# 行政院國家科學委員會專題研究計畫　成果報告

## 運用獨立元件分析方式評估正常人與巴金森氏病的腦血流差異

計畫類別：個別型計畫
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## Abstract

This study investigates regional cerebral blood flow (rCBF) changes in patients with Parkinson's disease using independent component analysis (ICA) followed by statistical parametric mapping (SPM). **Methods:** $^{99m}$Tc- hexaemethyl-propyleneamine oxime ($^{99m}$Tc-HMPAO) was used as the CBF tracer for rCBF measurements. A single photon emission computerized tomography (SPECT) study was performed on 27 patients with Parkinson's disease in various disease stages, and also on 24 aged-matched controls. SPECT images were first spatially normalized to standard space, concatenated, and then subjected to ICA decomposition. The resulting image components were then separated by logistic regression into two sets: disease-related components, whose subject weights differenced between groups and non-disease related components, whose subject weights exhibited no group difference. Components of each set were back-projected and summed across components. The resultant rCBF images were normalized to the global CBF for each subject and then analyzed using SPM to compare the rCBF values changes between Parkinson's disease and control subject. **Results:** In the disease-related image subspace, patients with Parkinson's disease exhibited significantly higher adjusted rCBF in the subthalamic nucleus, putamen, globus pallidum, thalamus, brainstem, and anterior lobe of cerebellum, and significant hypoperfusion in the supplementary motor plus dorsolateral prefrontal, pariteo-occipital cortex, insula, and cingulate gyrus. In the non-disease related image subspace, very few regions showed a significant group difference. Using SPM only without ICA separation gave significantly lower peak t value and at a smaller number of image voxels. Some of the regions revealed by ICA to be affected by Parkinson's disease have not shown significant changes in previous HMPAO-SPECT studies, though those are central to the pathophysiological model of Parkinson's disease. **Conclusion:** In a HMPAO-SPECT study, ICA-based separation of normalized images into disease-related and unrelated subspaces revealed more disease-related brain regions than applying SPM directly. The diseased-related regions indicated by ICA are consistent with the current model of pathophysiology in Parkinson's disease, though their rCBF changes in Parkinson's disease have not been fully demonstrated by any previous single functional imaging study. Thus ICA provides a new and more comprehensive method for testing functional and brain circuit models in Parkinson's disease.


Key words: SPECT, Parkinson's disease, regional cerebral blood flow, Independent component analysis, statistical parametric mapping



中文摘要:
目前已有相當多的研究指出巴金森氏病人的腦血流與正常人有所不同，然而對於血流異常區域卻有許多不一致的發現，本研究試圖運用新的分析方法-獨立元件分析來分析巴金森氏病與正常人之單光子電腦斷層造影之不同。本研究收集 24 位正常人與 27 位不同程度之巴金森氏病人。腦血流測量使用 HMPAO 試劑，病人與正常人之腦影像，先使用標準化的模版做標準化。使每個影像的空間位置相同後，再把所有影像輸入做獨立成分分析，經由此分析後，以邏輯迴歸找出與疾病有相關之成分後，再以 SPM 的方法找出疾病箱關之腦血流異常區域，與過去的方法相比較，本研究不但發現傳統上在巴金森氏病典型的變化，包括

基底核與小腦的腦血流增加，額葉與枕顳葉的腦血流下降，我們更發現輔助運動區與尾核的腦血流於病人有異常的下降，此發現能與疾病的病理生理學相符合。說明以此方法可以有效的發現疾病相關之異常腦血流區域。

關鍵詞：巴金森氏病、腦血流、獨立成分分析

## Introduction

Parkinson's disease (PD) is a common neurodegenerative disease with four cardinal motor features: resting tremor, bradykinesia, cogwheel rigidity and postural instability. 99mTc-HMPAO SPECT is a well-established method of assessing rCBF. SPECT data have been analyzed utilizing either Region Of Interest (ROI) analysis (*4*), which investigates blood flow abnormalities in predefined regions, or using statistical parametric mapping (SPM), which can generate images of blood flow abnormalities for each pixel in the whole brain image(*5*). Results of previous reports about rCBF differences in PD and control have been mixed. Independent component analysis (ICA) is a recently developed data-driven approach to imaging data analysis. It has been widely applied to the analyses of functional neuroimaging data, including EEG/MEG, ERP, fMRI (*11*) and other biomedical signals. In the previous literature, ICA methods has been shown to effectively remove eye-blink artifacts in ERP study (*12*) and to separate artifact components from fMRI data *(11)*. This study used ICA to remove the non-disease related SPECT activity including artifacts and rCBF unaffected by PD from the data followed by voxel-based statistic parametric mapping (SPM). We hypothesized that this method would reveal more areas of significant rCBF difference in PD.

## MATERIALS AND METHODS

### Subjects

Twenty-seven PD patients and twenty-four age-matched control subjects participated in this study. Patients were diagnosed with PD according to the research diagnostic criteria of Ward and Gibb (*13*). Then stage of disease was assessed using the method of Hoehn and Yahr (*14*). The 27 PD patients (21 male, 6 female; mean age of 65.6+ 10 years) were divided into three groups; six patients at Hoehn-Yahr stage I, ten at stage II, and eleven at stage III. Patients were clinically evaluated using the motor-unified Parkinson's disease rating scale (UPDRS) prior to the SPECT study (*15*). Patients imaged had been maintained at least one month on stable anti-parkinsonian therapy with optimized clinical benefit. Patients were receiving anti-parkinsonian therapy including various combinations of L-DOPA with decarboxylase inhibitor (carbidopa), anticholinergic agents, amantadine hydrochloride and dopamine receptor agonists. Twenty-four control subjects (8 male, 16 female; mean age of 61.8 ± 9 years) were healthy volunteers without major neurologic or psychiatric disorder (including alcoholism, substance abuse, head trauma with consciousness loss or cerebral vascular disorder). All subjects were given information about the procedure and gave signed informed consent prior to participating in the study.

**Experimental Protocol**

Patients and control subjects were injected with 740MBq (20 mCi) of (99mTc) HMPAO 30

minutes prior to scanning. The acquisition matrix was 128x128; zoom, 1.5. The reconstruction of SPECT images was achieved using a filtered back projection algorithm with a Metz filter of power 3 and a system resolution of 8 mm intrinsic full width at half maximum (FWHM), resulting in 80 contiguous 128x128 transaxial image slices with in-plane resolution of 1.77x1.77 mm and slice thickness of 1.8 mm. Attenuation correction based on Chang's method (*16*) was performed on each slice, with a uniform attenuation coefficient of 0.11.

**Image Transformation and ICA Pre-Processing**

All images were first converted to Analyze format from their native image format using MRIcro software. Each individual SPECT image was then re-oriented and spatially normalized to the standard Montreal National Institute (MNI) template included in SPM2 http://www.fil.ion.ucl.ac.uk/spm/ using a 12-parameter affine transformation. As a result, each subject's image was re-sampled into 2x2x2 mm voxels in a cube with axes right-left, anterior-posterior, and superior-inferior, respectively. After spatial normalization, the individual SPECT images from normal controls (1~24) and patients (25~51) were concatenated, forming a SPECT data matrix, *X*, with 51 (the number of subjects) and 79*95*69 columns (the total number of voxels). ICA decomposition was performed under FMRLAB. Within FMRLAB, the off-brain voxels were first removed based on an image intensity threshold selected interactively through a graphic user interface. Then, the Bell-Sejnowski information-maximization (Informax) algorithm as implemented by Makeig et al. *(17)* was used to derive the spatially maximally independent components.

**Independent Component Analysis**

Applied to our SPECT data matrix, *X*, ICA found an 'unmixing' matrix, *W*, that decomposed or linearly unmixed the concatenated SPECT data into a sum of spatially independent components, $U = W \times X$, where *U* was a matrix of spatially fixed independent component SPECT images. Since the unmixing matrix *W* was invertible, $X = W^{-1} \times U$. The columns of W-1 represent relative signal strengths of the component map in each of the observed subject SPECT maps *X*. That is, the signal amplitudes in the columns of $W^{-1}$ represent the relative adjusted rCBF strength of the brain regions recruited by the corresponding component maps in each subject image. We expected that some of the resultant components would account for the differences in rCBF between (normal vs PD) groups, while other components would account for inter-subject variability in anatomy or rCBF. After ICA training converged, we applied logistic regression to the subject weights for each component, with a probability threshold of $p < 0.05$, to find "disease-related" components exhibiting a significant difference between patients (columns 25~51) and controls (columns 1~24). The remaining components were considered "non-disease-related" components. Thus, all the components were classified into two sets - "disease-related" or "non-disease-related". Components in these two sets were separately back-projected and summed to reconstruct the disease-related and un-related portions of the individual subject images.

**Data analysis**

SPM analysis was perform on both the raw SPECT images and on the reconstructed "disease-related" data pre-processed by ICA method described above. Before processing the raw data images, each image was spatial normalized using linear and non-linear parameters as in the ICA pre-processing step described above. Then a 3-D Gaussian filter (8 mm width) was used to smooth each image. The mean CBF of each image was scaled to 50 for each subject. Between-group comparisons (controls and PD), were performed on a voxel-by-voxel basis using as general linear model based on the theory of Gaussian fields (*18,19*), within SPM. The first comparison sought areas of increased perfusion, the second, areas of decreased perfusion. The resulting set of voxel values for each comparison constituted a statistical parametric map or SPM{t}. The SPM{t} maps were then transformed to unit normal distribution, SPM{z}. In these between-group comparisons, significant voxels were defined as those surviving a probability threshold of $p < 0.01$ after correction for multiple comparisons. In evaluating the data preprocessed by ICA, the two partial data sets (summing disease-related components and non-disease related components respectively) were submitted to SPM analysis separately as described above. SPM results on the raw and ICA preprocessed data were then overlaid on a normalized MR image.

## Results:

There was no significant difference in age between controls and patients. In the ICA-preprocessed data, 9 components were classified by logistic regression as "disease-related" and 42 components as "non-disease related".

In whole image analysis by SPM, patients with Parkinson's disease showed significantly increased adjusted rCBF in the putamen, globus pallidus, ventral lateral nucleus, brainstem, and cerebellum, while decreased adjusted rCBF was most prominent in the parieto-temporal and medial frontal cortex . Significant affects of Parkinson's disease-related changes in ICA-preprocessed data were more extensive. In the "non-diseased related" component subspace, only one area (right middle frontal gyrus, 41 voxels) showed significantly decreased ($p < 0.01$) adjusted rCBF by SPM analysis, and only one area (right midbrain, 78 voxels) showed significantly increased ($p < 0.05$) adjusted rCBF. When the significance level was set to $p < 0.001$, no brain area showed any disease-related changes. In contrast, in the "disease-related' component set, Parkinson's disease patients showed increased adjusted rCBF in the bilateral subthalamic nucleus, globus pallidus and putamen, ventral lateral and posterior nucleus of thalamus, brainstem, cerebellum, precentral gyrus, superior and inferior frontal cortex, as well as hypoperfusion in the bilateral middle frontal gyrus (dorsolateral prefrontal cortex), parieto-occipital cortex, temporal cortex, and cingulate gyrus. Details of the brain areas involved and a comparison of raw and Compared with the results from whole image data analysis, results on ICA- preprocessed data showed higher peak T values and more extensive regions of disease-related rCBF difference.

In patients, rCBF in the bilateral caudate head and tail, parahippocampus gyrus, right pulvinar, right insula, left anterior cingulated, posterior cerebellar lobe, and parieto-temporal lobe were

negative correlated with motor UPDRS scores, while rCBF in the right putamen, fusiform gyrus, inferior occipital gyrus, and superior parietal lobule were positively correlated.

## Discussion

**Regions of rCBF increase in PD**

Our data imply that in Parkinson's disease, rCBF is increased in the basal ganglia, thalamus, orbital frontal cortex, the brainstem, and the cerebellum. Among these, increased rCBF in the bilateral putamen, globus pallidum, thalamus, subthalamic nucleus, and pons are expected from the basal ganglia circuit model (*2*,*3*) and are consistent with previous studies using SPECT and FDG-PET(*10*,*22*).

**Regions of rCBF decrease in PD**

A widely distributed decrease in rCBF in the cerebral cortex was found in PD from our result. The involved cortices included the posterior parieto-temporal cortex, precuneus, cingulate, insula, dorsolateral prefrontal cortex, and supplementary motor cortex. In addition, the caudate and the medial dorsal nucleus of the thalamus also showed decreased rCBF.

The symptomatology in Parkinson's disease can be partially explained by a disturbed cortical-basal ganglia-thalamic-cortical circuit activity resuting from degeneration of dopaminergic nigrostriatal neurons. If such is the case, a consistent alteration of local rates of regional cerebral metabolism (rCMR) or regional cerebral blood flow (rCBF) would be expected. However, up to now, the findings of rCMR or rCBF changes in the brain of Parkinson's disease patients have been inconsistent. In this present study, we assess the rCBF changes between PD patients and normal controls using Independent Component Analysis as data preprocessing method. The rCBF changes in brain various brain areas shown in this study can well be incorporated into the suggested pathophysiological model in PD. In contrast to using SPM alone, the combination with ICA processing can reveal significant rCBF changes in areas that have been largely overlooked previously.

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計畫成果自評：

巴金森氏病是老年常見的神經退化性疾病，然而其缺乏有意義的生物學指標，使得診斷常需依靠臨床症狀診斷，如果能夠利用影像學的工具，找出與疾病相關連的異常區域，以此作為診斷參考指標，則能夠提高診斷的正確性，同時對於疾病的病理生理學將可提供更深入的了解，本研究發現以此方法，不但可以與過去的研究結果相符合，更可以找到過去研究無法發現，但從疾病的病理生理學可推論得知的異常區域，顯示以此新的方法更能有效的找到與疾病相關之異常區域。

附件二

# 可供推廣之研發成果資料表

□ 可申請專利　□ 可技術移轉　日期：94 年 10 月 26 日

| | |
|---|---|
| **國科會補助計畫** | 計畫名稱：運用獨立元件分析方式評估正常人與巴金森氏病的腦血流差異<br>計畫主持人：徐建業<br>計畫編號：NSC 93-2320-B-038-033　學門領域：醫學工程 |
| **技術/創作名稱** | 運用獨立元件分析方式評估腦血流之方法及步驟 |
| **發明人/創作人** | 徐建業、徐榮隆、邱泓文 |

| | |
|---|---|
| **技術說明** | 中文：本研究試圖運用新的分析方法-獨立元件分析來分析巴金森氏病與正常人之單光子電腦斷層造影之不同。本研究收集 24 位正常人與 27 位不同程度之巴金森氏病人。與過去的方法相比較，本研究不但發現傳統上在巴金森氏病典型的變化，包括基底核與小腦的腦血流增加，額葉與枕顳葉的腦血流下降，我們更發現輔助運動區與尾核的腦血流於病人有異常的下降，此發現能與疾病的病理生理學相符合。 |
| | 英文：Independent component analysis (ICA) is a recently developed data-driven approach to imaging data analysis. This study used ICA to remove the non-disease related SPECT activity including artifacts and rCBF unaffected by PD from the data followed by voxel-based statistic parametric mapping (SPM). We hypothesized that this method would reveal more areas of significant rCBF difference in PD. |
| **可利用之產業<br>及<br>可開發之產品** | Medical Image, Image processing algorithms, Medical Decision support system |
| **技術特點** | 目前已有相當多的研究指出巴金森氏病人的腦血流與正常人有所不同，然而對於血流異常區域卻有許多不一致的發現，本研究運用獨立元件分析來分析巴金森氏病與正常人之單光子電腦斷層造影之不同。腦血流測量使用 HMPAO 試劑，病人與正常人之腦影像，先使用標準化的模版做標準化。使每個影像的空間位置相同後，再把所有影像輸入做獨立成分分析，經由此分析後，以邏輯迴歸找出與疾病有相關之成分後，再以 SPM 的方法找出疾病箱關之腦血流異常區域。 |
| **推廣及運用的價值** | 如果能夠利用影像學的工具，找出巴金森氏病之神經退化相關連的異常區域，以此作為診斷參考指標，則能夠提高診斷的正確性，同時對於疾病的病理生理學將可提供更深入的了解。本研究成果可應用於醫學影像及醫學決策支援系統。 |