I was sitting by the fire, happily reading the nice paper by Ryan Petrulli and friends (Transl Psychiatry, 2017) when I came to this statement:

> The interaction between an immune response and DA signaling may carry unappreciated risks. If in the presence of inflammation, a dopaminergic medication or other stimulus with addiction potential produces higher DA elevation in the dorsal striatum than without, then it is reasonable to expect that the addiction liability of the stimulus may be increased through impaired response inhibition. Consider an individual experimenting with illicit stimulants or an adolescent prescribed Ritalin (MP), either of whom are experiencing short-term neuroinflammation. Both could be at increased risk for addiction due to reduced inhibitory control caused by a supraphysiologic DA elevation. We believe our findings call for further investigation of patient populations who may be suffering from neuroinflammation and are using or abusing stimulants.

I jumped! Stressful situations drive some people to seek out their drug of choice? Maybe it’s not that they lack willpower? It’s a cytokine-mediated (?) amplification of their dopamine system. ‘

But how does it work?
Impulsivity play a role.
I vaguely remembered reading something(s) that had linked low Dopamine D2 receptors to poorer response inhibition. I could even see the picture in my mind.

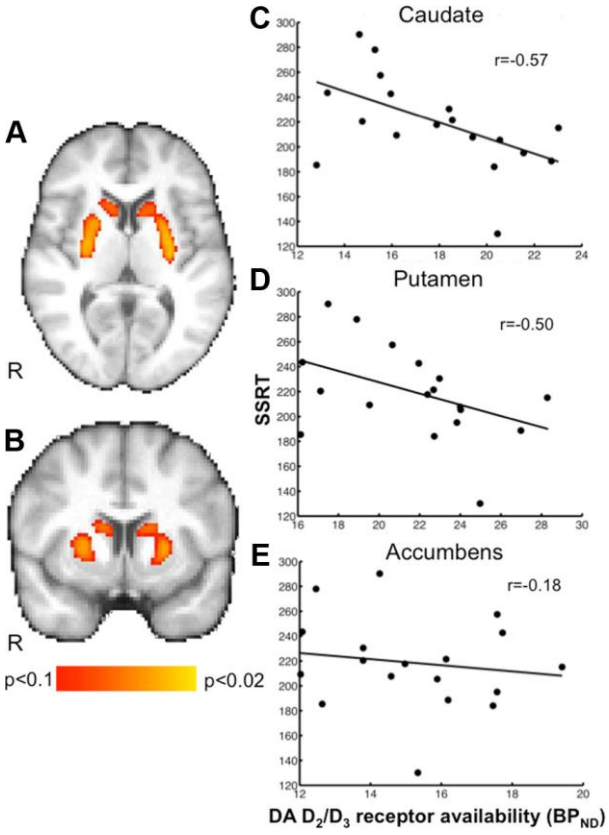

Figure 1. Correlations between striatal dopamine D2/D3 receptor availability (BP_{ND}) and SSRT (*n*_18). Participants who stopped more quickly showed greater D2/D3 receptor availability in caudate and putamen. ***A***, ***B***, Results from voxelwise nonparametric regression of BP_{ND} on SSRT. TFCE probability maps (corrected for multiple comparisons) are overlaid on the MPRAGE anatomical image. Maps show SSRT was negatively correlated with BP_{ND} in caudate and putamen but not nucleus accumbens. Voxelwise height threshold is set at *p* _ 0.1 for illustration purposes. Images are presented in radiological orientation (right _ left). ***C–E***, Scatterplots indicating relationship between SSRT and BP_{ND} extracted from anatomically defined caudate (*p* _ 0.02), putamen (*p* _ 0.04), and nucleus accumbens (*p* _ 0.47) VOIs. Because left and right BP_{ND} values were highly correlated (all *r* _ 0.71 and all *p* _ 0.001), volume-weighted averages of left and right values were used.

Where had I read that? And how exactly did they demonstrate it?

I was starting to believe that it might not be so wacky to think that an amplified dopamine response could predispose (or trigger) someone to drug seeking.

Finally, I thought, "motor response inhibition" is all well and good. But to really lock this down, I'd also want to show that the real-world behavior is altered by stressor-induced neuroinflammatory response.

Now what sort of real-world addictive behavior should I examine? (Alas, there is not yet a validated lab test of addiction to the Red Sox - although when one is invented, it will surely test how long people are willing stay up into the wee hours of the morning to watch an interminable baseball game.)

Then I remembered Sherry McKee's laboratory model to test smoking cessation.

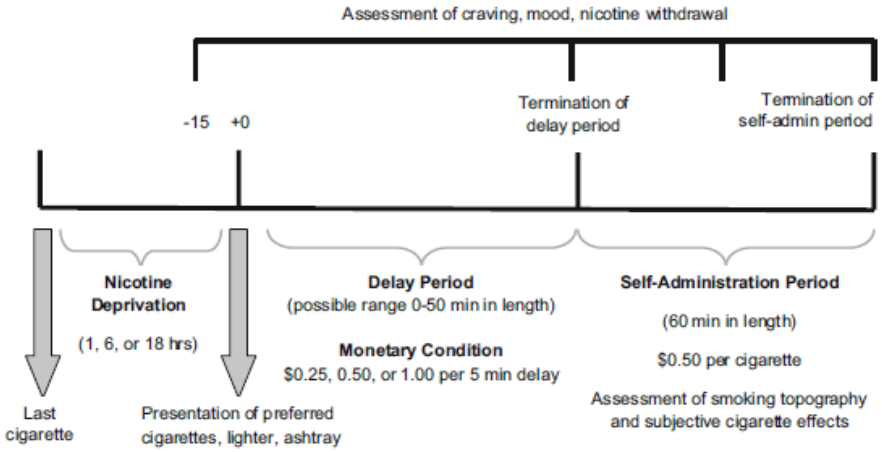

Figure 1. Design and timeline of STUDY 1 procedures. Nicotine deprivation was a within-subject condition and monetary condition was a between-subject variable. The delay period commenced at 4 p.m. Study 2 was of identical design but subjects were randomized to placebo, bupropion, or varenicline; only completed one laboratory session following 18 hr of nicotine deprivation; and were reinforced $1.00 for every 5 min they could resist smoking.

Sure, I thought, let's study smokers! My friend Kelly Cosgrove (rumored to be making a cameo appearance at a design-a-thon near you) studies smoking. Smokers aren't as tough to recruit as alcoholics or cocaine users (or so I thought.) I know Sherry McKee. I bet she can help too.

<u>So here is the goal:</u>
Build on the Petrulli findings. Propose an experiment (or series of experiments) to connect neuroinflammation (aka, 'immune stress') to amplified dopamine transmission to disinhibition and smoking lapse.

Be mindful of your design decisions.
Who are the subjects? What tools will you use? Have they been validated? By whom? (rigor)
What is novel about your approach (innovation)?
What are the calculated endpoints at the first level of analysis?
What are the comparisons to be made at the second level of analysis? (approach)
What are the aims of your study?
What do you hope to show in the end? **Why should anyone care (significance)?**