基礎および臨床分野における AutomatedImage Registration による3次元脳 SPECT 画像の解剖学的標準化手法の研究

著者	Muhammad Babar Imran
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氏　名（本籍）	ムハッマッド　ババール　イムラン Muhammad Babar Imran
学位の種類	博　　士（医　学）
学位記番号	医博第　1647　号
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論文審査委員	（主　査） 教授　福田　　寛　　教授　糸山泰人 教授　高橋昭喜

論 文 内 容 要 旨

SPECT can effectively and non-invasively measure regional cerebral blood flow (rCBF). Its role in advancing our understanding of pathophysiological mechanisms of brain disorders and in the clinical assessment of patients with these disorders is expanding. There is often a need to compare CBF SPECT images for robust evaluation of various parameters. A pre-requisite for accurate comparison is precise three dimensional registration of data sets. In our present research work, use of an automated image registration (AIR) program for the standardization of brain SPECT data has been elaborated. AIR is an operator independent program that can register any brain image with respect to any other specified image. During its working, it does not require anatomical information of the images, rather, only voxel data is enough to complete the registration.

Before applying AIR to SPECT data, accuracy of this program for SPECT-SPECT transformation was evaluated and then relative uptake values for Tc-99m HMPAO in various regions of the normal brain was calculated by region of interest method. Intersubject accuracy was evaluated on brain images of 17 normal subjects (age 64.9±8.7 yrs). These were aligned and registered to a standard size and shape with the help of AIR. Realigned images were overlaid on the reference image to determine the overlap areas. Intrasubject accuracy was evaluated by realigning 20-degree rotated brain images with an index calculated as the overlap area/overlap+non overlap area. Anatomical variability between realigned target and reference images was evaluated by measurements on corresponding X-ray CT scans, realigned using transformations established by the SPECT images. Realigned brain SPECT images of 30 normal subjects (age 50.7±18.7 yrs), including those subjects examined in the accuracy validation study were used to generate mean and standard deviation images based on voxel values and mean values for rCBF calculations. Images based on the mean value of each voxel (n=30) were compared with other mean images prepared by the human brain atlas (HBA) standardization technique on a voxel-by-voxel basis to generate T maps. Accuracy indices were 98.2%±0.6 and 99 %±0.2 respectively, from the intersubject and intrasubject evaluations. The maximum anatomical variability was 4.7 mm after realignment. Student's t-test comparisons of mean HBA and AIR images revealed statistically significant differences for the deep white matter, pons and occipito-temporal regions. These differences could be explained by variation in the population being studied and the protocol for data handling by AIR and

HBA. Hence it was concluded that AIR aligns and registers brain SPECT images with acceptable accuracy without the necessity of MRI or X-CT scans.

Next, image registration concept was applied to establish the pattern of distribution of Tc-HMPAO in patients with Alzheimer's disease and to evaluate the effects of various covariants by correlation analysis. Twenty patients of Alzheimer's disease (age 71.1±7.4 yrs, CDR 1-3, MMS 17.8±5.3) and fifteen age matched normal subjects (age 70.2±8.4 yrs) were enrolled. Tc-99m HMPAO brain SPECT and X-ray CT scans were acquired for each subject. SPECT images were transformed to a standard size and shape with the help of AIR. Realigned brain SPECT images of patients and controls were used for group comparison with the help of SPM96. Significant differences were displayed on the respective voxel to generate three dimensional Z-maps. X-ray CT scans of individual subjects were evaluated by computer program for brain atrophy. Voxel-based covariance analysis was performed on standardized images taking age of patients, severity of disease (CDR, MMS) and atrophy indices as independent variables. Z-maps showed significantly decreased rCBF in the frontal, parietal and temporal regions in patient group ($p<0.001$), more marked in those patients having severe dementia. Covariance analysis revealed that aging and severity of disease have pronounced effect on rCBF especially that of left parietal region.

Finally, an objective method for the assessment of rCBF deficits in standardized brain SPECT images was developed, using a statistical image analysis protocol. The algorithm was validated for its effective use in the clinical practice. Tc-99m HMPAO brain SPECT images were acquired for 60 subjects (normal, n=40, patients with Alzheimer's disease, n=10, patients with depression, n=10). AIR was used to standardize the size and shape of the brain structures for all the subjects. The images of the first 30 normal subjects were used to construct a normal database. The CBF images of the other 10 normal and the 20 patients were compared voxel by voxel with the normal database to map CBF abnormalities by statistical evaluation. The results were compared with clinical evaluation reports of CBF images. The expert system detected all the rCBF deficits reported by the nuclear physicians. Some additional areas with special information like atrophy and bilateral asymmetry were also pointed out by the expert system. We concluded that this expert system can delineate CBF deficits with sufficiently high accuracy, differentiating normal from abnormal CBF images by voxel-based comparisons. The use of an expert system improves rCBF SPECT image evaluation.

審 査 結 果 の 要 旨

本研究は日常臨床に広く使用されている脳血流SPECT画像を解剖学的に標準化することによって画像データベースを作成し，次にデータベース間の画素ごとの統計検定により客観的に診断するシステムの開発を行ったものである。研究は以下の3つのパートに分けられる。

(1) 解剖学的標準化の手法は従来，若年健常者を対象としたポジトロンCTを用いる脳賦活研究に用いられてきたものである。著者はまず最初にこの手法を分解能の低いSPECT画像に適用することの妥当性，脳萎縮の程度が若年にくらべて大きい壮年～老年者に適用する場合の精度の検討を行い，標準化の誤差は装置の分解能以下であることを示した。この結果を踏まえて健常者30名の脳血流画像データベースを作成した。

(2) 次に20名のアルツハイマー痴呆患者の脳血流画像の解剖学的標準化を行い，痴呆群の画像データベースを作成した。また同様の手法で年齢を一致させた健常老年者の画像データを作成し，これと痴呆群画像データベースを画素ごとに統計検定することにより，痴呆群で有意に血流が低下している部位を客観的に抽出した。その結果，従来から指摘されてきた前頭，頭頂，側頭連合野の血流低下を明らかにした。また，患者の年齢，脳萎縮の程度と脳血流の低下との相関について検討した結果，痴呆群における脳血流低下は単に加齢や脳萎縮だけでは説明できず，疾患そのものに起因する可能性を指摘した。さらに，痴呆の重症度（CDRスコア）と脳血流の低下との相関について検討した結果，左頭頂葉に相関が見られることを示した。

(3) 最後に，これらの研究成果を踏まえて，正常画像データベースとある患者一例を比較することにより，自動診断を行うシステム（エキスパートシステム）を構築した。すなわち画素ごとに平均値と標準偏差（SD）を持つ正常画像データベースからの隔たりを偏差値｛=（観測値－平均値）／SD＋50｝で表現し，画素ごとに計算する。一定の偏差値以下を異常と定義すれば，自動的に血流低下部位を抽出することができる。このシステムによる自動診断の結果と核医学専門医の診断を比較して，自動システム同等以上の診断能を有することを示した。

以上，方法論の検討から疾患への応用，自動診断システムの開発まで極めて独創的な研究を発展させた。本研究は診断の客観化につながる重要かつ先駆的な仕事であり，学位論文にふさわしいと判断する。