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## Serotonin 1B receptor imaging in pathological gambling

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### Abstract

**Objectives**—Although serotonergic mechanisms have been implicated in pathological gambling (PG), no ligand-based imaging studies have assessed serotonin receptors in individuals with PG. Given its role in substance addictions and its abundance in brain regions implicated in PG, we evaluated serotonin 1B receptors (5-HT<sub>1B</sub>Rs) in PG.

**Methods**—Ten medication-free subjects with PG (mean ± SD age = 36.3 ± 9.4 years, nine men) and ten control comparison (CC) subjects (mean ± SD age = 35.8 ± 9.9 years, nine men) underwent [<sup>11</sup>C]P943 positron emission scanning on a high resolution research tomograph.

**Results**—5-HT<sub>1B</sub>R *BP*<sub>ND</sub> values were similar in PG and CC subjects (*P* > 0.1). Among PG subjects, scores on the South Oaks Gambling Screen (SOGS) correlated positively with 5-HT<sub>1B</sub>R *BP*<sub>ND</sub> values in the ventral striatum (*r* = 0.66; *P* = 0.04), putamen (*r* = 0.67; *P* = 0.03) and anterior cingulate cortex (*r* = 0.73; *P* = 0.02).

**Conclusions**—These findings provide the first evidence that PG severity in humans is linked to increased levels of 5-HT<sub>1B</sub>Rs in regions previously implicated in functional neuroimaging studies of PG. These findings indicate a potential role for serotonergic function in the ventral striatum and anterior cingulate cortex contributing to problem gambling severity and warrant further studies to investigate whether numbers of available 5-HT<sub>1B</sub>Rs might represent a vulnerability factor for PG or develop in relationship to problem gambling.

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### Statement of Interest

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## Keywords

Pathological gambling; brain imaging; serotonin 1B receptor; positron emission tomography; South Oaks Gambling Screen

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## Introduction

Pathological gambling (PG), a disorder with prevalence estimates of about 1%, shares clinical and biological features with substance addictions (Potenza 2008). However, in comparison to substance addictions, less is known regarding the neurobiology of PG as animal models of the disorder have only recently been developed and comparably few human investigations have been performed (Potenza 2009). An improved understanding of the neurobiology of PG could lead to the development of improved treatment strategies for PG, a significant need as no medications are currently approved by the Food and Drug Administration for the disorder.

Genetic, clinical, neural and neurochemical data link PG with substance addictions like alcohol dependence. Shared genetic contributions partly underlie the co-occurrence of these two disorders, opioid antagonists have been found to be helpful in randomized clinical trials for each disorder, and individuals with each disorder demonstrate relatively diminished ventral striatal activation during reward anticipation or simulated gambling (Potenza 2008; Beck et al. 2009). Studies of PG and alcohol dependence have implicated ventral striatal and anterior cingulate function in each disorder (Potenza et al. 2003; Reuter et al. 2005; Beck et al. 2009). Individuals with alcohol dependence and PG each have shown low levels of the serotonin metabolite 5-hydroxy-indole acetic acid in some but not all studies (Bergh et al. 1997; Nordin and Eklundh 1999), and the serotonergic ligand meta-chlorophenyl piperazine (m-CPP), a drug which agonizes multiple 5-HT<sub>1B</sub>R, similarly generates a more positive subjective response in individuals with these disorders than in those without (Potenza 2008). Together, these findings suggest a possible role for 5-HT<sub>1B</sub>R function in PG.

5-HT<sub>1B</sub>R function in cortico-limbic regions has been implicated in other psychiatric disorders, including ones characterized by mood dysregulation, stress vulnerability and impaired impulse control. Individuals with major depression have shown relatively diminished 5-HT<sub>1B</sub>R binding potential in the ventral striatum (Murrough et al. 2011) and individuals with post-traumatic stress disorder (PTSD), particularly those with co-occurring major depression, have shown relatively diminished 5-HT<sub>1B</sub>R binding potentials in multiple cortico-limbic regions, including the anterior cingulate cortex (Murrough et al. in press). In the latter study, 5-HT<sub>1B</sub>R binding potential in the anterior cingulate cortex correlated with age of first trauma, suggesting that markers associated with illness severity in psychiatric disorders might correlate with regional 5-HT<sub>1B</sub>R binding potentials. In contrast to PTSD and major depression, elevated 5-HT<sub>1B</sub>R binding potential was observed in the ventral striatum in alcohol dependence (Hu et al. 2010). These findings indicate that 5-HT<sub>1B</sub>R function may contribute in differential fashions to specific psychiatric disorders. Alcohol dependence has multiple similarities with PG, including with respect to biological and behavioral responses to m-CPP (Potenza 2008) and in demonstrating shared genetic and environmental contributions (Slutske et al. 2000). The findings linking the biological underpinnings of alcohol dependence and PG may be particularly relevant to men as participants in these studies were predominantly or solely male and PG in women has shown stronger links to trauma (Petry et al. 2005a), gambling to escape dysphoria (Blanco et al. 2006) and internalizing disorders like depression (Desai and Potenza 2008).

In the current study, we assessed 5-HT<sub>1B</sub>Rs in a largely male cohort of individuals with PG. Given the data summarized above and findings that: (1) show expression of the 5-HT<sub>1B</sub>R in the ventral striatum and anterior cingulate (Varnas et al. 2005); (2) similarly link impulsivity with both ventral striatal and anterior cingulate responses during reward processing in alcohol dependence (Beck et al. 2009); (3) implicate anterior cingulate cortex and ventral striatum dysfunction in PG (Potenza 2008), and (4) link gambling severity with activations in brain regions including the ventral striatum (Reuter et al. 2005), we hypothesized that: (1) PG subjects (versus control comparison (CC) subjects) would show elevated [<sup>11</sup>C]P943 BP<sub>ND</sub> measures in ventral striatum and anterior cingulate cortex; and (2) [<sup>11</sup>C]P943 BP<sub>ND</sub> measures in these regions would correlate positively with South Oaks Gambling Screen scores in the PG group.

## Methods and materials

### Subjects

Ten PG subjects (mean ± SD age = 36.3 ± 9.4 years, nine men, seven white) and 10 matched CC subjects (mean ± SD age = 35.8 ± 9.9 years, nine men, eight white) provided written informed consent for this study that was approved by the Yale Human Investigation Committee. Subjects were recruited through advertising and were evaluated via Structured Clinical Interview for DSM-IV (First et al. 1995) and Structured Clinical Interview for Pathological Gambling (Grant 2004). Subjects were medication-free. Three PG and two CC were current daily tobacco smokers. With the exception of PG for the PG group, no subjects met criteria for any current psychiatric diagnoses. No CC subjects met criteria for any lifetime psychiatric diagnoses. One PG subject met criteria for remitted panic disorder without agoraphobia. With the exception of tobacco, no PG subjects met lifetime dependence criteria for any substance. Four PG subjects met criteria for remitted alcohol abuse, one of whom also abused cannabis previously. Subjects provided written, informed consent to participate in the protocol that was approved by the Yale Human Investigations Committee. Evaluations included physical examinations, electrocardiograms, urine toxicologies and other standard laboratory tests, as described previously (Hu et al. 2010). Individuals were excluded for histories of medical or neurological illnesses, head trauma with loss of consciousness, or metal in body precluding MRI. Subjects (all PG and a minority of CC subjects ( $n = 2$ )) completed the South Oaks Gambling Screen (Lesieur and Blume 1987), a widely used screening instrument with a range extending from 0 to 20 and a score of 5 or more suggesting pathological gambling (Lesieur and Blume 1987) and whose German correlate has been used previously as a measure of problem gambling severity in neuroimaging analyses (Reuter et al. 2005).

### Imaging

Imaging methodologies followed those employed in our prior work (Hu et al. 2010). MRI scans for localization and detection of structural anomalies were performed with a 3T Trio Siemens magnet. PET imaging procedures involved indwelling intravenous (IV) catheter placement and a transmission scan with a <sup>137</sup>Cs point source. Subsequent emission scans were obtained for 120 min at rest with a single IV injection of high specific activity [<sup>11</sup>C]P943, a selective 5-HT<sub>1B</sub>R antagonist radiotracer (Nabulsi et al. 2010), using a high-resolution research tomography (HHRT) scanner (207 slices, resolution at < 3 mm full-width-at-half-maximum in 3-D acquisition mode). Dynamic scan data were reconstructed with corrections (attenuation, normalization, scatter, randoms, and dead time). Motion-correction was performed by co-registering each reconstructed frame to an early summed image (0 – 10 min after injection) with 6-parameter mutual information algorithm and FMRIB's Linear Image Registration Tool (FLIRT, FSL 3.2, Analysis Group, FMRIB, Oxford, UK).

For each individual, a summed image (0 – 10 min following injection) derived from motion-corrected PET data was co-registered with their MR image, which then was registered (12-parameter affine transformation) to an MR template in Montreal Neurological Institute space. The regions of interest for the ventral striatum, involving the nucleus accumbens and globus pallidum, and anterior cingulate cortex, involving its subgenual and pregenual segments, were taken from the template (Anatomical Automatic Labeling (Tzourio-Mazoyer et al. 2002) for SPM2 [<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>]) and applied to the PET data to generate time-activity data. Similarly defined control comparison regions included other striatal regions (putamen, caudate) and cortical regions (prefrontal and occipital cortices). Pixel-by-pixel analysis was done using a multilinear reference tissue model (Ichise et al. 2003) to produce images of  $BP_{ND}$  (Innis et al. 2007). The interpretation of  $BP_{ND}$  is  $f_{ND} \times B_{avail}/K_d$ , where  $f_{ND}$  is the tracer-free fraction in a region without specific binding,  $B_{avail}$  is the unoccupied receptor concentration, and  $K_d$  is dissociation equilibrium constant of the tracer. The cerebellum was used as the reference region as it is virtually devoid of 5-HT  $1B$ Rs (Varnas et al. 2005) and to allow comparability across studies (Hu et al. 2010). Assuming there is no change in affinity or non-specific binding between subject groups, changes in  $BP_{ND}$  were interpreted as changes in receptor concentration. The  $BP_{ND}$  values from multilinear reference tissues models have yielded highly comparable results to those obtained with arterial input functions (Gallezot et al. 2010).

### Statistical analyses

Between subject groups, unpaired two-tailed t-tests compared clinical and demographic variables and a Mann – Whitney *U*-test compared  $BP_{ND}$  values. Relationships between  $BP_{ND}$  values and SOGS scores were investigated using Spearman correlation coefficients. Analyses were not corrected for multiple comparisons given the specific hypotheses being tested.

### Results

Demographic and smoking measures did not differ between the PG and CC groups (Table I). Individuals with PG had mean(SD) SOGS scores of 14.00(2.71). CC subjects had SOGS scores of zero. PET injection measures (injected dose, specific activity, and injected mass) did not differ between groups (each  $P > 0.05$ ). Between-group [ $^{11}C$ ]P943  $BP_{ND}$  values did not differ (each  $P > 0.05$ ) in ventral striatum (CC:  $1.64 \pm 0.27$ ; PG:  $1.64 \pm 0.43$ ) and anterior cingulate (CC:  $0.94 \pm 0.14$ ; PG:  $0.90 \pm 0.17$ ) nor in comparison regions of putamen (CC:  $0.87 \pm 0.07$ ; PG:  $0.88 \pm 0.20$ ), caudate (CC:  $0.50 \pm 0.15$ ; PG:  $0.50 \pm 0.23$ ), frontal cortex (CC:  $0.75 \pm 0.16$ ; PG:  $0.73 \pm 0.15$ ) or occipital cortex (CC:  $0.76 \pm 0.08$ ; PG:  $0.81 \pm 0.10$ ). In PG subjects, SOGS scores correlated positively with  $BP_{ND}$  values in ventral striatum ( $r = 0.66$ ;  $P < 0.05$ ) and anterior cingulate ( $r = 0.78$ ;  $P < 0.02$ ) (Figure 1) as well as in putamen ( $r = 0.67$ ;  $P < 0.05$ ), but not in caudate ( $r = 0.45$ ;  $P > 0.1$ ) or frontal ( $r = 0.52$ ;  $P > 0.1$ ) or occipital ( $r = 0.57$ ;  $P = 0.09$ ) cortices.

### Discussion

Our a priori hypotheses in this investigation of 5-HT  $1B$ Rs in PG were partially supported. The hypothesis that 5-HT  $1B$ R  $BP_{ND}$  values would differ in PG and CC subjects was not observed for either the ventral striatum or anterior cingulate. However, the hypothesis that 5-HT  $1B$ R  $BP_{ND}$  values within these regions would correlate positively with SOGS scores, reflecting problem gambling severity, was observed in both regions. Additionally, SOGS scores also correlated with 5-HT  $1B$ R  $BP_{ND}$  values in the putamen but not the caudate or occipital or frontal cortices, suggesting specificity to regions of the striatum and anterior cingulate. Interpretations and clinical implications are discussed below.

No significant between-group differences in 5-HT<sub>1B</sub>R  $BP_{ND}$  values were observed in the PG and CC groups. This result contrasts with a previous finding in alcohol dependent subjects in whom elevated 5-HT<sub>1B</sub>R  $BP_{ND}$  values were seen (Hu et al. 2010). Both similarities and differences between alcohol dependence and PG have been reported. For example, alcohol dependent and problem gambling subjects show similar impairments in risky decision-making but differences in cognitive function (Lawrence et al. 2009), and the extent to which 5-HT<sub>1B</sub>R might contribute to these processes in PG and alcohol dependence warrants additional investigation.

The observation of no between-group differences in 5-HT<sub>1B</sub>R  $BP_{ND}$  values observed in the PG and CC groups in the ventral striatum and anterior cingulate cortex suggests that 5-HT<sub>1B</sub>R availability in these regions is not a defining feature of the disorder. However, significant inter-individual variability was observed in the PG group, particularly with respect to the ventral striatal findings. These findings are consistent with the notion that, like many psychiatric conditions, PG is a heterogeneous disorder. Several subtypes of PG have been proposed, with different groups characterized by high impulsivity and sensation-seeking and others by emotional vulnerability who may be motivated to gamble to escape from distress or dysphoria (Blaszczynski and Nower 2002). Such typologies may explain PG's frequent co-occurrence with both externalizing disorders like substance dependences and internalizing disorders like depression (Petry et al. 2005b). It is tempting to speculate that impulsive, sensation-seeking individuals with PG may show elevated 5-HT<sub>1B</sub>R  $BP_{ND}$  values, akin to those with alcohol dependence (Hu et al. 2010), and emotionally vulnerable individuals with PG may show depressed 5-HT<sub>1B</sub>R  $BP_{ND}$  values, akin to those with major depression (Murrough et al. 2011). The latter group may be particularly important to consider with respect to sex differences as women with PG are more likely than men with PG to acknowledge gambling for negative reinforcement motivations, consistent with sex differences in the relationships between problem/PG and depression (Blanco et al. 2006; Desai and Potenza 2008). Further study is needed to investigate these possibilities.

Although serotonergic differences have been observed in PG and CC groups (Potenza 2008), drugs that influence serotonergic function have shown in randomized clinical trials either negative results (e.g., antagonists like olanzapine) or mixed findings (e.g., for serotonin reuptake inhibitors like paroxetine and fluvoxamine) (Brewer et al. 2008). It is tempting to speculate that some variability in treatment response to SRIs in PG might relate to differences in 5-HT<sub>1B</sub>R function, although direct investigation of this idea is needed. Such investigations seem timely given current interest in developing gene therapies that alter 5-HT<sub>1B</sub>R function in the ventral striatum for depression based on findings that in the nucleus accumbens region of the ventral striatum, increasing levels of p11, a 5-HT<sub>1B</sub>R-binding protein that enhances cell surface location of the 5-HT<sub>1B</sub>R, have been associated with remission of depressive features (Alexander et al. 2010; Chen et al. 2010). It is possible that drugs that influence 5-HT<sub>1B</sub>R function may operate to indirectly modulate activity in the ventral striatum. As indirect modulation of dopamine function in the striatum has been proposed to underlie the effects of opioid antagonists that have in multiple placebo-controlled trials shown efficacy in the treatment of PG (Wareham and Potenza 2010), the development of tolerable drugs targeting the 5-HT<sub>1B</sub>R may represent a novel approach in the treatment of PG. However, variability in 5-HT<sub>1B</sub>R function as might be related to different subtypes of PG warrant consideration in this process.

The significant inter-individual variation in 5-HT<sub>1B</sub>R  $BP_{ND}$  values in the PG group provided a range that facilitated correlations with SOGS scores. The mean SOGS score in the PG group was similar to that reported in other PG samples and reflects significant gambling problems (Potenza et al. 2003). The positive correlation between 5-HT<sub>1B</sub>R  $BP_{ND}$  values and SOGS scores in the ventral striatum differs from the inverse correlation observed

between scores on a German analog of the SOGS and ventral striatal activation during simulated gambling in PG subjects (Reuter et al. 2005). Together, these findings raise the question whether the number of 5-HT<sub>1B</sub>R might correlate inversely with gambling-related activation of the ventral striatum, a supposition consistent with a role for 5-HT<sub>1B</sub>R in the nucleus accumbens in regulating mesolimbic pathways (Ferguson et al. 2009). Given the influence of stress on 5-HT<sub>1B</sub>R modulation of mesolimbic function (Ferguson et al. 2009), future studies should investigate the extent to which 5-HT<sub>1B</sub>R function relates to stress and trauma in PG (Petry et al. 2005a; Elman et al. 2010). Other intermediary phenotypes that are relevant to PG, such as those relating to impulsivity and mood state or tendencies, warrant investigation in future studies to determine their relationship with 5-HT<sub>1B</sub>R function in PG.

As with the ventral striatum (Potenza 2008), relatively diminished activation of the anterior cingulate cortex has been observed in PG subjects when viewing gambling-related stimuli (Potenza et al. 2003). Thus, the similar patterns of positive correlations between 5-HT<sub>1B</sub>R  $BP_{ND}$  values and SOGS scores in the ventral striatum and anterior cingulate are not surprising. The anterior cingulate cortex has been implicated in phenomena relevant to PG including emotional and motivational processing and cognitive control. Given a role for 5-HT<sub>1B</sub>R expression in the anterior cingulate in depression (Svenningsson et al. 2006) and strong biological relationships between depression and PG (Potenza et al. 2005) and negative mood states and gambling urges (Thomsen et al. 2009), future research should investigate the relationship between 5-HT<sub>1B</sub>R in the anterior cingulate and affective dysregulation in PG. Also, given data associating p11 levels in the ventral striatum with remission of depressive features, studies should investigate the relationship between ventral striatal 5-HT<sub>1B</sub>R and depressive symptomatology in PG. However, the nature of the relationship between PG, major depression, 5-HT<sub>1B</sub>R, and ventral striatal function appears complex given that increased numbers of 5-HT<sub>1B</sub>R appear associated with greater problem gambling severity in the current study and improved mood in other studies (Alexander et al. 2010; Chen et al. 2010). Given the reduced 5-HT<sub>1B</sub>R  $BP_{ND}$  values observed in major depression (Murrough et al. 2011), the frequent co-occurrence of PG and major depression (Potenza et al. 2005) and the clinical implications of the relationship, additional studies should clarify the nature of a potential role for 5-HT<sub>1B</sub>R in individuals dually diagnosed with PG and major depression. Additionally, therapies that target mood improvement through elevating ventral striatal 5-HT<sub>1B</sub>R should consider the potential influence on problem gambling and other addictive behaviours like alcohol abuse or dependence (Hu et al. 2010).

5-HT<sub>1B</sub>R influence GABAergic and dopaminergic neurotransmission in the mesolimbic pathway (Yan and Yan 2001a,b). For example, infusion of a 5-HT<sub>1B</sub>R agonist into the nucleus accumbens increases local dopamine concentration in a dose-dependent fashion (Yan and Yan 2001a). Thus, in individuals with PG, increased availability of 5-HT<sub>1B</sub>R in the ventral striatum could increase levels of ventral striatal dopamine. Increased ventral striatal dopamine release has been reported during performance of gambling tasks both in PG as compared to CC subjects losing money and, amongst individuals with Parkinson's disease, in those with PG as compared to those without PG (Steeves et al. 2009; Linnet et al. 2010). Future studies should investigate the interaction between serotonin and dopamine systems in PG, particularly as also data suggest complementary roles for the two neurotransmitters in gambling behaviours (Zeeb et al. 2009; Campbell-Meiklejohn et al. 2011).

The current study has limitations including small samples and co-occurring tobacco smoking. Given the small sample of PG subjects, statements relating to inter-individual variability should be considered cautiously. Although the groups did not differ on smoking status, future studies should investigate 5-HT<sub>1B</sub>R in tobacco smoking. Additionally, SOGS

scores were not collected on most CC subjects as we had envisioned the SOGS scores and their neurobiological and clinical correlates to be mainly relevant to the PG group. The existing data and our prior experience with CC imaging subjects denying heavy gambling problems suggest that most if not all CC subjects would score zero. Nonetheless, future studies should assess gambling severity using the same structured scales in both PG and CC subjects. Despite these limitations, the current study represents the first to investigate with radiotracers 5-HT<sub>1B</sub>R in PG and provides important initial data with respect to a role for 5-HT<sub>1B</sub>R function in PG.

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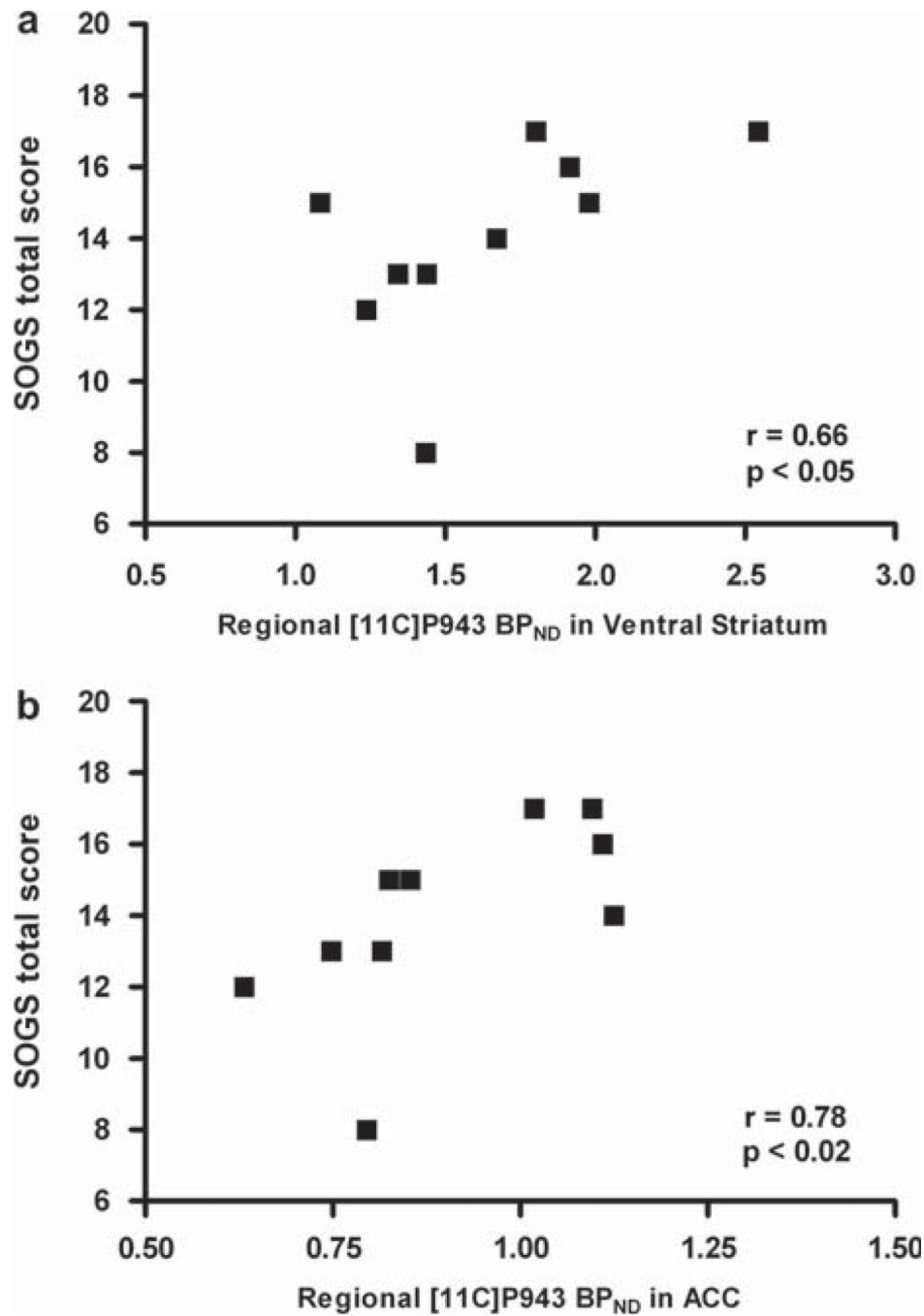
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**Figure 1.** Correlations between 5-HT<sub>1B</sub>R BP<sub>ND</sub> values and SOGS scores in PG subjects in the ventral striatum (a) and anterior cingulate (b).

**Table I**

Demographic and clinical characteristics of PG and CC subjects.

<b>Group</b>	<b>PG (n = 10)</b>	<b>CC (n = 10)</b>	<b>P</b>
Age, years (mean $\pm$ SD)	36.3 $\pm$ 9.44	35.80 $\pm$ 9.875	0.91
Gender, male (n; %)	9; 90%	9; 90%	1
Race, white (n; %)	7; 70%	8; 80%	0.62
Current tobacco smoker, yes (n;%)	3; 30%	2; 20%	0.62

PG, pathological gambling; CC, control comparison.