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Bibliographic survey of the clinical application of magnetoencephalography (II): stroke

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Measuring local cerebral blood flow and metabolism by various mapping methods such as positron emission tomography or perfusion computed tomography helps us to evaluate detailed functions of brain areas containing a focal ischemic lesion, but does not necessarily represent neural activities of the areas. Scalp electroencephalography (EEG), reflecting volume-conducted neural activities, demonstrates that slow wave activity is dominant in an acute ischemic cerebral region; but, this technique presents major problems with the lack of objective indices for brain functions and low spatial resolution. Magnetoencephalography (MEG), an important new method in neuroscience to directly detect neural activities with high spatial resolution, has been applied in stroke patients. However, the usefulness of MEG for assessing neural activities in an ischemic brain area has not been fully established as yet. The present study reviewed MEG studies of cerebral stroke using internet searches of the bibliography to identify scientific evidence for the clinical effectiveness of MEG. We searched for stroke-related manuscripts published before July 2010 on MEDLINE using

the keywords (stroke OR cerebral ischemia) AND (MEG OR magnetoencephalography), and retrieved 58 papers. We narrowed the search to 25 papers based on the levels of evidence and abstract contents. Then, we selected 12 papers with evidence level higher than 2 to assess the clinical utility of MEG. Most papers stressed the clinical usefulness of MEG, but a few claimed the superiority of MEG compared to EEG for the diagnosis or treatment indication for ischemic conditions. Therefore, more objective analysis of MEG findings in ischemic conditions is needed for future development.

Key Words: magnetoencephalography, stroke, bibliographic survey

皮質脳波による視覚認知ネットワークの解明

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Visualization of a Functional Visual Cognition Network by Electrocorticogram

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In order to better interpret spatial and temporal changes on electrocorticograms (ECoG) taken during semantic tasks, we developed software to visualize semantic-ECoG dynamics on individual brains. Twenty patients with intractable epilepsy underwent implantation of subdural electrodes (more than 80 channels) bilaterally. Semantic-ECoGs were then recorded during word, figure and face recognition tasks. The ECoG raw data was processed by averaging and time-frequency analysis and the functional profiles were projected on individual brain surfaces. Acquired ECoG was classified by Support Vector Machine and Sparse Logistic Regression to classify brain signals evoked by different stimuli. Because of electrode location variations, we normalized the ECoG elecrtrodes using SPM8. The basal temporal-occipital cortex was activated within 250 msec after visual object presentations. Face stimulation evoked significantly higher ECoG amplitudes than other stimuli. The prediction rate of ECoG-classification reached 90%, which is sufficient for clinical use. Semantic-ECoG is a powerful technique to detect and decode human brain functions.

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Key words : electrocorticogram, ECoG, epilepsy, language, normalization
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はじめに

近年の脳機能画像研究は飛躍的に発展しているが，基礎科学のみならず臨床医学の分野においても得られた画像結果の報告とその解釈にのみ主眼が置かれている．現在脳全体から発生する微小磁界を検出する脳磁図とblood oxygenation level dependent (BOLD) 効果を反映した機能 MRI，さらに拡散テンソル解析による白質画像 (tractography) が普及しつつある．これらにより非侵襲的にヒト脳機能をとらえることができるようになり，さまざまな機能の画像化などが試みられるようになった．しかし，機能画像の著しい進歩に比してその結果の検証はほとんど行われていない．特に言語機能はヒトにとって quality of life にかかわる重要な中枢機能であり，信頼性の高い高次脳機能ネットワークの画像化は臨床医学に大いに貢献するものと期待される．

わが国のてんかん患者総数は約 100 万人と推定され，そのうちの 20 万人は薬剤抵抗性の難治性てんかんとされている．一般に海馬硬化を主体とする典型的内側側頭葉てんかんに対しては，海馬を含む側頭葉切除術により

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68%で発作消失，24%が改善と良好な結果が得られている[9]．しかし，内側側頭葉てんかん以外の症例には種々の手術法が用いられているが，てんかん焦点の病態の多彩性のため手術効果はさまざまである[1)2)]．この治療ではてんかん学，神経科学が複雑に絡み合っているため，その病態，ヒト認知機能局在を明らかにすることで，より確実な治療方針の立案が可能となる．外科治療のために焦点を電気生理学的にとらえるために頭蓋内電極を留置することが多い．通常はこの留置した頭蓋内電極をてんかん発射源の同定，および脳皮質電気刺激による言語機能マッピングに応用している．

本論文では頭蓋内電極を用いてさまざまな視覚刺激により誘発された脳皮質電位（electrocorticogram：ECoG）を計測することにより，言語関連機能の画像化を試みた．個々の患者において計測されたECoGの時間・空間的広がりを個人脳に投射することで機能ダイナミクスを画像化した．さらに複数の自動判別関数を用いて課題別ECoG反応のクラス分けに応用し[8]，より効率的な脳信号の抽出を試みた．また，患者間で留置電極位置にばらつきがあるため，標準脳にECoG電極位置座標を変換・重畳した[4]．これにより標準脳上に高解像のECoGの時間的変化過程を描画した．これらを組み合わせることにより，言語機能野の同定，および典型的な認知ECoG反応ダイナミクスの解析法を開発したので報告する．

対象および方法

1 対　象

旭川医科大学，および東京大学医学部附属病院において難治性てんかん外科治療のために頭蓋内電極を留置した20例を対象にした．患者の内訳は，側頭葉てんかん16例，前頭葉てんかん3例，後頭葉てんかん1例であった．患者年齢は32.4±10.3歳であり，男女比は9：11であった．全例Wada testを施行し言語優位半球，記憶優位半球（言語性，視覚性）を同定した．また術前にWAIS-R，WMS-Rを全例に施行し高次機能評価を行った．本研究は旭川医科大学倫理委員会（承認番号693，平成22年7月12日）により承認された．

2 頭蓋内電極留置

てんかんの焦点精査目的に両側側頭葉底面，前頭葉外側面，側頭葉外側面などに硬膜下電極を留置した．側頭葉内側（鉤～海馬傍回にかけて）に留置した8極電極は術中に透視で位置を確認した．

術前MRIから脳表データをDr. View（AJS，日本）を用いて抽出した．電極位置が含まれる術後CTデータはDr. Viewにより術前MRI座標に変換してリスライスを行った．座標の一致している術前MRIと術後CTをEMSE（Source Signal Imaging，米国）上で脳表と電極位置とを融合表示し，電極位置はすべて番号を付して登録した（**Fig. 1A**）．

3 頭蓋内電極による誘発ECoG計測

ECoG記録はシールドルーム内でBMSI6000（Nicolet-Biomedical Inc, Wisconsin，米国）脳波計（128ch）を用いて行った．サンプリング周波数は400 Hzとし，ECoG計測時にはノッチ，またはバンドパスフィルターは使用しなかった．言語課題を含む視覚刺激は，縞模様-アラビア語-単語（平仮名3文字の単語の具象・抽象語弁別課題）-顔-物品写真の視覚提示，具象語と判断した時は，非利き手によるボタン押しを行った．すべての課題は視覚提示時間500 msec，刺激提示間隔を2,800～3,200 msec，平均120回の提示回数とした（**Fig. 1B**）．各刺激別にtransister-transister-logic信号を脳波計チャンネルに入力して，刺激タイミングトリガーとした．

4 ECoG解析

取得ECoGはテキストファイルに変換後Matlab-2010b＋Simulink（Mathworks，米国）に読み込んだ．Matlab内のツールを用いてshort-timeフーリエ変換を行った．刺激提示前～500 msecをベースラインとして，60～120 Hzのγ帯域成分がpermutationテスト上統計的に有意（$p<0.05$）に変化している電極を選択した．各電極の周波数成分の時間的変化量を解析した．解析結果はEMSE上で登録した電極にカラーマップとして表示して，γ帯域成分の時間-空間的変化を画像化した．

5 ECoGクラス分け学習

課題であるアラビア語-単語（平仮名3文字）-顔の3課題に対する反応（chance rate：33.3%）をクラス分け解析に用いた．各15回の学習セッションを登録した後に，Matlabのツールである Support Vector Machine（lib-SVM）とSparse Logistic Regression（ATR，日本）を用いてクラス分けを行った．

6 ECoG標準化

電極位置の標準化はSPM8（Wellcome Trust Centre for Neuroimaging，英国）を用いて行った．標準脳MRIに各患者脳MRIを非線形座標変換により変形する．この変形パラメータを患者頭部CTデータ変換に用いること

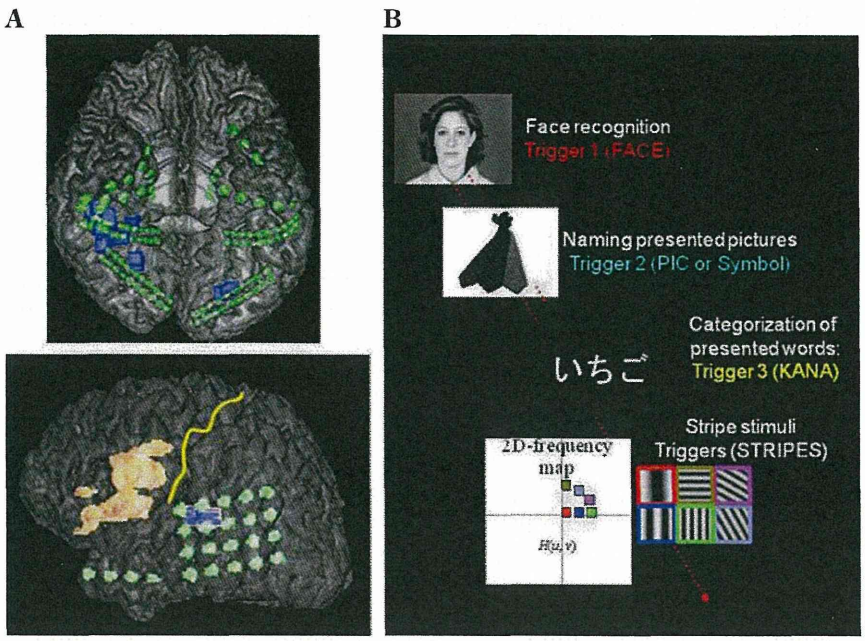


Fig. 1　Overview of semantic-ECoG recording

A：Fusion images of individual brain (MRI) and ECoG electrodes (CT),where the orange and blue areas indicate fMRI activation and MEG dipoles during the reading task, respectively.

B：Visual stimuli for semantic tasks.

で，標準脳 MRI 上に各患者 ECoG 電極を重畳する（**Fig. 2A**）．各電極はすべて番号を付して登録し，γ帯域成分の時間ごとの変化量を表示するようにした（**Fig. 2B**）．1 cm^3単位空間内に分布する電極数で帯域成分値を除すことにより，電極密度分布による成分の空間的広がりを補正した．

結　果

① 課題遂行度

20 症例中 12 症例ですべての課題を適切に行うことができた．その具象・抽象課題における正答率は平均 94.4.±6.4%であった．

② 誘発 ECoG 解析結果

課題：視覚提示刺激に対する 60～120 Hz のγ帯域成分の経時的（150，175，300 msec），空間的な広がりを可視化した．典型例を提示する．**Fig. 3A** は，両側側頭葉底部に電極を留置している症例である．比較的単純な縞模様刺激では 150～300 msec の間後頭極に活動が限局していた．一方，顔刺激では 150 msec から両側側頭葉底部均等に活動，300 msec になると縞模様刺激に比して右優位，かつ後頭極から前・外側の活動が強くなった．単語読みでは後頭極 150 msec にやや縞模様刺激より強いγ帯域成分の上昇を認め，最終的に 300 msec では優位半球（左）の活動が続いた．意味を有していないアラビア語刺激でははじめは単語刺激と同様の反応を認めたが，両側側頭葉底部の活動が続いた．しかし，その活動範囲は顔認知領域に比して内側・後方であった．**Fig. 3B** は優位半球側頭葉底部に通常の電極間距離 10 mm を 5 mm とした高密度電極を留置した例である．縞模様刺激では 150～300 msec の間後頭極にのみ活動を認めている．顔刺激では 300 msec ほどから側頭葉底面外側にγ帯域成分が広がるのが特徴的であった．一方，単語読み課題では後頭極～側頭葉内側部に活動を認め，外側に広がる顔認知反応と活動パターンが明らかに異なっていた．アラビア語では **Fig. 3A** と同様に顔認知と文字認知パターンが混在し，無意味図形に対して側頭葉底部が活発に活動していることが判明した．これらの反応の傾向は計測可能であった 12 症例全例で同様の傾向であった．

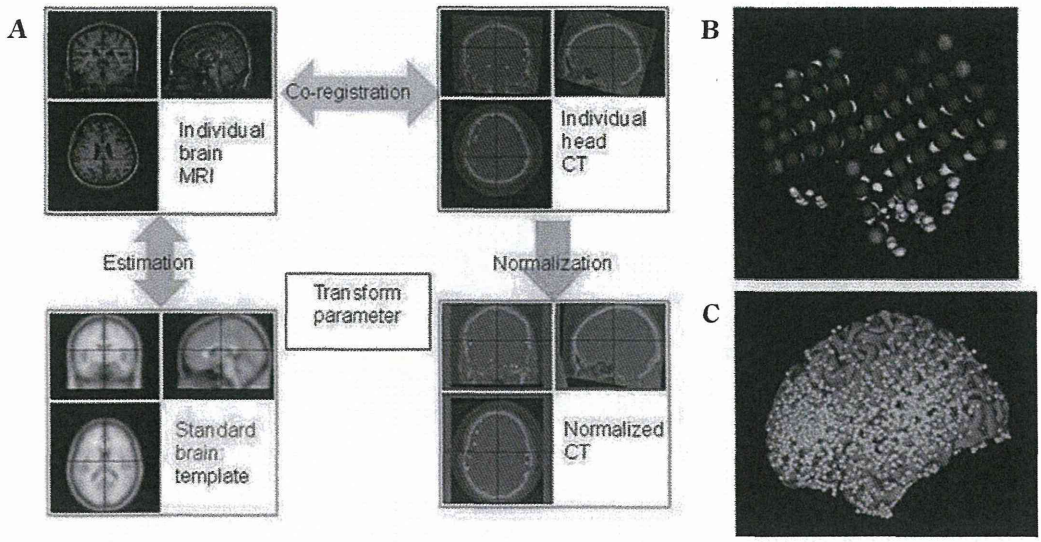


Fig. 2　Overview of ECoG electrode normalization
A：Transformation of MRI and CT coordinates by SPM8.
B：Registration of transformed ECoG channels.
C：Normalization of 20 brains with 1,323 ECoG electrodes.

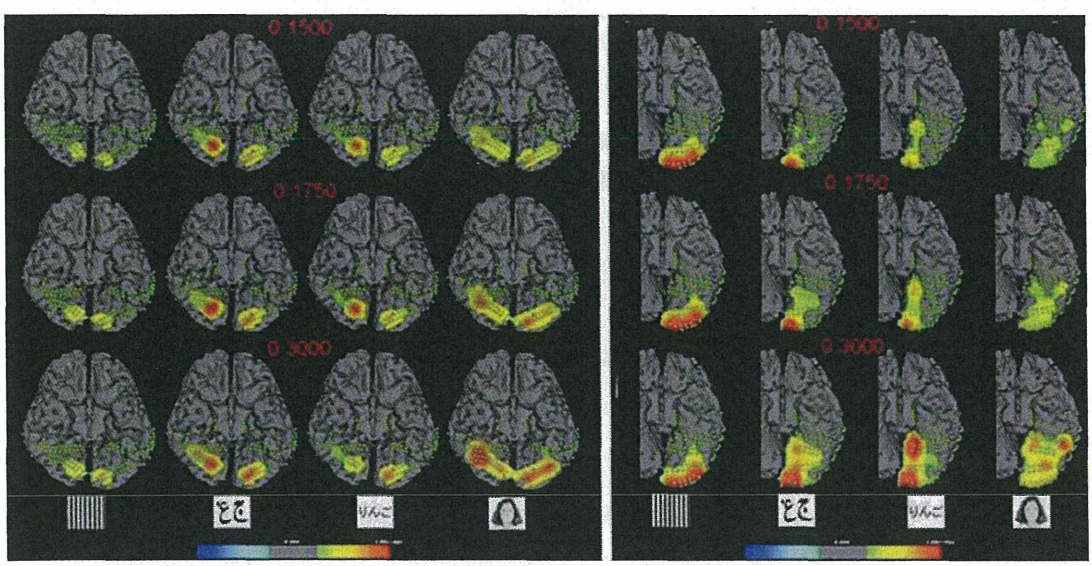


Fig. 3　Gamma band maps related to different visual stimuli
A：A patient with ECoG electrodes in the bilateral temporal bases.
B：A patient with a high density ECoG electrode in the left temporal base. Face stimulation excited the antero-lateral temporal bases more than other stimuli. There are significant differences among visual stimuli.

3 ECoG クラス分け学習

異なる 3 種類の視覚刺激（chance rate：33.3%）のクラス分け解析を行った．予測正答率は Support Vector Machine では 91.1〜97.7%，Sparse Logistic Regression は 80.2〜89.3%であった．全 ECoG データに対して特殊な処理（周波数，潜時設定など）を加えることなく読み込み処理を行った結果，それぞれの計算時間はおよそ 2 秒以内に終了した．

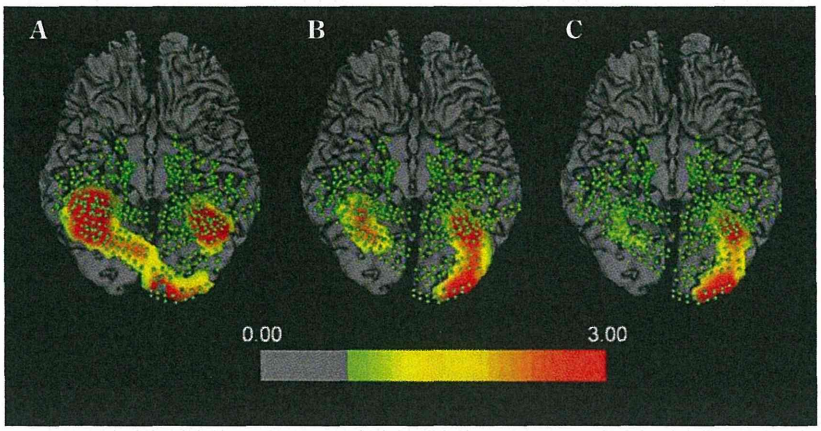


Fig. 4 Typical distribution of Gamma band components related to visual stimuli on the standard brain

A：Face stimuli activated the bilateral temporal base including the inferior temporal and fusiform gyri with right hemispheric dominancy.

B：Arabic stimuli evoked the intermediate pattern between Face (**A**) and Kana (**C**) stimuli.

C：Kana stimuli evoked Gamma band components only in the left fusiform and parahippocampal gyri.

④ ECoG 標準化

電極位置の標準化は全 20 症例を用いて行った．標準脳の側頭葉底面，優位半球外側面を 1,323 極の電極で覆うことができた（**Fig. 4A**）．電極密度は下前頭回，上側頭回近傍に高い傾向があった（**Fig. 4B**）が，密度補正を行うことで均一な電極分布状態にすることができた（**Fig. 4C**）．

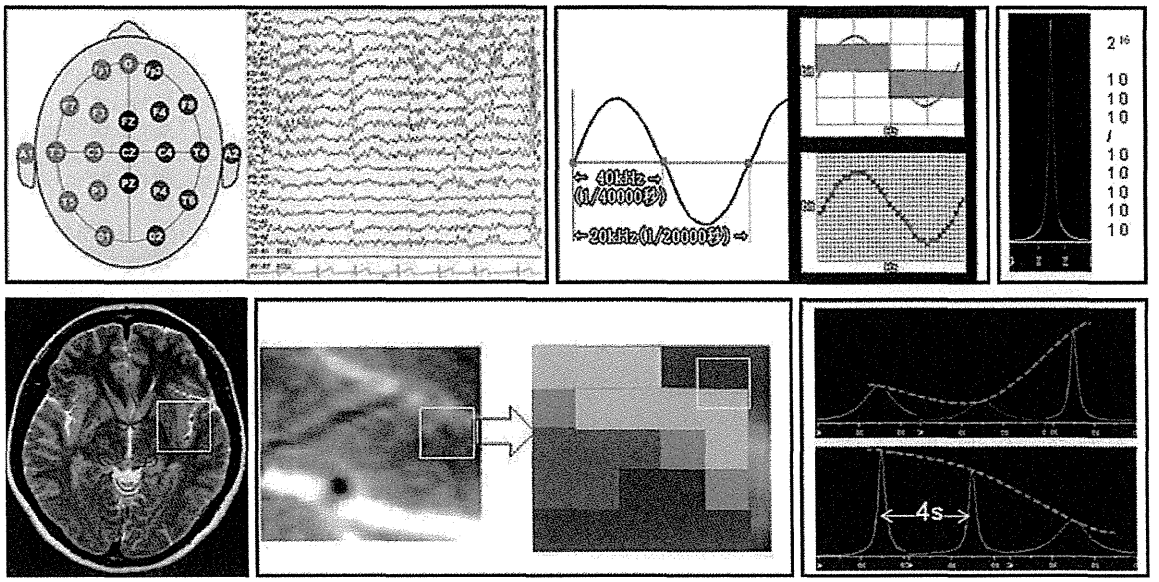
標準化した結果の視覚刺激別γ帯域成分の分布状態を示す．顔認知（Face）では両側の紡錘状回の前，外側の強い活動を認めた．特に右側への強い側方性があった．一方，文字読み（Kana）では顔認知に比してやや内側の紡錘状回-海馬傍回後部に活動が限局し，右側にはほとんど活動を認めなかった．アラビア語認知（Ara）は右側頭葉底部内側，広範に左側頭葉底部の活動を認めたが，明らかに顔認知，または文字読み課題による反応とは異なっていた（**Fig. 4**）．

考　察

本研究では異なる視覚刺激を提示しながら広範に脳表を覆った頭蓋内電極より ECoG を計測した．さらに ECoG の加算平均，時間-周波数解析結果を患者ごとに脳表に投射するソフトウェアを作成した．側頭葉底部では視覚刺激が単純であればあるほど，後頭極側にγ帯域成分が局在する傾向があった．一方複雑な刺激になると反応する領域が広がっていた．顔刺激では右優位であり，かつ両側側頭葉底部の前外側に活動が強くなっていた．電極位置の標準化は視覚刺激による側頭葉底部の典型的な反応パターンを可視化することを可能とした．文字認知では左紡錘状回～海馬傍回に，顔認知では右紡錘状回～下側頭回にγ帯域成分が出現していた．

近年頭蓋内電極によるγ帯域成分の変化に着目した報告が散見される．これらの検討では主に運動，文字読みなどに関連したγ帯域成分のダイナミクスに着目している．特に文字読み課題では文字提示後約 500 msec 後に左下前頭回，運動野近傍にγ帯域成分の増加を認めるとされている．Sinai ら[7]は脳皮質電気刺激マッピングで抑制される言語関連機能とγ帯域成分局在を検討し，その局在感度は 84% と高いことを報告している．しかし，側頭葉底面，および内側側頭葉領域のγ帯域成分ダイナミクスに関する検討はいまだ十分に行われていない．

一方，これらのヒト高次脳機能解析が Support Vector Machine のようなコンピュータ学習ソフトウェアを応用することで，より客観的に行われることも期待できる．本報告では主に脳波（ECoG）を用いたが，近年の画像を含むすべてのデジタルデータは同様の処理が可能である．**Fig. 5** で脳波と MRI のデジタル処理の原理を示す．**Fig. 5A** では一般的な脳波モンタージュと 1 チャンネルの脳波形を示す．**Fig. 5B** は 20,000 Hz の周波数のサイン波である．20,000 Hz の関心周波数の 1.5 倍のサンプリ



A|B|C
D|E|F

Fig. 5 Principles of digital data sets
A：Routine EEG montage and EEG waveforms.
B：Nyquist sampling rate for frequency of interest rate.
C：16 bit sampling for voltage amplitude.
D：MR image.
E：Magnified images consisting of pixels with various brightness.
F：Signal changes of each pixel over time on 4-dimensional images.

ング点では **Fig. 5B** のように平坦な波として認識してしまう．この波形変化を正確にとらえるために，サンプリング点を 2 点追加する必要があり，その結果関心周波数の最低 2 倍以上のサンプリング周波数は必要になる(Nyquist 周波数)．さらにその波の振幅を 2 のべき乗で表す（2 の 16 乗：16 bit）ことで，デジタル脳波データとなる（**Fig. 5C**）．一方画像においても拡大すると細かい画素（ピクセル）に分割されて，そのピクセルを脳波チャンネルと考えることができるため，脳波に比して空間分解脳はきわめて高いが（**Fig. 5D, E**），その一方で機能 MRI では 4 秒ごとに撮像を行うため，脳波に比して時間分解能ははるかに劣る（**Fig. 5F**）．各ピクセルの信号強度を 12～16 bit で表現しているため，基本的に脳波と画像のデジタルデータを同等に扱うことが可能である．このように今回用いたコンピュータ学習ソフトウェアは脳波のみならず，機能 MRI などの時系列データを有する 4 次元画像にも応用できる．

頭蓋内電極は画像診断，臨床症候に基づいて，その留置位置と範囲が決定される．診断的目的で電極が留置されるために，患者ごとにその留置範囲が異なることが脳機能解析面における課題であった．本報告では SPM8 を用いて頭蓋内電極位置を標準脳上に変換することで，高密度の電極分布による解像度の高い ECoG 解析を可能とした．本方法により異なる視覚刺激による側頭葉底面の誘発電位パターンを明らかにすることができた．SPM8 による“標準化”は機能 MRI を始め，拡散テンソル解析，脳血流シンチグラムなどに応用され，アルツハイマー病，脳虚血疾患診断に応用されてきた[3)6)]．しかし，ECoG を標準化し，高い空間解像度，および時間分解能で典型的な電気的活動の表示を可能としたのは本報告がはじめてである．特に顔認知では右側優位，かつ紡錘状回外側，および下側頭回のγ帯域成分の広がりが特徴的であった．側頭葉底部の機能分布に関する検討は機能 MRI で行われている．Puri ら[5)]は側頭葉底部外側は顔認知で強く活動する fusiform face area（FFA），さらに内側部は物品認知などに関連する parahipocampal place area（PPA）と分類している．われわれの検討では FFA と PPA の局在を電気生理学的に検証することができた．今後本方法を用いることにより電気的活動の空間的広がりに加え，周波数帯域別の変化およびそれぞれの時間的ダイナミクスをより詳細に解明することができる．頭蓋内電極を用いた脳機能マッピングは現在のところ脳皮質電気刺激法が gold-standard である．しかし，この電気刺激法では刺激強度，時間の制限，痙攣発作誘発のリスクを

伴うため，できる限り刺激頻度を減らし，検査時間を短時間にすることが最も患者の負担軽減につながる．本研究で施行した認知課題誘発 ECoG の計測，データ処理，画像化は今後脳皮質電気刺激法の代替法となり得る．また，内側側頭葉活動をとらえることで記憶機能の評価に応用できる可能性もある．さらに標準化 ECoG 法により，ヒト脳機能ダイナミクスを詳細に検討することができ，神経科学への貢献も期待できる．

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要　旨

皮質脳波による視覚認知ネットワークの解明

鎌田　恭輔　　國井　尚人　　太田　貴裕　　川合　謙介　　斉藤　延人

ヒト高次脳機能画像化を目的として頭蓋内電極留置された患者に，さまざまな課題を行いながら electrocorticogram (ECoG) を計測した．対象は診断目的に頭蓋内電極留置を行った難治性てんかんをもつ 20 症例である．異なる視覚刺激を提示しながら広範に脳表を覆った頭蓋内電極より ECoG を計測し，加算平均，時間-周波数解析処理を行った．また，コンピュータ学習ソフトウェアを応用して，ECoG 生データから刺激に応じた自動判別を行った．さらに 20 症例に留置した全電極を標準脳座標に変換，重畳することで高密度の電極配置と典型的な脳機能ダイナミクスの画像化をした．側頭葉底部では視覚刺激が単純であればあるほど後頭極側にγ帯域成分が集積する傾向があった．顔刺激では右優位であり，かつ両側側頭葉底部の前外側にγ帯域成分の増加が広がっていた．自動判別関数では 3 種類の異なる視覚刺激を 90%以上の正答率で判別が可能であった．電極位置の標準化により文字認知では左紡錘状回-海馬傍回に，顔認知では右紡錘状回から下側頭回にγ帯域成分が出現していた．本研究で示したように誘発 ECoG 計測を解析することにより，今後てんかん術前評価目的の新たなマッピング法として期待できるものと考えられる．

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Research Report

Neuroprotective effects of focal brain cooling on photochemically-induced cerebral infarction in rats: Analysis from a neurophysiological perspective

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ABSTRACT

Although systemic hypothermia provides favorable outcomes in stroke patients, it has only been adopted in a limited number of patients because of fatal complications. To resolve these issues, focal brain cooling (FBC) has recently drawn attention as a less-invasive treatment for brain injuries. Therefore, we investigated whether FBC has a favorable effect on focal cerebral ischemia (FCI). Male-adult-Wistar rats were used. Under general anesthesia, a small burr hole was made and FCI was induced in the primary sensorimotor area (SI-MI) using photothrombosis. An additional craniotomy was made over the SI-MI and FBC was performed at a temperature of 15 °C for 5 h. Electrocorticograms (ECoG) were recorded on the border cortex of the ischemic focus. Thereafter, rats were sacrificed and the infarct area was measured. In another experiment, rats were allowed to recover for 5 days after cooling and neurobehavioral function was evaluated. FBC suppressed all ECoG frequency bands during and after cooling ($p<0.05$), except for the delta frequency band in the precooling versus rewarming periods. The injured areas in the cooling and non-cooling groups were 0.99 ± 0.30 and $1.71\pm0.54\,mm^2$, respectively ($p<0.03$). The grip strength at 2 days after surgery was preserved in the cooling group ($p<0.05$). We report the novel finding that epileptiform discharges were suppressed in the ischemic border, the infarct area was reduced and neurobehaviour was preserved by FBC. These results indicate that FBC is neuroprotective in the ischemic brain and has demonstrated therapeutic potential for cerebral infarction.

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1. Introduction

Several experimental studies have indicated that a decrease in brain temperature reduces cerebral infarction and is neuroprotective to the brain, while a mild increase in brain temperature can exacerbate the extent of ischemic neural injury (Busto et al., 1987; Minamisawa et al., 1990; Ginsberg et al., 1992; Kim et al., 1996; Baena et al., 1997). Therefore, previous studies have emphasized the clinical feasibility of systemic hypothermia for patients with brain injury and ischemia (Ginsberg et al., 1992; Clifton et al., 1993; Baena et al., 1997; Yanamoto et al., 1996; Schwab et al., 2001). Despite these favorable outcomes, systemic hypothermia can also lead to fatal complications, such as infection, cardiac arrhythmia, and disruption of blood coagulation (Clifton et al., 1993; Marion et al., 1993; Schubert, 1995).

To resolve these issues, focal brain cooling (FBC) has recently drawn attention as a minimally invasive treatment for brain injuries (Oku et al., 2009; Wagner et al., 2005; Zhang et al., 2007; Clark et al., 2009). Compared with systemic hypothermia, FBC has the advantage of reducing the cooling temperature below 30 °C, without producing permanent brain damage or systemic complications (Yang et al., 2006). The initial clinical application of FBC was performed for patients with brain tumor or epilepsy from 1959 to the early 1960s and its effectiveness was demonstrated (FAY T, 1959; Ommaya and Baldwin, 1963). Despite these initial studies supporting the therapeutic potential of FBC, FBC has not been optimized for clinical use. However, in the 21st century, FBC has received much attention for the treatment of severe brain injuries, as described above, along with advancements in medical engineering technology. Our recent experimental studies have also indicated the effectiveness of FBC against focal epilepsy and nociceptive pain (Imoto et al., 2006; Tanaka et al., 2008; Fujioka et al., 2010a).

Under these circumstances, the aim of this study was to investigate the effect of FBC on focal cerebral ischemia. We employed a photothrombotic model of focal cerebral ischemia because photothrombotic occlusion of cerebral microvessels using Rose Bengal dye is a highly-reproducible and a less-invasive method of simulating the ischemic infarct pattern in humans (Yao et al., 2003; Grome et al., 1988).

Furthermore, in acute focal ischemia, high extracellular potassium and excess glutamate release from the ischemic core leads to depolarization and increased metabolic demand on the neighboring cortex. These conditions can induce periodic epileptiform discharges (EDs) along the ischemic border (Hartings et al., 2003; Iijima et al., 1992). These repetitive EDs could play a key role in the progression of brain injury from the regions of primary ischemic insult to adjacent regions of secondary injury (Hartings et al., 2003; Mies et al., 1993). Therefore, in this experiment we also evaluated, for the first time, whether FBC could suppress periodic EDs in acute focal ischemia.

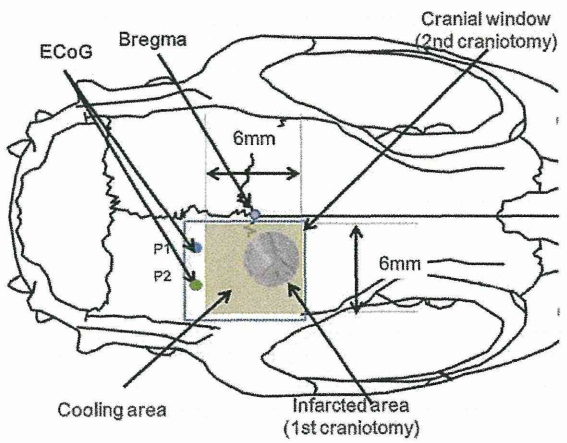

Fig. 1 – Schematic drawing of the experimental design. A small burr hole for photothrombosis and an additional craniotomy for cooling are indicated. Recording sites of electrocorticogram (ECoG) are also indicated (P1 and P2).

2. Results

2.1. *Effect of FBC on perifocal EDs*

Typical examples of the ECoG changes after focal ischemia are shown in Fig. 3. Soon after the induction of focal ischemia,

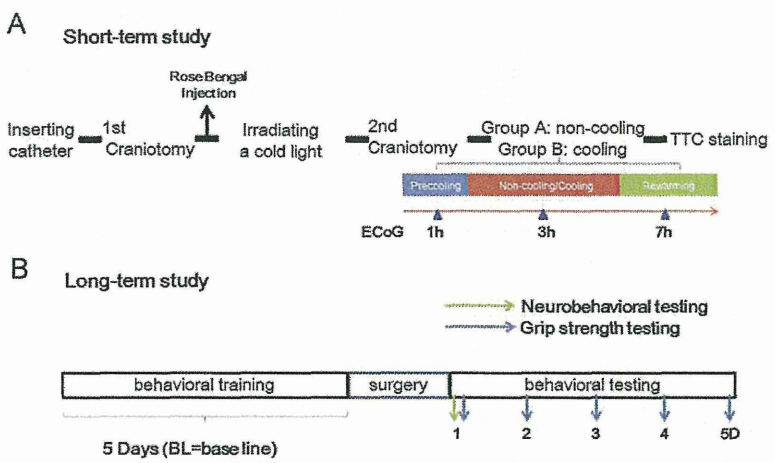

Fig. 2 – Experimental protocols of the short-(A) and long-(B) term studies. As noted in the experimental procedure.

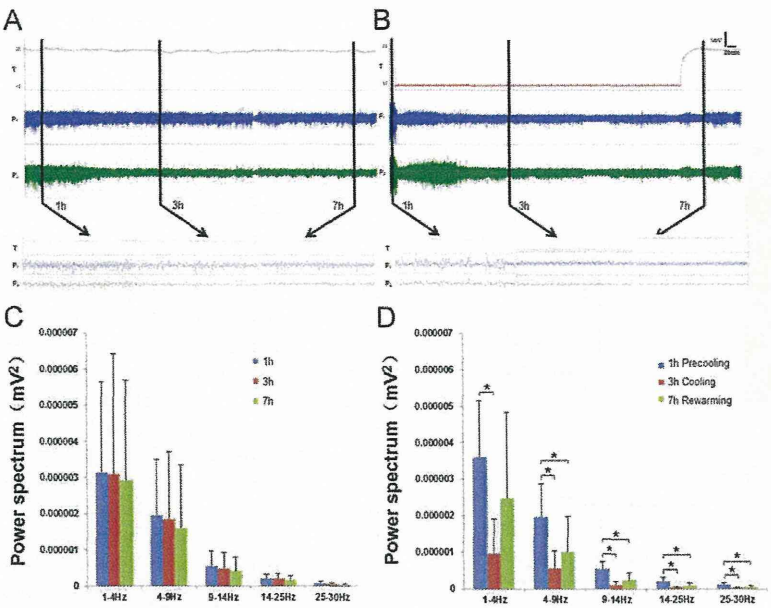

Fig. 3 – Typical examples of electrocorticogram (ECoG) changes after the onset of infarction were showed. (A) Non-cooling sampling and (B) cooling sampling (T: temperature, P1 and P2 indicates the recording sites). Bottom tracings indicate magnified ECoG at 1 h (precooling), 3 h (cooling) and 7 h (rewarming) after the onset of infarction). The power spectrum analysis of the ECoG data in 60 s epochs at 1 h (precooling), 3 h (cooling) and 7 h (rewarming) after the development of focal ischemia. (C) Non-cooling group and (D) cooling group ($n=6$ $^*p<0.05$ by ANOVA followed by a LSD post-hoc test). Note that in the cooling group, epileptiform discharges (EDs) were remarkably suppressed during brain cooling at 15 °C, and incomplete suppression of EDs persisted throughout the rewarming period.

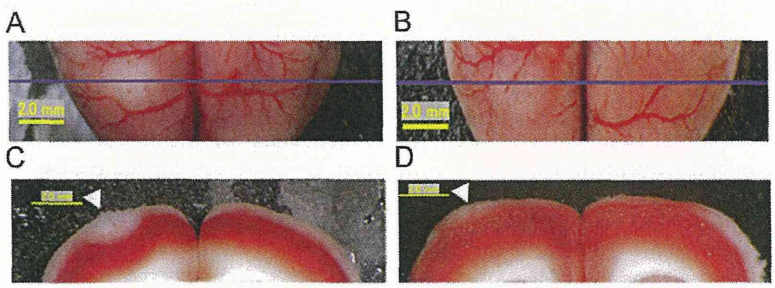

Fig. 4 – Typical delineations of ischemic damages with TTC (triphenyltetrazolium chloride) staining, 24 h after photochemically-induced infarction in the non-cooling (A, C) and cooling (B, D) groups. (A, B): gross appearance of the cortical surface; (C, D): coronal section. These delineations indicate that the ischemic zone is smaller and shallower in the cooled cortex.

periodic EDs were recorded from the peripheral cortex of the infarct zone. In the non-cooled group, EDs were recorded continuously for 8 h throughout the experiment (Fig. 3A). However, in the cooling group, EDs were remarkably suppressed during brain cooling at 15 °C, and incomplete suppression of EDs persisted throughout the rewarming period (Fig. 3B).

The average power spectra of ECoG in the cooling and non-cooling groups in 60 s increments are shown in Fig. 3C and D. In the non-cooling group ($n=6$), there were no significant differences in the power spectra in all frequency ranges (1–30 Hz) among the power spectra at 1 h, 3 h and 7 h after production of focal ischemia (Fig. 3C). However, in the cooling group ($n=6$), there were statistically-significant differences between the power spectra at 1 h (precooling) and 3 h (cooling) at all frequency ranges (1–30 Hz) by ANOVA with LSD post-hoc test ($n=6$, $p<0.01$) (Fig. 3D). Furthermore, there were also statistically-significant differences between the power spectra at 1 h (precooling) and 7 h (rewarming) in all frequency bands ($p<0.01$), except for the delta frequency range (1–4 Hz) ($p<0.03$, Fig. 3D).

2.2. *Effect of FBC on the infarct area*

Typical delineations of ischemic damages with the triphenyltetrazolium chloride (TTC) staining 12 h after photothrombotic occlusion of cerebral microvessels in the cooling and non-cooling groups are shown in Fig. 4. When comparing the macroscopic gross appearance of the cortical surfaces, the

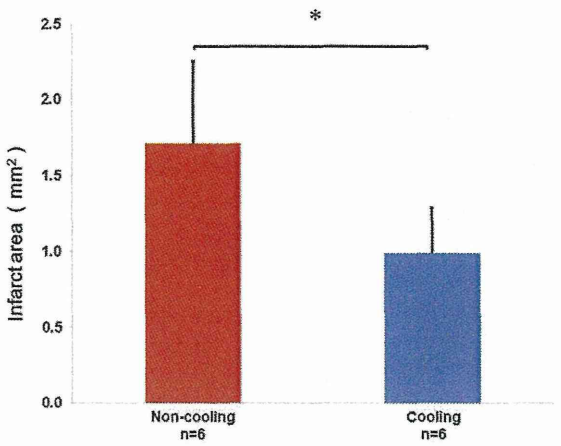

Fig. 5 – Infarct areas in the non-cooling and cooling groups at 24 h post-ischemia ($n=6$). The injured area of the cooling group was statistically-significantly smaller than that of the non-cooling group ($^*p<0.03$ by Mann–Whitney *U* test).

ischemic zone was sharply demarcated in the non-cooled cortex (Fig. 4A). However, the ischemic zone was indistinct in the cooled cortex (Fig. 4B). Furthermore, coronal sections of the cortices at the center of the ischemic zone indicated that the ischemic zone was smaller and shallower in the cooled cortex (Fig. 4C and D).

After taking photographs of coronal sections of the cortices, the injured areas were calculated using Image *J* software. Injured areas in the cooling and non-cooling groups ($n=6$, each) were 0.99 ± 0.30 mm^2 and 1.71 ± 0.54 mm^2, respectively (Fig. 5). The injured area of the cooling group was statistically-significantly smaller than that of the non-cooling group ($p<0.03$).

2.3. *The impact on neurobehavioral function*

In the neurobehavioral function, the neurologic score of the cooling group was significantly better than that of the non-cooling group at 24 h after the ischemic onset (Fig. 6A. $p<0.05$ by Mann–Whitney *U* test).

The grip strengths of both forelimbs were analyzed for 5 days after surgery. In the ipsilateral forelimb, there was no difference in grip strength after surgery between the cooling and non-cooling groups (Fig. 6B). In the contralateral-to-stroke forelimb, grip strengths were decreased after the ischemic event and recovered to baseline at 3 days after onset. On the other hand, in the cooling group, grip strengths were preserved at the baseline level after the ischemic event. There was statistically-significant difference in the grip strength of the contralateral forelimb between the cooling and non-cooling groups ($p<0.05$ by paired t-test) at 2 days after surgery (Fig. 6C).

3. Discussion

We obtained the novel findings that periodic EDs in the ischemic border were suppressed, infarct area was reduced and neurobehaviour was preserved by FBC. These results indicate that FBC acts neuroprotectively to the ischemic brain and has therapeutic potential for the cerebral infarction.

We selected the 15 °C cooling as an optimal temperature, because our previous study indicated that this cooling temperature suppressed EDs induced by penicillin G with minimal influence on neurobehavioral function and histology in the seizure model (Fujioka et al., 2010b; Fujii et al., 2012). Power spectrum analysis of ECoG indicated that focal cooling to 15 °C suppressed all the frequency bands, which is consistent with the results of our previous study (Fujii et al., 2012). Kida et al. (2012)confirmed that cooling the brain to 20 °C suppressed faster (alpha and beta) ECoG bands, and that cooling the brain to 15 °C suppressed both the faster and slower (theta and delta) frequency EEG bands . From these results, we speculate that because 15 °C cooling suppressed neuronal activity in the subcortex, all the frequency bands that originate from neuronal networks in the cortex would be suppressed. The reason the delta frequency of the power spectra alone did not show differences between precooling and rewarming periods in the cooling group (15 °C) is explained by the finding in our previous study that slower frequency bands of ECoG are insusceptible to the FBC because the origin of the slower frequency component is deeper in the cortical layer than that of the faster frequency components (Kida et al., 2012).

As described briefly in Section 1, the hypoxic/hypoglycemic condition caused by ischemic metabolic failure leads to neuronal membrane depolarization, further glutamate release, spreading ionic imbalances, and eventual cell death (Mies et al., 1993; Nedergaard and Hansen, 1993; Lipton, 1999). ECoG seizure activity is a pathological sequela of ischemic brain injury reflecting hyperexcitability in the neuronal networks and can sometimes occur without overt clinical manifestations (Vespa et al., 1999). Suppression of EDs by FBC suggests that FBC would be protective in the focal cerebral ischemia, as well as systemic hypothermia.

Several studies have reported the reductions of infarct size after systemic hypothermia (Karibe et al., 1994; Markarian et al., 1996; Maier et al., 1998; Berger et al., 2007; Kollmar et al., 2007; Sakurazawa et al., 2012). In previous studies, mild hypothermia (32–34 °C) has been selected to prevent the development of systemic complications and reduce the infarct size. We confirmed that FBC also reduced the infarct size with TTC staining. Thus, FBC is also neuroprotective and can be better applied to the treatment of focal ischemia with a lower temperature (15 °C) compared with systemic hypothermia, and does not induce complications.

In evaluating behavioral function, two assessments related to motor functions were used in this study, because focal ischemia was induced in the SI-MI area (Lee et al., 2002; Bertelli and Mira, 1995). Deterioration of motor function also reflects pathological insults. Thus, the grip strength test provides a sensitive quantitative technique for assessing recovery of motor function.

In our study, although reduction of grip strength was observed in the contralateral forelimb 2 days after the ischemic onset, grip strength was preserved in the cooled group. There was a statistically-significant difference in grip strength 2 days after surgery between the cooling and non-cooling groups. These findings also suggest that the FBC suppresses the brain injury caused by focal ischemia.

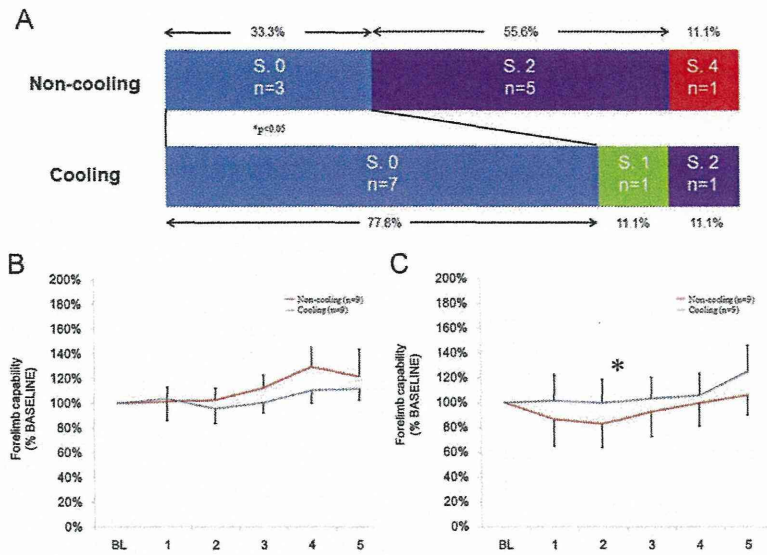

Fig. 6 – (A) Neurobehavioral test at 24 h post-ischemia, the neurologic score of the cooling group was better than that of the non-cooling group ($n=9$ $*p<0.05$ by Mann–Whitney U test. S. indicates scores of motor function. Score 0: best, score 4: worst. N: number of rats.). Forelimb capability (B. ipsilateral forelimb; C. contralateral forelimb) measured by a grip strength meter from 5 days before surgery to 5 days after surgery. Note that in the contralateral forelimb (bottom tracing), a significant difference was observed between the cooling and non-cooling groups at 2 days after surgery. Data are expressed as mean±SD ($n=9$ $*p<0.03$ by paired t-test. BL=baseline average grip strength 5 days before the surgery.)

Motor function was restored to baseline at 3 days after the ischemic event and there was no statistically-significant difference between the cooling and non-cooling groups. This phenomenon is supported by previous studies showing that most animals recover from their impaired function, more or less after brain injury because of active neuroplasticity (Alexis et al., 1995).

While the neuroprotective effect of FBC was confirmed in our study, further proof is still necessary to confirm the optimal cooling temperature, cooling period and rewarming times, as well as comparison of the efficacy of FBC and systemic hypothermia (Steiner et al., 2001; Clark et al., 2008; Colbourne et al., 2000; Yanamoto et al., 2001).

In our institute, we have initiated development of an implantable focal cooling system, including a cooling component, temperature control system, battery, and a fail-safe system. Recently, a focal cooling system, the ChillerPad^{TM}, was applied to a monkey model of traumatic brain injury and in patients with stroke or aneurysm (King et al., 2010; Wagner and Zuccarello, 2005). However, several issues remain and must be resolved from the medical engineering point of view before this neuromodulation can be used clinically. With the continued development of such apparatuses, clinical application of this implantable local cooling system may thus be realized in the near future.

4. Experimental procedure

4.1. Animals

Healthy adult male Wistar rats (350±50 g) housed in a temperature-controlled room (23.0±2.0 °C) were used in the study ($n=30$ in total). Animal experiments were performed using protocols that were approved by the Institutional Animal Care Committee at Yamaguchi University School of Medicine.

4.2. *Surgical procedures and the focal cerebral ischemia model*

Rats were anesthetized with sevoflurane (3% for induction via a face mask, 2% after intubation and maintenance in an 80%/20% mixture of oxygen and air by a ventilator (A.D.S.1000 Engler Engineering Corporation. USA). During the procedure, rectal temperature was monitored and kept constant at 37±0.2 °C by a temperature-controlled heating pad (NS-TC10, Neuroscience Inc., Japan). The femoral artery and femoral vein were cannulated for continuous monitoring of arterial blood pressure, obtaining blood gas samples and drug administration. Systemic blood pressure was maintained at 100–120 mmHg, and blood-gas data in the non-cooling and cooling groups were controlled at pH 7.44±0.04 and 7.43±0.03, pO_2 of 202.6±36.0 and 215.3±37 and pCO_2 of 40.7±2.2 and 40.5±3.0.

The skull was fixed using a stereotactic apparatus (SR-6N, Narishige, Japan). A scalp incision was performed at the midline following injection of lidocaine (2%), and both the Bregma and Lambda points were exposed after dissection of the pericranial tissue. A small burr hole, 3 mm in diameter, was made 4 mm lateral to the right and 0.5 mm anterior to the Bregma and the dura matter remained intact. Focal cerebral ischemia was achieved by the photothrombotic method (Yao et al., 2003; Grome et al., 1988; Fujioka et al., 2010b), illumination was initiated through the burr hole with

a fiber optic bundle of a cold light source (Fiber-Lite series 180 Dolan-Jenner Industries. Inc., USA) just after the Rose Bengal injection (1.3 mg/100 g body weight in 0.9% sterile saline) via the right femoral vein, and lasted for 20 min. In this manner, focal cerebral ischemia of the primary sensorimotor (SI-MI) cortex of the right hemisphere (2.5–5.5 mm lateral, 2.0 mm anterior, 1.0 mm posterior to the Bregma) was photochemically-induced (Fig. 1).

4.3. *Focal brain cooling*

An additional craniotomy, including the burr hole, was made over the ipsilateral SI-MI cortex (1.0–7.0 mm lateral, 3.0 mm anterior, 4.0 mm posterior to the Bregma) just after induction of the focal cerebral ischemia. A cooling device composed of a thermoelectric chip that was originally developed in our laboratory, and has been described previously (Fujioka et al., 2010a, 2010b), was placed on the SI-MI cortex (Fig. 1). We focally cooled the SI-MI cortex above the dura matter to a temperature of 15 °C for 5 h from 1 h after the development of focal ischemia. After the cooling period ended, the cortex was spontaneously rewarmed and the temperature was maintained for 1 h. The 15 °C cooling was selected because it represents the borderline temperature affecting neurobehavioral function (Fujii et al., 2012). Sham-operated rats underwent craniotomy and placement of the cooling device.

The focal cooling experiments were composed of short- and long-term studies. The short-term study evaluated the periodic epileptiform discharges in the border zone of the ischemic focus and of the infarct area. The long-term study assessed the impact on neurobehavioral function (Fig. 2).

4.4. *ECoG recordings and the spectral analysis*

We placed a pair of ball-type electrodes (impedance 500 kΩ at 500 Hz) to detect the ECoG on the cortex at the boundary of the ischemic area after placement of the cooling device (Fig. 1). Thereafter, ECoGs were recorded continuously for 8 h in two channels (monopolar recording; with a reference electrode inserted in the scalp) and analyzed using PowerLab Chart 5 software (PowerLab Chart5; AD Instruments) at a sampling rate of 2 kHz (low-cut filter 5 Hz, high-cut filter 60 Hz) for visual examination. To quantify the frequency profiles, the power spectrum was calculated by fast Fourier transform (FFT) analysis, which was performed for ECoG data in 60 s intervals at 1 h (precooling), 3 h (cooling) and 7 h (rewarming) after the development of focal ischemia (Fig. 2). We analyzed the ECoG components in all conventional frequency bands, including delta, theta, alpha and beta (delta=1–4 Hz; theta=4–9 Hz; alpha=9–14 Hz; beta1=14–25 Hz; beta2=25–30 Hz). Six rats were used in each of the cooling and non-cooling groups.

4.5. *Measurement of the infarct area*

All of the rats in both the cooling and non-cooling groups ($n=6$) were sacrificed after the recording of ECoG for 8 h. The brains were immediately removed and incubated in a 2% solution of 2,3,5-triphenyltetrazolium chloride (TTC Lot KWG 6634, Wako Pure Chemical Industries, Ltd., Japan) at 4 °C for 12 h (Hatfield et al., 1991). Three serial sections from each brain were cut at 1 mm intervals from the center of the infarct zone and photographs of the sections were taken at the middle of the 3 sections.

4.6. *The impact on neurobehavioral function*

After the focal cooling for 5 h, cortices were naturally rewarmed and the temperature was maintained at the baseline for 1 h (cooling group, $n=9$). Thereafter, the scalp was closed without repairing the cranial window. The rats awakened from anesthesia were placed back in the cages. To distinguish the effect of the sensorimotor injury, appropriate control experiments were also conducted (non-cooling group, $n=9$).

Neurobehavioral function of each rat was evaluated after surgery by an observer who was blinded to the experimental procedure. Neurobehavioral function was assessed by five categories of motor neurological findings, as follows: score 0: no observable deficit, score 1: forelimb flexion, score 2: forelimb flexion and decreased resistance to lateral push, score 3: forelimb flexion, decreased resistance to lateral push and unilateral circling, and score 4: forelimb flexion, unable or difficult to ambulate (Lee et al., 2002). Neurobehavioral function was assessed 24 h after the induction of focal ischemia in the cooling and non-cooling groups (Fig. 2).

Grip strength test was also employed in the assessment of neurobehavioral function. An inverted T-type bar 63 mm in length and 103 cm wide connected to a grip strength meter (Ugo Basile Comerio (VA), Italy) was used to measure graded changes in the forelimb grip strength of the rats. Rats held the bar and were gently pulled away from it in a smooth manner, by grasping of the tail, in a steady motion, until they released the bar. The grip strength meter measured the force [g] required to break the rat's grip. Prior to the surgery, rats were trained on the apparatus for 5 days ($n=9$). Each rat was allowed to grasp the apparatus for three consecutive times, to determine the strength of the forelimbs of the left, right and both sides, respectively. The average grip strength for all patterns was used as the baseline force. From 1 to 5 days after surgery, three readings were taken for each rat and the average force required was recorded as the individual grip strength score for that rat (Fig. 2) (Bertelli and Mira, 1995).

4.7. *Statistical analyses*

The Mann–Whitney U test was used for comparison of the infarction area, neurobehavioral test between groups. The grip strength test was performed by paired t-test. The power spectrum was analyzed with one-way analysis of variance (ANOVA), followed by a LSD post-hoc test. These tests were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA). The data are expressed as the mean±SD. p-values<0.05 were considered significant.

Disclosure

None of the authors have any conflicts of interest to disclose.

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Focal Brain Cooling: Revisiting a Potential Therapeutic Option for Intractable Epilepsy

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Abstract Seizure control is not achieved in approximately one-third of patients with epilepsy, even with the best available medications. Surgical treatment can be performed for these patients, however this is also not always successful. Under these circumstances, the potential for seizure suppression by focal brain cooling has gained attention. Brain cooling was first proposed about 50 years ago, and has come into the spotlight in recent years with advances in technology. Recent studies indicate that focal cooling of the brain to a cortical surface temperature of 20 to 25°C terminates epileptic discharges without inducing irreversible neurophysiological dysfunction or neuronal damage. These results have promoted development of implantable focal cooling devices, but some aspects of the hardware in these devices require optimization. However, advances in precision machining have enabled optimization of an implantable focal cooling system, and this suggests that brain cooling therapy may become a reality in the near future.

Key words: epilepsy, focal brain cooling, seizure, device, neuromodulation

Introduction

Epilepsy is usually treated with medication, but approximately one-third of epilepsy patients do not attain seizure control, even with the best medications.[1] Surgical treatment is also used, but is not always successful. Furthermore, surgical resection is impossible if the epileptogenic focus is in critical areas such as the motor and speech cortices. Under these circumstances, several clinical trials of neuromodulation technology for treating refractory epilepsy have recently been performed. Vagal nerve stimulation has been used for the past decade[2] and electrical stimulation of the brain has been proposed as an alternative to surgical resection. The anterior nucleus of the thalamus or hippocampus has been chosen as a stimulation target. Clinical pilot stimulation studies have been performed, but the results remain unsatisfactory.[3-5] A unique clinical study with an implantable, responsive, closed-loop stimulation system is currently in progress.[6] This device can terminate seizures by delivering a burst of stimulation after detecting a seizure with an electroencephalogram (EEG) algorithm through an implanted electrode.[7] The preliminary efficacy of this method was demonstrated in a feasibility trial, but further clinical investigation and optimization are required.

Focal cooling of the brain is another attractive and nondestructive approach for treatment of patients with epilepsy. Brain cooling was first proposed about 50 years ago as an effective method for suppressing epileptic discharges (EDs),[8,9] and has recently been revived with advances in technology and medical engineering.[10,11] At our institution, we have obtained interesting results in practical use of brain cooling as a new therapy, which we refer to as "thermal neuromodulation", for patients with intractable epilepsy.[12,13] In

this review, we discuss the historical background of focal cooling, the influence of focal cooling on epileptic seizure and the normal brain, the mechanisms of seizure termination due to focal cooling, and the practicality of use of an implantable cooling system based on our experimental data and results published in the literature.

Historical background

The therapeutic value of focal cooling initially gained attention in the 1950s. At that time, local cooling of the nervous system was achieved in animal models using perivascular methods.[14,15] Local cooling was also used to treat patients with head trauma, cancer, and pain, and the findings emphasized the utility of this method.[16] The effect of cooling on epilepsy was first demonstrated by suppression of EDs in the primate temporal lobe using systemic hypothermia.[8] Thereafter, local cooling with the gas method was shown to suppress EDs in human.[9] Ventricular irrigation with cold Ringer's solution was also found to suppress seizures.[17] Another early study indicated that systemic hypothermia suppressed seizures in patients with refractory epilepsy.[18]

Despite these initial studies indicating that brain cooling has the potential to terminate seizure activity, the method was not optimized for clinical use because of the difficulty in improving the cooling system. Initial cooling methodologies such as local refrigeration with gas and cold water or ventricular irrigation had many problems for clinical use. These methodologies increased the chance for infection and are difficult to use over long periods or permanently. Severe systematic hypothermia can suppress seizures,[18,19] but also has fatal complications including infection, cardiac arrhythmia, and blood coagulation disturbances.[20]

Focal brain cooling has recently gained attention because of advances in technology. In recent studies, evidence for an anticonvulsant effect of focal cooling has been obtained in neocortical and hippocampal epilepsy models[10,11,21-23] and in humans.[24,25] Clinically, Sartorius et al. found that focal seizure activity induced by direct cortical stimulation mapping was rapidly halted by irrigation of the brain surface with cold Ringer's solution.[26] In recent studies, including our work, a thermoelectric device has been used because of its small size and strong cooling effect.[10-13,27] This kind of focal-cooling device is implantable and can be combined with a seizure detection system.[28] Use of this technology has caused new interest in focal brain cooling as a therapy for patients with intractable epilepsy.

Inhibitory effect of focal cooling on epileptic seizure

We investigated the effect of focal brain cooling on EDs in rat neocortical and hippocampal seizure models.[12,13] A Peltier chip was used as the basis of the thermoelectric device. This chip consists of two conductors, which are connected in parallel. Passing an electric current between the conductors causes cooling of one conductor and heating of the other because of the electronic refrigeration phenomenon (Peltier effect). A heat sink made of aluminum with a water channel is attached to the chip to help dissipate the heat generated. Two silicone tubes are connected to the heat sink to circulate water through the channel.[12]

A neocortical seizure model was made in adult male Sprague-Dawley rats. After craniotomy, a cooling device was placed on the surface of the sensorimotor cortex. Kainic acid (KA) was injected into the cortex just beneath the cooled area to provoke EDs. Reduction of the temperature of the cortical surface to 30°C, 28°C, and 25°C caused the frequency of EDs to decrease as the temperature of the cortex was lowered, with final disappearance of EDs at 25°C during the cooling period.[12] Rapid termination of EDs by focal cooling of the neocortex has previously been shown in rats with 4-aminopyridine-induced epilepsy.[11] Our results are also consistent with reports showing that the optimum temperature of the cortical surface for terminating seizures is approximately 20 to 25°C.[11,27]

We also investigated the inhibitory effect of selective hippocampal cooling on KA-induced hippocampal seizures in rats.[13] Control of the temperature of the cooling site at 20°C caused significant suppression of the amplitude of the EDs. These results are also con-

sistent with previous findings.[21-23]

Influence of focal cooling on brain tissue and neurophysiological function

Focal brain cooling has an inhibitory effect on EDs and a protective effect on brain tissue.[29] However, the mechanisms underlying the influence of focal cooling on brain tissue and neurophysiological function have not been investigated in detail. Therefore, we examined the pathological and neurophysiological consequences of focal cooling in the neocortices of rats.[30] Pathologically, focal cortical cooling at -5°C for 1 hour caused irreversible histological changes that were consistent with cryoinjury. However, focal brain cooling above 0°C for 1 hour did not cause histological damage of the cortex. Yang et al. found that cooling of the rat brain to 5°C every 2 minutes for 30 seconds for a total duration of 2 hours and cooling of the cat brain to 3°C for 1-2 hours every day for 7-10 months had insignificant pathological consequences.[31] These findings agree with our results, and we also showed that irreversible neuronal damage was not caused by focal brain cooling above 0°C for 1 hour.[30]

Several studies have described the effects of cooling on the electrophysiology of the normal brain. Cooling of cortical tissue to temperatures between 0 and 20°C disrupts local synaptic activity without causing permanent injury to brain tissue.[32] The motor response is preserved after cold saline is applied for termination of EDs caused by cortical stimulation mapping.[24] Focal cooling of the somatosensory cortex in rats at 20°C for 5 minutes induces recognizable changes of somatosensory evoked potentials, but these are fully reversible after warming the tissue.[33] These studies suggest that reversible neurophysiological dysfunction is induced at a threshold temperature of approximately 20°C.

Mechanisms of seizure termination

Focal brain cooling is generally thought to reduce transmitter release,[34] alter the kinetics of voltage-gated ion channels,[21,35] and cause network desynchronization.[36] The precise antiepileptic mechanisms remain to be determined, but it is generally recognized that suppression of synaptic transmission is involved in reduction of seizures.

In our study, EDs were selectively inhibited, but motor function was preserved when the cortical surface was cooled to 20-25°C.[30] An explanation of this phenomenon is needed. An *in vitro* study showed that synaptic transmission begins to decrease below 20°C.[35] In a case in which the temperature is <20°C at 1 mm under the cortical surface, but >20 °C at a depth of 2 mm, it is reasonable to assume that synaptic transmissions and EDs in the shallow cortex (layer II/III) are selectively suppressed because of the spread through neurons in the shallow layer with horizontal connections to the ipsilateral or contralateral cortex. Selective suppression of synaptic transmission due to a cooling-induced thermogradient in the cortex may have contributed to the vulnerability of somatosensory processing, as indicated by the reduction of receptive fields during cooling. Since the motor cortex lies deep in the sensorimotor cortex (layer V), selective transmission failure may have occurred during surface cooling.[37]

Practicality of use of an implantable cooling system

Our previous studies and those of others have demonstrated termination of EDs by focal brain cooling and indicate the therapeutic potential of this method for patients with intractable epilepsy, as an alternative to invasive surgery. Focal brain cooling may be applied for patients with an epileptic focus on the eloquent cortex (i.e., motor or language area). In our institute, we have initiated development of an implantable focal cooling system including a cooling component, an automatic electrocorticogram (ECoG) analytical system, a heat processing system, a rechargeable battery, and a fail-safe system (Fig. 1). However, several hardware issues remain to be resolved before this system can be used clinically on a large scale. First, an optimal fluid is required for use as the circulating fluid for heat dissipation. Second, the cooling device with Peltier chips requires large amounts of electricity, and development of electricity supply technology for the device is required. Third, miniaturization of the cooling device may be necessary. Smaller ancillary devices such as the electric power sup-