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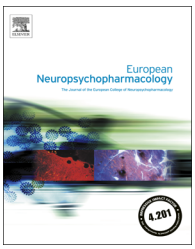

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Imaging the D_3 dopamine receptor across behavioral and drug addictions: Positron emission tomography studies with [^{11}C]-(+)-PHNO

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Abstract
Chronic drug use has been associated with dopaminergic abnormalities, detectable in humans with positron emission tomography (PET). Among these, a hallmark feature is low D_2 dopamine receptor availability, which has been linked to clinical outcomes, but has not yet translated into a therapeutic strategy. The D_3 dopamine receptor on the other hand has gained increasing attention, as, in contrast to D_2, chronic exposure to drugs has been shown to up-regulate this receptor subtype in preclinical models of addiction—a phenomenon linked to dopamine system sensitization and drug-seeking. The present article summarizes the literature to date in humans, suggesting that the D_3 receptor may indeed contribute to core features of addiction such as impulsiveness and cognitive impairment. A particularly useful tool in investigating this question is the PET imaging probe [^{11}C]-(+)-PHNO, which binds to $D_{2/3}$ dopamine receptors but has preferential affinity for D_3. This technique has been used to demonstrate D_3 up-regulation in humans, and can be applied to assess pharmacological interventions for development of D_3-targeted strategies in addiction treatment.

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1. Pathophysiology of the dopamine system in addictions

Addiction is a chronic relapsing disorder involving progressive changes in the brain that underlie clinical symptoms such as tolerance and withdrawal, as well as changes in motivation, compulsive drug-seeking, and a loss of control over drug use. Moreover, addiction is linked to personality traits that can confer vulnerability, such as impulsivity, externalizing behaviour, and risky decision-making. While originally understood in the context of substance use, the notion of addiction has now expanded to include behavioural addictions, most notably pathological gambling, which has been re-categorized to "Substance-Related and Addictive Disorders" in the DSM-5. Diagnostic criteria for pathological gambling in DSM-5 parallel those for substance use disorder, including, for example, a need to gamble with increasing amounts of money to achieve the desired effect (tolerance), irritability/restlessness when attempting to cut down (withdrawal), chasing losses (motivation), or repeated unsuccessful efforts to stop (loss of control). Other proposed behavioural addictions include compulsive eating, shopping, sexual activity, and internet use. However, the evidence for neurobiological and clinical overlap with substance use disorder is not yet well supported.

The pathophysiology of addiction is complex and involves nearly every neurochemical system in the brain, but the dopamine (DA) system has received particular attention due to its role in reward and reinforcement (although non-stimulant addictions may rely more on non-DA mechanisms). Human positron emission tomography (PET) studies have described consistent dopaminergic abnormalities across addictions that form some of the cardinal pathological features detectable with neuroimaging. For example, $D_{2/3}$ DA receptor availability in striatum (measured with the PET radiotracers [^{11}C]raclopride, [^{18}F]fallypride, or [^{11}C]-(+)-PHNO) has been found to be lower in individuals addicted to cocaine, methamphetamine, alcohol, heroin, and nicotine (Fehr et al., 2008; Martinez et al., 2004, 2005, 2011, 2012; Payer et al., 2013; Volkow et al., 1990, 2001), as well as in overweight and obese individuals who binge-eat (Wang et al., 2004) compared to healthy controls. This feature has been related to addiction-relevant behavioural traits, including behavioural impulsivity (Lee et al., 2009), emotional impulsivity/urgency (Clark et al., 2012), overeating (Zorick et al., 2011), response inhibition (Ghahremani et al., 2011), and importantly, has been linked to relapse following clinical intervention (Martinez et al., 2011; Wang et al., 2011). Interestingly, a number of studies have investigated this question in pathological gambling, but none found the expected difference in striatal $D_{2/3}$ DA receptor availability between gamblers and non-gamblers (Boileau et al., 2012a; Clark et al., 2012).

Another DA system feature that is consistently linked to addiction, is abnormal DA release in response to a challenge with a DA-releasing agent (e.g., amphetamine or methylphenidate), measured as PET radiotracer displacement compared to pre-challenge baseline. Here, the consistent finding is blunted DA release, which has been demonstrated in cocaine, alcohol, methamphetamine and heroin addiction (Martinez et al., 2005, 20011, 2012; Volkow et al., 2001; Wang et al., 2011) and is thought to contribute to a hypodopaminergic state that perpetuates drug-seeking. Notably, however, this too has not been replicated in pathological gambling; in fact, this population showed evidence for greater DA release than healthy individuals (i.e., sensitization), which related to greater subjective excitement from gambling and gambling severity (Boileau et al., 2013b).

In contrast to these hallmark D_2 findings, the D_3 DA receptor – a member of the D_2-like family – has shown a paradoxical *upregulation* in animal (Le Foll et al., 2005a, 2005c; Neisewander et al., 2004; Spangler et al., 2003; Vengeliene et al., 2006) and human *post mortem* studies (Segal et al., 1997; Staley and Mash, 1996). With new in vivo imaging tools such as [^{11}C]-(+)-PHNO (Wilson et al., 2005), it is now possible to investigate this question in living humans. In support of the preclinical and *post mortem* data, D_3 receptor availability has been found to be heightened in addiction, and to relate to impulsiveness (Payer et al., 2013), drug wanting (Boileau et al., 2012b), cognitive function (Nakajima et al., 2013), and symptom severity (Boileau et al., 2012a), and it has shown potential clinical utility, as described below.

2. Addiction and key features of the D_3 dopamine receptor system

The D_3 dopamine receptor was cloned and characterized for the first time almost 25 years ago, and was classified in the D_2-like family of G protein-coupled receptors based on amino acid sequence and gene organization (Sokoloff et al., 1990). Even before the development of D_3-selective research tools (e.g., knock-out mouse models, imaging probes, specific antibodies, and pharmacological agents), a key feature of the D_3 system had attracted considerable attention: its anatomical localization was remarkably restricted to limbic 'reward' circuitry, spurring the hypothesis that D_3 involvement could contribute to the pathophysiology of neuropsychiatric disorders, including substance abuse (Sokoloff et al., 2006).

D_3 receptors are co-expressed in D_2-containing regions of the brain, but their anatomical distribution contrasts with that of D_2, which is found in significantly higher numbers in the basal ganglia, thalamus, and hypothalamus (Gurevich and Joyce, 1999; Murray et al., 1994). Conversely, the largest population of D_3-containing neurons is found in a group of granule cells located within the ventral part of the striatum, called the Islands of Calleja, and in medium-sized spiny neurons co-expressing the D_1 receptor (as well as dynorphin and substance P) in the shell of the nucleus accumbens and extended amygdala (Diaz et al., 1995; Le Moine and Bloch, 1996). Both cell groups receive inputs from the ventral tegmental area, and heavily project to prefrontal cortex as well as relay nuclei in the mediodorsal thalamus and ventral pallidum. These limbic loops, and D_3 presence within them, have been theoretically associated with emotionality and motivational states (Nestler and Carlezon, 2006), as well as memory and cognitive functions (Floresco and Magyar, 2006). Other regions in which high D_3 receptor concentrations have been identified include the olfactory tubercle, ventral pallidum, globus pallidus, medial mammillary nucleus, and dentate gyrus of the hippocampus, as well as the nucleus basalis of