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学 位 論 文 題 名

MEG time-frequency analyses for pre- and post-surgical evaluation of patients with epileptic rhythmic fast activity

(てんかん性律動性棘波を有するてんかん症例における術前術後の周波数解析を用いた脳磁図解析に関する研究)

学位論文内容の要旨

Background: Magnetoencephalography (MEG) is applied to localize the source of epileptiform discharges in patients with refractory epilepsy, particularly in symptomatic localization-related epilepsy, as it is noninvasive and exhibits excellent temporal and spatial resolution. MEG localization of epileptiform discharges has been successfully achieved by single dipole modeling (SDM), which is mainly used to analyze interictal epileptiform spikes. However, the application of SDM appears to be limited to patients with localized spikes, since the algorithm is based on the presumption that the current epileptic discharge originates from a single spot. Rhythmic electroencephalography (EEG) activities are often the hallmarks of underlying epileptogenesis. Rhythmic polyspike activities have been reported as indicative of an irritative epileptogenic zone in the EEG. However, the resolution of EEG is not powerful enough to properly evaluate rhythmic activity because EEG activity is affected by the conductivity of brain structures, and in some cases EEG is unable to detect notable pathological activity. Recently, time-frequency analyses of EEG and MEG have been used to investigate rhythmic activities. Short-time Fourier transform (STFT) applies a short-time window to the signal and performs a series of Fourier transforms within this window as it slides across the recorded data. This technique can be used to estimate the time-frequency components of the signal and visualize the spectral distributions. It has been proposed to apply this technique to patients with epilepsy, as it provides temporal changing information on the time-frequency domain.

Purpose: To evaluate the effectiveness of surgery for epilepsy, we analyzed rhythmic fast activity by magnetoencephalography (MEG) before and after surgery using time-frequency analysis. To assess reliability, the results obtained by presurgical MEG and intraoperative electrocorticography were compared.

Patients and Methods: Four children with refractory symptomatic localization-related epilepsy caused by circumscribed cortical lesion were enrolled in the present study using 204 channel helmet-shaped MEG (Neuromag Vectorview; Elekta-Neuromag Oy, Stockholm, Sweden) with pairs of orthogonal planar gradiometers. The MEG data were collected at a sampling rate of 600 Hz. A scalp EEG was recorded simultaneously using the international 10-20 system. One patient had dysembryoplastic neuroepithelial tumor (DNT) and three patients had focal cortical dysplasia (FCD). Single spikes were analyzed by SDM. The dipole-fit software (Neuromag, Helsinki, Finland) was used to calculate the equivalent current dipoles (ECDs) with SDM. STFT was used to reveal the distributions of MEG fast activity and the MATLAB (MathWorks, Natick, MA, USA)

program was used to execute the STFT for the MEG signals. The time-frequency distributions are displayed as graphs. A spectrum was considered to be aberrant when it was observed in the graph to be isolated from the background frequency spectrum. An aberrant frequency spectrum on the graph was superimposed onto the reconstructed 3-D MRI. The ECoG studies were performed during surgery.

Results: In three patients, short-time Fourier transform (STFT) analyses of MEG showed rhythmic activities just above the lesion with FCD and in the vicinity of DNT. In one patient with FCD in the medial temporal lobe, rhythmic activity appeared in the ipsilateral frontal lobe and temporal lateral aspect. In three patients, the EEG showed bilateral fast activity. In one patient, the EEG showed only a spike or polyspike and a slow wave complex that corresponded to the MEG fast activity. These MEG findings correlate well with the results obtained by intraoperative electrocorticography. After the surgery, three patients were relieved of their seizures, and the area of rhythmic MEG activity disappeared or become smaller. One patient had residual rhythmic MEG activity, and she suffered from seizure relapse.

Discussion: This study indicate that time-frequency analyses using STFT can reveal the distributions of rhythmic fast activity on MEG. This method is useful for presurgical and postsurgical evaluation. To improve outcomes from epileptic surgery, it is essential to define the precise location of the epileptogenic zone and the margin of surgical resection by the presurgical evaluation. For these purposes, MEG analysis is considered to be a suitable technique, as it offers good temporal and spatial resolution and noninvasive. SDM has been used mainly to analyze the interictal epileptiform spikes on MEG. In the present study, isolated interictal spikes were scarce in two patients, and few in one patients. The data obtained from the SDM were, therefore, insufficient for presurgical evaluation in our patients. In our study, epileptic rhythmic activity was demonstrated more clearly by MEG in all patients. STFT analysis of fast activity is thus clearly beneficial for predicting the epileptic foci in patients with poor or several ECDs and for placing the ECoG electrodes. Our study analyzed the changes in epileptic rhythmic activity before and after surgery for epilepsy and demonstrated the clinical value in predicting the outcome of surgery. Postoperative MEG showing normal or notably improved aberrant rhythmic oscillation suggests a favorable outcome, whereas postsurgical residual MEG polyspikes may indicate a risk of seizure relapse. Our findings from MEG correlated with seizure outcome. Thus, MEG provides a useful postsurgical evaluation procedure to indicate the need for a secondary operation. In this way, MEG avoids redundant resection and is a safe and noninvasive procedure. Concerning the correlation between the MEG and ECoG findings, the MEG fast activity locations demonstrated by STFT colocalized well with the ECoG polyspikes in patients, while MEG areas were rather wider. This could be due to the distance (several cm) between the cortical surface and the MEG sensors, the size of the planar gradiometer sensor, and the distance between sensors. Recent studies showed the clinical value of MEG for the epileptic rhythmic activities in correlation with ECoG. Consistent with the results of previous studies, our findings suggest that STFT of MEG data can depict fast activity that indicate epileptogenic zones associated with FCD and DNT, which are the most significant etiologies of pediatric intractable symptomatic localization-related epilepsy. The excellent postsurgical outcomes achieved for our patients strongly support the predictive value of noninvasive MEG analysis. The rhythmic activities that are closely correlated to the ictogenesis in the cerebral cortex can be demonstrated stereoscopically by noninvasive MEG.

Conclusion: MEG can detect fast activity in symptomatic localized-related epilepsy more clearly and accurately than conventional EEG. STFT reveal the frequency and location of MEG fast activity that could not be analyzed by SDM. The MEG fast activity findings correlated well with the intraoperative ECoG findings and are therefore useful for presurgical evaluation. Ascertaining the presence of fast activity after epilepsy surgery could predict the prognosis of seizures. This

noninvasive evaluation provides valuable information for pre- and post-surgical evaluations to define surgical strategies for patients with symptomatic localization-related epilepsy induced by circumscribed cortical lesions.

学位論文審査の要旨

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（てんかん性律動性棘波を有するてんかん症例における術前術後の周波数解析を用いた脳磁図解析に関する研究）

脳磁図は脳内の神経活動により生じた磁場を測定する。脳磁図が測定する磁場は頭蓋骨、脳脊髄液など脳と頭蓋骨の間の組織による影響を受けにくい長所があり、また非侵襲的であり、時間、空間分解能に優れている。脳磁図はてんかん患者のてんかん性活動の信号源を求めるのに使われ、その解析にはひとつの磁場源を仮定した単一双極子法：Single dipole modeling（SDM）が使われる。SDM は磁界発生源を脳内に一つと仮定し、実際に測定された磁界から等価電流双極子：Equivalent current dipole（ECD)を推定する。律動性棘波：Rhythmic fast activity は脳波においてんかん原性を示すと報告されるが、S/N 比（信号雑音比）が低く、広汎性で伝播しやすいため SDM での解析は困難である。本研究は限局性皮質病変を有する症候性局在関連てんかん症例の従来法 SDM では解析できない術前術後の脳磁図の発作間欠時律動性棘波を、短時間フーリエ変換：Short-time Fourier transform（STFT）による時間周波数解析を用いて解析し、これらの手法の整合性、妥当性を検討するため手術症例で術中の皮質脳波所見と比較検討を行った。対象は 4 名の小児で、204ch ヘルメット型脳磁図計 Vector View を用い、sampling rate は 600Hz で記録した。STFT により律動性棘波の局在を表現が可能となり、限局皮質異型性 Focal cortical dysplasia (FCD)では腫瘍部より、胚芽異形成性神経上皮腫瘍： Desembryoplastic Neuroepithelial Tumor（DNT）では腫瘍の近傍から出現しており、律動性棘波の周波数、出現部位ともに皮質脳波所見とほぼ一致した。術後の脳磁図で律動性棘波が著明に改善した場合は術後の予後がよく、残存した場合は発作が再発した。STFT による時間周波数解析により脳磁図の律動性棘波を表現し解析できるようになり、この方法は限局皮質病変を有する局在関連てんかん患者において、てんかん手術の術前術後の評価に大変有用であった。

学位論文公開発表は、スライドを用いながら約 15 分に渡って学位論文内容の発表を行った。副査生駒一憲教授から、STFT の時間幅を約 400ms に選んだ理由、今後の臨床的発展性についての質問があった。STFT の幅は、周波数分解能と時間分解能のバランスが

よいところを選らんだこと、北大ではすでに律動性棘波を有する患者の解析やその他の症例においても用いられていると回答した。非常にきれいな明確なデータであり今後さらに臨床応用の発展を期待すると評価された。次いで副査佐々木秀直教授から、脳磁図における信号の感度、どれほどの振幅の信号を捉えられるか、律動性棘波の伝播拡延を表現することによる手術様式の変化について質問があった。脳磁図は脳波よりは感度がよいことが多く、とくに律動性棘波は脳磁図においてより明瞭であったこと、背景波に埋もれない振幅の信号は捉えやすいこと、伝播拡延の様式の把握により特に皮質脳波の電極の配置や腫瘍の鑑別に有用であると回答した。本研究が臨床に役立つ点で大変すばらしいと評価された。最後に主査有賀正教授より、SDM のみでてんかん原性が分かる例もあるのか、SDM と STFT はルーチンで両方施行されるのか質問があった。SDM のみで分かる例もあるが、本研究の例のように律動性棘波のみがみられる例、ECD が 2 箇所に集積したため SDM のみではてんかん原性が分からない例において特に威力を発揮したこと、単発の棘波に対しては必ず SDM を用いていること、律動性棘波があれば STFT で解析していると回答した。DNT において FCD のケースと異なって、律動性棘波が腫瘍の近傍から出現していたことが大変印象的であったこと、臨床において患者の評価に役立ち、脳磁図の臨床応用の可能性を広げた点において大いに評価された。

この論文は、これまでの方法 SDM では解析できない脳磁図のてんかん性律動性棘波の解析が可能になり、てんかん手術における術前術後の評価に大変有用である点、脳磁図の臨床応用の幅が広がった点において高く評価され、今後限局病変を有さないてんかん性律動性棘波を有するてんかん症例におけるてんかん原性の評価、手術適応の決定、てんかん症候群の決定、さらに症候性局在関連てんかんに限らず全般てんかんの律動性棘波の解析などさらなる臨床応用が期待される。審査委員一同は、これらの成果を高く評価し、大学院過程における研鑽や取得単位なども併せ申請者が博士（医学）の学位を受けるのに充分な資格を有するものと判定した。