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Hippocampal and Amygdalar Volumetric Differences in Pathological Gambling: a Preliminary Study of the Associations with the Behavioral Inhibition System

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The behavioral inhibition system (BIS) and behavioral activation system (BAS) are hypothesized to underlie motivated behavior, relate to hippocampal and amygdalar function, and link to pathological gambling (PG). Prior studies have not investigated hippocampal and amygdalar volumes in PG and their relationships to BIS/BAS measures. Structural MRI scans and BIS/BAS and other clinical measures were obtained from 32 PG individuals and 47 healthy comparison (HC) individuals. Volumetric measures of the hippocampus and amygdala were assessed using FreeSurfer and related to BIS/BAS measures. PG relative to HC individuals demonstrated diminished volume in the left hippocampus and right amygdala and higher BIS and BAS scores. BIS scores were positively correlated with left hippocampal and left amygdalar volumes in PG individuals. The findings of relatively diminished hippocampal and amygdalar volumes in PG individuals resonate with findings from substance-dependent groups. Relationships between amygdalar and hippocampal volumes and BIS measures in PG suggest that individual differences in these structures may contribute to avoidance behaviors in PG.
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INTRODUCTION

Gray's theory regarding the neural pathways that underlie motivated behaviors encompasses two parallel systems—a behavioral inhibition system (BIS) and a behavioral activation system (BAS; Gray, 1987). According to Gray, the BIS is sensitive to punishment, novelty, and negative affective states including anxiety and depression (Gray, 1987; Gray and McNaughton, 2000). It has been postulated that the neural correlates of the BIS include the amygdala and septo-hippocampal systems, with high activity in these areas associated with anxiety (Gray, 1987; Gray and McNaughton, 2000). Conversely, the BAS is sensitive to reward signals and is associated with positive affective states like happiness and elation (Carver and White, 1994; Gray, 1987). Gray proposed the BAS to be imbedded primarily in the septal area and the hypothalamus (Gray, 1987). However, the neural underpinnings of the BAS are not as well elaborated as the BIS, although dopaminergic pathways may contribute (Carver and White, 1994; Depue and Collins, 1999; Gray, 1987).

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Structural studies investigating reward and risk assessment and emotionally motivated behavior support the BIS/BAS function in regions initially proposed by Gray. For example, voxel-based-morphometry studies found that hippocampal and amygdalar volumes were positively correlated with BIS activity, whereas dorsal striatal and superior frontal gyral volumes were negatively correlated with BAS activity (Barros-Loscertales *et al*, 2006a, b). Additionally, larger hippocampal volumes have been associated with increased anxiety, whereas reduced hippocampal volumes have been implicated in increased impulsivity (Rusch *et al*, 2001; Zetzsche *et al*, 2007). In a large sample ($n = 430$) of healthy adults, BIS activity correlated with hippocampal volumes (Cherbuin *et al*, 2008). These studies support a relationship between hippocampal and amygdalar volume and BIS/BAS function.

BIS/BAS function is relevant to multiple psychiatric disorders. For example, increased BIS activation and decreased BAS activation have been associated with depression and anxiety (Hundt *et al*, 2007; Johnson *et al*, 2003). BAS-reward-responsiveness (BAS-RR) and BAS-drive (BAS-D) subscale scores are low in depressed adults (McFarland *et al*, 2006). Substance-use disorders have also been associated with BIS/BAS function (although see van Toor *et al* (2011)), with BAS-fun-seeking (BAS-FS) and BAS-D activity associated with the substance use and/or lifetime drug dependence (Franken *et al*, 2006; Johnson *et al*, 2003), and BIS function inversely related to binge-drinking

behavior. BIS, BAS-RR, and BAS-FS activity have also been positively associated with impulsivity and hazardous drinking in a community sample of adults (Hamilton *et al*, 2012).

Pathological gambling (PG) may also be considered within this framework. PG is characterized by impaired impulse control and altered risk assessment, which suggests that BIS/BAS may relate to PG (Potenza, 2008; Potenza *et al*, 2003; Tanabe *et al*, 2007). PG is associated with poor physical and psychiatric health in both adults and adolescents (Potenza *et al*, 2001; Rahman *et al*, 2012; Shaffer and Korn, 2002). As gambling in PG may be motivated by negative or positive reinforcement tendencies, BIS and BAS systems may relate importantly to PG as they do to substance-use disorders (Grant and Kim, 2002).

Several studies have described the relationship between BIS/BAS function and gambling behaviors. Among college students, negative affect was associated with problem-gambling severity and with scores on the BIS assessment, whereas BAS-RR was inversely correlated with problem-gambling severity (Atkinson *et al*, 2012). Problem gamblers also score higher on the BIS and BAS scales, with higher BIS/BAS scores associated with worse performance on the Iowa Gambling Task (Goudriaan *et al*, 2006). In non-problematic adult gamblers, BIS scores were more closely related to risky betting than were BAS scores (Demaree *et al*, 2008). PG individuals also scored higher than healthy comparison (HC) subjects on the BAS-FS and BAS-D scales, with BAS-FS scores inversely correlated with the white matter integrity in the left and right genu of the corpus callosum (Yip *et al*, 2013).

Although hippocampal and amygdalar volumes have been linked to BIS and PG to BIS/BAS measures, no studies have investigated brain volumes in PG as related to BIS/BAS measures. Few studies have investigated brain volumetric differences in PG and HC subjects, with one small study finding no between-group differences (Joutsa *et al*, 2011; Leeman and Potenza, 2012). However, studies of other groups with addictions (eg, those with cocaine dependence) have shown smaller hippocampal and amygdalar volumes in addicted *vs* comparison samples (Makris *et al*, 2004; Rando *et al*, 2013). Here we sought to examine volumetric measures in a larger sample of PG and HC subjects and explore relationships with BIS/BAS. We hypothesized that: (1) PG *vs* HC participants would score higher on BIS and BAS scales; (2) PG *vs* HC participants would have diminished hippocampal and amygdalar volumes; and (3) Hippocampal and amygdalar volumes would positively associate with BIS activity, particularly within PG participants.

MATERIALS AND METHODS

Participants

Both HC and non-treatment-seeking PG individuals were recruited via advertising. Final enrollment included 32 PG (12 female) and 47 HC (19 female) individuals. Participants were assessed using the Structured Clinical Interview for DSM-IV (SCID; First *et al*, 1995). PG status was determined using the Structured Clinical Interview for Pathological Gambling (SCI-PG; Grant *et al*, 2004). Exclusion criteria for this study included: current or planned pregnancy, current non-substance-use Axis I disorders, or unstable medical conditions. All participants provided written informed consent before enrolling and all study procedures were approved by the Yale Human Investigation Committee.

Demographic data collected included: age, gender, race/ethnicity, and education. Smoking status was categorized as either current smoker or not. Alcohol and drug dependence were assessed during structured interviews. Drug categories included sedatives, marijuana, stimulants, opiates, cocaine, hallucinogens, and 'other.' The HC group had no individuals that had current or prior alcohol or drug dependence, whereas the PG group had 11 individuals, including one each with current alcohol and cocaine dependence. The specific prior disorders in the PG group included one individual with prior alcohol dependence, cocaine dependence, and sedative/hypnotic dependence (in remission from all for greater than a year), two individuals with prior opiate dependence (in remission for over 2 years and 10 years, respectively), one individual with prior alcohol dependence (in remission for 9 years), one individual with prior cocaine dependence (in remission for 19 years), one individual with prior alcohol dependence, cannabis dependence and cocaine dependence (in remission for 7 months), one individual with prior cannabis dependence (in remission for 4 months), one individual with prior alcohol and cocaine dependence (in remission for 7 years), and one individual with prior alcohol, opiate and cocaine dependence (in remission for 10 years, 7 years and 4 months, respectively).

Measures

The BIS and BAS (BIS/BAS) Scale. The BIS/BAS scale is a reliable and valid 24-item scale that measures behavioral inhibition and approach (Carver and White, 1994; Jorm *et al*, 1998). The scale assesses behavioral tendencies with regard to risk aversion or reward seeking. Participants select from a Likert-style scale the degree to which they agree or disagree with the statements. The measure generates two subscale scores relating to BIS and BAS. The BIS measures inhibition to negative affective outcomes, whereas the BAS measures response to positive affective outcomes (Carver and White, 1994). High BIS and BAS scores reflect high BIS and BAS activity, respectively.

The alcohol use disorders identification test. The alcohol use disorders identification test (AUDIT) is a valid and reliable 10-item screen that identifies hazardous alcohol use (Babor *et al*, 2001). Respondents can select between five response choices which are given specific scores, with higher total scores associated with increased severity.

The beck anxiety inventory. The Beck Anxiety Inventory (BAI) is a valid and reliable 21-item instrument that assesses anxiety (Beck *et al*, 1993). Respondents select between four responses per question, and higher total scores reflect increased severity.

The beck depression inventory II. The beck depression inventory II (BDI) is a valid and reliable 21-item instrument that assesses depression (Beck *et al*, 1996). Respondents select between four responses per question, and higher total scores reflect increased severity.

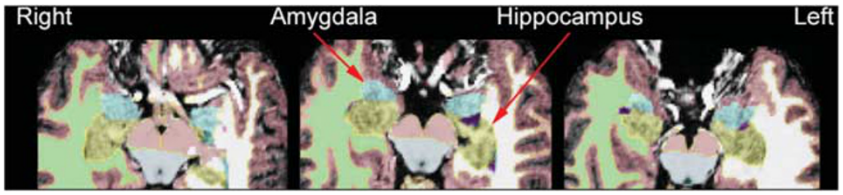

Figure 1 Volumetric differences in mesial temporal structures. Both right amygdalar and left hippocampal volumes were significantly decreased in pathological gambling (PG) subjects ($n = 32$) compared with healthy comparison (HC) subjects ($n = 47$). High-resolution T1-weighted anatomical images were acquired using a 3-T scanner (Trio; Siemens) and mesial temporal structures outlined using FreeSurfer software (http://www.surfer.nmr.mgh.harvard.edu).

Image Acquisition and Processing

High-resolution T1-weighted anatomical images were acquired using a 3-T scanner (Trio; Siemens, Erlangen, Germany) with the following parameters: TR = 1500 ms, TE = 2.83 ms, flip angle = 7°, FOV = 256 × 256 mm^2, matrix = 256 × 256, 1 mm^3 isotropic voxels, 176 slices. The hippocampus and amygdala were automatically segmented using the software FreeSurfer version 5.1.0 (http://surfer.nmr.mgh.harvard.edu) (Fischl *et al*, 2001) (Figure 1). The validity and reliability of the FreeSurfer package have been found to be very good (Morey *et al*, 2009; Shen *et al*, 2010). FreeSurfer scripts autorecon1, 2, and 3 were run in sequence on all imaging data. In brief, processing consisted of removal of the non-brain tissue, Talairach transformation, segmentation of subcortical volumetric structures including hippocampus and amygdala, intensity normalization, tessellation of the gray-matter/white-matter boundary, and labeling of each voxel based on previous probabilistic information. Intracranial volume was generated during this processing. The detailed procedure has been described previously (Fischl *et al*, 2002).

Data Analysis

All data were double-entered and randomly spot-checked for accuracy. Subsequent analyses were conducted in SPSS (version 20.0; IBM; Chicago, IL). Gender comparisons between groups utilized χ^2 analysis and showed the groups to be well matched. Means for age and education were analyzed using *t*-tests. Mean volumes were compared using the general linear model, correcting for age, education, and intracranial volume. Gender was typically not included as a covariate given that groups were evenly matched. All scores on behavioral assessments (BDI, BAI, BAS, and BIS) were compared using the general linear model and adjusted for age and years of education. Partial correlations were conducted between volumes and relevant behavioral assessments, correcting for age, and years of education. Multiple regression models were created for BIS and BAS scores and split by clinical group (HC and PG). All models included age, gender, years of education, intracranial volume, BAI scores, BDI scores, left amygdalar volume, right amygdalar volume, left hippocampal volume, and right hippocampal volume as predictor variables. Additionally, for the PG group, AUDIT score, past/present smoking status, past/present alcohol dependence, and past/present drug dependence were also included as predictor variables. Statistical significance was set at $P < 0.05$ unless otherwise indicated.

RESULTS

Demographics

Most PG and comparison participants were male: 62.5% and 59.6%, respectively (Table 1). There was no between-group difference in gender ($x^2 = 0.068$, $P = 0.794$). PG individuals differed from healthy individuals on age ($t = -2.78$, $P = 0.007$) and education ($t = 4.40$, $P < 0.001$), with PG individuals being older and having less education.

Clinical Measures

PG individuals scored higher on the AUDIT ($F = 12.00$, $P = 0.001$), BDI ($F = 18.75$, $P < 0.001$), BAS ($F = 11.618$, $P = 0.001$), and BIS ($F = 4.47$, $P = 0.039$) (Table 1).

Hippocampal and Amygdalar Volumes

PG individuals had smaller volumes in the right amygdala ($F = 4.31$, $P = 0.041$) and left hippocampus ($F = 5.49$, $P = 0.022$) (Table 1). PG individuals did not differ from healthy individuals in intracranial volume ($F = 0.984$, $P = 0.325$), left amygdalar volume ($F = 2.91$, $P = 0.092$), or right hippocampal volume ($F = 2.33$, $P = 0.131$).

Correlations Between Brain Volumes and Clinical Assessments

No significant correlations were observed in HC subjects (Supplementary Table 1). For PG individuals, a positive correlation was detected between BIS scores and left amygdalar volumes ($r = 0.606$, $P < 0.01$) and BIS scores and left hippocampal volumes ($r = 0.457$, $P < 0.05$).

Multiple Regression Analyses

For the HC group, volumes of the amygdala and hippocampus were not related to BIS nor BAS scale scores when adjusting for the modeled variables including age, gender, years of education, intracranial volume, and BAI and BDI scores (Table 2). For the PG group, left amygdalar volumes were related to BIS scores ($\beta = 0.846$, $P = 0.038$), and the relationship between right hippocampal volumes and BIS scores strengthened but did not reach significance at $p < 0.05$ ($\beta = 0.728$, $P = 0.082$) when adjusting for variables including age, gender, years of education, intracranial volume, BAI, BDI, AUDIT, past/present smoking status, past/present alcohol dependence, and past/present drug dependence (Table 3). The relationship between BIS scores and left hippocampal volumes in

unadjusted analyses ($r = 0.475$, $P < 0.05$) was no longer observed in the adjusted model ($\beta = -0.132$, $P = 0.703$).

DISCUSSION

This study investigated hippocampal and amygdalar volumes and BIS/BAS tendencies in PG and HC subjects. Partially consistent with our *a priori* hypotheses, PG subjects showed relatively smaller hippocampal and amygdalar volumes, with findings reaching statistical significance in the right amygdala and left hippocampus. As hypothesized, PG subjects scored higher than HC subjects on the BIS/BAS scales, and partially consistent with our hypotheses, left amygdalar, and hippocampal volumes correlated with BIS scores in PG but not in HC subjects. When covarying for clinical factors, findings persisted between left amygdalar volumes and BIS scores in PG subjects. Clinical implications are discussed below.

Table 1 Demographic, Volumetric, and Behavioral Differences between Groups

Demographics	HC ($n = 47$)	PG ($n = 32$)	df	x^2	P
	N (%)				
Females	19 (40.4%)	12 (37.5%)	1	0.068	0.794
	Mean values		df	*t*	P
Age (years)	29.62	36.47	77	−2.787	0.007
Education (years)	14.72	13.03	77	4.404	<0.001
Volumes	Mean values		df	*F*	P
ICV (l)[a]	1.073	1.066	1	0.984	0.325
LA (ml)[b]	1.729	1.602	1	2.912	0.092
RA (ml)[b]	1.828	1.715	1	4.318	0.041
LH (ml)[b]	4.061	3.873	1	5.495	0.022
RH (ml)[b]	4.201	4.034	1	2.337	0.131
Behavioral					
AUDIT[a]	3.240	6.140	1	12.003	0.001
BAI[a]	3.850	5.760	1	2.930	0.092
BDI[a]	2.37	9.14	1	18.752	<0.001
BAS total[a]	37.68	42.38	1	11.618	0.001
BIS total[a]	18.02	19.86	1	4.471	0.039

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BAS, behavioral activation system; BIS, behavioral inhibition system; ICV, intracranial volume; HC, healthy controls; PG, problem/pathological gamblers; LA, left amygdala; RA, right amygdala; LH, left hippocampus; RH, right hippocampus.
[a]Adjusted for age and years of education.
[b]Adjusted for age, years of education, and intracranial volume.

Behavioral Tendencies—BIS/BAS Scores

Consistent with our first hypothesis and with prior findings in problem gamblers, PG individuals scored higher on BIS and BAS measures (Goudriaan *et al*, 2006). Higher BIS scores in the PG group indicate greater BIS activity (Carver and White, 1994; Gray, 1987). As the BIS works to inhibit behaviors that may result in negative outcomes, greater activity is associated with tendencies to inhibit behaviors and might reflect internalizing features observed in PG, as is evidenced by frequent co-occurrence of depression and anxiety disorders (Giddens *et al*, 2012; Potenza *et al*, 2005). Moreover, PG individuals score higher on the BAS, suggesting higher activity in this system. Within Gray's proposed motivational framework, the BIS and BAS are considered separate systems, however, they are not diametrically opposed and are, perhaps, more orthogonal as evinced by the current findings and others finding BIS and BAS scores positively relating to the AUDIT scores (Hamilton *et al*, 2012). Accordingly, higher BIS and BAS scores indicate that PG individuals are not only more inclined to demonstrate greater avoidance but also more highly motivated by external rewards (Johnson *et al*, 2003). Consistent with this notion, during gambling tasks (Cavedini *et al*, 2002; Goudriaan *et al*, 2006; Petry, 2001; van Holst *et al*, 2010), PG individuals typically make risky decisions for monetary rewards despite potential negative outcomes. The replication in PG of findings previously observed in problem gamblers suggests BIS/BAS tendencies relate to excessive gambling across diagnostic boundaries, cultures, and geographic locations and imply that both avoidance and approach tendencies relate to PG, perhaps through motivational tendencies underlying gambling behaviors.

Hippocampal and Amygdalar Volumes

In support of our second hypothesis, PG individuals showed relatively decreased hippocampal and amygdalar volumes. These findings are consistent with those in other addictive disorders like stimulant dependence (Makris *et al*, 2004; Rando *et al*, 2013). Additionally, the findings are consistent with an association between PG and elevated stress exposure (Elman *et al*, 2010) and stress and smaller hippocampal volumes (Gilbertson *et al*, 2002). To our knowledge, only one study has investigated volumetric differences in PG and showed no between-group differences, perhaps as the study involved a small sample (Joutsa *et al*, 2011).

The positive correlation between BIS scores and hippocampal volumes reflects a general relationship observed in non-PG populations (Cherbuin *et al*, 2008). In a model adjusting for clinically relevant variables (including those

Table 2 Multiple Regression Analyses Describing the Effects of Relevant Variables on BIS/BAS Scores—HC

	Age	Gender	Edu	ICV	BAI	BDI	LA	RA	LH	RH
	β (P)	β (P)	β (P)	β (P)	β (P)	β (P)	β (P)	β (P)	β (P)	β (P)
BIS total	0.123 (0.423)	−0.011 (0.962)	0.296 (0.075)	−0.373 (0.166)	0.089 (0.585)	0.235 (0.16)	0.054 (0.807)	0.14 (0.577)	−0.251 (0.369)	0.107 (0.682)
BAS total	−0.303 (0.061)	0.14 (0.542)	0.223 (0.18)	−0.574 (0.037)	−0.105 (0.522)	−0.067 (0.682)	−0.02 (0.927)	0.395 (0.122)	0.331 (0.234)	−0.268 (0.295)

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; Edu, education; ICV, intracranial volume; HC, healthy comparison; LA, left amygdala; LH, left hippocampus; RA, right amygdala; RH, right hippocampus.

Table 3 Multiple Regression Analyses Describing the Effects of Relevant Variables on BIS/BAS scores—PG

	Age	Gender	Edu	ICV	BAI	BDI	AUDIT	Smoker	AD	DD	LA	RA	LH	RH
	ß (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)	*ß* (P)
BIS total	0.178 (0.298)	−0.51 (0.058)	0.025 (0.89)	−0.589 (0.073)	−0.087 (0.651)	0.327 (0.058)	−0.33 (0.096)	0.447 (0.08)	−0.359 (0.086)	0.072 (0.675)	0.846 (0.038)	−0.199 (0.44)	−0.132 (0.703)	0.728 (0.082)
BAS total	0.289 (0.228)	−0.013 (0.961)	0.421 (0.083)	0.065 (0.882)	−0.096 (0.732)	0.144 (0.634)	−0.179 (0.661)	−0.029 (0.939)	0.21 (0.646)	0.179 (0.73)	0.289 (0.228)	−0.013 (0.961)	0.421 (0.083)	0.065 (0.882)

Abbreviations: AD, past/present alcohol dependence; AUDIT, Alcohol Use Disorders Identification Test; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DD, past/present drug dependence; Edu, education; ICV, intracranial volume; LA, left amygdala; LH, left hippocampus; PG, pathological gambling; RA, right amygdala; RH, right hippocampus; Smoker, current smoker.

relating to substance-use disorders), the association between BIS scores and left hippocampal volumes weakened and that between BIS scores and right hippocampal volumes strengthened, suggesting that co-occurring substance-use exposure/behaviors/disorders may influence/and/or alter laterality relationships between hippocampal volumes and BIS tendencies, although this possibility warrants further examination. The positive direction of the correlations suggests that greater hippocampal volume is associated with greater behavioral inhibition, as assessed through the BIS scale. Thus, although the PG group as a whole exhibited greater BIS scores and smaller hippocampal volumes, the tendency on an individual basis for larger volumes to associate with greater BIS activity was observed in the PG sample as has been reported in non-PG groups. This raises the possibility that the overall group effect relating to elevated BIS scores in PG may not be driven by hippocampal volumes (with perhaps other mechanisms underlying a group effect), but rather that individual differences in BIS-related tendencies in PG subjects relate positively to hippocampal volume as has been observed in other populations. The most robust correlation within the PG group was between BIS scores and left amygdalar volume and is also consistent with prior studies in which PG was not assessed (Barros-Loscertales *et al*, 2006a), suggesting that this pattern relating behavioral activation to amygdalar volumes reflects a more general relationship across groups, whereas the between-group difference relating to PG diagnostic status displays a different relationship. Identification of structural or functional influences that might be driving the group effects in BIS measures remains an important endeavor. Clinically, the finding suggests that individual differences relating to BIS tendencies within PG may be similar to those in the general population and might respond to interventions targeting the BIS more generally.

Limitations and Future Directions

Several limitations exist. First, although the sample is considerably larger than in a prior PG report (Joutsa *et al*, 2011), the sample size remains relatively modest, which may impact power and generalizability. It may be that some variables that approached significance might become significant if a larger sample was studied. Additionally, although all statistical analyses corrected for age, the HC group was younger than the PG group, and age has been related to amygdalar and hippocampal volumes. Future investigations should investigate age-matched samples of PG and HC subjects, and ultimately study groups of varying ages. Moreover, given the preliminary nature of this study (particularly with respect to BIS/BAS relationships), a liberal threshold was used in analyses, which could possibly lead to false discovery. None of the current findings survive a Bonferroni correction, with the most robust finding (between left amygdalar volume and BIS scores) significant at $p<0.01$. Future studies employing larger and better-matched samples are indicated to seek to replicate and extend the current findings. Although this study's hypotheses focused on hippocampal and amygdalar volumes, future studies should also consider examining whole-brain differences between PG and HC subjects. Furthermore, self-reports were used to assess behavioral tendencies. Although

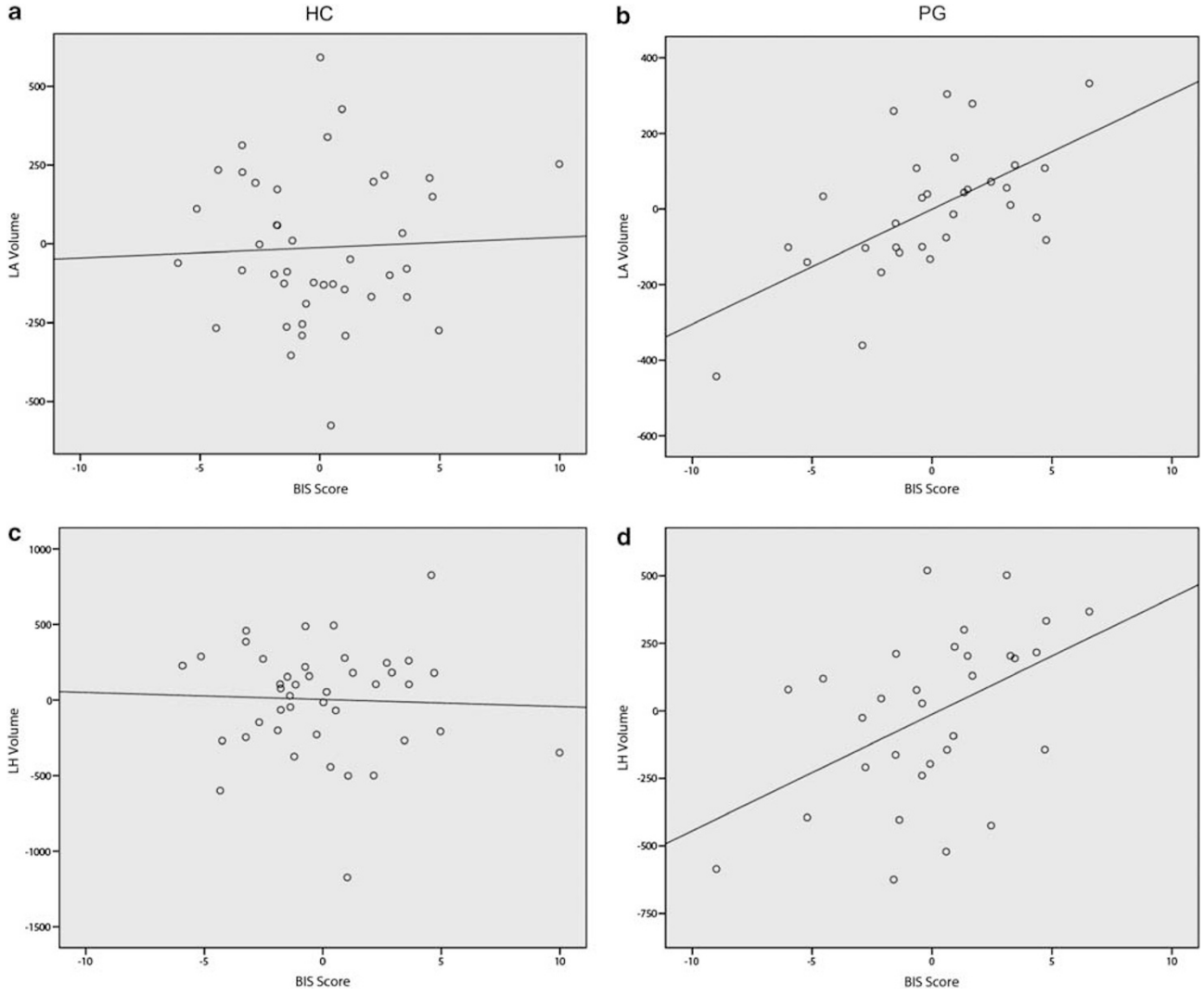

Figure 2 Correlations between behavioral assessments and structural volumes in both HC and pathological gambling (PG) subjects. Although there was no correlation between behavioral inhibition system (BIS) and left amygdalar volume in healthy comparison (HC) subjects (a), a positive correlation was observed in PG subjects (b). Similarly, there was no correlation between BIS and left hippocampal volume in HC subjects (c), but there was a positive correlation in PG subjects (d). Plots were generated using residual values after controlling for age, years of education, and intracranial volume.

the scales employed have been shown to be valid, reliable, and yield valuable clinically relevant information (Babor *et al*, 2001; Beck *et al*, 1996; Beck *et al*, 1993; Carver and White, 1994), future studies should examine hippocampal and amygdalar function with respect to actual behaviors in individuals with PG. Additionally, future studies should investigate the clinical implications of the observed findings. For example, the relationship between amygdalar and hippocampal volumes as related to treatment outcome should be examined. Prior studies have found that among individuals with depression, those with smaller hippocampal volumes demonstrated poorer treatment outcome prospectively (Frodl *et al*, 2008). Although brain activation measures relating to cognitive control have been preliminary linked to treatment outcome in PG (Potenza *et al*, 2013), future imaging studies employing larger samples are needed to investigate the biological factors underlying vulnerability and biological mechanisms underlying clinical improvement. Finally, the factors leading to smaller hippocampal and amygdalar volumes should be studied. For example, if stress exposure might underlie the finding of smaller hippocampal volumes in PG, then early interventions that reduce stress might provide protection from neural insults in people with PG.

CONCLUSIONS

The current study is the first to our knowledge to identify between-group differences in brain volumes in PG as compared with HC subjects. Additional research is needed to determine the extent to which smaller hippocampal and amygdalar volumes might result from or confer vulnerability to PG, and the extent to which differences in hippocampal and amygdalar volumes relate to clinically relevant features of PG-like treatment outcomes.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)