A neural circuit selective for fast drug reward in humans

Peter Manza[1], Dardo Tomasi[1], Kai Yuan[1], Ehsan Shokri-Kojori[1], Corinde Wiers[1], Michele Vera-Yonga[1], Jamie Burns[1], Danielle Kroll[1], Dana Feldman[1], Katherine McPherson[1], Catherine Biesecker[1], Evan Dennis[1], Allison Johnson[1], Rui Zhang[1], Gene-Jack Wang[1], Nora Volkow[1,2]

[1]National Institute on Alcoholism and Alcohol Abuse, [2]National Institute on Drug Abuse, National Institutes of Health

Introduction

The faster that drugs enter the brain, the more rewarding they are. Hence drugs that are administered quickly, e.g., intravenously (IV) have greater abuse potential than when administered more slowly, e.g., orally. [1,2]

How does human brain function change as a function of drug brain uptake speed? (Marker of misuse potential?)

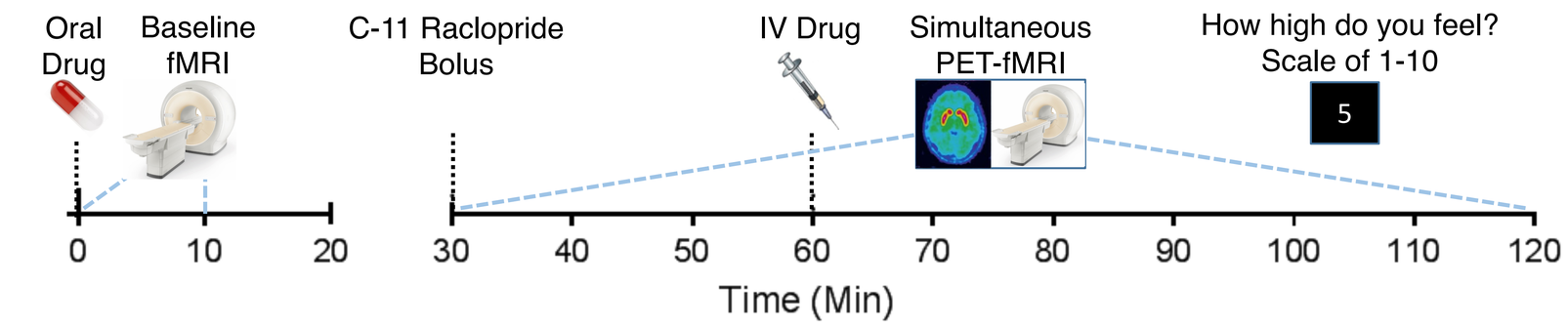
We used simultaneous PET-fMRI[3,4] to examine brain activity and dopamine signaling to IV (fast) versus oral (slow) doses of methylphenidate (MP)

We hypothesized that oral and IV MP would evoke decreases and increases in striatal activation, respectively, because slow dopamine release would be more likely to stimulate high-affinity inhibitory D2 receptors, whereas fast dopamine release would be sufficient to stimulate the lower-affinity excitatory D1 receptors.

Methods

n = 20 healthy adults (11/9 Male/Female; Age 36 ± 10 years)

DESIGN



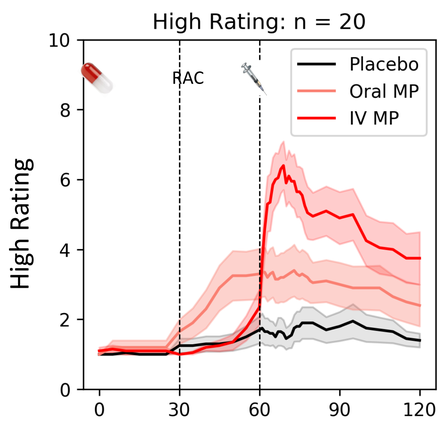
Double-blind, Counterbalanced, Within-Subject Design

Session	Oral Drug (60 mg)	IV Drug (.25 mg/kg)
ORAL	MP	Placebo
IV	Placebo	MP
PLACEBO	Placebo	Placebo

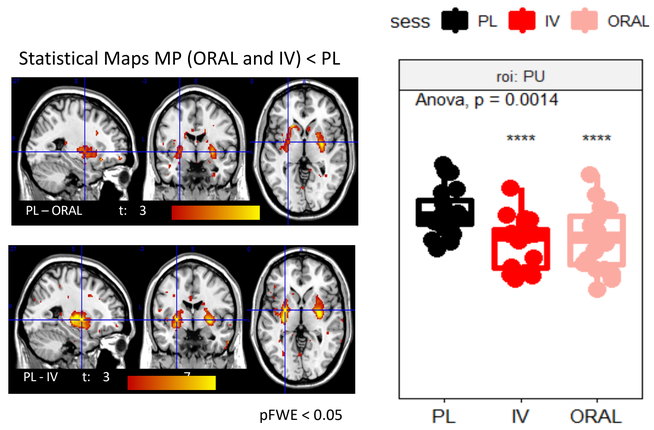
Resting fMRI: 3x3x4mm voxels, TR = 3s
Human Connectome Project Minimal Preprocessing Pipeline[5]

PET: Attenuation correction
Cerebellum reference region

1) Subjective 'High' ratings to MP



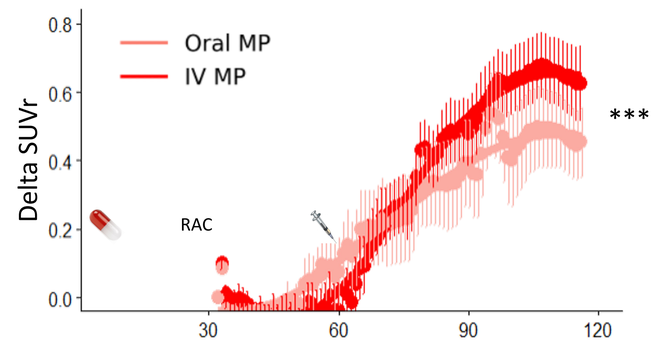
2) "Static" PET Results: Dopamine D2 Receptor Binding - Striatum



- IV and oral MP significantly decreased specific binding of [^{11}C]raclopride (BP_{ND}) in striatum, consistent with striatal dopamine increases
- No differences in overall magnitude of dopamine changes between Oral and IV.
- **Can we detect differences in <u>speed</u> of dopamine increases?**

3) "Dynamic" PET Results: Speed of dopamine increases

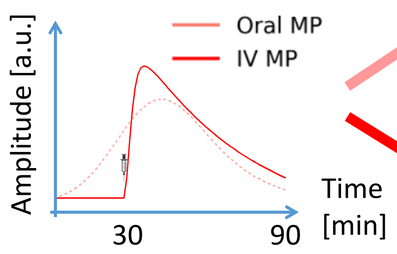
Change in standardized uptake value ratio (SUVr), minute-by-minute, versus placebo



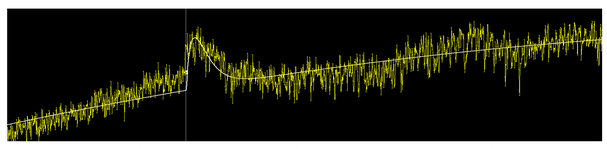
4) fMRI Results: GLM: Brain Activation to speed of dopamine increases

For each fMRI session, we used two regressors to model the BOLD signal: the speed of dopamine increases to slow (oral) and fast (IV) MP, as estimated from dynamic PET analysis

We fit a gamma regressor to fMRI data based on average speed of dopamine increases from PET (plot to the right shows average 'speed of dopamine increases' for all 20 subjects – the derivatives of the curves in panel 3).

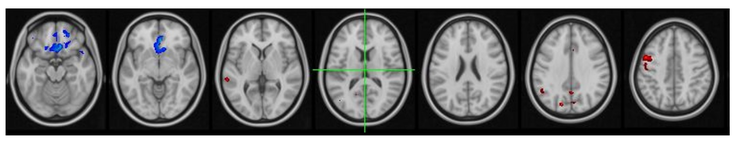


IV MP Example: voxel in caudate



Repeat this procedure for every voxel in the brain, in whole-brain GLM analysis

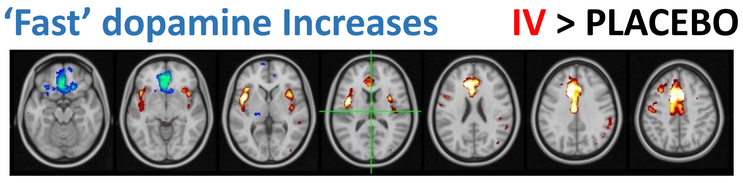
'Slow' dopamine increases **ORAL > PLACEBO**



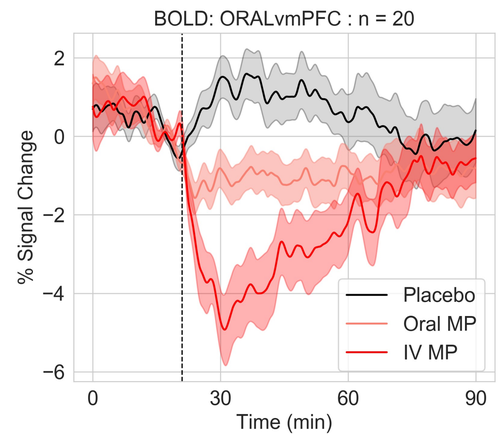
Paired t-test

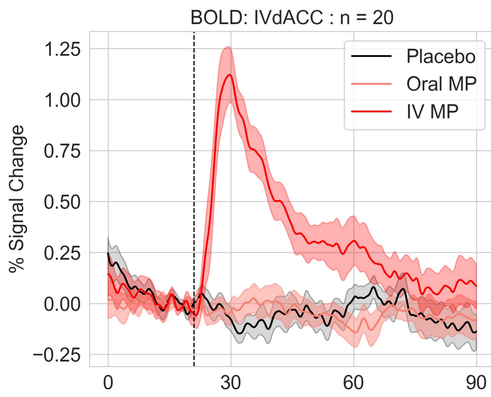
t
-6 -3 3 6

'Fast' dopamine Increases **IV > PLACEBO**



- The ventromedial prefrontal cortex (vmPFC) showed graded decreases in activation: modest decreases to slow (oral) and large decreases to fast (IV) dopamine increases.
- In contrast, dorsal anterior cingulate cortex (dACC) and bilateral insulae showed ***a selective increase to fast (IV) dopamine increases***.

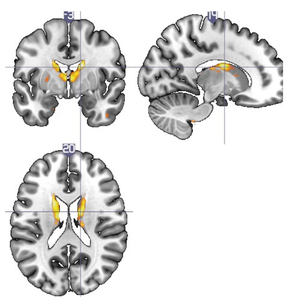




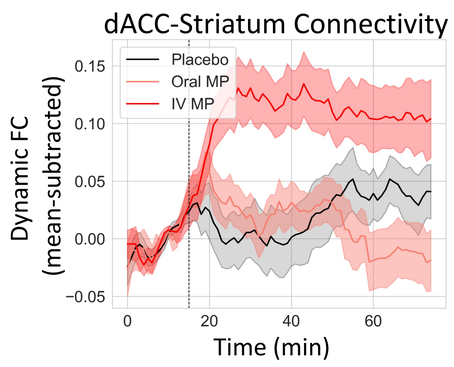
5) fMRI Results: Dynamic functional connectivity to speed of dopamine increases

dACC seed region from "fast" dopamine analysis. Method: 5-min bins with 4-min overlap, for an estimate of functional connectivity every 1 min. Then use same regressor as the prior analysis. (i.e., which regions does dACC increase its connectivity to in association with speed of dopamine increases?)

In whole-brain analysis, only one region emerged: the dorsal striatum, which was significantly connected with dACC only to FAST (IV) but not SLOW (oral) dopamine increases.



P < .001 voxel, p < .05 FWE cluster-corrected



Summary

- Two distinct mesolimbic circuits emerged for slow vs. fast dopamine kinetics
- The ventral (vmPFC) and dorsal (dACC) nodes of these networks have homologous regions in the rat brain (infralimbic and prelimbic cortex, respectively), suggesting reverse translation potential.
- Positive nodes (saliency network): possible location for focal lesions or for inhibition to treat addiction. Negative nodes (vmPFC): **brain stimulation target**?
- Further studies are needed to determine if repeated drug stimulation results in neuroadaptation of positive (salience network) and negative (vmPFC) connections that promote drug taking

References

1. Fowler, J. S. *et al.* Fast uptake and long-lasting binding of methamphetamine in the human brain: Comparison with cocaine. *Neuroimage* (2008) .
2. Koob, G. F. & Volkow, N. D. Neurocircuitry of Addiction. *Neuropsychopharmacology* **35**, 217–238 (2010).
3. Sander, C. Y. M. *et al.* Neurovascular coupling to D2/D3 dopamine receptor occupancy using simultaneous PET/functional MRI. *Proc. Natl. Acad. Sci.* **110**, 11169–11174 (2013).
4. Judenhofer, M. S. *et al.* Simultaneous PET-MRI: a new approach for functional and morphological imaging. *Nat. Med.* **14**, 459–465 (2008).
5. Glasser, M. F. et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* **80**, 105–124 (2013).

For correspondence, contact: **peter.manza@nih.gov**

This work was accomplished with support from the National Institute on Alcohol Abuse and Alcoholism (Y1AA-3009).