# Dopamine: A Tale of Two Cities

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Prescription drugs, and how they work in our bodies to treat different disorders, are fascinating.

Here, we present one way to illustrate why a relatively common prescription drug (stimulants) affect two different areas of the brain so differently.

Dopamine (DA) is an important neurotransmitter in many brain regions including: prefrontal cortex (PFC) and the striatum.

**ADHD,** which involves **lower levels of DA in the brain,** is characterised behaviorally by hyperactivity/impulsivity and/or inattention and impaired executive functions (EFs).

**Stimulants** are often used to **treat ADHD** as stimulants **increase DA levels,** with evidence of reduced hyperactivity and improved **EFs** (which include attention, self-control, cognitive flexibility, problem-solving, and working memory).

**In PFC, the optimal level of DA is an intermediate one**. If a drug raises DA levels too much in PFC, that is not helpful.

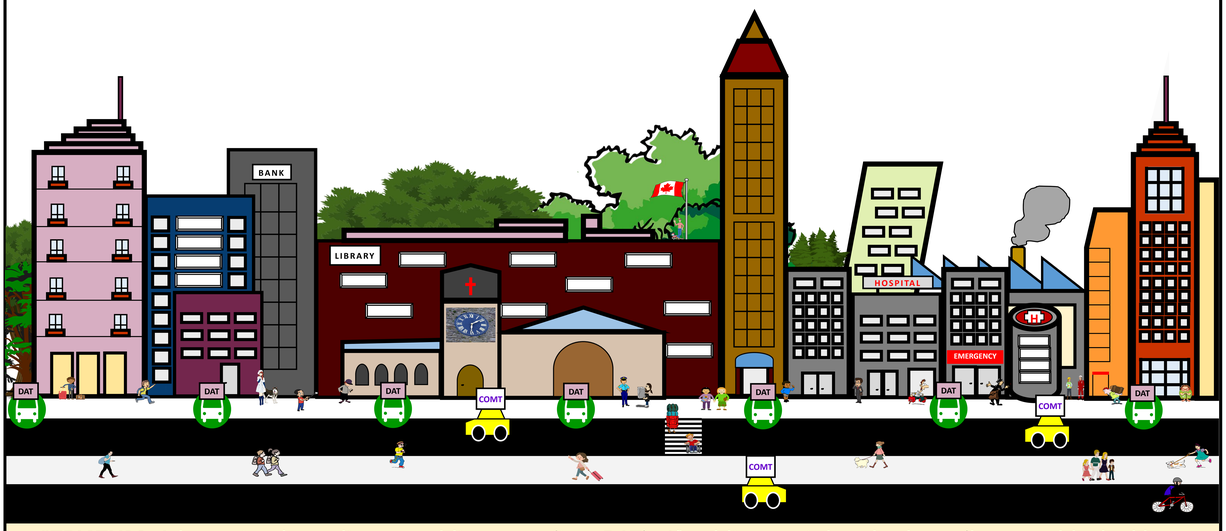
Drugs that raise DA do not necessarily lead to better PFC function or improved cognition (improved EFs).

**The best mechanism for clearing excess DA is through DA Transporters (DAT).**

**At *moderate to high doses*, stimulants work by blocking DAT from taking DA back up (blocking re-uptake).**

**That primarily helps the striatum, which is implicated in *hyperactivity and impulsivity*, because DAT plays a major role in the striatum.**

**Thus, improvements in behavior are seen.**




**STRIATUM**: A busy city that relies on public transit (i.e., DAT). If public transit breaks down (because blocked by a stimulant), pedestrians will pile up (i.e., DA levels increase)

**But stimulants work differently in PFC.**

**PFC has little DAT, causing it to rely more on other clearance mechanisms such as the catechol-o-methyltransferase (COMT) enzyme.**

**Thus, blocking reuptake of DA by DAT using moderate to high doses of stimulants produces little benefit here and might actually impair PFC.**

**But at *low doses*, stimulants work differently. They selectively improve signal-to-noise in PFC.**

**PFC is critical for EFs. Thus, low doses of stimulants (because they improve PFC functioning), improve EFs of persons with ADHD.**


**PREFRONTAL CORTEX**: There is little public transit (i.e., DAT) to be affected by blocking DAT. The city is forced to rely more on cars (i.e., COMT).

**For neurotypical persons (who already have PFC DA levels near optimal), however, even at low doses, stimulants can push PFC DA levels too high and then can impair, rather than improve, EFs.**

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Program in Developmental Cognitive Neuroscience, Dept. of Psychiatry, UBC

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

NSERC CRSNG

UBC IMH Institute of Mental Health

NIH National Institute on Drug Abuse Advancing Addiction Science