

A disruption of brain energy metabolism as a driver for delirium

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Introduction & aims

- Delirium is an acute neuropsychiatric condition characterised by **hypoactive or hyperactive behaviour**.
- Widely neglected and poorly understood, delirium is extremely common, with an overall **prevalence of 20% in hospital inpatients**.
- Explored the **lack of cerebral glucose availability or its impaired uptake** and relationship with sudden changes in cognitive status of the patient. This was assessed by means of a **literature review** that is currently progressing towards submission of a review article.
- Nuclear magnetic resonance (NMR) spectroscopy** is a highly specific tool used for global metabolic profiling. Establishing the metabolic profile of a pathology can help distinguish it from others.
- NMR spectroscopy was used to **assess metabolic profiles** of patients with an **acute inflammatory trauma**, and with or without dementia and/or delirium, to realise pathways affected by the different clinical states, and where these might overlap or diverge.

Materials and Methods

- 20 cerebrospinal fluid (CSF) samples** (Group 1 and Group 2) were processed via **Nuclear magnetic resonance (NMR)** to reveal important biomarkers.

Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=10)	Group 4 (n=10)
Hip fracture	Hip fracture	Hip fracture	No hip fracture
Dementia	No dementia	No dementia	No dementia
Confused	Not confused	Confused	Not confused

Table 1: Patient cohorts of CSF samples

- All ¹H NMR spectra were acquired on an **18.8 T NMR spectrometer**. The spectra were preprocessed using **NMRProcFlow 1.4.10**. Data filtering, data normalization, and data scaling were applied using **MetaboAnalyst 5.0**.
- Data was analysed with **Principal Component Analysis (PCA)** and **Partial Least Squares Discriminant Analysis (PLS-DA)**. The PLS-DA model was validated by 5-fold cross-validation. This analysis was used to **compare metabolic profiles** of both groups.

Discussion and limitations

- It can be derived that a different metabolic pattern exists between Group 1 and Group 2 samples.
- This indicates that post systemic inflammation, **biomarkers observed in dementia/ confusion are different to those in a cognitively balanced state**.
- The current sample size **does not produce a predictive model**, possibly due to low number of samples.
- While delirium remains relatively misunderstood, it is apparent that **any energy shift**, possibly one caused by systemic inflammation can **drive cognitive imbalance**.
- Further analysis may be carried out to explore metabolically important spectral regions and determine the **concentration changes** of particular metabolites.
- These results aim to **improve prognosis outcomes of delirium** and hopefully even **garner more awareness** on the subject.

Results

Pairwise comparisons of patients with acute inflammation but with/without dementia and/or confusion are as follows-

PLS-DA plot

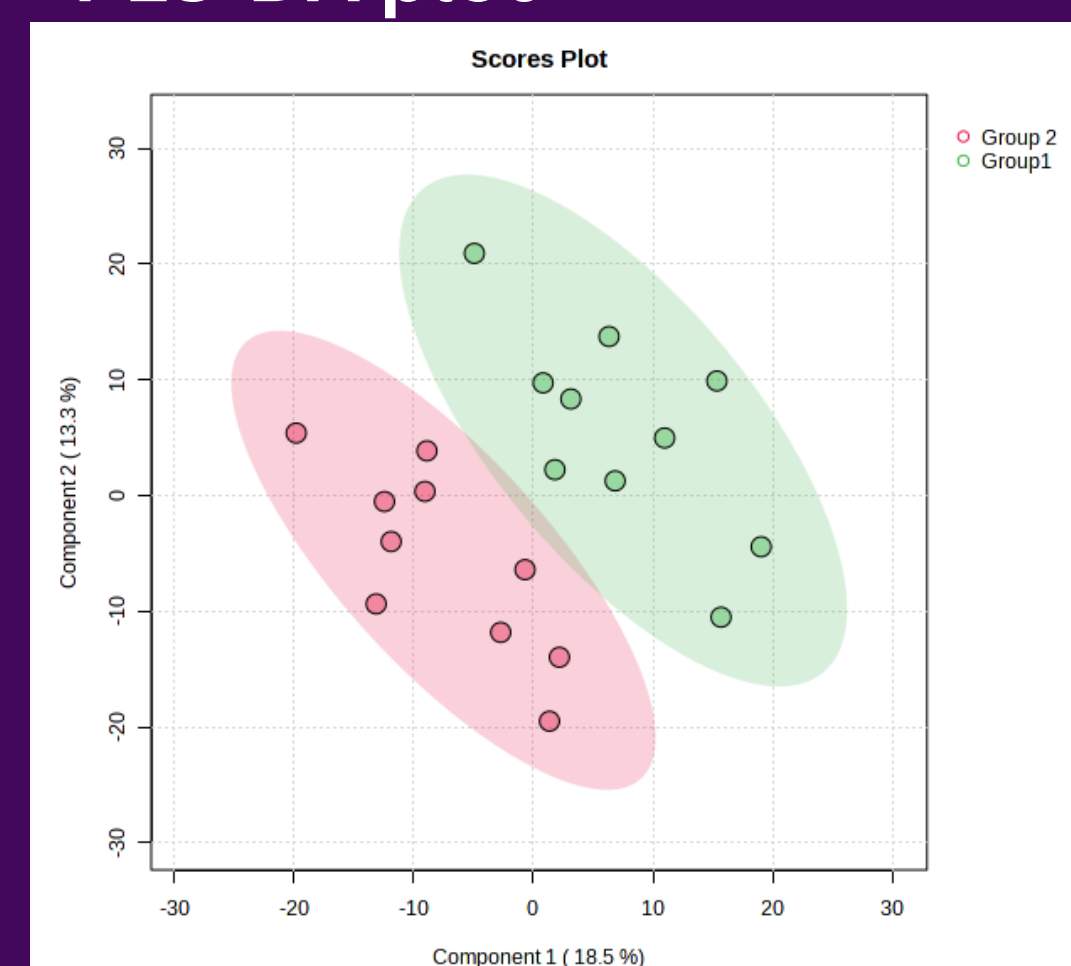


Figure 1: Pairwise analysis of Group 1 (green) and Group 2 (red) by PLS-DA

Cross Validation

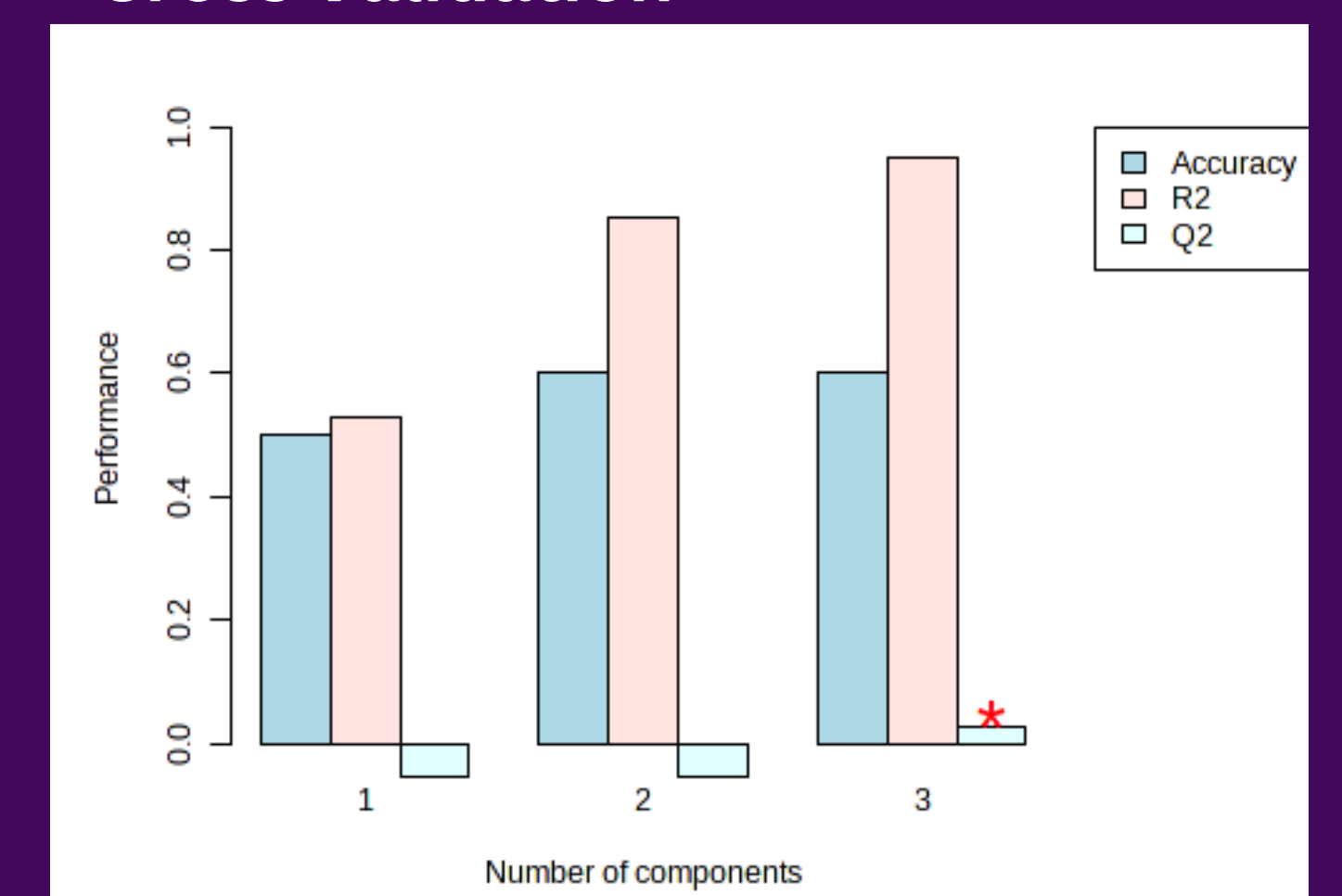


Figure 2: 5-fold cross validation of PLS-DA model

- PLS-DA indicates difference between Group 1 and 2 samples, indicating **different metabolic profiles of dementia and confusion** post systemic inflammation.
- Based on the multivariate analysis of Q2 values as a part of cross validation, the current sample size **does not appear** to be sufficient to provide a **predictive model**.

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References:

- Wilson et al. (2020). Delirium. *Disease Primers, Nature Reviews*. 6:90
- Engel, G. L., & Romano, J. (2004). Delirium, a syndrome of cerebral insufficiency. 1959. *The Journal of neuropsychiatry and clinical neurosciences*, 16(4), 526–538.