Estimation of Control Modulated by Dopamine in Parkinson's Disease

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INTRODUCTION

- **Depression is highly prevalent in Parkinson's disease** (PD)[1]
- Aberrant **dopamine** signaling is a factor impairing the ability to **learn statistical regularities** in the environment[2,3,4]
- **Estimating the controllability of the environment** is a key environmental statistic fundamental to the **learned helplessness** model of depression[5]
- We **hypothesize that dopamine plays a crucial role in estimating the controllability of the environment**
  - Does dopamine signaling affect the estimation of environmental controllability in persons with PD?
- We conducted an **online study with 90 individuals** diagnosed with PD
  - Perform a task designed to assess their ability to estimate the controllability of the environment[6]
  - Prior to the task participants were asked to self-report how medicated they felt

Key Concept: Controllability - The influence actions have over the environment

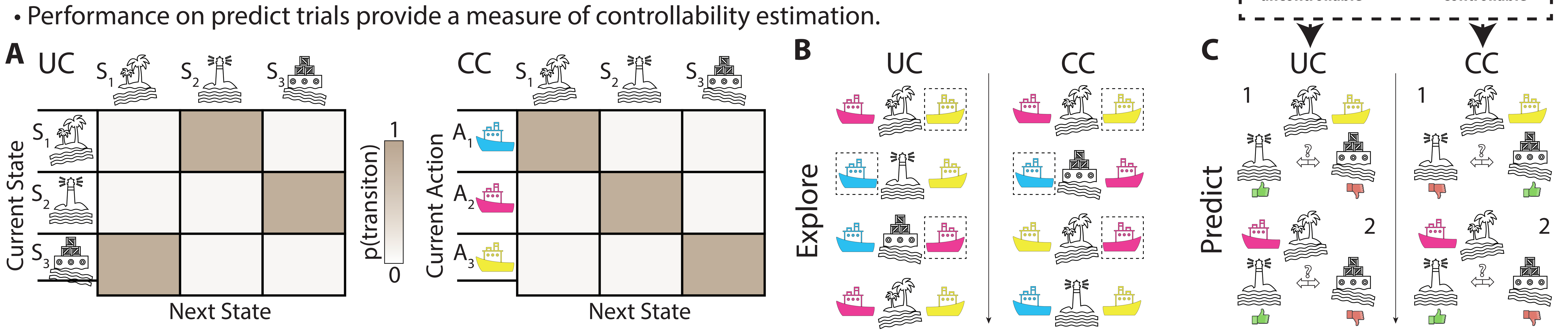
TASK

- On each trial, participants see 1of 3states (island, lighthouse, harbor) and are instructed to predict the state on the next trial.
- They are told that the next state can depend on which boat they choose (in controllable task-phases) or only on which state they are in now (in uncontrollable task-phases). To predict the next state, they need to choose between boats to find out whether they are in a controllable or uncontrollable phase.

- **A**: State-state transition matrices for uncontrollable (UC) and controllable (CC) task-phases
- **B**: Explore trials - participants choose between boats to infer controllability and to predict the next state
- **C**: Predict trials - participants indicate their prediction of the next state (given a current state and boat)
- Performance on predict trials provide a measure of controllability estimation.

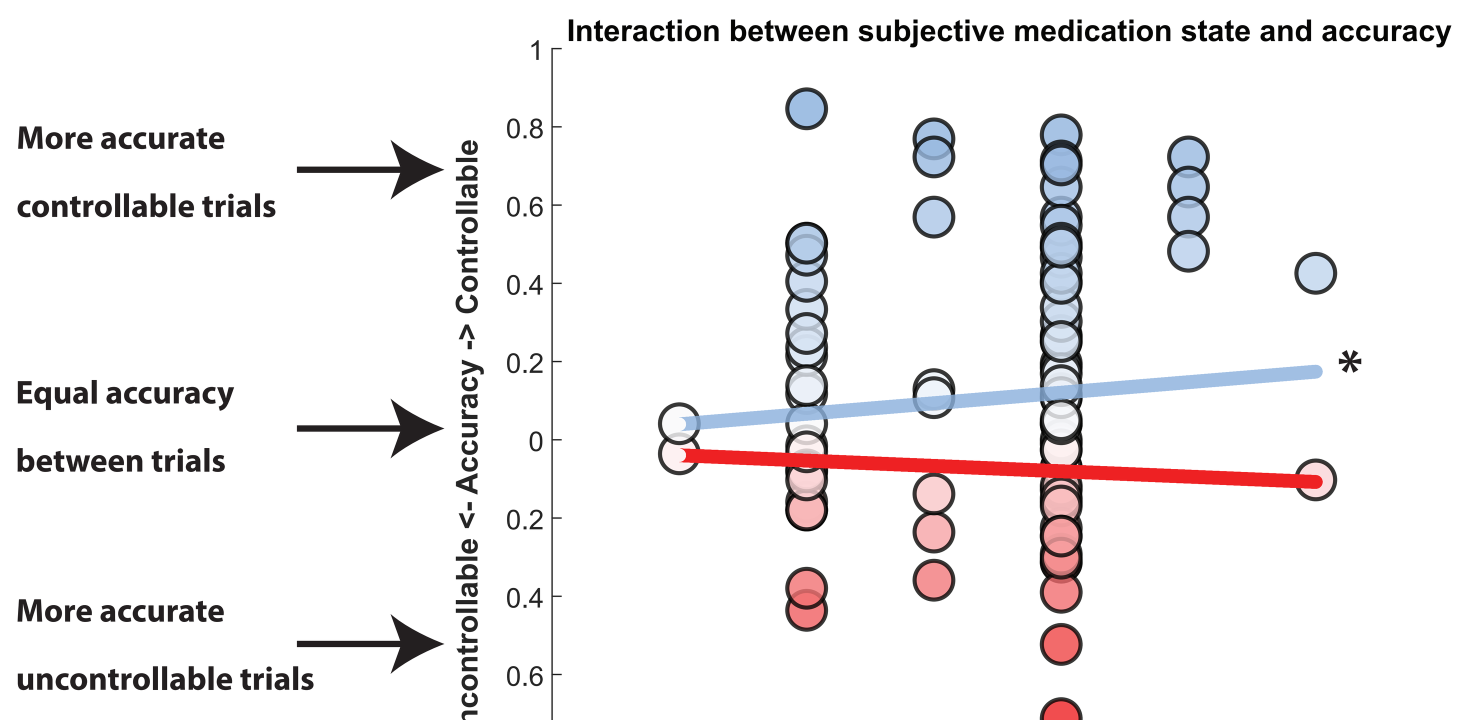
Key Insight

Same answer on both trials = acting as if **uncontrollable**	Different answer on both trials = acting as if **controllable**



RESULTS

Higher subjective medication state is associated with higher controllability estimates, leading to higher accuracy of controllability estimates in controllable task-phases, but lower accuracy of controllability estimates in uncontrollable task-phases.



	Estimate	t-Stat	p-Value	Lower	Upper
Intercept	-0.05	-0.26	0.79	-0.40	0.30
Condition	0.35	**7.31**	>0.01	0.26	0.45
ONESS	-0.04	-0.26	0.80	-0.38	0.29
MDS-UPDRS II	-0.01	-1.13	0.22	-0.04	0.01
Condition:ONESS	0.17	**2.18**	0.03	0.02	0.33

CONCLUSIONS

- The current results show an interaction between environmental controllability estimation and dopaminergic function. This suggests that there is a potential link between dopamine and the estimation of control in PD.
- This work may offer insight into the mechanisms underlying psychiatric symptoms like **depression** in PD and provide potential avenue for refining therapeutic approaches that target cognitive aspect of the disease.
- We are continuously collecting more data on this task from cohorts involved in the CONTROL-PD consortium.
- Further research is required to confirm these preliminary findings and explore the underlying neural mechanisms in more detail. To identify the specific mechanism being modulated by dopamine a **computational model** needs to be fit to the data.

REFERENCES

1. Reijnders, J. S. A. M., Ehrt, U., Weber, W. E. J., Aarsland, D., & Leentjens, A. F. G. (2008). A systematic review of prevalence studies of depression in Parkinson's disease. Movement Disorders, 23(2), 183–189. https://doi.org/10.1002/mds.21803

2. Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. Science, 275(5306), 1593–1599. https://doi.org/10.1126/science.275.5306.159

3. Robbins, T. W., & Everitt, B. J. (2007). A role for mesencephalic dopamine in activation: Commentary on Berridge (2006). Psychopharmacology, 191(3), 433–437. https://doi.org/10.1007/s00213-006-0528-7

4. Gershman, S. J., & Uchida, N. (2019). Believing in dopamine. Nature Reviews Neuroscience, 20(November), 703–714. https://doi.org/10.1038/s41583-019-0220-7

5. Maier, S. F., & Seligman, M. E. P. (2016). Learned helplessness at fifty: Insights from neuroscience. Psychological Review, 123(4), 349–367. https://doi.org/10.1037/rev0000033

6. Ligneul, R., Mainen, Z. F., Ly, V., & Cools, R. (2022). Stress-sensitive inference of task controllability. Nature Human Behaviour, 6(6), 812–822. https://doi.org/10.1038/s41562-022-01306-w

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