Correspondence

Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD

To the Editor: Xu et al. report that they failed to prove the hypothesis that MRI-derived measures of the entorhinal cortex (EC) are superior to hippocampal measures in the early diagnosis of AD.[1] They compared their published MRI hippocampal volume method against their adaptation of two published anatomically validated MRI methods to evaluate the EC. The first EC method, developed by Insausti, was a volume determination.[2-4] The second method, developed at New York University, measured the surface area of the EC. Xu et al. concluded that little difference was observed between the measurements, and that after considering the anatomic ambiguities and artifacts associated with EC measurement, overall, the hippocampal measure was preferred.

As the authors of the two prior MRI-EC publications, we are writing to express our concern that Xu et al. did not correctly employ our methods and, therefore, that their conclusion is premature.

By taking the rostral limit of the hippocampus as the anterior boundary of the EC, one neglects a considerable anterior portion of the EC (figure).

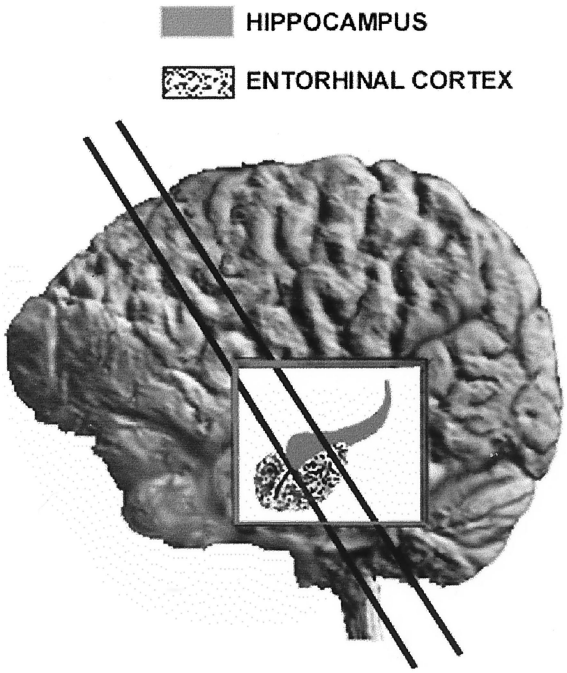

Figure. MRI depicts size, shape, and orientation of the entorhinal cortex (EC) and the hippocampus. The fraction of the EC examined by the Mayo group (between the two parallel lines running perpendicular to the long axis of the hippocampus) is compared with the total EC previously defined.[3,5]

Our articles reference the frontotemporal junction (limen insula) to identify the rostral boundary (not the sulcus semiannularis, as misstated by Xu et al). Furthermore, by using the crural cistern rather than the sulcus semiannularis as the superiomedial boundary of the EC, in the anteriormost sections one further neglects the periamygdala portion of the EC. It was stated that the basis for this decision was that the sulcus semiannularis was not always clearly depicted. We offer that their apparent difficulty is related to section angulation. The coronal plane of section used by Xu et al. was orthogonal to the long axis of the hippocampus, not, as we had published, to the AC-PC line. This results in sections that differ in orientation by 30–40 degrees, altering the appearance and the extent of anatomy sampled.

In seven patients we estimated the effect of the modifications to the surface area method. The modification undersampled the rostrocaudal length of EC by about 1 cm of a total of approximately 2.5 cm, and underestimated the surface area by 46% (range −37% to −59%).

The hypothesis that the anatomic sequence of AD affects the EC prior to the hippocampus remains to be adequately addressed by MRI.

Mony de Leon, Maciek Bobinski, Antonio Convit, *New York, NY*, Oliver Wolf, *Duesseldorf, Germany*; Ricardo Insausti, *Pamplona, Spain*

Reply from the Authors: de Leon et al. indicate that by selecting the anterior border of the EC to be coincident with the anterior excursion of the hippocampal head, our entorhinal measurements do not include the anterior portion of the histologic entorhinal cortex. We agree with this comment.

The reason that we selected that landmark as the anterior boundary of the entorhinal cortex was to improve the precision of our measurements. Using the method of de Leon et al.[3,5] the supra medial border of the anterior portion of the EC is defined by the sulcus semiannularis. We were unable to clearly see the sulcus semiannularis on MRI slices in a significant portion of our subjects and hence elected to use the boundary criteria in our article that in our hands were more reliable.[1]

de Leon et al. claim that the sulcus semiannularis is more clearly depicted if the MRI data are reformatted perpendicular to the AC-PC line than if the data are oriented perpendicular to the long axis of the hippocampus. In response to this comment, we reformatted several cases both ways and were unable to confirm the contention that the angle at which the data are reformatted has a significant impact on the visibility of the sulcus semiannularis. What we find is that on the MRI sections just posterior to the position of the limen insula, it is typically very difficult, if not impossible, to identify the sulcus semiannularis, regardless of the orientation of the reformatted data. Therefore, we disagree with de Leon et al. on this point. Interested readers may want to replicate the simple experiment we describe above and decide for themselves.

The fact that AD pathology begins in the EC and not the hippocampus, and therefore entorhinal cortical MRI measures should in theory be more sensitive to the earliest changes of AD, is not in dispute. In our study, however, we failed to find that entorhinal measures could discriminate controls from patients with mild cognitive impairment better than hippocampal measurements.[1] We attribute this largely to the greater difficulty with precise boundary definition for the EC than for the hippocampus. In fact, the group that has published most extensively on MRI-entorhinal volume measurements concluded precisely this. We quote from an article by Juottonen et al: "The volumetric measurements of both the entorhinal cortex and hippocampus have comparably high discriminative power in diagnosing Alzheimer's disease. In clinical practice, hippocampal volumetry may be more feasible, because the method is easier to use and has less variability."[6]

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Table *Patient data*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age, y/sex	58/M	24/F	15/M	33/M
Structural lesion	Left parietal stroke, age 58	Traumatic right frontal porencephaly, birth	Left frontal cysticercus, age 15	Gunshot wound, right parietal, age 32
Clinical or EEG evidence of true epileptic seizures	No	No	No	No
Side of neurologic deficit	Right hemiparesis and aphasia	Mild left hemiparesis	Right pronator drift	Left hemiparesis
Side of symptoms during the episodes	Tremors/shaking right arm	Difficulty moving left arm, followed by side to side head and torso movements	Stiffening of the body followed by generalized jerkings of extremities	Left-sided weakness and left shoulder and arm jerkings
Aura/triggers	Yes/stress—public places	Yes/argument with mother	No/no	Yes/bright lights
Frequency of episodes	Several times a week	One episode every 3–5 d	One episode every 2–3 mo	Initially 8–10 episodes/d; frequency decreased to once every 2–3 mo
Duration of episodes	Minutes to hours	Minutes; rarely 1 h	20–60 min	Most last 2–5 min; rarely >15 min
Onset of episodes after injury	3 mo	19 y	5 wk	5 d
EEG abnormalities	Left hemispheric slow	Focal slow, right frontal	No	Focal slow, breech rhythm, right parietal
Epileptogenic EEG abnormalities	No	No	No	No
Seizure induction	Positive	Positive	Positive	Positive
Change in symptoms with AED treatment	No	Transient improvements	No	No
Psychosocial issues	Lost job; marital problems	Social withdrawal	Academic difficulties; high parent expectations	Unemployed; cared for by parents
Psychiatric diagnosis	Anxiety disorder without panic features	Conversion disorder	Anxiety disorder	Adjustment disorder, conversion disorder

and perirhinal cortices in Alzheimer's disease. Neurobiol Aging 1998;19:15–22.
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Transplantation of cultured human neuronal cells for patients with stroke

To the Editor: Kondziolka et al.[1] report the results of a study in which LBS-Neurons were transplanted into the brains of 12 stroke patients. LBS-Neurons are produced from a cell line, derived from human teratocarcinoma by Layton Bioscience (LBS) (Atherton, CA). Although this study may prove a landmark in the clinical management of stroke, the conclusions drawn by the authors should be viewed with caution.

The choice of cells for this therapy raises serious concern. LBS-Neurons are theoretically capable of unlimited proliferation but are treated "in the dish" with retinoic acid to induce differentiation into postmitotic neurons prior to transplantation. The methods by which these cells are considered postmitotic are not described by Kondziolka et al. After transplantation, recipient patients were immunosuppressed for 8 weeks. The authors report no adverse events after the procedure as assessed by "laboratory, radiographic, or electrocardiographic abnormalities" over a period of 12 months. However, a closer reading of the text reveals that the radiologic assessment consisted of MRI performed at 24 weeks and PET scans performed at 24 and 52 weeks. Such radiologic assessment seems scanty and does not include MRI at 52 weeks. Why a 12-month period should be chosen as the time frame to determine that this procedure is safe is also dubious; most patients would not be considered "cured" of a treatable malignancy for at least 5 years.

An increase in ^{18}fluorodeoxyglucose (FDG) uptake was noted in six of the patients. The authors claim that this suggests the presence of viable cells. Another explanation could be the presence of inflammatory cells in reacting to the graft. It is certainly an inadequate test on which to conclude there is graft survival.

Neurologic outcome was based on National Institutes of Health Stroke Scale, European Stroke Scale (ESS), Barthel index, and SF-36 scale scores which were assessed prior to transplantation and again at 24 weeks. The authors claim a "significant improvement in function" as based on an average 2.9-point increase in ESS score. However, it would be reasonable to expect such an improvement in functional outcome in a group of stroke patients regardless of whether or not they underwent a transplantation procedure. Without a properly designed trial, it is impossible to ascribe any such improvement to the transplanted cells, if indeed to make any functional connections.

We are concerned that this study does not satisfactorily ad-

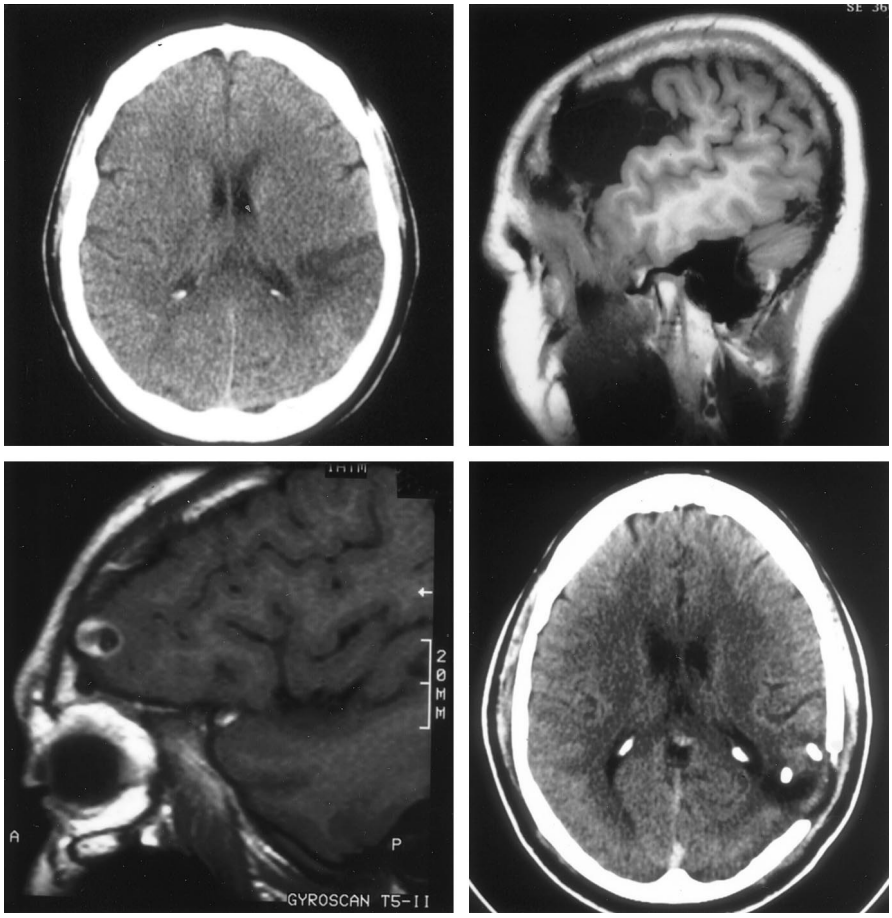

Figure. MRI and CT findings of four patients with "intractable seizures" and CNS lesions referred for epilepsy surgery who were found to have psychogenic seizures only. Patient 1: wedge-shaped stroke in the left MCA territory; Patient 2: right frontal porencephaly; Patient 3: neurocysticercosis, left frontal; Patient 4: remnants of bullet wound trauma to the right parietal region. See table for additional patient details.

dress the safety of transplanting cells from a differentiated malignant tumor cell line into patients. Patient assessment and follow-up were inadequate. The claims for safety of the procedure, patient improvement, and graft survival are not adequately substantiated. We applaud the Editors[2] of *Neurology* for expediting publication of this research and bringing it to the notice of the wider neurologic and medical community because cell therapy holds great potential in the clinical management of stroke. It would be unfortunate if such therapy was ultimately denied to patients because of a calamity resulting from inadequate and poorly designed trials. The rapidity with which our understanding of neuronal regeneration and repair has advanced in recent years means that there is great potential for the development of safe methods of production of cells for such therapy, but currently "primum non nocere" remains the maxim.

Alastair M. Buchan, Dan Warren, *Calgary, Alberta, Canada;* Rowan Burnstein, *Cambridge, UK*

Reply from the Authors: We thank Buchan et al. for their brief discussion about some important issues from our phase 1 clinical trial. The authors argue for caution in review of this article, a recommendation that we have always embraced during the conduct of our research. First, they discuss the source of cells and the length of follow-up. LBS-Neurons are well characterized and have been studied both in vitro and in vivo for years. Because this article was published as a "brief communication," we were limited to 10 references. Nevertheless, references 2 and 3 discuss the cell biology in detail. I would recommend these references to the authors. In this investigation imaging studies were performed at 6 months because that was the length of observer blinding. In addition, all patients underwent MRI at 1 year, and patients have now had MRI at 2 years. In no patient have cell-related adverse effects been identified. The long-term assessment of patients will be the subject of a separate report. Buchan et al. also discuss the reasons why increased FDG uptake could be noted on PET scans. It appears they did not read paragraph 4 of the discussion section in which we raised the same questions as these authors. Finally, the authors believed it "reasonable" to expect an improvement in functional outcome in a group of stroke patients whether or not they underwent a transplantation procedure. We do not know how they obtained this conclusion. I would ask that the authors share any natural history functional outcome data in patients with stroke. We believe it would be more reasonable to expect a *decline* in stroke scores because of further neurologic disability, depression, muscle atrophy, or new ischemic events. Late improvements would be unlikely. In this study, all patients underwent repeated stroke scale assessments for 2 months prior to surgery and did not show improvement.

We agree that there is great potential for the development of cellular therapies for neurodegenerative diseases. As a novel study, we hope that our work has provided the foundation for additional clinical and basic research. Our work has opened the door for further research in this field. Our own plan is to conduct a larger safety study that will also provide further information on the functional response to neurotransplantation. We hope that our work will encourage other investigators to enter this field.

Douglas Kondziolka, *Pittsburgh, PA*

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MRI evidence of mesial temporal sclerosis in patients with psychogenic nonepileptic seizures

To the Editor: A number of epidemiologic studies have confirmed the importance of postnatal insults as a cause of epilepsy.[1] Neuroimaging has been an increasingly important diagnostic tool, and it has been stated that the demonstration of "epileptogenic lesions" strongly supports the diagnosis of epilepsy in these individuals.[2] The article by Benbadis et al. is a timely reminder of the pitfalls of diagnosing epilepsy based on neuroimaging findings alone.[3] As the authors stated, EEG remains the standard diagnostic test in these and cases of suspected epilepsy. Whereas many risk factors for psychogenic nonepileptic seizures have been identified,[4] isolated psychogenic nonepileptic seizures in patients with CNS lesions have only rarely been reported.[5,6] Benbadis et al.'s patients presented with a history of "seizures" and were found to have brain lesions (MTS).[3] The opposite situation, namely patients with a CNS lesion who present with stereotypic symptoms that are assumed to represent epilepsy, is an equally difficult and probably a more common dilemma. The diagnosis of epilepsy in these patients, as with the cases reported by Benbadis et al., is frequently based on history and "confirmed" by the demonstration of CNS abnormalities on neuroimaging.[3] We recently had four patients with well-defined CNS lesions and "refractory seizures" referred to us for epilepsy surgery in whom appropriate EEG studies showed only psychogenic nonepileptic seizures (table).

Psychogenic nonepileptic seizures in the absence of epilepsy have been reported in children with head injuries but have not been well studied in adults with CNS lesions.[5] All our patients had clinical manifestations that were "neurologically correct" with the paretic side being the one initially involved at the onset of the psychogenic attacks. In contrast, focal psychogenic neurologic symptoms (paralysis, dysesthesias) in patients without CNS lesions seem to randomly involve either right or left sides of the body.[6] None of our patients had epilepsy; all had a positive seizure induction that reproduced their "typical seizures." Attacks were often but not always precipitated by situations of stress; all patients felt that the residual neurologic deficits limited their ability to cope with life situations. Neuroimaging in each case showed obvious lesions involving cortex and underlying white matter (figure). Telemetry evaluation showed no epileptogenic abnormalities in any of them. However, previous EEG in one postcraniotomy case had been incorrectly interpreted as showing "epileptogenic" abnormalities which in retrospect represented breech rhythms. Whereas patients with psychogenic seizure series are predominantly adults, particularly women, psychogenic seizures and CNS lesions seem to be more common in boys[5] and men.

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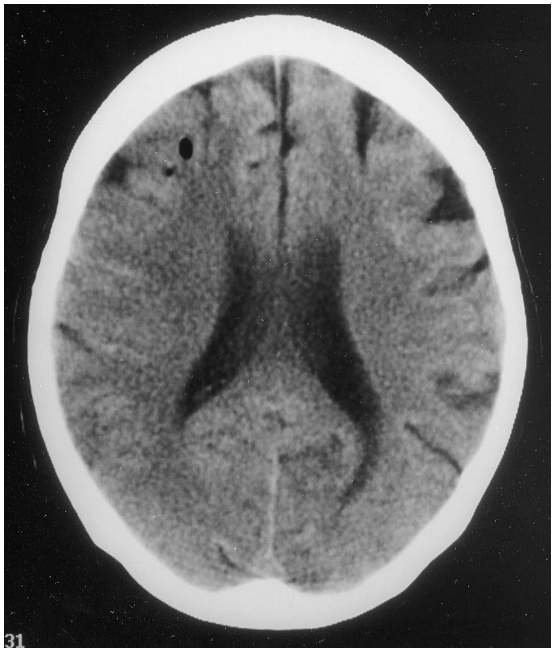
Corrections

Cerebral artery air embolism following an esophagogastroscopy: a case report

In the article "Cerebral artery air embolism following an esophagogastroscopy: a case report" by Akhtar et al. (Neurology 2001;56:136–137), an incorrect figure 1 was printed. The correct figure is printed below.



Familial occipital calcifications, hemorrhagic strokes, leukoencephalopathy, dementia, and external carotid dysplasia

In the article, "Familial occipital calcifications, hemorrhagic strokes, leukoencephalopathy, dementia, and external carotid dysplasia" by Iglesias et al. (*Neurology* 2000;55:1661–1667), figure 4 was printed incorrectly. The figure is reprinted below.