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Comment on “Human Neuroblasts Migrate to the Olfactory Bulb via a Lateral Ventricular Extension”

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Curtis *et al.* (Research Articles, 2 March 2007, p. 1243) claimed discovery of a human neuronal migratory stream to the olfactory bulb along a putative lateral ventricular extension. However, high levels of proliferation reported with proliferating cell nuclear antigen were not confirmed using different markers, neuronal chain migration was not demonstrated, and no serial reconstruction shows a true ventricular extension.

In a recent study, Curtis *et al.* (1) claimed to have discovered extensive proliferation of neuronal progenitors along the lateral wall of the human lateral ventricles, massive neuroblast migration to the olfactory bulb (OB) through a putative rostral migratory stream (RMS), and a novel anatomical structure connecting the human subventricular zone (SVZ) to the OB via a continuous open ventricle. Their data, however, do not support these conclusions, and in some cases similar observations have been previously reported with more cautious interpretations.

Curtis *et al.* suggest that tens of thousands of dividing cells exist at the base of the anterior horn of the human lateral ventricle. In figure 1 in (1), it appears as if every cell is labeled with proliferating cell nuclear antigen (PCNA). Were any of these cells mitotic or expressing Ki-67, a more reliable marker for proliferation in humans (2)? If these cells are neuroblasts, as in the rodent brain (3), they should coexpress β III-tubulin (TuJ1) or polysialylated–neural cell adhesion molecule (PSA-NCAM), but no co-labeling or ultrastructural analysis was shown to characterize these putative neuronal precursors. Was this large mass of PCNA-positive cells observed in all brains studied? The evidence that these cells are all dividing or that they are neuronal precursors seems weak, yet Curtis *et al.* inferred from this data that these cells are the source of new neurons in the human OB. However, despite the numerous PCNA-positive cells they reported, Curtis *et al.* demonstrated only a single cell positive for neuronal nuclei (NeuN) and 5-bromo-2'-deoxyuridine (BrdU) in the OB [figure 4L in (1)]. The patient's age, cause of

death, survival since treatment, and total number of labeled cells were not indicated (were BrdU⁺NeuN⁺ cells observed in more than one patient?), nor do the authors comment on the atypical cytoplasmic NeuN localization (4), on what type of OB neuron this was, or where in the OB it was found.

The presence of new human OB neurons has been previously suggested (5), but studies have also raised the possibility that human OB neurogenesis may be a local phenomenon (5, 6). Curtis *et al.* (1) neither commented on these data nor provided direct evidence that putative new neurons are born in the human SVZ and migrate through an RMS to the OB, even though this is the central conclusion of their paper. Because it is not possible to identify a human RMS by grafting or labeling human SVZ progenitors, the histological data should at least be consistent with what previous mammalian studies have shown (3, 7), namely (i) cells with migratory morphologies coexpressing markers specific to migrating young neurons (β III-tubulin, PSA-NCAM, and double cortin), (ii) migratory neuroblasts existing continuously between the SVZ and OB, (iii) young neurons capable of chain migration, and (iv) migratory neuroblasts with the ultrastructure of Type A cells. Instead, Curtis *et al.* supported their claim of a human RMS by primarily showing elongated cells expressing either PSA-NCAM [figure 3 in (1)] or β III-tubulin [figure 4, A to C, in (1)]. Clear double-labeling was only shown in the absence of convincing migratory morphology [figure 4, D to F, in (1)], whereas an image filled with β III-tubulin–positive fibers contained only a single cell ostensibly coexpressing PSA-NCAM [figure 4, G to J, in (1)]. Are all of these β III-tubulin–positive fibers part of the putative RMS, or only the single colabeled cell? How do we know that β III-tubulin staining is not indiscriminately labeling all the olfactory tract white matter fibers? Even with access to “large numbers of normal, well-preserved, perfused, whole human brains,” the authors showed no serial reconstructions of this region or the histological (3) or in vitro (8) features of chain migration. Finally, their ultra-

structural analysis lacks the essential elements that identify young migratory neurons (free ribosomes, microtubule networks, and leading processes containing growth cones) (3), and some of the cells they described as young neurons have the ultrastructure of oligodendrocytes [figure 4K in (1)]. Elongated young neurons have been previously described in the adult human SVZ and OB (5, 9–11). However, these putative migratory cells are sporadic and bear little resemblance to the massive chain migration that defines the RMS in other studied mammals (3, 7).

Finally, Curtis *et al.* claim to have discovered a new anatomical structure in the adult human brain. However, what the authors term the “ventriculo-olfactory neurogenic system” was previously described by Bernier *et al.* (11) and Weickert *et al.* (10), who called it the “ventral-lateral extension,” and further characterized by our group as the “SVZ-olfactory trigone connection” (12). We are all referring to the same location: a region where the olfactory ventricle existed early in human development. Our serial reconstruction, however, did not reveal a contin-

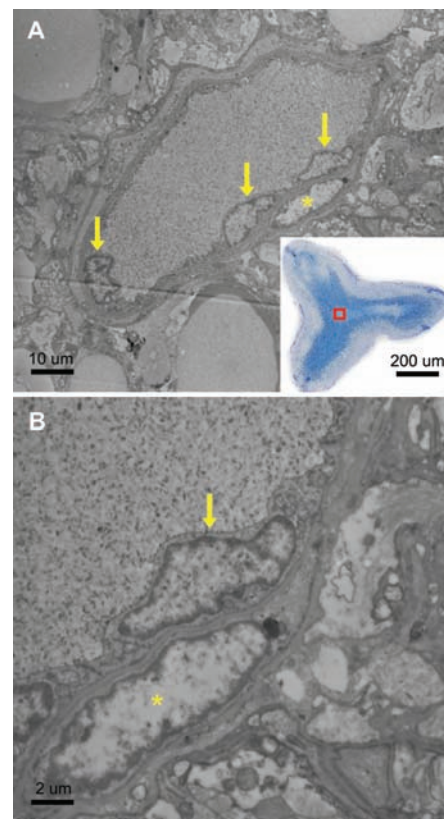


Fig. 1. (A) Examination of three adult human olfactory tracts in 1- μ m plastic sections by electron microscopy revealed no evidence of an open ventricular system. (B) A lumen in the core of the olfactory tract corresponds to a blood vessel surrounded by endothelial cells (arrows) and smooth muscle (*). However, no evidence of ependymal cells or cavities continuous with the ventricular system was observed.

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uous open cavity—an observation shared by previous studies (6, 10, 11). Instead, careful histology has shown that the human olfactory ventricle closes during fetal development (13). In contrast, Curtis *et al.* showed an irregular hole in the core of one olfactory tract that they interpreted as a “hollow tube” [figure 5D in (1)], yet this tissue appears damaged. No serial reconstruction is presented, no ependymal lining is identified, and it is unclear whether such an opening exists in all their specimens. Their use of magnetic resonance imaging (MRI) to corroborate their inference is inconclusive because skull base imaging varies greatly with image acquisition settings, and previous MRI studies of the human olfactory system contradict their findings (14). Therefore, we believe that the authors’ claims to have discovered a

new anatomical entity in the adult human brain are unsubstantiated. We have reexamined adult human olfactory tracts at the light and electron microscope to look for an open ventricle. As before, no such structure was found, but a large blood vessel lined by endothelial cells can be seen in the olfactory tract core (Fig. 1) in the same location as that shown in figure 5D in (1).

Although a clear demonstration of large-scale neurogenesis and long-range neuronal chain migration in the adult human brain would be of great interest, we suggest that the available evidence warrants much more caution.

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