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Memory decline from hippocampal electrodes? Let's not forget statistics and study design

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To the Editor

We have significant concerns regarding the manuscript by Ljung et al.¹ recently published in *Epilepsia*, entitled “Verbal memory decline from hippocampal depth electrodes in temporal lobe surgery for epilepsy.” In this study, the authors examined neurocognitive performance in patients with epilepsy who received video–electroencephalography (EEG) monitoring with or without intracranial implants, including left hippocampal depth electrodes. They report verbal memory deterioration in 56% of 16 patients who received intracranial monitoring, and conclude that there is a direct causal link between left hippocampal electrodes and neurocognitive decline. This conclusion implies that temporary hippocampal electrodes convey a risk of verbal memory decline even greater than that associated with left hippocampal removal in epilepsy surgery.² Moreover, it is inconsistent with studies of long-term hippocampal depth electrode placement for responsive neurostimulation treatment, in which no patients showed diminished, but many showed improved, verbal memory performance.³

Of greatest concern, the article by Ljung et al. has substantial statistical and analytical flaws that limit drawing any sound conclusions:

- *Lack of statistical correction and power.* The authors perform 19 univariate statistical tests to compare neuropsychological test results between the study and reference groups, but do not correct for multiple comparisons, leading to a 62.6% likelihood of uncovering spurious “significant” differences. The smallest *P*-value (.03) reported by the authors is approximately 10 times what would be required for significance using the Bonferroni correction method (0.0027), suggesting no

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None. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

significant differences. Furthermore, the small patient sample makes the study grossly underpowered to perform 19 comparisons.

- *Unmatched groups.* The “matched” patient groups are poorly matched. Study group patients were 10 years older ($P = .009$), had a longer duration of time between neuropsychological evaluations ($P = .05$), and had higher initial naming scores ($P = .02$). Furthermore, although all the study group patients received intracranial monitoring, none of the reference group subjects did. Inherent disease-related differences are likely in patients requiring intracranial monitoring, and the specific need for left hippocampal electrodes itself suggests a higher suspicion of left mesial temporal lobe epilepsy.
- *Inappropriate patient pooling.* One fourth of the subjects had right temporal lobe resection prior to final neurocognitive testing. These should be excluded from both patient groups if the goal is to evaluate the effects of intracranial electrodes alone.
- *Selection bias.* After patient attrition or removal, only 33%–36% of “eligible” patients remained in each group, suggesting significant selection bias that limits the interpretability of any group differences.
- *Flawed interpretation.* It is scientifically inappropriate to invoke causation in an uncontrolled study examining associations (eg, “This study showed a risk of verbal memory deterioration from longitudinal hippocampal depth electrodes. . .”). It is also unclear how the authors conclude that neurocognitive changes were specifically related to left hippocampal electrodes, when all patients in the study group had intracranial electrodes in multiple locations.

Intracranial monitoring with depth electrodes is associated with low complication rates and often provides important localizing information necessary for safe and effective epilepsy surgery.^{4,5} While Ljung et al. argue that “caution regarding depth electrodes in the language-dominant hemisphere hippocampus seems advisable,” the data that they present do not support this recommendation.

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