域のパワー減少を認めた。これらの脳表分布は運動種類に応じて統計的に有意な変化を示した。これを用いて，麻痺患者でも，3種類の運動が最大90％以上の精度で推定された。しかし，完全麻痺患者では推定精度に個人差が大きく，麻痺肢の運動をイメージできない患者では推定精度も著しく低下した。

【結論】大脳皮質再構築後でも運動に伴った皮質活動は定性的に保たれるが，定量的には個体差が大きいことが明らかになった。特に，運動イメージと皮質脳波の変化との間に関係性が示唆された。

索引用語：脳・マシーン連結；ロボットハンド；神経義手；皮質脳波；運動機能補填

[1] 大阪大学大学院医学系研究科　脳神経外科学教室
〔〒565-0871 大阪府吹田市山田丘2-2 / Tel.06-6879-3652 / Fax.06-6879-3659〕
[2] ATR脳情報研究所
[3] 東京大学大学院情報学環
[4] 医誠会病院　脳神経外科

機能的脳神経外科 50(2011)124-128

はじめに

運動制御に関わる神経活動の詳細が明らかになるにつれ，BMIによる運動機能再建の可能性は高まってきた。2000年，Nicolelisらはサルの一次運動野のニューロン活動から2次元の画面上でカーソル制御を行わせることに成功した[19]。さらに2008年にはSchwartzらが同様のシステムを用いて，サルが「考えるだけで」ロボットアームを操作し，任意の場所にある餌を自力摂取させることに成功している[18]。また，Donoghueらはこの技術を頸髄損傷による四肢麻痺患者に臨床応用し，コンピュータのカーソル操作や簡単な義手制御を行わせることに成功している[8]。

これらの成果は微小な針電極を脳に刺入し神経細胞活動を記録・解析することで達成された。しかし，刺入電極は脳への侵襲性が大きく，長期留置による瘢痕形成などで信号が劣化するなどの問題があり臨

Table 1 Clinical profiles

No.	Age / Sex	Diagnosis	Duration of disease (yr)	Paresis on affected limb (MMT)
N1	34 / F	R intractable epilepsy	19	none
N2	14 / M	R intractable epilepsy	7	none
N3	20 / F	R intractable epilepsy	6	none
N4	22 / F	R intractable epilepsy	10	none
N5	33 / M	R intractable epilepsy	33	none
N6	13 / M	L intractable epilepsy	11	none
P1	49 / M	R putaminal hemorrhage	2	slightly spastic (5–)
P2	66 / F	R subcortical infarction	3.3	spastic (4)
P3	64 / M	R thalamic hemorrhage	7	spastic (4)
P4	65 / M	ruputured spinal dAVF	8	spastic (4)
C1	31 / M	L brachial plexus avulsion	5	complete (0) (except biceps 3*)
C2	49 / M	L brachial plexus avulsion	6	severe (1) (except biceps 4–*)
C3	47 / M	No limb (amputation) phantom limb pain	3.3	hard to image movement of the phantom limb

Abbreviations: MMT, manual muscle test; dAVF, dural arteriovenous fistula
*post transplantation of intercostal nerve

床応用への障壁となっている[11]。そこで，脳への侵襲が比較的少なく，信号安定性に優れている皮質脳波（electrocorticogram, ECoG）が注目されるようになった[11]。皮質脳波は各電極から得られる情報量で刺入電極に劣るが，刺入電極よりも広い範囲の脳活動を一度に計測することができる上，信号が1年以上にわたって安定して計測できることが示されている[2]。また，てんかん患者を用いた研究では，皮質脳波からリアルタイムに脳情報を読み出し外部機器を制御できることが示されている[13,17]。皮質脳波は臨床応用可能なBMI信号の一つと言える。

一方，てんかん患者のように運動障害がない患者で得られた皮質脳波に関する知見が，実際にBMIを必要とする重度運動機能障害患者についても同様に適応できるかどうかは明らかでない。実際，脊髄損傷[1,7,12]や切断肢[3,15,16]，脳卒中後[5,6,14]などの患者では，感覚運動野に大脳皮質再構築が生じることが知られている。大脳皮質再構築により運動機能[14]や感覚機能，身体の認知[3,4,15]などが変容することも知られている。これらの変化に伴い皮質脳波がどのように変化するか，また大脳皮質再構築後もBMI信号として適応可能であるかは明らかでない。我々は難治性疼痛の治療目的で硬膜下電極を感覚運動野に留置した患者より皮質脳波を計測し，麻痺の程度による皮質脳波への影響を運動情報解読の視点から定量的に検討した。

症例と方法

大阪大学脳神経外科にて硬膜下電極を留置された患者13人（女性4人，男性9人；年齢13歳から66歳）が本臨床研究に参加した（Table 1）。麻痺の程度により患者を3つのグループに分類した。てんかん患者などで運動機能が正常な6人の患者は“運動機能正常群”（N1–N6）。脳卒中などで半身不全麻痺や痙性を伴うが感覚運動野皮質に著明な障害がない4人は“中等度運動機能障害群”（P1–P4）。腕神経叢引き抜き損傷や切断肢などで重度の運動機能障害がある3人は“重度運動機能障害群”（C1–C3）とした。このうち，重度運動機能障害群の3人は麻痺肢の運動をイメージする能力において違いが認められた（Table 2）。各患者は難治性てんかんや難治性疼痛の治療目的で感覚運動野に15〜60極の硬膜下電極（直径3 mm,

Table 2 Summary of the decoding results

Patient no.	imagining movements	% correct
N1		81.6
N2		80.0
N3		74.8
N4		76.7
N5		78.0
N6		76.3
P1		60.0
P2		68.2
P3		65.0
P4		84.2
C1	easy	74.2
C2	slightly difficult	51.3
C3	extremely difficult	49.6

電極間距離 0.7 mm, Unique Medical. Co., Tokyo, Japan) を留置された。本臨床研究は大阪大学医学部付属病院倫理委員会の承認と，参加者全員からの書面を用いた十分なインフォームドコンセントを得て行った。

患者が 3 種類の上肢運動課題(手を握る・開く・つまむなど) を留置した電極の対側上肢で施行した際の皮質脳波を記録した。患者は 4 秒毎に提示される音刺激に合わせて課題を施行した (Fig.1)。各運動は患者が 3 種類から任意に選んで行われ，それぞれ 20〜40 回程度施行された。また，重度運動機能障害群においては 3 種類の運動から 1 つずつ選んで患者に示し，指示された運動を施行するつもりで想起させた。皮質脳波は臨床用のデジタル脳波計 (EEG 2000; Nihon Koden Co., Tokyo, Japan) で計測された。

皮質脳波から運動内容を推定する方法として線形の support vector machine (SVM) を用いた[9,10,20]。運動開始の音より 1 秒間の皮質脳波より γ 帯域の平均パワーを全電極について求めた。施行された運動種類と γ パワーの分布を用いて SVM が学習を行い，新たな皮質脳波に対して SVM が運動種類を推定した。

結　果

各グループの代表的な皮質脳波を Fig.2 に示す。患者が手を握るもしくは握るイメージを行っている際の皮質脳波を時間周波数解析すると，全ての患者で運動開始直後に 80 から 150 Hz の γ 帯域のパワーが増加し，30 Hz 以下の α, β 帯域のパワーが減少する特徴が認められた。このような特徴は完全麻痺患者が運動をイメージする場合でも認められた。

運動種類の情報を最も反映するとされる γ 帯域のパワーに含まれる運動情報量を比較するために，SVM を用いた decoding 解析を行った。つまり，皮質脳波の γ 帯域パワーを用いて施行 (想起) した運動種類を推定し，推定結果が実際に施行 (想起) された運動と一致している確率を比較することで，皮質脳

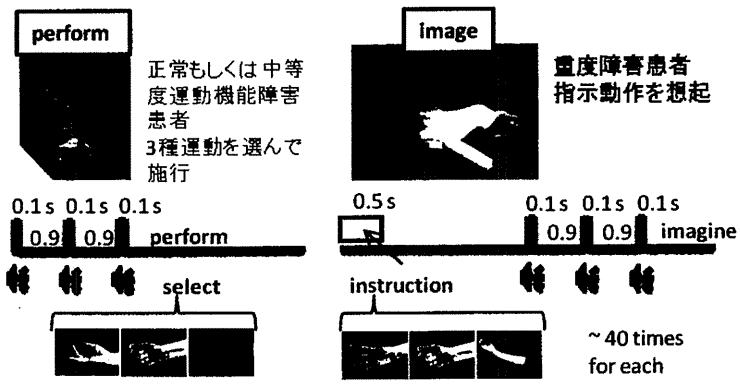

Fig.1 Task paradigm.

In the execute task, patients selected and executed 1 of 3 movements after the sound cue. The cue consisted of 3 beeps 1 second apart that recurred every 5.5 seconds. The movements were performed with the arm contralateral to the implanted electrodes. In the attempt task, patients were instructed which of the 3 movements to attempt.

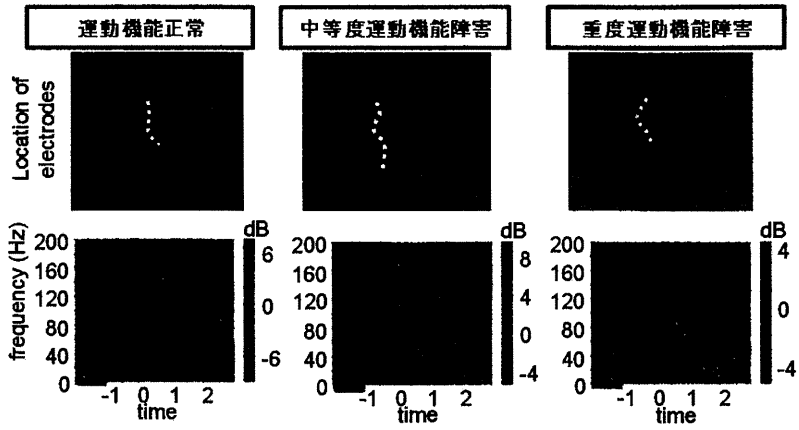

Fig.2 Representative results of time-frequency analysis.

Upper panel: Locations of implanted electrodes for patients N1, P4, and C2 are indicated by the green (implanted on the brain surface) and red (implanted within the central sulcus) filled circles on the 3-dimensional brain renderings of MRI volumes. The dashed white line indicates the location of the central sulcus. Only the electrodes used for the analysis are shown. Lower panel: Power spectra of the ECoG signals recorded during grasping (execute) or attempt to grasp from the electrodes on the primary motor cortex indicated by the orange arrows. The black horizontal bars show the 1000-millisecond period used for normalization. Time 0 corresponds to the onset cue.

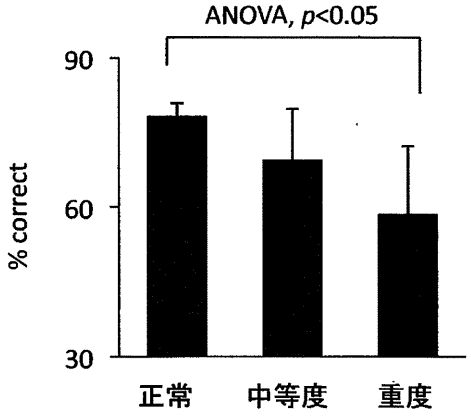

Fig.3 Averaged classification accuracy with gamma band power.

Classification accuracies with gamma band power were averaged for the patients of each group.

波に含まれる運動情報の量を比較した。

γ帯域パワーを用いた運動推定の結果を Table 2 に示す。全ての患者で偶然の一致よりも有意に高い確率で運動推定が可能であった。その推定精度は麻痺がない患者で最も高く，完全麻痺患者では有意に低下していた（Fig.3）。特に，完全麻痺患者3名について，その内訳を詳細に検討すると，完全麻痺でも麻痺した上肢の運動をイメージできる患者では推定精度が高く，イメージができない患者では推定精度が低い傾向が見られた。

まとめと今後の展望

本研究では，世界で初めて麻痺患者の皮質脳波を定量的に解析した。BMI の適応患者である重度運動機能障害患者でも，γ帯域のパワーなど，これまで運動機能障害がない患者で詳細に調べられている皮質脳波の特徴が保存されていることが明らかになった。また，運動機能障害患者でも皮質脳波だけから運動意図を推定できることが示された。しかし，運動イメージができなくなった患者では皮質脳波による運動推定も困難になることが示された。今後，このような患者に BMI を適応する場合，運動イメージを改善する何らかのリハビリテーションが必要になると考える。

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Degeneration of ECoG signals in sensorimotor cortex of paralyzed patients

Takufumi Yanagisawa[1,2] / Masayuki Hirata[1] / Youichi Saitoh[1] / Haruhiko Kishima[1] / Tetsu Goto[1] Ryohei Fukuma[2] / Hiroshi Yokoi[3] / Yukiyasu Kamitani[2] / Toshiki Yoshimine[1]

[1] Department of Neurosurgery, Osaka University Medical School
[2] ATR Computational Neuroscience Laboratories
[3] The University of Tokyo Interfaculty Initiative in Information Studies Graduate School of Interdisciplinary Information Studies

Abstract: *Objective:* Paralyzed patients may benefit from restoration of movement afforded by prosthetics controlled by electrocorticography (ECoG). Although ECoG shows promising results in human volunteers, it is unclear whether ECoG signals recorded from chronically paralyzed patients provide sufficient motor information.
Methods: We recorded ECoG signals from sensorimotor cortices of 12 patients while they executed or attempted to execute 3 simple hand movements. Sensorimotor function was severely impaired in 3 patients due to peripheral nervous system lesion or amputation, moderately impaired due to central nervous system lesions sparing the cortex in 4 patients, and normal in 5 patients. Time-frequency and decoding analyses were performed with the patients' ECoG signals.
Results: In all patients, the high gamma power (80 – 150 Hz) of the ECoG signals during movements was clearly responsive to movement types. The classification performance was significantly better than chance in all patients even though differences between ECoG power modulations during different movement types were significantly less in patients with severely impaired motor function.
Interpretation: ECoG signals appear useful for prosthetic arm control and may provide clinically feasible motor restoration for patients with paralysis but no injury of the sensorimotor cortex.

Key words: Brain-machine interface; Robot hand; Neural prosthesis; Electrocorticogram; Motor restoration

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Subthalamic nucleus stimulation for attenuation of pain related to Parkinson disease

Clinical article

Hideki Oshima, M.D., Ph.D.,[1,3,4] Yoichi Katayama, M.D., Ph.D.,[1,4] Takashi Morishita, M.D., Ph.D.,[1] Koichiro Sumi, M.D., Ph.D.,[1] Toshiharu Otaka, M.D., Ph.D.,[1] Kazutaka Kobayashi, M.D., Ph.D.,[1] Yutaka Suzuki, M.D., Ph.D.,[2] Chikashi Fukaya, M.D., Ph.D.,[4] and Takamitsu Yamamoto, M.D., Ph.D.[4]

Departments of [1]Neurological Surgery, [2]Neurology, and [3]Functional Morphology, and [4]Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine, Tokyo, Japan

Object. The objective of this study was to evaluate the efficacy of chronic subthalamic nucleus (STN) stimulation for alleviating pain related to Parkinson disease (PD).

Methods. Among 163 consecutive patients undergoing STN stimulation, 69 were identified as experiencing pain preoperatively that was related to their PD. All 69 patients suffering from pain were followed up prospectively for 12 months after surgery. All patients described the severity of their pain according to a visual analog scale (VAS) preoperatively and at 2 weeks, 6 months, and 12 months postoperatively. Pain unrelated to PD was not studied.

Results. Several types of pain related to PD, the categories of which were based on a modification of 2 previous classifications (Ford and Honey), can occur in such patients: 1) musculoskeletal pain, 2) dystonic pain, 3) somatic pain exacerbated by PD, 4) radicular/peripheral neuropathic pain, and 5) central pain. The overall mean VAS score was significantly decreased postoperatively by 75% and 69% at 2 weeks and 6 months, respectively ($p < 0.001$). The mean VAS score at 12 months was also decreased by 80%, but 6 instances of pain (3 reports of somatic back pain and 3 reports of radicular/peripheral neuropathic pain) required additional spinal surgery to alleviate the pain severity. The results were analyzed using the Wilcoxon signed-rank test and demonstrated a significant reduction in VAS scores at all follow-up assessments ($p < 0.001$). Musculoskeletal pain and dystonic pain were well alleviated by STN stimulation. In contrast, somatic pain exacerbated by PD and peripheral neuropathic pain originating from lumbar spinal diseases, such as spondylosis deformans and/or canal stenosis, often deteriorated postoperatively despite attenuation of the patients' motor disability. Patients with central pain were poor responders.

Conclusions. This study found that STN stimulation produced significant improvement of overall pain related to PD in patients with advanced PD, and the efficacy continued for at least 1 year. The present results indicate that musculoskeletal pain and dystonic pain responded well to STN stimulation, but patients with back pain (somatic pain) and radicular/peripheral neuropathic pain originating from spinal disease have a potential risk for postoperative deterioration of their pain. *(DOI: 10.3171/2011.7.JNS11158)*

Key Words • **subthalamic nucleus** • **brain stimulation** • **Parkinson disease** • **pain** • **functional neurosurgery**

Functional stereotactic surgery is now a well-established procedure for treating the motor symptoms of advanced PD. In particular, DBS of the STN and globus pallidus can greatly attenuate the cardinal motor symptoms and functional disability of PD.[6,9,17,20,22,25] Pain is also a common symptom of patients with PD and often contributes to deterioration in their quality of life.[2,3,10,14,15,19,24,27,28,30,33] The prevalence of patients suffering pain attributable to their PD (PD-related pain) is variable and has been estimated to be between 27% and 65%.[3,15,24,27,33] Several types of PD-related pain have been described and categorized on the basis of their origin, such as musculoskeletal pain, dystonic pain, central pain, radicular/peripheral neuropathic pain, somatic pain exacerbated by PD, and pain related to akathisia.[12,15,16] Whereas many investigators have reported improvements of pain related to levodopa-induced dystonic dyskinesia (dystonic pain) following functional stereotactic surgery of the STN[20,21,25] and globus pallidus,[1,16,23,26] few studies have addressed the effects of functional stereotactic surgery on each type of PD-related pain.[16,18,26,34] Furthermore, there is little information concerning the effects of STN stimulation on such pain, despite the increased popularity of STN-DBS

Abbreviations used in this paper: DBS = deep brain stimulation; PD = Parkinson disease; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analog scale.

surgery. Only Kim et al.[18] have described the effects of STN stimulation on these various types of PD-related pain, although their follow-up period was only 3 months. The aims of the present study were to assess the effects of STN stimulation on PD-related pain and to investigate how this stimulation therapy might affect the various types of PD-related pain.

Methods

Patient Population and Surgical Criteria

Advanced idiopathic PD was diagnosed in all patients who were referred to us by neurologists with an intimate knowledge of the pharmacological treatment of PD. All patients were clearly responsive to levodopa. However, their parkinsonian symptoms could not be controlled sufficiently with clinically optimal pharmacological therapy, and they displayed levodopa-induced side effects, such as on-off motor fluctuations and dyskinesias. Our surgical indication criteria for STN stimulation were as follows: 1) clinically diagnosed advanced idiopathic PD that demonstrated evidence of a good response to levodopa, and 2) a Hoehn and Yahr staging that was within the range of Stages III–V during the off-period and Stage III or less in the best on-condition, despite treatment with optimal pharmacological therapies as described in a previous publication by our group.[17] Patients with major depression or cognitive dysfunction (Mini-Mental State Examination score < 23) were excluded as candidates for surgery. In the present study, 163 consecutive patients with PD, who were candidates for STN stimulation, were interviewed preoperatively.

We defined pain as PD-related pain in cases in which the pain severity changed with motor fluctuations. Pain unrelated to PD was excluded from the analysis. Most of the pain unrelated to PD was joint pain caused by osteoarthritis of the knee joint or back pain caused by spinal spondylosis deformans. Sixty-nine patients were identified as having pain related to their PD. Twenty-three patients had more than one type of pain or multiple pains, so that a total of 94 instances of pain were categorized and investigated (Table 1). The mean patient age ± SD was 63.0 ± 7.8 years, and the mean duration of disease was 11.8 ± 7.7 years. All patients were receiving medication for PD (mean duration 11.0 years). The preoperative mean levodopa and levodopa equivalent daily doses were 671.3 ± 356.1 mg/day and 463.1 ± 224.7 mg/day, respectively.

Clinical Assessments

The PD-related pain was grouped into categories based on a modification of both the Ford[12] and Honey et al.[16] classifications. In our classification, PD-related pains were categorized into 5 groups as follows: 1) musculoskeletal pain, 2) dystonic pain, 3) somatic pain exacerbated by the PD, 4) radicular/peripheral neuropathic pain, and 5) central pain. When the pain presented itself in the body part with higher muscle tone without any dystonic dyskinesias (abnormal posture and/or involuntary movement), this pain was defined as musculoskeletal pain. In contrast, dystonic pain was defined as the pain presented only in association with dystonic dyskinesias. When the musculoskeletal pain was accentuated for a certain period by dystonic dyskinesia, this pain was defined as mixed musculoskeletal and dystonic pain. Somatic pain had a defined apparent origin of pain, such as osteoarthritis or tendonitis, and was indirectly caused by the PD. Since somatic pain (exacerbated by PD) was not categorized in Ford's classification[12] and was included in musculoskeletal pain, we delinked the category of "somatic pain exacerbated by the PD" from this classification following the example of the classification given by Honey et al.[16] Radicular/peripheral neuropathic pain, which had a defined organic origin of pain such as spinal spondylosis and/or spinal canal stenosis, was distinguished from central pain without any obvious somatic cause. According to the definition of central pain by the International Association for the Study of Pain,[31] a high prevalence of central pain can be estimated in patients with PD who invariably have CNS (basal ganglia) dysfunction.[7] In the present pain series, central pain was categorized last. Only 2 instances of pain originating without apparent lesions could be categorized as central pain, because their origin had no other explanation but to be dysfunction of the CNS, and their features resembled the main features of central pain described in the International Association for the Study of Pain classification.[31] In Ford's classification,[12] akathisia was recorded as another type of PD-related pain. We also noted the patients experiencing akathisia and symptoms of restless leg syndrome. However, because they did not complain of pain symptoms, we did not categorize akathisia as a pain subtype in the present study.

Preoperative and postoperative assessments of motor disability were performed using the methods described previously by our group.[17] Briefly, the UPDRS was scored during the on-period and off-period with sustaining antiparkinsonian agents. The levodopa-induced dyskinesias were categorized into 3 groups: off-period, diphasic, and on-period dyskinesia. The dyskinesia severity rating scale was used to evaluate the severity of each case of levodopa-induced dyskinesia, scoring the dyskinesia in 6 body parts (neck, trunk, and each of the 4 extremities) on a 5-point scale (range 0–4, 0 = absent, 4 = severe). The mood of each of the patients was rated using the Hamilton Depression Rating Scale, and cognitive function was assessed using the Mini-Mental State Examination.

Statistical Analysis

Data were collected from the present cohort prospectively. All patients described the severity of their pain using a VAS (range 0–10.0 points) preoperatively and at 2 weeks, 6 months, and 12 months postoperatively. The pain scores on the VAS were then analyzed using the Wilcoxon signed-rank test. Differences between the 3 groups were evaluated using the Kruskal-Wallis test. The correlations between the various parameters were calculated by univariate linear regression analysis and expressed according to the Pearson correlation coefficient. A p value < 0.05 was considered statistically significant.

Results

Overall Pain

The overall pain severity at the preoperative assess-

TABLE 1: Location and number of instances of PD-related pain

Type of Pain	No. of Patients*	Location of Pain						Total Instances of Pain
		Face	Neck	Upper Limb	Abdomen	Back	Lower Limb	
musculoskeletal	30	0	5	4	6	6	18	39
dystonic	17	0	3	1	0	0	17	21
dystonic & musculoskeletal	15	0	3	3	0	0	12	18
somatic	11	0	0	0	0	9	2	11
radicular/peripheral neuropathic	3	0	0	0	0	0	3†	3
central	2	1	0	0	0	1	0	2

* Nine patients had multiple pains.
† Two patients also had buttock pain.

ment and 3 follow-up assessments is summarized in Table 2. The overall mean VAS score was significantly decreased by 75% at 2 weeks postoperatively and by 69% at 6 months postoperatively ($p < 0.001$). The mean VAS score at 12 months was also decreased by 80%, but 3 patients suffering from somatic pain (back pain) with radicular/peripheral neuropathic pain (sciatic pain) required additional spinal surgery to alleviate their pain.

The mean on-period (on-medication, best-on motor condition) and off-period (on-medication, worst-off motor condition) UPDRS Part III scores were reduced by 29% and 51% at 12 months, respectively. The mean levodopa daily dose and levodopa equivalent daily dose were decreased by 47% and 32%, respectively. The mean Hamilton Depression Rating Scale score was significantly decreased, but no correlation was observed between the decrease in score and improvement of pain.

Of the total 94 instances of pain, 39 (41.5%) were categorized as musculoskeletal pains, 21 (22.3%) as dystonic pains, 18 (19.1%) as mixed musculoskeletal and dystonic pains, 11 (11.7%) as somatic pains, 3 (3.2%) as radicular/peripheral neuropathic pains, and 2 (2.1%) as central pains (Table 1).

Musculoskeletal Pain

Thirty patients had musculoskeletal pain in our series. This type of pain was the most frequent in our series. Among the cases, lower limb pain was the most common (Table 1). The locations of pain corresponded well with the locations of severe rigidity and occurred during the off motor condition ("off-pain"). At 2 weeks after bilateral chronic STN stimulation, almost all patients described resolution or marked relief of their pain. At 6 and 12 months postoperatively, this pain relief effect was still evident (Table 2). The patients' motor symptoms, especially rigidity, were markedly improved at 12 months postoperatively. A correlation was noted between the percentage improvement of the UPDRS subscore for rigidity (Item 22) and the VAS score ($r = 0.49$, $p < 0.0001$; Fig. 1) in 23 patients with neck or limb pain (27 instances of pain excluding abdominal wall pain and back pain).

Seven patients had received some type of medication (such as NSAIDs and/or muscle relaxants) before surgery. Four patients stopped taking such drugs early after the surgery, and none of the remaining 3 patients required any additional dose of medicine to alleviate their pain after the surgery.

Dystonic Pain

Seventeen patients experienced pain related to levodopa-induced dyskinesias (21 instances total). All dyskinesias of the limbs with pain included a dystonic component. Most of the dystonic pains were presented during the off period or were diphasic dyskinesias, although 1

TABLE 2: Changes in severity of different types of PD-related pain after chronic STN stimulation

Type of Pain	Instances of Pain	VAS Score (% Change)			
		Preop	2 Wks Postop	6 Mos Postop	12 Mos Postop
musculoskeletal	39	4.6 ± 2.1	0.7 ± 1.2 (−85)*	1.0 ± 1.3 (−80)*	0.9 ± 1.2 (−81)*
dystonic	21	5.2 ± 2.1	1.0 ± 2.0 (−80)*	0.5 ± 1.1 (−90)*	0.2 ± 0.6 (−96)*
dystonic & musculoskeletal	18	5.8 ± 2.2	1.3 ± 1.4 (−77)*	1.3 ± 1.9 (−82)*	0.6 ± 1.0 (−90)*
somatic	11	4.7 ± 1.4	2.9 ± 1.9 (−36)*	4.4 ± 3.2 (−6)	2.7 ± 1.9 (−49)*†
radicular/peripheral neuropathic	3	6.8 ± 1.8	4.8 ± 0.8 (−30)	8.3 ± 1.6 (+22)	1.7 ± 1.6 (−75)†
central	2	6.9	4.0	5.9	6.1
total pain	94	5.2 ± 2.1	1.3 ± 1.8 (−75)*	1.6 ± 2.4 (−69)*	1.0 ± 1.5 (−80)*‡

* $p < 0.001$.
† Including 3 patients (3 instances of pain) who underwent spinal surgery.
‡ Including 3 patients (6 instances of pain) who underwent spinal surgery.

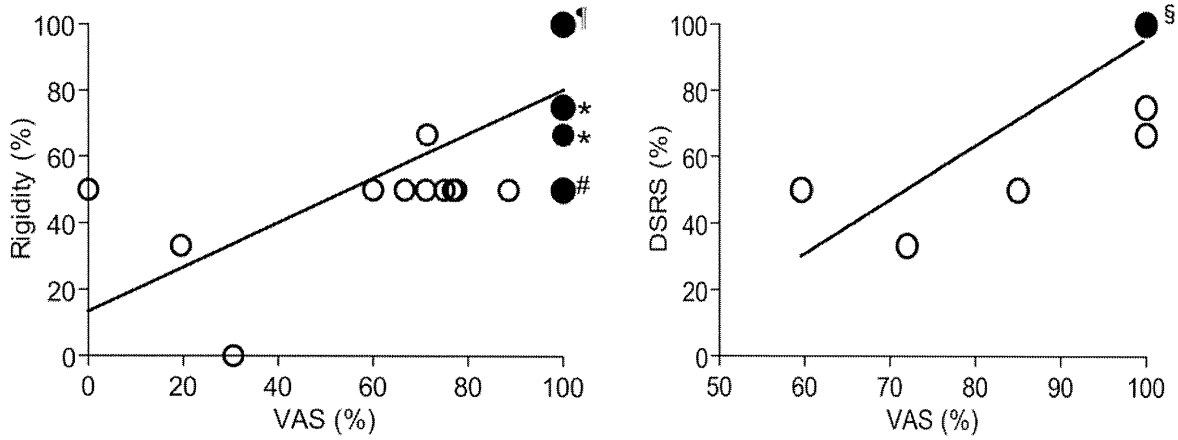

Fig. 1. Correlations between improvement rates in severity of musculoskeletal pain (percentage improvement in VAS score) and limb rigidity score (UPDRS Item 22 subscore; **left**), and between improvement rates in severity of dystonic pain (percentage improvement in VAS score) and dyskinesia severity rating scale (DSRS) score **(right)**. Simple regression analysis revealed a significant positive correlation between the percentage improvement of VAS score in musculoskeletal pain and percentage improvement of rigidity severity score ($r = 0.49$, $p < 0.0001$). Such a positive correlation was also evident for the relationship between improvement in dyskinesia and severity of dystonic pain ($r = 0.69$, $p < 0.0001$). Regression lines are indicated by *solid lines*. There were some overlaps of data points, as indicated by *closed circles*. §16 patients, ¶9 patients, #3 patients, *2 patients.

patient complained of the pain during on-period choreodystonia. The overall mean VAS score for the dystonic pain was significantly decreased at 2 weeks, 6 months, and 12 months postoperatively (Table 2). Every pain in each type of dyskinesia was significantly improved postoperatively. The percentage improvement of the pain severity in diphasic dyskinesia was smaller than that in off-period dyskinesia, but the difference was not statistically significant. A strong correlation was observed between the percentage improvement in each pain severity and that of the dyskinesia severity ($r = 0.69$, $p < 0.0001$; Fig. 1).

Mixed Musculoskeletal and Dystonic Pain

Fifteen patients complained of pain during the off-motor condition with severe limb rigidity. Off-period dystonia was presented in all patients, and this aggravated their pain. Because it was often difficult to distinguish between the 2 types of pain in such patients, we categorized their pain as mixed musculoskeletal and dystonic pain. The overall mean VAS score for this type of pain was significantly decreased at 2 weeks, 6 months, and 12 months postoperatively (Table 2).

Central Pain

Central pain was noted in only 2 of our patients. One patient, a 58-year-old woman, had suffered from burning pain of the face, tongue, and oral cavity throughout the day. The severity of the pain had distinctly fluctuated and had deteriorated during the off-motor condition (off period). The origin of her pain remained unidentified on neuroimages. The pain improved moderately at 2 weeks after surgery. However, it had redeteriorated toward the presurgical level by 6 months postoperatively (Case 1, Table 3), whereas the cardinal motor symptoms of PD and motor fluctuations were improved. Her pain remained at 12 months after surgery despite taking additional medications (amitriptyline and gabapentin).

The other patient, a 67-year-old woman, had suffered from burning and tingling pain in her back. The severity of the pain also fluctuated, reacting to the wearing-off phenomenon. The improvement effect of STN stimulation on her back pain was mild. The back pain remained at 6 and 12 months after surgery, whereas the motor fluctuations were improved completely (Case 2, Table 3).

Somatic Pain Exacerbated by PD

Eleven patients had somatic pain in the present study. Nine of the patients complained of low-back pain caused by lumbar spinal disease that often deteriorated in the immobility state during the off period (Table 1). Three of these patients also displayed radicular/peripheral neuropathic pain preoperatively. One patient complained of foot joint pain caused by serious joint deformities, which were considered to be striatal deformities. The remaining patient complained of knee joint pain caused by osteoarthritis, which had deteriorated through repetitive dyskinesias (choreodystonic movements).

Two contrary outcomes were presented with this type of pain. The overall mean VAS score for somatic pain was decreased by 36% at 2 weeks after surgery (Table 2). However, there was an increase in pain severity from 2 weeks to 6 months, because 4 patients (Cases 12–15, Table 4) complained of redeterioration of their pain after transient improvement despite the fact that their motor dysfunction was alleviated. All 4 had described pain reduction at 2 weeks after surgery (Table 4). Three patients (Cases 12–14, Table 4) then underwent spine surgery (posterior decompression of the lumbar spinal canal) at 6, 8, and 11 months after surgery, respectively. Thus, the overall mean VAS score at 12 months after surgery was improved compared with the 6-month postoperative scores.

In 8 of the 9 patients with spinal disease, their posture improved after STN stimulation (Table 4). In the remaining patient (a woman, Case 11, Table 4), her forward

TABLE 3: Summary of changes in severity of central and radicular/peripheral neuropathic pain*

Case No.	Type of Pain	Features of Pain/Origin	VAS Score (% change)			
			Preop	2 Wks Postop	6 Mos Postop	12 Mos Postop
1	central	burning mouth & face/unidentified	6.5	3.1 (–52)	6.1 (–6)	7.2 (+11)
2†	central	burning pain in wide back/unidentified	7.2	4.8 (–33)	5.7 (–21)	5.0 (–31)
3	radicular/peripheral neuropathic	sciatic pain/LSD, LSCS	6.2	5.1 (–18)	9.5 (+53)	1.8 (–71)‡
4	radicular/peripheral neuropathic	sciatic pain/LDSL, LSCS	5.3	3.9 (–26)	6.4 (+21)	3.2 (–40)‡
5	radicular/peripheral neuropathic	sciatic pain/LSD, LSCS	8.8	5.3 (–34)	8.9 (+1)	0.0 (–100)‡

* LDSL = lumbar degenerative spondylolisthesis; LSCS = lumbar spinal canal stenosis; LSD = lumbar spondylosis deformans.
† Case 16 in Table 4.
‡ Postoperative VAS score.

bent posture and pain were unchanged even after STN stimulation. This patient underwent spinal surgery (posterior decompression and fusion with instrumentation) for the spinal canal stenosis caused by lumbar degenerative spondylolisthesis ahead of the STN stimulation therapy. Since receiving the spinal surgery 2 years previously, her forward bent posture had become progressively worse and her lumbar spine had already become immobile before the STN stimulation therapy.

The improvement in severity of back pain categorized in somatic pain was smaller than that categorized in musculoskeletal pain (Table 4).

Six patients had received pain killers (NSAIDs) before the surgery. Three of the patients stopped taking the medications because their pain had improved. The remaining 3 patients required continuous taking of such drugs to alleviate their pains during the follow-up period.

Radicular/Peripheral Neuropathic Pain

Three patients had sciatic pain related to spondylosis deformans preoperatively (Cases 12–14, Table 4; see Table 3). Mild or moderate improvements of this type of pain were evident in all 3 patients at 2 weeks after surgery. However, their pain deteriorated from 2 weeks to 6 months postoperatively. They subsequently underwent spinal surgery, and the postsurgical (12-month) VAS score was then improved (Table 1; Cases 3–5, Table 3). All 3 of the patients had received NSAIDs and mecobalamin for their pain before surgery, and these drugs were used during the follow-up period.

TABLE 4: Summary of changes in severity of back pain*

Case No.	Age (yrs)	Type of Pain	Spinal Disease	Site of Pain	VAS Score				Posture Score (UPDRS Item 28)			
					Preop	2 Wks Postop	6 Mos Postop	12 Mos Postop	Preop	2 Wks Postop	6 Mos Postop	12 Mos Postop
1	71	MS	mild scoliosis	low back	6.7	0.0	0.0	0.0	2	1	1	1
2	64	MS	none	low back	7.8	0.0	0.0	2.8	2	0	0	1
3	64	MS	none	low back	2.5	0.0	0.0	0.0	2	0	1	0
4	65	MS	mild scoliosis	low back	4.0	3.7	1.6	0.0	3	1	2	0
5	62	MS	mild scoliosis	low back	5.6	2.2	3.7	1.3	2	1	1	1
6	67	MS	none	low back	4.7	0.0	2.6	0.0	2	0	0	0
7	61	somatic	LSD	low back	5.1	4.7	2.4	2.6	3	1	2	1
8	63	somatic	LSD	low back	2.6	0.9	1.7	1.3	2	0	1	0
9	65	somatic	LSD, scoliosis	back, low back	5.4	5.1	2.0	2.3	3	0	1	1
10	57	somatic	LSD, LSCS	low back	3.3	0.0	1.0	1.2	3	2	2	2
11	63	somatic	LDSL†	low back	5.9	3.8	4.6	5.3	4	4	4	4
12	65	somatic	LSD, LSCS	low back	4.8	3.2	4.9	2.7‡	3	1	1	1
13	61	somatic	LDSL, LSCS	low back	3.0	1.0	6.5	2.4‡	2	0	0	0
14	52	somatic	LSD, LSCS	low back	6.2	5.3	9.5	3.2‡	2	1	1	1
15	67	somatic	LSD, LSCS	low back	6.8	3.1	9.8	6.2	1	0	1	1
16	67	central	mild scoliosis	wide back	7.2	4.8	5.7	5.0	3	1	1	1

* MS = musculoskeletal.
† Underwent spinal surgery prior to STN stimulation.
‡ VAS score after spinal surgery.

Discussion

The present prospective study clearly demonstrates that chronic STN stimulation can significantly attenuate overall PD-related pain at 2 weeks, 6 months, and 12 months postoperatively. This finding is in agreement with the results of previous cohort studies on patients who underwent pallidal and STN surgery: a 71% reduction of pain score was noted at 12 months after pallidal stimulation,[26] a > 50% reduction of pain score was observed at 12 months after unilateral pallidotomy,[16] 20 (87%) of 23 patients with PD-related pain were found to be responders to STN stimulation,[18] and an 84% reduction of pain/sensory score (UPDRS Item 7 subscore) was noted at 12 months after STN stimulation.[34]

The present study also clearly demonstrates that the effects of chronic STN stimulation differ among different pain types even though the pains are all PD-related preoperatively. Little is known concerning whether the various types of pain accompanying PD (excluding dystonic pain) are attenuated by functional stereotactic surgery. Only 2 groups have investigated the efficacy of pallidotomy[16] or STN stimulation[18] for various types of pain related to PD. Honey et al.[16] reported different effects of unilateral pallidotomy on each type of pain. The results of their study indicated that "somatic pain which is exacerbated by PD" and "musculoskeletal pain" were prominently attenuated by pallidotomy rather than "dystonic pain" and "dysesthetic pain." The present data revealed an obvious difference in somatic pain, in which 2 contrary outcomes were observed for such pain, so that the mean percentage pain reduction noted in the present study was smaller than that given previously. In a 3-month follow-up study on the effects of STN stimulation on PD-related pain by Kim et al.,[18] these authors reported that dystonic pain (100%) and central pain (92%) were prominently responsive rather than radicular pain (63%) and musculoskeletal pain (61%). The numbers of patients with central pain and the responders to surgery in their series were far greater in comparison with the present study and previous investigations involving pallidal surgery.[16]

Musculoskeletal pain and dystonic pain were common in advanced PD and responded well to bilateral STN stimulation in the present study. The pathophysiological mechanisms underlying PD-related pain remain unclear. It has been postulated that PD-related pain, especially musculoskeletal and dystonic pain, may originate primarily from a sustained increase in muscle tone.[15] The present data also revealed that the percentage improvement of the pain severity score in musculoskeletal pain was positively correlated with the percentage improvement of the rigidity severity score. Such a positive correlation was also evident for the relationship between improvement in dyskinesia and dystonic pain. These findings suggest that the mechanism of action of STN stimulation on PD-related pain, especially musculoskeletal and dystonic pain, may be through improvement of a musculogenic nociceptive factor, although it has been reported that the origin of the pain could be multifocal including musculogenic and abnormal spinal/basal ganglia sensory processing.[8,11,29,32] Recent data have shown that PD patients with pain have a lower threshold for heat pain compared with both PD patients without pain and non-PD controls,[11] and levodopa has been found to raise their objective pain threshold.[4,13] It is well known that STN stimulation can lead to a reduced levodopa dose postoperatively in patients with advanced PD. Although the reduction in levodopa dose can lessen the levodopa-induced complications, such as on-off motor fluctuations and dyskinesia, it may increase the risk of pain deterioration. Pain was, however, improved in almost all patients in the present study with musculoskeletal pain and dystonic pain despite the fact that the levodopa dose in every PD patient was markedly reduced. This finding suggests that the beneficial effects of STN stimulation on the pain are greater in comparison with the unpleasant effects caused by a decreased dose of levodopa.

Central pain has been reported in 1.7%–10% of patients with PD.[3,10,33] In our series, only 2 patients (1.2%) with PD had central pain; this prevalence is thus similar to that in previous studies. Only in the series of Kim et al.[18] was a prominently high prevalence of central pain presented (37% of all 67 instances of pains). For this reason, they presumed that their patients had more advanced PD, so that the dysfunction of the basal ganglia would be more severe. We suggest another possible contributing reason, namely that they might have overrepresented the central pain category (see *Methods*).

Kim et al.[18] indicated that central pain is a good responder to STN stimulation after a 3-month evaluation period. Although each of our 2 patients with central pain also responded to STN stimulation in the present study, the effectiveness was transient, and no long-term satisfactory benefit was obtained in these 2 patients. Similar results have been reported previously by Honey et al.[16] In their study, pallidotomy afforded long-term benefit for central pain (their category name was "dysesthetic pain") in 2 patients with PD, although 1 of them showed a transient response at 6 weeks after surgery. We infer, therefore, that functional surgery of the basal ganglia, including the STN and globus pallidus internus, may provide no long-term beneficial effect. However, the number of cases of this type of pain treated by functional surgery is too small to reach a final conclusion.

Somatic pain exacerbated by PD was observed in 11 patients. All the pain had deteriorated during the off-motor condition. Such off-period pain deterioration may be caused by increasing and continuous joint stresses and a decreased pain threshold from a decrease in dopamine concentration. Of the 11 patients with PD-related somatic pain, 9 suffered from back pain. Honey et al.[16] reported that somatic pain and musculoskeletal pain responded best to treatment. In our series, however, 2 contrary outcomes were presented up to 6 months after surgery, whereas all pain was resolved or improved in all patients at 2 weeks postoperatively. The mean percentage reduction of the VAS score in this type of pain at 6 months was thus smaller than that of musculoskeletal and dystonic pain. In the series of Honey et al., this type of pain was located in the limbs in most patients. In contrast, 9 of our 11 patients had somatic back pain caused by lumbar spinal disease. We assume that this difference reflected a difference in the distribution of origins of each pain.

It is known that back pain in patients with PD can be caused by postural abnormalities and increased muscle tone.[5] In addition to such possibilities, we suggest that underlying spinal disease can also contribute to back pain in patients with PD. In two-thirds of the patients in this study with back pain (6 of 6 categorized as musculoskeletal pain and 4 of 9 categorized as somatic pain caused by spinal disease), the pain was markedly alleviated by STN stimulation with accompanying improvement of postural abnormalities. We believe that the abnormal muscle tone related to postural abnormalities could contribute to the pain in such patients. On the other hand, pain related to lumbar spinal disease, such as spinal spondylosis deformans and accompanying canal stenosis, deteriorated in 4 patients despite the fact that their forward bent posture was improved. Underlying spinal disease may be considered as the main cause of the pain in such patients, because it is known that extension (increased lordosis) of the lumbar spine increases the mechanical stress on the lumbar facet, resulting in a deterioration of the pain originating from lumbar spondylosis deformans. Increasing lordosis of the lumbar spine can also aggravate the stenosis of the lumbar spinal canal leading to a risk of deteriorating symptoms associated with spinal canal stenosis, such as lumbago and radicular/peripheral neuropathic pain.

A recent cohort study by Broetz et al.[5] showed that 74% of 101 patients with PD suffered from back pain. The prevalence of back pain in our study thus appeared to be smaller than that in their cohort study. This difference may reflect the difference in candidate selection used in each study. Whereas the study of Broetz et al.[5] included all patients complaining of back pain, we counted only those patients with PD-related pain in which there were clear alterations of pain in conjunction with their motor fluctuations. Similar to the results obtained in epidemiological studies, we have also encountered many PD patients suffering from back pain (non–PD-related pain), and their pain sometimes deteriorated after DBS surgery. Furthermore, we observed 3 patients who experienced asymptomatic lumbar spinal spondylosis deformans with canal stenosis preoperatively who complained of low-back pain postoperatively, and radicular/peripheral neuropathic pain appeared in 2 of them at several months after commencing STN stimulation (these patients were not included in the present study). These results indicate that PD patients with back pain originating from spinal disease, regardless of whether the pain is PD-related or not, may have a potential risk for developing postoperative deterioration of their pain. The present study sample was small, but we strongly suggest that presurgical evaluation of patients' spinal condition should be performed in all candidates for stereotactic surgery to assess the potential risk of postsurgical deterioration related to spinal disease.

Conclusions

We observed that STN stimulation provided significant improvement of pain related to PD in patients with advanced PD, and the efficacy continued for at least 1 year. The results of this cohort study demonstrate that musculoskeletal pain and dystonic pain respond well to STN stimulation. However, patients with back pain (somatic pain) and radicular/peripheral neuropathic pain originating from spinal disease have a potential risk for postoperative deterioration of their pain. Preoperative recognition of the type of pain can inform us of the postsurgical potential benefits and the risk of deterioration of the pain related to PD.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Oshima. Acquisition of data: Morishita, Sumi, Otaka, Kobayashi, Suzuki. Analysis and interpretation of data: Oshima, Otaka, Yamamoto. Drafting the article: Oshima. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fukaya. Study supervision: Fukaya, Katayama.

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Address correspondence to: Chikashi Fukaya, M.D., Ph.D., Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine, 30-1 Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan. email: fukaya.chikashi@nihon-u.ac.jp.

12 ケタミン

山本隆充* 深谷 親* 片山容一**

ポイント

- 麻酔用量と異なって低用量のケタミンは，選択的にNMDA受容体の非競合的拮抗薬として作用する．
- 低用量のケタミンは神経障害性疼痛の治療に有用であり，中枢性感作やワインドアップ現象の解除にも有効と考えられる．
- ドラッグチャレンジテストでketamine-sensitiveな症例を対象とすることで，不快な異常感覚や情動反応などの副作用を心配することなく，安全に低用量のケタミンを使用することができる．
- 神経終末から興奮性アミノ酸の遊離を抑制する作用のあるガバペンチンやプレガバリンは，ケタミンとの併用により効果を増強することができる．
- ケタミンはオピオイドには含まれないが，麻薬指定を受けているので，注意が必要．

キーワード ケタミン，中枢性疼痛，NMDAレセプター，ドラッグチャレンジテスト，低用量ケタミン点滴療法

＊日本大学医学部先端医学系応用システム神経科学分野 ＊＊日本大学医学部脳神経外科系神経外科学分野

◎神経障害性疼痛とNMDA受容体

知覚求心路の切断後に中枢側ニューロンに過剰放電が出現することは，脊髄後根切断後に脊髄後角内でニューロンの過剰活動を記録したLoeserら[1]（1967年）の報告以来，脊髄後角，三叉神経核，視床，大脳皮質知覚野など多くの部位で確認されている．中枢神経損傷後疼痛の出現には，①このニューロンの過剰活動が重要な役割を担っていること，②このニューロンの過剰活動の発現に興奮性アミノ酸が関与していること，③特に知覚求心路の遮断後に著明であること，などが報告されている[2]．また，求心路遮断後に出現するニューロンの過剰活動に対して，興奮性アミノ酸のNMDAレセプターのブロッカーであるケタミンの効果が確認されている．臨床的にも求心路遮断後に出現する中枢性感作（central sensitization）やワインドアップ現象に対するケタミンの効果が報告されている．

◎ドラッグチャレンジテストの目的と方法

神経障害性疼痛症例の治療方針を決定するためには，ドラッグチャレンジテストが有用である．私どもは，visual analogue scale（VAS）で痛みの評価を行い，薬物投与によるVASの変化を比較している．この評価法の特徴は，プラセボ投与から始め，少量ずつ段階的に薬物を投与するので，少量から連続的に多量投与までの効果を確認できることである．患者の訴える疼痛がどのような薬物にどの程度の投与量でどの程度反応するか，またはまったく反応しないかを明らかにすることができる[3]．

ケタラールテストは，5分間隔で生食を2回投与後，同様に5分間隔でketamine hydrochlorideを5mg，合計25mgまで静脈内投与する．(薬物投与後VAS÷薬物投与前のVAS)×100%＝%VASとして，%VASが60%以下となったもの，すなわち薬物投与前と比較して，VASが

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表 1 ケタミンテストによる副作用

ketamine	-sensitive	-resistant
症例数	55	65
副作用の種類		
不快な感覚ならびに情動反応	0 (0%)	17 (26.1%)
	0 (0%)	17 (26.1%)
めまい感	2 (3.6%)	5 (7.7%)
軽い頭痛	0 (0%)	3 (4.6%)
疲労感	0 (0%)	3 (4.6%)
嘔気	1 (1.8%)	2 (3.1%)
	3 (5.4%)	13 (20.0%)

ketamine-sensitive 群と ketamine-resistant 群でのケタミンテストによる副作用の比較.

40%以上減少したものを sensitive case，40%以下のものを resistant case としている[4].

◉ドラッグチャレンジテストの対象と結果

脳血管障害後疼痛の 120 例では，自発痛に対しては 120 例中 55 例（45.8%）が ketamine-sensitive で，アロデニアなどの誘発痛を含めると 120 例中 63 例（52.5%）が ketamine-sensitive と判定された．また，幻肢痛，断端痛，神経根損傷などの末梢神経系に損傷を有する神経障害性疼痛では，23 例中 20 例（86.9%）が ketamine-sensitive であった．ケタミンテストによって，不快な異常感覚や情動反応が出現した症例が脳血管障害後疼痛の 120 例中 17 例存在したが，全例で問題なくテストを行うことができた．この 17 例はいずれも ketamine-resistant な症例で，ketamine-sensitive な症例ではこのような反応を呈した症例は存在しなかった．ketamine-sensitive 群では，めまい感や嘔気を訴えた症例を認めたが，ketamine-resistant 群に比較すると少数であった（**表 1**）．このような結果から，低用量ケタミンの使用は，ketamine-sensitive な症例には安全で有効な方法であると考えられる．

◉低用量ケタミン点滴療法

ドラッグチャレンジテストで ketamine-sensitive な 55 例に対して，100 mL の生食に 20 mg のケタラール® (0.33 mg/kg) を加え，約 1 時間かけて点滴する低用量ケタミン点滴療法を行った．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 1～6 時間以内がもっとも多く，24 時間以内が 69%であったが，24 時間以上持続するものも 31%存在した．

ketamine-sensitive 症例に限って 2～4 週ごとに低用量ケタミン点滴を行った．開始 6ヵ月後に行った患者満足度調査では，疼痛のコントロールに有用であることを自覚し，6ヵ月以上の継続を希望したもの 39 例（80%），疼痛のコントロールが一過性のため中止を希望したもの 10 例（20%）であった．

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，20 mg で開始した 39 例中，6ヵ月後も 20 mg が 31 例，21～30 mg が 6 例，10～19 mg が 2 例で，モルヒネのような耐性は認めなかった[4]．

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．また，血液・生化学検査で異常が出現し，治療を中止した症例はいなかった．

◉低用量ケタミン点滴療法の意義

ケタミン点滴療法では効果の持続時間に個人差があり，わずか数時間のものから数日間持続するものまで存在した．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，中枢性感作の解除にも有効であると考えられる．ケタラール®の持つ解離性麻酔薬としての性質から情動面の変化を呈する症例も存在したが，適切な投与量と投与時間を選択することによって，有効な治療効果を得ることができる．わが国でも使用可能となったガバペン

チンやプレガバリンには，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[5]．

◉低用量ケタミン点滴療法の特徴

これまでにケタミンが麻酔薬として使用される場合は，ケタミン1～2mg/kgを1分以上かけて静注，あるいは5～10mg/kgを筋注する方法が用法，用量として推奨されている．一方，ケタミン点滴療法は，ケタミン0.3mg/kgを100mLの生食に加え，1時間かけて点滴投与する方法で，まったく別の使用法である．ケタミンの点滴中でも覚醒状態で患者さんの状態を確認し，精神状態ならびに疼痛の変化を確認することができる．また，神経障害性疼痛では，この程度の投与量で十分な除痛効果を得ることができる．ケタミンに対する感受性の違いから，このような少量投与でも意識レベルが低下する症例も存在するが，このような症例では点滴速度を遅くすることによって，対処することができる．ケタミン点滴療法の明らかな除痛効果は数時間のことが多いが，疼痛が持続して難治性となっている症例においては，一時的であっても疼痛から開放される時間を提供することによって，増大した痛みの感覚をリセットすることができ，日常の生活も改善される．さらに，抗うつ薬，抗不安薬，抗けいれん薬の内服を併用することによって，持続的な除痛効果を得ることができ，患者さんの負担も少なく，日常の生活改善を図ることができる．

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