# BLIND RECOVERY OF 1H MRSI SPECTRAL SIGNATURES OF BATTEN DISEASE AND MELAS

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## Introduction

The availability of multi-planar and/or fast spectroscopic imaging techniques now allows the acquisition of high spatial resolution MRSI data in clinically acceptable scan times. Moreover, both spatial and temporal resolution are also likely to increase dramatically with the recent availability of high field MR systems and phased-array coils, which provide substantial gains in detection sensitivity and acquisition speed. However, these high gains in spatio-temporal resolution of MRSI data are also rapidly leading to an unintended or undesired side effect: The resulting spectroscopic imaging datasets are becoming so large that their analysis and interpretation has begun to tax most available data analysis methods. Therefore, for such large MRSI datasets to become of widespread practical utility, spectral analysis methods which can quickly recover the important features within a dataset will be required to allow clinicians to quickly glean the diagnostic information. Recently, we introduced constrained non-negative matrix factorization (cNMF) [1], an advanced data analysis method for recovering physically meaningful spectral signatures by decomposing the observed spectral data into two non-negative matrices, representing (a) the underlying tissue specific spectral patterns and (b) the spatial distribution of their concentrations. This study demonstrates the utility of cNMF in being able to blindly discriminate, on the basis of their multislice $^1$H MRSI data, two neurodegenerative diseases affecting children: Batten disease (BD: Late infantile neuronal ceroid lipofuscinosis) and MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke like episodes). In their early stages, BD and MELAS have similar clinical symptoms, though the relevant treatments and survival morbidity are very different. In the later stages, BD and MELAS have nearly identical structural patterns on MRI - great loss of brain tissue -- when evidence of infarcts are lacking in MELAS. These phenotypic and radiologic similarities can make it difficult to differentiate between the two diseases without extensive and costly genetic analyses. Here, we demonstrate that applying cNMF to multislice $^1$H MRSI data of the two disorders results in both extraction of their respective spectral patterns as well as the spatial distributions of lesion patterns critical for differentiation.

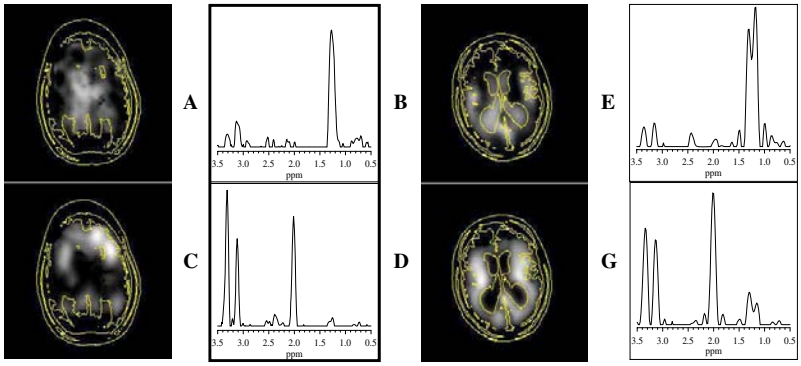
## Methods

Blind Spectral Recovery using cNMF. cNMF, an extension of NMF [2][3], has been described in detail previously[1]. It seeks a representation of the original data-matrix as a mixture of several constituent spectral patterns. Let **X** represent a spectral data-matrix consisting of N rows, each row representing a voxel having L spectral points (L columns). Two matrices are recovered simultaneously: **A** and **S**, such that their product optimally reconstructs **X** given noise in the data. Each row of **S** is seen as one of the M constituent spectra with the columns in **A** representing the mixing coefficients, corresponding to the concentration of the constituent material. Our long TE (280 ms) MRSI protocol is such that **A** and **S** are constrained to be non-negative. Given that the noise in the data can be modeled as Gaussian, one can formulate the problem as a maximum likelihood estimation. The cNMF algorithm constructs a gradient descent over a negative log-likelihood objective function thus optimizing **A** and **S**. Active data selection is used to remove voxels which are due to artifacts and confounding metabolites/tissues (e.g. lipids and water) [4] for analysis with high specificity.

MRS methods. The cNMF method is demonstrated retrospectively on Batten disease and MELAS cases, whose spectra had been acquired on a 3.0 T LX MR system and on a 1.5 T GE 5.x MR system, respectively, using the multislice MRSI sequence of Duyn et al [5]. Following acquisition of localizer MRI series, a 4-section $^1$H MRSI scan was performed, with 15-mm thick slices, 3.5-mm gaps, TE/TR 280/2300 ms, FOV 240 mm, 32x32 phase-encoding steps with circular k-space sampling. These sequence parameters were identical for the two field strengths except that 512 sample points and a spectral width of 2500 Hz were used at 3.0 T, whereas 256 sample points and a spectral width of 1000 Hz were used at 1.5 T. The resulting raw data were separated into individual slices and then processed using standard fast Fourier transform algorithm.

## Results and Discussion

Figure 1 shows the recovered spectral patterns and their corresponding concentration images for BD (left four panels, A-D) and MELAS (right four panels, E-H). The MELAS data are characterized by a large ventricular lactate (Panel F), and a significantly elevated brain lactate and decreased N-acetyl-aspartate (NAA) (Panel H). For BD, the spectrum recovered from brain parenchyma (Panel D) shows a decreased NAA resonance and a mildly increased choline resonance, with a small elevation of lactate. Though a ventricular lactate is also visible in the BD (Panel B), it is significantly smaller than that recovered for MELAS, and while both disorders are always fatal, their recovered spectral patterns are clearly different. MELAS, which is due to a point mutation at nucleotide 3243 of the mitochondrial DNA, is characterized by severe lactic acidosis. The recovered MELAS spectra, which show a highly elevated lactate peak in the brain parenchyma, as well as in the ventricular cerebrospinal fluid (CSF), are consistent with a profound mitochondrial energy metabolism dysfunction in this disorder. The presence of a smaller lactate peak in the brain and CSF of BD suggests a milder mitochondrial energy dysfunction.




Both disorders are neurodegenerative and this is consistent with their recovered spectral patterns, which show neuronal loss as assessed by the levels and distribution of NAA. Choline is significantly more elevated in BD than in MELAS, suggesting axonal demyelination, in addition to neuronal damage. The cNMF-recovered spectral patterns can clearly form the basis for discriminating between BD and MELAS, regardless of the field strength at which the data were acquired.

## Conclusion

Matrix factorization methods based on very general constraints and minimal prior information, such as non-negativity, can be applied to $^1$H MRSI for simultaneously recovering spectral patterns and their spatial distributions, enabling fast and accurate differentiation between neurological diseases.

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## References

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