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Quantifying Global-Brain Metabolite Level Changes with Whole-Head Proton MR Spectroscopy at 3 T

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Abstract

BACKGROUND AND PURPOSE—To assess the sensitivity of non-localized, whole-head ¹H-MRS to an individual's serial *changes* in total-brain NAA, Glx, Cr and Cho concentrations – metabolite metrics often used as surrogate markers in neurological pathologies.

MATERIALS AND METHODS—In this prospective study, four back-to-back (single imaging session) and three serial (successive sessions) non-localizing, ~3 minute ¹H-MRS (*TE/TR/TI*=5/10⁴/940 ms) scans were performed on 18 healthy young volunteers: 9 women, 9 men: 29.9±7.6 [mean±standard deviation (SD)] years old. These were analyzed by calculating a within-subject coefficient of variation (CV=SD/mean) to assess *intra*- and *inter*-scan repeatability and prediction intervals. This study was Health Insurance Portability and Accountability Act-compliant. All subjects gave Institutional Review Board-approved written, informed consent.

RESULTS—The *intra*-scan CVs for the NAA, Glx, Cr and Cho were: 3.9±1.8%, 7.3±4.6%, 4.0±3.4% and 2.5±1.6%, and the corresponding *inter*-scan (longitudinal) values were: 7.0±3.1%, 10.6±5.6%, 7.6±3.5% and 7.0±3.9%. This method is shown to have 80% power to detect changes of 14%, 27%, 26% and 19% between two serial measurements in a given individual.

CONCLUSIONS—Subject to the assumption that in neurological disorders NAA, Glx, Cr and Cho *changes* represent brain-only pathology and not muscles, bone marrow, adipose tissue or epithelial cells, this approach enables us to quantify them, thereby adding specificity to the assessment of the total disease load. This will facilitate monitoring diffuse pathologies with faster measurement, more extensive (~90%) spatial coverage and sensitivity than localized ¹H-MRS.

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Keywords

MR Spectroscopy; Whole Brain MR spectroscopy; metabolic quantification; Proton MR Spectroscopy; Diffuse neurological disorders

INTRODUCTION

Proton MR spectroscopy (^1H -MRS) facilitates non-invasive detection of several neuro-metabolites, most prominently, the total *N*-acetylaspartate (NAA), glutamate+glutamine (Glx), creatine (Cr) and choline (Cho), with single- or multi-voxel sequences available on all modern scanners [1,2]. These are used as surrogate markers for neuronal integrity [3], neurotransmitter dynamics [4], energy metabolism, membrane-turnover [5] and gliosis [2]. Localized ^1H -MRS, however, suffers several limitations: (a) it covers just a fraction, typically 1–10% and rarely up to 70% of the brain [6,7], precluding assessment of the total disease load [8]. Consequently, (b) it relies on the assumption that metabolic changes occur only at MRI-visible abnormalities, resulting in MRI-occult pathologies being missed. Furthermore, ^1H -MRS (c) is sensitive to repositioning errors, even when automatic, image-based repositioning is applied [9]; (d) requires long, 4 – 30 minutes, acquisition to achieve sufficient SNR; and (e) often assumes the same T_1 and T_2 relaxation-times in patients and controls [10].

These issues can all be addressed using a non-localizing ^1H -MRS sequence that acquires the signal from the whole-head [8,11,12] and been shown to capture >90% of the brain's signal with ~10% loss to susceptibility gradients at air-tissue interfaces [13]. Unfortunately, it can only practically quantify the levels of NAA, since this is the only metabolite implicitly localized by its physiology exclusively to neurons and their processes, *i.e.*, to just the brain [14], ascribing to the method the name “whole-brain NAA” (WBNA) [11]. Since Glx, Cr, and Cho are also present in all other tissue types [15], the brain's contribution to their whole-head non-localized signals cannot be separated from that of muscles, bone marrow, adipose tissue and epithelial cells.

However, when the WBNA technique is applied to neurological disorders, which are often progressive, follow-up acquisitions are sometimes also acquired, to monitor progression and treatment response [8,16]. In these cases, if we assume that these neurological conditions affect only the brain's biochemistry, and not any of the patient's other head tissue, then *differences* between measurements taken at different times will also localize their Glx, Cr and Cho *changes* to just the brain. This is because their (unchanged) contributions from other tissue types to the head's ^1H -MRS signals will destructively interfere.

The recent availability of full spectral-modeling software yielding ~7% *intra*-subject WBNA reproducibility [12] prompted this study. Specifically, the purpose of this study was to assess the technique's sensitivity to individual serial changes in total-brain NAA, Glx, Cr and Cho concentrations – metabolite metrics often used as surrogate markers in neurological pathologies [1,2] – by obtaining serial whole-head ^1H -MRS in healthy young adults.

METHODS

Human subjects

Eighteen healthy young adults [9 men, 9 women, 29.9 ± 7.6 (mean $\pm$ standard deviation, range: 14 – 44 years old)] were prospectively enrolled in this study. Their “healthy” status was based on self-reported exclusion of neurological conditions and MRI contraindications before the scan and an unremarkable MRI, confirmed by a board-certified neuroradiologist afterwards. The study was Health Insurance Portability and Accountability Act-compliant. All participants gave Institutional Review Board-approved written, informed consent.

MR spectroscopy – whole-head metabolite quantification

All experiments were done in a 3 T MR scanner (Trio, Siemens AG, Erlangen, Germany) with a circularly-polarized transmit-receive head-coil (TEM3000, MR Instruments, Minneapolis, MN). Each subject was placed head-first supine into the magnet, and its field homogeneity adjusted using the scanner’s 1st and 2nd degree shims automatically with non-iterative $\mathbf{B}_0$ map based shimming (Bolero - “B0 loop encoded readout”) that included the whole brain from the vertex to the brainstem, excluding all other non-brain head tissue [17]. The global amounts of NAA, Glx, Cr and Cho were then obtained with a non-localizing, $TE/TI/TR = 0/940/10^4$ ms ^1H -MRS sequence, whose structure and principles of operation are described in detail elsewhere [11,12]. Its long $TR \gg T_1$ and short $TE \approx 0$ minimize its sensitivity to metabolites’ typically unknown T_1 and T_2 variations [18].

The ^1H -MRS spectral fitting were performed with Versatile Simulation, Pulses and Analysis (VeSPA) software (available at: <https://scion.duhs.duke.edu/vespa/project> [12,19]). The VeSPA-Analysis application extracted the ^1H -MRS data from the scanner’s file format and applied a standard set of preset processing and spectral fitting parameters: even time-signals were subtracted from odd, the 8 pairs summed and the spectral data fitted parametrically using an automated algorithm [12,20,21]. The metabolites’ basis set for the parametric fit (synthesized with the VeSPA-Simulation application using the actual radio-frequency pulses and timings from the WBNA sequence), comprised total-NAA (NAA+NAA-glutamate at 7:1 ratio [22]), Glx, total-Cho, total-Cr and *myo*-inositol, as shown in Fig. 1. The *inter*- and *intra*-subject WBNA signal variability with this approach has been shown at $\pm 12\%$ and $\pm 7\%$ [12]. Since only within-subject metabolite *changes* are sought, percent changes in peak areas for each metabolite was obtained without normalizing for brain volume:

$$\frac{p_j - p_1}{p_1} \cdot 100, \quad j \neq 1$$

where p_1 is the baseline value and p_j any subsequent scan’s value for that metabolite. Note that this metric has the advantages that it is (a) units-free; (b) independent of a subject’s head or brain sizes; and (c) requires neither of the volumes to be segmented from the MRI.

Acquisition strategy

We wish to assess both *intra*- (back-to-back in a single session) and *inter*-scan (acquired at different times) reproducibility. The former accounts for post-processing (intrinsic) noise,

whereas the latter contains the former plus additional possible instrumental variations, *e.g.* scanner gain. To obtain the *intra*-scan variations, four back-to-back whole-head ^1H -MRS scans (~10 minutes total) were performed without moving the subject or changing any measurement parameters for all 18 participants. To quantify the *inter*-scan variation, 13 subjects were also taken out of the magnet for ~15 minutes and then repositioned back in to undergo the same protocol with only one ^1H -MRS acquisition, two more times. To ascertain changes over longer periods, which may also include biological “noise,” five additional subjects were scanned three times, each a week apart.

Statistical analyses

Since the direction of metabolic changes in a given already diagnosed disease are known *a priori*, one-sided statistics are appropriate to determine when a metabolite’s change exceed its prediction interval’s (PI) upper limit, indicating that a subject is most likely not from the sampled population. Assuming the within-subject differences follow a normal distribution, a PI with coverage probability $1-\alpha$ can be constructed for each metabolite using the standard formula:

$$\text{PI} = \bar{X} \pm S \sqrt{1 + \frac{1}{n}} T_{n,\alpha}$$

where S denotes the sample SD, n is the sample size and $T_{n,\alpha}$ is the critical value such that a random variable T following a t distribution with $n-1$ degrees of freedom has probability $\alpha/2$ of being greater than $T_{n,\alpha}$. Since the magnitudes of the changes are inherently non-negative, one-sided PIs can be constructed as: Left-sided: $[X_L, \infty)$; Right sided: $[0, X_R]$, where:

$$X_L = \bar{X} - S \sqrt{1 + \frac{1}{n}} T_{n,\alpha} \quad ; \quad X_R = \bar{X} + S \sqrt{1 + \frac{1}{n}} T_{n,\alpha}$$

These represent a PI for the expected change for that metabolite within a single subject from the sampled population. Note that for the purpose of this study, we expect no concentration changes in our cohort of healthy young subjects.

RESULTS

The auto-shim procedure yielded 25 ± 3 Hz whole-head water linewidths in under 5 minutes. Given the high SNR of the whole-head ^1H -MRS signals, VeSPA analysis spectral fitting yielded Cramer-Rao lower bounds $\ll 1\%$ for all metabolites in all subjects. The *intra*-scan (back-to-back) NAA, Glx, Cr and Cho coefficients of variation ($\text{CV} = \text{SD}/\text{mean}$) for all 18 participants were: $3.9 \pm 1.8\%$, $7.3 \pm 4.6\%$, $4.0 \pm 3.4\%$ and $2.5 \pm 1.6\%$ (mean $\pm$ SD). The *inter*-scan CVs for the three measurements separated by 15 minutes in each of 13 subjects were: $7.5 \pm 3.8\%$, $11.3 \pm 5.6\%$, $8.1 \pm 4.3\%$ and $8.3 \pm 5.7\%$; and for the three scans, each a week apart, in 5 more subjects: $6.5 \pm 3.0\%$, $10.1 \pm 4.4\%$, $6.6 \pm 3.8\%$ and $5.0 \pm 4\%$. Since these two groups’ CVs are $\sim 1\%$ apart, much smaller than even the intrinsic *intra*-scan CV, and an unpaired t -test between them revealed no significant differences, therefore the two groups were pooled, yielding *inter*-scan CVs of $7.0 \pm 3.1\%$, $10.6 \pm 5.6\%$, $7.6 \pm 3.5\%$ and $7.0 \pm 3.9\%$, as shown in Fig. 2. The resulting prediction intervals for the least changes detectable for NAA, Glx, Cr and

Cho with 80%, 90% and 95% power, are compiled in Table 1. Based on the estimates of the SD for the within-subject changes, a table of the sample sizes needed to achieve 80% or 90% power to detect 10%, 15% and 20% mean within-subject change from baseline to follow-up, is compiled in Table 2.

DISCUSSION

MR-derived metrics are increasingly being used as biomarkers in diagnoses, management and in clinical trials of neurological disorders [7,23,24]. To be useful, a marker needs to be: (a) easy to implement, (b) clinically meaningful, (c) pathology specific, (d) reproducible and (e) sensitive to temporal changes [25]. Since whole-head ^1H -MRS takes under 3 minutes to acquire and requires minimal post-processing, it meets requirement (a). Points (b) and (c) have already been well-established [7,23,24]. Our goal, therefore, is to examine and quantify the method with respect to the remaining requirements: (d) which implicitly defines (e).

Since its inception, the WBNA method suffered two central limitations. First, total partial volume admixture, due to complete lack of localization except implicitly to just the brain [11]. Second, although the other whole-head spectrum visible metabolites' concentrations, *e.g.*, Glx, Cr, and Cho are often sought for added specificity to MRI and clinical diagnoses [1,2,24], the brain's contributions to their signal could not be distinguished from the head's other tissue types [8,11,12]. Here we address this issue by leveraging the fact that, in studies of the mostly chronic neurological disorders, (i) there often will be follow-up ^1H -MRS; and (ii) it can be assumed that these disorders affect just the brain and not other head tissue physiology. Specifically, we show that from two or more follow-up scans we can ascribe the non-localized whole-head *inter-scan changes* also for Glx, Cr, and Cho (and not only the NAA) to evolving brain pathology.

The prediction intervals obtained beg the question whether they delineate sufficient sensitivity to global changes that are actually observed in various neurological disorders. Specifically, whether the overall magnitude of the % changes from assumed "healthy" at baseline to the reported values for patients with the disease would put an individual outside the PIs reported in Table 1. (The time needed to "build up" this change, which is typically not reported in the literature, is discussed in the limitations section below). Indeed, 14% NAA changes detectable with 80% power between two measurements is sufficient for the global >40% declines reported in multiple sclerosis (MS), 26% in primary brain tumors [26], 20% in Alzheimer's disease (AD) [8,27,28], 10–20% in HIV [29,30] and 20–50% in its associated dementia [31,32]. Similarly, the 19% Cho change detectable with 80% power is sufficient to monitor the substantial elevation reported in AD [33,34], >30% increase in MS [35], 10–50% in HIV and HIV associated dementia [29–32] and well upwards of 30% in large progressive multifocal leukoencephalopathy (PML) lesions that spread quickly through the brain [36,37]. Diffuse Cr changes on the order of its 26% prediction interval have also been seen, *e.g.*, a 22% increase in MS [35]; and >90% decreases in Cr deficiency syndromes [38].

Furthermore, when metabolite *ratios* are considered, in primary brain tumors, 30% and 70% changes have been reported in NAA/Cr and Cho/Cr that extend beyond the mass into regions

of perifocal edema and even distant normal-appearing white matter [39]. In the normal appearing tissue in the contralateral hemisphere, NAA/Cr and Cho/NAA changes of 15–25% have also been reported, suggesting a diffuse infiltrative component throughout the brain [23,40].

Note that the *intra*-scan CVs are, as expected, very low, all <5% and all approximately half the *inter*-scan ones for that metabolite. This suggests that there is little added-value to the precision from collecting back-to-back scans and averaging their outcomes. Rather, the ability to acquire a robust and relevant ^1H -MRS measurement in under 3 minutes, *i.e.*, adding little overhead to a typical clinical MRI of patients with neurological disorders, is the primary advantage gained.

Admittedly, the proposed methodology is also susceptible to several intrinsic limitations: First, is the lack of localization remains and with it the inability to discern regional from multi-focal from global diffuse pathology, forcing the assumption that changes are uniform over the whole brain. Second, no localization also precludes local or regional corrections for static, $\mathbf{B}_0$, and radio-frequency, $\mathbf{B}_1$ variations. However, it has been shown that $\mathbf{B}_0$ inhomogeneity leads to just ~10% signal underestimation, mostly near the air filled sinuses and auditory canals [13]; and the up to $\pm 15\%$ $\mathbf{B}_1$ variations over the head affect quantification negligibly [12]. Third, this application requires at least two acquisitions separated by enough time for the metabolites to change by more than the prediction interval, which, in some diseases, such as high-grade primary brain tumors, may be just months, and in other diseases, *e.g.* MS, may take years. Fourth, the underlying assumption of no change in non-brain head tissues in neurological disorders may not always be correct, *e.g.*, Amyotrophic Lateral Sclerosis and stroke affect the facial muscles, as do various myopathies.

CONCLUSIONS

Limitations notwithstanding, by monitoring the serial changes in NAA, Glx, Cr, and Cho concentrations, whole-head ^1H -MRS can be an effective tool in assessment of neurological disorders' progression and treatment response. This is especially germane to clinical applications, given the established sensitivity in a single individual (versus group effects). Combined with acquisition speed, SNR, global spatial coverage (*i.e.*, immunity to serial misregistration), long TR and short TE , which minimize unknown T_1 - and T_2 -weighting variations in pathologies, this method is well-suited to monitor diffuse neurological disorders.

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Fig. 1.

VeSPA analysis of three serial (*inter-scan*) whole-head ^1H -MRS from a 35-year-old male.

Top, a: The raw spectrum and the NAA, Glx, Cr, Cho and *myo*-inositol (mI) model functions used in the VeSPA analyses, all on the same intensity and chemical shift scales.

Center, b: Raw data overlaid with VeSPA fitted baseline and model functions in a. Bottom, c: Residual from the difference between the “fitted+baseline” and “raw” data. Note the effective lipid suppression performance of the sequence, the exceedingly high SNR, reflecting signal from the entire head, the visually similar raw data between the three serial scans, reflecting the repeatability of the sequence, and the near vanishing residual, reflecting the goodness of VeSPA’s spectral modeling performance.

Fig. 2.

Box plots showing the first, second (median) and third quartiles, $\pm 95^{\text{th}}$ percentiles (whiskers), outliers (*) and means (+) of the *inter-scan* measurement (white) and *intra-scan* measurement (gray) mean CV distributions of the four metabolites in $N=18$ subjects. Note that: (i) all metabolites' *inter-scan* CVs are typically lower than 10%; and (ii) the *intra-scan* CVs are, as expected, much lower ($<5\%$) than the *inter-scans*', leading to the prediction intervals in the Table 1.

Table 1

One-sided 95, 90 and 80% Confidence Intervals (CI) to detect a relative % changes in NAA, Glx, Cr and Cho in any given subject at the indicated Power.

Power	NAA	Glx	Cr	Cho
95%	30%	42%	41%	32%
90%	21%	35%	34%	25%
80%	14%	27%	26%	19%

Estimated sample size (number of subjects) needed to achieve 80% or 90% power to detect a mean within-subject change of 10%, 15% and 20% from baseline to follow-up.

Table 2

%Change	10%		15%		20%	
	80%	90%	80%	90%	80%	90%
Power Metabolite						
NAA	17	22	9	11	6	8
Glx	43	57	21	27	13	16
Cr	33	43	16	21	10	13
Cho	23	30	12	15	8	10