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Commentary on Boileau *et al*. (2013): Distinguishing D2/D3 dopaminergic contributions to addictions

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Boileau and colleagues address a clinically and scientifically important topic: the role of dopamine D2-like (particularly D2/D3) receptors in pathological gambling (PG) [1]. As the authors note, PG is recommended for reclassification in DSM-5, with a proposed move from the category of 'Impulse Control Disorders Not Elsewhere Classified' to one entitled 'Addiction and Related Disorders' [2]. This move is supported by epidemiological, phenomenological, clinical, behavioral and biological similarities between substance-use disorders and PG [3,4]. Despite these similarities, it is only recently that investigators have used positron emission tomography (PET) to investigate the neurobiology of PG.

Given the importance of dopaminergic projections from the ventral tegmental area to ventral striatum in substance addictions, it was reasonable to hypothesize a similar involvement in PG [5]. The absence of between-group differences in D2/D3 [11C]-raclopride binding is consistent with findings from two other studies of community PG subjects [6,7], although one study suggested a between-group difference (lower binding in PG) among individuals performing less advantageously on the Iowa Gambling Task. Additionally, among Parkinson's disease patients, those with PG versus those without demonstrated lower [11C]-raclopride binding in the ventral striatum at baseline and greater [11C]-raclopride displacement during a gambling task [8]. Thus, the extent to which D2/D3 receptor availability relates to gambling-related decision-making warrants further consideration.

The associations between D3-related [11C]-(+)-PHNO binding and impulsivity and problem-gambling severity in the present study are important. These findings resonate with others, indicating in limbic regions and ventral striatum an inverse correlation in PG between mood-related impulsivity and [11C]-raclopride binding [7] and a positive correlation between problem-gambling severity and [11C]-P943 binding [9]. [11C]-P943 assesses the availability of serotonin 1B receptors, implicated in striatal dopamine regulation and showing increased availability in alcohol-dependent subjects [10]. The impulsivity related findings suggest that this important construct (one that has been linked to addiction risk and addictive disorders) may relate to D3 function in PG, whereas the latter findings suggest that PG severity may link both to aspects of dopamine and serotonin function in the striatum, although conjoint PET imaging of PG subjects using dopaminergic and serotonergic radioligands has yet to be performed to examine their interrelationships. Additionally, as impulsivity has multiple aspects (e.g. relating to response and choice [4]),

future studies should examine howfacets of impulsivity relate to neurochemical functioning and addictive processes.

The dual radiotracer approach performed here, which used a D3-preferring radioligand ([11C]-(+)-PHNO) [11] and the D2/D3 receptor radioligand ([11C]-raclopride), is a novel aspect of the study and potentially represents an emerging line of research in the molecular imaging field. Given knowledge about regional receptor binding of these radioligands [12,13], the ratios of D3 to D2 receptors and high- to low-affinity D2/D3 receptors were evaluated, as were overall D2 and D3 levels. Although overall binding potentials of either radioligand did not differ between participants with and without PG, this approach demonstrated a positive correlation between D3 receptor density and problem-gambling severity and impulsivity in the PG group. The specificity of the positive finding was facilitated by the dual-receptor approach and prior data demonstrating that 100% of PHNO binding in the substantia nigra relates to D3 receptor binding [13]. Together, the observed range of relationships between clinical features and D2 versus D3 receptor availabilities may help to explain why medications having affinities for D2 and D3 receptors show limited efficacy in the treatment of substance and non-substance addictions [14].

With increasing availability of reliable radioligands for neuroimaging, the dual radioligand approach with PET provides insight into relationships between molecules and behavior. In one study examining both the pre-synaptic serotonin (5-HT) transporter and post-synaptic 5-HT(2A) receptor [15], impulsive aggression was associated with higher brainstem pre-synaptic 5-HT transporter levels and lower post-synaptic 5-HT(2A) levels, implying overactive serotonin release. In another study [16], current ecstasy [3,4-methylenedioxy-N-methylamphetamine (MDMA)] users demonstrated lower 5-HT transporter binding and higher 5-HT(2A) receptor binding in cortical regions, implying that MDMA use leads to damage in 5-HT neuron terminals innervating the cortex. In a third study [17], no differences were found in serotonin transporter or receptor levels between those with and without Asperger's disorder.

In addition to allowing for detailed associations between neurotransmitter systems and behavior, dual radiotracer approaches may provide insight into receptor profiles of antipsychotic [18] and antidepressant [19] medications, yielding more detailed accounts of receptor occupancies *in vivo*. Thus, the use of more than one radiotracer in a single study to gain detailed information about neurotransmitter systems of known importance is a novel area of research for which the Boileau *et al.* study is a strong addition to the field of PG. Additionally, using single and dual radioligand PET information in conjunction with other imaging modalities (such as magnetic resonance imaging approaches that investigate volumetric, white matter and functional characteristics), genetic assessments and other clinical information, such as treatment outcome, will help to advance prevention and treatment approaches for PG and substance addictions.

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Declaration of interests

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