COMMENTARY

Individual Differences in Cognitive Flexibility

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Is it better to be flexible, or persistent? A colleague once said that the secret to success in science is perseveration (no, not mere perseverence—that wouldn't get you very far at all). Yet we all believe that the highest levels of cognitive function are associated with extreme flexibility—the ability to juggle many things at once and not get hung up on just one. Indeed, this ability to juggle the many demands of being a scientist are seemingly even more important these days than perseverating on one important deep problem. Clearly, these two poles of flexibility and perseverence (aka stability) both have benefits and costs (even in the world beyond the ivory tower), and it would make sense that, at a population level, individuals might be differentially distributed across this spectrum to cover our collective bases (1).

Samanez-Larkin *et al.* (2) provide an important advance in understanding the biological basis for these individual differences, leveraging the powerful technique of dopamine (DA) receptor availability measurements under radioligand positron emission tomography (PET) imaging. This technique is uniquely important for understanding the function of DA (and other neuromodulators) in humans, by virtue of being able to non-invasively assess both DA receptor availability and differences in DA levels, across different brain areas. Interestingly, they found that individual differences in cognitive flexibility were predicted by baseline DA D2/D3 receptor availability in the prefrontal cortex (PFC), parietal cortex, and thalamus, whereas amphetamine-induced DA release in the anterior striatum additionally predicted individual differences (and partially mediated the cortical and thalamic effects).

Interpreting these results requires wading into a complex sea of countervailing effects of dopamine and dopamine receptors across the striatum and PFC, as nicely reviewed by Cools and D'Esposito (3). Broadly speaking, consistent with a variety of data, D1 receptors in the PFC are associated with greater stability, whereas D2 receptors promote flexibility. However, the opposite pattern seems to hold in the striatum: D1 receptors promote flexibility, and D2 promotes stability. Furthermore, in the striatum, DA activation of D2 receptors has an overall inhibitory effect, whereas it is excitatory on D1. Putting this all together, we see that Samanez-Larkin *et al.* (2) bowled a perfect strike: they found D2 baseline availability effects on flexibility in PFC but not in the striatum, whereas they found increased DA levels in the striatum associated with greater flexibility, which would presumably lead to greater D1 receptor activation. If someone ever figures out a way to image D1 receptor availability using PET, then one would predict the opposite pattern, in which flexibility is associated with greater D1 baseline availability effects in striatum and lower levels of D1 availability in the PFC. As emphasized by Cools and D'Esposito (3), these opposing dynamics in PFC versus striatum provide a nice opportunity for the commonly seen U-shaped curves in DA effects; these were not, however, observed by Samanez-Larkin *et al.*, presumably because of the dosage of amphetamine used.

Digging down deeper, what do we think is really going on here? The opposing effects of D1 and D2 are nicely explained by a detailed computational model of the underlying biology (4,5). At the striatal level, our computational models of the D1 effects on the direct or Go pathway, and D2 effects on the indirect or NoGo pathway provide a useful account (6,7). We hypothesize that the Go pathway firing has a net effect of updating working memory representations in the PFC, whereas NoGo opposes the update and enables information to continue to be stably maintained. Thus, enhanced D1 activation promotes updating and flexibility, whereas enhanced D2 activation promotes stability and maintenance.

Furthermore, it is essential to consider the temporal dimension, which is unfortunately not well resolved through the PET methodology. As suggested in Frank and O'Reilly (8), there is likely to be another division here between the PFC and striatum. The PFC-level effects depend on longer time-scale diffusion of DA to activate more distal D1 receptors (5), whereas the Go and NoGo pathways in the striatum exhibit rapid phasic firing, and DA dynamics are similarly rapid (6). Thus, DA in PFC is likely to be more about longer time-scale cognitive-state effects (e.g., level of engagement, arousal, etc.), whereas DA in striatum likely plays a more phasic, moment-to-moment role. Another complicating factor entering here is that longer-term tonic levels of DA likely play a role in regulating phasic release, in part through the presynaptic subtype of D2 receptors. Sorting through these various opposing effects of D2 can be a complicated but potentially rewarding process (9).

What does this all have to say about self-medicating our cognitive functions through dopaminergic drugs? Two things clearly matter. First, what are you trying to achieve? If you want to be rapidly juggling different things, then in general increasing your dopamine levels is likely to help. But if you want an enhanced ability to focus on one important thing, you might be disappointed. I know I always find myself jumping all over the place doing all kinds of irrelevant things if I overdose on my morning coffee, in vain hopes of getting the next paper written. Second, it matters who you are, and along multiple dimensions. Individuals can vary in their D1 versus D2 balance in both cortex and striatum and in their baseline levels of dopamine, potentially in an area-specific manner as well. Thus, there are many potential cognitive profiles, with potentially different time scales and dynamics in interactions with dopaminergic drugs such as amphetamine. For example, if you happen to have a greater D2 versus D1 balance in PFC, then increasing dopamine levels may always promote greater flexibility there. But this same D2-weighting in striatum will cause greater stability—and perhaps, less coherent coordination between striatum and PFC, which might have its own implications.

It is hoped that further developments in the kind of research conducted by Samanez-Larkin *et al.* will help to fill in the many missing pieces of this overall puzzle. Maybe someday we will be able to order a custom-made cocktail of just the right cognitive

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enhancers tailored for our own individual dopaminergic profile, but perhaps this will lead to a cognitive monoculture, potentially emphasizing flexibility over good old-fashioned perseveration, subverting whatever wisdom appears to be manifest in the considerable individual differences across the population, presumably under some kind of evolutionary drive.

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