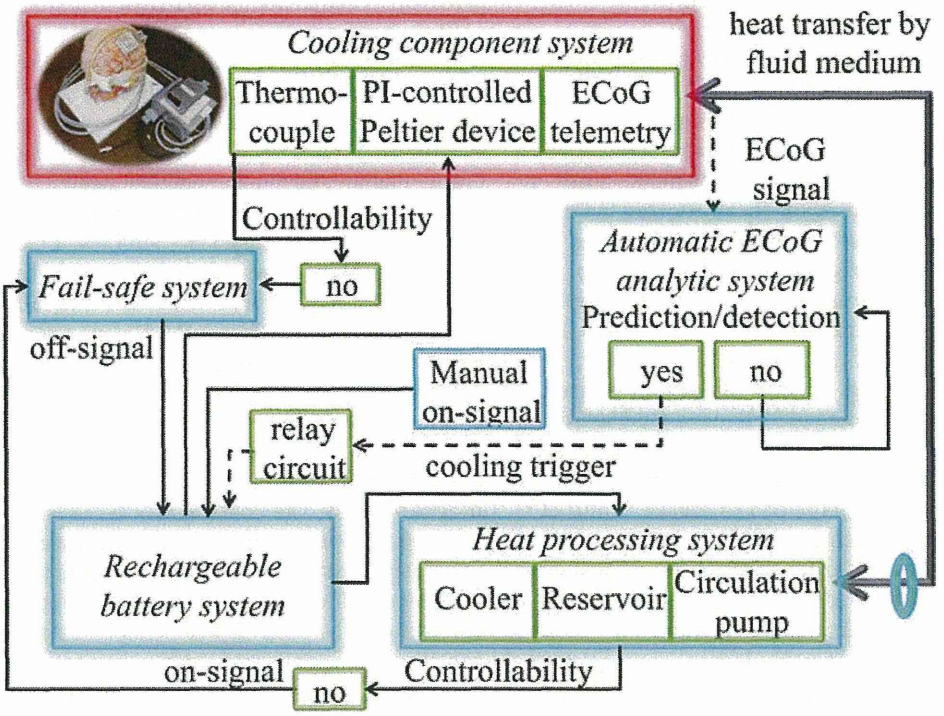

Fig. 1 Flow chart of an implantable focal brain cooling system for intractable epilepsy. ECoG; electroencephalogram.

ply, EEG detection system, and thermometer are also required. However, precision devices and micro-electromechanical technology have made remarkable advances that are likely to facilitate development of micropumps, microbatteries, and microcharging systems. The continuing development of this equipment suggests that an implantable local cooling system may become available in the near future.

Proposal for "thermal neuromodulation"

In this review, we discussed brain cooling for treatment of intractable epilepsy. However, clinical demand for a focal-cooling device will not be limited to the epileptic field; other potential applications include treatment of cerebrovascular diseases in post-stroke rehabilitation,[38,39] neurotrauma,[38] and pain,[40] all of which depend on "thermal modulation" of neuronal excitability. Therefore, thermal neuromodulation has considerable potential as a new therapy for serious neurological disorders.

Conclusion

Focal brain cooling terminates EDs and modulates seizures. These findings have promoted development of implantable focal cooling devices with a closed-loop system (seizure detection and focal cooling) for use in neuromodulation. However, several hardware components of these devices require optimization before clinical use can be considered.

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Conflict of Interest

The author states no conflict of interest.

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光トポグラフィー装置を用いた無侵襲言語優位半球の同定法について ～Wada testとの比較～

丸田雄一[1),2)]　藤井正美[1),2)]　野村貞宏[1),2)]　井本浩哉[1),2)]
岡　史朗[1)]　出口　誠[1)]　吉川功一[1)]　米田　浩[1)]
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要旨　光トポグラフィーを無侵襲性言語優位半球同定に応用し，Wada testの結果との一致状況を検討した。対象は，13歳から81歳の患者11例（脳動脈瘤3例，脳腫瘍6例，てんかん1例，脳動静脈奇形1例），男性7例，女性4例である。課題はブロックデザインの単語想記記述課題を用いた。左右6種のROI（関心領域）を設定し，LI（Laterality Index）算定によりWada testの結果との対比から判定に至適なROIの決定を行った。その後，至適ROIのLIに基づき，光トポグラフィー法で言語優位半球の判定を行った。光トポグラフィー法の結果は，左側優位8例，右側優位2例，両側優位1例，判定不能0例であり，Wada testの結果は左側優位8例，右側優位1例，両側優位1例，判定不能1例であった。両検査法の一致率は，90%（9/10例）であった。また，光トポグラフィー法では，Wada testの実施が困難であった1例についても評価が可能であった。以上より，本法は言語優位半球の同定法として臨床応用が可能と考えられた。

はじめに

脳神経外科治療に際して，術前に脳機能局在を同定し，機能の温存を図ることは，患者のQOL保持においてきわめて重要である。そこで，近年，各種脳機能評価技術によって感覚野・運動野・聴覚野・視覚野などの同定法が確立されてきている[1~5)]。

現在実施されている言語優位半球の決定法の標準試験は，Wada test[6)]であるが，侵襲性の問題から，非侵襲性言語優位半球決定法の確率が切望されている。これを受けて，機能磁気共鳴画像（fMRI）[7)]や脳磁図記録（MEG）[8)]といった脳機能画像を中心とした言語優位性評価が試みられている。ところが，上述の技法では，認知能の低下した患者や幼児といった，安静状態の維持が困難な症例では，実施が困難である。このため，我々は，体動による影響を受けにくく，特別な設備や薬物の使用を必要としない近赤外分光法（NIRS）に着目し，光トポグラフィー（多チャンネル近赤外線分光計測）による非侵襲性言語優位半球決定法の有効性を検証した。併せて，Wada testの結果と比較し，その特性について報告する。

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対象と方法

1. 対象

対象は当院当科にて，開頭手術を施行した患者11例である。年齢は13歳～81歳（平均57歳），男性7例，女性4例である。疾患内訳は，脳腫瘍6例，脳動脈瘤3例，脳動静脈奇形1例，てんかん1例である（表1）。

本研究は，山口大学医学部附属病院治験・臨床研究

表1 症例のまとめ
Table 1 Summary of the patients

症例	性別	年齢	臨床診断
1	M	39	右中大脳動脈動脈瘤
2	F	80	右後頭部悪性膠腫
3	M	78	左蝶形骨平面髄膜腫
4	M	63	右頭頂後頭部神経膠芽腫
5	F	50	右動静脈奇形
6	F	53	右前頭葉乏突起膠腫
7	M	72	右前大脳動脈巨大動脈瘤
8	M	41	右内頸動脈巨大動脈瘤
9	F	57	左前頭葉神経膠芽腫
10	M	13	左症候性てんかん
11	M	81	右頭頂後頭部神経膠芽腫

審査委員会の承認を得て実施し，患者本人もしくは患者の判断が困難な場合には，患者家族から同意を得て実施した。

2. 方法

(1) Wada Test

大腿動脈を穿刺し，左右の内頸動脈に対して個別にカテーテルを挿入後，両腕を挙上させた状態で，1，2，3…とカウントさせながらプロポフォール（1 mg/mL）をゆっくり，麻痺が出現するまで動注した。その後，5つの物品を見せて呼称をしてもらった。優性大脳半球の評価は，物品呼称・カウント停止をスコア化し，スコアが小さい方を優位半球とした。

(2) 光トポグラフィー

課題は，定常課題として風景画の模写を30秒行った後に，標的課題として，提示したひらがな一文字に対する，単語想起記述（時間内複数回答）15秒を1セッションとする5セッションのブロックデザインを採用した。この単語想起時に提示する一文字は，その都度異なる文字を提示した。

課題の提示は，パソコン画面にWatanabeらが開発した単語想記課題ソフトを使用して行った[9]。この際，患者には絵は書きたい部分から自由に書き始めるように指示し，模写が難しいという訴えがあった場合には，絵のなかの好きな部分の四角でも三角でも良いので書くように指示を与えた。

計測は，光トポグラフィ装置ETG7100（日立メディコ社製）で行った。プローブは3×5個のプローブホルダー（縦10 cm 横16 cm プローブ接地間隔3 cm）を用いて，ホルダー内側下部をFp1，Fp2に相当する領域に，外側下部が耳の上部（T3，T4）にかかる位置に配置し，左右それぞれ22チャンネル（図1）からサンプリング周波数10 Hzで記録を行った。

得られたデータに対し，まずintegral解析（Fittingによるベース補正処理，つまりデータをTask区間毎に切り出し，PreとPost区間に対して最小二乗法近似でFitting線を引き，次にタスクに伴うHb濃度変化をFitting線からの変化として最小二乗法近似で補正し平均加算波形として表示したもの）を行った。

次に，外耳孔と眼窩下外側縁の2点を底辺とする正三角形の頂点（B点）が，area 45と一致する[11]ことを利用して，B点（本設定のROI6とほぼ一致）周辺に，図1に示す左右の6か所の関心領域ROIを設定した。この6種のROIに対して，課題遂行中のmean Oxy-Hb値から，偏性指数laterality index（LI）を算出した。LIは，課題遂行中の左右のmean Oxy-Hb値をそれぞれ，L，Rとするとき，LI＝(L－R)/(L＋R)の式で計算した。このとき，LもしくはRがマイナスを示した場合には，これを0とした。また，L，Rが共に0の場合のLIは，判定不能とした。

優位半球の判定は，Rutenらの判定法[12]に従い，0.25より大きい場合を左優位，－0.25以上0.25以下を両側性，－0.25より小さい場合を右優位と判定した。優位半球決定に用いる至適ROIの選定は，Wada testとの一致率が高く，MRI上area 45の近傍に位置することが確認できたものとした。

結果

測定により得られた11例の光トポグラフィー画像を図2に示す。一見して活性化の状況を確認することは可能である。しかし，実際の優位半球の判定に際しては，例え視認により判定するとしても，半球全域の評価ではなく，機能分担領域で行う必要がある。また可能な限り主観を排除した方法で判定すべきである。そこで，LIを客観的指標として用いることで機能局在部位の明示を試みた。

1. LI判定に用いるROI解析用チャンネルの決定

光トポグラフィー法による6か所のROIでの判定結果とWada testによる判定結果の一致状況を表2に示す。各ROIに対する一致率は，それぞれ，40%，

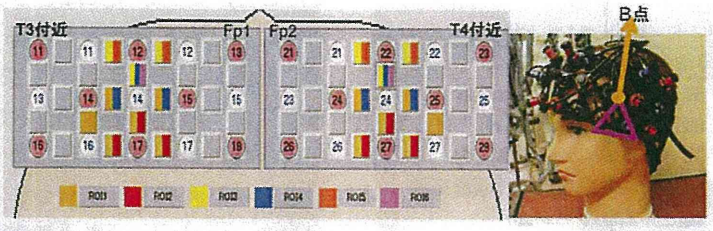

図1　プローブの配置とROIの位置関係
プローブは3×5個のプローブホルダーを用いて，内側下部をFp1，Fp2に相当する領域に，外側下部が耳の上部（T3，T4）にかかる部分に配置した。そして，図に示す6か所のROIを設定した。図に示す三角は，先行文献のプローブ配置のメルクマールであり，B点がarea 45付近と考えられている。

Fig. 1　The placement of the probe and relations of ROI. Using the 3×5 unit probe folders, medial inferior probe was located at Fp1 and Fp2, and external inferior probe was located at superior region of the ear (T3 and T4). And we set six places of ROI to show in the figure. The point B was marked on the top of equilateral triangle, and supposed to be introductive of area 45. The triangle was plotted as the prior literature[10].

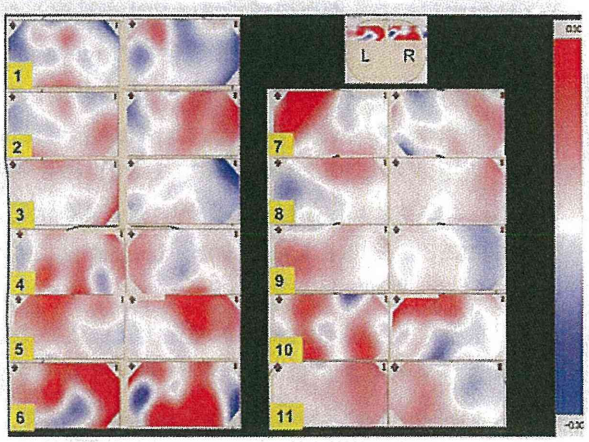

図2　課題遂行中のOxy-Hbの光トポグラフィー2D画像
integral解析後，Oxy-Hbが最大値を示した時間帯での全患者の光トポグラフィー2D画像を図に示す。一見して，優位半球を決定するのは，難しい。

Fig. 2　2D images of optical topography based on Oxy-Hb during task accomplishment. The figure shows the 2D optical topography images of all patients with maximum Oxy-Hb value after integral analysis. It is difficult to determine the dominancy at a glance of these pictures.

表2　各ROIにおけるlaterality index（LI）値およびWada testとの一致率

Table 2　The laterality index (LI) value in each ROI and agreement rate with Wada test

	ROI1	ROI2	ROI3	ROI4	ROI5	ROI6	Wada
1	L(0.66)	L(0.78)	X(0)	L(1)	X(0)	L(1)	L
2	R(−1)	R(−0.33)	R(−0.56)	R(−1)	B(−0.03)	R(−0.81)	R
3	B(−0.09)	R(−0.6)	L(0.97)	L(1)	L(1)	L(0.61)	L
4	L(0.84)	L(0.56)	L(0.81)	L(1)	L(0.94)	L(0.5)	L
5	R(−0.42)	L(0.75)	R(−0.29)	R(−0.44)	B(−0.21)	R(−0.48)	L
6	R(−0.86)	R(−1)	L(0.58)	B(−0.12)	L(0.56)	L(0.65)	L
7	B(0.14)	L(0.30)	L(0.84)	B(0.03)	L(0.96)	B(0.12)	L
8	R(−1)	R(−1)	L(1)	R(−0.82)	L(1)	L(0.73)	L
9	L(0.77)	B(0.06)	L(1)	L(0.48)	L(1)	L(0.33)	NOT
10	L(1)	L(1)	B(−0.18)	L(1)	B(0.06)	R(−1)	L=R
11	L(0.33)	R(−0.36)	L(1)	L(0.86)	L(1)	L(0.46)	L
一致率（%）	40%	50%	80%	50%	70%	80%	

50%，80%，50%，70%，80%であり，ROI3，ROI5，ROI6で高い一致をみた。次に課題に反応し，Oxy-Hbの増加が認められた領域が，脳皮質上どの部位に相当するかを確認するために，3例の患者に対して光トポグラフィーとMRIの合成画像を作製した。3例とも，ROI3とその構成領域であるROI5，ROI6の領

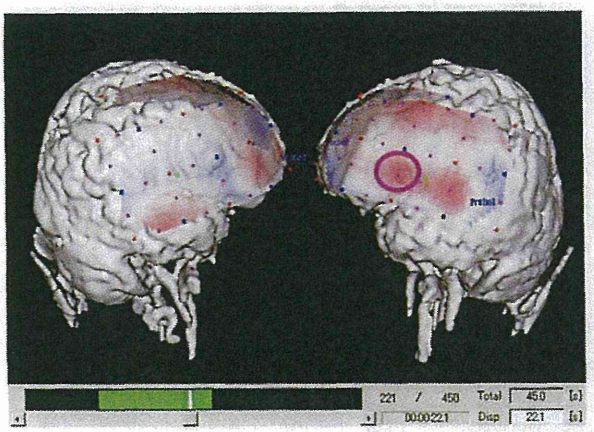

図3　課題遂行中のOxy-Hbの光トポグラフィーとMRIの合成画像
41歳男性，右内頸動脈巨大動脈瘤（判定：左優位；LI＝0.94）。integral解析後，Oxy-Hbが最大値を示した時間帯での代表患者の光トポグラフィー3D MRI合成画像を図に示す。ROI3, 5, 6に一致した左area 45近傍に血流の増加を認めた。

Fig. 3　The 3D fusion image of optical topography based on Oxy-Hb and MRI during task accomplishment. The case is a 41 year-old male with right internal carotid giant aneurysm (determination: left dominant; LI = 0.94). The figure shows the 3D optical topography images of the typical patient with maximum Oxy-Hb value after integral analysis. The cerebral blood flow (CBF) increase at ROIs 3, 5 and 6 where were close to the area 45.

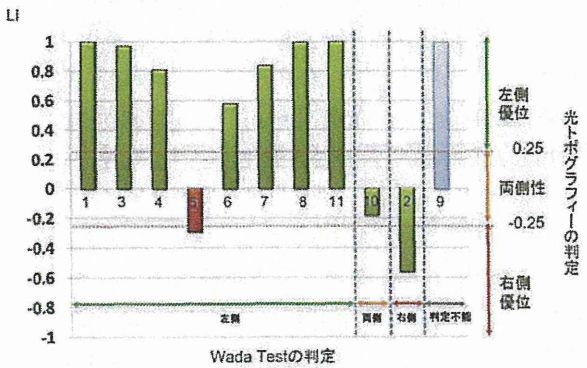

図4　各症例のWada testと光トポグラフィーの結果の一致状況
*X*軸方向にWada testの結果を，*Y*軸方向にLI値を示す。Wada testと光トポグラフィーの結果が一致したものは緑で，不一致であったものは赤で，Wada test判定不能例は青で示した。

Fig. 4　The agreement situations of each case between Wada test and optical topography. *X*-axis direction indicates the results of Wada test, *Y*-axis indicates LI values. The green bar indicates agreement of the optical topography and Wada test, the red bar indicates mismatch, and blue bar indicates inability case of Wada test.

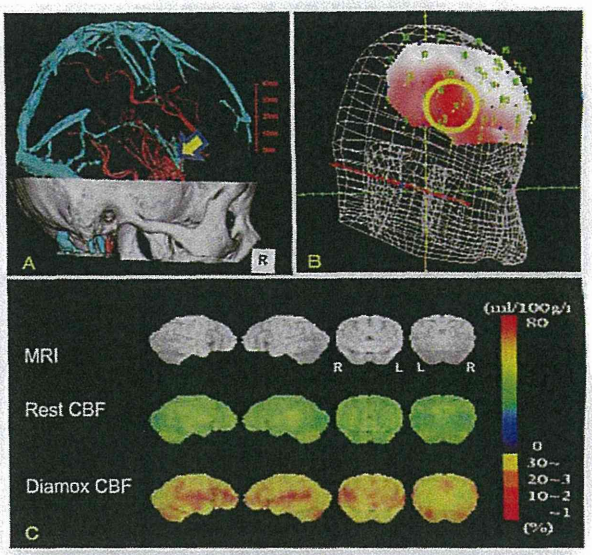

図5　判定不一致症例の脳血流評価
50歳女性，area 45に近接する動静脈奇形。
5-A：area 45近傍に異常血管が存在している。
5-B：異常血管の存在する部位の近傍に血流の増加がみられる。
5-C：ダイアモックス負荷試験においても同部位に容易に血流の増加が認められた。

Fig. 5　The cerebral blood flow evaluation of the case with determination mismatch. The case is a 50 year-old female with arterio-venous malformation (AVM) adjacent to the area 45. 5-A: An abnormal blood vessels are located adjacent to the area 45. 5-B: The CBF increases at the area of AVM. 5-C: The CBF after acetazolamide administration has been enhanced at the area of AVM.

域のOxy-Hbの増加が認められた。また，この領域はarea 45とほぼ一致していた（図3）。

以上より，一致率が高くarea 45近傍と考えられたROI3，ROI5，ROI6を至適ROIとした。また，優位半球決定は，3箇所の至適ROIの全領域をカバーするROI6から算出したLI値をもとに行うこととした。ただし，判定に際し，ROI6の波形にアーチファクトの混入がある場合には，アーチファクトの混入の最も少ない残りの至適ROIからLI値を計算し，優位半球を決定した。

2. Wada testとの比較

全症例の光トポグラフィーとWada testの一致状況を図4に示す。Wada testが実施可能であった10例では症例5を除く9/10例（90%）でWada testの結果との一致がみられた。また，Wada testの実施が困難であった1症例（症例9）においても，光トポグラフィー

では優位半球の決定が行えた。

3. 代表症例

(1) Wada test で判定の乖離がみられた症例

症例は 50 歳女性で，area 45 近傍の動静脈奇形に対して手術を施行した。本例での LI は－0.29 で右優位半球と判定したが，Wada test では左半球優位であった。本症例では，area 45 近傍に異常血管が増生していた。また，同部位は，ダイアモックス負荷試験において，明らかな血流増加が認められた（図 5）。

(2) Wada test の実施が困難であったが光トポグラフィーで言語優位半球が決定できた症例

症例は 57 歳女性で，左前頭葉膠芽腫の症例である。本例に対して Wada test を試みたが，麻酔導入に伴い患者が不穏状態となり，実施が困難であった。そこで，光トポグラフィー検査を実施したところ ROI3 で LI が 1，ROI5，ROI6 で LI が 0.33 となり 左優位と判定した。

考察

1. Wada test の非侵襲性代替法としての光トポグラフィー検査

頸動脈内アモバルビタール法/Wada test は，危険と不快を伴う観血的な試験であり，加えて再検査が困難である。また，その評価に際しても患者の意識水準の変動，行動および情動反応により結果が不明瞭となるなどの問題を有する[13]。現在，Wada test の代替法として，言語皮質の非活性化を利用した方法，構造的非対称を利用した方法，言語作業によって直接的に事象関連脳活性化を検出する方法および言語皮質の血行力学応答を検出する方法などが報告されている（表 3）。これらの報告での，RTMS（Repetitive transcranial magnetic stimulation），MRI，MEG，光トポグラフィー，PET，fMRI と Wada test の一致率は，それぞれ，71％(12/17)，100％(12/12)，87％(74/85)，88％(9/11)，96％(23/24)，91％(91/100) である[8,9,14~17]。代替法に求められる絶対条件としては，一致率の高さに加えて，臨床応用にあたって各種方法の特性を考慮する必要がある。臨床的観点から，PET では安全に投与できる放射能量が制限される。このため，時間分解能は 1～2 分程度で，加えて再検査が容易に行えないなどの問題がある。fMRI と NIRS は無侵襲であるので，安全面からの制限は少ない。

次に，rCBV の変化に着目して fMRI と NIRS の違いを考察する。rCBV は血管床の面積と rCBF の速さの積で表される。この点で，rCBF の増加には 2 種類のパターンが想定される。1 つは血管床の面積の増加に起因した rCBV の増加が起こる場合である。この場合には，Oxy-Hb と deoxy-Hb の双方の増加が見込まれる。もう 1 つは，rCBF の速さの増加に起因した rCBV の増加である。この場合には，流入した動脈血により deoxy-Hb は wash out されてしまい，Oxy-Hb の増加と deoxy-Hb の減少が見込まれる。光トポグラフィーでは，Oxy-Hb と deoxy-Hb の両者の増減による変化を検出可能である。これに対して，fMRI では後者の変化をとらえた BOLD 効果そのものを検出原理としているため，前者の rCBV の変化の検出は困難である。この理由により，感度においては光トポグラフィーの方が高いことが想定される。事実，fMRI により検出不能であった脳活動を，同時記録の NIRS で検出したとする報告がなされている[10]。したがって，光トポグラフィーは，空間分解能では fMRI には及ばないものの，時間分解能と賦活部位の検出感度において，fMRI より優勢であると考えられる。加えて，MEG や fMRI のように磁場を必要としないため，人工内耳やペースメーカー装用者への検査も可能である。

表 3　各種言語優位半球決定法の原理と Wada test との一致状況

Table 3　The determination methods of language lateralization: the principle and agreement situation with Wada test

方法	判定原理	直接性	和田試験一致率	著者
RTMS	電気干渉による非活性化法	直接的	71% (12/17)	Epstein et al, 2000[14]
MRI	形態的優位性と関連	間接的	100% (12/12)	Foundas et al, 1994[15]
MEG	直接活性化と関連した磁性束密度法	直接的	87% (74/85)	Papanicolaou et al, 2004[8]
光トポグラフィー	活性化に対する血行力学反応法	間接的	88% (9/11)	Watanabe E et al, 1998[9]
PET	活性化に対する血行力学反応法	間接的	96% (23/24)	Tatlidil et al, 2000[16]
fMRI	活性化に対する血行力学反応法	間接的	91% (91/100)	Woermann et al, 2003[17]

また，NIRSは体動に比較的強い検査法であるとされ[18]，安静状態保持が困難な症例に対しても測定できる可能性を有する。我々の事例においても右後頭部に悪性膠腫を有した80歳の認知機能低下患者（症例2）および13歳の自閉症患児（症例10）でも検査が遂行でき，麻酔により不穏状態となった症例においても優意半球の決定ができた点は臨床的意義が大きい。これらを総合的に考えるとき，光トポグラフィー法はWada testの有力な代替法になりうると考える。

2. LIの判定値の設定

Rutten らはfMRIでLIを算出し，Cohen's kappaテストで0.25，0.50，0.75の場合のカットオフ値の妥当性について検討している[12]。この結果として，LI 0.25のカットオフで最善の一致が示され，強い左側方化（LI>0.50），わずかに左側方化（0.25<LI≦0.50），両側性（−0.25<LI≦0.25），弱い右側方性（−0.50<LI≦−0.25），強い右側方性（LI<−0.50）を規定した。我々は，これをもとに，LIの判定基準として「0.25」を採用したが，実際にはさらに症例を増やして0.25の妥当性の評価をする必要がある。

3. 光トポグラフィー検査の標準化

渡辺らは，外耳孔と眼窩下外側縁（infraorbital point）の2点を底辺とする正三角形の頂点（B点）を同じデータで作製した脳表像の上に投射することで，area 45の後端周辺に集まることを確認し[11]，これをメルクマールとしてプローブを配置している。今回我々は，さらに簡便な方法として図1のプローブ配置法を採用した。この部分は，渡辺らの示したarea 45を含む正三角形領域と重複しており，また彼らが設定したROIと本検討のROI3は，ほぼ一致している。本検討では，MRI画像と光トポグラフィーの合成画像を作製した3例全例でROI3にOxy-Hbの増加が認められ，9/10例（90%）でWada testの結果との一致がみられた。以上より，プローブの配置法と判定法は，適切であると考えられ，本プローブの配置法は，簡便であるため検査の標準化に寄与することが考えられた。

4. 判定乖離例から考えられる光トポグラフィーの特性

本研究においては，1例（11%）の患者にWada testと乖離がみられた。その原因は，脳動静脈奇形が右前頭側頭部に存在しており，中大脳動脈の灌流異常が結果に反映されたものであると考えられる。同様の事例として，Lehéricy らは動静脈奇形の患者の血流異常がfMRIの言語優位性を妨げることを報告している[19]。光トポグラフィー検査の誤判定については，上述の原因以外にも，腫瘍，発達時の問題に伴う言語野の偏移などが考えられる。また，Wada testとの乖離については，麻酔薬による脳機能抑制を利用したWada testに対して，言語皮質の血行力学応答を間接的に検出する光トポグラフィーの原理的違いが表現された可能性も，不一致の要因として否定できない。

結語

1. プローブ配置の簡便化とarea 45に相当する適切なROIの決定を行い，設定ROIの有効性を確認した。
2. 光トポグラフィー装置による無侵襲性言語優位半球の同定はWada testと90%（9/10例）の一致率をみた。
3. 中大脳動脈領域の病変の存在は，判定に影響を及ぼす可能性がある。
4. 本法の導入によりWada testの判定不能症例であっても優位半球の決定できる可能性が示唆された。

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Non-invasive determination of language dominance with optical topography: comparison with the intracarotid amobarbital procedure

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Background; During neurosurgical treatment, it is extremely important to localize of cerebral function to preserve cerebral function and maintain the quality of life of the patients. Recently, hemispheric dominance for language has been assessed using the Wada test in which amobarbital is injected into the carotid artery. However, this is an invasive technique with considerable risk of complications. Herein, we attempted optical topography (OT) along with the findings of the Wada test.

Methods; Eleven patients who underwent craniotomy in this hospital were tested with optical topography during a word generation task. These patients included 3 patients with cerebral aneurysms, 6 with brain tumor, 1 with epilepsy, 1 with cerebral arteriovenous malformation, who were from 13 year to 81 years of age, and comprised of 7 men and 4 women.

Word generation task: Each subject was given 15 seconds to write down as many words as possible, beginning with a randomly presented letter on a computer monitor. In between presentation of letters, subjects were instructed to focus on copying a picture for 30 seconds during which the NIRS baseline was established.

NIRS measurements: We measured the relative changes in oxygenated (Oxy-Hb) deoxygenated hemoglobin (deoxy-Hb) and total hemoglobin, which were calculated by combining the two parameters following collection of NIRS data (ETG-7100; Hitachi Medical Corporation, Tokyo, Japan) during performance of the Word generation task. We subsequently used a region of interest (ROI) and laterality index (LI). Six ROIs were set to determine the useful ROI, and the agreement rate with the Wada test was calculated. The LI, for Oxy-Hb was calculated from L and R, the sum of the concentrations for the activated ROIs over the left and right inferior frontal regions bilaterally, according to the following formula: $LI = (L - R)/(L + R)$. The LI ranged from -1 to 1, where a positive value (0.26 to 1) indicated left language lateralization and a negative value (-1 to -0.26) indicated right language lateralization. A value between -0.25 and 0.25 inclusively was considered to reflect bilateral language dominance.

Results; The results indicated a high agreement ratio in ROI 3, 5, and 6, of which 5 and 6 were included in ROI 3. We subsequently determined the language dominant hemisphere from the foregoing ROI and LI. The results based upon the optical topography were eight left-sided predominance, right predominance in two, and one case of bilateral predominance. Meanwhile, the results of Wada test were eight left-sided predominance, one case each of right and bilateral predominance, and inability to determine in one. The agreement between the techniques was 90% (9/10 case). One evaluation that was impossible by determination using Wada test was possible.

Conclusions; Therefore, this study demonstrates that OT is a feasible clinical application for the identification of the language dominant hemisphere.

Key Words : near-infrared spectroscopy, optical topography, Wada test, language dominance, non-invasive measurement

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Focal brain cooling terminates the faster frequency components of epileptic discharges induced by penicillin G in anesthetized rats

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HIGHLIGHTS

- Epileptic discharges (EDs) in superficial layers were induced with penicillin G.
- Focal brain cooling preferentially terminated the faster frequency components of EDs.
- Frequency analysis demonstrated that cooling below 25 °C may be an effective treatment for epilepsy.

ABSTRACT

Objective: The goal of the study was to investigate the effects of focal brain cooling on epileptic discharges (EDs) and background rhythms in the sensorimotor cortex of anesthetized rats using spectral analysis of electroencephalography (EEG).
Methods: Penicillin G was administered intracortically into superficial layers of the left sensorimotor cortex and EDs were induced. Focal brain cooling was achieved using a cooling device attached to the cortical surface. The cortical surface was cooled to 25 °C, 20 °C and 15 °C, and EEG was continuously recorded just beneath the cooling device. EEG spectral powers were determined using fast Fourier transform before and during cooling.
Results: Penicillin G induced EDs and increased the Alpha and Beta power spectra. Cooling suppressed EDs with an effect that depended on the brain temperature. Cooling to 25 °C attenuated Beta powers, cooling to 20 °C attenuated Alpha and Beta powers, and cooling to 15 °C suppressed spectral powers ranging from Delta to Beta bands.
Conclusions: These results suggest that focal brain cooling can terminate EDs in the cortex and suppress spectral powers with a temperature-dependent effect.
Significance: These findings may contribute to development of a new clinical treatment for patients with epilepsy.

1. Introduction

Epilepsy is a neurological disorder characterized by recurrent brain abnormalities that result in seizures and can be detected by electroencephalography (EEG). Epilepsy is usually treated with medication, but approximately one-third of epilepsy patients do not attain seizure control (Guidelines for epidemiologic studies on epilepsy, 1993). Surgical treatment is also used, but is not always successful. Brain cooling has been proposed for suppression of epileptic discharges (EDs) for over 50 years (Baldwin and Frost, 1956; Ommaya and Baldwin, 1963; Sartorius and Berger, 1998; Yang and Rothman, 2001; Rothman, 2009). Our previous studies demonstrated that use of a focal brain cooling device could suppress EDs induced by cerebral infusion of kainic acid without causing histological damage in rats (Imoto et al., 2006; Oku et al., 2009). However, little is known about the profile of the EEG frequency spectrum during suppression by focal brain cooling.

Experimental epilepsy induced by penicillin is a classical model of epileptic activity mediated by GABA A receptor antagonism and has been widely used in animal experiments (Schwartzkroin and Prince, 1977; Chen et al., 1986; Fisher, 1989; Bertsche et al., 2010). Recently, it was reported that intracerebroventricular (i.c.v.) infusion of penicillin G potassium shifted the EEG spectral

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distribution from slow to fast frequency bands (Canan et al., 2008). In this study, we investigated whether focal brain cooling at different temperatures can attenuate EDs of any frequency.

2. Methods

Male Sprague–Dawley rats (body weight 500–600 g, Chiyoda. Kaihatsu, Japan) were housed in individual plastic cages (*L* 40 cm, *W* 25 cm, *H* 25 cm) at a constant temperature (22 °C) under a 12-h light/dark cycle with access to water and food ad libitum. The animals were 11–12 weeks old at the start of the study. All experiments were performed according to the Guidelines for Animal Experimentation of Yamaguchi University School of Medicine.

2.1. Preparation

The animals were anesthetized with urethane (1.25 g/kg, i.p.). Lidocaine, a local anesthetic, was applied at pressure points and around the area of surgery. After the initial surgery, the animals were fixed in a stereotaxic apparatus (SR-6, Narishige Co., Tokyo, Japan). Body temperature was maintained at 37 ± 1 °C with a heating pad (BWT-100, Bio Research Center Co., Japan). The depth of anesthesia was monitored throughout the experiment by testing for reflexes and monitoring changes in heart rate in response to tail pinching.

2.2. Epilepsy model

Penicillin G potassium (Sigma, Japan) was dissolved in 0.9% saline at a concentration of 400 IU/μl. A rectangular opening (4 × 10 mm) in the cranium was made above the left sensorimotor cortex to allow insertion of a guide cannula and placement of the cooling device (a Peltier chip with a heat sink) (Imoto et al., 2006) on the dura-arachnoid membrane. A thin thermocouple (IT-24, Physitemp, Japan) was placed between the Peltier chip and the brain surface. A small slit in the dura was made and the injection cannula (0.4 × 19 mm, NN-2719S, Terumo, Japan) was inserted at a depth within 1 mm from the brain surface. Penicillin G was administered into the left sensorimotor cortex for 5 min at a rate of 5 μl/min (total 2000 IU). Administration was performed via a 10-μl Hamilton syringe (MS-10 type, Ito Corp. Fuji, Japan) attached to a microinfusion pump (ESP-64, Eicom, Japan), after the dura-arachnoid membrane had been carefully incised at the point of entry of the needle. The stereotactic coordinates relative to the bregma were 1 mm (posterior) and 3 mm (lateral).

2.3. Electrophysiological recording

Continuous EEG recordings were made during each experiment, as previously described (Imoto et al., 2006). An Ag/AgCl electrode for recording EEGs (Unique Medical Co., Fukuoka, Japan) was positioned stereotactically on the cortical surface at the left

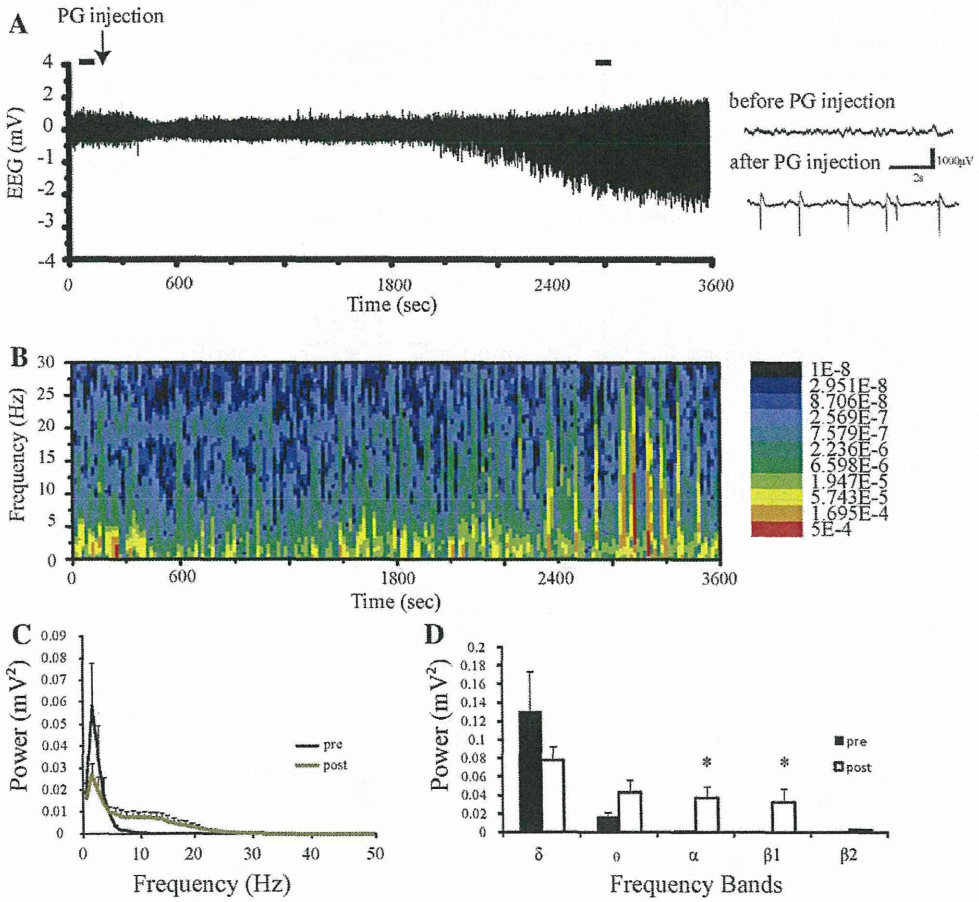

Fig. 1. (A) An example of epileptic discharges produced by intracortical administration of penicillin G. Bars indicate durations for EEG spectral analysis pre- and post-penicillin injection (arrow), respectively. EEG traces (right). (B) FFT analysis. (C) Spectral profiles of epileptic activity (n = 5, mean ± SE) pre- (black) and post- (gray) penicillin injection. (D) Average EEG power (n = 5, mean ± SE) pre- (black) and post- (white) penicillin injection for each frequency band. *P < 0.05 (paired t-test).

sensorimotor cortex, just beneath the cooling device. A reference electrode was inserted in the neck muscle and EEGs were recorded continuously by a digital electroencephalograph (GE Healthcare, Japan). An ED was determined as a sharp wave with a duration <70 ms (Chatrian et al., 1974). The conditions for recording EEGs were time constant: 0.3 s; high-frequency filter: 10 kHz; notch filter: on.

2.4. Cooling conditions

We previously reported that cooling the cortical surface to 15 °C increased the latency for withdrawal in limbs contralateral to the cooling cortex in thermal withdrawal tests (Fujioka et al., 2010), suggesting that cooling below 15 °C induces sensorimotor dysfunction. Therefore, the temperatures targeted by the focal brain cooling device were 25 °C, 20 °C, and 15 °C.

2.5. Data analysis

Before induction of EDs, EEGs were obtained for 1 min within the first 3 min as basal activity. EEGs during EDs were recorded for 1 min when the amplitude reached a supramaximal level. In cooling, fast Fourier transform (FFT) analysis was performed for spontaneous discharges for the first 1 min after the cortical temperature reached the target value. The sampling rate of the EEG recording was 2000 Hz. Frequency analyses were performed using FFT (one epoch of 100 s) with a Hamming window. After FFT, the absolute band power was calculated for prominent EEG spectral bands (Delta: 1–4 Hz, Theta: 4–9 Hz, Alpha: 9–14 Hz, Beta 1: 14–24 Hz and Beta 2: 24–30 Hz).

2.6. Statistical analysis

All results are expressed as means ± standard error of the mean. For spectral analysis, a paired *t*-test was used for comparison of pre- and post-drug injection or non-cooling and cooling data. The level of significance for all analyses was set at $P < 0.05$.

3. Results

First, we investigated the changes in the power spectrum after penicillin G injection. A typical example of EDs induced by penicillin G is shown in Fig. 1. No EDs were observed prior to injection. At 30 min after drug injection, the amplitude of EDs began to increase

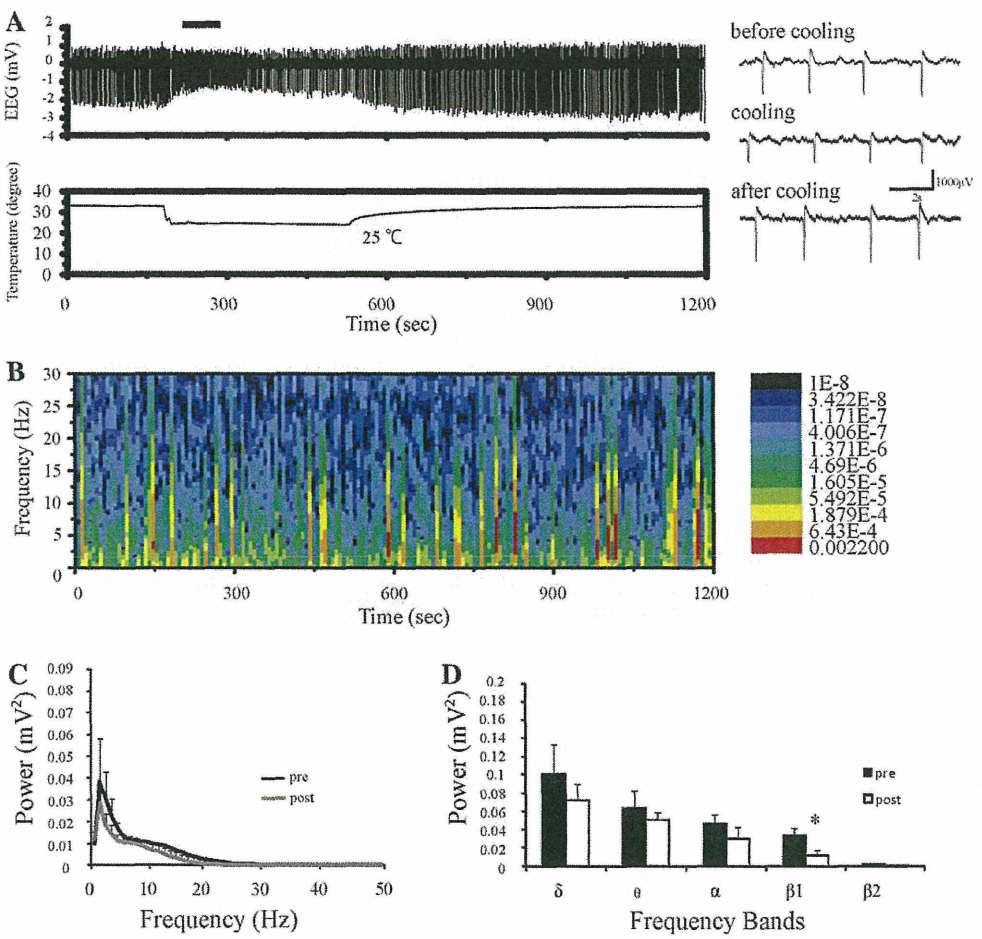

Fig. 2. (A) An example of a change in epileptic discharge (top) with the temperature of the cortical surface (bottom) controlled at 25 °C. The bar indicates the duration of EEG spectral analysis after focal cooling. EEG traces (right). Note that the decreased spectral power recovered to the level before focal cooling. (B) FFT analysis. (C) Spectral profiles of pre- (black) and post- (gray) cooling treatment for epileptic activity ($n = 5$, mean ± SE). (D) Average EEG power ($n = 5$, mean ± SE) pre- (black) and post- (white) cooling for each frequency band. *$P < 0.05$ (paired *t*-test).

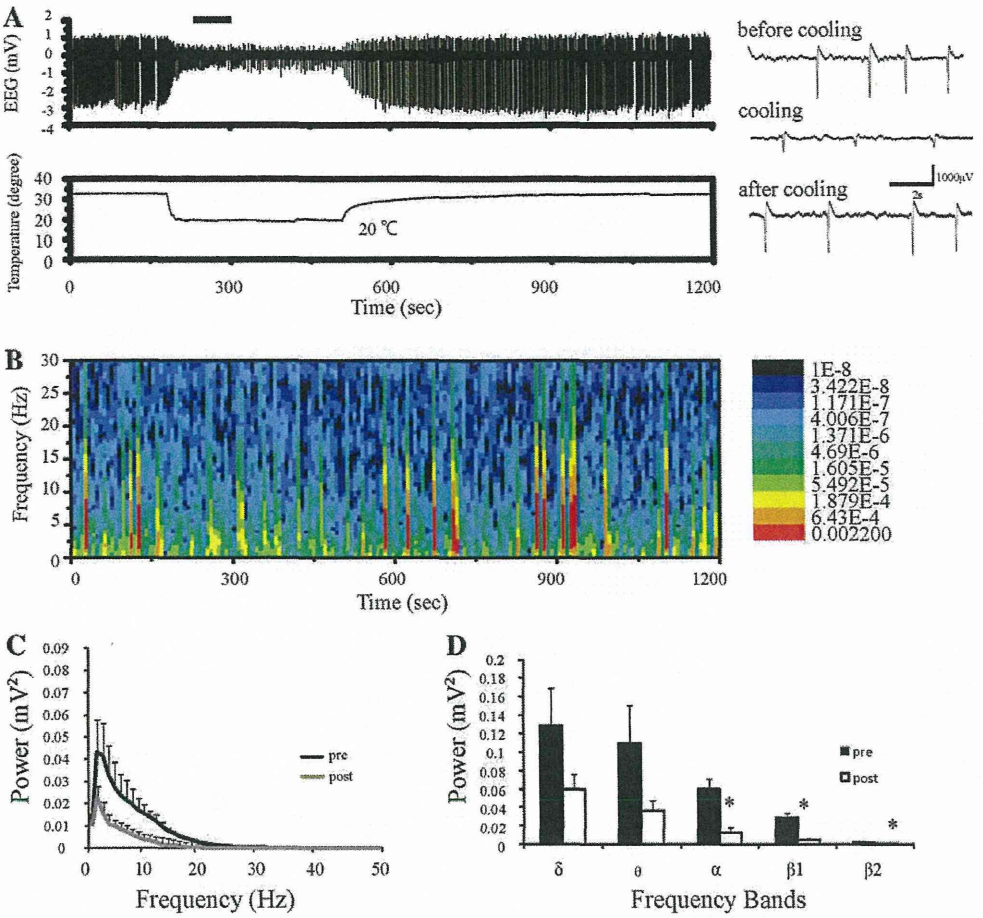

Fig. 3. (A) An example of a change in epileptic discharge (*top*) with the temperature of the cortical surface (*bottom*) controlled at 20 °C. The bar indicates the duration of EEG spectral analysis after focal cooling. EEG traces (right). (B) FFT analysis. (C) Spectral profiles of epileptic activity ($n = 5$, mean ± SE). (D) Average EEG power ($n = 5$, mean ± SE) pre- (black) and post- (white) cooling for each frequency band.* $P < 0.05$ (paired t-test). Other notations are the same as those in Fig. 2.

and lasted at least 1 h (Fig. 1A). The mean ED rate was 0.64 ± 0.07 Hz. There was a significant increase in the number of EDs per min between pre and post-drug infusion ($P < 0.01$). To quantify the frequency profiles, the power spectrum was calculated by FFT analysis for all animals ($n = 5$). A power distribution within 10 Hz was predominant during pre-treatment, while the distribution shifted toward faster frequency bands after injection of penicillin G (Fig. 1B and C). There was a significant increase in spectral power for the Alpha wave (pre 0.002 ± 0.0002 vs. post 0.037 ± 0.012 mV^2) and Beta1 wave (0.001 ± 0.0002 vs. 0.032 ± 0.015 mV^2) bands (Fig. 1D, $P < 0.05$). To investigate the frequency components in the EDs, FFT analysis was performed for each ED. Wave bands other than the Delta wave exhibited significant increases (Theta wave, 5.7 times; Alpha wave, 22.6 times; Beta1 wave, 12.2 times; Beta2 wave, 5.2 times).

Focal brain cooling was performed after adequate EDs were observed. Compared with pre-cooling, EDs were weakly and insignificantly suppressed by cooling to 25 °C (pre 0.68 ± 0.07 vs. post 0.63 ± 0.09 Hz, $P = 0.44$; Fig. 2A); moderately but significantly suppressed at 20 °C (0.70 ± 0.01 vs. 0.59 ± 0.06 Hz, $P < 0.05$; Fig. 3A); and completely attenuated at 15 °C (0.62 ± 0.01 vs. 0.47 ± 0.06 Hz, $P < 0.05$; Fig. 4A). The temperature of the cortical surface was maintained at 34 °C before cooling and decreased to the target temperature within 3 min in all cooling protocols (Figs. 2A, 3A, and 4A).

To examine changes of EEG frequency during cooling, FFT analyses were performed, as shown in Fig. 1B. We verified that the changes in spectra were reversible (Figs. 2B, 3B and 4B). At 25 °C, only the Beta1 band was significantly suppressed (pre 0.033 ± 0.009 vs. post 0.011 ± 0.006 mV^2, $P < 0.05$; Fig. 2C and D). At 20 °C, the Alpha band (0.059 ± 0.001 vs. 0.013 ± 0.006 mV^2) and Beta1 band (0.028 ± 0.004 vs. 0.004 ± 0.002 mV^2) were significantly suppressed ($P < 0.05$, Fig. 3C and D). At 15 °C, every spectral band was significantly suppressed ($P < 0.05$, Fig. 4C and D).

4. Discussion

This is the first study to use frequency analysis to investigate the effects of focal cooling in rats with EDs. The results are summarized as follows: (1) penicillin G increased faster frequency components (Alpha range: 9–14 Hz; Beta range: 14–30 Hz), (2) cooling the brain to 25 °C suppressed the Beta EEG bands, (3) cooling the brain to 20 °C suppressed not only the Beta EEG bands but also the Alpha EEG bands, and (4) cooling the brain to 15 °C suppressed both the fast and slow frequency EEG bands.

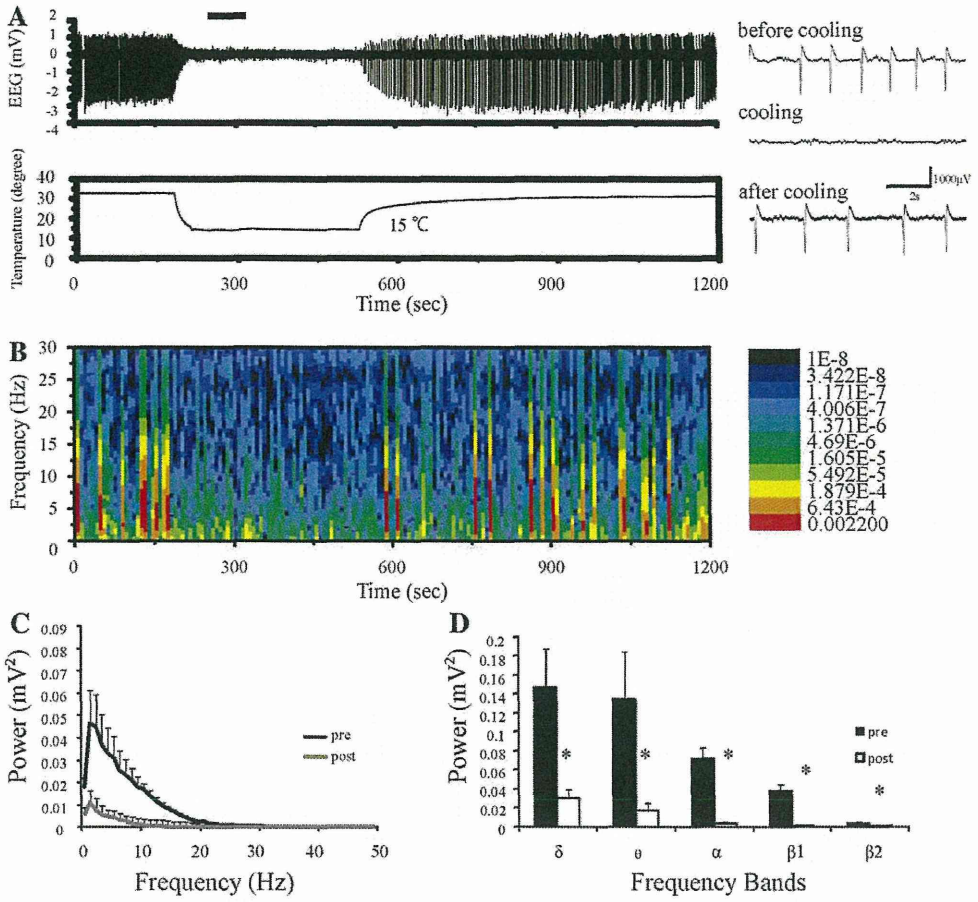

Fig. 4. (A) An example of a change in epileptic discharges (*top*) with the temperature of the cortical surface (*bottom*) controlled at 15 °C. The bar indicates the duration of EEG spectral analysis after focal cooling. EEG traces (right). (B) FFT analysis. (C) Spectral profiles of epileptic activity ($n = 5$, mean ± SE). (D) Average EEG power ($n = 5$, mean ± SE) pre- (black) and post- (white) cooling for each frequency band.* $P < 0.05$ (paired *t*-test). Other notations are the same as those in Fig. 2.

The spectral shift from slow to fast frequency induced by penicillin G was responsible for disinhibition of synchronous firing activity in the cortex, consistent with previous studies (Canan et al., 2008). Penicillin G was infused into the superficial layers through a small slit in the dura, after which the drug gradually diffuses into deep layers within 15 min (Ludvig et al., 2008). However, the origin of faster frequency components was not considered to be due to hyperactivity in deep layers. This is because i.c.v. infusion in a previous study (Canan et al., 2008) and intracortical administration in this study induced faster frequency components in Alpha and Beta wave bands, while GABA A receptor disinhibition with bicuculline in neocortical layer V generates discharges of at most 1 Hz (Castro-Alamancos, 2000). Therefore, induction of faster frequency components may be organized in superficial layers.

In this study, the cooling device predominantly reduces the temperature in superficial layers, since a previous study showed that there is a temperature difference of approximately 5° between the cortical surface just under the cooling device and deep layers (Oku et al., 2009). Therefore, mild cooling at 20 °C could terminate Alpha waves in the cortex, while 25 °C cooling suppresses only Beta wave bands. Because 15 °C cooling suppressed neuronal activity in the subcortex, there may be a faster frequency of neuronal networks in the cortex than in the subcortex. The exact mechanism of the antiepileptic effects of focal brain cooling has not been elucidated. However, we have obtained preliminary results (Fujii et al., 2011) that suggest that reductions of metabolism, cerebral blood flow and glutamate release are involved in termination of seizures, in addition to suppression of synaptic transmission (Eilers and Bickler, 1996) and/or the difference of activity in response to cooling between pyramidal neurons and inhibitory interneurons (Motamedi et al., 2012).

In the rat sensorimotor cortex, including the barrel cortex, there are widespread horizontal excitatory connections among functional columns in layers II/III and V/VI (Feldmeyer et al., 2002; Petersen et al., 2003). Our previous study demonstrates even cooling to 15 °C above brain surface cannot decrease the temperature below 20 °C in layers V/VI (Fujii et al., 2012), suggesting that the effect of focal cooling on termination of ED is within layers II/III. It is reasonable to assume that even cooling at 25 °C can terminate the conductance of faster frequency EEGs along layers II/III, although we did not record an EEG from each layer directly. Accordingly, axons in layers II/III may be involved in routes for propagating EDs. In addition, maintenance of the temperature of the cooling site at 20 °C caused significant suppression of the amplitude of the EDs. Our results are also consistent with reports showing that the optimum temperature of the cortical surface for terminating seizures is approximately 15–25 °C (Yang et al., 2002, 2003; Fujioka et al., 2010). A recent study demonstrated that focal brain cooling from 20 to 15 °C did not suppress normal

function (Fujii et al., 2012). Therefore, we conclude that focal brain cooling to at least 20 °C does not affect normal EEG activity.

High EEG frequency spectra (>30 Hz) did not appear in the current study, in contrast to experiments performed under arousal conditions (Buzsaki et al., 1988; Bragin et al., 1999). Additionally, epileptic seizures were not observed, in contrast to a recent report using a similar method (Rothman, 2009). Our method differs from those previous studies in that we selected a stable and prolonged urethane anesthesia. Nevertheless, we considered that the observed epileptic discharges in our study were interictal (Holmes et al., 1987; de Guzman et al., 2010), although induction of seizure may depend on the degree of anesthesia. These disagreements are due to the limitation of performing experiments in anesthetized animals, and further work is required to test the effects of cooling in free moving rats established in our laboratory (Fujioka et al., 2010; Fujii et al., 2012). A recent study demonstrated that high frequency oscillation is linked to seizure onset (Bragin et al., 2010), and therefore it is possible that focal cooling at a suspected epileptogenic focus can terminate EDs and seizures.

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Intra-operative monitoring of lower extremity motor-evoked potentials by direct cortical stimulation

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HIGHLIGHTS

- We advocate a new method for lower-limb motor evoked potential (MEP) monitoring.
- This method is available in the supratentorial surgery.
- Lower-limb MEPs were consistently recorded by direct cortical stimulation.
- Optimal stimulation site was 2 cm lateral from the midline on the motor cortex.
- This monitoring technique can be applied to standard pterional craniotomy.

ABSTRACT

Objective: Motor-evoked potentials (MEPs) are commonly recorded from upper-extremity muscles, whereas lower-extremity MEP (LE-MEP) monitoring has not been adequately established. The goal of the study was to develop a MEP monitoring method using direct cortical stimulation (DCS) for predicting motor deficits of lower extremities.

Methods: Intra-operative LE-MEP monitoring was performed in 22 patients. After craniotomy, a subdural electrode was placed on the cortex so that the optimal contact was positioned 2 cm lateral from the midline on the motor cortex. The electrodes for stimulation consisted of a cathode at Fpz and an anode at the optimal contact site on the motor cortex. After stimulation was performed with short trains of five stimuli, LE-MEPs were recorded from the lower-limb muscles.

Results: LE-MEPs were consistently recorded in all patients. Disappearance or amplitude reduction of MEP waveforms was observed in five patients, but the MEP waveforms had recovered and remained at the control level by dural closure, and no permanent motor deficit was observed in any patient.

Conclusions: We accomplished LE-MEP recording during supratentorial surgery using monopolar DCS with a subdural electrode placed on the convex side of the motor cortex.

Significance: A useful method of intra-operative LE-MEP recording was described.

1. Introduction

Intra-operative monitoring of the motor evoked potential (MEP) has become common during neurosurgical procedures to avoid the occurrence of motor deficit, especially following the manipulation of the peri-rolandic area (Burke and Hicks, 1998; Kombos et al., 1999, 2001, 2009; Sala et al., 2007; Sloan et al., 2008; Suzuki et al., 2003; Szelényi et al., 2005; Tanaka et al., 2007; Taniguchi et al., 1993). The MEPs are commonly recorded from upper-extremity muscles or the spinal cord at the cervical epidural space (the so called D-wave) after transcranial electrical stimulation or direct stimulation of the motor cortex (Cedzich et al., 1996; Chen et al., 2007; Fujiki et al., 2006; Journée et al., 2007; Kaneko et al., 1988; Krammer et al., 2009; Nagle et al., 1996; Rothwell et al., 1994; Suzuki et al., 2003; Szelényi et al., 2005, 2007a,b; Szelényi et al., 2010; Taniguchi et al., 1993; Yeon et al., 2010). Recently, MEP monitoring using direct cortical stimulation (DCS) has been recommended for supratentorial surgery, because transcranial stimulation may stimulate the motor tracts deep to the motor cortex and therefore miss ischaemia in the cortical region (Rothwell et al., 1994).

The hand area of the motor cortex is usually selected as a DCS site when recording MEPs with DCS (Chen et al., 2007; Neuloh and Schramm, 2004a; Neuloh et al., 2007). However, this monitor-

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ing method is difficult for detecting blood-flow insufficiency in the anterior cerebral artery (ACA) during aneurysm surgery or motor deficit of the lower extremities during procedures for peri-rolandic tumour resection. Furthermore, the few studies of MEP monitoring of the lower extremities have indicated a low success rate of monitoring (Neuloh and Schramm, 2009; Szelényi et al., 2005). Therefore, we herein describe a useful monitoring method using DCS for predicting motor deficits of the lower extremities. The methodology and results of intra-operative monitoring of the lower-extremity MEP (LE-MEP) are described in this technical study.

2. Clinical material and methods

All protocols were approved by the Yamaguchi University Ethical Review Committee. Written informed consent to intra-operative monitoring and surgical procedures was obtained from each patient or their legal guardian.

2.1. Patient population

Intra-operative LE-MEP monitoring was applied to 22 consecutive patients (nine males and 13 females) ranging in age from 40 to 85 years (mean 63.0 ± 10.8 years). These patients were undergoing surgical procedures for aneurysms of the ACA territory and for brain tumours that were adjacent to the primary motor cortex for the lower extremities. Ten patients had an anterior communicating artery (AcomA) aneurysm, four had an ACA aneurysm, three had an internal carotid artery (ICA) aneurysm, one had a middle cerebral artery (MCA) aneurysm, three had meningiomas and one patient had a glioblastoma. The backgrounds and symptoms of the patients are summarised in Table 1.

2.2. Neurophysiological monitoring methods

2.2.1. Placement of subdural electrodes for cortical stimulation

We applied LE-MEP monitoring for three types of craniotomy: a standard pterional craniotomy, a bifrontal craniotomy and a craniotomy in the range of which the motor cortex was exposed. Depending on the location of craniotomy, the placement of subdural electrodes for DCS was arranged as follows. In a standard pterional craniotomy for ICA, MCA and AcomA aneurysms, 'Corkscrew' electrodes (CS electrodes; Nicolet Biomedical, WI, USA) were placed at the Cz′ of the International 10–20 System on the scalp (2 cm posterior from the midpoint of the nasion–inion line) and C3/C4 of the International 10–20 System (approximately 7–7.5 cm lateral from the midline on the central sulcus line) as landmarks for the insertion of a subdural grid and were also used as stimulation sites before craniotomy for recording of MEPs. After the craniotomy, a 3 × 4 grid electrode (12 contacts, each 5 mm in diameter with a 10-mm centre-to-centre inter-electrode distance; Unique Medical Co. Ltd., Tokyo, Japan) was subdurally inserted toward C1/C2 of the International 10–20 System and between the two

Table 1
Background, stimulus parameters, MEP changes during surgery and postoperative outcome in 22 patients.

Case no.	Age/sex	Diagnosis	Symptoms/signs	Stimulation		MEP change during surgery	Postoperative *de novo* motor deficit (duration)
				Intensity (mA)	Duration (ms)		
1	40/M	ICA thrombosed giant aneurysm	No	23.0–26.6	1	Disappeared for 30 min	Recovered (35 days)
2	44/M	SAH, AcomA aneurysm	Headache	14.5–16.5	05	No change	No
3	52/F	SAH, ICA–AchA aneurysm	Headache/vomiting	18.0	05	No change	No
4	52/F	SAH, AcomA aneurysm	Headache/vomiting/consciousness disturbance	18.0–22.0	0.5	No change	No
5	53/F	Parietal glioblastoma	Left clumsy hand/left sensory disturbance	19.0	0.5	No change	No
6	56/M	Frontal parasagittal meningioma	Partial seizures of right fingers	19.0	0.5	No change	No
7	56/M	Frontal falx meningioma	No	21.0	0.5	No change	Transient (8 days)
8	59/F	SAH, AcomA aneurysm	Headache/vomiting	12.5	0.5	Disappeared for 8 min	No
9	62/F	Unruptured AcomA aneurysm	No	22.5	05	No change	No
10	62/M	SAH, ApomA aneurysm	Headache/vomiting/consciousness disturbance	155	05	No change	No
11	65/F	SAH, AcomA aneurysm	Headache/consciousness disturbance	16.0	05	No change	No
12	66/F	SAH, AcomA aneurysm	Consciousness disturbance	16.0–17.0	1	No change	No
13	67/M	SAH . AcomA aneurysm	Headache	20.0	0.5	No change	No
14	68/F	Unruptured AcomA aneurysm	No	20.3	0.5	No change	No
15	69/M	SAH, distal ACA aneurysm	Headache/vomiting	23.5	0.5	20–50% reduction for 15 min	No
16	70/F	Frontal parasaggital meningioma	Right hemiparesis	20	0.5	No change	No
17	70/F	Unruptured ICA–PcomA aneurysm	No	20.5	05	No change	No
18	72/M	ACA thrombosed giant aneurysm	Disorientation/left hemiparesis	20.0–22.0	1	Disappeared for 20 min	Recovered (26 days)
19	72/F	SAH, distal ACA aneurysm	Headache	30.0	05	80% reduction for 90 s	No
20	72/M	SAH, AcomA aneurysm	Headache/vomiting	20.0	0.5	No change	No
21	76/F	SAH, distal ACA aneurysm	Headache	16.0	05	No change	No
22	85/F	SAH, MCA aneurysm	Headache	24.5	0.5	No change	No

ICA; internal carotid artery, SAH; subarachnoid haemorrhage, AcomA; anterior communicating artery, ACA; anterior cerebral artery, AchA; anterior choroidal artery, PcomA; posterior communicating artery.