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Editorial

KALPANA: Advanced Spectroscopic Signal Processing Platform for Improved Accuracy to Aid in Early Diagnosis of Brain Disorders in Clinical Setting

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Abstract. Magnetic resonance spectroscopy (MRS) plays a substantial role in the non-invasive detection of brain neurochemicals, antioxidants, and neurotransmitters. Quantitative monitoring of these neurochemicals and neurotransmitters in the brain has a profound application for the understanding of brain disorders. Significant progress in the MR scanner as well as MR pulse sequence development to detect *in vivo* neurochemicals has been accomplished. The processing of MR signal from these low abundant neurochemicals/neurotransmitters should be very robust and sensitive in order to provide distinctive observations of disease-related neurochemical alterations and their absolute quantitation to aid in early clinical diagnosis. We highlight the diversity in currently available MRS processing tools, and recently introduced, KALPANA, a promising package integrating the end-to-end processing as well as robust quantitation of neurochemicals in a user-friendly approach through a graphical user interface. This further necessitates the futuristic need for advanced MRS processing pipeline and the respective readout can help in early diagnosis and prognosis of diseases in the clinical environment.

Keywords: Absolute quantitation, clinical study, KALPANA, magnetic resonance spectroscopy, Matlab, platform, signal processing

INTRODUCTION

Dementia is the fifth leading cause of global death and according to a recent survey, the number of individuals living with dementia has doubled from 1990 to 2016 [1]. In absolute terms, about 35.6 million people are living with dementia worldwide with 7.7 million new cases added every year, with the highest estimated projections in south Asian nations such as India and China [2]. Moreover, the number of people with dementia worldwide is projected to double by 2030 and increase more than three times by 2050, with the majority in developing countries like India [3].

The average life expectancy of the Indian population has increased to 68.3 years. Hence, with the increasing elderly population, a proportionate rise in the prevalence of dementia among the elderly has reached up to 5%–7% [4]. The World Health

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Organization (WHO) recognizes dementia as a public health priority and in May 2017, WHO endorsed an 8-year global action plan emphasizing diagnosis and information for dementia, including research and innovation as one of the highlighted areas [1].

The number of aging people is increasing rapidly, and reports of aging associated disorders are multiplying specifically due to dementia, such as Alzheimer's disease (AD), Parkinson's disease, frontotemporal dementia, dementia with Lewy body disease, etc. The causal process of these neurodegenerative disorders is not known yet. However, oxidative stress is considered as one of the possible key factors [5–7]. On the other hand, the number of brain disorders with neurodevelopmental deficits such as autism spectrum disorders [8], epilepsy [3], attention deficit hyperactivity disorder [9], and psychiatric disorders such as schizophrenia [10] is increasing rapidly with increasing complexity of lifestyle. The exact cause of all these disorders is unknown and hence cures are not found yet. Neuroimaging techniques such as positron emission tomography and magnetic resonance imaging (MRI) are used on a regular basis to help in clinical diagnosis, while other modalities such as diffusion tensor imaging and functional MRI are still being investigated to identify the respective disease specific biomarkers for early diagnosis [11].

Metabolic changes including alterations in antioxidant levels as well as receptor modulation being the primary focus areas for brain disorders, magnetic resonance spectroscopy (MRS) is the only available non-invasive investigative tool to monitor this critical neurochemical information at an early stage. Neurodegenerative and neurodevelopmental disorders as the two major health issues in elderly as well as young age groups, need urgent attention to identify the causal molecular processes, and MRS can help immensely in the investigation of disease specific early diagnostic markers [12]. Despite the special capabilities of MRS, it has largely faced limitations due to its large scan time, issues with availability of hardware, and lack of trained manpower in a multidisciplinary setting. Research to cope with these limitations require focused innovations, development of new pulse sequences with multiple metabolites in a single shot, specific transmit/receive coil development, and expertise in the aforementioned areas. This specific domain of imaging modality needs the involvement of scientists from physical sciences, electrical and electronics as well as biomedical engineering. There are still a limited number of specialized centers in MRS and sincere efforts are required to put this highly promising technology upfront, so the outcome of this technique can find applications in clinical environments like the widely used technique MRI.

MOLECULAR DETAILS USING NON-INVASIVE MRS

MRS is extremely useful to extract information about various molecular processes using ^{1}H MRS, [13] ^{31}P MRS [14, 15], and ^{13}C MRS [16]. The neurochemical information from MRS is correlated with clinical condition and quantitation of neurochemicals to help in the generation of the receiver operating curve (ROC). ROC indicates specificity and sensitivity, an important indicator for the disease accuracy in clinical settings.

MRS PROCESSING PIPELINE: EFFECT ON QUANTITATIVE NEUROCHEMICAL MEASUREMENT

Multi-nuclear (^{1}H, ^{31}P, ^{13}C, ^{19}F, etc.) MRS from N-acetyl aspartate, choline, creatine, myo-inositol, adenosine-tri-phosphate, adenosine-di-phosphate, glucose, receptors (gamma-aminobutyric acid (GABA), glutamate, glutamine, etc.) and antioxidants (glutathione (GSH), ascorbic acid, etc.) can provide a wealth of information relating to various neurological, psychiatric, and developmental disorders [17]. There is a profound improvement of pulse sequence (e.g., DQ-Filter [18], L-COSY [19], MEGA-PRESS [20], etc.) for *in vivo* detection of neurochemical signals. Consequently, signal processing of a very small amplitude signal arising from these receptors due to low abundance needs utmost care while extracting information with a focused approach. The metabolic quantitation from MRS signals from the low abundance neurotransmitters is highly influenced by the choice of processing parameters, basis sets, and signal processing software. Moreover, the locally chosen processing parameters in individual software have also shown variability in the assessed metabolic outcomes.

MR signal processing packages such as GANNET [21], jMRUI [22], KALPANA [5], LCModel [23], TARQUIN [24], and MIDAS [25] are mostly being used to process MRS data at clinical centers. Among these, individual packages other than KALPANA have their dedicated data processing

pipelines and restrictive application in research areas, where the comparison of individual processing schemes is desirable. Initial efforts to check the variability of MRS data processing using various existing packages involving GANNET, jMRUI, KALPANA, LCMODEL, and TARQUIN on the selected GABA data (blinded) were reported in a recent ISMRM meeting [26]. This study also shows the variability in estimated outcomes generated from the same data.

KALPANA: MRS PROCESSING PACKAGE AND PLATFORM FOR COMPARATIVE PROCESSING ANALYSIS

The initial framework of the KALPANA package was developed in the NINS laboratory with the objective of easy handling and multi-nuclei (^{1}H, ^{31}P, ^{19}F, etc.) data processing across various types of scanners (Philips, General Electric, and Siemens), KALPANA works in unified-platform based upgradation bringing additional features later on (such as, calibration choices, relaxation time correction, and partial volume correction) for absolute quantitation within the KALPANA platform. KALPANA works in the MATLAB environment (compatible with all versions after MATLAB 2014b) and uses built-in MATLAB functions that include signal/image processing toolbox for MRS signals, as well as optimization toolbox for minimizing non-linear least square functions and peak area peak fitting.

The KALPANA package is user friendly and provides a variety of processing choices to the users for the MRS signal such as eddy current compensation, initial point correction, filtering (exponential, Gaussian, Mixed), zero-filling, auto/manual peak labelling, interest peak/water/lipid suppression (HSVD, HLSVD), baseline correction (SSA, spline, wavelet), and peak fitting (TD, FD, TDFD, VARPRO) for accurate quantitation of metabolites. KALPANA implements an iterative baseline estimation and fitting approach [27] to maximize quantitation accuracy, whereby baseline estimation and removal of

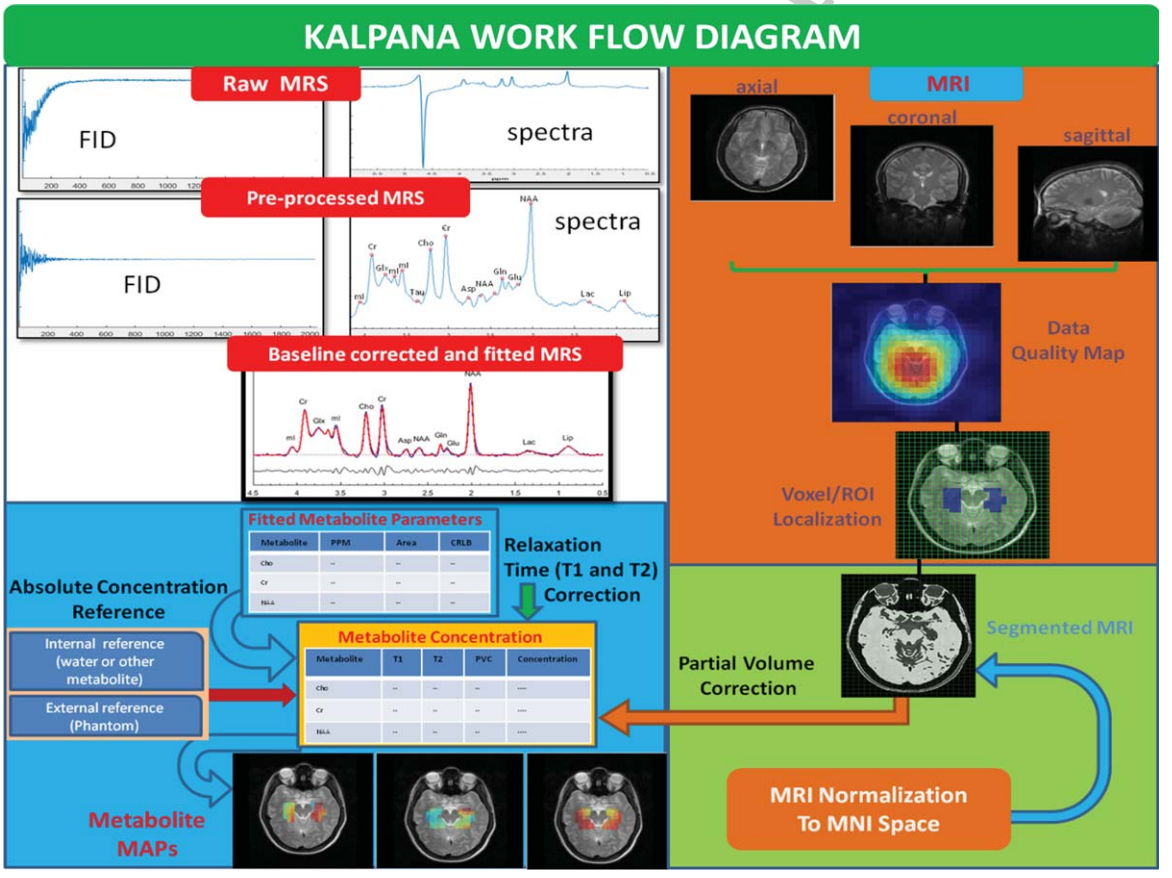

Fig. 1. An illustrative representation of the multi-nuclei data processing, metabolic quantitation, and outputs generated using the KALPANA package.

alternates with peak fitting until optimal peak fitting is achieved and provided the quality of peak fitting from Cramer-Rao lower bound values is also reported. The availability of a various processing choices provides an additional advantage of comparison of the processing schematics on a single platform making KALPANA unique from the other MRS processing packages. It also has numerous post-processing features including segmentation, partial volume correction, group normalization, and absolute quantitation of the neurochemicals. An illustrative picture for the processing features of KALPANA is shown in Fig. 1. This package integrates the processing pipeline in manual and automated mode for group analysis of PRESS and edited sequence, i.e., MEGA-PRESS data obtained from Philips, Siemens, and GE scanners. It can be used to process single voxel and multi-voxel MRS data (^{1}H, ^{31}P, ^{19}F) for a variety of purposes such as GABA quantitation, pH mapping, and antioxidant GSH quantitation [28, 29].

Recently it was discovered that the brain microenvironment has a role in modulating the conformations of GSH, a master antioxidant involved in the neutralization of the harmful radicals in the brain. GSH exists in two conformational states (extended and closed) in the brain [30, 31]. It is, therefore, paramount to identify novel imaging based disease biomarkers [32] involving antioxidants, neurotransmitters, and physiological parameters that can aid in identifying the causal processes of these brain disorders. Further, it can be translated into clinical practices for simplified diagnostic tests and advocating appropriate lifestyle changes to delay the onset of symptoms.

EARLY DIAGNOSIS MARKER FOR THE CONVERSION OF HEALTHY TO MILD COGNITIVE IMPAIRMENT AND PROGNOSIS OF AD USING MRS: AN URGENT NEED

A healthy old person converts to mild cognitive impairment (MCI) when the closed form of GSH level (GSH_{cl}) in the hippocampus is depleted significantly as reported in our earlier work [5]. When the GSH_{cl} level of the frontal cortices deplete significantly, the MCI patient converts to AD [5]. Here, we show that the transition of a normal elderly person to MCI and then AD is correlated with the depletion of GSH_{cl} level in the hippocampus (Fig. 2). This is validated by measuring GSH_{cl} in the frontal cortices and quantified using KALPANA. Based on the assessment of GSH_{cl} non-invasively in the healthy old and MCI patients, the progression of disease and transition as well as prognosis can be monitored by measuring the MCI patients longitudinally. This scheme can also be extended to investigate the efficacy of the drugs on patients currently prescribed with respective medications.

This editorial emphasizes the critical need of an advanced signal processing tool for the standardiza-

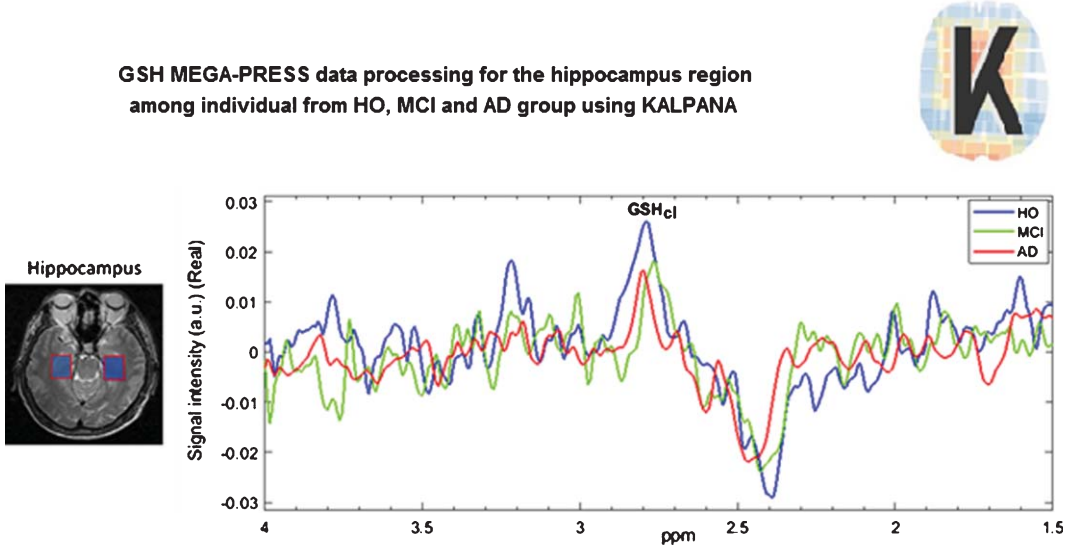

Fig. 2. The depletion of the closed form of GSH (GSH_{cl}) from the hippocampal area of healthy old (marked in Blue color), MCI (marked in **Green** color), and AD (marked in **Red** color) patients. GSH data was collected using the MEGA-PRESS pulse sequence (3T Philips Scanner) at NBRC and processed using the KALPANA package.

tion of metabolic quantitation and its application in identifying the diagnostic biomarkers for disease so that MRS can be utilized in a clinical setting. We are hopeful that MRS will be utilized as a routine tool for patient care in a few years' time.

Web-link: Information related to the KALPANA package is available for academic use at http://www.nbrc.ac.in/newweb/research/groups/PM.

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