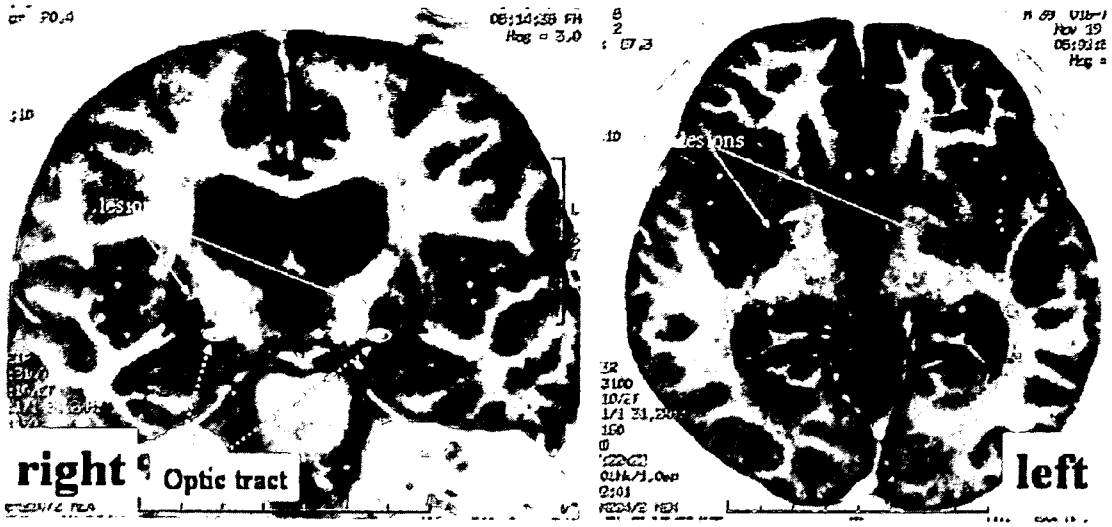

Fig. 2 MRI of patient 2. Symmetrical atrophy of the caudate nucleus and putamen. The left and right thermal lesions are located in the ventral GPi

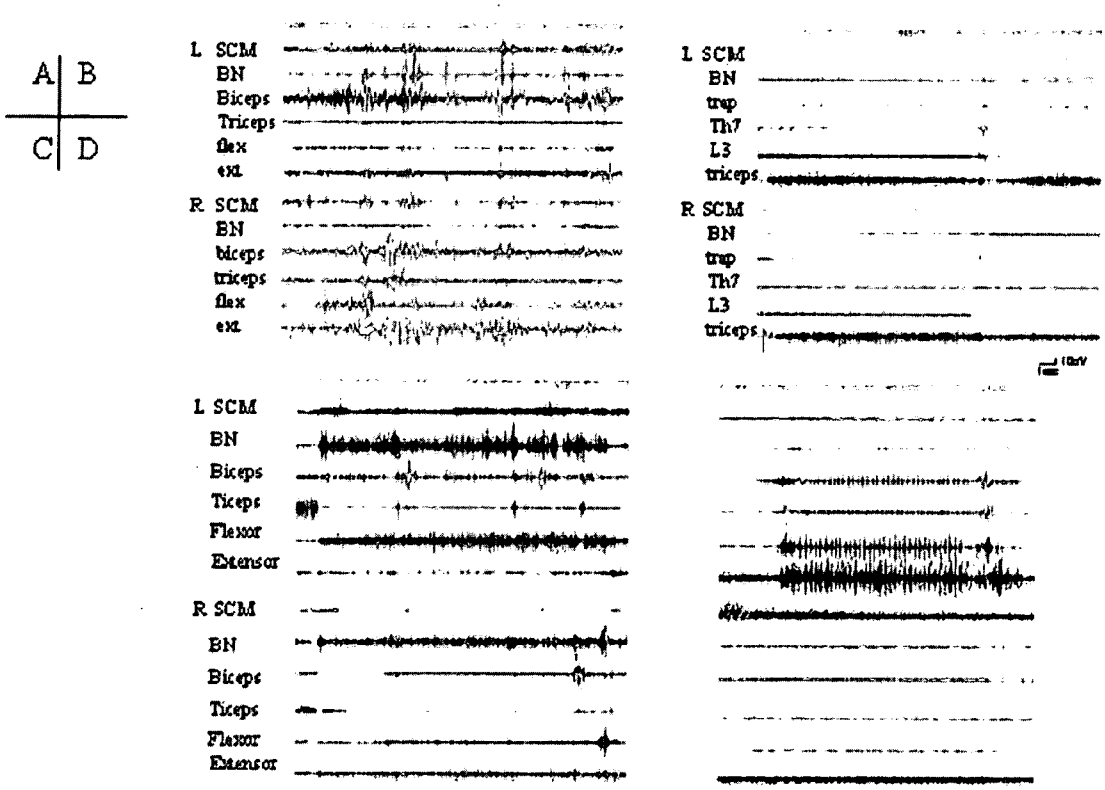

Fig. 3 Surface EMG recording of patient 2 before and 3 months after pallidotomy. A and B were obtained in a sitting position. Before pallidotomy (**a**) there were rapid and synchronous involuntary movements, which were not observed after pallidotomy (**b**). Before pallidotomy the patient was unable to perform diadochokinesis with the left hand (**c**), but after pallidotomy he was able to perform diadochokinesis without involuntary movements (**d**)

followed by the other side. Surgery was performed on patient 1 in 1995 and on patient 2 in 2001. The surgical procedure differed between the two patients.

Patient 1 was operated using the Sugita stereotactic frame without microrecording. The coordinates of the proposed target in the posteroventral part of the GPi as measured by ventriculography were 2 mm anterior to the midpoint of the intercommisural (AC-PC) line (Y), 4.8 mm inferior to the AC-PC line (Z) in the lateral view and 21 mm lateral to the midline of the third ventricle (X) in the AP view. The angle of the lesioning radiofrequency electrode was 60° to the AC-PC line. The location of the optic tract was confirmed using visual evoked potentials, and three thermal lesions were made starting at 2 mm dorsal to the optic tract, and at intervals of 1.5 mm proceeding dorsally from this. The thermal lesions were made at 70 °C for 50 s.

Patient 2 was operated using the Leksell stereotactic frame. The dorsal surface of the optic tract was identified as the tentative target, being immediately ventral to the GPi, and was determined by MRI. The coordinates of the tentative target were Y:1 mm anterior to the midpoint of the AC-PC line, Z:5 mm inferior to the AC-PC line and X:23 mm lateral to the midline. During the operation, neuronal activity was recorded by microrecording, and the specific location of the target was confirmed by neurophysiological and radiological methods. The distance to the optic tract was determined by recording the neural activity of the optic tract in response to a flashed light. Three thermal lesions made at 70 °C for 50 s using a radiofrequency electrode positioned away from the optic tract at an angle of 70° to the AC-PC line.

2.1.3 Results

Patient 1 showed a significant, albeit not completely satisfactory, improvement in his clinical condition after bilateral procedures, with reduction in lingual dyskinesia and involuntary movements of the trunk. After surgery, he was able to eat and stand with less assistance, although still with difficulty. Self-biting disappeared. The lesions as observed on MRI were very small and were not located in the GPi (Fig. 1). The right lesion involved the optic tract, and the location of the left lesion was unclear.

Six months after surgery, he committed suicide. He had not been noted to shows signs of depression. Before committing suicide, he did not complain of any defects or problems in his visual fields. The pathological findings confirmed the diagnosis of NA. The lesion on the right involved the optic tract.

For patient 2, following the right-side pallidotomy, the flexion and extension movements of the trunk improved and he could stand by supporting himself. The involuntary movements of his left hand and his tendency to hit his head against the wall both disappeared. Three months after bilateral pallidotomy, he was partially independent. He could eat without assistance in a sitting position. He could stand alone by holding on a bar, but it was difficult for him to remain standing and to walk without support because of contractures of the ankle joints. The non-purposeful limb movements and involuntary trunk movements gradually reduced in frequency

Fig. 4 Patient 2 standing before and after pallidotomy. Before pallidotomy patient 2 was unable to stand even with support because of his truncal movements (**a**). Three months after pallidotomy he could stand without involuntary movements with support (**b**). Four years after pallidotomy he could stand by himself (**c**)

until they disappeared completely. He continued to show an anteflexed posture while standing. His ADLs gradually improved until he was able to perform all indoor activities independently. There was no change in his cognitive functions. He had no difficulty in swallowing food or water, but he was bradykinetic. Four years after undergoing bilateral pallidotomy, he was able to sit, walk or stand and maintain these positions easily without any involuntary movements (Fig. 4). Five years after undergoing pallidotomy, he continued to perform his ADLs independently, and exhibited no involuntary movements.

On MRI, the left and right lesions in the GPi were located in the ventral part of the pallidum (Fig. 2). The surface electromyography (EMG) recorded before and after pallidotomy showed a marked effect of the surgery with a decrease in involuntary movements and improved ability to perform voluntary movements (Fig. 3).

2.2 *Deep Brain Stimulation*

2.2.1 Patients

Patient 3 was a 32-year-old man with an 8-year history of a choreatic-dystonic syndrome, dysarthria and generalized epileptic seizures who presented with recurrent distressing tasteless belching [29]. The frequency of belching had progressively increased over the previous year and had become extremely debilitating leading to severe depression. The patient also exhibited dramatic tongue-biting. Feeding was problematic and he had lost 20 kg during the previous year. Walking was disturbed by intermittent dystonia of the left foot and bilateral choreatic movements causing a jerky gait. Trunk flexion movements and a moderate back-arching dystonia were occasionally observed. Moderate cognitive impairment was obvious on clinical examination but neuropsychological testing was impossible because of dysarthria.

The patient had 10% of acanthocytes among the circulating red blood cells and a single intronic mutation in the *VPS13A* gene was detected, suggestive of the diagnosis of ChAc. Brain MRI, thoracic radiography and endoscopy of the upper gastrointestinal tract were normal. Videofluoroscopy showed normal deglutition and slight hypotonia of the inferior esophageal sphincter confirmed by manometry. EMG of the diaphragm demonstrated prolonged, recurrent, arrhythmic contractions of both diaphragmatic domes. Recording of respiratory muscles with surface electrodes revealed severely dyskinetic breathing frequently associated with violent belching (Fig. 5). Risperidone (up to 8 mg per day) was ineffective.

Patient 4 exhibited a progressive choreatic syndrome associated with muscular weakness at the age of 41 [13]. A brother and maternal uncle also had chorea. Investigations revealed 10% acanthocytes among the circulating red blood cells, compensated chronic hemolysis with splenomegaly, increased muscle enzymes and a sensory axonal neuropathy. Weak expression of red blood cell Kell antigens and a mutation in the *XK* gene were consistent with MLS. MRI revealed moderate atrophy of the caudate and putamen. Six years later the patient presented with progressive deterioration with severe generalized chorea, predominantly on the left, with hypotonia, postural instability causing repeated falls. He had moderate cognitive impairment (Mini mental state 28/30, Mattis scale 127/140). Tiapride (maximum dose 150 mg/d), risperidone (maximum dose 5 mg/d), and olanzepine (maximum dose 30 mg/d) were introduced without benefit, but with adverse sedative and cognitive effects.

2.2.2 Neurosurgical Procedures

For patients 3 and 4, the targets and entry point coordinates were calculated with regard to the AC-PC line reference system obtained through stereotactic 3D T1-weighted MRI as described elsewhere [7]. Under general anesthesia, per-operative electrophysiological recordings were performed using five parallel micro-electrodes

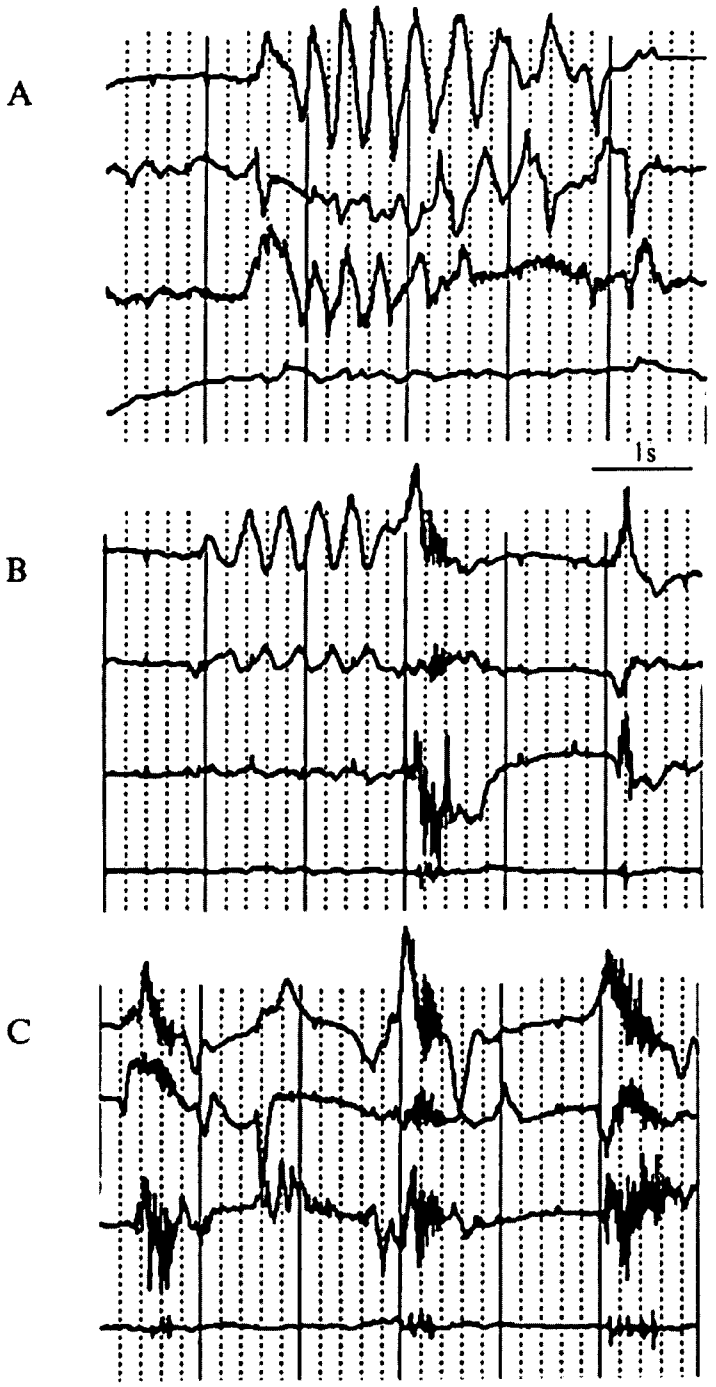

Fig. 5 EMG of axial symptoms in patient 3. Surface polygraphic recording of thoracic muscles recorded before surgery (from top to bottom; right intercostal, right paravertebral, left intercostal, left paravertebral). (**a**) Respiratory rhythms were disturbed by polypneic episodes of 2–3s. (**b**) Polypnea led to a series of violent belching indicated by the *white arrows*. (**c**) Belching appeared spontaneously in a series of violent spasms

(FHC, Bowdoinham, ME, USA) with an Alpha-Omega system (Micro-guide, Nazareth, Israël). At the end of each track, micro-stimulations were performed through the same micro-electrodes with a current intensity up to 10 mA in order to detect the per-operative occurrence of adverse effects. The final implantation sites

of the definitive electrodes for chronic stimulation (DBS – 3387 electrode Medtronic®) were guided by the longest recording of GPi neuronal activity and the absence of visible side-effects after micro-stimulation. Electrodes were secondarily connected to a pulse generator (Kinetra, Medtronic®) internalized in the subclavicular region (Medtronic, Model 7425). A cerebral CT scan was performed three days after electrode implantation to identify electrode positions, and images were combined with the pre-operative 3D T1-weighted MRI. The post-operative location of electrode tracks was determined on a basal ganglia atlas consisting of the contours of basal ganglia structures traced and digitized from a brain specimen obtained at autopsy (Fig. 6). Three-dimensional surfaces constructed from these contours were co-registered with the patient's MRI by using specially designed algorithms [36].

2.2.3 Results

For Patient 3, initial stimulation settings involved the two lowest contacts with a voltage of 2.5 V, a frequency of 120 Hz and a pulse width of 90 µs. Within a few days after the onset of stimulation, a dramatic decrease in belching frequency and dyskinetic breathing was observed. Choreic and dystonic movements involving the lower limb and axial muscles completely disappeared, as did tongue-biting. However, after 2 months a partial relapse occurred, and belching and breathing dyskinesia reappeared, although tongue-biting did not. Changes in stimulation settings (voltage, frequency, contacts) were ineffective. MRI revealed that the right electrode was positioned at the border of the putamen and globus pallidus external segment (GPe). We therefore decided to re-operate on this patient in order to reposition the electrode. The first right electrode was left in place and a second electrode was introduced more medially on the same side. After the second implantation, contacts 0 and 1 (the two lower contacts) were located within the GPi on both sides. Contact 2 was at the border between the GPi and GPe and contact 3 within the GPe, bilaterally (Fig. 6). A double-blind evaluation was performed 3 months after this second intervention. Chorea, belching and dysarthria were improved by GPi 40 Hz stimulation compared to the "off" condition. The dystonia sub-score was slightly improved by 120 Hz GPi stimulation but at this frequency, chorea and dysarthria were worsened with drooling. There was no effect on gait whatever the settings used. GPi stimulation at 10 Hz was ineffective.

For patient 4, dysarthria was less pronounced and both the dystonia and choreic symptoms were improved at 40 Hz stimulation compared to the "off" condition. However, GPi 120 Hz stimulation clearly worsened chorea and induced drooling. There was no apparent improvement in hypotonia, and walking remained impossible without help whatever the stimulation parameters used. GPi stimulation at 10 Hz was ineffective. Contacts 0 and 1 were located within the GPi. Contact 2 was at the border between the GPi and GPe on the left, and in the GPe on the right (Fig. 6). Contacts 3 were within the GPe bilaterally. All of the contacts were located slightly more laterally in patient 1 than in patient 2 due to larger ventricles.

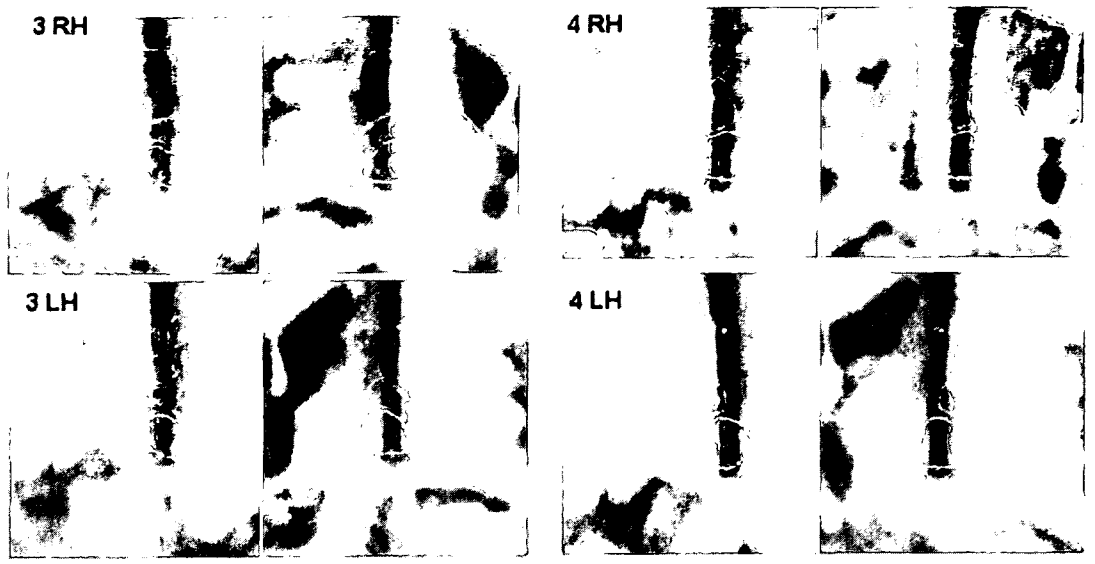

Fig. 6 Localization of the electrodes in patients 3 and 4. RH: right hemisphere; LH: left hemisphere. For each electrode a sagittal (*left*) and a frontal (*right*) view reformatted along the electrode trajectory is presented. Contacts for each electrode are indicated by small circles. The contours of the registered atlas comprise the putamen, and external and internal globus pallidus (from [13])

3 Discussion

These preliminary data obtained on a small series of patients reveal that functional surgery might be a useful tool in the treatment of choreatic and dystonic symptoms in NA syndromes.

The clinical outcome of pallidotomy in patient 1 was partial, however, his lingual dyskinesia and involuntary trunk movements improved and self-biting disappeared. After the surgery, he was able to eat and stand with less assistance, although still with difficulty. The clinical outcome of pallidotomy in patient 2 was better, as 3 months after his bilateral pallidotomy he became partly independent, and 5 years after undergoing pallidotomy he was able to sit, walk or stand easily without any involuntary movements. The difference between these two patients is likely to be due to the location and size of the thermal pallidotomy. In patient 2 the lesion was located in the sensory motor area of the GPi, i.e. the posteroventral area, whereas the lesion in patient 1 was located more anteriorly, and it is unclear as to whether there was actually any lesion of the GPi. In the treatment of levodopa-induced dyskinesia, careful anatomical analysis revealed a strong correlation between location of the lesion in the ventral GPi, its volume and the clinical improvement in contralateral limbs [16]. This is confirmed by data from high frequency stimulation (HFS) of the GPi. Stimulation with the most ventral contacts, located in the ventral part of the GPi, led to a complete arrest of the levodopa-induced dyskinesia [17].

In patients 3 and 4, bilateral GPi stimulation at 40 Hz gave the most reduction of chorea. This is in accordance with a recent finding on Huntington's disease using

the same frequency [24]. In patient 3, belching appeared to be due to the combination of a hypotonic internal oesophageal sphincter and diaphragmatic dyskinesias [29]. GPi stimulation dramatically decreased the diaphragmatic dyskinesias, which is the most likely explanation for the improvement in belching [13]. The severe tongue-biting was responded to surgery independently of stimulation, probably through a pallidotomy effect. GPi 130Hz stimulation worsened chorea and dysarthria, both patients becoming pallilalic with drooling, in line with a previous report showing that HFS did not improve chorea in an NA patient [35]. There was a modest effect on dystonia, but in our study dystonic symptoms were mainly observed in patient 3 and remained moderate.

The effect of GPe stimulation was more complex to interpret. Higher contacts were located at the border between the GPi and GPe thus some current might have reached the GPi, giving confusing data. Moreover, because of the angle of electrode track, these contacts were located in a medial part of the GPe leaving unstimulated a large part of the nucleus. Consequently, the effect of GPe stimulation in NA requires further investigation.

The mechanism by which pallidotomy or chronic stimulation of the GPi modifies chorea remains highly speculative. If HFS (130Hz) is taken to have an inhibitory effect, as suggested by previous studies in parkinsonian patients [18, 21, 22], such GPi stimulation could worsen chorea, possibly by increasing the activity in the thalamo-cortical pathway. On the other hand, exogenous 40Hz stimulation applied on the GPi could lead neurons to fire at a subnormal frequency allowing new dynamics in the cortico-subcortical network, thereby restoring a more physiological pattern of discharge, as previously proposed [11, 23]. However, contradictory data have been reported regarding the firing rates of GPi neurons in hyperkinetic syndromes. Whereas low discharge rates were initially found in a hemiballistic patient [32], high discharge frequencies comparable to those observed in parkinsonian patients have been recently reported in two choreic patients [30]. It is likely that further neuronal recordings, taking into account the nature of the anaesthesia used, are necessary to resolve this question.

Alternatively, pallidotomy, which totally suppresses the information passing through the pallido-thalamo-cortical pathway may improve chorea. This was illustrated by the good clinical outcome observed in patient 2 and is consistent with the previous reported case of improvement of back-arching movements in NA with HFS of the motor thalamus [2]. Finally, it seems that the therapeutic effect on chorea is obtained with several methods which have in common the capability of suppressing (with pallidotomy) or regulating (with DBS) an abnormal neuronal firing pattern. The choice between the two techniques could ultimately be dependent on the patient's preference or financial capability.

To conclude, although pallidotomy or pallidal DBS might be considered for the treatment of NA syndromes, it should be kept in mind that this progressive disease has a wide spectrum of symptoms. The decision to perform surgery involves full assessment of the risk of side-effects and the clinical features of each patient. The latter must also guide the choice of target and stimulation parameters. For example, DBS could have opposite effects on movement disorders such as chorea and dysto-

nia that could limit the efficacy of a given target. An alternative could be to use several electrodes with different targets (e.g. GPi, GPe, motor thalamic nuclei) to treat specific symptoms (e.g. chorea, dystonia, hypotonia). In any case, study of a large series of patients with homogeneous clinical features is necessary to investigate this topic. This must be performed in the context of randomized, double-blind, controlled studies with optimal anatomo-clinical correlations.

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連続磁気刺激の実際

武智詩子　魚住武則　辻　貞俊

はじめに

経頭蓋磁気刺激法 transcranial magnetic stimulation (TMS)は，1985年 Barker ら[1]により開発されて以来，様々な脳機能評価に応用されてきた．1990年代に刺激装置の改良が進み，TMS を連続して用いる反復経頭蓋磁気刺激法 repetitive TMS(rTMS)の方法論が確立し，パーキンソン病をはじめ脊髄小脳変性症，うつ病，ジストニアなど様々な神経疾患の治療効果が検討されている．ここでは rTMS を用いたパーキンソン病に対する治療の試みについて述べる[2,3]．

反復経頭蓋磁気刺激法 repetitive TMS(rTMS)

rTMS とは3発以上規則正しく反復される TMS と定義されている．rTMS には2種類あり，刺激頻度が1 Hz を越えるものを高頻度 rTMS(fast rTMS)，1 Hz 以下のものを低頻度 rTMS(slow rTMS)と区別している．5 Hz 以上の fast rTMS ではコイル直下の大脳皮質の興奮性が増大し，slow rTMS では大脳皮質の興奮性は低下すると考えられている．

rTMS はてんかん発作を誘発する可能性があり，また大脳皮質に強いパルス磁場を与えるため，てんかん患者，脳動脈瘤クリッピング術後患者，および心臓ペースメーカー埋込術後患者には禁忌となる．

パーキンソン病における rTMS

1994年に Pascual-Leone らは初めてパーキンソン病への rTMS の応用を報告した．off 状態のパーキンソン病患者の手の運動野へ fast rTMS を与えると，有意に反応時間が改善することを報告し，rTMS がパーキンソン病の治療に使用できる可能性を主張した[4]．日本では Shimamoto らが，両側前頭部に運動閾値の1.1倍の強度で0.2 Hzの slow rTMS を週1回繰り返すことにより著明な症状の改善が認められたと報告した[5]．また Fregni らは，224例を対象に行ったメタアナリシスにおいて，統計学的に TMS は運動機能改善に効果があったと報告している[6]．一方有効性を論じる論文が多い中，Ghabra らは5 Hz の rTMS を運動野に与えたが有意な変化は認められないと報告した[7]．上記以外にもパーキンソン病に対する rTMS の治療効果については多くの報告があるが(表)，効果に関しては疑問視するものも少なくなく，結論が出ていない状態である．

2000年度には厚生労働省特定疾患対策研究事業として，われわれの施設も含めた全国25施設において sham 刺激をコントロールとして rTMS の有効性の検討が行われた．刺激方法は運動野刺激・後頭部刺激・sham 刺激(頭皮に微弱な電気刺激を与え磁気刺激の音を聞かせる)の3方法を無作為に割り振り，週1回8週間3種類の刺激のいずれかを施行した．運動野刺激は両側手の運動野に円形コイルを用いて弱収縮時の1.1倍の強度で0.2 Hz の低頻度刺激を100回/週，連続8週間行った．評価は Unified Parkinson's Disease Rating Scale(UPDRS)・Hamilton Rating Scale for Depression(HRSD)・自覚症状の3者について毎週1回行い，評価時のバイアスを排除するため治療実施者と評価者は別の医師が行った．結果は運動野刺激では経過とともにパーキンソン症状の臨床症状の改善が認められた．しかしながら後頭部刺激・sham 刺激でも改善を認めた．すなわち，コントロール群と運動野刺激群で明らかな有用性の差は認められず，改善効果は placebo 効果を越えるものではないという結論であった[17]．これはパーキンソン病患者が placebo 効果を受けやすいという[9]理由によるものとも考えられる．

しかし，最近でも Strafella らの前頭部 rTMS により線条体のドパミンレベルが増加するとする報告[19]や，高頻度 rTMS では筋強剛や動作緩慢が改善するという報告[20]があり，刺激部位や強度，頻度といった刺激パラメータを変えることにより有効な治療法となりうる可能性はいまだ残っている．

今後の課題

rTMS の治療効果に関する報告は多いが，対照と比較した研究は少ない．また刺激頻度，刺激強度，刺激回数，刺激間隔等の刺激条件や刺激部位は様々であり，現在までのところ rTMS が治療法として確立されるには至っていない．rTMS による大脳皮質興奮性の変化の持続が短いこと

たけち うたこ　産業医科大学/神経内科
うおずみ たけのり　同 助教授
つじ さだとし　同 教授

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表1　パーキンソン病の磁気治療に関する過去の報告(玉川ら[2]より)

報告者	人数(人)	刺激頻度(Hz)	刺激強度	コイル種類	刺激部位	刺激回数(回)	治療効果
Pascual-Leone ら(1994)[4]	6	5	0.9×rMT	8の字	一次運動野	(記載なし)	改善
Siebner ら(1999)[8]	12	5	0.9×rMT	8の字	一次運動野	750	改善
Ghabra ら(1999)[7]	11	5	0.8〜0.85×rMT	8の字	一次運動野	(記載なし)	不変
Mally ら(1999)[9]	49	1	0.2×rMT	円形	Cz	60回/日×10日	改善
Mally ら(1999)[10]	10	1	0.34〜0.8×rMT	円形	Cz	60回/日×7日	改善
Tergau ら(1999)[11]	7	1, 5, 10, 20	0.9×rMT	円形	Cz	1000	不変
Siebner ら(2000)[12]	10	5	0.9×rMT	8の字	一次運動野	750	改善
Boylan ら(2001)[13]	10	10	1.1×rMT	8の字	補足運動野	2000	増悪
Shimamoto ら(2001)[14]	9	0.2	700 V	円形	Cz	60回/週×8週	改善
Sommer ら(2002)[15]	11	1	1.2×rMT	8の字	一次運動野	900	改善
Ikeguchi ら(2003)[16]	12	0.2	700 V	円形	F3, F4	30回×2/日×2週	改善
*Okabe ら(2003)[17]	85	0.2	1.1×aMT	円形	Cz	50回/週×8週	Placeboと同等
Lefaucheur ら(2004)[18]	12	10	0.8×rMT	8の字	一次運動野	2000	改善
Lefaucheur ら(2004)[18]	12	0.5	0.8×rMT	8の字	一次運動野	600	改善

rMT：安静時運動閾値，aMT：活動時運動閾値，＊は本文中の厚生労働省特定疾患対策研究事業のもの

や，長期的な影響や作用機序の解明など治療法として確立するために解決しなければならない問題が多く残されている．

パーキンソン病は薬物治療が有効な疾患であるが，長期間の薬物治療で様々な副作用が出現することは避けられない．近年脳深部刺激療法が実用化されるなど，パーキンソン病の治療に様々なアプローチ法が試されている．rTMSの最適刺激条件と有効刺激部位が明らかになり，長期的な影響や作用機序の解明など治療法として確立すれば，パーキンソン病に対する薬物治療の有効な補助的治療法になりうることが期待できる．

むすび

rTMSを用いたパーキンソン病に対する治療の試みについて解説した．現時点では治療効果は確立されていないが，rTMSの最適刺激条件と有効刺激部位が明らかになれば，パーキンソン病に対する薬物治療の補助となりうることが期待できるため，今後も臨床研究が必要である．

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Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials

Seiko Ishikawa [a], Kaoru Matsunaga [b,*], Ryoji Nakanishi [b], Kazumi Kawahira [a], Nobuki Murayama [c], Sadatoshi Tsuji [d], Ying-Zu Huang [e], John C. Rothwell [f]

[a] *Department of Rehabilitation and Physical Medicine, Kagoshima University, Kagoshima, Japan*
[b] *Department of Neurology, Kumamoto Kinoh Hospital, 6-8-1 Yamamuro, Kumamoto 860-8518, Japan*
[c] *Department of Graduate School of Science and Technology, Kumamoto University, Japan*
[d] *Department of Neurology, University of Occupational and Environmental Health, School of Medicine, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan*
[e] *Department of Neurology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taipei, Taiwan*
[f] *Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, 8-11 Queen Square, London WC1N 3BG, UK*

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Abstract

Objective: To study the after-effect of theta burst stimulation (TBS) over the left sensorimotor cortex on the size of somatosensory as well as motor evoked potentials evoked from both hemispheres in healthy human subjects.
Methods: We used a continuous TBS paradigm for 40 s (600 pulses) in which a burst of 3 transcranial magnetic stimuli at 50 Hz is repeated at 5 Hz [Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6]. Somatosensory evoked potentials (SEPs) following electrical stimulation of right or left median nerve and motor evoked potentials (MEPs) in the right or left first dorsal interosseous (FDI) muscles were recorded before and after TBS over the left motor cortex (M1) or a point 2 cm posterior to left M1.
Results: Amplitudes of P25/N33 (parietal components) following right median nerve stimulation were significantly increased for at least 53 min after TBS over the left M1, whereas this component was suppressed for 13 min after TBS over a point 2 cm posterior. MEPs in right as well as left FDI muscles were suppressed with a similar time course after TBS over the left M1.
Conclusions: A single-session of TBS over the sensorimotor cortex can induce a short-lasting change in the size of ipsilateral cortical components of SEPs as well as MEPs evoked from both hemispheres.
Significance: TBS is an interventional tool that can induce rapid reorganization within cortical somatosensory as well as motor networks in humans.
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Keywords: Theta burst stimulation; Transcranial magnetic stimulation; Motor evoked potentials; Somatosensory evoked potentials; Neuroplasticity; Cortical excitability

1. Introduction

In animal experiments, repetitive electrical stimulation of central nervous pathways with "theta burst" paradigms (3–5 pulses at 100 Hz repeated at 5 Hz) has been used to induce changes in the efficacy of synaptic transmission that outlast the period of stimulation. Such effects involve long-term potentiation (LTP) and depression (LTD) of synaptic connections (Larson and Lynch, 1986; Huemmeke et al., 2002). Recently Huang et al. (2005) developed a "theta burst" paradigm to condition the human motor cortex using low intensity repetitive transcranial magnetic stimulation (rTMS). This theta burst stimulation (TBS) produces a long-lasting effect on motor cortex physiology

* Corresponding author. Tel.: +81 (0) 96 345 8111; fax: +81 (0) 96 345 8188.
E-mail address: K.Matsunaga@juryo.or.jp (K. Matsunaga).

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and behaviour after an application period of only 20–190 s in humans.

The pattern of delivery of TBS (continuous TBS versus intermittent TBS) is crucial in determining whether the excitability of the motor cortex, as monitored by the amplitude of transcranial motor evoked potentials (MEPs), is increased or decreased. Continuous TBS (cTBS) decreases the amplitude of MEPs, while they are increased by intermittent TBS. The duration of the after-effect of cTBS depends on the duration of the train: the effect of cTBS given for 20 s (300 pulses) lasts about 20 min, while the effect of the same paradigm given for 40 s (600 pulses) lasts about 60 min. cTBS has been shown to inhibit specific excitatory circuits in the human motor cortex (I1-wave inputs to corticospinal neurones; Di Lazzaro et al., 2005). In addition to the effect on the motor cortex (M1), TBS has also been shown to have an effect on the human premotor (Mochizuki et al., 2005) and visual cortex (Franca et al., in press).

One question we address here is whether TBS has any lasting after-effect on somatosensory cortex. A variety of previous works have shown that several kinds of interventions such as a single-pulse TMS (Kujirai et al., 1993), 1 Hz rTMS (Enomoto et al., 2001), paired associative stimulation (PAS) (Tsuji and Rothwell, 2002; Wolters et al., 2005) or transcranial direct current stimulation (Matsunaga et al., 2004) modulate the amplitude of cortical components of the median nerve somatosensory evoked potentials (SEPs) during or after the interventions. In many previous studies, conditioning was applied to M1 whilst SEPs were recorded from S1 (Kujirai et al., 1993; Enomoto et al., 2001; Matsunaga et al., 2004; Tsuji and Rothwell, 2002). In contrast there are fewer reports in which SEPs were examined after conditioning was applied to the somatosensory cortex (S1) (e.g., Wolters et al., 2005; Enomoto et al., 2001).

A related question is whether TBS over one sensorimotor cortex has any after-effect on excitability of the contralateral sensorimotor cortex. Several kinds of rTMS such as 1 Hz (Wassermann et al., 1998; Schambra et al., 2003; Plewnia et al., 2003) or 5 Hz rTMS (Gilio et al., 2003) have been reported to have after-effects on the contralateral motor cortex excitability. However, the direction of the effect was different among reports and seems to depend on the frequency and stimulus intensity of the rTMS.

The aim of the present paper was to test whether TBS over the human sensorimotor cortex has after-effects on SEPs as well as MEPs evoked from both hemispheres. The results suggest that it may be possible to target the somatosensory cortex separately from the ipsilateral motor cortex; in addition we found that TBS has after-effects on excitability of contralateral motor, but not sensory-cortex.

2. Subjects and methods

2.1. Subjects

Twelve healthy volunteers (10 men and 2 women; mean age (±SD), 42.0 ± 6.3 years; range, 33–51 years) were studied. All subjects were right handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects gave their informed consent to the studies, which were approved by the local Ethical Committee and conformed to the requirements of the Declaration of Helsinki.

2.2. Experimental paradigms

Two different experiments were performed. In order to assess the time course of the TBS effect over the sensorimotor cortex, SEPs or MEPs were recorded before and immediately (0), 10, 20, 30, 40, 50 and 60 min after the end of the TBS trains in each experiment. TBS was performed over the scalp location of M1 or S1 in each experiment: M1 was defined as the "motor hot spot" for the right hand muscle determined by a single-pulse TMS and S1 was a point 2 cm posterior from this site. The latter position was chosen since a previous result (Okamoto et al., 2004) using a neuronavigation system revealed that this position overlies the postcentral gyrus. Wolters et al. (2005) also reported that rTMS over this position using a PAS protocol had after-effects on the cortical component of SEPs.

2.2.1. Experiment (1): assessment of the after-effect of TBS on SEPs

Eleven subjects (9 men and 2 women; mean age (±SD), 42.8 ± 5.8 years) were studied in this experiment. TBS was performed over two different scalp positions: one was the "motor hot spot" for the right abductor pollicis brevis (APB) muscle and the other was a point 2cm posterior from this point. We recorded two baseline sessions of the SEP from stimulation of each arm before TBS to ascertain their reproducibility. A single SEP average was then obtained after stimulation of each arm for each time point after TBS. All subjects participated in two SEP experiments on different days, one for each of the two different scalp positions for TBS conditioning.

2.2.2. Experiment (2): assessment of the after-effect of TBS on MEPs

Ten subjects (9 men and 1 women; mean age (±SD): 42.3 ± 6.9) were studied in this experiment. Nine out of 10 subjects had participated in experiment (1). TBS was applied over two different scalp positions: one was the "motor hot spot" for the right first dorsal interosseous (FDI) muscle and the other was a point 2 cm posterior from this point. Twenty MEPs were recorded with an interstimulus interval of 5 s from the FDI muscle on each side in each session. We recorded two baseline sessions before and one session at each time point after TBS. All subjects participated in two MEP recording experiments with the conditioning TBS over two scalp positions on different days. Experiments 1 and 2 were performed on different days and the interval between each experiment was over 7 days in any one subject.

2.3. Somatosensory evoked potential (SEP) recording

During the sessions, subjects lay down in a bed and were observed continuously. Subjects were requested to close their eyes but to remain awake during recording SEPs. SEPs were recorded following electrical stimulation of the right or left median nerve at the wrist at 3 Hz with a pulse width of 0.2 ms. The intensity of stimulation was fixed at the motor threshold and was checked throughout the course of the experiment by monitoring the evoked EMG response in the APB muscle. At this stimulus intensity, scalp recorded SEPs are usually submaximal in amplitude. SEPs were recorded from scalp Ag–AgCl surface electrodes 2 cm posterior from C3 or C4 (parietal component) and 5 cm anterior from C3 or C4 (frontal component) referred to the contralateral earlobe according to the 10–20 electrode system for EEG placement. Recordings were made with a band-pass of 5 Hz to 1 kHz using a Synax 1200 (NEC, Japan). All data were collected at a sampling rate of 5 kHz for a 120 ms period beginning 20 ms before each stimulus. 500 responses were averaged in each session.

2.4. Motor evoked potential (MEP) recording

MEPs were recorded from Ag–AgCl surface electrodes over the right or left FDI or APB muscles. The signal was amplified and band-pass filtered (20–3000 Hz) by a Synax 1200 (NEC, Japan) and acquired at a sampling rate of 5 kHz on a personal computer for off-line analysis (Signal Software, Cambridge Electronic Design, Cambridge, UK). During the experiments EMG activity was continuously monitored with visual feedback to ensure complete relaxation at rest.

MEPs were evoked at rest by a single-pulse TMS with a High Power Magstim 200 machine and a figure of eight coil with mean loop diameters of 70 mm (Magstim Co., Whitland, Dyfed, UK). The magnetic stimulus had a nearly monophasic pulse configuration with a rise time of approximately 100 μs, decaying back to zero over approximately 0.8 ms. The coil current during the rising phase of the magnetic field flowed toward the handle. The coil was placed tangentially to the scalp with junction region pointing backwards and laterally at a 45° angle away from the midline, approximately perpendicular to the line of the central sulcus inducing a posterior–anterior current in the brain. We chose this orientation since motor threshold is minimum when the induced electrical current in the brain flows approximately perpendicular to the line of the central sulcus (Brasil-Neto et al., 1992; Mills et al., 1992). We determined the optimum position for activation of the FDI or APB muscles by moving the coil in 1 cm steps around the presumed M1. The site at which stimuli of slightly suprathreshold intensity consistently produced the largest MEPs in the target muscle was marked with a grease pencil as the "motor hot spot". Stimulus intensities for TMS were determined at the beginning of each experiment so that the amplitude of the MEP was about 1 mV peak to peak for the baseline before TBS. We recorded the MEP from the right as well as the left FDI muscles after a single-pulse TMS of the contralateral M1.

2.5. Theta burst stimulation (TBS)

We applied a continuous TBS paradigm (cTBS) for 40 s (600 pulses) to the left sensorimotor cortex. The main element of cTBS is a burst of 3 stimuli at 50 Hz which is repeated at 5 Hz as described by Huang et al. (2005). TBS was performed using a figure of eight coil with mean loop diameter of 70 mm, connected to a Magstim Super Rapid stimulator (Magstim Co., Whitland, Dyfed, UK). The magnetic stimulus had a biphasic waveform with a pulse width of approximately 300 μs. During the first phase of the stimulus, the current in the centre of the coil flowed toward the handle. Each individual's active motor threshold (AMT) over the M1 for the right FDI or APB muscle was determined prior to TBS using the Magstim Super Rapid stimulator and the coil orientation with the handle pointing backwards and laterally at a 45° angle away from the midline. AMT was defined as the lowest stimulus intensity at which 5 of 10 consecutive stimuli elicited reliable MEP (about 200 μV in amplitude) during slight (about 20% maximum) tonic contraction of the target muscle. A total number of 600 stimuli at 80% AMT for the FDI or APB muscles were applied during a single TBS session.

2.6. Data analysis

SEPs and MEPs were stored on a personal computer for off-line analysis. Peak-to-peak amplitudes of SEP components and MEPs were measured. Mean amplitudes of each component of two SEPs or 40 MEPs recorded before TBS were used as baseline values. The amplitude of SEPs or the mean amplitude of 20 MEPs recorded on each side at each time point after TBS was compared to the baseline values. Because the absolute latencies of SEP components varied among subjects, grand average waveforms were constructed by adjusting the time scale with respect to the peak latencies of the P14 far-field component of each waveform.

The effects of TBS on SEPs or MEPs were evaluated employing three-way repeated measures ANOVA (analyses of variance) with time course, side of stimulation or recording (SEPs evoked from the right vs. left median nerve stimulation, MEPs recorded from the right vs. left FDI muscles) and position of TBS (motor cortex vs. site 2 cm posterior to the motor cortex) as within-subject factors. In addition, the effects of TBS on SEPs or MEPs were evaluated employing separate two-way or one-way repeated measures ANOVA (analyses of variance) as within-subject factors. When necessary the Greenhouse-Geisser correction was used to correct for non-sphericity. Post hoc tests to compare the baseline values before TBS with those after TBS employed Bonferroni correction for multiple comparisons. A p value of <0.05 was considered significant for all statistical analyses.

3. Results

No subjects reported any side effects during or after the experiments.

3.1. After-effects on SEPs

Grand average waveforms of SEPs following right median nerve stimulation obtained from 11 subjects are shown in Figs. 1 and 2. The P14, N18, P22 and N30 in the frontal leads and P14, N20, P25, N33 and P40 peaks in the parietal leads are all clearly visible. After TBS over the left M1, the amplitudes of P22/N30 and P25/N33 components increased, whereas P14/N18, N18/P22, P14/N20 and N20/P25 components were relatively unaffected (Fig. 1). In contrast, TBS over the point 2 cm posterior to the left M1 reduced P22/N30 and P25/N33 (Fig. 2). Peak latencies of all components were unchanged.

The results of the three-way repeated measures ANOVA for each component are shown in Table 1. The clearest effects were on the parietal P25/N33 component (see mean data in Fig. 3) which showed significant two and three-way interactions for time course × position ($p = 0.002$) and time × side × position ($p = 0.011$). Follow-up ANOVAs showed that these interactions were due to the fact that (a) TBS had an effect on SEPs evoked from right but not from the left median nerve, and (b) for right median nerve stimulation, TBS over M1 increased the P25/N33 whereas it was decreased by TBS over the site 2 cm posterior. Thus, two-way repeated measures ANOVAs on the data from the right and left median nerve separately revealed a significant time × position interaction after right median nerve stimulation ($F_{7,70} = 5.7$, $p < 0.001$), but no significant main or interaction effects after stimulation of the left median nerve. One-way ANOVAs on the data from right median nerve stimulation following TBS over M1 or 2 cm posterior revealed a significant increase in P25/N33 after TBS over the M1 ($F_{7,70} = 3.4$, $p = 0.004$) whereas it decreased after TBS over the point 2 cm posterior ($F_{3,32} = 4.3$, $p = 0.01$). Post hoc tests indicated that the P25/N33 component of the SEPs from the right arm was facilitated for up to 53 min after the end of the TBS over M1, whereas this component was suppressed for up to 13 min after the TBS over the point 2 cm posterior. There was no effect on SEPs from the left arm after TBS over either scalp position.

There was a tendency for the frontal P22/N30 to behave in the same way as the parietal P25/N33, but we did not analyse this in detail because the three-way interaction time × side × position was only marginally significant ($p = 0.051$) and there were no other significant interaction or main effects.

The N33/P40 component was also influenced by TBS, although in this case, the lack of significant effects involving stimulation site in the three-way ANOVA (Table 1) indicated that any changes were the same after TBS at both sites of stimulation. There was a significant time × side interaction ($p = 0.018$) that was due to the fact that TBS only affected SEPs evoked from right but not left median nerve. Separate two-way repeated measures ANOVA on left and right median nerve stimulation with factors of time and position revealed a marginal time x position interaction for right median nerve ($p = 0.07$) but no significant main or interaction effects for the left. Finally, separate one-way repeated measures ANOVA revealed a significant effect of time only for right SEPs with post hoc tests showing facilitation for up to 53 min after the end of the TBS over the M1 (Fig. 4).

Finally the ANOVA showed a significant main effect of time course for the parietal P14/N20 component. The lack of any other effects suggests that this was due to a gradual

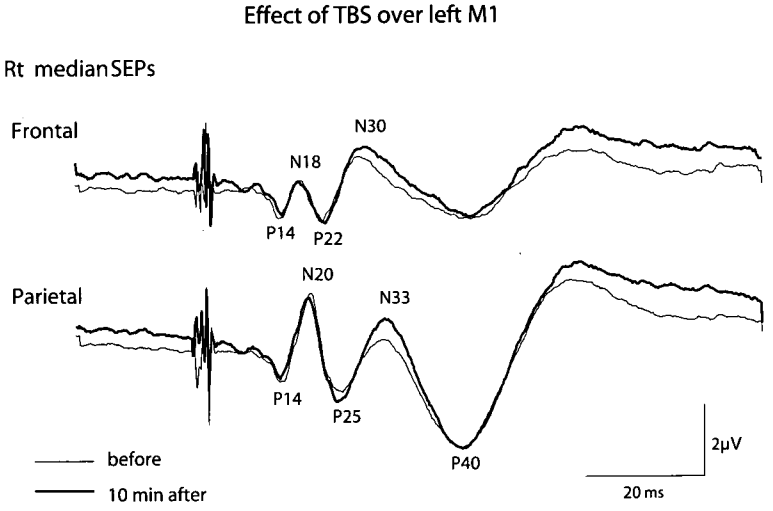

Fig. 1. Grand average waveforms of SEPs following right (Rt) median nerve stimulation ($n = 11$) before and after theta burst stimulation (TBS) over left motor cortex (M1). Two traces are superimposed: the thin line represents the response before conditioning, the thick line shows the response 10 min after conditioning. Amplitudes of P22/N30 and P25/N33 increased after TBS, whereas P14/N18, N18/P22, P14/N20 and N20/P25 components were relatively unaffected. Frontal: SEPs recorded from the fontal lead (5 cm anterior to C3), parietal: SEPs recorded from the parietal lead (2 cm posterior to C3).

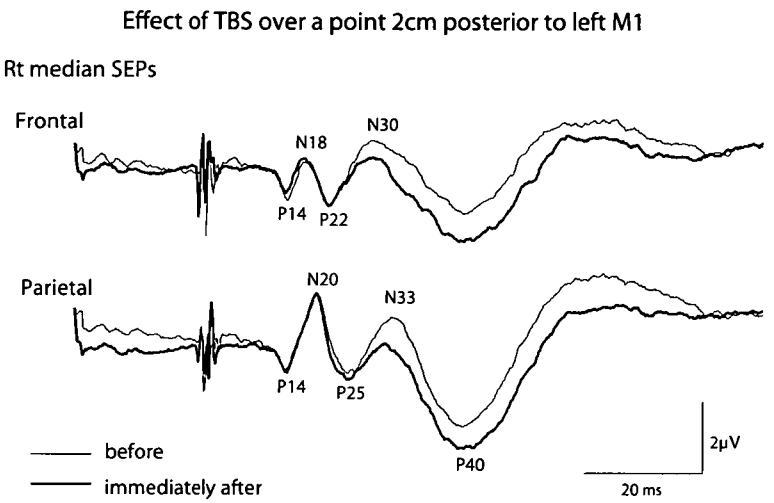

Fig. 2. Grand average waveforms of SEPs following right (Rt) median nerve stimulation ($n = 11$) before and after theta burst stimulation (TBS) over a point 2 cm posterior to left motor cortex (M1). Two traces are superimposed: the thin line represents the response before conditioning, the thick line shows the response just after conditioning. Amplitudes of P22/N30 and P25/N33 components decreased after TBS, whereas P14/N18, N18/P22, P14/N20, N20/P25 and N33/P40 components were relatively unaffected. Frontal: SEPs recorded from the fontal lead (5 cm anterior to C3), parietal: SEPs recorded from the parietal lead (2 cm posterior to C3).

decrease in amplitude over the time of the experiment that was independent of TBS at either site. However, the effect was small since separate one-way repeated measures ANOVA with time course as the main factor revealed no significant effect after TBS over either position on SEPs evoked from right or left median nerve.

3.2. After-effects on MEPs

Fig. 5 summarizes the after-effects of TBS on the MEPs. TBS over the left M1 decreased the amplitude of MEPs evoked by a single suprathreshold TMS stimulus in both the right and left FDI muscles, whereas there was no significant effect after TBS of the point 2cm posterior to M1. Thus, a three-way repeated measures ANOVA with time course, side of recording and position of TBS revealed a significant main effect of position ($F_{1,9} = 9.1$, $p = 0.015$) and significant interactions of position × time ($F_{7,63} = 3.4$, $p = 0.004$) and side × time ($F_{7,63} = 2.3$, $p = 0.036$). A separate two-way repeated measures ANOVA on the MEP data before and after TBS over left M1 with time and side of recording as main factors showed a significant main effect of time ($F_{7,63} = 3.8$, $p = 0.001$), but failed to show a significant interaction of side and time ($p = 0.7$). This was due to the fact that MEPs recorded from right and left FDI muscles decreased with a similar time course after TBS over left M1. Post hoc tests indicated that the MEPs in the right FDI muscle were significantly suppressed for up to 42 min after TBS over left M1 and the MEPs in the left FDI muscle were significantly suppressed for more than 50 min starting about 12 min after TBS (Fig. 5).

In contrast, two-way repeated measures ANOVA on the MEP data before and after 2 cm posterior TBS with main factors of time and side of recording failed to show any significant effects, suggesting there is no effect of TBS at this site on MEPs in either hand.

Table 1
Results of the three-way repeated measures ANOVA for the effect of TBS on SEPs

Variables	df	Frontal components				Parietal components							
		N18/P22		P22/N30		P14/N20		N20/P25		P25/N33		N33/P40	
		F	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
Time course	7	0.469	0.854	0.674	0.57 (df 2.887)	2.307	0.036*	1.07	0.392	1.138	0.35	1.416	0.267 (df 1.686)
Side of stimulation	1	0.017	0.898	0.006	0.94	0.489	0.5	0.181	0.68	1.285	0.283	0.12	0.736
Position of TBS	1	4.706	0.055	2.117	0.176	0.002	0.967	0.002	0.968	3.62	0.086	0.428	0.528
Time course × side	7	0.579	0.771	0.362	0.812 (df 3.545)	0.899	0.513	0.715	0.659	1.171	0.331	2.631	0.018*
Side × position	1	0.111	0.746	0.018	0.897	2.053	0.182	1.415	0.262	0.087	0.773	1.435	0.259
Time course × position	7	1.696	0.124	1.911	0.081	0.746	0.634	1.468	0.193	3.619	0.002*	1.821	0.097
Time course × side × position	7	0.437	0.876	2.138	0.051	1.748	0.112	1.493	0.184	2.874	0.011*	0.643	0.719

df, degrees of freedom; *F*, *F* values; *P*, *p* values (significance level); Underlined *p* values and df, corrected *p* values and df after Greenhouse Geisser correction.

* $p < 0.05$.

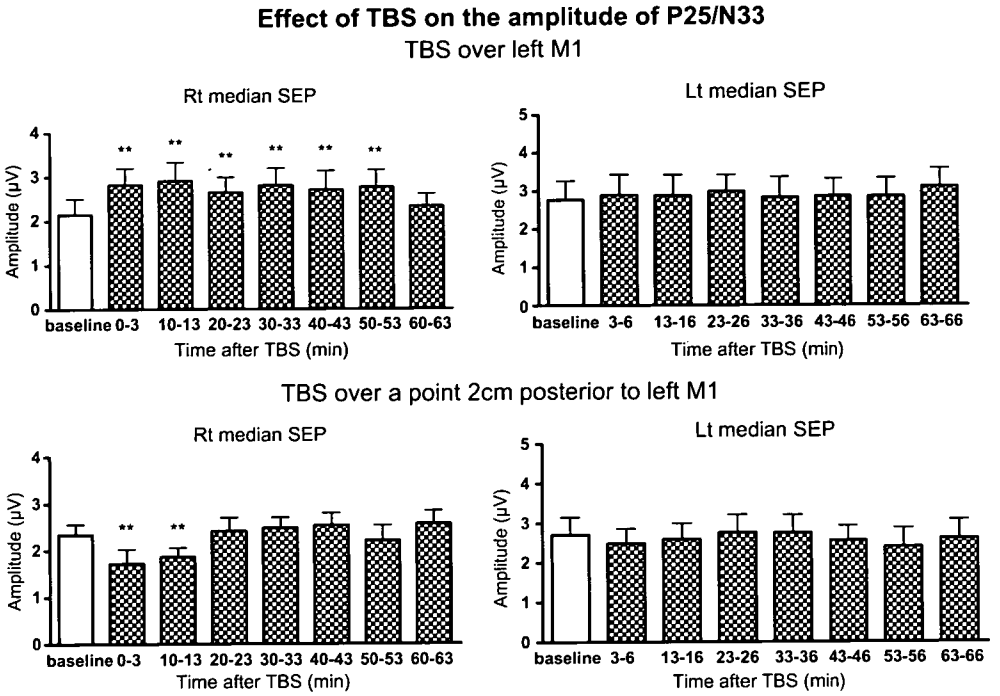

Fig. 3. Mean (±standard error) time course of effects of theta burst stimulation (TBS) on the amplitude of P25/N33 component of SEPs. Note that short-lasting (53 min) increase in amplitude of this component following right (Rt) median nerve stimulation was induced after TBS over left motor cortex (M1), whereas this component was suppressed for 13 min after TBS over the point 2 cm posterior to left M1 ($^{*}p < 0.05$, $^{**}p < 0.01$, Bonferroni correction). There was no effect on this component produced by left (Lt) median nerve stimulation.

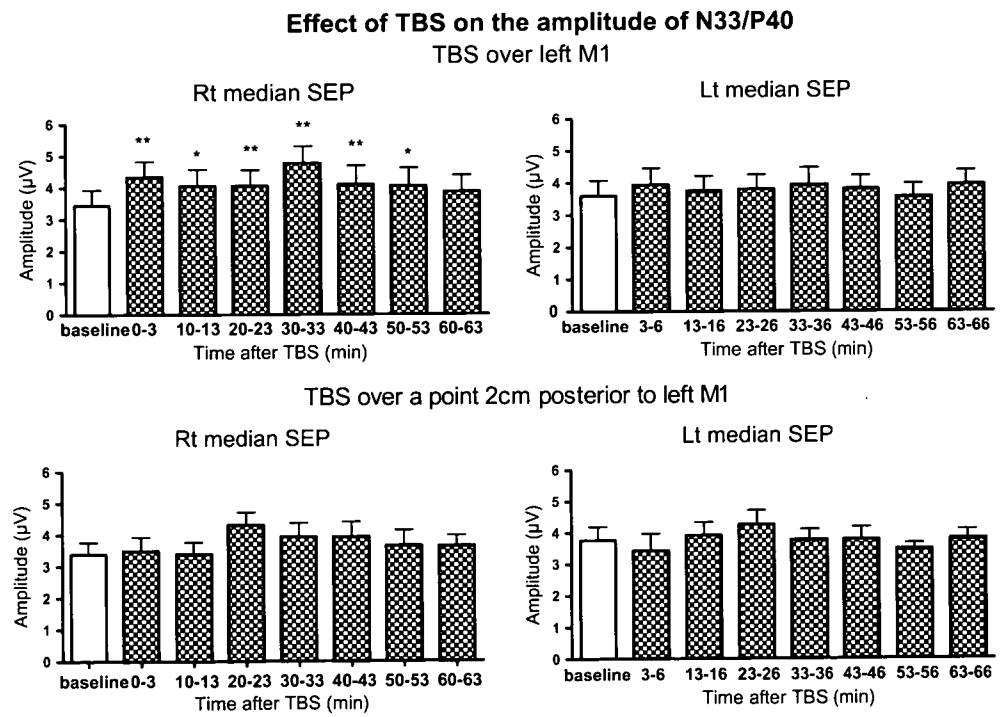

Fig. 4. Mean (±standard error) time course of effects of theta burst stimulation (TBS) on the amplitude of N33/P40 component of SEPs. Note that short-lasting increase (53 min) in amplitude of this component following right (Rt) median nerve stimulation was induced after TBS over left motor cortex (M1) ($^{*}p < 0.05$, $^{**}p < 0.01$, Bonferroni correction). There was no effect on this component from left (Lt) arm or after TBS over the point 2 cm posterior.

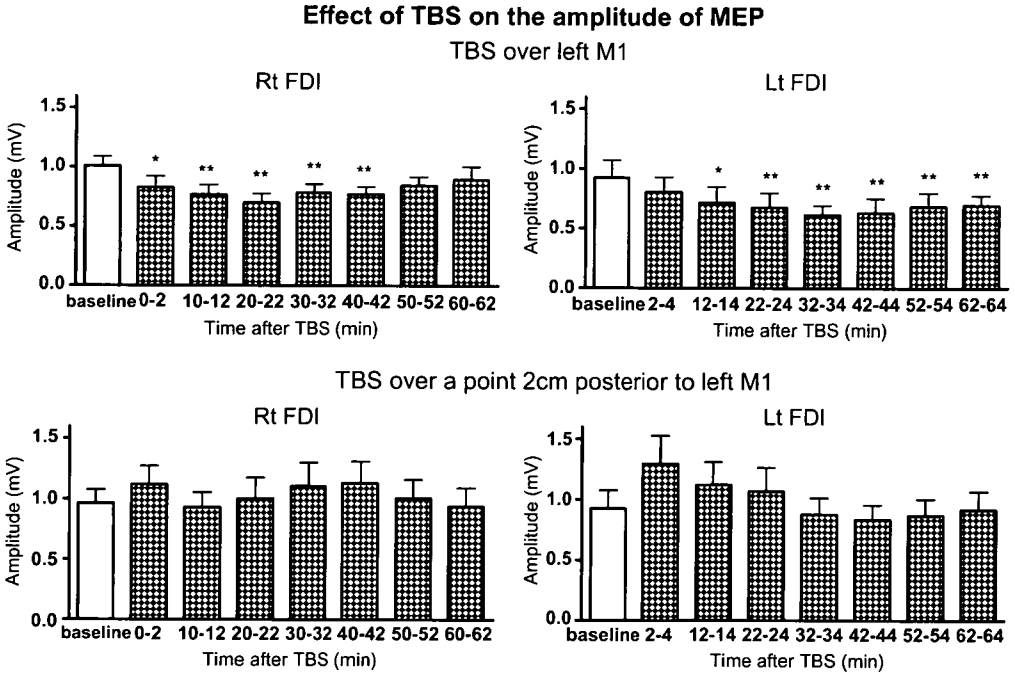

Fig. 5. Mean (±standard error) time course of effects of theta burst stimulation (TBS) on motor evoked potential (MEP) amplitude. Note that short-lasting suppression in MEP amplitude in the right (Rt) as well as left (Lt) first dorsal interosseous (FDI) muscles was induced after TBS over left motor cortex (M1) ($^{*}p < 0.05$, $^{**}p < 0.01$, Bonferroni correction).

4. Discussion

4.1. After-effects on SEPs

The present results show that TBS over the sensorimotor cortex changes the amplitude of later components of the SEP, particularly the P25/N33, evoked from the contralateral but not ipsilateral median nerve. However, the direction of the after-effects depended on the scalp position of the TBS. Following TBS over M1, the P25/N33 component was facilitated for about 50 min, which was similar to the time course of its effects on contralateral MEPs (experiment 2). However, TBS at the same intensity over a point 2 cm posterior to left M1 suppressed the P25/N33 component for at least 13 min, and had no effect on MEPs. We conclude that a short period of TBS at a low intensity can affect processing in somatosensory cortex.

The lack of effect of TBS on the P14/N20, N20/P25 and N18/P22 components suggests that its action is limited to cortical rather than subcortical structures. If so, then the cortical areas most likely to be affected by TBS are those on the surface of the brain directly under the stimulating scalp position. Neuroimaging studies (Terao et al., 1998) have shown that the motor "hot spot" for the hand lies over rostral area 4 on the crown of the precentral gyrus; Okamoto et al. (2004) using a neuronavigation system revealed that stimulation 2 cm posterior overlies areas 1 and 2 on the crown of the postcentral gyrus. TBS at these two points may then explain why there was little effect of TBS on the N20 component, since this is generated at some depth from the cortical surface in area 3b where cells will experience a smaller voltage gradient from the TMS (Allison et al., 1989, 1991). In contrast there was a clear effect on the P25/N33 component that involves generators in superficial area 1 (Jones et al., 1978). Previous studies have shown that continuous TBS has an inhibitory effect on the excitability of primary motor (Huang et al., 2005) and visual cortices (Franca et al., in press). Thus the TBS over a point 2 cm posterior to M1 may have suppressed excitability of area 1, leading to a reduction in amplitude of the P25/N33 component.

The effect of TBS over M1 on the P25/N33 component presumably reflects action in a cortico–cortical connection from the motor to sensory cortex. In fact, Enomoto et al. (2001) used a similar argument to explain the effect of 1 Hz rTMS on SEPs. They found that the largest effect on the SEP came from rTMS over the motor cortex hand area rather than a point 3 cm posterior, over sensory cortex. They reasoned that activation of projections from motor to sensory cortex was responsible for the effects they observed. Since these projections are mainly to areas 1 and 2 (Jones et al., 1978), this also explained the predominance of effects on the P25/N33 components and the smaller effect on N20.

The question is why the direction of the after effect of TBS over M1 on the P25/N33 component was facilitatory even though the TBS at the same site suppressed the amplitude of MEPs (experiment 2). One possible explanation is that TBS of motor cortex induces a compensation in sensory processing mechanisms, facilitating the latter while motor cortex excitability is suppressed. In fact, the time course of the effect on this component is very similar to