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Cause and effect in cortical folding

David C. Van Essen

In their article on neurogenesis and cortical development, Kriegstein *et al.*[1] propose that regional differences in neuronal proliferation in the subventricular zone (SVZ) lead to differential expansion of superficial cortical layers, thereby causing gyral folds near regions of increased SVZ thickness and sulcal folds near regions of decreased SVZ thickness. I contend that this hypothesis is problematic in some respects and that Kriegstein *et al.* might have reversed cause and effect in their attempt to explain cortical folding. The hypothesis of tension-based cortical folding[2] provides an attractive alternative for their observations, as it predicts that variations in thickness of the SVZ can arise as a consequence rather than a cause of cortical folding.

Kriegstein *et al.* provide only anecdotal and fragmentary evidence for a correlation between variations in SVZ thickness and the location of cortical folds in both macaque and human. For the macaque (their figure 3a), they point to a change in SVZ thickness in the vicinity of the lunate sulcus. However, the SVZ is relatively thick over the full extent of presumptive area V1 (REF. 3), suggesting that SVZ thickness correlates more closely with areal identity than with specific folding patterns.

In considering their human data, it is first necessary to point out an unfortunate mis-labelling and mis-categorization of the fibrous and cellular strata of the intermediate zone as part of the SVZ. In their figure 3b, Kriegstein *et al.* categorized as 'SVZ*' a broad swath originally identified as layers 2–6 of the stratified transitional field (STF) within the intermediate zone[4]. Regional variation in the thickness of the STF reflects differences in the distribution of fibres of passage, as well as the density of migrating postmitotic neurons[5]. Furthermore, since neurogenesis has not been reported in the intermediate zone[5,6], it is inappropriate to equate the SVZ* with the STF in an analysis that considers the SVZ to be a region of ongoing neurogenesis. Inspection of the correctly identified SVZ[4] reveals that the correlation between developing cortical folds and SVZ thickness is relatively weak.

The observed pattern of variations in the thickness of both the STF and the SVZ is a natural outcome of the hypothesis of tension-based cortical folding[2]. By this hypothesis, mechanical tension generated by the axons of cortico-cortical projection neurons tends to cause gyral folds along boundaries between strongly interconnected regions (for example, areas V1 and V2 in many species), whereas neighbouring regions that are relatively weakly interconnected allow sulci to form in-between. The fact that deep (infragranular) cortical layers are relatively thick in gyral regions and relatively thin in sulcal regions can be attributed to tension-induced shearing forces within the cortical sheet (see figure 2d in REF. 2). Similarly, tension-induced shearing would tend to make the STF and the SVZ thicker near gyral regions and thinner near sulcal regions, with a weaker effect on the SVZ because of its greater distance from cortical folds.

If cortical folding were dictated by patterns of subcortical neurogenesis in the SVZ, as proposed by Kriegstein *et al.*, a complex pattern of differential neurogenesis in the SVZ, induced by an elaborately choreographed set of developmental instructions, would be required to account for the tremendous complexity of human cortical convolutions and their variability from one individual to the next[7]. By contrast, tension-based cortical folding provides a simple and efficient strategy for generating cortical folds using experimentally verified cell biological properties of developing neurons[8]. An added benefit is that tension-based folding would tend to reduce the aggregate length of cortico-cortical connections and thereby contribute to compact wiring of the brain.

The tension-based morphogenesis hypothesis[2,9] can account for both the degree and the pattern of cortical folding, given the number of cortical neurons and their connectivity patterns. This provides a sound mechanistic framework for understanding the remarkable diversity in the extent and pattern of cortical convolutions within and across species.

David C. Van Essen is at the Anatomy & Neurobiology Department, Washington University, St. Louis, Missouri, USA.

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