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Quadri-pulse stimulation (QPS) induced LTP/LTD was not affected by Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene

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ABSTRACT

It has been reported that the brain derived neurotrophic factor (BDNF) has some functional roles in inducing plasticity in the adult human brain and the Val66Met BDNF polymorphism affects the plasticity induction. In contrast, some long lasting effects were not fully induced in subjects with non-Val–Val polymorphism. In this communication, we retrospectively investigated whether this polymorphism affects the plastic changes induced by a newly developed stimulation method (quadripulse stimulation (QPS)) in 12 subjects. Both long-term potentiation (LTP) and long-term depression (LTD) like effects were induced by QPS for 30 min in any types of BDNF Val66Met polymorphisms. This finding presents a striking contrast to the previous results, which showed reduced long-term effects elicited by some other induction methods in subjects with non-Val–Val polymorphism. Although we are not able to make a final conclusion about the effect of Val66Met BDNF polymorphism on QPS because of the small number of subjects studied, QPS may be less affected by the BDNF polymorphism than several other protocols for inducing LTP/LTD-like effects in humans. Several possibilities may explain this difference. One candidate possibility is that QPS may be long enough for inducing the late LTP/LTD like effect whereas the other stimulation methods may be long enough for early but not enough for late LTP/LTD like effect. It is conspicuous that the QPS for 30 min does elicit stable bidirectional long-term effects even in subjects with non-Val–Val polymorphism of BDNF.

The brain-derived neurotrophic factor (BDNF), which is originally considered to have some important functions in the development of nervous systems in the fetal period and childhood, has been shown to have some roles in plasticity induction in the adult brain [2]. Its precursor peptide, pro-BDNF, has also been shown to play some roles in plasticity induction. The BDNF induces long-term potentiation (LTP), and pro-BDNF induces long term depression (LTD). Therefore, the bidirectional plasticity depends on whether BDNF or pro-BDNF is dominantly present [10]. Another impact of BDNF is the report that the Val66Met BDNF polymorphism has some influence on the activity-dependent BDNF secretion and its processing and also on human hippocampal function [4].

Several stimulation methods have been reported to induce LTP/LTD like effects on the human motor cortex, and their application to the treatment of neurological disorders is promising. We have described a newly developed stimulation method to induce long-term effects using monophasic pulses of TMS, which is called QPS (quadri-pulse stimulation) [5]. Its metaplastic changes were also induced by the priming stimulation over the primary motor cortex (M1) [5] and supplementary motor area (SMA) [6]. These results suggest that QPS can induce LTP/LTD like effects on M1. In the meantime, one paper recently demonstrated that the theta bust stimulation (one of long term effects inducing methods) did not induce significant plastic changes in the human motor cortex in some BDNF polymorphism carriers even though it induced significant changes in subjects with other BDNF polymorphisms [3]. This finding has been confirmed by a following study [1]. It also showed

Abbreviations: BDNF, brain derived neurotrophin factor; TMS, transcranial magnetic stimulation; LTP, long term potentiation; LTD, long term depression; QPS, quadripulse stimulation.

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that different stimulation methods were variously affected by BDNF polymorphism, and stressed the need to consider BDNF polymorphism in the interpretation of the long-term effects [1]. To explore whether this polymorphism affects QPS in a similar manner, we retrospectively compared the QPS effects between two groups of BDNF polymorphism.

We studied 12 subjects, who participated in our previous two studies [5,6] and gave written informed consent to take part in genetic analyses. As a parameter of QPS effect, in the present study, we use the relative motor evoked potential (MEP) size at 30 min after QPS5 or QPS50 to the baseline response before QPS (size ratio 30 min) as a representative value of LTP or LTD because we used this parameter to draw a relation between the inter-stimulus interval of QPS and its main effect [5,6]. We also compared the whole time courses of the LTP/LTD effects between subjects with different BDNF polymorphism. The genomic DNA was extracted from peripheral leukocytes by standard procedures. Polymerase chain reaction (PCR) and the PCR-based restriction fragment length polymorphism (RFLP) assay were performed to determine the genotype of the DNA sequence variant, Val/Met polymorphism of the BDNF gene as reported previously [8]. The subjects were classified into two groups according to the BDNF polymorphism: Val–Val group and non-Val–Val group (Val–Met or Met–Met). The size ratios at 30 min were compared between these two groups using Student's *t*-test. The time courses for LTP or LTD were independently compared between the two groups of subjects using two factorial analysis of variance (ANOVA) test using GROUP (Val–Val and non-Val–Val) as between-subject factor and TIME (5, 10, 15, 20, 25, and 30 min after the end of QPS) as within-subject factor. Post hoc analyses were performed using the Bonferroni method to compensate for multiple comparisons. Statistical analyses were performed using a commercial software SPSS (ver. 16.0). These procedures were approved by the Ethics Committees of Fukushima Medical University, the University of Tokyo and Chiba University.

The 12 participants were genotyped as follows: 5 participants were found to be homozygous for the Val allele (Val66Val), 5 were Val66Met heterozygotes, and 2 were homozygous for the Met allele. The two groups, therefore, consisted of 5 subjects with Val–Val polymorphism and 7 subjects with non-Val–Val polymorphism. In QPS5 experiments, the mean (±SD) size ratio at 30 min after QPS was 2.07 (±0.96) for the Val–Val group and 2.22 (±0.61) for the non-Val–Val group (Fig. 1A). In QPS50 experiments, they were 0.53 ± 0.45 for Val–Val and 0.70 ± 0.38 for non-Val–Val groups (Fig. 1A). These were not significantly different between the two groups (*t*-test: $P > 0.3$ for both QPS5 and QPS50). The time courses of LTP/LTD like effects are shown in Fig. 1B and C. ANOVA revealed no significant effect of GROUP on the size ratio ($P = 0.955$ for QPS5, $P = 0.735$ for QPS50). The TIME had a significant effect on the size ratio ($P = 0.046$ for QPS5, $P = 0.034$ for QPS50). No significant interaction between these factors was seen ($P = 0.535$ for QPS5, $P = 0.680$ for QPS50). Post hoc analyses corrected for multiple comparisons revealed that significant potentiation was elicited by QPS 5 (Bonferroni method: $P = 0.034, 0.037, 0.008, 0.017, 0.0005, 0.0008$ for 5, 10, 15, 20, 25, 30 min after QPS, respectively), and significant suppression by QPS 50 (Bonferroni method: $P = 0.004, 0,006, 0.001, 0.0006, 0.003, 0.01$ for 5, 10, 15, 20, 25, 30 min after QPS, respectively).

We showed that normal amount of LTP and LTD like effects were induced by QPS for 30 min in any types of BDNF Val66Met polymorphisms. This finding presents striking contrast to the previous two papers [1,3]. They showed that, in non-Val–Val polymorphism subjects, some long-term effects were reduced in TBS, transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and paired associative stimulation (PAS) protocols.

Several possibilities may explain this discrepancy between their and our results.

The difference in duration of stimulation may be one important factor to explain this discrepancy. The QPS protocols gave TMS pulses for 30 min, and during this period the subjects should keep the target muscle relaxed. On the other hand, iTBS takes only 190 s, and tDCS, tRNS or PAS takes 10–13 min in total. The importance of QPS duration has been shown in our previous paper [5]. In contrast to the bidirectional after-effects of QPS for 30 min, QPS5ms for 10, 20 and 40 min unaffected MEP sizes after the protocols even though some of them had a priming effect. Why is the duration of stimulation so important? Two observations may explain the importance of duration of stimulation. One is the time needed for protein synthesis contributing to the synaptic plasticity, and the other is the fact that some target muscle voluntary contraction abolishes LTP/LTD like effects in humans. Some protein synthesis needed for late LTP/LTD begins around 30 min after stimulation [11], and actual synaptic morphological changes were seen 30 min, at shortest, after the burst stimulation in slice experiments [13]. In QPS experiments, MEP size changes were first accessed 30 min after QPS stimulation onset. In the other methods, however, they were measured 190 s to 13 min after the onset of their protocols. Measurements at these short intervals after stimulation may miss the effects. In addition, it is well known that target muscle contraction during a protocol abolishes the long term effects induced by TBS [7]. In the following MEP measurements, unintentional target muscle contractions sometimes occur. These unintentional contractions should disturb some cascade for the long-term effects. In contrast, the subjects should keep the target muscle relaxed in QPS stimulation for 30 min. It ensures complete relaxation of the target muscle for 30 min. Combination of these two factors should explain the importance of stimulation duration in LTP/LTD like effects induction in humans. The BDNF polymorphism may have a comparatively strong influence on the secretion of BDNF but no influence on its function [4]. If the duration of repetitive stimulation or the duration of stimulation and complete relaxation after stimulation is long enough for inducing the secretion of the total amount of BDNF for later LTP or LTD cascade even though the secretion is slow, normal magnitude of LTP or LTD must eventually be induced even in subjects with non-Val–Val polymorphism of BDNF. The usual LTP/LTD induction protocols elicit BDNF secretion which enhances its secretion presynaptically and postsynaptically by themselves [9], and the BDNF secretion may continue even after the protocols have ceased. This cascade must be blocked at some part when voluntary contraction contaminates. Based on these arguments, we suppose that QPS for 30 min in a completely relaxed state may be long enough for stable LTP/LTD like effects to be induced even in subjects with non-Val–Val BDNF polymorphism.

The second possible explanation for the discrepancy is the strength of LTP/LTD like effects. The LTP/LTD like effects induced by QPS may be stronger than those by the other methods. If so, strong QPS effects may not be affected by the Val66Met polymorphism in BDNF. The weak priming effects by shorter duration QPS may be affected by this polymorphism.

Another possible explanation is that there are differences in some parts of the cascade for LTP/LTD like effects induction between several induction methods, and some of them are affected by BDNF polymorphism, and some other part may be affected by another polymorphism. Many investigations have studied the influence of BDNF Val66Met polymorphism on LTP/LTD like effects. It is well known that several other factors affect these long-term effects, such as dopamine or serotonine [12]. Some polymorphisms of dopaminergic, serotonergic or other genes may also affect QPS.

This study has a few limitations. The first is the small number of subjects studied. Our subjects were not sufficient to make a firm conclusion about the BDNF polymorphism effects on QPS

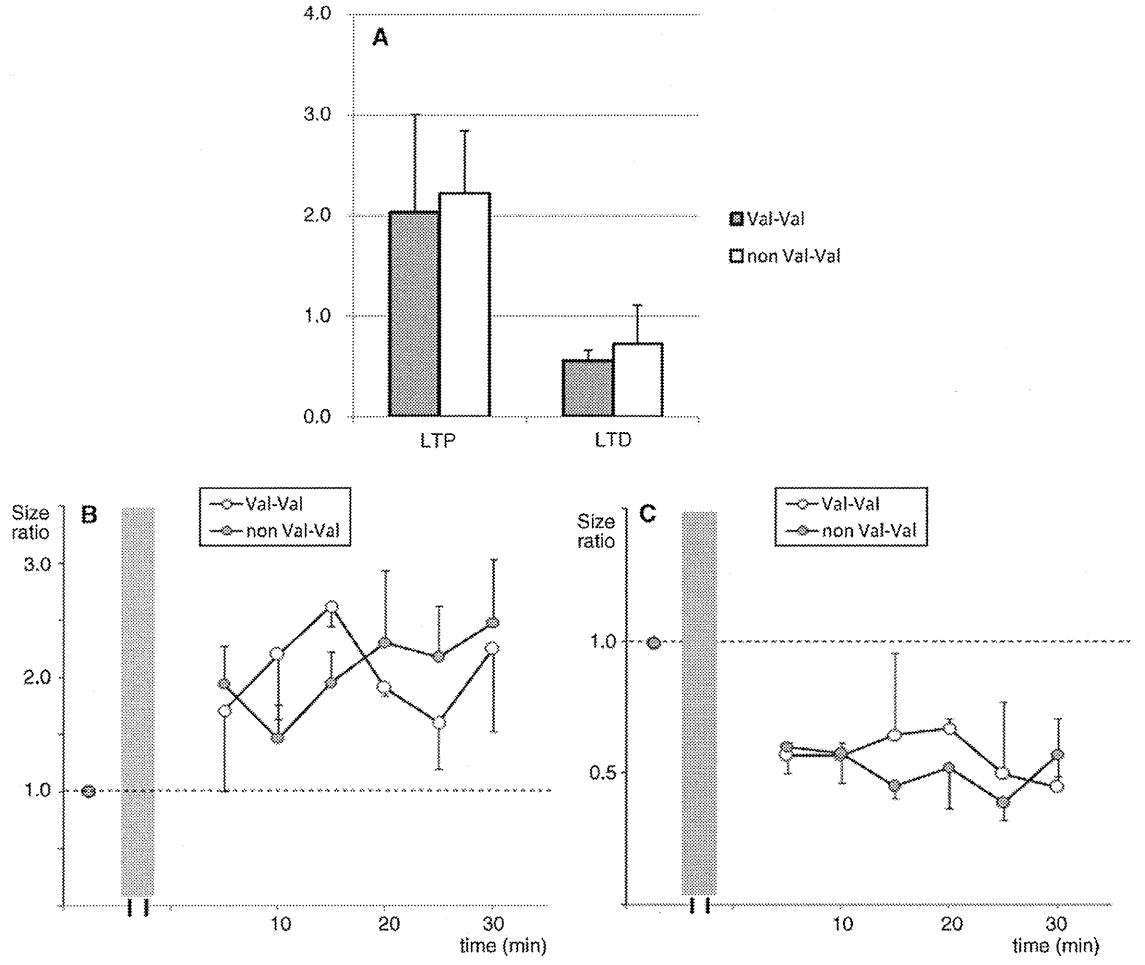

Fig. 1. (A) MEP size ratio at 30 min after QPS. The filled bars show the mean ± standard error (SE) size ratios after QPS5, and white bars those after QPS50. There were no significant differences between the subjects groups of Val–Val and non-Val–Val. (B) The mean ± standard error (SE) time courses of LTP like effects induced by QPS5 in Val–Val and non-Val–Val groups. Similar potentiation was induced in both groups of subjects. The time course did not significantly differ between the two groups of subject. (C) The mean ± standard error (SE) time courses of LTD like effects induced by QPS50 in Val–Val and non-Val–Val groups. Similar depression was induced in both groups of subjects. The time course did not significantly differ between the two groups of subject.

induced plasticity. We will study more subjects prospectively in the future. Another drawback is the lack of studies of effects of stimulation duration on QPS results. We should study several stimulation durations of QPS and compare their results. This is also one of the future research projects on QPS. As mentioned above, investigations of other genetic polymorphisms are also one of future projects.

Even with these limitations, it is a conspicuous point of this study that QPS for 30 min does elicit stable bidirectional long-term effects even in subjects with non-Val–Val polymorphism of BDNF.

Disclosures statement

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RESEARCH ARTICLE

Triad Stimulation Frequency for Cortical Facilitation in Cortical Myoclonus

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ABSTRACT: Background: Abnormally enhanced cortical rhythmic activities have been reported in patients with cortical myoclonus. We recently reported a new triad-conditioning transcranial magnetic stimulation (TMS) method to detect the intrinsic rhythms of the primary motor cortex (M1). Triad-conditioning TMS revealed a 40-Hz intrinsic rhythm of M1 in normal subjects. In this investigation, we study the motor cortical facilitation induced by rhythmic triple TMS pulses (triad-conditioning TMS) in patients with cortical myoclonus.

Methods: Subjects were 7 patients with cortical myoclonus (28–74 years old) and 13 healthy volunteers (30–71 years old). Three conditioning stimuli over M1 at the intensity of 110% active motor threshold preceded the test TMS at various interstimulus intervals corresponding to 10–200 Hz. The resulting amplitudes of conditioned motor evoked potentials recorded from the contralateral hand muscle were compared with those evoked by the test stimulus alone.

Results: The facilitation at 25 ms (40 Hz) observed in normal subjects was absent in patients with cortical myoclonus. Instead, triad-conditioning TMS induced facilitation at a 40 ms interval (25 Hz) in cortical myoclonus.

Discussions: This change in the timing of facilitation may be explained by a shift of the most preferential intrinsic rhythm of M1, or by some dysfunction in the interneuronal network in cortical myoclonus. © 2011 *Movement* Disorder Society

Key Words: transcranial magnetic stimulation; motor evoked potentials; cortical intrinsic rhythm; gamma band; beta band

Cortical myoclonus is a brief muscle jerk generated by abnormal activation of the sensorimotor cortex. Some patients with cortical myoclonus show rhythmic electromyographic (EMG) bursts. These rhythmic myoclonus jerks consist of EMG bursts with frequencies of 10,[1] 20,[2] or 50 Hz.[3,4] Jerk-locked back averaging (JLA)[5,6] and electroencephalography (EEG)-EMG coherence analyses[4,7] have revealed the same rhythmic cortical activities. Brown et al. (1999)[4] considered that the cortical rhythmic activities at frequencies of around 20, 40, and up to 175 Hz play important roles in the generation of cortical myoclonus. Of all these frequencies, 20 Hz has been considered especially important in cortical myoclonus.[2,8–10] However, the physiological significance of 20 Hz is still unclear. We have recently shown the presence of a 40-Hz intrinsic motor cortical rhythm in normal subjects using a newly developed triad-conditioning transcranial magnetic stimulation (TMS) method.[11] In this article, we applied this triad-conditioning TMS method to patients with cortical myoclonus.

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TABLE 1. Patients' data

No.	Gender	Age	Diagnosis	AED
1	M	74	Benign myoclonus epilepsy	Phenytoin sodium
2	M	64	Benign myoclonus epilepsy	Clonazepam, valproic acid, phenytoin sodium
3	M	42	Benign myoclonus epilepsy	Clonazepam, valproic acid, primidone
4	F	59	Benign myoclonus epilepsy	Valproic acid
5	F	51	Benign myoclonus epilepsy	Clonazepam
6	F	51	Benign myoclonus epilepsy	Phenytoin sodium
7	M	28	Autoimmune-mediated encephalopathy	Carbamazepine, valproic acid

M: male, F: female, AED: antiepileptic drug.

Methods

Subjects

Seven patients with myoclonus epilepsy (4 men and 3 women; mean age 56.8 ± 11.3 years; age range 28–74 years; Table 1) and 13 age-matched healthy volunteers (7 men and 6 women, mean age 49.2 ± 13.6 years; age range 32–75 years) participated in this study. Six patients were diagnosed with benign myoclonus epilepsy because lysosomal enzyme activities, analyses of mitochondrial genes, and brain MRI were all normal. Another patient had autoimmune encephalitis. All the patients were on some antiepileptic drugs (AEDs: clonazepam, valproic acid, phenytoin sodium, phenobarbital, and primidon) during our study. The diagnoses of cortical myoclonus were made based on clinical features and electrophysiological studies. All patients had spontaneous, reflex, and action myoclonus in their hands, but none of them had rhythmic myoclonus. They all had paroxysmal abnormal EEG discharges and abnormally enhanced median nerve somatosensory evoked potentials (SEPs) (giant SEPs: the amplitude of P25–N33 was 17.9–37.5 μV) with enhanced long-loop reflexes. No patients in the present study were participants in our previous study.[12] Healthy volunteers had neither neurological disorders nor episodes of seizure. Written informed consent to participate in this study was obtained from all the subjects. The experiments were performed according to the Declaration of Helsinki; the procedures were approved by the Ethics Committee of the University of Tokyo. No adverse effects were noted in any individuals.

Electromyographic Recordings

Surface EMG signals were recorded from the right first dorsal interosseous muscle using 9-mm-diameter Ag-AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified (Biotop; GE Marquette Medical Systems Japan, Japan) through filters set at 100–3 kHz, digitized at a sampling rate of 20 kHz, and stored on a computer (TMS bistim tester; Medical Try System, Japan) with which we performed a randomized conditioning test paradigm and off-line averaging. Because muscle relaxation was very important in this experiment, EMG activities were monitored on an oscilloscope during the experiments. Subjects kept the right first dorsal interosseous muscle relaxed throughout the experiments by monitoring EMG activity on the oscilloscope. Trials in which EMG activity appeared during data collection were not used in the analysis.

Transcranial Magnetic Stimulation

Four Magstim 200^2 magnetic stimulators (The Magstim Company, UK) were used to deliver TMS. We placed a figure-8-shaped coil (7-cm external diameter at each wing; The Magstim Company, UK) over the primary hand motor area (M1) of the left hemisphere. Induced currents in the brain flowed in the posterior to anterior direction. To determine the hot spot for the first dorsal interosseous muscle in each subject, we changed the stimulation site in 1-cm steps starting at a point 5 cm lateral to the vertex and determined the location at which the largest responses were elicited by the same intensity stimulation. This position was marked on the scalp using a red pen to guide repositioning of the coil throughout the experiments. Outputs from four magnetic stimulators were connected with a special device (Combine module, The Magstim Company, UK) that enabled us to deliver four monophasic pulses through the same coil.

We determined the threshold for evoking EMG activities in the active target muscle (active motor threshold: AMT) when the subject contracted the target muscle at 5–10% of maximum contraction. The stimulation intensity was changed in steps of 1% of the maximum stimulator output until we determined the lowest intensity that evoked a small response at the amplitude of 200 μV, compared with the prestimulus background activity in half of the trials.

Short Interval Intracortical Inhibition and Intracortical Facilitation

To evaluate the cortical excitability changes, we studied the short interval intracortical inhibition (SICI)

and intracortical facilitation (ICF) using the paired pulse TMS method first reported by Kujirai et al.[13] In the SICI experiment, we used the conditioning stimulus at 90% AMT and interstimulus intervals (ISIs) of 3, 4, and 5 ms. We set the conditioning stimulus at 110% AMT and used ISIs of 7, 8, and 10 ms in the ICF experiment.

Triad-Conditioning TMS

We used the same method as has been reported previously.[11] Here, we describe it briefly. Three subthreshold conditioning TMS pulses were set at 110% AMT. The test stimulus was set to elicit an MEP as large as 0.3 mV in the relaxed muscle when given alone. The final pulse of the conditioning triad preceded the test pulse by the same interval as that between the conditioning pulses. The ISIs between the pulses were 5, 7, 8, 10, 15, 20, 25, 30, 40, 50, and 100 ms (corresponding, respectively, to 200, 143, 125, 100, 66, 50, 40, 33, 25, 20, and 10 Hz). We used a randomized conditioning test paradigm. In one session, several conditioned trials in which a triad of conditioning pulses with several ISIs preceded the test stimulus were intermixed randomly with control trials in which the test stimulus was given alone. The intertrial interval was set at 12–15 s. Two blocks of trials were performed to investigate all intervals. In the first block, the ISIs were 5, 7, 8, and 10 ms; in the second block, the ISIs were 15–100 ms. Ten responses were collected and averaged for each condition in which four stimuli were given; 20 responses were collected for the control condition. For each subject, we calculated the ratio of the mean amplitude of the conditioned response to that of the control response at each ISI. The time course of the effect of the conditioning triad was plotted with this ratio on the ordinate and the ISI on the abscissa.

Single Pulse Conditioning TMS

To study whether a single-pulse conditioning stimulus is able to elicit the same effect evoked by the triad-conditioning stimulus, we performed a single-pulse conditioning TMS experiment in 6 patients, in which only a single TMS pulse was given instead of triad conditioning. The intensity of the conditioning stimulus was fixed at 110% AMT.

Statistical Analysis

Statistical analyses were performed using SPSS v. 14.0 for Windows (SPSS, Chicago, USA). To compare the effects of triad-conditioned MEPs between patients with cortical myoclonus and healthy volunteers, we used two-way repeated measures analysis of variance (ANOVA) for two experimental blocks separately (first block: 5–10 ms; second block: 15–100 ms) [Group (myoclonus and normal); ISI (control, ISIs of 5, 7, 8, and 10 ms or control and ISIs of 15, 20, 25, 30, 40, 50, and 100 ms)].

The dependent variable was the MEP size. When necessary, the Greenhouse-Geisser correction was used to correct for nonsphericity. Tukey's test was used for multiple comparisons in post hoc analyses; *P*-values less than 0.05 were considered significant. If there was significant interaction between two factors, we used a paired *t*-test to compare MEP sizes at two intervals judged as having some physiological meaning (ISIs of 25 or 40 ms).

To compare the amount of SICI or ICF between patients with myoclonus and healthy volunteers, we used two-way repeated measures ANOVA [Group (myoclonus and normal); ISI: 3, 4 and 5 ms for SICI and 7, 8, and 10 ms for ICF]. The dependent variable was the MEP size ratio.We compared the MEP size ratios between the triad and single-pulse conditioning stimulus experiments at ISI of 40 ms using a paired *t*-test.

Data are described as mean ± standard error (SE) in the following presentations, unless otherwise indicated.

Results

The mean AMT was 35.8 ± 3.36% (SE) in cortical myoclonus, which was not significantly different from that of healthy volunteers (37.2 ± 1.75%). The amount of SICI[12] was abnormally reduced in all of them and significantly different from that of healthy volunteers [Group F (1, 48) =12.5 $P < 0.05$; ISI F (2, 48) = 5.25, $P < 0.05$; ISI × Group F(2, 48) = 3.43, $P < 0.05$]. The mean average size ratio (3–5 ms) was 1.03 ± 0.14 in cortical myoclonus patients and 0.59 ± 0.06 in healthy volunteers. There were no significant differences in the ICF between cortical myoclonus patients and healthy volunteers [Group F (1, 32) = 2.35, $P > 0.05$; ISI F (2, 32) = 0.729, $P > 0.05$; ISI × Group F (2, 32) = 0.184, $P > 0.05$]. The mean average-size-ratio (7–10 ms) was 1.54 ± 0.45 in cortical myoclonus patients and 1.29 ± 0.13 in healthy volunteers.

Figure 1 depicts how the MEP amplitude to a test TMS was modulated by triad-conditioning stimuli in patients with cortical myoclonus and healthy volunteers.

For the first interval block of 5–10 ms, two-way repeated measures ANOVA revealed a significant effect of ISI, [ISI 5–10 ms ISI – F (4, 72) = 8.62, $P < 0.01$] but no interaction between the subject group and ISI [(ISI × Group)—ISI 5–10 ms F (4, 72) = 0.961]. For the second interval block of 15–100 ms, two factor ANOVA revealed a significant interaction between ISI and group (F (7, 126) = 4.995, $P < 0.01$] and a significant effect of ISI [F (7, 126) = 2.203, $P < 0.05$]. At ISI of 5–10 ms, MEPs were significantly

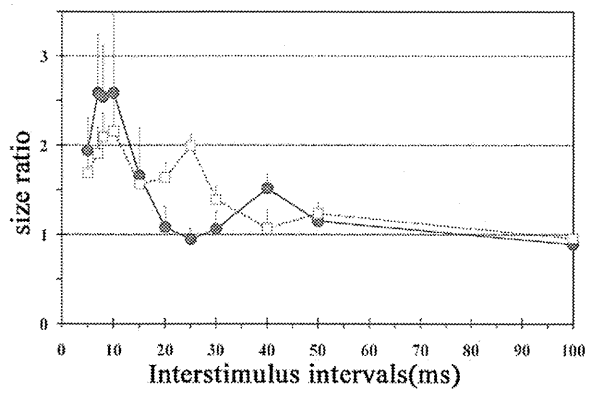

FIG. 1. Time courses of the size ratio of conditioned MEP to control MEP for the triad-conditioned TMS experiment in normal subjects (squares) and patients with cortical myoclonus (dots). The ordinate displays the size ratio of conditioned MEP to control MEP; the abscissa shows the ISIs between successive pulses. Two peaks demonstrate facilitation at ~ 7–8 ms and at 25 ms in healthy volunteers. In patients with cortical myoclonus, the facilitation was absent at 25 ms but present at 40 ms.

larger than control MEPs in both subject groups. Significant enlargement was seen at 20 and 25 ms in healthy volunteers but not in cortical myoclonus patients. In contrast, MEP enlargement was seen at 40 ms ($P < 0.05$) in cortical myoclonus.

To confirm the necessity of triad-conditioning stimulus for inducing the facilitation, we compared the facilitation at a 40-ms interval between the triad and single-pulse conditioning stimulus experiments (Fig. 2). The size ratio at an ISI of 40 ms was significantly larger in the triad-conditioning experiment than in the single-pulse experiment. Significant facilitation was evoked by the triad-conditioning stimulus but not by the single-pulse conditioning stimulus.

Discussion

The triad-conditioning stimulus facilitated test MEPs at two intervals (7–10 ms and 25 ms) in healthy volunteers, as shown in our previous report.[11] In cortical myoclonus, the early peak at ISIs of 7–10 ms was normally present, but the later facilitation at 25 ms was absent. Instead, MEP was significantly enlarged at an ISI of 40 ms in patients with cortical myoclonus.

All patients took their daily AED regimens during this study. AEDs must alter cortical excitability and may affect the amount of inhibition or facilitation studied by TMS. In fact, many articles have shown that AEDs reduce motor cortical excitability or enhance motor cortical inhibition,[14–17] but none reported any enhancement of the motor cortical excitability. We therefore consider that AEDs may explain neither the facilitation at an ISI of 40 ms shown by triad-conditioning TMS nor the reduced SICI in cortical myoclonus.

Reduction of SICI in Cortical Myoclonus

Consistent with previous reports,[18,19] the amount of SICI was smaller in patients with cortical myoclonus than in normal subjects. The reduction of SICI is most likely due to dysfunction of the inhibitory interneuronal network because pathological studies have revealed involvement of GABAergic interneurons of the motor cortex.[20] We used ISIs of 3–5 ms to study SICI based on our previous report.[21] Peurala et al.[22] suggested that short interval intracortical facilitation could overlap with SICI at these ISIs and may affect the results of SICI experiment. However, this overlap is usually seen when using a stronger conditioning stimulus (greater than 95% AMT).[22] Based on these arguments, we consider that this possibility less likely explains the reduced SICI because lower conditioning stimuli were used in the present experiments.

Facilitation at 7–8 ms

We[11] have previously proposed that the facilitation at 7–10 ms is produced by the same mechanism as the intracortical facilitation (ICF) in paired pulse magnetic stimulation.[23,24] This 7–10 ms facilitation is unrelated to rhythmic activities because even a single conditioning stimulus can evoke this facilitation.[11] In patients with cortical myoclonus, both the ICF and the 7–8 ms facilitation in the triad-conditioning stimulus experiment were normally elicited. This is consistent with normal ICF in cortical myoclonus reported previously.[24]

Facilitation at 40 ms without 25 ms Facilitation in Cortical Myoclonus

Instead of facilitation at 25 ms (40 Hz), the triad-conditioning stimulus elicited facilitation at 40 ms (25 Hz) in cortical myoclonus. Several mechanisms

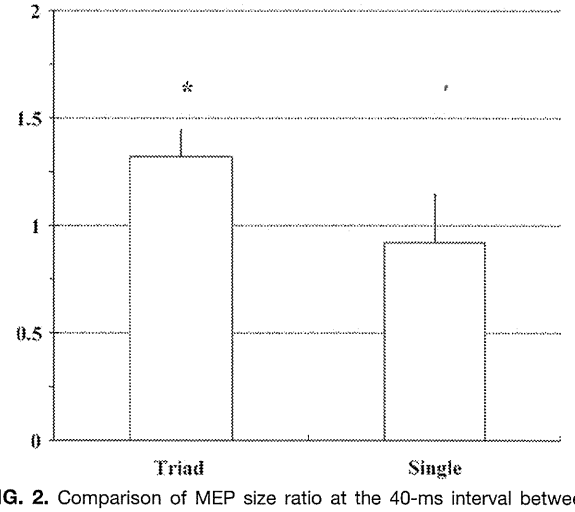

FIG. 2. Comparison of MEP size ratio at the 40-ms interval between triad and single-pulse conditioning stimulus experiments. The ratio in the triad-conditioning experiment differs significantly from that of the single-pulse conditioning experiment.

that may explain these findings correlate strongly with which mechanism produces the facilitation shown by triad conditioning experiments.

Following our previous hypothesis,[11] the motor cortical intrinsic rhythm and its changes may explain the present whole results. The rhythmic triad conditioning stimulus is originally considered to enhance a certain intrinsic rhythm generated by interneurons or some neuronal loops. The simple explanation for the present results directly following our hypothesis is that the normally undetectable 25 Hz intrinsic rhythm is enhanced and the normally present 40 Hz intrinsic rhythm is reduced in cortical myoclonus because several previous reports have revealed these rhythmic activities in cortical myoclonus.[2,6]

Another possibility is that the triad-conditioning TMS may change the frequency of the cortical intrinsic rhythm to a new rhythm synchronizing with the stimulation frequency. This rhythm after modulation by the triad conditioning stimulus (triad modulated rhythm) may be detected by our experiment. The triad modulated rhythm is 40 Hz in normal subjects and 25 Hz in cortical myoclonus. Even in this case, the motor cortex must tend to synchronize to 25 Hz for some reason. Several previous papers support this explanation of the intrinsic rhythm. Some patients with cortical myoclonus have rhythmic EEG activities at a frequency of 20 Hz coupled with myoclonic jerks.[2] In such patients, single conditioning stimuli of 100% RMT were able to induce facilitation at 50 ms. We also revealed 20 Hz oscillatory EEG potentials preceding the myoclonic jerk in jerk-locked averaging methods in patients with rhythmic myoclonus.[6] Some animal data also support this hypothesis. Animal studies have revealed that the beta rhythm (including 25 Hz) is produced in layer V of the cortex,[25] the gamma rhythm (including 40 Hz) originates from cortical layer II/III,[26,27] and both layers mutually modulate each other.[28] In cortical myoclonus, dysfunction of cortical inhibitory interneurons at layer II/III may reduce the gamma rhythm,[29] and the preferential rhythm may shift to the usually masked beta rhythm.

A nonintrinsic rhythm mechanism may explain our results. The motor cortical excitability is simply enhanced at 40 ms in cortical myoclonus, independent of changes in the intrinsic cortical rhythm. The triad-conditioning stimuli may be strong enough to induce facilitation at 40 ms even though a single stimulus is not strong enough. Some interneuronal dysfunction of the motor cortex may cause this facilitation.

Either or both of the above-mentioned intrinsic rhythm and nonintrinsic rhythm mechanisms may explain the lack of 25 ms facilitation and the occurrence of 40 ms facilitation. Whichever mechanism explains our results, we conclude that the motor cortex tends to be activated by multiple stimuli at a certain interval. Our new stimulation method must be useful to investigate some motor circuit abnormalities, including intrinsic rhythmic changes in humans. ■

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SUPPLEMENT

Inclusion and Exclusion Criteria for DBS in Dystonia

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ABSTRACT:

When considering a patient with dystonia for deep brain stimulation (DBS) surgery several factors need to be considered. Level B evidence has shown that all motor features and associated pain in primary generalized and segmental dystonia are potentially responsive to globus pallidus internus (GPi) DBS. However, improvements in clinical series of ≥90% may reflect methods that need improvement, and larger prospective studies are needed to address these factors. Nevertheless, to date the selection criteria for DBS—specifically in terms of patient features (severity and nature of symptoms, age, time of evolution, or any other demographic or disease aspects)—have not been assessed in a systematic fashion. In general, dystonia patients are not considered for DBS unless medical therapies have been previously and extensively tested. The vast majority of reported patients have had DBS surgery when the disease was provoking important disability, with loss of independence and impaired quality of life. There does not appear to be an upper age limit or a minimum age limit, although there are no published data regarding the outcome of GPi DBS for dystonia in children younger than 7 years of age. There is currently no enough evidence to prove that subjects with primary-generalized dystonia who undergo DBS at an early age and sooner rather than later after disease onset may gain more benefit from DBS than those undergoing DBS after the development of fixed skeletal deformities. There is no enough evidence to refuse or support consideration of DBS in patients with previous ablative procedures. ©2011 *Movement* Disorder Society

Key Words: DBS; dystonia; pallidal stimulation; surgery; thalamic stimulation

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Dystonia is a movement disorder characterized by involuntary, sustained muscle contractions causing twisting and repetitive movements.[1] Dystonia may affect only certain regions of the body or may be generalized and can be primary, heredodegenerative, or secondary.[1,2] Drug treatment for generalized dystonia is often unsatisfactory or is limited by adverse effects.[3] Surgical treatments for dystonia, such as thalamotomy, pallidotomy, and deep brain stimulation (DBS), have improved in their efficacy to safety ratio through a combination of technological advances and better understanding of the role of the basal ganglia in dystonia.[3,4]

In this chapter, the evidence is reviewed regarding the factors that influence the selection of patients with various types of dystonia for treatment with DBS. Included in five sections are the following factors: patients characteristics (appropriate time for DBS with

respect to age and duration of disease, comorbidities that may present risks for adverse events during or after DBS or may predict a poor outcome); clinical features of dystonia (degree of severity and disability, type and nature of the dystonia, predictive factors of outcome, relationship with the surgical target, features that might not respond to DBS); previous medical treatment; predicted outcome if previous surgical procedures for the dystonia were attempted; and genetic factors.

Methods

Search Strategy

The literature search was performed using PubMed, CINAHL, and the Cochrane Collaborative databases initially from 1980 to January 2008 using the terms: dystonia and DBS; pallidal stimulation and dystonia; subthalamic stimulation and dystonia; thalamic stimulation and dystonia; secondary dystonia and DBS; neurodegenerative diseases and DBS. The search was combined with the one used for neuropsychology, neuropsychiatry, microelectrode recording, neuroimaging, electrophysiology, surgical techniques, complications, and targeting. Only English-language publications involving human subjects were considered. A total of 235 articles were retrieved. To facilitate the committees' work, the articles were divided in three groups, which often overlapped: preoperative, intraoperative, and postoperative. A PDF file was created for each article obtained from the search and put in a CD that was mailed to the members. During the writing phase, additional 71 articles were added to update the search, covering the period from January 2008 to September 2009.

Process of Generating Clinical Recommendations

The Consensus Committee members of the Task Force included neurologists, neurosurgeons, neurophysiologists, psychiatrists, neuropsychologists, nurses, and mid-level practitioners with expertise and experience in DBS. The experts were also chosen from different countries in Asia, Europe, North and South America, to provide a more comprehensive contribution to the Task Force. The authors of each chapter were selected taking into account their specific expertise in the field. The steering committee prepared a list of questions related to preoperative, intraoperative, and postoperative issues and established two chairs responsible for each of these three areas (subcommittees). These chairs then assigned a few questions to be addressed by each member of the subcommittees. The answers to the questions had to be formulated after reviewing the available literature (provided on CD) and combining their expertise. As the level of evidence for most of the DBS studies was low, the responses were organized following the template previously used for the Special Supplement on DBS for Parkinson's disease (PD): (1) available data, (2) conclusions, (3) pragmatic recommendations, and (4) points to be addressed.[5] A first document was prepared from this initial work and was reviewed and discussed by the entire Task Force group during a 1-day meeting. During this meeting the Task Force members provided further feedback and agreed on additional refinements of the whole document adding the comments and remarks collected during the meeting. Special attention was paid to formulate pragmatic recommendations in absence of available studies. A second version of the project was sent to the entire working committee for final approval. The Executive Committee then met again to refine the Special Issue document before submission.

Patients' Characteristics

Age

What Is the Best Age for Surgery? Is There Any Age Limit for Surgery (A "Critical" Age)?

Available Data

The influence of age on the selection of patients for DBS varies for different forms of dystonia. Therefore, these will be reviewed separately.

Primary-Generalized Dystonia. Several class IV studies have assessed the factor of age as a variable regarding the outcome of DBS in primary-generalized dystonia (PGD), and enough data is provided in other articles to make a statement on outcome versus age.[6–8] Age considerations include age of dystonia onset or the age at the time of surgery. Most studies have looked at the age at the time of surgery; however this variable is linked to the duration of symptoms.

Some studies have found an association between outcome and age at the time of surgery. Alterman et al.[8] reported a retrospective study of 15 patients with PGD who underwent bilateral globus pallidus internus (GPi) DBS. They found a significant correlation with outcome based on the age at time of surgery ($r^2 = 0.63$, $P < 0.001$). Subjects who were <21-year-old (n = 8) experienced a median improvement in the Burke–Fahn–Marsden dystonia rating scale—motor score (BFMDRS-M) of 97% (range 84–100%) at 1 year. Subjects >21-year-old (n = 7) experienced a 69% (range 40–89%) improvement in BFMDRS-M at 1 year after DBS. The significant difference between the groups was maintained even when the three DYT-1 mutation negative subjects (all older than 21) were excluded from the analysis. The youngest age at operation was 10 years. There was also a negative correlation with outcome based on the durations of symptoms

($r^2 = 0.63$, $P = 0.011$), with the older group having had a longer duration of symptoms (mean of 20.7 years versus 5.1 years in the younger group). The same authors had previously found predictive value of post surgical benefit of age of onset in a larger group of 39 patients (children and adults) with primary dystonia.[9] Of note the same patients may have contributed to both studies. Patients >21 years at surgery (n = 17) improved 15% less ($P < 0.001$) than those <21 years (n = 15) at 12 months after surgery.

Coubes et al.[10] reported the outcome of seven patients with DYT-1 mutation. Six were children (age 14 or less) and one was an adult (age 27). The youngest at operation was 8 years of age. No duration of disease was given. The six children walked again after surgery, but the adult did not, due to "secondary skeletal deformities of the spine and lower limb." Coubes et al.[11] also reported the 2-year outcome from 31 patients with PGD who underwent bilateral GPi DBS. The group comprised 12 adults (17 years of age or older) and 19 children. Children showed significantly better improvement in motor scores (BFMDRS-M) than adults ($P = 0.04$), but there was no significant difference between children and adults in level of improvement in disability scores (BFMDRS-D) ($P = 0.95$). This age-related finding was not a function of being positive or negative for the DYT-1 mutation. There was no specification of the ages of the children, but a comment in the article mentioned a subject who was 6 years of age. This appears to be the youngest patient operated on in the literature of PGD.

Halbig et al.[12] reported the 3–12 months outcome of 13 patients with PGD. The youngest subject was 13 year-old at the time of operation (disease duration of 5 years, improvement in BFMDRS-M of 65%). The oldest subject, 68 at surgery, had the least improvement (disease duration of 18 years, improvement in BFMDRS-M of 25%). Five other PGD patients were above 50 and had a 43–67% improvement.

Other class IV studies have found that a longer duration of symptoms was associated with a worse outcome. Cersosimo et al.[13] reported the outcomes of 10 patients with PGD (9 of 10 tested positive for the DYT1 gene mutation). They did not report outcome by age, but 9 of 10 patients were under 20 and the other was 28. Unlike the study from Alterman et al.,[8] the 28-year-old patient had a short duration of symptoms (4 years) and showed the fastest time of the whole group to achieve maximal benefit (24 hours). The outcome of the 28-year-old was better than that of the youngest subject (9 years old; 69.7% improvement in BFMDRS-M after 3 years vs. 53.3% after 2 years). Both were DYT-1 mutation positive.

A correlation with disease duration was found by Isaias et al.[9] Disease duration negatively correlated with clinical outcome and with disability scores at 1 year after surgery ($P < 0.05$). Seven patients with fixed skeletal deformities had a significant poorer outcome at 12 months after surgery.

Eltahawy et al.[14] compared the outcomes of pallidal lesions (four subjects) versus pallidal DBS (two subjects) in PGD patients. The authors found a tendency for better outcome scores in patients who were younger and had an early onset of dystonia and shorter duration of disease before surgery.

In contrast, the prospective class III study reported by Valldeoriola et al.[15] found a positive association ($P = 0.001$) between motor improvement with DBS and patients' age at the moment of surgery in a group 24 PGD patients with bilateral GPi DBS but not with disease duration or age at onset of dystonic symptoms.

In a meta-analysis of DBS for all types of dystonia, Holloway et al.[16] found a significant correlation between duration of symptoms and outcome ($P = 0.003$). Age at onset and age at the time of surgery did not influence the outcome. However, a multiple regression analysis performed using nucleus stimulated, aetiology of dystonia, and duration of symptoms was highly significant for nucleus stimulated and aetiology but not duration of symptoms ($P = 0.117$).

Cervical Dystonia. The age at the time of operation for cervical dystonia (CD) tends to be older than for PGD due to the nature of the disease, which usually presents in adulthood. Two independent class IV studies with 10 patients at 1 year[17] and at 3 years[18] after bilateral GPi DBS did not find correlation between age and duration at time of surgery with outcome or adverse effects of GPi DBS, but these findings might be related to the small sample of patients. From small case series regarding the outcome of GPi DBS for CD there is not enough data to make any statement about age at the time of surgery as a predictive factor of outcome, except that the surgery appeared to be safe in elderly subjects (the oldest subject was 78 year-old at the time of surgery).[17–20] Of note, however, is the association of the duration of CD and the risk of the development of cervical myelopathy, which may suggest that DBS for CD should be considered before this occurs. Tonomura et al.[21] reported a case of a 53-year-old patient with CD since childhood who developed atlantoaxial rotatory subluxation. GPi DBS was performed first, followed by atlantoaxial transarticular screw fixation and fusion. GPi DBS improved the CD so that the spinal fusion could be done. The authors warn that subjects with severe CD can develop unstable necks with severe morbidity.

Other Focal Dystonias. DBS surgery has been performed for other focal dystonias, many of which occur in adulthood and no formal recommendation concerning age as a predictive factor has been reported.[20,22–26] However, the same recommendations concerning increasing age and duration of symptoms as well as

risks for medical comorbidity and fixed skeletal deformities can apply. So DBS, if indicated, should be performed before these occur.

Pantothenate Kinase-Associated Neurodegeneration. This group is included because it can benefit from bilateral GPi DBS. The age of onset of pantothenate kinase-associated neurodegeneration (PKAN) is variable but usually starts in childhood. Castelnau et al.[27] reported the outcomes of GPi DBS in six subjects with genetically confirmed PKAN whose ages at the time of surgery were 10–39 years. The 10-year-old had symptom onset at age 1 year (the youngest age of onset) and had the least improvement (46% in BFMDRS-M; compared with mean of group of 74.6%) despite not having the longest duration of symptoms. This was the only subject who could not return to walk, unlike three other wheelchair bound subjects who resumed independent walking with DBS. The oldest subject at the time of surgery (39-year-old) had an 82% improvement, disease duration 22 years, and had spasticity.

Secondary Dystonia. No study has systematically determined age to be a factor in patient selection in secondary dystonias, including tardive dystonia, hemidystonia, and postanoxic dystonia.

Conclusions

Primary-Generalized Dystonia. From the studies available, mostly class IV, there is no enough evidence to prove that subjects with PGD who undergo GPi DBS at an earlier age may gain more benefit from DBS for PGD than those operated at a later age. There is also controversy in the literature regarding whether symptom duration is an independent factor associated with outcome One class IV study found that duration of symptoms rather than age at the time of surgery was inversely correlated with outcome even after the patients with fixed skeletal deformities had been removed from the analysis,[9] although a class III study found that age at the time of surgery and not symptom duration was predictive of outcome.[15] From these mostly retrospective studies it is suggested that DBS should be considered before the development of fixed skeletal deformities, the presence of which was associated with a poorer outcome. As there is not enough evidence to support this suggestion, larger prospective studies are needed to further address this issue.

Cervical and Other Segmental and Focal Dystonias. Subjects with CD tend to be older than those with PGD. No statement can be made regarding age as a predictive factor for DBS, from the few class IV case series published. However, DBS appeared to be safe in the older subjects (65–78 years). For focal dystonias, a longer duration of symptoms appears to pose a risk of subsequent fixed skeletal deformities, such as cervical myelopathy or spine instability in CD and limb contractures for other focal dystonias. DBS should be considered before these complications are irreversible.

Pantothenate Kinase-Associated Neurodegeneration and Secondary Dystonias. There is no available data to predict whether age or symptom duration is predictive of outcome of DBS.

Minimum and Maximum ages for DBS for Dystonia. Currently there are no data regarding the outcome of DBS for dystonia in children younger than 7 years of age. From experience and comments in the surgical literature, implanting neurostimulators (even in the abdominal region) in very small children, especially those emaciated from disease such as PKAN, may lead to skin erosion. However, the procedure is well tolerated in young children and the extension connecting the DBS lead to the neurostimulator appears to allow for growth. As far as an upper age limit is concerned, there have been no reports of increased risk of intracranial haemorrhage in older patients with dystonia. However, patients with dystonia are usually younger than patients with PD at time of surgery.

Pragmatic Recommendations

Age itself should not be used as an inclusion or exclusion criterion for GPi DBS: children as well adults can benefit from the procedure. No data are available on children under 7 years of age. A practical approach is that any subject with a progressive generalized or CD should consider surgery before developing fixed skeletal deformities or cervical myelopathy.

Points to Be Addressed

Future large randomised and prospective studies should tease out the relative contribution of age and symptom duration on surgical outcomes.

Comorbidities

Are There Patients Who Are Not Eligible for Surgery due to Comorbidities? Are There Absolute and Relative Comorbidity Contraindications?

Available Data

Brain Imagin. From a systematic review of the diagnosis and treatment of dystonia by a European Task Force,[28] it is suggested that brain imaging should be mandatory in order to determine the aetiology of dystonia and should be done before considering a patient for DBS. No major structural abnormalities are detected with conventional brain CT or MRI studies

in subjects with primary dystonia, although certain basal ganglia and cerebellar abnormalities, such as changes in volume and grey matter density, have been found.[28–30] Secondary and neurodegenerative dystonias may show structural abnormalities such as stroke, demyelination, tumor, brain atrophy, and so forth. There are no studies specifically addressing the impact of these abnormalities on the surgical outcomes, although abnormal brain MRI was associated with less postsurgical improvement (after pallidotomy and pallidal DBS) in a small class IV series of 15 patients with primary and secondary dystonia.[14] As DBS is largely considered to be more effective for primary dystonias than secondary dystonias,[14] the main purpose of conventional brain MRI in surgical candidates is to support or refute the diagnosis of a primary dystonia and to rule out other incidental findings.

Psychiatric Issues. Most published studies have used exclusion criteria for patients with severe depression or "major psychiatric disorders." No study has examined the rate of suicide in subjects with dystonia post-DBS. There are few anecdotal reports of suicide after DBS for dystonia. Burkhardt et al.[31] reported the suicide of one patient with postanoxic dystonia and a prior history of depression, suicide ideation and attempt, aggressive behavior, and drug dependency. Foncke et al.[32] reported suicide in two dystonia patients with GPi DBS with a previous history of depression.

These three cases of suicides after DBS for dystonia may represent an exception to the general experience reported in published series. Furthemore, GPi DBS has been used safely in tardive dystonia patients with history of depression and psychosis.[33,34] There is also one case report of remarkable mood improvement in a patient with severe depression who underwent bilateral GPi stimulation for tardive dyskinesia.[35]

A specific article in Section II of this Supplement will further address psychiatric issues in patients with dystonia and DBS.[36]

Dementia. Certain class IV studies of PGD used exclusion criteria similar to those used for PD and included a cut-off on the Mattis Dementia Rating Scale (<120/144).[37] Other studies of PGD did not screen subjects for dementia due to their young age. There are no available studies focusing on patients with dystonia and dementia who have had DBS surgery. However, some studies have reported on patients with secondary dystonias and preoperatively impaired neuropsychological evaluation. No major differences in cognitive performances were observed after surgery.[38,39] A specific article in Section II will further address this issue.[36]

Fixed Skeletal Deformities. Several studies have reported that patients with PGD who have fixed skeletal deformities do not improve as much from GPi or subthalamic nucleus (STN) DBS as those who do not as addressed above.[9,40]

Conclusions

Minor structural abnormalities in the basal ganglia in primary dystonia do not seem to be a contraindication for GPi DBS surgery. Brain MRI is considered mandatory in the preoperative selection process for subjects with dystonia, who are considering DBS in order to support the diagnosis of primary or secondary dystonia. From the class IV studies available, the incidence of suicide after DBS is very low and occurred in patients with preoperative psychiatric disease. Preoperative evaluation of any fixed skeletal deformities is required, as the latter may limit the benefit from DBS. In secondary dystonia patients, the degree of spasticity and possible other neurological deficits need to be carefully assessed to provide a realistic prediction of outcome.

Pragmatic Recommendations

Screening for psychiatric comorbidities, including depression and suicide attempts, is recommended. If the premorbid psychiatric symptoms are deemed severe this may be a contraindication to surgery. For older patients, comorbidities such as hypertension and cognitive impairment should be taken into account in the risk/benefit analysis. Careful assessment of other neurological deficits should be included in the preoperative evaluation, especially in cases of secondary dystonia. Prediction of functional outcome should be carefully assessed and discussed with the patient and care givers.

Points to Be Addressed

Issues regarding psychiatric comorbidities and vulnerabilities suggest that this area needs more study.

When to Operate on Patients, Taking into Account Possible Remission of Dystonia over the Years?

Available Data

The relationship between dystonia duration, severity or disability, and outcomes of DBS is not well known. As previously discussed, and based on small class IV series, the symptoms' duration and age at time of surgery[15] may be inversely correlated with the surgical outcome.[8,9,16]

In general, spontaneous remission of dystonia can occur, possibly in up to 15% of patients. For instance, 10–20% of patients with CD may have spontaneous remissions.[41] However, most of these patients have recurrent dystonia within 5 years with no further remissions. There is a report of an individual with

spontaneous resolution of hemidystonia 4 years after onset and another whose hemidystonia resolved after 3 months of medical treatment.[42] Chuang et al.[43] examined 33 cases of hemidystonia after stroke, trauma, perinatal injury, infection, congenital lesion, and tumor. Using follow-up telephone interviews they found that 11 patients were unchanged or improved, whereas none had resolution of dystonia. Of note, this was at very different times after the onset of hemidystonia, as the range of dystonia duration was 1–58 years. In their review of the literature, the authors found that most cases of acquired hemidystonia progress and then stabilize but do not resolve spontaneously.[43]

Conclusions

Currently, there is not enough evidence of spontaneous persistent resolution of dystonia to delay DBS surgery if it is otherwise indicated. Even in patients who experience symptomatic remission within the first 5 years from the onset, dystonia usually relapses and become permanent. However, it is prudent to wait until the symptoms have stabilized, especially in relatively acute new onset of dystonia.

Pragmatic Recommendations

DBS for dystonia should be considered as a treatment option once it has become clear that medical therapy provides insufficient symptom control.

Points to Be Addressed

None.

Clinical Features of Dystonia

What Are the Specific Indications for Surgery (Mobility and Activities of Daily Living Scores, Pain Score, and Degree of disability)?

Available Data

There are no studies that directly assess, in a prospective fashion, which characteristics of dystonia are ideal for surgery. In most of the original class IV case series concerning DBS for dystonia, inclusion criteria for DBS were: disabling motor symptoms, impairment in activities of daily living (ADL), severe pain, and progression of symptoms, in the context of unsatisfactory response to medical treatment.[37,44] From these studies it remains unknown which specific characteristics would respond better to DBS.[12,44–49]

Conclusions

The question of which patient features define a good candidate remains unanswered, as this issue has not been systematically examined. Severity of motor impairment, pain, limitations in quality of life, and ADLs are currently the most frequent indications for DBS.

Pragmatic Recommendations

At the present time, DBS can be recommended for dystonia patients with limitations of functions (caused by motor impairment, pain and disability). There is no recommendation about the severity of dystonia or any cut off scores for the same. Both the patient and the treating physician should agree on the impairment of ADL (especially motor function), reduced quality of life, and severity of pain.

Points to Be Addressed

Future studies need to assess which clinical features are predictive of response to DBS in a more rigorous fashion. Outcomes should include disability, quality of life (QoL), and nonmotor symptoms.

Are There Specific Types of Dystonia (Primary, Secondary, Neurodegenerative, etc.), Which Better Support the Indication of Surgery and Why?

Available Data

Primary segmental and generalized dystonia generally have good surgical outcome. One class I study[37] and several class III studies using blinded assessment and larger numbers of patients were done in patients with primary dystonia (generalized or cervical, positive, and negative for the DYT-1 gene).[17,44,48–50] The postoperative improvement of patients with primary dystonia who receive GPi DBS or ablative treatment is within a range of 40–90% using standard dystonia rating scales.[6,8,10,13,15,16–18,37,44–45] Adults with primary dystonia (DYT-1 positive and negative) and children with DYT-1 positive dystonia can achieve similarly good outcomes from GPi DBS.[8,10,44] Meige's syndrome[23–26,51] has also shown a good response to bilateral GPi DBS from class IV series.

There is a single class IV study comparing retrospectively the surgical results in patients with primary versus secondary dystonia and concluding that the outcome is better in patients with primary dystonia.[14]

Other types of dystonia, such as PKAN,[27,52–54] tardive dystonia,[33–35,55–59] Lubag,[60,61] and myoclonus-dystonia[62–64] may respond to DBS favorably in a consistent fashion, especially the mobile dystonic features.

In contrast, there are a number of case reports and small series of patients with secondary dystonia who obtained little or no benefit from DBS.[14,65,66] However, a class III, prospective study of 13 adults with dystonia-choreoathetosis from cerebral palsy without cognitive impairment, reported a mean improvement of 24.4% at 1 year with significant improvement in disability, pain, and mental health-related QoL.[67]

There was no worsening of cognition or mood. Accurate placement of the DBS lead in the posteroventral segment of the GPi was important for outcome. A small class IV study reported improvement of 41.4% in the motor and 29.5% in the disability scores of the BFMDRS in 8 subjects with different types of secondary dystonia.[68] Secondary dystonias associated with a previous encephalitis or structural brain lesion may respond less favorably.[14,69]

Conclusions

Level B evidence suggests that patients with primary dystonia experience benefit from DBS, whether it is generalized or segmental. Level C evidence of benefit is provided for CD and GPi DBS. Other types of dystonia (secondary, neurodegenerative, and dystonia-plus) may have more variable outcome. This latter evidence is from open label retrospective case series. However, one prospective series has shown that patients with hyperkinetic cerebral palsy without cognitive impairment may have modest but significant functional improvement in their QoL from GPi DBS.[67]

Pragmatic Recommendations

GPi DBS should be considered for patients with PGD who do not respond adequately to medical therapy and who are limited in their ADL. GPi DBS can be considered for primary CD associated with pain or severe retrocollis or laterocollis and without adequate response to botulinum toxin. In other dystonic syndromes, especially those secondary to other causes, DBS might be considered in cases of tardive dystonia, hyperkinetic cerebral palsy, and/or cases with severe disability, although more large prospective trials are needed to support evidence of benefit. Secondary dystonia from encephalitis and/or structural lesions may not respond well to DBS.

Points to Be Addressed

Well designed trials (prospective, randomized, controlled, blinded evaluation, large series) are needed in secondary dystonia syndromes to address the question of the efficacy of DBS.

Is There Any Predictor of Response to Surgery (Mobile Dystonia vs. Fixed Dystonic Postures, etc.)?

Available Data

In most of the studies of DBS in primary or secondary dystonia, phasic hyperkinetic movements respond more rapidly and better than tonic or fixed postures; patients who had little improvement tended to have severe tonic posturing.[9,20,37,44,48,70,71] In some of these subjects fixed skeletal deformities may have contributed to the worse outcome with tonic dystonic posturing.[8] Primary dystonia patients respond well to DBS regardless of the presence of the DYT-1 mutation.[44]

One center has suggested that a pattern of electromyographic activity with repeated bursts could indicate better or earlier response to GPi DBS.[72,73] As stated above age at time of surgery and duration of dystonia may predict postsurgical outcomes, at least at 1 year follow-up.[9] Secondary dystonia may respond less favourably to DBS surgery but this issue needs further study before a recommendation can be made.[14]

Conclusions and Pragmatic Recommendations

Primary dystonia predicts a good outcome. Level B evidence suggests that phasic hyperkinetic movements generally respond faster and better than tonic postures.

Points to Be Addressed

Different clinical features of dystonia may not be adequately captured by current clinical rating scales (such as tremor, type of dystonic movement). In addition, especially in secondary dystonia, primary outcomes may need different scales or other evaluation instruments.

Are There Specific Types of Dystonia or Indications that Encourage Preferential Choice of One Target Over Another (Thalamus, GPi, and STN)?

Available Data

No prospective randomized study has compared one target to another for primary dystonia. The choice of GPi as the target of choice in primary dystonia emerged from the successful treatment of dystonia in PD with pallidotomy, followed by the early case series showing dramatic improvement in DYT-1 positive PGD patients with GPi DBS.[10,14] The GPi and ventrolateral thalamus have been considered suitable targets for secondary dystonia,[3,4,74,75] although in one class IV study stimulation of GPi was associated with better outcomes compared with thalamic stimulation.[65] The STN has also been considered for primary and secondary dystonia in small case series with controversial outcomes.[40,76,77] Thalamic DBS has also been used to treat writer's cramp and musician's dystonia with success.[78]

Conclusions

There is Level B evidence that confirms the efficacy of GPi DBS in the treatment of primary (generalized and segmental) dystonia and level C evidence for GPi DBS in treating medically refractory CD. Because of the paucity of data with thalamic or STN DBS, no conclusions can be made at this time on the preferred target for the treatment of dystonia. There are no comparative studies for the other targets and for secondary dystonia.

Pragmatic Recommendations

GPi DBS can be recommended for dystonia patients who are candidates for DBS surgery. Further studies of DBS performed at other targets, including STN and thalamus, are warranted.

Points to Be Addressed

Randomized, controlled studies are now mandatory to better assess the target for DBS in the treatment of severe dystonia. Future studies of DBS in secondary dystonia need to specifically define the aetiology and features of the dystonia for each patient, rather than collectively grouping these disparate conditions together.

Are There Motor and Nonmotor Features that Reliably Do Not Respond to Surgery? When Should These Be Sufficiently Important to Contraindicate Surgery?

Available Data

A class I study of 40 patients with primary generalized and segmental dystonia showed statistically significant motor improvement of all body regions (face, speech/swallowing, neck/trunk, arms/legs), as well as improvement in pain.[45] Depression/anxiety/psychiatric scores were generally low at baseline and did not significantly change after 3 months. The physical component of the QoL scale improved but the mental one did not. An open-label evaluation after 6 months revealed improvement in depression and both the physical and mental components of the quality of life scale. A class IV study of generalized dystonia reported significant motor improvement in neck, trunk, arm, and leg regions but not in face or speech.[70] In another study with 22 patients at 3-year follow-up of PGD treated with bilateral GPi DBS, axial, limb, and face scores significantly improved from baseline, although speech did not (though baseline scores were quite low to start).[44,49] The study of 10 patients with CD by Kiss et al.[17] showed improvement in CD and related pain. Numerous other studies referenced in earlier sections of this article support the efficacy of GPi DBS for the reduction of motor signs and pain in various types of dystonia.

Conclusions

Level B evidence has shown that all motor features of primary dystonia are potentially responsive to GPi DBS, although response of speech is less consistent or robust. Pain also showed improvement. Other nonmotor features of dystonia are not well studied or reported in the literature. Thus, there is no evidence that specific motor or nonmotor features such that when present would contraindicate treatment with DBS.

Pragmatic Recommendations

At the present time, each patient's clinical situation needs to be assessed on a case-by-case basis to determine the extent and severity of motor features and associated dysfunction or disability when making a risk/benefit calculation and recommendation to the patient regarding DBS.

Points to Be Addressed

Further study of the nonmotor features of dystonia and associated response to DBS is desirable.

More objective and quantitative assessment of speech and swallowing dysfunction and its response to DBS is needed.

Previous Medical Therapy for Dystonia

What Medical Treatment Should Be Mandatory Before Considering Surgery? How Many Drug Trials and How Long Should Have Been Attempted?

Available Data

Virtually all the reports of DBS for dystonia referenced in earlier sections indicate that patients have failed "appropriate" or "optimal" pharmacological therapy, but the details are often not defined. Similarly, in series focused on focal or segmental dystonia, an entry criterion is typically failure of adequate or continued response to chemodenervation treatment with botulinum toxin.

Conclusions

Evidence-based data do not currently inform the answer to this question, largely because pharmacological treatment tends to be individualized to each patient's needs and tolerability of treatment.

Pragmatic Recommendations

Medical management using appropriate pharmacological therapy needs to be tailored to the patient before considering surgery. It is not mandatory to try all the available medications for primary dystonia. Clinical practice generally suggests that patients with dystonia should undergo trials of maximally tolerated doses of appropriate medications, including one or more of the following classes of drugs: dopaminergic, anti-cholinergic, and benzodiazepine. In children high doses of anticholinergic drugs may be very beneficial. This therapy has to be weighed with the evidence that performing GPi DBS in PGD should be considered sooner rather than later in the duration of disease and before the formation of fixed skeletal deformities. High dose anticholinergic therapy may not be tolerated in adults due to adverse cognitive side effects.

Affected muscle regions that can be effectively targeted with botulinum toxin(s) should be so treated in a manner that optimizes localization and dose.

Points to Be Addressed

Rigorous study of the efficacy of pharmacotherapy on various types of dystonia is needed, with the goal of developing probabilistic models of response to inform appropriate timing of surgical intervention.

Previous Surgery for Dystonia

Does previous functional surgery (thalamothomy, pallidotomy, peripheral denervation, myectomy, etc.) influence the outcome from DBS and if so should this influence whether or not to offer DBS?

Available Data

The only data available on DBS in patients who had previous surgery (lesions or previous DBS) for dystonia is from small observational case series. In fact, previous surgery, such as thalamotomy, pallidotomy, and peripheral denervation, is rarely stated as exclusion criterion for DBS.

Katayama et al.[79] studied five cases of PGD treated with bilateral GPi DBS. Two of the patients had been treated previously with bilateral thalamotomy or unilateral pallidotomy. They found a marked effect of GPi DBS even in patients who had previously undergone ablative procedures. Vercueil et al.[65] performed thalamic (VLp) DBS in 12 patients, three of whom later underwent a second operation with GPi DBS lead implantation because of lack of efficacy. Two of these patients had secondary dystonia. After the second DBS surgery, the benefit was reported as moderate in two and marked in one out of three patients.

On the other hand, a level IV study pointed out that a history of multiple thalamotomies is a negative outcome predictor for GPi DBS in patients with dystonia.[8] These authors studied 31 patients with medically refractory primary dystonia (20 DYT-1 positive) who underwent GPi DBS. Three patients had undergone multiple thalamotomies before DBS. An average improvement in all the patients was 69.4% at 12 months. They found that previous thalamotomy was the major factor showing a significant negative correlation with clinical outcome at 1 year ($P < 0.01$).

As for combination of pallidal or thalamic DBS and contralateral lesioning, Cersosimo et al.[13] reported the long-term follow-up data of pallidal DBS in 10 patients with PGD: five of them had unilateral pallidotomy and contralateral GPi DBS. The authors conclude that combined DBS with pallidotomy may be more effective than bilateral pallidal DBS.

There are no data on previous peripheral surgeries such as denervation or myotomy regarding their influence on the outcome of DBS.

Conclusion and Pragmatic Recommendations

There is no enough evidence to prove that previous surgical treatments (i.e., thalamotomy, pallidotomy, and peripheral denervation) should prevent consideration of DBS. There are only a few retrospective case series on the effect of previous surgical treatment. Patients who have undergone peripheral denervation for CD with unsatisfactory results and/or with symptoms that have extended to other parts of the body may be considered as candidates for GPi DBS.

Genetic Causes of Dystonia

Should Patients with DYT-1 Dystonia or Other Genetic Causes of Dystonia Be Treated Any Differently with Respect to the Issues Listed Above?-Available Data

There are no prospective studies specifically addressing the question whether patients with genetic dystonia have different postoperative outcomes after DBS surgery. Genetic testing is usually done to specify diagnosis,[2] for counseling and research purposes. It is not routinely performed in every patient with dystonia considered for DBS, although the DYT-1 mutation was tested in PGD patients in many studies reporting outcomes after DBS surgery.

DYT-1. Initial class IV studies suggested that DYT-1 mutation positive patients would have better outcomes compared to DYT-1 negative patients. In 2000, Coubes et al.[10] reported the 1 year outcomes after bilateral GPI DBS in 7 PGD patients (6 children and 1 adult) with DYT-1 mutation. The motor benefit was on average 90.3% (range 60–100). Krauss et al.[66] subsequently reported 2 non-DYT-1 PGD patients who improved by 74% at 2-year follow-up. Similarly, several other studies reported somewhat lower results in non-DYT1 patients.[19,73,79]

However, other subsequent series, including a follow-up report by Coubes et al.,[11] have not identified significant differences between DYT-1 patients and other PGD cases.[37,44] In 2004, Coubes et al.[11] reported the 2-year follow-up of 31 PGD patients with GPi DBS and found no difference in the motor outcome (79% improvement) in the DYT-1 positive subjects compared with the DYT-1 negative subjects. In a level III, prospective controlled multicenter study with GPi DBS in PGD, there was no difference (50% improvement) in the benefit at 1 year and 3 years in

the 7 DYT-1 positive patients compared to the 17 DYT-1 negative patients.[44,49]

Recently, DYT-1 mutation status has again been implicated as a predictor of better DBS outcome in children and adolescents. Borggraefe et al.[6] described 6 PGD paediatric patients having GPi DBS and also reviewed the literature finding 44 reported PGD cases with surgery occurring before age 21 years, known DYT-1 status, and postsurgical evaluations at 4 weeks or more. The authors found DYT-1 positive patients (29/50) improved significantly more than mutation negative patients.

DYT-11. There are a small number of class IV reports of DYT-11 (myoclonus-dystonia) patients undergoing thalamic or GPi DBS. Thalamic DBS was reported effective in one patient with myoclonus dystonia,[61] as well as bilateral GPi DBS in another two patients.[62,64]

Other Genetic Dystonias. Several case reports about GPi DBS in secondary dystonias due to inherited disorders have been published. Bilateral GPi DBS in Huntington's disease,[80–82] neuroacanthocytosis,[83] Lubag (X-linked dystonia-parkinsonism, DYT-3),[60,61] Lesh-Nyhan syndrome,[84] PKAN,[52–54] and Type 3 gangliosidosis[85] has been performed so far. The surgical outcomes have been heterogeneous, but no worsening of preoperative conditions has been reported.

Conclusions

Most class III and IV studies have not found that DYT-1 mutation positive PGD patients differ in their clinical benefits from GPi DBS compared with mutation negative PGD patients, although one recent meta-analysis of children and adolescents undergoing GPi DBS suggests DYT-1 positive patients have better outcome. The role of DYT-1 genetic testing and determination of gene status in PGD as a predictor of surgical outcome, therefore, remains to be determined and may differ in paediatric and adult populations. There are few data available for other genetic dystonias. Secondary dystonias due to genetic disorders have differing outcomes.

Pragmatic Recommendations

Testing for DYT-1 dystonia or myoclonus dystonia (DYT-11) is helpful to confirm the diagnosis and for counselling the patient regarding outcomes of treatment.

Points to Be Addressed

Other genetic PGD (e.g., DYT-6) might have a different response to DBS surgery. Further prospective studies that systematically test PGD patients for both DYT-1 and DYT-6 should clarify whether surgical outcomes are associated with mutation status.

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