From neurons to large-scale networks, hierarchical coding appears to be a ubiquitous functional property

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Introduction

❖How the brain enables primates to plan and sequence cognition and behavior across time remains unclear.

❖Duncan and colleagues found that the lateral prefrontal cortex (both dorsolateral and ventrolateral) coded sequential task events hierarchically: i.e., general task phases were coded separately, and within each phase, specific stimulus information was coded.[1,2]

❖To determine whether other related brain regions represent sequential events hierarchically, we recorded from individual neurons in ten brain regions in primates in a task that required both cognitive and action control.

Methods

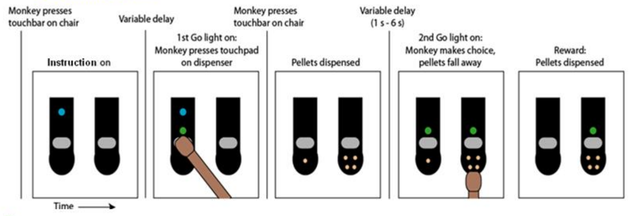
❖ We tested two male rhesus monkeys (*Macaca mulatta*), denoted A & W. Each monkey sat in a custom-made primate chair with his head fixed, his left arm comfortably restrained, and his right arm free to reach.

❖ The monkeys were trained on two rules[8] using a custom-made pellet dispenser system:
- ❖ A ***conventional*** prepotent rule (**PP**) to select the larger of two quantities (see ***A***)
- ❖ An ***unconventional*** reverse-reward rule (**RR**), in which they must select the smaller quantity to receive the larger (see ***B***)

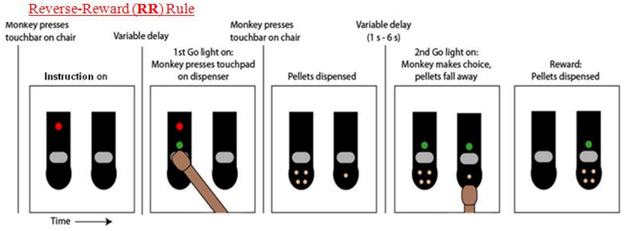
❖ The task also required two responses: once to touch a touchpad mounted underneath the instruction cue, and a second time to make a choice at the end of the trial.

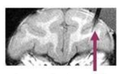
❖ Thus, there were multiple task phases as well as specific cognitive and action demands.

A. Conventional: Prepotent (**PP**) Rule

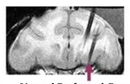


B. Unconventional: Reverse-Reward (**RR**) Rule

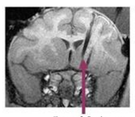




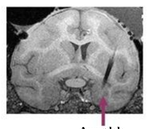
Lateral Prefrontal Cortex



Ventral Prefrontal Cortex



Dorsal Striatum (caudate)



Amygdala

❖We conducted the test sessions in both *block* and *mix* conditions. In *block*, there were 12 prepotent rule trials, then 24 reverse-reward trials, then 12 prepotent trials. In *mix*, both rules were pseudo-randomly interleaved. In our analyses, the block and mix conditions are combined.

❖Along with the two *rules*, we also denoted two spatial goals, based on the monkey's reaching direction: *left* or *right* touchpad or dispenser.

❖While the two monkeys performed the choice task, we used a multi-electrode system *(Plexon, Inc., Dallas, TX)* to record single neurons from different frontal cortical and limbic structures.

❖We used (a) magnetic resonance imaging (MRI), (b) a monkey brain atlas and (c) neurophysiological signals to verify that the electrodes reached the targeted sites for both monkeys. The figures to the left show four coronal slices of one subject's brain, with arrows indicating electrode tips.

Results

	Brain region	MONKEY	TOTAL NEURONS	TASK-RELATED	PERCENTAGE (%) TASK-RELATED
1.	Dorsolateral prefrontal cortex	A	96	85	89
		W	106	74	70
2.	Ventrolateral prefrontal cortex	A	81	66	81
		W	134	93	69
3.	Medial prefrontal cortex (Anterior Cingulate)	A	101	72	71
		W	170	101	59
4.	Orbitofrontal cortex	A	77	48	62
		W	46	22	48
5.	Dorsal premotor cortex	A	104	94	90
		W	276	180	65
6.	Dorsomedial striatum	A	152	104	68
		W	104	60	58
7.	Ventral striatum	A	84	52	62
		W	76	44	58
8.	Mediodorsal thalamus	A	94	69	73
		W	9	6	67
9.	Agranular insula cortex	A	97	71	73
		W	39	26	67
10.	Basolateral amygdala	A	120	74	62
		W	16	11	69

❖The first three columns of the table to the left show the recorded brain regions and the number of recorded neurons for each monkey.

❖The *Task-related* column shows the number of neurons with significant firing rate modulation (ANOVA, $p \leq 0.01$) across eight time periods: (1) instruction light, (2) prior to the 1st response requirement; (3) after the first 'go' cue; (4) pellet presentation, (5) pre-reach, (6) reach, (7) end-of-reach (or goal acquirement); and (8) the reward period (500 ms windows). Only these neurons were used for further analysis. The last column shows the percentages of task-related neurons.

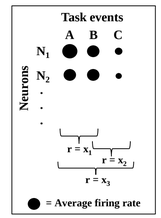
❖ We then conducted a two-way ANOVA ($p \leq 0.01$) in each time period with rule and spatial goal as factors. For neurons showing significant rule-related activity, we further classified them as PP or RR rule neurons based on highest firing rate.

❖Next, to characterize the modulation patterns in the firing rates across the task, we conducted modularity analysis (Louvain method) on all neurons together, and then on all neurons within each brain region.

❖The graphs below show the results, in which general modulation patterns are organized into "communities".

❖As illustrated to the right, we next sought to determine how the brain regions represented the sequential task events.

❖ Following Sigala et al., 2008, we then performed clustering analysis on the task periods: *i.e.* for each period, producing a vector, with each component of the vector representing each neuron in the given brain region, with each value being the average firing rate across correct trials for the neuron.

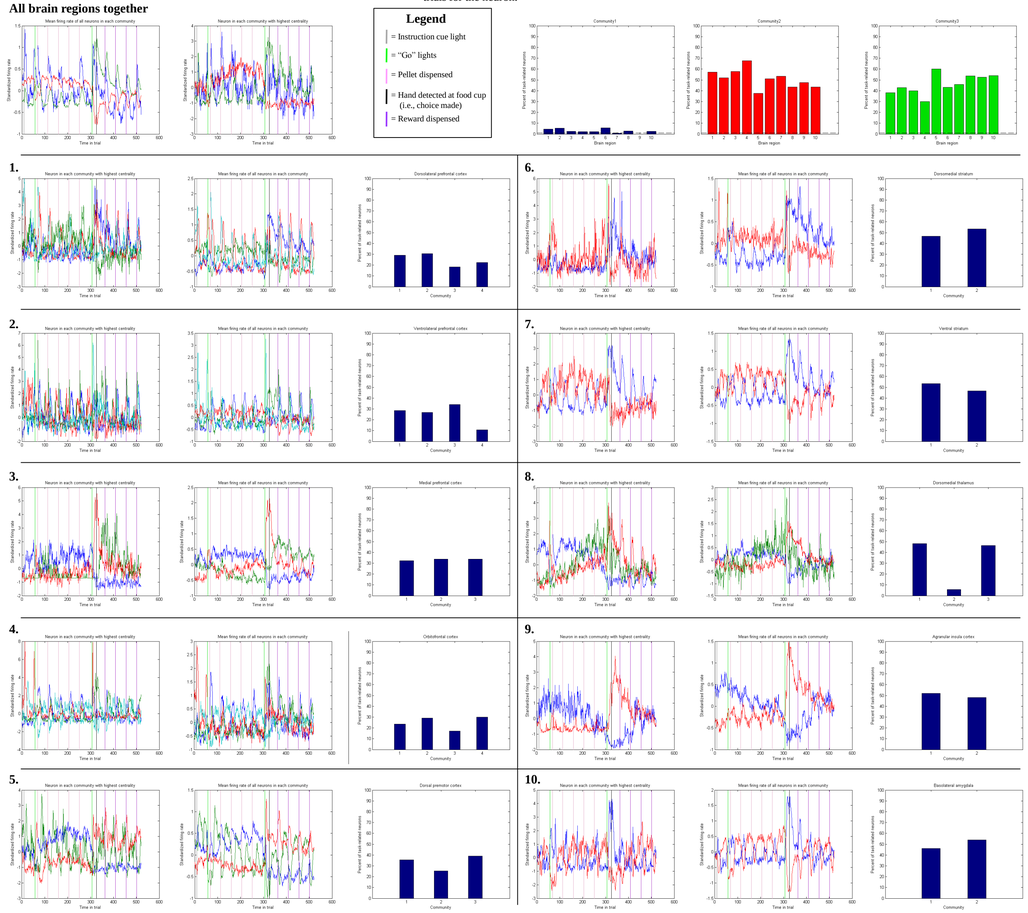


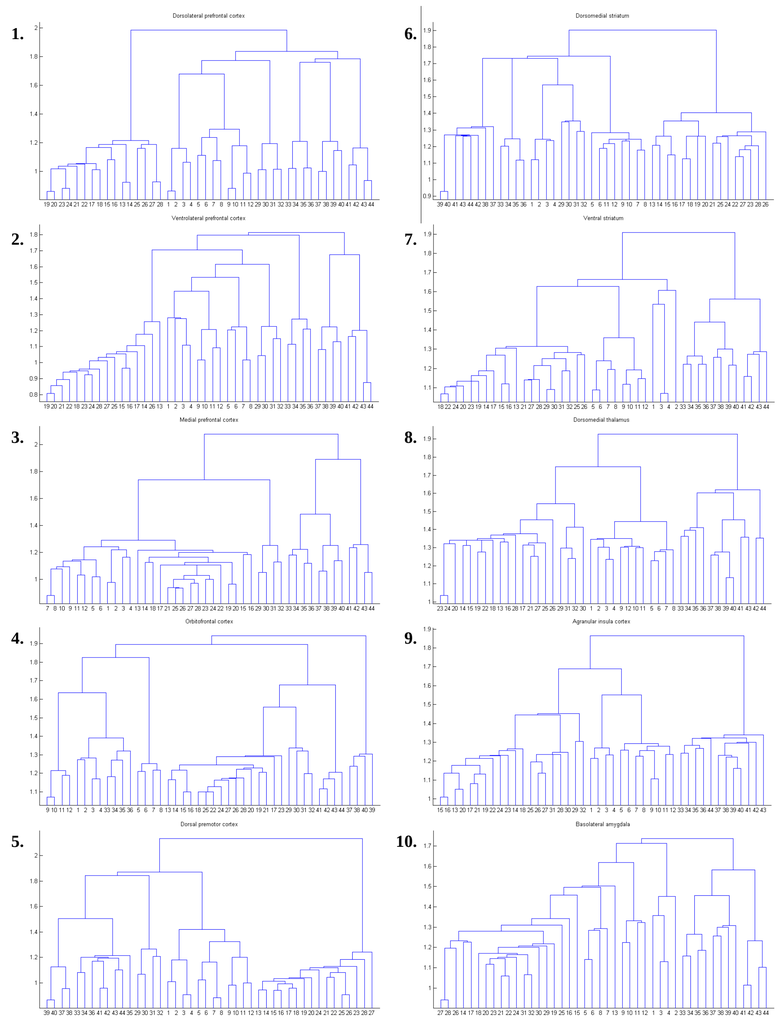
Average firing rates:
- **Prepotent Rule trials**
- **Reverse-reward Rule trials**
- **Left Choice trials**
- **Right Choice trials**

Task events:

1-4	Instruction cue on
5-8	Pre-reach to touchpad
9-12	Reach to touchpad
13-16	2nd Pellet dispensed
17-20	3rd Pellet dispensed
21-24	4th Pellet dispensed
25-28	5th Pellet dispensed
29-32	Pre-reach
33-36	Reach/Choice
37-40	End of reach
41-44	1st Reward pellet

All brain regions together





Summary & Conclusions

❖ We found strong *hierarchical clustering* of the task requirements.

❖ Overall, the first main cluster of the task components was based on the general task phases: all instruction cue periods clustered together, *etc.* Within each cluster for task phases were subclusters for the specific rule (Prepotent or Reverse-reward) and spatial goal (left or right dispenser).

❖ Thus, neuronal activity at the population level was primarily modulated by the task phases, followed by the cognitive and action control requirements of the specific rule and location.

❖ We found hierarchical clustering in every brain region.

❖ Thus, hierarchical coding appears to be a ubiquitous functional property in the brain.

❖ It has been argued that this hierarchical structure is necessary for proper planning and sequencing of cognition and behavior. [1,2]

References

1. Sigala et al., (2008). *PNAS.*
2. Duncan, (2010). *TICS.*

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