以獨立元件分析方式評估巴金森病之腦血流異常

Assessing rCBF Changes in Parkinson’s Disease Using Independent Component Analysis on SPECT Image

中文摘要

過去二十年，生物醫學及工程上最重要的進展之一就是在非侵式記錄技術的突飛猛進。嶄新的技術讓我們能設計、從事各種複雜的實驗，記錄高精密度的腦電波、心電圖、肌電圖、磁振造影及功能性磁振造影。但是，當生醫技術繼續向時空精密度極限挑戰的同時，生醫訊號分析方法的進展卻沒能趕上技術開發的腳步。對腦神經科學而言，一個可信度高的分析方法與一項革命性的生物技術同等重要，我們需更好的分析方法來從龐大複雜的數據（包括時間)中，擷取有意義的資訊。本研究使用一個目前最受訊號處理領域矚目的『獨立元件分析』(Independent Component Analysis, ICA)演算法爲主，來分析單光子電腦斷層攝影影像訊號。獨立元件分析是一種可以將多管道 (concurrent multiple-channel)生醫訊號分解成完全獨立的訊號(independent component)，並進一步探討這些獨立訊號與實驗行爲(task behavior and performance)的相關性的分析工具。這個分析方法在過去幾年已經應用到各種基礎腦神經科學的數據分析，包括腦電波(ＥＥＧ)、肌電圖(ＥＭＧ),及功能性磁振造影,獨立元件分析的提出原是爲了要解決「雞尾酒會問題」(cocktail-party problem)，或稱爲「分離未知訊號源問題」(blind source separation)。ICA 是一個可以將被一個未知轉換 (matrix)線性混在一起的訊號，一個個分離出來的工具。其大致之原理是利用神經網路演算法去找到另外一個轉換(W matrix)，使其所有輸出（Y）的焗 (joint entropy)到達它的最大值，此W就可以把原來的訊號還原回來。過去 ICA 應用到分析 fMRI 訊號如 McKeown et al 展示了如何用 ICA 去分析 fMRI 的資料。ICA 的最大優點是它不需要事先知道腦部會對各種不同的事件做如何的反應，而能自動的找到不同區域所作的活動，不像其它的分析方法往往依賴一個事先可以預測的活動變化來尋找哪些區域會產生這變化。本研究將運用此分析方式（獨立元件分析）來比較正常人與巴金森氏病人其大腦中的局部腦血流差異。

方法:巴金森氏病是老年常見的神經退化性疾病，其主要的症狀爲動作遲緩、僵直、姿態不穩與顫抖。雖然經過數十年的研究，對於巴金森氏病的腦血流變化仍然未有定論，而目前的單光子電腦斷層攝影對於評估局部的腦血流與了解疾病的病理生理學是一項有用的工具。在本研究中我?將運用 ICA 分析一組正常人與巴金森氏病人的單光子電腦斷層攝影影像資料，來比較正常人與巴金森氏病人其大腦中的局部腦血流差異的位置，並探討此差異與臨床症狀的關係。我們收集了 27 位不同程度的巴金森氏病人與 24 位對照組的單光子電腦斷層攝影影像資料，病患的臨床症狀與疾病嚴重度依英國巴金森氏病評估量表(United Kingdom of Parkinson’ s Disease Rating Scale)與荷雅氏分級(Hoehn and Yahr)。以 ICA 分析出

9 個與疾病相關的獨立訊號和 42 個與疾病不相關的獨立訊號，再經由影像統計分析的方法(Statistic Parametric Mapping, SPM)找出巴金森氏病與正常人有統計顯著差異的區域，同時我們也以病患的臨床症狀指標找出與疾病有顯著關聯的相關腦功能區。
結果:我們的研究顯示運用此方法可以找到比傳統分析方式更多的疾病相關聯腦功能區，且這些有顯著意義的區域與臨床症狀有著顯著相關，並且與疾病的病理生理學相符合。同時我們也發現邊緣系統(limbic system)中的扣帶迴(cingulated gyrus)與腦島(insula)和臨床症狀有顯著相關，這在過去的文獻並未被提出。
討論: 由於傳統的分析方式是以選擇區域性(region of interest)來進行比較，我們的研究顯示應用獨立成份分析方式可提供一個不同且較完全的方式來評估巴金森氏病的腦血流變化區域。然而我們的病人數並不是很多，另外病人服用藥物可能產生的影響是本研究在解釋時須注意的。未來將須更充份評估此方法的優劣並做廣泛的測試以期於臨床上的使用。

英文摘要

The emergence of non-invasive recording during the current decade is one of the most important developments in biomedical sciences. As technologies continue to push the boundaries of spatial-temporal resolutions of bio-signal recordings, analytic tools need to keep pace with these advances. However, analytic tools for exploring and modeling the wealth of data collected during functional imaging experiments do not yet capture or model the rapidly shifting dynamics of brain systems during complex cognitive activity. Methods are needed to analyze this wealth of data and to separate out machine noise and physiological artifacts to examine functionally independent physiological systems. Based on a recently developed signal-processing tool, Independent Component Analysis, we can implement methods for linear separation of activity originating in functionally distinct physiological systems by using the relative temporal independence of these activities across sufficient recording time and experimental conditions. This approach has resulted in very promising results in analyzing electroencephalogram (EEG), electrocardiogram (EKG), electromyography (EMG), or functional magnetic resonance imaging (fMRI) data. Materials and Methods: Despite extensive studies in Parkinson’s disease (PD) in recent decades, the neural mechanisms of this common neurodegenerative disease remain incompletely understood. Functional brain imaging technique such as single photon emission computerized tomography has emerged as a tool to help us understand the disease pathophysiology by assessing regional cerebral blood flow (rCBF) changes. We suggest that tools based on decomposition of biomedical time series data into a mixture of temporally or spatially independent components can further provide us more information in the analysis of biomedical image signals. In present study, we collected 27 PD patients in various stage of disease and 24 health controls. Clinical staging and motor symptoms in PD were measured by UPDRS scores (United Kingdom of Parkinson's Disease Rating Scale) and Hoehn and Yahr stage. 99mTc-HMPAO SPECT (single photon emission computerized tomography) image was arranged for both patients and controls. We applied Independent Component Analysis (ICA) to assess the difference in rCBF between PD patients and healthy controls to identify brain regions involving in PD. Finally, statistic parametric mapping (SPM) tool was use to identified statistic significant regions between PD and controls. We also applied motor part UPDRS score to correlate with these significant regions and find brain areas responsible for clinical scores.

Results: After ICA decomposition, 9 independent components were classified as "disease related" subset and 42 as "non-disease related" subset. In "disease-related" subset, SPM revealed many brain areas identified by ICA included the basal ganglia, the brainstem, the cerebellum, and the cerebral cortex. Some of the regions have been largely overlooked in neuroimaging studies using region-of-interest approaches, yet they are consistent with previous pathophysiological reports. Besides, rCBF in limbic system included cingulated gyrus and limbic lobe had demonstrated not only had significant difference between PD and controls, but also had significant correlated with disease symptoms. These had not been reported in previously literatures.

Conclusions: Our study had showed that use ICA as image preprocessing step followed by SPM statistic analysis could significant improve image analysis results. However, our patients were on medication and patient number was not large, which should be caution in further interpretation our results. Since ICA has the ability to solve the blind source separation problem of recovering independent source signals after they are linearly mixed by an unknown matrix, we expect that ICA might be valuable to suggest a new alternative and more comprehensive disease and brain circuit models in PD.