Cognitive and action control neuronal signatures reveal functional properties of large-scale brain systems in primates

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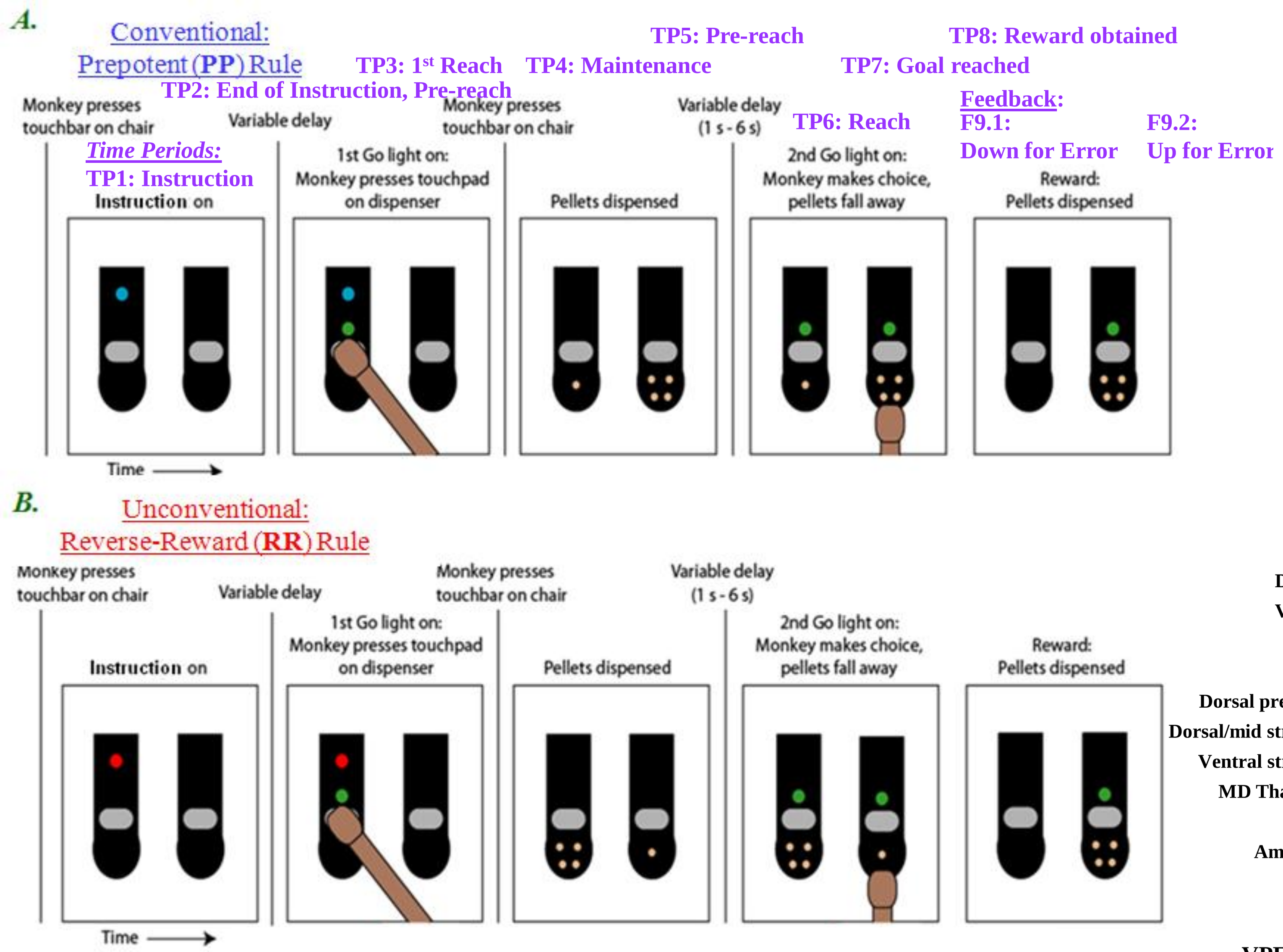
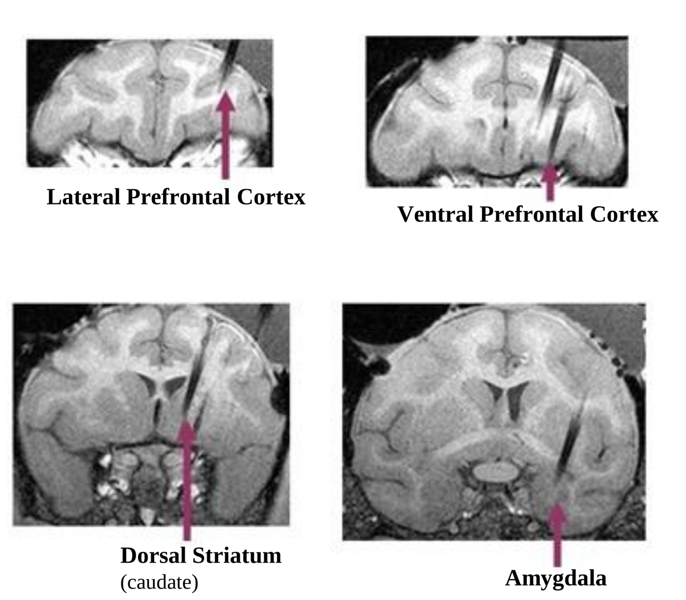
Introduction

- ❖Functional imaging and anatomical connectivity studies are revealing large-scale networks in the brain.[1-6]
- ❖However, the functional significance of these networks remains unclear.
- ❖We build on work that identifies networks in part based on brain regions that share particular cognitive and behavioral control signatures.[2, 3, 7]
- ❖We also attempt to bridge the gap between imaging and neuroanatomical findings, on the one hand, and neurophysiological results at the single neuron level, on the other.
- ❖We recorded from individual neurons in ten brain regions in primates and examined whether the neuronal population in a given region exhibited similar functional properties to other regions, which might suggest participation in large-scale brain systems.

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 time periods to test for different cognitive and action control signals:[2,3]





❖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.

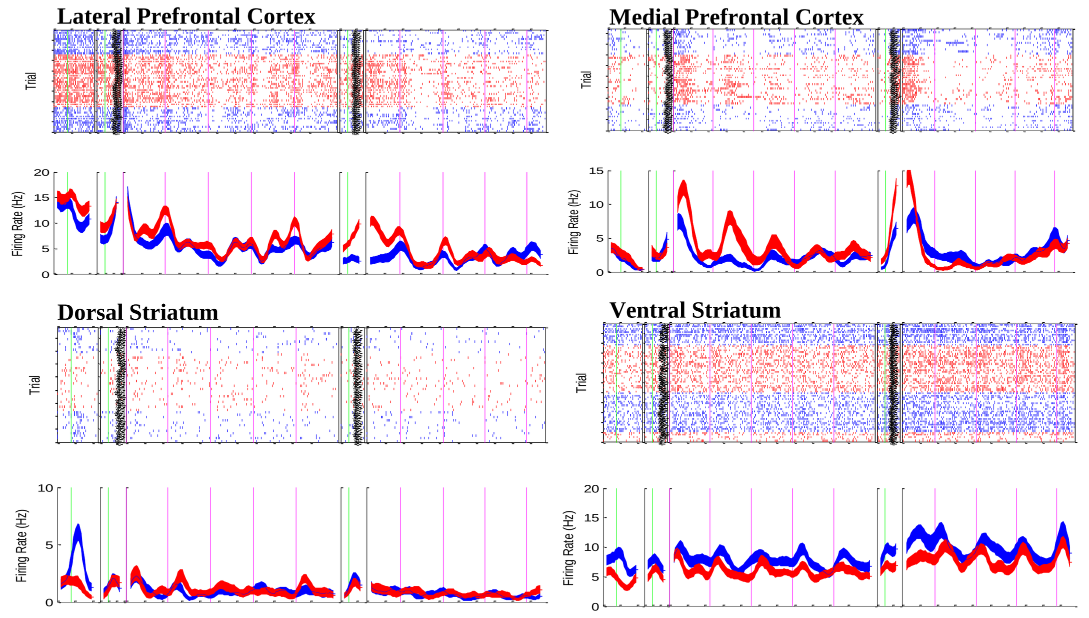
❖While the two monkeys performed the choice task, we used a multi-electrode system (*Plexon, Inc., Dallas, TX*) to record single neurons from different frontal cortical and limbic structures.

❖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

	AREA	MONKEY	TOTAL NEURONS	TASK-RELATED	PERCENTAGE (%) OF TASK-RELATED
1.	Dorsolateral Prefrontal	A	96	85	89
		W	106	74	70
2.	Ventrolateral Prefrontal	A	81	66	81
		W	134	93	69
3.	Medial Prefrontal (Anterior Cingulate)	A	101	72	71
		W	170	101	59
4.	Ventral Prefrontal	A	77	48	62
		W	46	22	48
5.	Premotor cortex	A	104	94	90
		W	276	180	65
6.	Dorsal/medial 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.	Insula (agranular)	A	97	71	73
		W	39	26	67
10.	Amygdala	A	120	74	62
		W	16	11	69

Rule Selective Neurons



Legend:

- = Light: 1st is Instruction cue, 2nd and 3rd are "go" cues)
- = pellet dispensed
- ✱ = response detected at food cup
- = RR (Reverse-Reward) trials
- = PP (Prepotent) trials

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

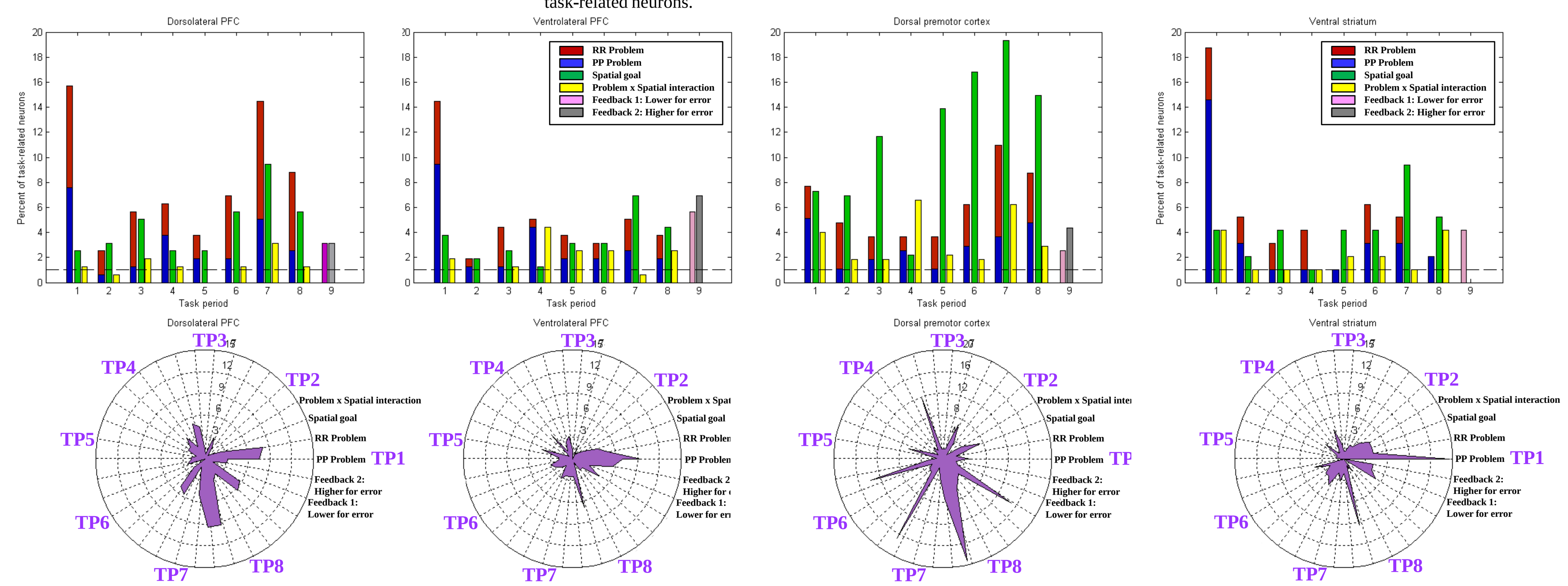
❖The *Task-related* column shows the number of cells with significant firing rate modulation (ANOVA, $p \leq 0.01$) between the eight time periods: (1) instruction light, (2) prior to the 1st response requirement; (3) after the first 'go' cue; (4) pellet presentation, (5) pre-reach, (6) reach, (7) post-reach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

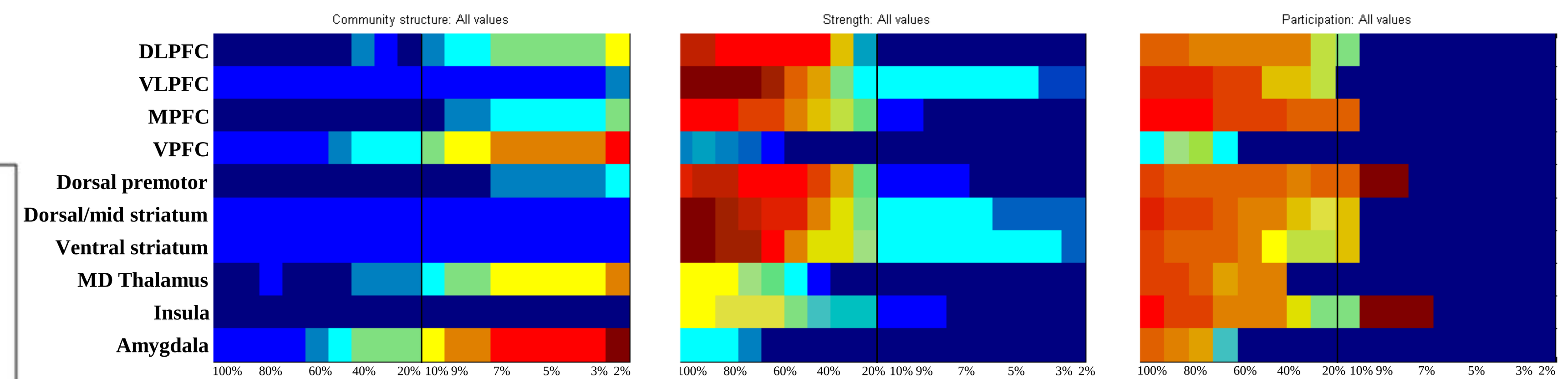
❖Raster plots and histograms are shown for four example neurons.

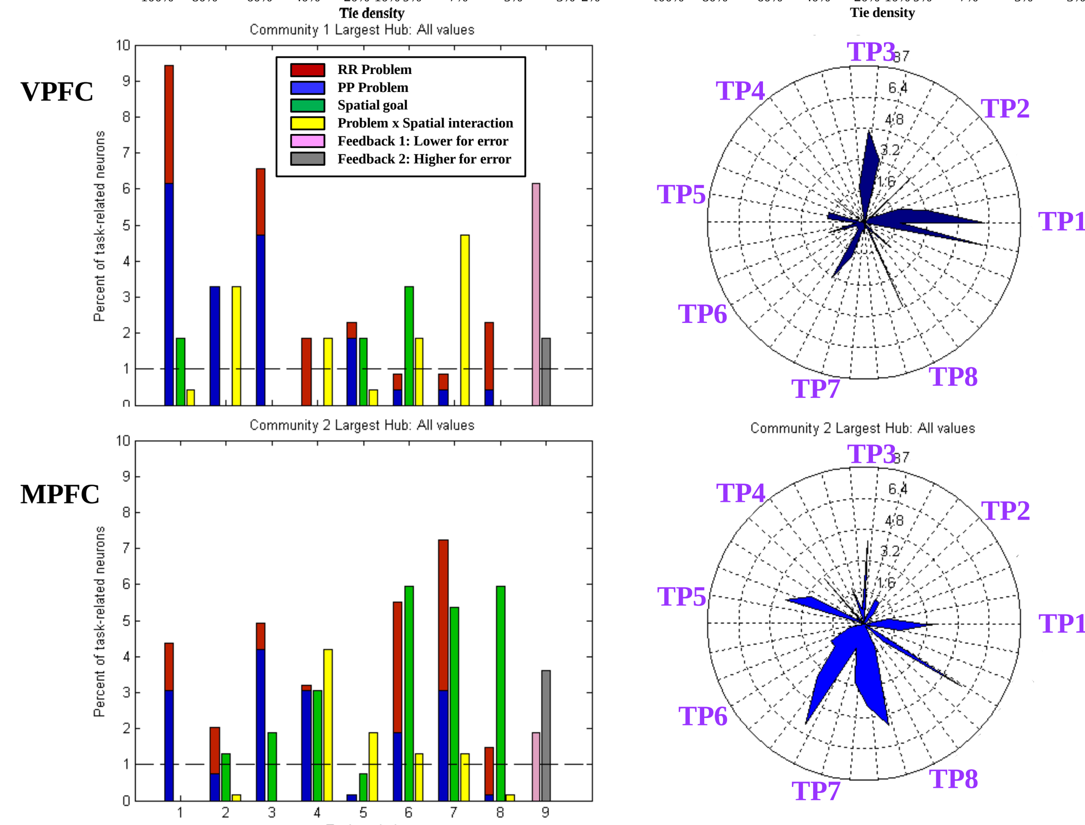
❖We then conducted a two-way ANOVA ($p \leq 0.01$) in each time period with rule and spatial goal as factors. For neurons showing significant rule-related activity, we further classified them as PP or RR neurons based on firing-rate preference.

❖We also conducted an *error analysis* in the feedback period (after the second reward pellet was or would be dispensed) (student's *t* tests, $p \leq 0.01$). Significant neuronal activity for correct versus error trials was further classified based on direction of firing-rate preference.

❖The bar graphs to the left below show the results for four example brain regions.



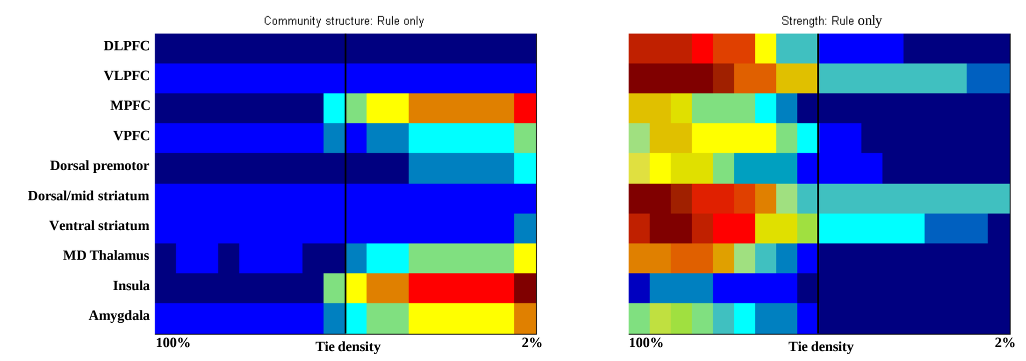


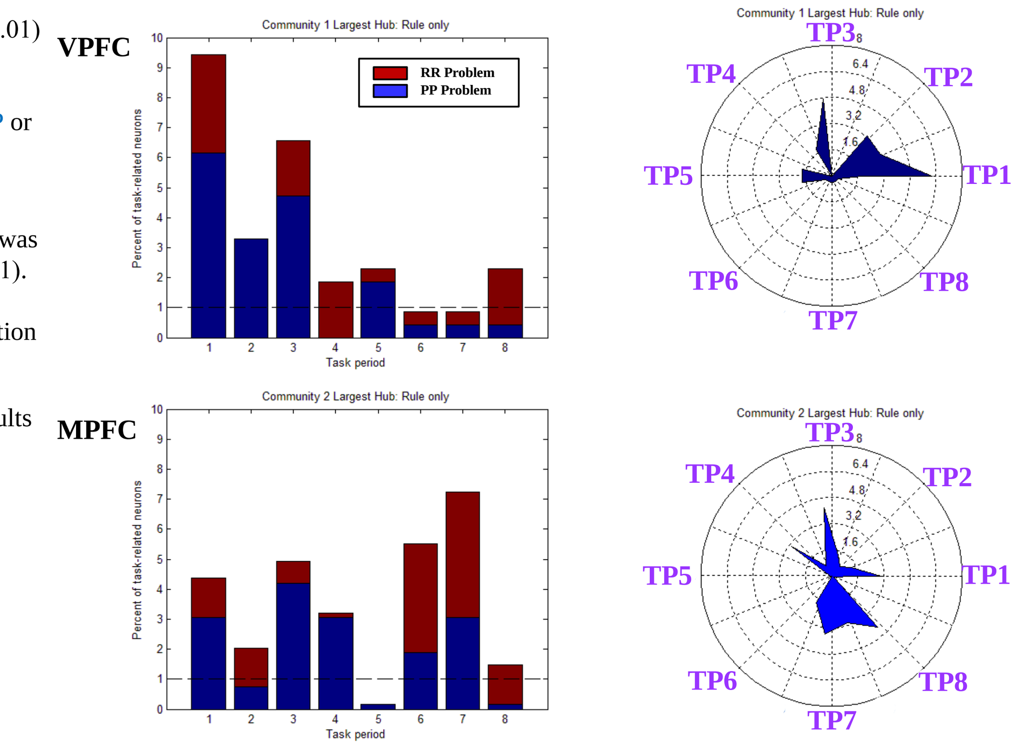


Community 1	*Community 2*
VLPFC	DLPFC
VPFC	MPFC
Dorsal/mid striatum	Dorsal premotor
Ventral striatum	MD Thalamus
Amygdala	Insula
Centrality order (highest to lowest):	*Centrality order (highest to lowest):*
VPFC	MPFC
Amygdala	Dorsal premotor
Dorsal/mid striatum	DLPFC
Ventral striatum	MD Thalamus
VLPFC	Insula
Strength order (highest to lowest):	*Strength order (highest to lowest):*
Ventral striatum	Dorsal premotor
VLPFC	MPFC
Dorsal/mid striatum	DLPFC
VPFC	Insula
Amygdala	MD Thalamus

- ❖ Each brain region can be characterized with a specific cognitive and action control 'signature' across the time periods that can also been seen as a "fingerprint" in a polar plot of the same results.[1,9]
- ❖ Note that larger values to the East represent initial instruction cue processing, whereas to the South represent activity later in the trial.[2,3]
- ❖ We next examined the similarities in functional processing across brain regions using network/graph theory analysis.[1-4]
- ❖ First, we generated a10x10 correlation matrix of all brain regions using the 34 percentages shown in the example graphs above.
- ❖ We next conducted modularity analysis to determine whether there were subcommunities among the regions. The analysis conducted on the correlations (i.e. no thresholding) produced two communities, listed to the right.
- ❖ Thresholding based on correlations (also called ties, links, edges, or connections) being above a given percentile helped determine the strength of connections between the regions[4]. The left color plot shows community membership across different threshold values. In our results, regions began to fall out of the correlation matrix and classifed as their own community, whereas strong relationships remained.
- ❖ The middle color plot shows individual *strengths* (i.e. the sum of all connection weights, i.e. correlations, for a given region).
- ❖ *Participation* (3rd color plot) shows the degree a region was associated with regions outside of its community.
- ❖ *Hubs* and *centrality* determine the extent to which a region is broadly associated with multiple areas. The results to the left represent *centrality* and *strength* within the given community.

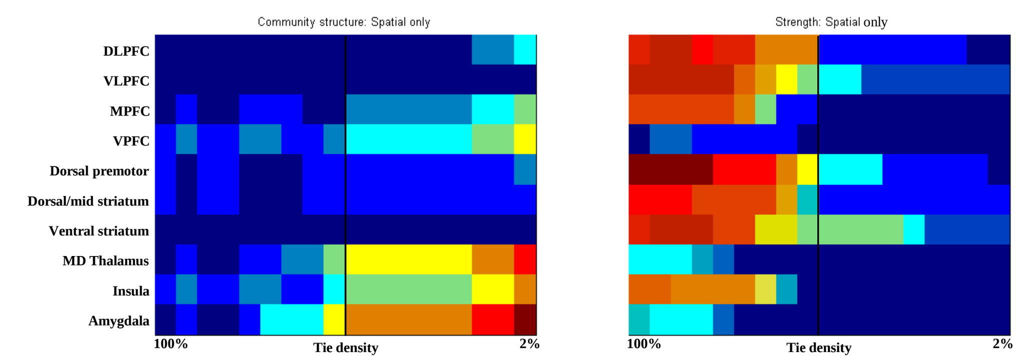
> ❖ A major characteristic of *Community 1* appears to be a larger initial instruction cue response; whereas *Community 2* appears to be more active later in the trial, notably during the reach and post-reach periods.

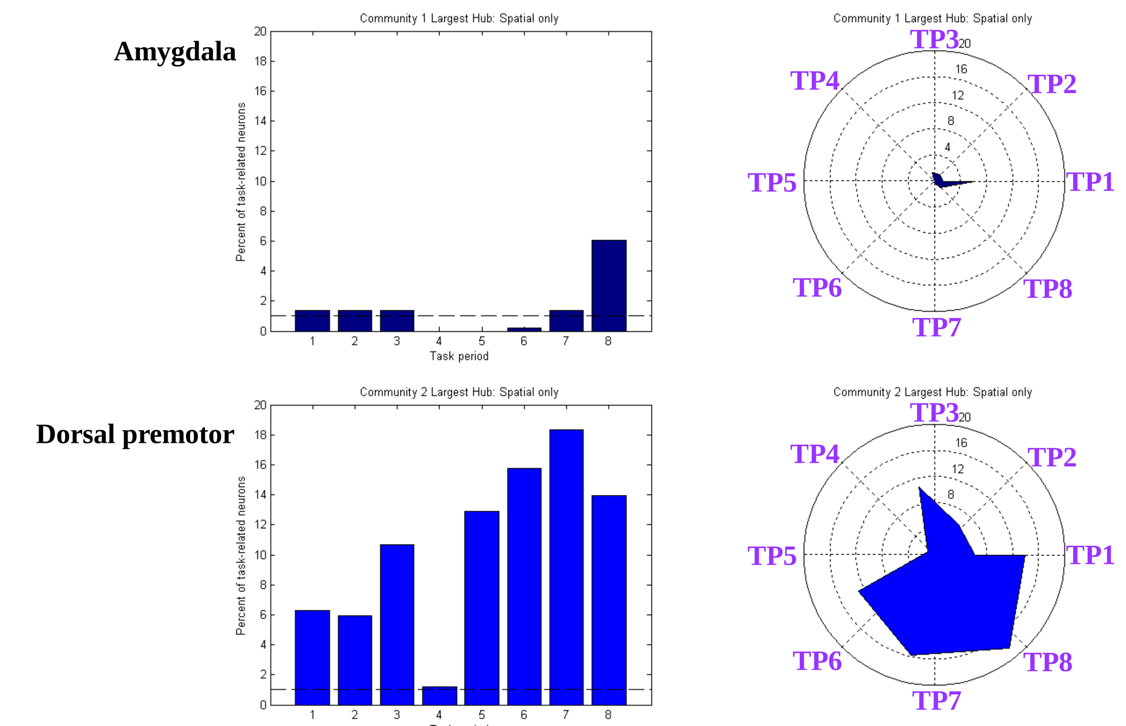




- ❖Although one might suspect that motor signals may be driving the findings, this was not the case.
- ❖We next analyzed the data with only the rule results: i.e. two percentages, for PP and RR neurons, across the eight time periods (16 values).
- ❖The community results were the same as those with all values, including community membership, as well as specific rankings of centrality and strength within the communities.

> ❖ Again it appears that a main characteristic of *Community 1 is* a larger initial instruction cue response; whereas *Community 2* is less so, and appears to be more active later in the trial, notably during the reach and post-reach periods.





- ❖Finally, we analyzed only the spatial data: the eight percentages across the time periods.
- ❖Some regions such as DLPFC, VLPFC, and ventral striatum showed a strong correspondence in spatial goal signature, as did Dorsal premotor and Dorsal/mid striatum.
- ❖Other regions such as VPFC showed little spatial goal activity, and likely should have been placed in a separate community. We will explore other analyses to help differentiate and clarify the spatial results.

Community 1	*Community 2*
DLPFC	VPFC
VLPFC	Dorsal premotor
MPFC	Dorsal/mid striatum
Ventral striatum	Insula
MD Thalamus	
Amygdala	*Centrality order (highest to lowest):*
	Dorsal premotor
Centrality order (highest to lowest):	Insula
Amygdala	Dorsal/mid striatum
Ventral striatum	VPFC
MD Thalamus	
VLPFC	*Strength order (highest to lowest):*
MPFC	Dorsal premotor
DLPFC	Dorsal/mid striatum
	Insula
Strength order (highest to lowest):	VPFC
VLPFC	
DLPFC	
Ventral striatum	
MPFC	
MD Thalamus	
Amygdala	

Summary & Conclusions

- ❖ We have taken the first steps in bridging the gap between analyses conducted at the broader fMRI/BOLD signal scale with recordings at the single neuron level in monkeys.
- ❖ We found similarity in cognitive (e.g. rule) and action (spatial) control signals across several brain regions, enabling us to identify two communities, as well as stronger associations within these communities.
- ❖ These findings appear similar to others that have identifying relationships between brain regions on a larger scale.
- ❖ Future work should also record baseline (i.e. resting state) activity as well as local field potentials to compare with the task-related results.
- ❖ It will be critical to elucidate the neuronal mechanisms that give rise to the large-scale functional relationships observed at higher levels of analysis (such as in fMRI BOLD signals).

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