Prefrontal Cortical Microcircuits for Cognitive Control

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Abstract: The prefrontal cortex of the primate brain has a modular architecture based on the aggregation of neurons in minicolumnar arrangements having afferent and efferent connections distributed across many brain regions to represent, select and/or maintain behavioral goals and executive commands. Prefrontal cortical microcircuits are assumed to play a key role in the integration of signals across cortical layers and the selection of executive variables. Recent research suggests that cognitive abilities emerge from corticocortical interactions between interlaminar prefrontal cortical microcircuits, while their disruption are involved in a broad spectrum of neurologic and psychiatric disorders like autism, and drug addiction. Based on recent technological progress it has been demonstrated that microstimulation of infragranular cortical layers with patterns of microcurrents derived from supragranular layers led to an increase in cognitive performance. This suggests that interlaminar microcircuits are playing a causal role improving cognitive performance. The objective of this paper is to shed light on the new interest in cortical modularity coming from the impressive progress in understanding anatomical, physiological and pathological facets of cortical microcircuits and the promise of neural prosthetics for patients with neurological and psychiatric disorders.

1. Introduction

The rich repertoire of cognitive, emotional and sensorimotor behaviors, mastered by both humans and animals, is a surprising and still poorly understood outcome of development and learning (Mountcastle, 1955, 1997). A key anatomical structure, the prefrontal cortex, at the top of executive hierarchy in the primate brain, uses a modular architecture based on minicolumnar aggregates of neurons with afferent and efferent connections distributed across many brain regions, to represent, select, maintain and coordinate thought and behavioral goals (Opris et al., 2012a, 2012b). Recent research suggests that executive abilities emerge from corticocortical interactions between interlaminar prefrontal microcircuits, the posterior parietal cortex, and cortico-striatal-thalamo-cortical circuits (Opris et al., 2013).

These prefrontal microcircuits also play a key role in the perception to action cycle that integrates relevant information about the environment, and then selects and enacts behavioral responses. This review focuses on how cortical modularity, as a key organizational principle, embraces both anatomy and physiology in coordinating executive facets of behavior. Here, we look specifically at evidence from the structural, functional, and pathological perspectives investigating intact as well as disrupted cortical minicolumns. Vernon Mountcastle described for the first time the electrophysiological basis of the cortical minicolumn and suggested it as an elemental unit of information processing (Mountcastle, 1957, 1997). According to this model of cortical organization, neurons and their connections form part of a vertical system which unites the cells of each minicolumn (Fig. 1) into a coordinated functional unit

(Mountcastle, 1997). In this context, the smallest unit of cortical organization is the minicolumn, usually defined in Nissl stained sections by a narrow radial array of pyramidal neurons transversing laminae II-VI (Mountcastle, 1997). The human neocortex is composed of a large number of minicolumns displayed in parallel vertical arrays (Casanova et al., 2007). Minicolumns are the first step in a nested series of nodes or echelons of increasing complexity. Other levels of modular organization include multiple minicolumns, macrocolumns, and large-scale networks of macrocolumns that are interconnected with the entire brain (Buxhoeveden and Casanova, 2002). The somas of pyramidal cells are not randomly distributed in space; rather, they are organized into both layers and different-sized columns or modules. Minicolumns are often considered highly repetitive, even clone-like, units; however, they display considerable heterogeneity between areas and species, perhaps even within a given macrocolumn. According to Buxhoeveden & Casanova (2002), and in agreement with Favorov and coworkers (1987, 1990) and Mountcastle (1957,1997), the estimated width of cortical macrocolumns is 350-600 μm.

Role of cortical minicolumns in cognitive function

1. Integration and selection within inter-laminar microcircuits: The functional role of the cortical minicolumn is a continuing source of research and debate more than half a century after it was identified as a component of brain organization (Mountcastle, 1955,1957,1997). Nevertheless, in agreement with the optimal principle of design (Leise, 1990), segregating neurons into modules can reduce the cost of wiring. This allows a large number of cells to be connected by fewer axons.). The resulting short-range connections are then poised to participate in behavioral tasks requiring integration and selection of neural signals during executive control (attention, working memory and decision making), sensory discrimination and time-critical responses.

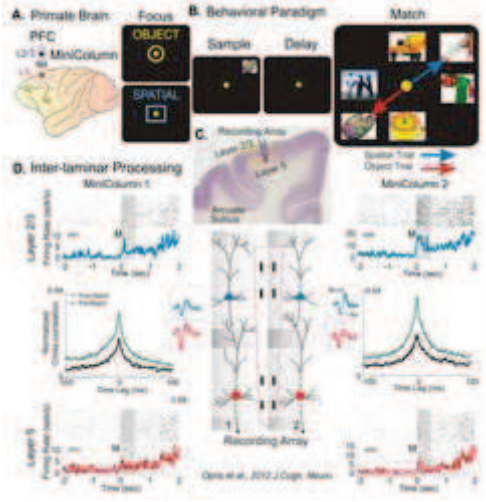

Figure 1. Illustration of columnar laminar neural activity during a cognitive task. A. Primate brain with PFC cortical minicolumn and the layers L2/3 and 5. B. Behavioral delayed match to sample (DMS) task with the sequence of events (Focus, Sample presentation, Delay period, Match array and the arrows representing target selections in object and spatial trials). C. Interlaminar display of recording array. D. Minicolumnar inter-laminar processing of target selection during the match phase of the task. Peri-event and cross-correlation (post- vs. pre-match) histograms depict the functional role of prefrontal layers & minicolumns in integration and selection (Opris, Casanova, 2014).

The integrative role of cortical minicolumns (Fig 1B) as a module (Leise, 1990) stems from connecting the horizontal and vertical components of the cortex within the same columnar space. The supragranular layers L2/3 which are the major source of corticocortical projections also receive sensory information, while the infra-granular layer L5 is the output to subcortical structures involved in behavior.

Thus, inter-laminar connections form microcircuits that bind sensory-related signals with behavior/movement related outputs (Opris et al., 2011). This sensory-motor integration was demonstrated by Opris et al. (2011, 2013) by means of inter-laminar correlated firing between supra-granular layers that carry perceptual/visual spatial information and the infra-granular layers that carry action related information. Such transformations of neural signals may likely reduce the output degrees of freedom within the cortical minicolumn by selecting only the relevant signals for action/behavior. This integrative process that occurs in canonical microcircuits binds/segregates parallel streams of minicolumnar processing within the 'executive cognit' network (Fuster and Bressler, 2012).

The available evidence suggests that the prefrontal cortical minicolumn might be the first stage bottleneck in the cortical-striatal-palidal-thalamo-cortical loop (Alexander et al., 1986). It is obvious that layers 2/3 and 4 cells integrate a lot of inputs from virtually all of the brain, while the number of outputs from layer 5/6 pyramidal cells to subcortical structures participating in behavior is much less. Also, a key role in selection is played by the GABAergic interneurons of minicolumns (Raghanti et al., 2010) that shape the tuning for preferred direction/location by means of lateral inhibition. The minicolumnar role in plasticity is associated not only with the tuning (Fig 2) of synaptic activity states but also with optimal selection among alternate sub-networks of microcircuits developing within a given context. Such parallel subnetworks may process complementary submodalities within a defined receptive/memory field; alternatively they may provide overlapping response characteristics to a common input. Competition among networks allows for circuit optimization (selection), in particular by means of learning.

We hypothesize that minicolumnar diversity provides the substrate for this competition and the basis for adapting learned behavior to context.

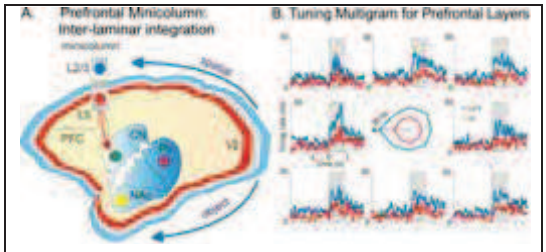

Figure 2. Role of prefrontal cortical minicolumn in integration and selection of information. .A. The laminar structure of the neocortex is depicted in blue (layer 2/3), gray (layer 4) and red (layer 5/6). A prefrontal cortical minicolumn is depicted with the projection to striatum. The two arrows show the flow of visual spatial/object information on the dorsal and ventral streams, respectively. B. Tuning multigram for a pair of prefrontal cortical neurons from layers 2/3 and 5. Overlay mean firing rate depict the preferred activity of layer 2/3 (blue) and layer 5 (red) for the target located on the left (180o). The tuning vectors are in the center. (Opris and Casanova, 2014)

During development, neurogenetic programs interact with epigenetic factors to regulate formation of cortical microcircuit templates (Rakic, 1988; Jones 2000; Jones and Rakic, 2010), which are then shaped and pruned by differential patterns of sensory activity. Thus, increased minicolumnar diversity may give rise to greater potential for combinatorial activity of microcircuits within overlapping networks, resulting in enhanced learning and behavioral flexibility (Casanova, 2008). Cortical minicolumns may therefore play a crucial role in behavioral selection that is in fact the substrate of executive function (e.g., attention, decision making). A decision circuit is defined as a closed neural network that measures the probable value of a signal element and makes an output signal based on the value of the input signal and a predetermined criterion or threshold. Minicolumns in PFC are interconnected to

each other through horizontal "long range" projections in layer 2/3 (Kritzer and Goldman-Rakic, 1995) and interlaminar mini-loops (Takeuchi et al., 2011). The loop is then closed ("reverberatory loops") through projections to the subcortical basal ganglia nuclei and thalamus (Alexander et al., 1986; Swadlow et al., 2002). Such "reverberatory loops" may be regarded as the "basic functional unit" of cognitive/executive mechanism because they: i. combine incoming signals of different input layers (Casanova et al., 2007); ii. store mnemonic information through feedback connections in "persistent" spiking activity; and, iii. compare input signals to a threshold criterion triggering an output response (selection), which constitutes the ability to make a decision. Thus, a cortical minicolumn with integrative, selective and threshold abilities can play the role of a decision module.

2. Inter-laminar interactions within prefrontal cortical microcircuits. The relevance of minicolumnar activity to executive function has been investigated with different approaches under several conditions (Opris et al., 2011, 2012a, 2012b, 2013; Hampson et al., 2012). Our recent results in nonhuman primates show for the first time interlaminar processing in PFC (Fig. 1,C & D) during target selection (Opris et al., 2011, 2012a, 2012b) and sensorimotor integration (Opris et al., 2011). An example of this interlaminar interaction during target selection (Opris et al., 2012a, 2012b) in delay match to sample (DMS) task is shown in Fig. 1B for two cell pairs with rasters and perievent histograms (PEHs) bracketing the temporal interval of image presentation (Match Phase onset) and completion of the target selection Match Response (0 - 2s). The cell pairs were recorded on appropriate sets of adjacent pads (minicolumns 1&2) in the conformal multiple electrode array (MEA) shown in the illustration (Opris et al., 2011, 2012a, 2012b) of both interlaminar cell pairs in L2/3 and L5 (Fig. 1D). Neurons in both layers showed significant increases in mean firing in supra- and infragranular layers as a function of Match presentation (Post Match: 0 to +2s) and during subsequent movements associated with target selection. Demonstration of precise functional connections between individual cells within each minicolumn was provided by cross correlation histograms (CCHs; Opris et al., 2011, 2012a, 2012b); constructed for individual L2/3 and L5 cell pairs recorded on vertically positioned pads of the MEA.

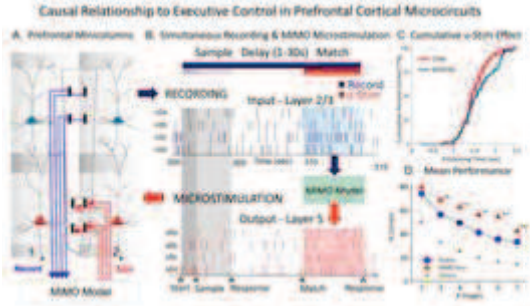

Figure 3. Causal relationship of PFC Interlaminar microcircuit to executive control. **A**: Diagram shows the interfacing of MIMO model with conformal MEAs shown in Figure 2 between L2/3 and L5 during task performance. Electrical stimulation delivered to MEA pads in L5 via patterns of pulses (biphasic) recorded and derived from the same L5 locations on successful trials by the MIMO model. **B**. Firing of L2/3 and L5 located columnar neurons as shown in Fig 2 recorded on line and fed to MIMO model shown in A. Shaded areas indicate time of Match Response execution during DMS trial, and the illustrated firing in L5 which is the same pattern as the delivered stimulation on trials with inappropriate L2/3 firing. **C**. Changes in cumulative performance as a function of processing time from Match phase onset during trials with stimulation delivered in the manner shown in A&B. **D**. Increase in performance across trials with increasing difficulty as a function of the number of Match phase distracter images on trials that received MIMO stimulation in the manner shown in A (Opris and Casanova, 2014).

Normalized CCHs for both minicolumn cell pairs are shown in Fig 1 for cell firing in the displayed PEHs: i) prior to (black) Match phase onset (2s to 0, Pre) or ii) after (green) Match phase onset (0 to +2s, Post) for the same cell pairs. Both CCHs show significantly correlated firing (Opris et al., 2012a).

3. Inter-laminar regulated microstimulation. The unique properties of conformal MEAs together with prior microstimulation work (Opris et al., 2001, 2005) has provided a basis for showing functional relationships to executive function in prefrontal cortex of nonhuman primates. The conformal MEAs also provide the basis for applying a system specific model to control firing of cells via application of electrical stimulation (Opris et al., 2012b, Hampson et al., 2012) to the same loci in which columnar firing has been detected and analyzed with respect to DMS task performance (Opris et al., 2012b, Hampson et al., 2012). This same model was implemented to test whether it could facilitate performance on trials that show a distinctive difference in correct performance as a function of the prior instructions as to type of response to make in the Match phase (i.e. Object vs. Spatial trials). Figure 4 shows the integration of a multi-input multi-output (MIMO) nonlinear math model to assess the patterns of firing in L2/3 and L5 cells recorded in the columnar manner with the MEA shown with adjacent vertical pads (Opris et al., 2011; 2012a, Hampson et al., 2012). Figure 3B reflects the type of input and output firing patterns recorded and analyzed by the MIMO model and also illustrates how the output pattern of L5 cell firing is duplicated via a multichannel stimulator that is capable of delivering predetermined patterns of pulses to the same L5 pads to mimic firing on correct trials.

The advantage of the MIMO model is that the online recording provides the means to detect when the inappropriate L2/3 firing pattern occurs which triggers the delivery of the appropriate L5 stimulation pattern providing the means to override errors and enhance performance (Hampson et al., 2012).

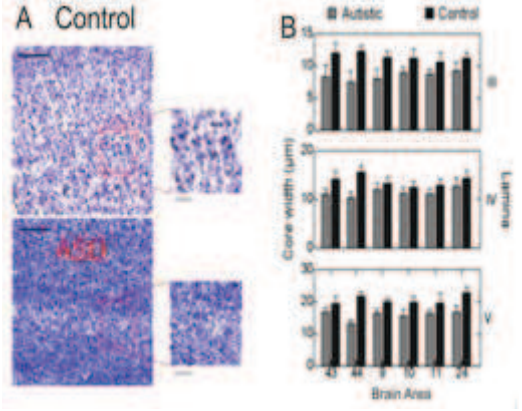

Figure 4. The pathology of cortical minicolumn in disease, **A**. Example of prefrontal cortical minicolumn in an autistic patient compared to normal control (left panel). **B**. Comparison of the minicolumnar width in autism vs. normal control subjects for layers III, IV and V, across prefrontal Brodmann areas 9,10,11,24,43 & 44. ASD, autism spectrum disorder. (Opris and Casanova, 2014).

Stimulation consisted of 1.0 ms bipolar pulses (20-50 μA) delivered to L5 recording locations following presentation of the Match phase screen and prior to the completion of the Match Response.The results of microstimulation delivery are shown in Figures 3C&D, in which the effects on performance are compared to trials in which stimulation was not delivered, respective of trial type. Figure 3C compares the change in % correct performance as a function of processing time (reaction time + movement time) on stimulation (Stim) trials with respect to the no stimulation (No stim) case. Figure 3D showed for the first time the increase in correct performance on trials as a function of the number of distracter images in the Match phase. The results indicate that MIMO derived stimulation induces enhanced cognitive

processing (Opris et al., 2012b, 2013; Hampson et al., 2012) required to retrieve the ”rule” for successful selection of the appropriate item. This inter-laminar MIMO model is the blueprint for restoring cognitive ability in patients with executive dysfunctions.

Dysfunction of cortical minicolumns in cognitive disease. A growing amount of evidence points to the dorsolateral prefrontal cortex as the main region for executive control. Studies suggest that the monitoring mechanism of the dorsolateral prefrontal cortex (that provides a representation for action) and its direct connections to the anterior cingulate cortex (that monitors conflict/errors) and basal ganglia (that implement a corrective action) is abnormal in a significant number of psychiatric conditions. Thus, functional gradients emerging on rostral-ventral to caudal-dorsal part of the medial prefrontal cortex (Nee et al., 2011) turn into error negativity maps in autistic children (Shokadze et al., 2012). The monitoring mechanism of errors detects the conditions under which errors are likely to occur (Carter et al., 1998), by comparing actual vs. expected outcomes as distinct from actual vs. intended outcomes. Disordered brain function involving disruptions of minicolumnar processing have been linked to a range of neurological/psychiatric conditions like autism spectrum disorders that are characterized by the inability to consistently and accurately monitor ongoing behaviors. Recent reports indicate that children and adult patients with autism show reduced error processing and deficient behavioral correction after an error has been committed (Sokadze et al., 2012). There is solid evidence that dysfunctions of error/conflict monitoring are also present in drug addiction (Hampson et al., 2011; Opris et al., 2012a),. Several psychiatric conditions that involve aberrant aspects of social intercourse, high-level perception, and predicting consequences of actions have abnormalities in the conformation of minicolumns.

1. Minicolumnar pathology in autism. Computerized image analysis of pyramidal cell arrays have shown minicolumnar abnormalities in the brains of autistic patients (Casanova et al., 2002a, 2006a, 2006b). These studies have shown reduced horizontal spacing in-between minicolumns which is most salient within their peripheral neuropil space (Casanova et al., 2002a, 2003a). Evidence for this minicolumnopathy has been reproduced using the gray level index (GLI) (Casanova et al., 2002b). The specificity of the findings has been investigated in independent populations, some of which exhibit an autism phenotype, e.g., Asperger syndrome, Rett syndrome, dyslexia, Down syndrome (Buxhoeveden et al., 2002; Casanova et al., 2003b). These findings appear to hold when controlling for possible confounds such as mental retardation. Using the Delaunay triangulation method to parcellate the position of pyramidal cells within the cortex reveals the presence of intra- and inter-cluster distances that correspond to the separation of neurons within and between minicolumns (Casanova et al., 2006a). The result from this study indicates that in autism the total number of neurons per minicolumn appears normal but the distance between minicolumns is reduced (Fig. 4). The reduction, primarily within the peripheral neuropil space, appears to involve all layers of the minicolumn. The findings suggest the possibility that in autism an anatomical element in-common to all laminae is affected. Given the preponderance of inhibitory elements within the peripheral neuropil space and the increase in total number of minicolumns, it has been proposed that heterochronic divisions of periventricular germinal cells may lead to a desynchronization in the maturation of excitatory and inhibitory cells during corticogenesis (Casanova et al., 2013). Minicolumnar studies that have used neuronal morphometry for pyramidal cells have shown a diminished size for both the cell soma and nucleoli in autism (Casanova et al., 2006a). Both size of the soma and nuclei help define

the total metabolic capacity of a cell. Their reduction in autism suggests a bias in connectivity that favors short connections at the expense of longer ones. In autism, the findings may help explain the significant increase in the outer radiate white matter compartment at the expense of a smaller corpus callosum (Herbert et al., 2004). Altered minicolumnar circuits may thus be related to changes in transcortical and callosal white matter pathways linking together regional networks of minicolumns. Changes to the blue print of connectivity may help explain a weak drive for central coherence and peculiarities of information processing favoring local (detail focused) over global information (Happe′ and Frith, 2006).

2. Disruption of interlaminar processing in drug addiction. A study of antenatal exposure to cocaine in rats suggest its ability to modify the maturation of the ontogenetic minicolumn (Buxhoeveden et al., 2006). Rats antenatally exposed to cocaine were sacrificed at P21. The distance between both minicolumns and apical dendritic bundles were found to be narrower in all cortical areas examined. Administration of cocaine has a dramatic effect in the inter-laminar processing of cognitive information.

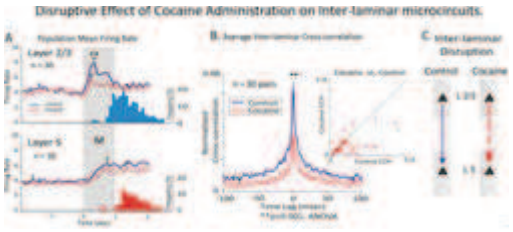

Figure 5. Disruption of inter-laminar interaction in cocaine addiction. **A**. Population peri-event histograms contrasting neural firing in prefrontal cortical layers before and after cocaine administration. **B**. Inter-laminar cross-correlation showing the decrease in interlaminar interaction induced by cocaine administration (Opris et al., 2012a). **C**. Diagram depicting interlaminar disruption.

Figure 5 shows that the loss in correlation produced by cocaine is most extreme for pairs of cells that exhibit high correlation values in the control (saline) half of the session while cell pairs with low normalized correlations (<0.04) were relatively unaffected by cocaine administration. These findings are in close agreement with prior studies showing marked influences of acute administered cocaine in altering task-related neural firing (Nestler, 2004; Opris et al., 2009;) and support the notion that dopaminergic modulation of PFC neuron firing may be responsible for regulating columnar processing in a manner that controls decision-making and target selection in cognitive tasks (Tomasi et al., 2010). The neuropathology of the "basic functional unit" of cognitive/executive mechanism shows for different psychiatric and neurological conditions: i. decrease minicolumnar width in autism (Opris and Casanova 2014); ii. disruption of interlaminar processing in drug addiction (Opris et al., 2012a).

Summary. The cell minicolumn is a basic architectural motif of the cerebral cortex. Such generic circuit within the cell minicolumn provides the elements necessary for redundancy and plasticity. A large number of studies implicate minicolumnopathies in different psychiatric conditions. Recent work on prefrontal minicolumns have shown clear evidence for their role in binding perception to executive control. Technological progress in developing multi-electrode arrays has allowed the simultaneous recording in cortical layers on adjacent minicolumns and the microstimulation of the deep cortical layerson adjacent minicolumns and the

microstimulation of the deep cortical layers. The implementation of the MIMO model (Hampson et al., 2012; Opris et al., 2013) has allowed the extraction of the code from supragranular layers in order to determine the optimal pattern of spikes that will be fed into the infragranular layers. It was thus

demonstrated that microstimulation of deep cortical layers led to increased cognitive performance, with the prefrontal interlaminar microcircuits playing a causal role in the improvement of cognitive performance. Furthermore, an important reason for the new interest in cortical modularity comes from the impressive progress in understanding anatomical, physiological and pathological facets of cortical microcircuits and potential implementation in cognitive neural prosthetics.

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