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Mapping dopamine with positron emission tomography: A note of caution

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Positron emission tomography (PET) imaging is uniquely suited to measuring neurotransmitter signaling in the human brain. PET tracers for neurotransmitter studies are ligands of the receptor or enzyme of interest labelled with positron emitting isotopes, usually ^{11}C of ^{18}F. By far the most frequent target of PET neurotransmitter imaging is dopamine, and the most commonly used tracer is [^{11}C]raclopride, an antagonist of the dopamine D2 receptor (D2R), first developed by researchers at the Karolinska Institute (Farde et al., 1986).

[^{11}C]raclopride has also been used to map dopamine release in the living brain (Egerton et al., 2009). This is because binding depends on both the density of D2R (B_{max}) and the tonic concentration of dopamine. Dopamine, unlike e.g. glutamate or GABA, is present outside neurons at constant levels. These so-called tonic levels of dopamine are maintained by constant low frequency firing of dopamine neurons and also by impulse-independent dopamine efflux (Sulzer et al., 2016). At baseline, the occupancy of D2R by dopamine is estimated at roughly 50–75% (Dreyer et al., 2010). The high affinity D2R is sensitive to these tonic concentrations, and therefore dopamine can exert bidirectional effects on D2R-bearing postsynaptic neurons. Both reductions and elevations in dopamine from its baseline are thought to convey information in the striatum, acting as signals for reinforcement learning (Cox et al., 2015; Frank and O'Reilly, 2006). It is because tonic occupancy is in the middle of the range that PET imaging with D2R ligands can be used to measure dopamine release, typically using a two-scan approach (baseline and "activation").

However, an inherent limitation in mapping D2R distribution or dopamine release with PET comes from the interaction of the properties that make a PET tracer suitable and the very large range of D2R densities across different brain areas. Indeed, there is a ten to one hundred-fold difference in the concentration of D2R between striatum and cortex (lower in cortex – see Fig. 1) (Hall et al., 1994). This is a problem because the affinity of a PET tracer needs to be optimum, that is neither too high nor too low. High affinity leads to slow equilibrium, while low affinity leads to low signal (Laruelle et al., 2003). A tracer whose affinity is optimum for the striatum will have too little binding in cortex to yield a signal that is detectable above noise. Conversely, a high affinity tracer may label cortical D2R but will be too slow to reach equilibrium in the striatum, requiring scan durations that are either impractical or impossible (given radioactive decay). [^{11}C]raclopride has moderately low affinity for D2R with a dissociation constant $K_D = 3.8$ nM (Farde et al., 1986) and is suitable for imaging D2R in the striatum, but is thought to yield no signal above noise in the cortex. On the other hand, tracers like [^{11}C]FLB 457 and [^{18}F]fallypride have affinities two orders of magnitude higher (0.018 nM and 0.030 nM respectively), and are thus suitable for imaging cortical D2R but less useful for studies of the striatum (Narendran et al., 2009). Indeed, an early study by the Karolinska group showed that cortical radioactivity detected after [^{11}C]raclopride almost certainly did not represent specific binding to D2R (Farde et al., 1988).

Nonetheless, these early studies were conducted with the first PET systems, which had relatively low sensitivity and spatial resolution. With the advent of more sensitive PET cameras several authors began to report mapping of extra-striatal D2R or dopamine release with [^{11}C]raclopride. This was sometimes met with controversy (Egerton et al., 2009) as the existing evidence was that this tracer could not detect a specific D2R signal in the cerebral cortex above noise (Hirvonen et al., 2003).

In this issue of Neuroimage, Svensson et al. attempt to once again lay this issue to rest (Svensson et al., 2019). They tested the ability of [^{11}C]raclopride to measure D2R density outside the striatum using a competition assay. They took advantage of existing datasets in which the receptor occupancy of the neuroleptic quetiapine was evaluated with [^{11}C]raclopride PET imaging in healthy individuals. Quetiapine is a D2/3 receptor antagonist approved for the treatment of psychosis. The goal of the original study was to compare the receptor occupancy of two formulations of quetiapine. Eight individuals had PET scans at baseline and following short course treatments with both immediate and extended release formulations of the drug. After quetiapine treatment, there were significant reductions in binding potential (BP_{ND}) in all three subdivisions of the striatum (caudate, putamen, accumbens) indicating 30–50% occupancy of the D2R by the drug. This confirms that [^{11}C]raclopride BP_{ND} in the striatum indicates specific receptor binding.

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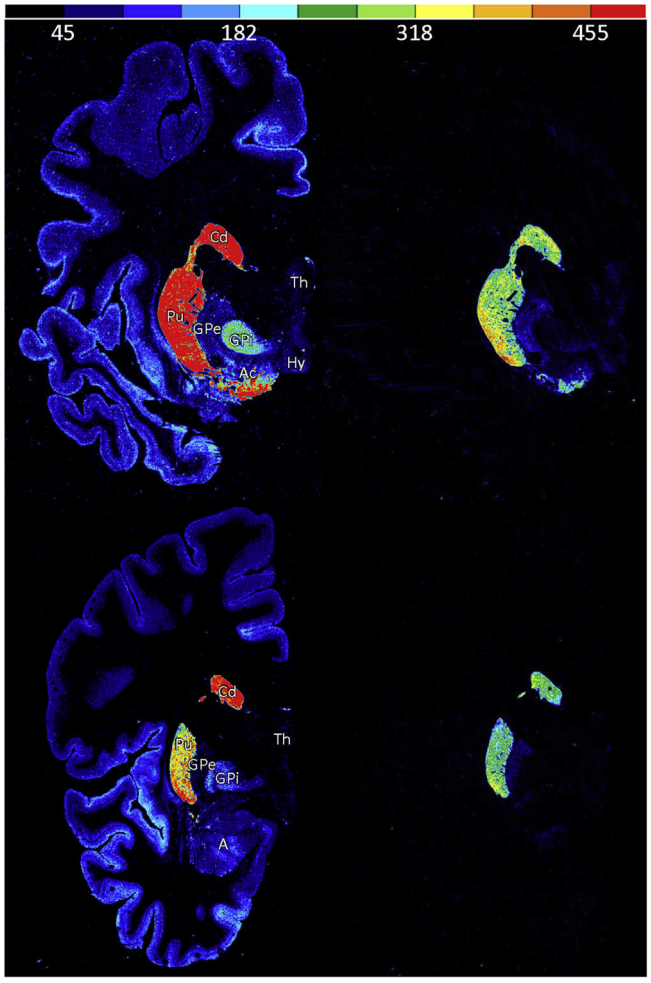

Fig. 1. Dopamine receptor density in post-mortem human brain.
Neighboring coronal sections through two human hemispheres processed by *in vitro* receptor autoradiography for visualization of the dopamine D_1 (left panels) and D_2 (right panels) receptors. The color bar codes for receptor densities in fmol/mg protein. Brains were obtained from subjects without a history of neurological or psychiatric illness through the body donor program of the Department of Anatomy, University of Düsseldorf, Germany (top row, 45-year-old male; bottom row, 72-year-old male). The D_1 receptors were labelled with 0.5nM [^{3}H]SCH 23390 in a 50 mM Tris-HCl buffer (pH 7.4) containing 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$ and 1μM mianserin for 90 minutes at 22 °C. This main incubation was preceded by a 20 minutes preincubation in the buffer at 22 °C, and followed by two washing steps with ice-cold buffer for 20 minutes each and a final dip in distilled water at 4 °C. The D_2 receptors were labelled with 0.55nM [^{3}H]raclopride in a 50 mM Tris-HCl buffer (pH 7.4) containing 150mM NaCl and 0.1% ascorbate for 45 minutes at 22 °C. This main incubation was preceded by a 20 minutes preincubation in the buffer at 22 °C, and followed by six washing steps with ice-cold buffer for 1 minute each and a final dip in distilled water at 4 °C. For methodical details see (Palomero-Gallagher and Zilles, 2018). A amygdala, Ac accumbens, Cd caudate nucleus, GPe globus pallidus pars externa, GPi globus pallidus pars interna, Hy hypothalamus, Pu putamen, Th thalamus.

However, in the cerebral cortex there was no change in [^{11}C]raclopride BP_{ND} after either quetiapine treatment. In the thalamus, binding was somewhat reduced, however the reduction was less than expected if tracer binding was fully specific; the authors estimate that only half of the [^{11}C]raclopride in thalamus was displaced by quetiapine.

In summary, the study by Svensson et al. supports the long-held view that [^{11}C]raclopride PET is only capable of measuring D2R (or dopamine release) in the striatum. These results were obtained on the most sensitive high-resolution PET camera currently available (HRRT, Siemens AG), and probably do not depend on the analytical method used to compute BP_{ND}. If the signal is not above noise no method can extract it from the data. Note also that cortical dopamine "activations" detected with [^{11}C]raclopride may represent changes in tracer delivery due to focal changes in cerebral blood flow, as shown in simulation studies (Dagher et al., 1998). However, there are caveats: the sample size of the Svensson et al. study (n = 8) is small, even though effect sizes from quetiapine displacement are expected to be very high. Also, the results, strictly speaking, only apply to the simplified reference tissue model method used by the authors. Nonetheless, this work raises the possibility that many studies reporting extrastriatal dopamine signaling with PET suffer from the all too familiar problems of small sample sizes and inadequate statistical methods (Bennett et al., 2009).

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