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The downside of downregulation

This scientific commentary refers to 'Reduced striatal dopamine synthesis capacity in patients with schizophrenia during remission of positive symptoms', by Avram *et al.* (doi:10.1093/brain/awz093).

Increased dopamine transmission in striatum is a core feature in the 'dopamine hypothesis of schizophrenia', which was first proposed in the 1960s. Since then, PET studies with DOPA decarboxylase substrates such as 6-^{18}F-fluoro-L-DOPA (^{18}F-DOPA) have consistently shown increased dopamine synthesis capacity (DSC) in striatum of unmedicated patients with schizophrenia compared to healthy controls. However, elevated DSC may represent a trait marker for schizophrenia remaining stable regardless of psychopathology, disease phase, or medication status, or it may rather be a state marker of a protein disorder and thus amenable to modulation. In this issue of *Brain*, Avram and colleagues present the results of an ambitious ^{18}F-DOPA PET study in a large group of medicated patients with schizophrenia, showing that those patients with remitted positive (but persisting negative) symptoms had a markedly reduced DSC in striatum, notably in the associative and sensorimotor divisions (Avram *et al.*, 2019).

The effect size of this reduction in DSC relative to findings in healthy controls (Hedges' g 0.89) was of the same magnitude as the increase reported in meta-analyses of PET studies in untreated patients with schizophrenia (Howes *et al.*, 2012). Tellingly, despite their substantial improvement in positive symptoms, the patients in the Avram *et al.* study had a distinct residual deficit in performing the Trail Making Test B; mediation analysis showed that reduced DSC mediated the cognitive difficulty. Similarly, we have previously shown that performance in tests of prefrontal cognitive function correlates positively with striatal DSC in healthy volunteers (Vernaleken *et al.*, 2007), and that subchronic treatment with haloperidol downregulates DSC in patients with schizophrenia, relative to their own unmedicated baseline (Gründer *et al.*, 2003). The new findings imply that patients with prolonged antipsychotic treatment may obtain their remission from positive symptoms at the cost of cognitive impairment, both being related to declining DSC. This clinically important implication raises new worries about the downsides of long-term treatment of patients with schizophrenia with dopamine $D_{2/3}$ antagonists. However, the Avram *et al.* study is of cross-sectional design, and thus cannot establish if the relationship between cognitive deficits and lower DSC in patients is a consequence of their drug treatment or is an inherent aspect of remission *per se*. To resolve this might require a challenging study design with baseline and follow-up ^{18}F-DOPA PET in groups of treated and untreated patients.

The Avram *et al.* study benefits from having group sizes of 24, and a stable molecular imaging endpoint, i.e. the DSC calculated by linear graphic analysis relative to ^{18}F-DOPA uptake in a cerebellum reference region, sometimes known as the Hartvig plot (Cumming, 2009) in recognition of the late Per Hartvig-Honoré, its first proponent. Avram *et al.* designate their metric as an influx constant k_i^{cer} (min^{-1}), but it might more properly be styled as a fractional rate constant, since there is no transfer of mass from cerebellum to the region of interest. Whatever one names it, the Hartvig slope is somehow an index of the local activity of DOPA decarboxylase, correlating with more physiologically precise parameters such as K_i, the net blood–brain clearance relative to the arterial input, or k_3^D, the relative activity of DOPA decarboxylase from compartmental analysis (Hoshi *et al.*, 1993). As Avram *et al.* concede, the k_i^{cer} is an imperfect measure of DSC due to its sensitivity to cerebral blood flow, uncorrected contamination of the brain signal from the plasma metabolite *O*-methyl-F-DOPA, and uncorrected loss of decarboxylated metabolites. Moreover, their claim that 'DSC measured with ^{18}F-DOPA is mainly a striatal measure, as reliability in the cortex seems to be poor', holds truer for k_i^{cer} than for the more physiologically defined measures noted above (Kumakura and Cumming, 2009).

The trade-off between the convenient k_i^{cer} analysis versus the technically more difficult arterial input methods lies at the heart of PET quantitation, and doubtless has some bearing on the discrepant ^{18}F-DOPA PET results reported in the literature, as cited by

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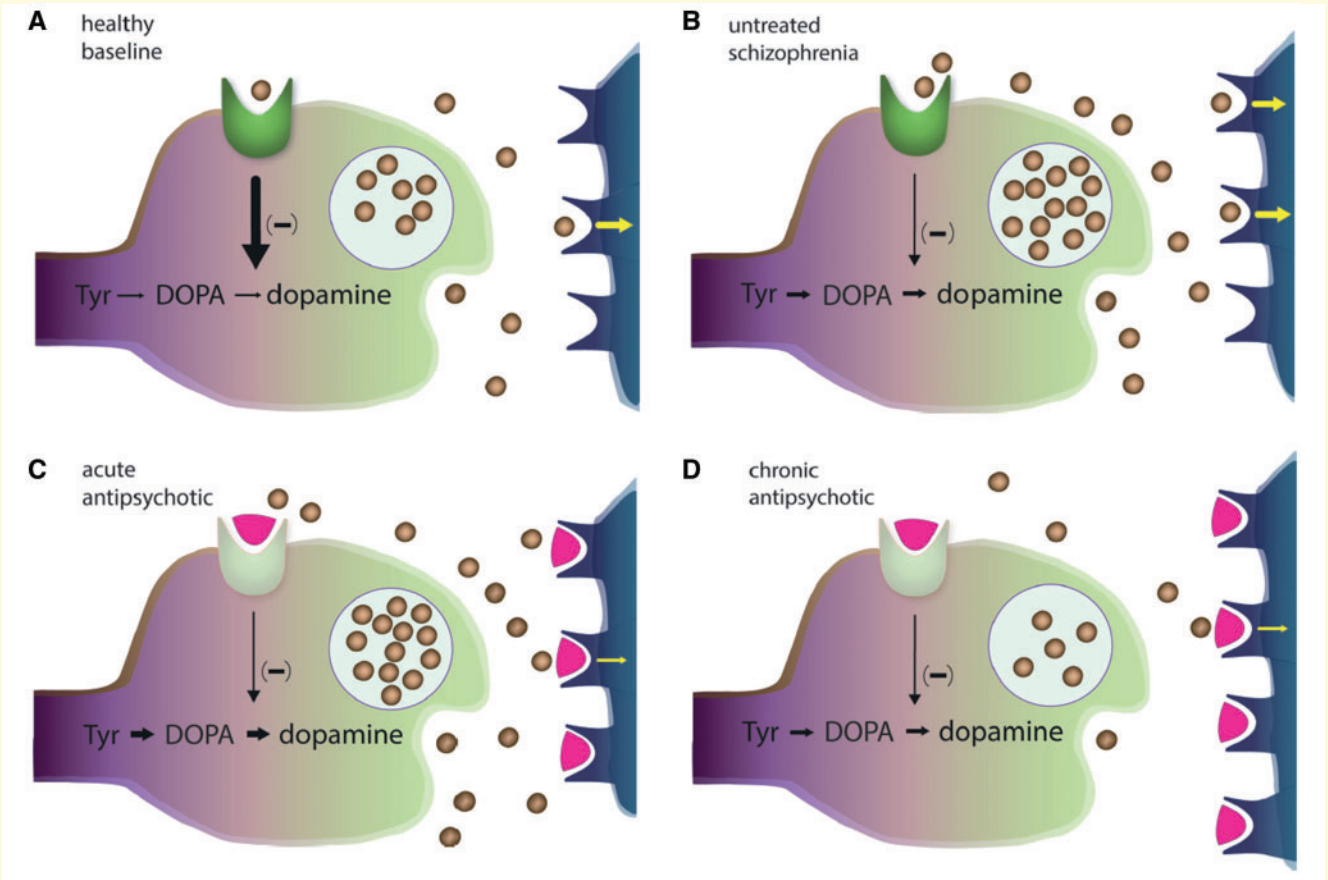

Figure 1 A schematic diagram depicting the dopamine pathway in (A) healthy controls (B) untreated patients with schizophrenia, (C) upon acute treatment with an antipsychotic dopamine $D_{2/3}$ receptor antagonist (pink symbols) and (D) chronic antipsychotic treatment, as assessed with ^{18}F-DOPA PET. In this scenario, presynaptic autoreceptors normally exert (**A**) a strong tonic inhibition of dopamine synthesis and release. Conjecturally, autoreceptors are functionally uncoupled in (**B**) patients with schizophrenia, resulting in disinhibited dopamine synthesis, high tonic and/or phasic dopamine release, and excessive dopamine signalling at postsynaptic receptors (thick yellow arrows). Acute treatment with antipsychotic medication substantially blocks pre- and postsynaptic dopamine receptors (**C**), provoking disinhibition of the dopamine synthesis pathway. Despite substantial blockade of dopamine $D_{2/3}$ receptors (60–80%), some dopamine signalling persists (thin yellow arrows). Chronic antipsychotic treatment maintains receptor blockade (**D**), despite possible upregulation of postsynaptic receptors (here increasing in number from three to four). However, the continuous antipsychotic treatment converts the dopamine neurons into a condition of depolarization block, in which dopamine synthesis and release decline.

Avram *et al.* A wide range of preclinical research has indicated that pharmacological blockade of dopamine $D_{2/3}$ receptors acutely activates DSC in living striatum (Cumming, 2009), and we have seen a 20% increase in striatal ^{18}F-DOPA-K_i in healthy volunteers exposed to haloperidol for 3 days, relative to their own baseline (Vernaleken *et al.*, 2006). Acute stimulation of DSC stands in contrast to the decreased magnitude of ^{18}F-DOPA-k_3^D seen in patients with subacute antipsychotic medication (Gründer *et al.*, 2003), and likewise the cross-sectional finding of reduced k_i^{cer} now reported by Avram *et al.* We have interpreted the phenomenon of late downregulation of DSC in human striatum to be consistent with depolarization block of nigrostriatal dopamine neurons, which is a cellular mechanism hitherto described in rats to explain the delayed response to treatment. Other supporting evidence for this downregulation in human brain is fragmentary and inconsistent. In one follow-up ^{18}F-DOPA PET study, Jauhar *et al.* (2019) found no effect of medication on the magnitude of k_i^{cer}, whereas Kim *et al.* (2017) found a decrease only in those patients receiving clozapine instead of first-line treatments. Completely discordant to the present report, McGowan *et al.* (2004) reported increased DSC among medicated patients compared to healthy control subjects, a difference comparable in magnitude to the elevated DSC seen in the meta-analyses of unmedicated patient studies. Although the patients in McGowan *et al.* were less well characterized than were the patients in the Avram *et al.* study, most likewise presented with similarly low positive symptoms. Among the other factors possibly contributing to

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the disparate ^{18}F-DOPA PET findings are smoking status, carbidopa/entacapone pretreatment, and duration of treatment, dosage, and type of antipsychotic medication. There is certainly a lack of knowledge of differential effects of specific compounds on DSC, and a need for studies of follow-up design for assessing changes in DSC relative to own baseline.

Our parsimonious explanation of the new results reported by Avram *et al.* is that the cohort of patients had indeed experienced downregulation of striatal DSC relative to their undocumented pre-medicated baseline condition, having entered into a condition analogous to the dopamine block seen in rats treated chronically with antipsychotic drugs. Our mentor, the late Arvid Carlsson, first suggested autoreceptors on midbrain dopamine neurons as potential targets for pharmacotherapy of schizophrenia. We suppose that a silver bullet for the perturbed dopamine system in schizophrenia might downregulate DSC without causing excessive blockade of postsynaptic dopamine receptors. The work presented by Avram *et al.* furnishes another piece in the puzzle of a better understanding of the regulation and dysregulation of dopamine systems in schizophrenia.

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Competing interests

The authors report no competing interests.

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