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Science **321**, 640d (2008);
DOI: 10.1126/science.1153997

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Comment on "Magnetic Resonance Spectroscopy Identifies Neural Progenitor Cells in the Live Human Brain"

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Manganas *et al*. (Reports, 9 November 2007, p. 980) reported the discovery of a biomarker specific for neural progenitor cells detectable using magnetic resonance spectroscopy. A new algorithm was developed to extract the biomarker from noisy in vivo data. We question how this algorithm was validated, because the biomarker overlaps with peaks from nonspecific lipid signals.

Manganas *et al*. (*1*) reported the discovery of a biomarker specific for neural progenitor cells (NPCs) detectable using magnetic resonance spectroscopy (MRS). Their findings, if reproduced independently, could have a major impact in clinical neurology and psychiatry, in particular for diseases exhibiting altered neurogenesis such as depression and mood disorders.

Manganas *et al*. reported that the 1.28-parts per million (ppm) biomarker is detectable using a standard clinical spectroscopy setup, by using a detection algorithm based on singular value decomposition (*2*). We have reservations toward the reported results, because it is unclear how accurately their detection technique has been validated. This algorithm is of key importance for the successful detection of the 1.28-ppm biomarker in noisy in vivo data. Therefore, more information on the quality of the original in vivo spectral data [in terms of signal-to-noise ratios (SNRs)] and the performance of the detection algorithm is highly desirable. For any quantification method, it is advisable to report error estimates and/or reproducibility values, in particular when they are presented as new. In this regard, specific data on the Cramer-Rao bounds, which give insight into the potential performance of quantitation estimators (*3*), would have been particularly useful.

Another concern is how the 1.28-ppm peak can be distinguished from nonspecific lipid signals. These lipid signals are typically present in in vivo spectra and have peaks that occur in this region (~1.3 ppm) of the spectrum. Furthermore, the intensities of these signals may vary among healthy individuals and are certainly known to vary among different brain regions (*4*). We believe that separation of the biomarker at 1.28 ppm and normal lipid signals at 1.3 ppm is essential for interpretation of the reported findings. MRS spectra from the hippocampus typically are of inferior quality to spectra from the cortex and display worse SNR properties (*5*). Therefore, we wonder if the detected differences in quantities of the biomarker within these regions could be due to nonspecific artifacts. An assessment of the effect of the spectral quality (i.e., SNR) on the detected concentration of the biomarker could be used to determine whether the SNR negatively influences the detection method at all (*6*). By performing these additional analyses on Cramer-Rao bounds and SNR effects, it is very likely that one may eventually rule out the possibility that the quantified differences were due to artifacts and not due to differences in quantities of the biomarker after all. However, until then, the results should be interpreted with great caution.

Our reservation toward the interpretation by Manganas *et al*. (*1*) is further supported by our published data on MRS spectra of metabolite extracts and lipid extracts of NPCs. We did not find any observable peak at 1.28 ppm of such a putative biomarker (*7*). We consider it highly unlikely that the difference between our cell preparations [NPCs enriched from embryoid bodies derived from mouse embryonic stem (ES) cells] and theirs (NPCs from fetal mouse brain) would form the basis for this discrepancy. If the result by Manganas *et al*. is validated, it not only represents a major technological breakthrough, but—based on our previous findings (*7*)—must also reveal a fundamental difference between ES-derived NPCs and those isolated and grown from the developing or regenerating brain.

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10 December 2007; accepted 2 July 2008
10.1126/science.1153997

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