CORRESPONDENCE

Attending to Striatal Ups and Downs in Addictions

To the Editor:

Altered striatal responses during monetary reward anticipation have recently been reported in pathological gambling (PG). Whereas van Holst *et al.* (1) reported an increased response, Balodis *et al.* (2) found a diminished response. Leyton and Vezina proposed that these divergent results may relate to cue specificity; in addicted populations addiction-related cues increase striatal activity, whereas in the absence of such cues, diminished striatal activity is observed. The authors suggested that the playing cards presented by van Holst *et al.* (1) may be more familiar/salient to PG participants, whereas the predominance of text presented by Balodis *et al.* (2) may account for the diminished striatal response. This explanation is complicated by several factors. First, the PG samples in both studies were heterogeneous in their gambling preferences. Second, the Monetary Incentive Delay Task used by Balodis *et al.* (2) included money symbols on each trial and references to currency, wins, and losses, all of which might be considered addiction-related stimuli in PG.

Multiple factors may underlie different findings in the two studies, including sample differences (e.g. gender distribution, treatment-seeking status), analytic strategies (e.g. contrasts of magnitudes versus contrasts of wins relative to neutral conditions). In addition, features of reward processing and decision-making inherent in gambling-related activities are different across studies, (e.g., risk, uncertainty, probability, response preparation, guessing, choice) and may influence the ventral striatal recruitment. Although these factors may have an impact on findings, we propose that the two studies' results are not discrepant but together provide insight into potential mechanisms of reward-processing alterations in PG. We posit that each study reports alterations in two different brain areas critical to reward processing: the ventral and the dorsal striatum.

Human and animal studies demonstrate dissociable roles of these areas, specifically as they relate to reward processing and instrumental conditioning (3–9). The ventral striatum is implicated in reward-related anticipation, prediction, and motivation, whereas dorsal areas are instrumental in the motor demands and cognitive control associated with the acquisition of stimulus-response-reward associations (3,4). Also, as addictive behaviors become habitual, striatal involvement may shift from ventral to dorsal (10,11). Dorsal striatal-related networks are implicated in habitual behaviors (12), most studied in addictions for cue-driven drug use and craving (13). For example, relative to healthy controls, altered striatal activation is observed in abstinent cocaine-dependent individuals during reward receipt in a risk-taking game; these activation differences are greatest in the right dorsal caudate and correlate negatively with compulsivity and reward/punishment sensitivity (9).

Van Holst *et al.* (1) administered a modified guessing task (14) during which participants indicated their likelihood of winning/losing €5 versus €1, given 30% or 70% probabilities. Imaging contrasts between PG and the control groups during the anticipatory phase of winning €5 versus €1 revealed greater bilateral dorsal striatum activity in PG participants. However, the corresponding Figure 1 and the abstract report this difference as the bilateral ventral striatum. The interpretation of the figure is complicated by the contrast-map threshold level differing from that reported in the results section and being uncorrected for multiple comparisons. Similarly, the results report greater gain-related expected-value activity in the dorsal striatum in PG participants, yet the corresponding Figure 2 refers to ventral striatal differences using a different contrast-map threshold uncorrected for multiple comparisons.

Ventral and dorsal striatal boundaries are difficult to demarcate in humans relative to rats. Ventral/dorsal striatum confusion may partially be explained by the 18-mm-diameter-sphere volume of interest centered on the ventral striatum used by van Holst *et al.* (1); a sphere of this size would likely also encompass dorsal striatum. The authors restricted their focus to subcortical and cortical areas. It could be informative to view task-related, whole-brain activations and whole-brain, between-group differences. Whole-brain information could be combined with smaller volumes of interest and keep thresholding levels constant and maintain corrections for multiple comparisons.

Nonetheless, between-group differences in gain-related, expected-value activity reported by van Holst *et al.* (1) in the dorsal striatum are important, given this area's role in reward-related learning. The coordinates and contrast maps correspond with the dorsal striatum, or specifically, the anterior caudate, a region signaling prediction error during instrumental conditioning (4). The dorsal striatum is also implicated in the perceived contingency between action and reinforcement (i.e., the extent to which an individual believes their performance determines the outcome [5,6]). This is noteworthy because the authors describe disconnections between action and outcome by informing participants that their performance would not influence the win/loss outcome of each trial. Therefore, in this context, greater anticipatory dorsal-striatal activity suggests that PG participants may have increased susceptibility to form action-outcome associations. Interestingly, the dorsal-striatal contribution for stimulus-response, reward-related activity occurs, even when the actual algorithm is suboptimal, such as during the gambler's fallacy (15). Furthermore, the dorsal-striatal area involved in learning stimulus-response associations is that recruited during choice (3,4,15), suggesting an increased propensity in PG to learn arbitrary associations between situations and actions. In the study by van Holst *et al.* (1), the PG group quickly recognized the greater magnitude of the €5 condition and performed the associated action (i.e., indicating their expectation). Rapid responding in PG relative to control participants supports this idea: mean reaction times were consistently more than 1 sec faster for each condition type (although between-group differences were not statistically significant). Accelerated responding may reflect this stimulus-response association, or differences in preparation and execution of motor responses because these were also incorporated in the expectation phase in this study. These results suggest more rapid action-outcome association acquisition in PG, and together with the results of Balodis *et al.* (2), indicated PG may involve greater inflexibility in modifying these associations (i.e., when ventral-striatal systems are hyporesponsive).

Functional roles of striatal subregions are dissociable and complex. Given the fundamental role of separate striatal subdivisions in different aspects of reward processing, careful attention should be given to anatomical distinctions. Dorsolateral and dorsomedial striatal regions are currently being further distinguished based on connectivity and function (16). To better understand anatomical and behavioral correlates of the striatum, we encourage a precise, nuanced approach in attending to striatal ups and downs.

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