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To the Editor:

The article by Kraguljac and colleagues presents a potentially important finding on the association between hippocampal glutamate levels and hippocampal morphology[1]. However, one aspect of the article requires correction. The authors report a significant positive correlation (r= +.39) between NAA/Cr and Glx/Cr in normal subjects that is lost in schizophrenia patients (r= -.19). Unfortunately, using "zero" correlation as the null hypothesis here is incorrect, since Glx/Cr and NAA/Cr are not independent numbers. Both include the Cr value in their denominator.

The statistical problem of correlations between such ratios (*P*) was identified by Pearson in 1897, who coined the term "spurious correlation" to describe it[2]. Pearson showed that for any three uncorrelated series of numbers (*x, y,* and *z)* with equal coefficients of variation (CoV), the calculated correlation *P* between *x/z* and *y/z* = 0.5. This relation can be inferred from Pearson's equation below (*r*= correlation between *x* and *y*, and *r'*= correlation between *x* and *z* and between *y* and *z* (which are assumed to be equal)):

(1) $$P = .5 + .5((r - r')/(1 - r'))$$

The null hypothesis will vary when these simplifying assumptions are not met. The following equation[3] applies when the CoVs of *x* and *y* are assumed equal while the CoV of *z* varies as some multiple "*a*" of that value, i.e. $CoV_x = CoV_y$ and $CoV_z = aCoV_x = aCoV_y$. Thus:

(2) $$P = (r + a^2 - 2ar')/(1 + a^2 - 2ar')$$

Using conservative assumptions about *a* and *r'* (i.e. $0.8<a<1.0$ and $-0.2<r'<0.2$), the value *P*= .39 reported by the authors in normal subjects approximates the null hypothesis, suggesting no true correlation between NAA and Glx in normal hippocampus. In contrast, the value *P*= -.19 in the patient

group appears significantly more negative than the null hypothesis, suggesting an inverse correlation between hippocampal NAA and Glx in patients. Furthermore, since *P* is substantially lower in patients than controls, one can infer a significantly more negative correlation in patients than controls (assuming similar values for *a* and *r'* in the two groups). The CoVs of metabolite ratios (supplementary eTable 2) provide additional relevant information. These will be relatively low when the numerator and denominator are positively correlated and relatively high when they are negatively correlated. Of the eight CoVs presented, the highest is for Glx/NAA in patients -- almost two standard deviations above the mean of the others. The Glx/NAA CoV in control subjects is near the mean. Altogether, these observations support the inference that a true negative correlation exists between hippocampal NAA and Glx in unmedicated schizophrenia patients, and not in normal volunteers. This converges with their volumetric finding and supports a model in which elevated hippocampal glutamate is associated with both structural and metabolic changes in unmedicated schizophrenia patients. Future studies examining correlations between MRS metabolites measured in the same voxel must take into account the problem of spurious correlation.

Citations

1. Kraguljac NV, White DM, Reid MA, Lahti AC. Increased Hippocampal Glutamate and Volumetric Deficits in Unmedicated Patients With Schizophrenia. *JAMA Psychiatry*. 2013;Published online October 9, 2013.

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3. Kuh E, Meyer JR. Correlation and Regression Estimates when the Data are Ratios. *Econometrica*. 1955;23:400-416.