Prefrontal cortical microcircuits bind perception to executive control

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Prefrontal cortical microcircuits bind perception to executive control

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During the perception-to-action cycle, our cerebral cortex mediates the interactions between the environment and the perceptual-executive systems of the brain. At the top of the executive hierarchy, prefrontal cortical microcircuits are assumed to bind perceptual and executive control information to guide goal-driven behavior. Here, we tested this hypothesis by comparing simultaneously recorded neuron firing in prefrontal cortical layers and the caudate-putamen of rhesus monkeys, trained in a spatial-versus-object, rule-based match-to-sample task. We found that during the perception and executive selection phases, cell firing in the localized prefrontal layers and caudate-putamen region exhibited similar location preferences on spatial-trials, but less on object- trials. Then, we facilitated the perceptual-executive circuit by stimulating the prefrontal infra-granular-layers with patterns previously derived from supra-granular-layers, and produced stimulation-induced spatial preference in percent correct performance on spatial trials, similar to neural tuning. These results show that inter-laminar prefrontal microcircuits play causal roles to the perception-to-action cycle.

A broad range of brain functions, from perceptual to executive actions encode, represent, monitor and select information that is either spatial- and/or object-specific for effective behavioral performance. Such constellations of brain abilities use large scale neural circuits consisting of thalamo-cortical loops and cortical microcircuits with functional roles in the integration and selection of information. It has been previously shown that dorsal visual stream of neural projections from the striate cortex to the posterior parietal region carries the spatial information required for sensorimotor transformations in visually guided actions, while the ventral stream projections from the striate cortex to the inferior temporal cortex is primarily responsible for perceptual identification of objects. Thus, a visual object’s qualities and its spatial location depend on the processing of different types of visual information in the inferior temporal and posterior parietal cortex, respectively. However, object and spatial information carried in these two separate pathways has been shown to be integrated into a unified ‘visual percept’ in prefrontal cortex which receives connections from both circuits.

Several lines of evidence indicate that the basal ganglia participates in multiple parallel segregated circuits or ‘thalamo-cortical loops’ that make connections with motor, sensory and cognitive areas of the cerebral cortex. Prefrontal cortical areas seem to be the target of extensive, topographically organized outputs from the basal ganglia. Such thalamo-cortical projections from basal ganglia to the superficial and deep prefrontal cortical layers can directly activate specific inputs to the re-entrant loop. Thus, the outputs from the inter-laminar microcircuits of prefrontal cortex are in ideal position to support the decision to act via the synchronous excitation of the constellation of circuits in the executive hierarchy.

Executive control is a fundamental function of the brain that mediates the integration of perception and action during behaviorally relevant environmental events. It has been proposed that executive control involves a broad network of brain areas, including frontal and parietal/temporal cortex, as well as striatum and other subcortical structures. These structures have been consistently associated with roles in sensorimotor integration and selection of task specific behavioral responses, commonly considered to be the regions necessary for ‘executive decisions’. However, what is not known is how such areas are synchronously activated via the inter-laminar
microcircuits that operate to segregate information in a manner consistent with control of movements necessary during the perception-to-action cycle that defines executive decision making in behavioral tasks.

Results

Prior evidence suggests that a critical role in this mechanism is played by inter-laminar microcircuits consisting of prefrontal cortical minicolumns in human and animal models. These minicolumns are composed of neurons whose dendrites form horizontal and vertical connections within the same cortical layer. The minicolumns receive inputs from the thalamus and other brain regions and send outputs to other cortical and subcortical areas. The minicolumns are organized in a well-defined hierarchical structure, with layers 2/3, 4, 5, and 6 forming distinct functional units. The minicolumns play a critical role in the integration of sensory information and the generation of motor responses.

Our approach to examine neural responses relevant to the perception-to-action information cycle involves the use of a delayed match to sample (DMS) task. The DMS task requires the subject to perform a series of trials in which they must remember the location of a sample stimulus and then choose the correct response to a test stimulus. This task is used to test the ability of the brain to integrate sensory information and generate appropriate motor responses.

In the DMS task, the subject is presented with a sample stimulus and then a delay period. During the delay period, the subject must keep the sample stimulus in mind. After the delay period, the subject is presented with a test stimulus and must choose the correct response to the test stimulus. The task is designed to test the ability of the brain to integrate sensory information and generate appropriate motor responses.

Our results show that the DMS task activates the prefrontal cortex, particularly the dorsal and ventral prefrontal regions. The dorsal prefrontal region is involved in the analysis of the sample stimulus, while the ventral prefrontal region is involved in the analysis of the test stimulus. The results also show that the DMS task activates the caudate-putamen, which is involved in the generation of motor responses.

In summary, our results suggest that the perception-to-action cycle is mediated by the prefrontal cortex and the caudate-putamen, which work together to integrate sensory information and generate appropriate motor responses. These findings have implications for the understanding of executive function and the treatment of diseases such as autism and Alzheimer’s disease.
phase of the task (Fig. 1C). The DMS task incorporated key features like the number of distracter images (2–4) which could appear in any of eight locations on the screen in the Match phase after variable durations of the intervening delay period (1 to 40 sec). These factors were reflected in the animal’s behavioral performance levels during encoding and selection of spatial or object stimuli as shown in Figure 1D.

Neurons were recorded simultaneously in PFC (n = 58 cells in layer L2/3 and n = 49 cells in layer L5) and in the striatum (n = 52 cells, caudate and putamen) while the animals performed the DMS task. Only prefrontal cortical pyramidal cells with excitatory (no inhibitory) firing correlates to sample and match DMS task events, and that demonstrated significant spatial tuning, were included in analyses. Consistent with previous reports,18,19 firing of cells in prefrontal layers and minicolumns reflected differential encoding of spatial and object trials in the DMS task. Figure 2A–F shows raster plots (A, B, C for perception and C, D, E for executive selection, right panels) depict firing preference, measured by the radial eccentricity (in spike/sec or Hz) in the polygonal contour for the eight different target locations on the screen where images appear. The overlay tuning plots compare firing preferences on Spatial (black arrow) vs. Object (pink arrow) trials for the same cells. The same tuning vectors also show the magnitude of firing for preferred locations during the encoding (left panel) and selection (right panel) phases of the task on Spatial and Object trials. Spatial trials tuning vectors (black) show the same preferred directionality (i.e. 270°) during the encoding and selection phases in both PFC layers and in caudate nucleus, suggesting parallel processing streams/loops through cortical minicolumns and striatum and likely through the entire thalamo-cortical loop. But when processing object information directional preference changes in the three cells tuning plots, suggesting that object information processing does not follow in the same “foot prints” as processing by the same cells on Spatial trials. The radius of polar plots is represented in Hz and tuning amplitude is measured in Hz, as well. Asterisks: **p < 0.001, ANOVA.

The polar plots in Figure 2 show that neurons in layer 2/3 and 5 fired similarly with caudate neurons and were synchronized and spatially tuned to the same screen locations (black arrows). However, when the same neurons fired on object trials (blue arrows) either a decrease or a direction change in tuning (firing to preferred location) occurred between the same 3 areas. When compared during match phase presentation (Match Tuning) neural tuning directions for the 3 regions were again similar on spatial trials (black arrows), but not on object trials (blue arrows), as shown previously19. This feature is extremely important because it dissociates spatial preference under these two trial conditions and indicates that increased firing in these particular microcircuit connections was sensitive to particular spatial locations where task-dependent responses are performed.

Figure 3A compares the average firing response during sample presentation (spatial perception) in PFC layers 2/3 and 5 with simultaneous cell firing in the striatum. In Figure 3B average firing responses of the same cells are compared during target selection in the match phase. Significant increases in firing rates of cells in PFC layers and striatum were obtained during spatial trials in both the perception (layer 2/3: F(1,1159) = 21.63, p < 0.001, n = 58; layer 5: F(1,979) = 6.73, p < 0.01, n = 49 cells; caudate: F(1,1039) = 7.32, p < 0.01, n = 52 cells; ANOVA) and selection (layer 2/3: F(1,1159) = 22.47, p < 0.001, n = 58; layer 5: F(1,979) = 15.56, p < 0.001, n = 49 cells; caudate: F(1,1039) = 9.13, p < 0.01, n = 52 cells; ANOVA) phases of the task (Fig. 3A&B), however, firing in these same areas was less during the perception phase on object trials (Fig. 3 A&C).
Figure 3 | Mean firing responses and population tuning of prefrontal cortical and striatal cells during Spatial and Object trials. (A&B) Spatial trials. Comparison of mean firing rates of neurons during encoding (A) and selection (B) across prefrontal cortical layers (L2/3 and L5 and Striatum (Caudate nucleus) during “Spatial” trials. Prefrontal cortical L2/3 cells (n = 58) showed elevated firing during encoding and selection on spatial trials. Striatal (Caudate nucleus) cells (n = 52) showed a higher firing rates at the trial start when the spatial rule entered in effect. PFC layer 5 cells (n = 49) displayed moderate involvement in perception and selection. (C&D) Object trials. Comparison of mean firing rates of the same cells during encoding (C) and selection (D) is shown during Object trials. Cells in both prefrontal layers and striatum had much lower firing rates during Object (image) encoding and higher rates during the match, target selection, phase. The F values for (PFC layer 2/3, PFC layer L5, caudate) in (A) Sample-Spatial (F(1,1159) = 21.63, p < 0.001; F(1,1039) = 6.73, p < 0.01; F(1,1039) = 7.32, p < 0.01), (B) Match-Spatial (F(1,1159) = 22.47; p < 0.001; F(1,979) = 15.56; p < 0.001; F(1,1039) = 9.13; p < 0.01), (C) Sample-Object (F(1,1159) = 1.46; p > 0.5; F(1,979) = 1.27; p > 0.5; F(1,1039) = 1.23; p > 0.5) and (D) Match-Object (F(1,1159) = 18.67; p < 0.01; F(1,979) = 16.51; p < 0.001; F(1,1039) = 14.31; p < 0.001). (E&F) Selection Phase. Comparison of neural tuning in prefrontal cortical layers and striatum during target selection on Spatial and Object trials. In (F) the arrangement of spatial locations/directions has been rotated so that the highest firing rates for all trials within the session correspond to 0° location/direction for every neuron. Error bars represent SEMs. Asterisks: **p < 0.001 ANOVA.

Figure 4 | Distribution of preferred prefrontal-striatal cell firing at each target selection location. (A–C). Polar plots showing the distribution of preferred firing directions for “Spatial” and “Object” trials in PFC layer 2/3 (A), layer 5 (B) and caudate nucleus (C) recorded simultaneously during the executive selection (match) phase of the DMS task. The average % of cell firing for each cell type tuning vector direction (in Figure 2) is represented by the corresponding target location in a circular histogram. The polar plot measures the percentage of cells with highest firing rates at those locations (tuning vectors) and the asterisks indicate the highest percentage of cells from the total population with firing rates at that particular location/direction. Asterisks: **p < 0.001, Rayleigh test.
Figure 3D shows significant increases (layer 2/3: \( F(1,1159) = 18.67, \) layer 5: \( F(1,979) = 16.51, \) caudate: \( F(1,1039) = 14.31, \) \( p < 0.001, \) ANOVA) in the firing of neurons in both PFC layers and in striatum for object trials during the target selection phase. Figure 3E&F shows a direct comparison of overall firing in the Perception and Selection phases across all 3 areas clearly indicating higher mean firing rates for spatial vs. object trials (F(1,1271) = 10.96; \( p < 0.001, \) n = 159, ANOVA; \( p < 0.001; \) Rayleigh test).

Figure 4A–C shows the polar distribution of the proportion of tuned firing across the population of cells (PFC layer 2/3, 5 and caudate) shown in Figure 3E&F, for the tuning vectors during spatial vs. object selection. Each cell’s tuning vector (see Fig 2) is mapped to the corresponding target location/direction in a polar plot histogram. The overall distribution of spatial tuning shows a general preference (layer 2/3: \( p < 0.001, \) n = 58; layer 5: \( p < 0.001, \) n = 49; caudate: \( p < 0.001, \) n = 52, Rayleigh test) for the contralateral targets with only a few cells showing ipsilateral preference, as expected\(^{24}\). In addition, this distribution on signaled spatial trials was clearly distinct from that when object selection was the rule, which is consistent with the perceptual dissociation of the task\(^{33}\).

To further test whether inter-laminar firing links spatial perception to executive selection we applied a novel type of closed loop patterned stimulation previously shown to facilitate performance of the same task\(^{29,35}\). This is shown in Fig. 5 as a functional diagram in which neural firing in PFC layer 2/3 was recorded with a multi-electrode array\(^{16,19}\) and fed into a nonlinear multi-input–multi-output (MIMO) math model (Fig. 5A & Fig. 3S Supplemental Information), which processed and simultaneously delivered a pattern of electrical pulses from a multi-channel stimulator that mimicked the correlated firing of PFC layer 5 cells on successful trials\(^{35}\). MIMO stimulation methods and associated control procedures proving columnar activation have been previously published in detail\(^{18,35}\). These controls included delivery of stimulation pulse patterns that were different than what the MIMO model derived for correct trials. In this case the intensity and the number of pulses, plus the area (L5) that was stimulated were identical, however the only factor that was different was the pattern that did not match the effective MIMO derived output shown in Supplementary Figure 3S.

Figure 5B shows a peri-event multigram the spatial preference firing of a PFC layer 2/3 cell during the selection phase in which the cell fired highest for spatial match targets located at 315°. Figure 5C shows behavioral tuning across stimulation sessions under spatial and object rules. Spatial trials showed improved accuracy when MIMO stimulation was delivered, but performance was...
enhanced more on trials in which the target was in the preferred firing location (315°) on the screen (p < 0.001; Rayleigh test). This puts neural (Fig. 4) with behavioral ‘tuning’ in good agreement as it is necessary for causal relation to the perception-to-action cycle.

The effectiveness of MIMO stimulation delivered to this particular region of PFC is shown in Figure 5D where the preference effect on stimulated (Stim) vs. nonstim trials is compared for all Spatial (n = 40 sessions) and Object type trials (n = 50 sessions) within the same session. The difference in mean % correct performance for all stim vs. nonstim trials (ALL) is shown in comparison to stim vs. nonstim trials in which performance at locations was significantly above that at all other locations (Facilitated). The marked difference (F(1,319) = 13.59, p < 0.001; ANOVA) in the degree of increase in % correct trials produced by MIMO stimulation at preferred vs. non-preferred (ALL) locations indicates that in addition to facilitating performance at all response locations, the stimulation enhanced the innate directional preference (spatial tuning) which corresponds to the anatomic location of the PFC layer 2/3 minicolumn. This demonstrated that the MIMO stimulation delivered during the match/selection phase of the task was likely to have facilitated discharge of Layer 5 neurons in the same recorded minicolumns and that is what improved spatial target selection in this phase of the task.

The unique feature of these experiments is that they allow us to tap into the perception-to-action cycle. As a final validation of microcircuit tuning in PFC and caudate we compared polar firing across the same three nodes in the perception and selection phases on spatial trials in which MIMO stimulation induced increases in performance. Figure 6 A–C shows nearly complete overlap (between 81% and 91%) in spatially tuned firing indicating that the majority of neural tuning vectors for the preferred microcircuit target location (315°) facilitated task performance when subjected to MIMO stimulation during spatial trials. The anatomic link between prefrontal cortex and striatum is demonstrated physiologically normalized cross-correlations pairs of cells in PFC layer 5 and Caudate displaying synchronized firing during Match target presentation epoch (0, 2 s; red) compared to the pre-Match epoch (−2 s, 0; blue). Therefore, such synchronized firing of PFC and Caudate neurons during the match phase (dealing with target selection and executive control; Fig. 6E) is telling us that these key nodes in the prefrontal cortical striatal loop show the modulation of executive control signals in the cortical-striatal executive loop.

![Figure 6](image-url) | Overlap of preferred firing and stimulation induced performance tuning during the perception-to-action cycle. (A), (B). Polar plots showing the distribution of preferred firing direction for "Spatial" trials in PFC layer 2/3, layer 5 and caudate during the perception phase (A), and the executive selection phase (B) as shown in Figure 4A–C. (C). Distribution of facilitated correct performance for spatial selection during MIMO stimulation sessions (Figure 5D). The red dotted contour of tuned activity of the neurons from PFC layer 5 is overlaid to indicate similar preferred locations for columnar tuning and MIMO-stimulation facilitated performance. (D). Prefrontal-striatal correlation. Normalized cross-correlations (overlay) between n = 54 pairs of cells in PFC layer 5 and Caudate depict synchronized firing during Match target presentation (0, 2 s; red) compared to the pre-Match epoch (−2 s, 0; blue). There was a marked difference between CCHs in Match vs Pre-Match conditions; F(1,107) = 21.82, p < 0.001; ANOVA. (E). Functional diagram showing a representation of the flow of information in the PFC-caudate tuned spatial relationship across brain regions and behavior in the perception-to-action cycle. Same symbols apply as in Fig. 1 A. Asterisks: **p < 0.001, ANOVA.
Discussion

These novel findings demonstrate a robust involvement of cortical layers and striatum in the perception-to-action cycle. This is supported by implementation of the MIMO model which extracts the percept from prefrontal layer 2/3 and imparts the appropriate signal to columnar related layer 5 cells, thereby strengthening activation via the executive loop through the caudate nucleus (shown in Fig. 6D) to manifest selection of a particular target location. Given these findings, the functional specificity of the perceptual circuit is likely determined via a "tuned" inter-laminar microcircuits connected to executive prefrontal cortico-striatal, thalamo-cortical loops, that are translated into action via "cogntis" that coordinate information in large scale networks.

The enhancement in cognitive performance by the MIMO stimulation may be explained by induced changes in the balance between excitation and inhibition in cortical-striatal loop and by the temporal specificity of the PFC layered L2/3–L5 firing pattern, since stimulation in a "scrambled" (random) pattern with the same pulses impaired performance in prior studies. The microstimulation current activates the neighboring minicolumns around the microelectrode pad/tip causing the preference of this group of minicol- umns to win the competition for the behavioral output. Consequently, the memory encoder for the encoded target may recruit more relevant inputs when stimulated compared to non-stimu- lated control trials. This view is supported by the fact that in the case of anti-phase stimulation, the % correct performance decreases below the normal (non-stimulation) level possibly because some of the attractors may become repellers under that condition. We do not exclude the potential limitations of the electrical microstimulat- ion, with respect to specificity of the effects, compared to optogeo- netics (for example), but the application of such methods to primates has not been accomplished yet.

Furthermore, perception and action seem consistent with a lam- inar segregation in gamma (40–60 Hz) and alpha (6–16 Hz) fre- quency coherence along the ventral stream, in which gamma coherence is confined to supra-granular layers and the alpha range to infra-granular layers. Similarly, in prefrontal cortex, rule-specific synchrony at "beta" (19–40 Hz) frequencies, suggests that synchrony of beta-frequency selects the relevant rule circuit, while alpha-fre- quency synchrony deselects a stronger, but currently irrelevant, ensemble in complex overlapping circuits. Therefore, these results clearly indicate the need for inter-laminar microcircuits to bind perception and action.

In summary, these experiments provide support for the cortical- ganglia loop model of executive control in key nodes of the loop including PFC layer 2/3, layer 5 and caudate nucleus, as well as a causal relationship involving the inter-laminar microcircuits of prefrontal cortex in tuned behavior. The results show that neuronal firing in supra-granular layers of prefrontal cortex increased during the perception phase of spatial vs. object trials while during the executive selection phase of the task both prefrontal layers and stria- tal cells show increases in firing rates on both types of trial (Fig. 2 & Fig. 2S). Model generated MIMO stimulation of layer 5 cells with a pattern of pulses derived from cell firing in layer 2/3 increased correct performance during selection of a spatial target at a particular spatial location during the session in which selection of targets at other locations was not improved as much. These findings suggest that prefrontal inter-laminar microcircuits play a causal role in linking perception to the executive selection of spatial targets (Fig. 6) that occupy the domain to which such microcircuitry has been tuned via past experience. In fact we were able to demonstrate activation of an innate PFC minicolumnar bias via MIMO model-controlled stimulation which resulted in improved performance on trials in which that specific type of information was required but only within a particular context. This discovery provides an important basis for building cognitive prosthetics in order to reverse cognitive deficits in a broad spectrum of diseases like schizophrenia, dementia, autism, ADHD, addiction, aging and executive dysfunction, in which inter-laminar processing is likely disrupted due to cortical tissue damage or malfunction.

Methods

Four male rhesus monkeys (Macaca mulatta) were utilized as subjects in all DMS sessions. Single neuron activity was recorded simultaneously from PFC and striatum (Caudate) using our tetrode microdrive and a costumed-designed multi-electrode array. ETM (Electrode Tip Marking) was specifically designed for this purpose (Center for Microelectrode Technology – CenMet, Lexington, KY). Each nonhuman primate was trained to perform a complex DMS task for juice rewards. Assessment of neuron activity within different PFC cortical layers and striatum was performed using recording activity (Figs. 1S & 2S Supplementary Information) and MIMO stimulation (Fig. 3S Supplementary Information) related to Match phase image presentation up until completion of the motor target selection response, as shown in Figs. 2, 3, 5 and 2S (Supplementary Information). All surgical and animal care procedures were performed in accordance with National Institutes of Health guidelines and were approved by the Wake Forest University Animal Care and Use Committee. Full Methods and associated citations are available in the Supplementary Material file associated with this manuscript.

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I.O., R.E.H. and S.A.D. designed experiments, I.O. analyzed data, I.O. and S.A.D. wrote the paper; L.M.S., I.O. and R.E.H. conducted and supervised experiments, G.A.G. provided the anatomical element in-common to multiple laminae. Brain Pathol. 20(2), 451–458 (2010).

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