

## Multimodal Integration of EEG, fMRI and Positron Emission Tomography Data Using Principal Component Analysis for Prognosis in Coma Patients

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**Abstract :** Introduction: So far, clinical assessments that rely on behavioral responses to differentiate coma states or even predict outcome in coma patients are unreliable, e.g. because of some patients' motor disabilities. The present study was aimed to provide prognosis in coma patients using markers from electroencephalogram (EEG), blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) and [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET). Unsupervised principal component analysis (PCA) was used for multimodal integration of markers. Methods: Approved by the local ethics committee of the Technical University of Munich (Germany) 20 patients (aged 18-89) with severe brain damage were acquired through intensive care units at the Klinikum rechts der Isar in Munich and at the Therapiezentrum Burgau (Germany). At the day of EEG/fMRI/PET measurement (date I) patients (<3.5 month in coma) were grouped in the minimal conscious state (MCS) or vegetative state (VS) on the basis of their clinical presentation (coma recovery scale-revised, CRS-R). Follow-up assessment (date II) was also based on CRS-R in a period of 8 to 24 month after date I. At date I, 63 channel EEG (Brain Products, Gilching, Germany) was recorded outside the scanner, and subsequently simultaneous FDG-PET/fMRI was acquired on an integrated Siemens Biograph mMR 3T scanner (Siemens Healthineers, Erlangen Germany). Power spectral densities, permutation entropy (PE) and symbolic transfer entropy (STE) were calculated in/between frontal, temporal, parietal and occipital EEG channels. PE and STE are based on symbolic time series analysis and were already introduced as robust markers separating wakefulness from unconsciousness in EEG during general anesthesia. While PE quantifies the regularity structure of the neighboring order of signal values (a surrogate of cortical information processing), STE reflects information transfer between two signals (a surrogate of directed connectivity in cortical networks). fMRI was carried out using SPM12 (Wellcome Trust Center for Neuroimaging, University of London, UK). Functional images were realigned, segmented, normalized and smoothed. PET was acquired for 45 minutes in list-mode. For absolute quantification of brain's glucose consumption rate in FDG-PET, kinetic modelling was performed with Patlak's plot method. BOLD signal intensity in fMRI and glucose uptake in PET was calculated in 8 distinct cortical areas. PCA was performed over all markers from EEG/fMRI/PET. Prognosis (persistent VS and deceased patients vs. recovery to MCS/awake from date I to date II) was evaluated using the area under the curve (AUC) including bootstrap confidence intervals (CI, \*:  $p < 0.05$ ). Results: Prognosis was reliably indicated by the first component of PCA (AUC=0.99\*, CI=0.92-1.00) showing a higher AUC when compared to the best single markers (EEG: AUC<0.96\*, fMRI: AUC<0.86\*, PET: AUC<0.60). CRS-R did not show prediction (AUC=0.51, CI=0.29-0.78). Conclusion: In a multimodal analysis of EEG/fMRI/PET in coma patients, PCA lead to a reliable prognosis. The impact of this result is evident, as clinical estimates of prognosis are inapt at time and could be supported by quantitative biomarkers from EEG, fMRI and PET. Due to the small sample size, further investigations are required, in particular allowing supervised learning instead of the basic approach of unsupervised PCA.

**Keywords :** coma states and prognosis, electroencephalogram, entropy, functional magnetic resonance imaging, machine learning, positron emission tomography, principal component analysis

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