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REVIEWS

[1]Department of Psychology, Yale University, New Haven, CT 06511, USA
[2]Department of Experimental Psychology, University of Oxford, Oxford, OX2 6HG, UK

*Correspondence:
molly.crockett@yale.edu (M.J. Crockett).

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Forum

Modelling the Human Cortex in Three Dimensions

Esther Kuehn[1,2,3,*] and
Martin I. Sereno[4]

In cognitive neuroscience, brain-behaviour relationships are usually mapped onto a 2D cortical sheet. Cortical layers are a critical but often ignored third dimension of human cortical function. Improved resolution has put us on the threshold of beginning to image human cognition in three dimensions.

From 2D to 3D Cognition

Cognitive neuroscience investigates the fascinating question of how neuronal computations give rise to mental processes such as sensory perception, learning, and memory. The cortex, which plays an important role in all of these processes, is often pictured as a 2D, folded sheet. However, this 2D model disregards the third (depth) dimension of the cortex, both anatomically and with respect to function (Figure 1). By contrast, modelling the human cortex as a 3D sheet takes into consideration the structured decomposition of laminar function long known from invasive experiments in rodents. Thus, this approach extends brain-behaviour mapping by one dimension. Recent developments in human neuroimaging technology (e.g., ultra-high field imaging at 7 Tesla) are finally making it possible to non-invasively investigate cortical depth-dependent computations in the living human brain. Here, we introduce '3D cognition' and discuss how this concept may help to unpack the 'hidden variables' of human cognition.

Columnar Overlap Does Not Mean Computational Equivalence

Brain parcellation atlases attempt to distinguish cortical areas using microarchitectonic features, such as the arrangement of cells or myelin. In early sensory areas, there is excellent correspondence between the boundaries of repeated neighbour-preserving maps of receptor sheets and architectonically-defined brain areas. There is no doubt that position tangential to the cortex is relevant for mental processes. However, cortical layers have strikingly different influences and functions, as revealed by experiments conducted with rodents and monkeys. Middle granular layers function as input layers for thalamic and earlier cortical area afferents; feedforward supragranular layers contribute to sensory signal elaboration, sensory memory, and have associative functions; deep infragranular layers are often involved in intra-columnar processing, important for perceptual sharpening and feedback; layer 5, containing neurons with huge dendrites, functions as an output layer and sends projections to subcortical areas; and finally, fibre-filled layer 1 receives both feedforward and feedback inputs (e.g., [1,2]).

The glutaminergic pathways in the cortex and thalamus were recently subdivided into two principal classes: 'drivers' and 'modulators' [2]. Whereas driver inputs carry sensory information, modulators modify or gate it (e.g., by control of firing mode, switching, or gain control). In the cortex, modulators often involve deeper cortical layers, particularly those in the deep layer 6. Critically, both driver and modulator inputs are topographically precise, and their tangential positions coincide, albeit at different depths, in a single cortical column.

Tangential overlap within a column does therefore not imply computational equivalence. Within the same columnar unit, different and perhaps even orthogonal functions may be computed. Though different hierarchical processing levels are typically assigned to different tangential cortical areas, different layers within one tangential area may perform computations at different levels, too. Advances in ultra-high field imaging now allow, for the first time, cortical depth-dependent non-invasive imaging in the living human brain. Continual optimisation of software and hardware components of ultra-high field MR scanners by MR physicists have
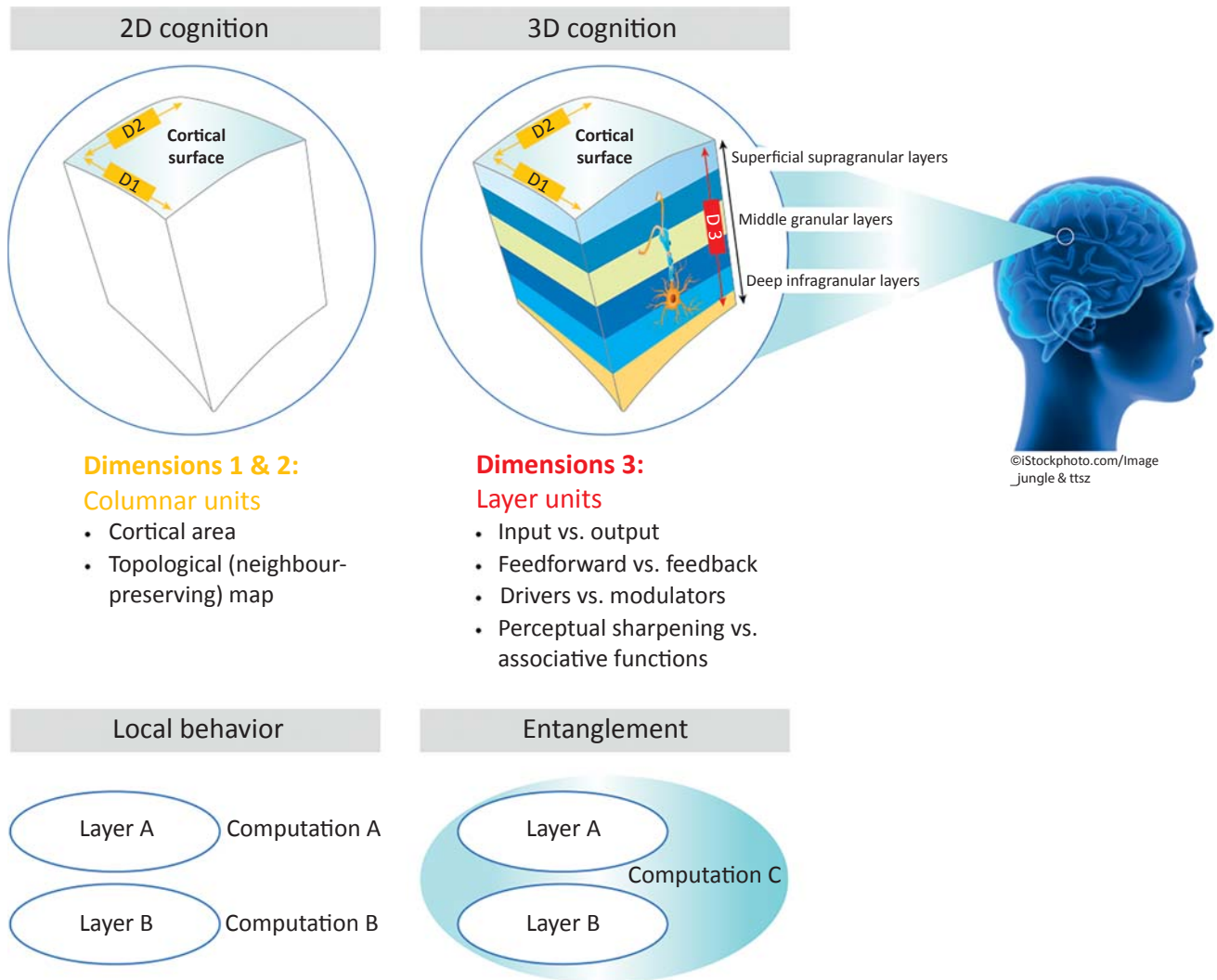
Figure 1. Three-dimensional Cognition in Humans. Whereas current brain-behaviour models of human brain function often map cognitive features onto a 2D cortical sheet, human brain function takes place in three dimensions: tangential to the cortical surface, and in cortical depth. Novel 3D models of human cortex function should take into account local behaviour versus entanglement to develop cortical depth-dependent brain-behaviour relationships.

provided us with *in vivo* structural and functional brain images at sub-millimetre resolutions that can now be acquired within a reasonable time frame [3]. This allows researchers a glimpse into the microstructural architecture of the living human cortex for the first time. Recent studies have demonstrated different laminar profiles of activation for encoding afferent versus non-afferent sensory inputs [4,5], have dissociated input versus output information flows in the motor cortex [6], and have identified septa in specific cortical depths of sensory and motor cortices [7]. These new results motivate us to more broadly and consciously incorporate the third, depth dimension of cortex function into new testable models and theories [3].

Perhaps the most striking demonstration of the fact that overlap in tangential position does not imply overlap in function can be found in primary sensory brain areas. While primary sensory cortices have obvious primary input modalities, they can also be activated by non-primary input modalities, such as touch in case of the primary visual cortex, or vision in the case of the primary somatosensory cortex [8]. This has led to the idea that sensory perception might be somehow 'amodal' or 'pluripotent' [9]. In this view,

even early sensory areas represent abstract environmental and object features, such as distance, shape, or surface texture, rather than modality-specific inputs. According to this view, we can 'feel with our eyes' and 'see with our hands'. However, amodality implies that the same computations take place in the same brain area irrespective of the sensory input channel; this is a view that may not be supported by a 3D model of cortex function (see Figure 1). An alternative view is that somatotopic, tonotopic, and visual maps are highly efficient formats for representing their respective sensory information content. Information may well be transformed from one map format to another, but may trigger different functions, or processes, at different cortical depths, dependent on input modality. A similar perspective can be taken with respect to the 'mirroring' of sensory or motor events, or with respect to the assumed 'invasion' of a deprived cortex by a non-native modality. We think it is likely that when the full 3D map structure is eventually interrogated in these other cases that we will find laminar differences between observation and sensorimotor experience, or between the native and non-native modality that may challenge some current models. Both high- and low-level processes may take place within the same columnar units.

Entanglement versus Local Behaviour

Though there is evidence for functional differences between cortical laminae, it is a deeper and more difficult undertaking to determine how entangled these local behaviours are. In quantum physics, the measurement process can find the projection onto one axis of the spin of a single particle. But prior to the measurement, the particle appears to be entangled with others. In the cortex, multiple interactions exist between cortical layers, and the computations that give rise to a particular brain function may be carried out within a specific cortical layer, or may be initially entangled between multiple layers (see Figure 1). The fine-grained temporal evolution at the level of a spiking network and the involvement of different layers for one specific function that links to cognitive processes may differ from case to case.

Future Challenges

Cortical layers are a critical but often ignored dimension of human cortical function. Improved resolution has put us on the threshold of beginning to image human cognition in three dimensions. However, at present, we can only measure temporally blurred hemodynamic signals at a few different depths; and given that neurons in different layers have metabolically active processes that extend to other layers, our measuring device is rather coarse. One possible way around some of these problems may be the development of computational models that implement prior knowledge on how neuronal signals in different cortical depths generate a hemodynamic signal [10]. Also critical is the development and usage of even more refined acquisition protocols, particularly of quantitative cerebral blood volume (CBV) based functional data [11]. Another promising way forward would involve combining measures of blood flow/blood volume with electrophysiological signals, which would allow deeper insights into frequency-dependent, microcircuit interactions [12]. In all cases, a key component of success will involve carefully considering which measurement parameters to choose in order to best answer a specific research question. With judicious respect for understanding complexity, these methods, in combination with behavioural paradigms that are easier to implement in humans than in non-human primates, may allow us to expand and differentiate our picture of human cognitive operations in the columnar direction.

[1]Aging and Cognition Research Group, DZNE, Magdeburg, 39106, Germany
[2]Center for Behavioral Brain Sciences Magdeburg, Magdeburg, 39106, Germany
[3]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, 04103, Germany
[4]Department of Psychology, San Diego State University, San Diego, CA 92182, USA

*Correspondence: esther.kuehn@dzne.de (E. Kuehn).

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