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Localized MRS reliability of in vivo glutamate at 3 T in shortened scan times: a feasibility study – Efforts to improve rigor and reproducibility

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Dear Editor,

We appreciate the opportunity to respond to the letter to the editor entitled, "*Localized MRS reliability of in vivo glutamate at 3 T in shortened scan times: a feasibility study – Methodological and statistical issue to avoid misinterpretation and mismanagement*" from Dr. Iranpour and Dr. Sabour[1], which was submitted in response to our publication in NMR in Biomedicine[2].

In recent years, there has been renewed interest in neural markers of psychopathology, which could be used to better parse the substantial heterogeneity of psychiatric disorders (e.g.,[3–6]) or predict treatment response (e.g.,[7,8]). A key methodological requirement for these endeavors is to use reliable assessments, which represents a *sine qua non* for the validity of any measurement. Toward this goal, in our recent publication in NMR in Biomedicine, we evaluated the test-retest reliability of glutamate and other metabolites levels, as estimated by a shortened and optimized magnetic resonance spectroscopy (MRS) protocol[2].

In their letter to the editor, Drs. Iranpour and Sabour offer helpful recommendations to improve evaluations of the test-rest reliability and stability of 6-minute J-resolved MRS

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Additional information: The first author of the original publication (Dr. John E. Jensen) died on August 8, 2017. The coauthors wish to dedicate this publication to him and the central role he played in this project.

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scans. Namely, it was suggested that the utilization of a repeated measure analysis of variance (RMANOVA) and Pearson correlations may not be sufficient to determine reliability and stability, and rather, these analyses would benefit from complementary analyses estimating the intraclass correlation coefficient (ICC). In line with their suggestion, we have calculated the ICC for all metabolites originally evaluated. ICC values were computed in SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) using two-way mixed models with absolute agreement. Table 1 summarizes results of the ICC calculations, along with the two metrics we had reported in our publication (see Table 2 in ref.[2]). All metabolites that had shown a percent difference (%diff) between scan 1 and scan 2 smaller than 10% were characterized by ICC values ranging from good (glutamate: ICC = 0.803) to excellent (N-acetylaspartate: ICC = 0. 975) (Table 1). Notably, although the mean % difference for N-acetyl-aspartyl-glutamate (19.53%) and scyllo-inositol (26.96%) was high, the new calculations suggest that these two metabolites have good to excellent test-retest reliability as measured by ICC (0.845 and 0.855, respectively). Collectively, these new analyses show that a brief J-resolved technique offers a reliable way to probe metabolites implicated in a wide range of mental disorders. Of note, the five metabolites we had highlighted in our original publication as showing adequate inter-scan variability (see metabolites highlighted with an asterisk in Table 1) all showed good to excellent ICC.

As a minor point of clarification, the Cohen's kappa coefficients included in the published manuscript reflect inter-rater reliability since the interviews were administered only once. As we agree with Drs. Iranpour and Sabour that Cohen's kappa coefficients are ill-suited for determining reliability of test-retest comparisons, we had not performed or reported such analyses for evaluating the reliability of the clinical diagnoses.

Taken together, we are appreciative of the feedback provided by Drs. Iranpour and Sabour, as we strongly believe that these dialogues are important for the scientific field. Through these constructive conversations, we can move closer to ensuring that methods employed strive for rigor and maximal reproducibility.

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Table 1.

Summary of metrics testing the reliability and stability of MRS-based metabolite levels among healthy adolescents ($n = 22$)[2]

Metabolites	ICC	ICC 95% CI	% Difference	Pearson *r*	*p*-value
Asp	−0.317	−2.470 – 0.472	13.28	−0.130	0.564
Cho *	**0.823**	**0.560 – 0.928**	**7.29**	**0.747**	**$<10^{-5}$**
GABA	−0.578	−2.550 – 0.325	43.98	−0.246	0.269
Glu *	**0.803**	**0.535 – 0.917**	**6.93**	**0.680**	**$<10^{-4}$**
Gln	0.395	−0.370 – 0.742	21.34	0.286	0.197
GSH *	**0.896**	**0.753 – 0.957**	**8.60**	**0.821**	**$<10^{-5}$**
Gly	−0.084	−1.675 – 0.554	45.05	−0.041	0.857
mI *	**0.843**	**0.625 – 0.935**	**6.48**	**0.748**	**$<10^{-4}$**
NAA *	**0. 975**	**0.941 – 0.990**	**3.47**	**0.953**	**$<10^{-11}$**
NAAG	0.845	0.600 – 0.938	19.53	0.774	$<10^{-4}$
Scy	0.855	0.647 – 0.940	26.96	0.738	$<10^{-4}$
Tau	0.682	0.217 – 0.869	30.21	0.530	0.011
Lac	−0.091	−1.639 – 0.548	35.77	−0.048	0.832

Note: Asp: aspartate; Cho: choline; GABA: γ-aminobutric acid; Glu: glutamate; Gln: glutamine; GSH: glutathione; Gly: glycine; mI: myo-inositol; NAA: N-acetylaspartate; NAAG: N-acetyl-aspartyl-glutamate; Scy: scyllo-inositol; Tau: taurine; Lac: lactate. *P*-values for Pearson *r* correlations.

*Metabolites that showed a percent difference (%diff) between scan 1 and scan 2 smaller than 10% in Jensen et al.[2], as assessed by the formula: %diff = (scan2 – scan1) / mean(scan2, scan1) x 100%. CI: Confidence Interval