

Pathological gambling is linked to reduced activation of the mesolimbic reward system

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By analogy to drug dependence, it has been speculated that the underlying pathology in pathological gambling is a reduction in the sensitivity of the reward system. Studying pathological gamblers and controls during a guessing game using functional magnetic resonance imaging, we observed a reduction of ventral striatal and ventromedial prefrontal activation in the pathological gamblers that was negatively correlated with gambling severity, linking hypoactivation of these areas to disease severity.

Gambling that interferes with interpersonal relationships and negatively affects financial and socioeconomic status has been defined as pathological gambling¹, a common disorder with a lifetime prevalence of 1.6% in adults¹ and important social consequences. Pathological gambling shares many features with drug addiction, such as the development of euphoria ('high'), craving and tolerance^{1,2}. The mesolimbic reward system is thought to play a crucial role in the development and maintenance of drug addiction^{2,3}, and several lines of evidence converge toward the hypothesis that drug addicts have a deficient reward system and that drug intake is an attempt to compensate for this deficit⁴. By analogy to drug addiction, it has been speculated that pathological gambling might also be related to a deficiency of the mesolimbic dopaminergic reward system⁴.

We addressed this question by studying 12 pathological gamblers and 12 closely matched healthy controls using functional magnetic resonance imaging (fMRI) and a guessing task known to robustly activate the ventral striatum^{5,6} (Fig. 1a,b and Supplementary Methods online). The study was approved by the local ethics committee, and all participants gave written informed consent before participating in this study.

The behavioral data (Supplementary Data online) showed that participants successfully completed all three runs. First, we verified that our task robustly activated the ventral striatum. We observed significantly greater activity during winning than during losing in the ventral striatum in both groups (Fig. 1c,d and Supplementary Table 1; activation maps of each individual subject can be found in Supplementary Figs. 1 and 2). At the same threshold, fewer voxels were activated in pathological gamblers than in the controls, and only the controls showed additional activation in the ventromedial and ventrolateral prefrontal cortex (VMPFC) (Fig. 1c). A direct comparison of both groups (Fig. 2) showed significantly lower activation of the right ventral striatum in pathological gamblers than in controls (peak x,y,z : 33, 12,

-6 mm; $t_{18} = 4.9$, $P < 0.05$, corrected) (Fig. 2b and Supplementary Table 2). The opposite comparison (testing for greater activation in pathological gamblers than in controls) revealed no significant signal differences. In addition, pathological gamblers showed significantly weaker activation in the VMPFC (peak x,y,z : $-3, 54, -12$ mm; $t_{18} = 4.7$, $P < 0.05$, corrected) (Fig. 2c).

We also performed a regression analysis trying to correlate signal changes in the ventral striatum with the severity of gambling in each patient. The severity of gambling in pathological gamblers (as assessed with a gambling questionnaire) showed a significant negative correlation with the response in the right ventral striatum ($r = -0.77$; $t_{10} = 3.8$, $P < 0.05$) and the response in the VMPFC ($r = -0.53$; $t_{10} = 2.0$, $P < 0.05$) (Fig. 2a,d). The patterns in areas demonstrating negative correlation are shown in Supplementary Figure 3, and peak voxels are summarized in Supplementary Table 3.

To ensure that this result was not related to depression in some pathological gamblers or to differences in smoking habits, we performed two additional analyses: (i) a categorical analysis comparing non-depressed pathological gamblers to a smaller control group perfectly matched for smoking, and (ii) a correlation analysis without the depressed patients.

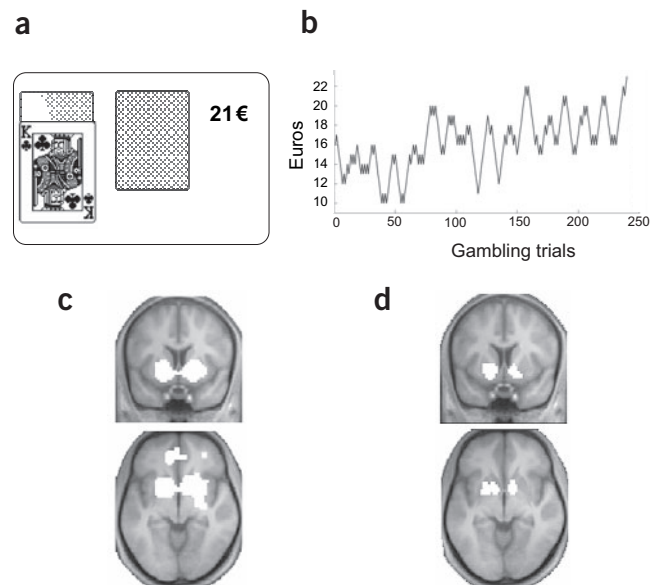


Figure 1 Layout of the guessing task and main effect of winning. (a) Volunteers had to choose a playing card (either right or left) by pressing a button. If the color of this card was red, they won €1.00; otherwise they lost €1.00. (b) Predetermined course of wins and losses. (c,d) Activation of the ventral striatum in the controls (c) and pathological gamblers (d) is superimposed on an averaged T_1 -weighted magnetic resonance image at a threshold of $P < 0.001$.

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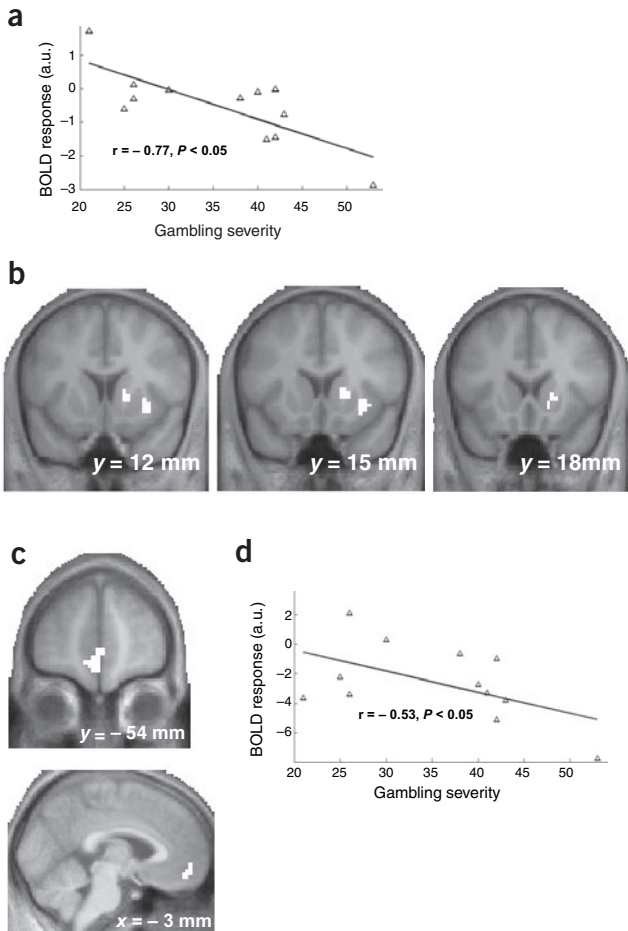


Figure 2 Differences in activation between the controls and the pathological gamblers. **(a)** Gambling severity of individual pathological gamblers. **(b)** Lower activation in the right ventral striatum of pathological gamblers compared with controls at $P < 0.001$ masked with the contrast winning > losing at $P < 0.001$. Activity within this area was negatively correlated with gambling severity of individual pathological gamblers **(a)**. **(c)** Pathological gamblers also showed less activation in the ventromedial prefrontal cortex. Again, activation was negatively correlated with gambling severity **(d)**. The y axes in **a** and **d** represent parameter estimates from the single subject analysis and are directly related to BOLD signal change.

of reward in win trials. This is in accordance with recent functional neuroimaging data showing that the nucleus accumbens is involved in coding unexpected arousing events¹³. Reward-related responses in the ventral striatum can also be augmented by saliency¹⁴, so a reduced activation of the ventral striatum in pathological gamblers might be the result of a lower saliency of rewards in that group.

Our guessing task is played at a fast pace and thus can best be studied with rapid event-related fMRI, which ensures a highly efficient design¹⁵. However, the efficiency for main effects such as winning or losing is extremely low in these designs. It is thus possible that a smaller difference between winning- and losing-related blood oxygenation level-dependent (BOLD) signals in the ventral striatum of pathological gamblers could stem at least partially from a higher BOLD signal during loss trials in this group. Indeed, a previous study has shown that the ventral striatum responds not only to rewarding but also to punishing stimuli in healthy controls⁶.

In summary, a decreased activation of the ventral striatum, which is a hallmark of drug addiction², and decreased VMPFC activation, which is related to impaired impulse control⁸, favor the view that pathological gambling is a non-substance-related addiction.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

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The categorical analysis revealed the same pattern as described above (Supplementary Table 4 and Supplementary Fig. 4). The additional correlation analysis confirmed our initial data and showed an even stronger relationship between gambling severity and hypoactivation of the right ventral striatum ($r = -0.88$; $t_6 = 4.5$, $P < 0.05$) and VMPFC ($r = -0.67$; $t_6 = 2.2$, $P < 0.05$).

Drug self-administration experiments have suggested that organisms try to maintain a homeostatic baseline level of dopamine in the ventral striatum³, which in normal volunteers can be maintained by weak reinforcers found in everyday life. In contrast, in pathological gamblers (who have reduced ventral striatal activation), natural reinforcers are not strong enough for dopamine to reach and maintain this homeostatic baseline level³. At this stage, organisms seek additional, stronger reinforcers, such as drugs of addiction or gambling, to compensate for the lack of activation.

Maintenance of drug addiction is linked to diminished impulse control, which is the reason that the addict is unable to quit despite adverse consequences emerging from the addiction^{1,2}. Several lesion and neuroimaging studies have identified the pivotal role of the VMPFC in impulse control⁷. It is thus not surprising that drug addicts perform similarly to patients with prefrontal lesions in tasks involving decision-making^{8,9}. Similarly to what has been observed in drug addicts, our data show a reduced activation in VMPFC in pathological gamblers. This is in accord with previous data¹⁰ and might represent the neural basis for impaired impulse control in pathological gamblers.

With reference to formal models^{11,12}, the strong activation of the ventral striatum in our paradigm might be explained by the difference of predicted reward in each trial (50%) and the unexpected delivery

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