Perspective authors' response: Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion

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A significant body of work has emerged from multiple laboratories over the past several years demonstrating cortical neurogenesis in the embryonic subventricular zone (SVZ). The role of SVZ precursor cells as a major source of cortical neurogenesis was not appreciated at the time that Van Essen formulated his hypotheses on cortical expansion and gyrification¹. Our basic premise concerns the potential significance of a newly described neuronal progenitor cell type found in the SVZ, referred to as an intermediate progenitor (IP) cell. IP cells have been best characterized in rodents, but similar cells have been described in primate cortex². In fact, the primate ventricular zone becomes very thin at the onset of cortical neurogenesis, and the SVZ might be the major source of neurogenesis in the primate visual system². Our paper speculates on the impact of IP cell neurogenesis on features of cortical development, particularly the generation of upper cortical layers, and cortical expansion. Our remarks about the possible evolutionary roles of IP cells owe much to the observation that the SVZ is practically non-existent in the simple three-layered reptilian cortex³, is appreciable in rodents and is extremely large in primates. If the primate embryonic SVZ harbours large numbers of IP cells, as we propose, the production of neurons from this region cannot be overlooked in models of cortical development and cortical expansion. It is not our intention to dismiss previous hypotheses, but to suggest that a revision that incorporates recent findings might be appropriate.

Dr Van Essen faults our work as reversing cause and effect, claiming that the width of the SVZ is dependent on the presence of axonal fibres, and thereby suggesting that it is not correlated with cortical neurogenesis. But one could argue that this is putting the cart before the horse, as the embryonic SVZ is a neurogenic compartment that produces the very cortical neurons that later send axonal projections through various cortical structures. Cause-and-effect relationships

between cell generation and cell maturation will need to be examined through experimentation and manipulation to determine the precise relationship between the size of the SVZ and cortical expansion. For example, absence of sonic hedgehog (SHH) during cerebellar development results in a smooth, unfoliated cerebellar cortex in which sulci are completely lacking. By contrast, overexpression of SHH produces extra foliation and tangentially expanded cerebellar lobules⁴. Interestingly, SHH appears to mediate this effect by stimulating the proliferation of precursor cells in the external granular layer⁴, providing a strong link between the degree of cortical folding and the levels of proliferation. These findings support our concept that proliferation might be relevant to gyral formation in the cerebral cortex as well.

Dr Van Essen is correct to point out that in our figure 3b, the brackets include stratified transitional fields, and should not have been identified as the SVZ *per se*. However, during stages of cortical neurogenesis in the rodent, the stratified transitional fields overlap with the SVZ and with the intermediate zone⁵, regions where many IP cells reside. Van Essen implies that neurogenesis does not occur in the intermediate zone. However, as pointed out by Altman and Bayer in the work cited by Van Essen, we know comparatively little about cortical neurogenesis in humans, and in the absence of hard data the best we can do is “extrapolate from the combined experimentally established sequence of cortical neurogenesis and transitional field stratification in rats to humans” (REF. 6). Most important for the arguments we make in our hypothesis, IP cells in rodents are not restricted to the SVZ, but are also found in the outer margin of the ventricular zone and in the intermediate zone (REF. 7 and S.C.N., V.M.-C. and A.R.K., unpublished observations). The development of markers for human IP cells will aid in determining to what extent IP cells are present in the human stratified fields, and to what extent cortical neurogenesis occurs in these compartments.

An understanding of the mechanism that produces the human smooth cortex disorder lissencephaly might be expected to shed light on our discussion. In classical lissencephaly the cortex is reduced to an agyric four-layered structure. Mutations in the *LIS1* gene are one of the causes of classical lissencephaly⁸, and the effects of reducing *LIS1* protein levels have been studied in the developing mouse cortex. In addition to defects in neuronal migration, IP cell production is severely reduced⁹, but there are also significant reductions in radial glial cell division and abnormalities in axon formation^{9,10}. Not only do these results not rule out the models of cortical expansion under discussion, they could even be interpreted as supporting each. In conclusion, we believe that our hypothesis does not contradict that of Van Essen. Instead, we believe that existing hypotheses must account for emerging data, and be flexible enough to incorporate new findings concerning cortical histogenesis.

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