PET assessment of brain metabolic recovery in aphasia

The paper by Cappa et al. deals with the important issue of the mechanisms of recovery from aphasia. The authors longitudinally assessed two patients both neuropsychologically and by $^{18}F$-2-fluoro-2-deoxy-D-glucose ($^{18}$FDG) PET measurements of the local cerebral metabolic rate of glucose (LCMRGl). Each patient was studied twice with a three-month interval. The LCMRGl values (19 brain regions on each side) were assessed for significant abnormalities at each study by comparison with values from a group of seven healthy subjects, while changes in LCMRGl from first to second PET study were assessed in each patient individually by an analysis of variance with one between-factor (acute and chronic stage) and one within-factor (left and right hemisphere). The authors conclude that (1) significant reductions in LCMRGl of many brain regions were present in both patients at initial evaluation, and in one patient at second evaluation only; (2) there was a significant increase in LCMRGl from first to second evaluation in each of the two patients.

We wonder whether the statistical procedures used were appropriate. Firstly, regarding the comparison with the control group, Cappa et al. used two standard deviations below control mean as the cut-off for $p < 0.05$; however, since the control group consisted of seven subjects, the two-tailed $t$ value for six degrees of freedom, or $t = 2.477$, should have been used instead. As this value is substantially larger than 2.0, it is likely that several of the LCMRGl values listed in tables 1 and 2, as statistically significantly reduced were, in fact, not. In addition, the authors do not acknowledge the fact that there is a multiple testing problem as they are simultaneously assessing the significance of 19 $t$-values. Secondly, the analysis of variance procedure used to assess changes in LCMRGl from one study to the next in each subject is of serious concern. Apparently, it was run on the following regions for each hemisphere (20 regions for each side, two determinations), and yielded inordinately low probability levels (down to $< 0.0001$) for single subject studies. Their way of using the analysis of variance in this and other studies would appear inadequate and possibly misleading. The authors do not point out the fact that region must also be a within-subject factor. In the case of measurements of LCMRGl, there exists a global scaling factor (the mean brain CMRGl), itself influenced by both physiological and methodological factors, that affects all regional values of a given subject. Thus, in the comparison of the two sets of LCMRGl data obtained in a single subject at two sequential studies, any change in this global factor will be repeated over all brain regions. As the more regions analysed, the larger the degrees of freedom and, in turn, the more statistically significant the findings. One way of turning around this problem would have been to carry out this global factor by, for example, an analysis of covariance.

When studying the changes in brain metabolism in a longitudinal fashion, more appropriate ways of testing whether a significant change in LCMRGl has occurred from one investigation to the next would be to assess each brain area either across a sufficiently large group of patients or, in single subjects, by following the numerical changes observed against confidence limits established for the same region in a set of control subjects studied twice at similar time intervals (that is, confidence limits for reproducibility). The results presented by Cappa et al. regarding recovery of LCMRGl must therefore be taken as descriptive only, pending confirmation from a better designed investigation.
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*J Neurol Neurosurg Psychiatry* 1994 57: 663
doi: 10.1136/jnnp.57.5.663

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