Identification of the neural stem cells in the human brain by magnetic resonance spectroscopy

L. Manganas[1], S. Zhang[2], P. Djuric[2], M. Wagshul[3], M. Maletic-Savatic[1]

[1]Neurology, Stony Brook University, Stony Brook, NY, United States, [2]Electrical and Computer Engineering, Stony Brook University, Stony Brook, NY, United States, [3]Radiology, Stony Brook University, Stony Brook, NY, United States

Abstract:

The ability to identify human neural stem cells (NSC) by brain imaging may have profound implications for diagnostic, prognostic, and therapeutic purposes. The study of human NSC *in vivo* is hindered by the absence of well-defined markers that can distinguish them from other neural cell types. We have, however, identified a NSC-specific metabolic peak using ^{1}H-NMR spectroscopy of cultured, purified neural cell types.[1,2] Herein, we explore the identification of human NSC using ^{1}H-MRS. We aim to develop novel imaging and signal processing methodologies that would enable non-invasive investigations of NSC behavior in healthy and disease states. This study is a first step toward that goal.

Introduction:

NSC are pluripotent cells that can differentiate into any of the neural cell type progeny such as neurons, astrocytes, or oligodendrocytes. Therefore, they have significant therapeutic capability both endogenously as reservoirs of potential replacement of damaged tissue, and exogenously as transplanted cells for gene/drug delivery or replacement of lost tissue. However, methodologies for identification of NSC in the living human brain are not yet available, and without the ability to identify them, the analysis of NSC fate and function is virtually impossible. Our preliminary experiments have demonstrated that we are able to identify the NSC on the basis of their ^{1}H-NMR metabolomic fingerprint.[2] NSC have a unique spectroscopic peak at 1.28ppm frequency, which is not present in the spectra of purified cultures of neurons, astrocytes, and oligodendrocytes. In addition, we can detect both endogenous and exogenous NSC in the living rat brain, using ^{1}H-MRS and 9.4T mMRI scanner.[2] Herein, we present our data on identification of NSC in the human hippocampus, where they normally reside within the dentate gyrus, using ^{1}H-MRS.

Methods:

We have obtained ^{1}H-MRS (3T Phillips Achieva MRI scanner) of the hippocampus, where endogenous NSC are localized, and cortex, where NSC are not normally found. The ^{1}H-MRS was acquired using TE 30ms, TR 2000ms, spectral width 2000 Hz, 1024 points, 128 averages, and total image time 4.55 minutes. The voxel size was 30 mm x 12 mm x 12mm oriented along the hippocampus and 16 mm x 16 mm x 16 mm within the gray matter in the cortex (the voxels have the same volume). The SNR was approximately 30-40.

Analysis:

To overcome the low SNR combined with low density of endogenous NSC, we have developed new signal processing methodologies for extraction of the peaks of desired spectroscopic frequency. The applied method for quantification is based on a frequency selective singular value decomposition (SVD) and enables analysis of the spectra in carefully selected frequency ranges (Fig. 1).[3-5]

Results:

Figure 1 shows an example of our methodology to detect endogenous NSC in the human hippocampus. Voxels are placed in the hippocampus (spectra on the right) and cortex (spectra on the left). The upper, raw spectra are processed via Fourier transformation (time-based domain) and major metabolites (NAA, creatine, choline, myoinositol) can be observed. The lower spectra are data processed via SVD frequency-based domain, isolating the NAA (2.02ppm), creatine (3.03ppm), choline (3.22ppm), myoinositol (3.52ppm) and NSC (1.28ppm) peaks. NSC peak is identified in the hippocampus only, as expected. In some cases, we have observed a small peak in the cortex if we extend the spectral range of interest between 1.25-1.31ppm. The results acquired to date are reliable and repetitive (N=5 subjects). Further development of the human MRI data processing is under way, particularly concentrating on SVD refinement so that the NSC peak is detected only when NSC are present within the tissue.

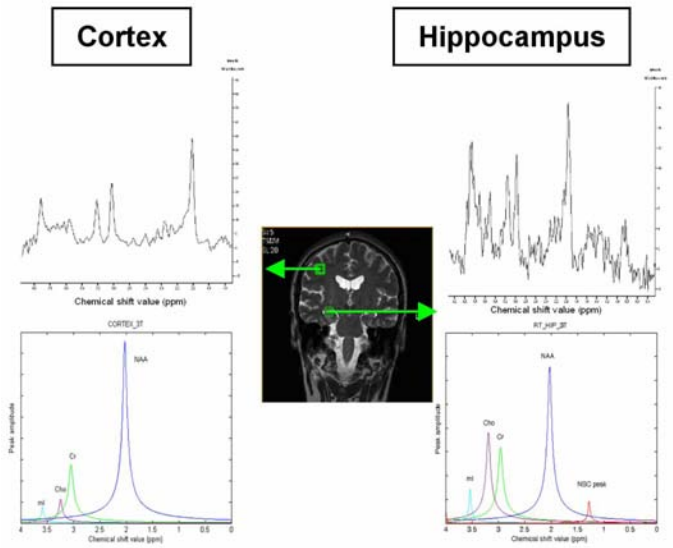

Figure 1. Identification of the NSC in the human hippocampus.

Discussion:

This is the first study that demonstrates our ability to visualize NSC in the living human brain, using MRI spectroscopy. Further clarification of the data and refinement of the MRI acquisition and processing methodologies are currently in progress. If successful, this methodology might eventually become a diagnostic routine in all age groups where NSC pathophysiology might be suspected as an etiologic factor. Furthermore, our research should be applicable to identification and tracking of exogenous NSC as well, which may be used as therapeutic reagents in certain disorders. Given the non-invasive nature and applicability of ^{1}H-MRS spectroscopy to infants and children, the results of our research will lead to essential clinical investigations of NSC behavior in normal human brains throughout development as well as in disease states.

References:

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