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Risky Decision-Making and Ventral Striatal Dopamine Responses to Amphetamine: A Positron Emission Tomography [¹¹C] Raclopride Study in Healthy Adults

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Abstract

Recent functional magnetic resonance imaging (fMRI) studies have provided compelling evidence that corticolimbic brain regions are integrally involved in human decision-making. Although much less is known about molecular mechanisms, there is growing evidence that the mesolimbic dopamine (DA) neurotransmitter system may be an important neural substrate. Thus far, direct examination of DA signaling in human risk-taking has centered on gambling disorder. Findings from several positron emission tomography (PET) studies suggest that dysfunctions in mesolimbic

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CONFLICT OF INTEREST

Drs. Kuwabara and Braši have no potential conflicts of interest to disclose.

SUPPLEMENTARY MATERIALS AND METHODS

Supplement to PET data analysis can be found online.

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DA circuits may play an important role in gambling behavior. Nevertheless, interpretation of these findings is currently hampered by a need for better understanding of how individual differences in regional DA function influence normative decision-making in humans. To further our understanding of these processes, we used [^{11}C]raclopride PET to examine associations between ventral striatal (VS) DA responses to amphetamine (AMPH) and risky decision-making in a sample of healthy young adults with no history of psychiatric disorder. Forty-five male and female subjects, ages 18–29 years, completed a computerized version of the IOWA Gambling Task. Participants then underwent two 90-minute PET studies with high specific activity [^{11}C]raclopride. The first scan was preceded by intravenous saline; the second, by intravenous AMPH (0.3 mg/kg). Findings of primary analyses showed that less advantageous decision-making was associated with greater right VS DA release; the relationship did not differ as a function of gender. No associations were observed between risk-taking and left VS DA release or baseline D2/D3 receptor availability in either hemisphere. Overall, the results support notions that variability in striatal DA function may mediate inter-individual differences in risky decision-making in healthy adults, further suggesting that hypersensitive DA circuits may represent a risk pathway in this population.

Keywords

Decision-making; Dopamine; Positron Emission Tomography (PET); Human; Amphetamine; Ventral Striatum

1.0 INTRODUCTION

Over the past decade, findings from a large body of functional magnetic resonance imaging (fMRI) studies have provided insights into the neuroanatomical substrates of human decision-making, leaving little doubt of the importance of corticolimbic brain regions, including the medial orbitofrontal/ventromedial prefrontal cortex (mOFC/VMPFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), amygdala, ventral striatum (VS), and insula (Fukui et al., 2005; Li et al., 2010). An important neurotransmitter system that serves as an interface between frontal and midbrain regions involved in decision-making is the mesocorticolimbic dopamine (DA) system (Koob and Volkow 2010). Growing evidence from preclinical studies suggests that DA signaling may subserve risky decision-making in rodents (Cocker et al., 2012; St Onge et al., 2012; Stopper, Khayambashi, Floresco 2013; Sugam and Carelli 2013). Notably, lesions and inactivation of the nucleus accumbens (NAcc) decrease preference for high risk choices (Cardinal and Howes 2005; Stopper and Floresco 2011); whereas, DA efflux in the prefrontal cortex (PFC) and NAcc signal reward value or the relative probability of obtaining a reward in rats performing risk-based decision making tasks (St Onge et al., 2012).

Derangements in corticolimbic DA function seem to be an underlying feature of most neuropsychiatric disorders characterized by maladaptive decision making (Christopher et al., 2013; Lau et al., 2013; Morales and Pickel 2012; Park and Kang 2013; Porcelli et al., 2011). Nevertheless, there is still a paucity of research to delineate the precise role that regional brain DA function may play in decision-making in either clinical or non-clinical populations. Part of the reason for the lag in translation of the preclinical findings probably

relates to the problems inherent in studying brain neurotransmitter function in humans. Two approaches that have been utilized with some success are pharmacological manipulation of DA activity with dopaminergic drugs (Antonelli et al., 2013; Boller et al., 2014; Burdick et al., 2014; Riba et al., 2008; Sevy et al., 2006) and examination of associations between risk-taking and variants of genes that affect DA neurotransmission (Amstadter et al., 2012; Heitland et al., 2012; Ibanez et al., 2003). Evidence from these human studies is generally consistent with the preclinical findings implicating DA neurotransmission in risky decision-making. However, a limitation of these methods is that they allow only indirect conclusions to be drawn about brain DA activity.

Recently, cognitive correlates of striatal DA function have begun to be examined more directly in humans with the use of positron emission tomography (PET) technology. To date, examination of the role that DA function plays in risk-taking behavior has centered on gambling disorder. A preponderance of early findings suggests that striatal DA circuits may be dysfunctional in this population (Boileau et al., 2013a; Linnet et al., 2010a; Linnet et al., 2011a; Linnet et al., 2012; Linnet 2013; Steeves et al., 2009). However, a question that remains unanswered is whether this dysfunction predates and increases risks for gambling addiction or whether it is a consequence of repeated exposure to gambling experiences (Boileau et al., 2013a). Recent evidence of an inverse relationship between risk-taking and striatal D2/D3 availability in healthy adults (Kohno et al., 2013) suggests that systematic variations in DA function may underlie individual differences in decision-making even in non-clinical populations. Nevertheless, knowledge about the neurochemical signaling mechanisms that underlie normal variability in human decision-making remains sparse. Better understanding of individual differences in such normative processes may lead to new insights into disease liabilities, potentially helping to guide the development of novel therapies designed to target decision-making deficits in neuropsychiatric conditions involving the striatum.

In the present study, we used [^{11}C]raclopride PET with intravenous amphetamine (AMPH) to examine associations between DA function and decision-making behavior in healthy young adults. Our primary region of interest was the ventral striatum (VS). A substantial body of preclinical and human fMRI literature has previously implicated this DA projection region in risk/reward-based decision-making (Basar et al., 2010; Clark and Dagher 2014; Li et al., 2010; Mitchell et al., 2014; St Onge et al., 2012; Sugam et al., 2012). Right (RVS) and left (LVS) sides were examined separately due to prior evidence of lateralization in findings related to decision-making. Findings of several studies have shown that risk-taking engages a primarily right-lateralized network (Bechara 2005; Bolla et al., 2003; Clark et al., 2003; Ernst et al., 2002; Joutsa et al., 2012; Knoch et al., 2006; Mohr, Biele, Heekeren 2010; van den Bos, Homberg, de Visser 2013). However, left lateralization (Linnet et al., 2010b; Steeves et al., 2009; Zald et al., 2004) or bilateral associations (Abler et al., 2006; Chase and Clark 2010; Linnet et al., 2011a; Linnet et al., 2011b; van Holst et al., 2012) have also been reported. We hypothesized that poor decision-making on the Iowa Gambling Task (Bechara et al., 1994) would be associated with increased DA responses to AMPH in one or both hemispheres of the VS. Directionality of the hypothesis was based on prior evidence that: a) VS DA circuits are hypersensitive in patients with impulse control disorders (Clark and Dagher 2014); b) amphetamine (Baarendse, Winstanley, Vanderschuren 2013; St Onge,

Chiu, Floresco 2010; Zeeb, Robbins, Winstanley 2009) and D2/D3 agonists (Morgado et al., 2014) increase risk-taking in animals; and c) D2/D3 agonists may lead to impulse control problems in patients with Parkinson's disease or restless leg syndrome (Driver-Dunckley et al., 2007; Riba et al., 2008; Voon et al., 2011).

2.0 MATERIALS AND METHODS

2.1 Participants

Forty-five healthy male ($n = 27$) and female participants, aged 18–29 years, were recruited through media advertisements in the Baltimore metropolitan area. Written informed consent was obtained under the oversight of the University of Maryland (UMB) and the Johns Hopkins Medicine (JHM) Institutional Review Boards. Intake assessment included administration of the Structured Clinical Interview for DSM Disorders (SCID-I/NP) (First et al., 2002), 90-day time-line follow-back (Sobell and Sobell 1992), Beck Depression Inventory (BDI) (Beck, Steer, Brown 1996), Perceived Stress Scale (PSS) (Cohen 1994); Shipley Institute of Living Scale-2 (Shipley et al., 2009), Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991), alcohol breathalyzer test, and urine toxicology. Eligible participants also underwent a history/physical examination, complete blood count, comprehensive metabolic panel, coagulation tests, electrocardiogram, urinalysis, and pregnancy screen (women). Some of the self-report and imaging data for 28 of the participants in the current study were reported previously (Oswald et al., 2014).

Exclusion criteria included: (a) younger than 18 or older than 29 years; (b) lifetime history of a major DSM-IV psychiatric Axis I disorder (American Psychiatric Association 2000); (c) BDI score > 18 ; (d) currently in need of psychiatric treatment; (e) illicit drug use during the past 30 days or lifetime stimulant use; (f) positive urine drug screen; (g) nicotine dependence or smokes > 10 cigarettes weekly; (h) alcohol use > 7 drinks per week for women or > 14 drinks per week for men; (i) oral contraceptive use, pregnant or lactating; (j) active medical conditions; (k) treatment (past 12 months) with antidepressants, neuroleptics, sedative/hypnotics, appetite suppressants, opiates, antihypertensives, dopamine or serotonergic agents, glucocorticoids, or propecia; (l) claustrophobia or fear of needles; (m) BMI < 20 or > 31 ; and (n) less than 5th grade reading level.

2.2 Decision-Making Task

The Iowa Gambling Task (IGT) is a decision-making paradigm designed to simulate real-life decisions in terms of uncertainty, risk, reward, and punishment (Bechara et al., 1994). In the computerized version of the task, subjects see four decks of cards on the computer screen. Each deck is programmed to have 60 cards. Subjects are instructed to win as much money as possible by picking one card at a time from any deck (A, B, C, and D) until the computer instructs them to stop (after 100 selections). Every time the subject clicks on a deck to pick a card, the computer generates a sound similar to a slot machine. A green bar on the top of the screen reflects the amount of hypothetical money won or lost across selections. The decks differ along two dimensions: Every card from decks A and B yields a gain of \$100 in play money and every card from decks C and D yields a gain of \$50. However, some of the cards in each deck also carry penalties such that accumulated losses

are larger than accumulated gains in decks A/B (disadvantageous); whereas accumulated losses are smaller than accumulated gains in decks C/D (advantageous). The optimal strategy is to minimize the overall loss by learning to avoid the short-term appeal of decks A/B in favor of the slower, but ultimately positive gain of decks C/D. The IGT is generally scored by calculating the number of cards selected from each deck across five blocks of 20 trials for a total of 100 trials. Dependent measures of performance in the current study were: 1) Net total score – the total number of cards selected from decks A and B (disadvantageous) subtracted from the total number of cards selected from decks C and D (advantageous) across all trials, and 2) Money won/lost - the cumulative amount of hypothetical money gained or lost during the task. Since the task requires participants to learn contingencies associated with each of the decks before they can fully express their risk preferences, the early blocks are considered measures of decision-making under ambiguity; whereas, the latter blocks are considered measures of decision-making under risk (Brand et al., 2007; Upton et al., 2011). Participants were paid for the session. To discourage indiscriminate responding, they were told that their earnings would depend on task performance. In reality, all participants were paid the maximum amount.

2.3 MRI Acquisition

A spoiled gradient (SPGR) sequence using the 3 T Siemens Trio MRI was obtained on each subject for anatomical identification of the structures of interest using the parameters: Repetition time, 35 ms; echo time, 6 ms; flip angle, 45°; slice thickness, 1.5 mm with no gap; field of view, 24 × 18 cm²; image acquisition matrix, 256 × 192, reformatted to 256 × 256.

2.4 PET Experiments

Participants were asked to arrive fasting, except for water, at our research office at Johns Hopkins at 08:30 hours on the day of the PET scans. A brief medical evaluation was conducted, including a toxicology screen, alcohol breathalyzer test, hematocrit level, and serum pregnancy tests for women. A light PET lunch was provided at 11:00. For women, we attempted to schedule PET scans during the follicular phase of their menstrual cycle. Cycle phase was confirmed by progesterone levels drawn on the day of the session. Women with levels < 2 ng/ml were classified as being in the follicular and those with levels ≥ 2 were classified as being in the luteal phase of the menstrual cycle. The median length of time between the IGT and PET sessions was 2.0 months; the interval was > 3 months for only 5 subjects (maximum 7.0 mos.).

PET data acquisition—PET scans were conducted at the Johns Hopkins Hospital Department of Radiology. Data acquisition commenced at 13:00 hours. A venous catheter was placed in the antecubital vein for the radioligand injection and saline/AMPH administration. Subjects were positioned in the scanner with their heads restrained by a custom-made thermoplastic mask to reduce head motion. A 6-min transmission scan was acquired using a rotating Cs-137 source for attenuation correction. Each subject had two scans performed on the High Resolution Research Tomograph scanner (HRRT, CPS Innovations, Inc., Knoxville, TN; spatial resolution 2 mm) (Rahmim et al., 2005; Sossi et al., 2005). A high specific activity IV bolus injection of [¹¹C]raclopride was administered over

one minute at the beginning of each scan. The first scan was preceded at -5 minutes by a bolus injection of saline; the second scan was preceded at -5 minutes by an equal volume bolus injection of AMPH (0.3 mg/Kg), each delivered over 3 minutes. Dynamic PET acquisition was performed in a three-dimensional list mode for 90 minutes following each injection of [^{11}C]raclopride. The [^{11}C]raclopride was prepared with minor changes in purification and formulation according to published procedure (Ehrin et al., 1985). Both scans were conducted on the same day. Because of potential carryover effects of AMPH, the order of drug administration was routinely fixed; saline was administered during the first scan and AMPH during the second. All participants were blind to order of drug administration. Participants were under continuous cardiovascular monitoring during the scans. A modification was made to the protocol about halfway through the study due to changes in IRB policies related to AMPH, which required participants to stay overnight on the Clinical Research Unit (CRU) at Johns Hopkins Hospital following the scans. Two participants did not complete both scans on the same day due to technical problems with the procedures. The AMPH scan was completed one day after the saline scan for one of these subjects and one week after the saline scan for the other.

No statistical differences were noted in injected activity (Mean $\pm$ SD: 19.3 ± 1.6 mCi for saline scans, and 19.7 ± 0.8 mCi for AMPH scans; $t = -1.81$; $p = 0.07$, paired t-test), non-radioactive mass (1.41 ± 0.50 and 1.36 ± 0.44 μg , respectively; $t = 0.83$; $p = 0.46$), and specific activities (5279 ± 1643 and 5477 ± 1568 mCi/ μmole , respectively; $t = -0.95$; $p = 0.34$) between saline and AMPH scans.

Reconstruction of PET data—Emission PET scans were reconstructed with the iterative ordered-subset expectation-maximization into 256 (left-to-right) by 256 (nasion-to-inion) by 207 (neck-to-cranium) voxels of 1.2188 mm cubic dimensions algorithm with attenuation, scatter, and dead-time corrected (Rahmim et al., 2005). The scans were re-binned to 30 dynamic PET frames of four 15-s, four 30-s, three 1-min, two 2-min, five 4-min, and twelve 5-min frames and were corrected for physical decay to the injection time. The final spatial resolution is expected to be less than 2.5 mm full-width at half-maximum in three directions (Sossi et al., 2005).

2.5 PET Data Analysis

Volumes of interest (VOIs)—The VOIs for putamen, caudate nucleus, and cerebellum were defined on MRI in the 3-D interactive-segmentation mode of a locally developed VOI defining tool (VOILand), as previously reported (Oswald et al., 2005). Striatal VOIs were subdivided into dorsal putamen (dPu) and caudate nucleus (dCN), and limbic VS subdivisions using a semiautomated method that incorporated anatomical guidance given by a cytoarchitronic study of post-mortem human materials (Baumann et al., 1999; Oswald et al., 2005). VOIs were transferred from MRI to PET space using MRI-to-PET coregistration parameters obtained with the coregistration module SPM5 (The Statistical Parametric Mapping 5; The Wellcome Trust Centre for Neuroimaging; available at www.fil.ion.ac.uk/spm) (Ashburner and Friston 2003), and applied to PET frames to obtain regional time activity curves (TACs).

Derivation of PET outcome variables—Nondisplaceable binding potential (BP_{ND}) (Innis et al., 2007) of [^{11}C]raclopride was obtained by the multilinear reference tissue method with two parameters (MRTM2) for striatum subdivisions (Ichise et al., 2003). Justifications of using MRTM2 are provided in the Supplementary Materials and Methods in detail. Then, intrasynaptic DA release, which represents the displacement of [^{11}C]raclopride by endogenous DA (DA_{Rel} in %) (Innis et al., 1992), was obtained using the following formula: $(BP_{ND}[S] - BP_{ND}[A])/BP_{ND}[S] \times 100$, where [S] and [A] stands for BP_{ND} of saline and AMPH scans, respectively. Images of BP_{ND} were generated by MRTM2 and spatially normalized to the standard space of SPM using SPM routines of this purpose (Ashburner and Friston 2003).

2.6 General Statistical Analyses

Paired *t*-tests were conducted to confirm that AMPH induced changes in [^{11}C]raclopride BP_{ND} across the scans. For the primary analyses we used repeated measures linear mixed models (LMM) to separately test the association of the two IGT performance variables (i.e., net total score and money won/lost; independent variables) with DA release (dependent variable). Each model included an indicator variable for VOI (LVS versus RVS) and an interaction term between the VOI indicator and IGT measure. Gender was included as a covariate due to prior evidence of associations with DA responses to AMPH, monetary reward, and performance on decision-making tasks (Martin-Soelch et al., 2011; Munro et al., 2006; van den Bos, Homberg, de Visser 2013). We also adjusted for levels of perceived stress (PSS) given our recent findings showing associations between PSS and VS DA responses to AMPH (Oswald et al., 2014). Although history of adverse childhood experiences (ACEs) was also reported to be associated with DA release in the prior paper, this variable was not included as an additional covariate in the current analyses since we previously found that the effects of ACEs were mediated by perceived stress. Covariate adjustment also required inclusion of covariate-by-region interaction terms to allow for differences in these effects across regions. Interactions of gender and perceived stress with IGT were included in the initial analyses, but if interactions were not significant, they were dropped from the analysis.

For each final repeated measures model, we first conducted the global test of an interaction between IGT performance and region and, if significant, we conducted separate post-hoc tests of associations between performance and DA release by region. For post-hoc tests we used a Bonferroni adjusted alpha level of $.05/2 = .025$ to accounts for tests of association in the two regions. Because the two IGT outcome measures are highly correlated, representing two slightly varied ways of examining the same construct, we did not make additional corrections for testing the two measures. Identical models were constructed to examine relationships between IGT performance and saline scan [^{11}C]raclopride BP_{ND} . To clarify the relative importance of DA function in early versus late trials of the IGT, we calculated Pearson Product Moment correlations, using net scores from the first and last blocks (20 trials each) to represent trials under ambiguity and trials under risk, respectively.

Although our primary region of interest was the VS, we also conducted exploratory repeated measures LMM – to examine associations between risk-taking and DA release or BP_{ND} in

four additional striatal regions: left dorsal putamen (LdPu), right dorsal putamen (RdPu), left dorsal caudate nucleus (LdCN), and right dorsal caudate nucleus (RdCN). Post-hoc analyses were conducted based on findings of the omnibus test as described for the primary analyses, using a threshold for statistical significance of $<.05/4 = .0125$ to account for multiple testing (4 regions).

3.0 RESULTS

3.1 Sample Characteristics

Sample characteristics are shown in Table 1. Participants were 45 young adults between the ages of 18 and 29 years, predominantly male, and mostly light to moderate drinkers, with the exception of six subjects who reported no alcohol use. Forty-two participants were non-smokers and three were non-dependent occasional smokers, two of these reported < 1 and the other < 5 cigarettes per week. Performance scores on the IGT were consistent with those previously reported for healthy adults (Bechara et al., 2001). Established normative data for a demographically corrected sample indicate that approximately 71% of individuals typically score in the non-impaired range (total scores $> 5-7$), 15% in the below average range (total scores -9 to $+4$), and 14% in the impaired range (total scores < -10). Comparable data for the present sample were 68%, 13%, and 20%, respectively. Consistent with the prior literature (van den Bos et al., 2013), males chose more cards from the advantageous decks than women; however, gender differences in performance were not significant.

Forty participants were right-handed; no differences were observed in DA release or BP_{ND} values in any of the primary or secondary regions of interest as a function of handedness. Associations between risk-taking and neuroimaging variables were examined both with and without the five left-handed participants. No meaningful differences were observed in findings when scores of the five left-handed participants were removed; therefore, data from all 45 subjects were included in the final analyses. No associations were found between measures of decision-making or DA function and demographic characteristics of age, BMI, drinking history, smoking status, or BDI scores; all of which were controlled to some degree by the study design. Measures of RVS and LVS baseline BP_{ND} and DA release did not differ between males and females. However, males had markedly higher baseline BP_{ND} values than females in the LdPu ($p < .02$), RdPu ($p < .04$), and LdCN ($p < .03$), as well as greater DA release, i.e., LdPu ($p = .004$), RdPu ($p = .008$), and LdCN ($p < .03$), consistent with findings previously reported by Munro et al. (2006). Evaluation of progesterone levels placed six of the female participants in the luteal and 12 in the follicular phase of the menstrual cycle on the day of the scans. No differences were observed in IGT scores or regional BP_{ND} or DA release values as a function of menstrual cycle phase. Therefore, data from all 18 women were included in subsequent analyses.

3.2 Binding Potential

Mean estimates of [^{11}C]raclopride BP_{ND} (i.e., D2 receptor occupancy) during the saline and AMPH scans are displayed in Table 2. A significant reduction in striatal [^{11}C]raclopride BP_{ND} from the saline to the AMPH scan was observed in each of the regions.

3.3 Associations between Risk-Taking (IGT) and Ventral Striatal Dopamine Function

Findings of post-hoc tests that followed a significant IGT by region interaction (Repeated Measures LMM -- effect of IGT net total score: $F=3.78$, $df=1,41$, $p=.058$; effect of region: $F=0.31$, $df=1,41$, $p=.58$; effect of gender: $F=2.76$, $df=1,41$, $p=.10$; effect of PSS: $F=3.49$, $df=1,41$, $p=.069$; effect of IGT net total score X region: $F=5.60$, $df=1,41$, $p=.023$; effect of gender X region: $F=0.51$, $df=1,41$, $p=.48$; effect of PSS X region: $F=0.49$, $df=1,41$, $p=.49$) indicated that lower IGT net total scores were associated with greater DA release (Table 3). Similar results were found for the amount of money won or lost (Repeated Measures LMM effect of money won/lost: $F=5.08$, $df=1,41$, $p=.030$; effect of region: $F=0.18$, $df=1,41$, $p=.68$; effect of gender: $F=3.17$, $df=1,41$, $p=.082$; effect of PSS: $F=3.29$, $df=1,41$, $p=.077$; effect of money won/lost X region: $F=5.01$, $df=1,41$, $p=.031$; effect of gender X region: $F=.53$, $df=1,41$, $p=.47$; effect of PSS X region: $F=0.34$, $df=1,41$, $p=.56$) with post-hoc tests showing that lower winnings were associated with greater RVS DA release (Table 3). Lower net total scores and lower winnings both reflect more disadvantageous IGT performance. Images of BP_{ND} (saline minus AMPH scans) are displayed in Figure 1 to visually illustrate the relationship between RVS DA release and IGT performance using scores of subjects in the highest and lowest quartiles of the IGT net total score distribution. The adjusted correlation between RVS DA release and IGT net total scores is shown in Figure 2.

We did not observe any associations between decision-making and LVS DA release and neither IGT net total scores nor money won/lost were associated with RVS or LVS BP_{ND} . No significant interactions were observed between IGT scores and gender in any of the repeated measures analyses, which suggests that the associations between risk-taking and DA function did not differ between males and females. Finally, although no association was observed between participants performance on the first block of the IGT (decision-making under ambiguity) and RVS or LVS DA release ($r=0.02$; $p=0.914$), more disadvantageous performance on the last block (decision-making under risk) tended to be associated with greater RVS DA release ($r=-0.28$; $p=0.063$).

3.4 Associations between Risk-Taking and Dorsal Striatal Dopamine Function

Findings of post-hoc tests that followed a significant winnings score by region interaction (Repeated Measures LMM -- effect of winnings score: $F=1.65$, $df=1,41$, $p=.21$; effect of region: $F=9.25$, $df=1,41$, $p<.001$; effect of gender: $F=5.95$, $df=1,41$, $p=.019$; effect of PSS: $F=3.11$, $df=1,41$, $p=.085$; effect of winnings score X region: $F=3.37$, $df=3,41$, $p=.028$; effect of gender X region: $F=0.24$, $df=3,41$, $p=.87$; effect of PSS X region: $F=0.92$, $df=3,41$, $p=.44$) indicated that lower IGT winnings were associated with greater DA release in the RdCN ($p=.011$ compared to the required Bonferroni corrected $\alpha = .05/4 = 0.0125$). The adjusted correlation between RdCN DA release and IGT net total scores is shown in Figure 3. Findings of post-hoc tests in the 4 regions are provided in Table 4. Similar associations were observed with IGT net total scores; however the results did not achieve statistical significance. No associations were found between IGT scores and dorsal striatal BP_{ND} . Associations between dorsal striatal DA function and performance scores on the first and last blocks of the IGT were also non-significant.

4.0 DISCUSSION

In recent years, there has been growing interest in gaining better understanding of the neural correlates of risk/reward-based decision-making due to growing awareness that variability in decision-making is both a core feature and a potential risk factor for the development of a variety of psychiatric disorders (Christopher et al., 2013; Lau et al., 2013; Morales and Pickel 2012; Park and Kang 2013; Porcelli et al., 2011). Findings from recent preclinical and human neuroimaging studies suggest that dysregulation in brain DA neurotransmission may underlie some of these relationships (Griffiths, Morris, Balleine 2014; Sweitzer, Donny, Hariri 2012). However, additional research is needed at both individual and population levels to fully elucidate the mechanisms. In the present study, we provide novel evidence that less advantageous IGT performance is associated with enhanced AMPH-induced RVS DA release in healthy young adults. Overall, the results support notions that variability in striatal DA function may mediate inter-individual differences in risky decision-making, further suggesting that hyper-responsive DA circuits may represent a risk pathway in this population. Associations between IGT performance and RVS DA response did not differ between males and females. No associations were observed between IGT scores and LVS DA release or BP_{ND} in either the RVS or LVS.

Individual differences in risk-taking propensity have been demonstrated in both human (Bechara 2005; Glicksohn, Naor-Ziv, Leshem 2007) and animal (Cocker et al., 2012; Simon et al., 2011; Sugam and Carelli 2013) samples. In rodents, pharmacological manipulation of systemic DA activity (Zeeb, Robbins, Winstanley 2009; van Enkhuizen, Geyer, Young 2013; Simon et al., 2011; Baarendse, Winstanley, Vanderschuren 2013; Cocker et al., 2012) and lesions of the NAcc (Stopper and Floresco 2011) both alter risk preference on decision-making tasks. Whereas low dose AMPH induces a dramatic increase in risk preference (Sugam et al., 2012); DA antagonists have the opposite effect, suggesting that normal DA tone promotes choice of larger, more costly rewards (Stopper et al., 2008). Greater risk preference is also associated with greater DA release in the NAcc core during task performance (Sugam et al., 2012). Notions that such differences may be genetically based are supported by preclinical evidence that biased decision-making is influenced by expression of D1 receptors in the NAcc shell (Simon et al., 2011) and D2/3 receptors in the striatum (Cocker et al., 2012). Analogous to the findings for rodents, dopaminergic drugs have been shown to modify risky decision-making in healthy humans (Antonelli et al., 2013; Boller et al., 2014; Burdick et al., 2014; Norbury et al., 2013; Scarna et al., 2005; Sevy et al., 2006). Associations between risk-taking and variants of genes affecting DA neurotransmission, including the DA transporter (DAT1), monoamine oxidase-A (MAOA) and catechol-O-methyltransferase (COMT) enzymes, and D4 receptor have also been reported (Amstadter et al., 2012; Frydman et al., 2011; Ha et al., 2009; Heitland et al., 2012; Ibanez et al., 2003; Mata et al., 2012).

To date, the majority of human PET studies that have evaluated the role of mesolimbic DA in decision-making have modelled risk-taking as a feature of gambling disorder, examining DA responses to behavioral stimulation during performance of the IGT or other gambling tasks. The preponderance of findings have revealed no differences in baseline D2 receptor availability (Boileau et al., 2013b; Clark et al., 2012; Linnet et al., 2010a; 2012; Peterson et

al., 2010) or task-induced DA release (Joutsa et al., 2012; Linnet et al., 2010b; Linnet et al., 2011a; Linnet et al., 2012) between gamblers and controls. However, Linnet et al. (2011a) found that gamblers who had increased task-induced DA release performed worse on the IGT than either gamblers with decreased DA release or healthy controls (HC). Curiously, a positive relationship was found between task-induced DA release and risky decision-making in gamblers; whereas, a negative relationship was found in controls. A significant quadratic relationship was observed between DA release and task performance in gambling disorder subjects in a later study (Linnet et al., 2012), suggesting that gamblers have greater dopaminergic sensitivity to uncertainty than controls. Greater task-induced DA release is also positively associated with gambling excitement (Linnet et al., 2011b) and gambling severity (Joutsa et al., 2012). Taken together, the findings have been interpreted as evidence that gamblers do not have DA hypersensitivity to gambling per se, but rather, experience a dopaminergic “reward” from uncertainty (Linnet 2013).

Boileau et al. (2013a) employed a different approach to study DA function in gambling disorder, using PET technology with the D3 receptor-preferring radioligand [^{11}C]-(+)-PHNO to examine individual differences in dopaminergic sensitivity to oral AMPH. Findings provided the first evidence of heightened dorsal striatal DA responsivity in gamblers as compared to controls. Dopamine release was also positively associated with gambling severity. In contrast to findings from the studies using behavioral challenges, the results supported hypotheses of a generalized *hyperdopaminergic* state in gambling disorder. The findings were notable in that they were in direct contrast with the accepted finding that drug addiction is associated with a *hypodopaminergic* state reflected by blunted striatal DA responses to psychostimulants (Martinez et al., 2005; Martinez et al., 2007; Volkow et al., 1997). The investigators suggested that the enhanced responses observed in gamblers may represent a risk phenotype that predates the compulsive pursuit of rewards. Gambling disorder may serve as a “model” for addiction vulnerability since DA circuits in gamblers may be less impacted by drug-induced neuroadaptations than those in chronic drug abusers.

Findings of the present study extend this line of research providing novel evidence that enhanced dopaminergic sensitivity to intravenous AMPH is positively associated with risky decision-making even in a non-clinical population. The evidence supports notions that alterations observed in studies on gambling disorder may predate the development of such problems, further suggesting that hyper-responsive DA circuits may represent a risk phenotype for both drug and behavioral addictions. The results are consistent with preclinical findings showing that high risk-taking rats have a more pronounced DA response to AMPH than low risk-taking rats (Palm et al., 2014). Greater DA responsivity is also associated with increased impulsivity and reward-seeking behaviors in rats and DA agonists may enhance such behaviors (Madden et al., 2010; Marinelli and White 2000; Marinelli 2005; Yates et al., 2012). Related findings from human fMRI studies have shown that high NAcc activation precedes risky choices in healthy adults (Kuhnen and Knutson 2005). Greater reward-related striatal activation is also associated with greater preference for immediate rewards in adult volunteers (Hariri et al., 2006; Sweitzer, Donny, Hariri 2012) and with externalizing behaviors in adolescents (Bjork et al., 2010). Positive associations have previously been reported between striatal DA release and fMRI activations, suggesting

that there is a quantifiable relationship between the neurochemical and hemodynamic responses in the VS (Buckholtz et al., 2010b; Schott et al., 2008)

Bechara (2005) previously noted that subgroups of normal controls show decision-making deficits that match those of drug abusers and patients with lesions of the VMPFC. In fact, up to 30% of healthy controls have been reported to exhibit poor performance on the IGT (Li et al., 2010). Examination of reported IGT scores in samples of drug abusers (Bechara et al., 2001) and healthy controls (van den Bos, Homberg, de Visser 2013) suggests that ranges are comparable, which provides further support for notions that poor decision-makers can be found in both populations. The reasons why some of these poor decision-makers go on to develop substance use problems but others do not have yet to be determined. One possibility is that neural alterations that underlie decision-making deficits may not be sufficient, but rather, may act additively or interactively with other genetic and/or environmental factors to influence vulnerability for addiction and related disorders. However, it should also be noted that even in the absence of psychopathology, maladaptive decision-making may lead to emotional distress, adverse health outcomes, and lack of personal and professional success (An et al., 2013; Apkarian et al., 2004; Morasco et al., 2006; Nguyen et al., 2013; Pawlikowski and Brand 2011).

A potential explanation for differences in findings between the present study and the studies conducted by Linnet and colleagues may have to do with differences in methodology, i.e., AMPH-induced versus task-induced DA release, respectively. Whereas Linnet et al. (Linnet et al., 2011a) reported that greater DA release was associated with adaptive behavior in healthy subjects (i.e., better IGT performance), we found that greater DA release was associated with maladaptive behavior (i.e., worse IGT performance). An established feature of the IGT is that the “risky” deck choices are disadvantageous options (i.e., possibility for large gains, but also for even greater losses). Thus, individuals who persist in making “risky” choices ultimately suffer more losses than those who choose the safer options. Findings from the gambling studies may reflect a diminished *sensitivity to loss* or *learning deficits* in the HC who exhibited poor decision-making (and lower task-induced DA release) while performing the task. In contrast, findings of the present study may reflect an enhanced *sensitivity to reward* among the poor decision-makers (i.e., greater AMPH-induced DA release). The enhanced DA response to AMPH in the risky decision-makers in our sample may be akin to enhanced response to the reinforcement value of risky decision-making or uncertainty in gamblers. Poor decision-making has previously been attributed to both diminished sensitivity to loss and/or hypersensitivity to reward in substance abusers and high sensation-seekers (Kruschwitz et al., 2012; Loxton and Dawe 2006; Noel, Brevers, Bechara 2013). Thus, the two sets of findings are not irreconcilable and, in fact, may reflect differences in processes engaged by each of the designs. Although speculative, it is also possible that a common neurobiological mechanism may underlie both sets of findings. On the one hand, striatal D2 receptors have been shown to facilitate avoidance learning in rodents (Clark and Dagher 2014; Frank 2005; Frank et al., 2007), which suggests that reduced function might lead to diminished sensitivity to negative or punishing outcomes. On the other hand, low D2 autoreceptor availability in the substantia nigra/ventral tegmental area

(SN/VTA) has been positively associated with AMPH-induced striatal DA release in healthy humans (Buckholtz et al., 2010a) and with novelty-seeking in rats (Tournier et al., 2013).

Kohno et al (2013) recently showed that healthy adults who made more risky choices after a reward on the Balloon Analogue Risk Task (BART) (Lejuez et al., 2002) had lower striatal D2/D3 BP_{ND} than those who took fewer risks. Parallel findings have been reported in rat models, which have shown inverse associations between striatal D2 receptor mRNA expression and risk-taking behavior (Mitchell et al., 2014; Simon et al., 2011). The lack of associations between IGT scores and striatal D2 BP_{ND} in the present study could be due to a lack of power to detect such effects. However, the differences in findings could also be related to differences in decision-making paradigms. Prior comparisons of the BART and IGT (Bornovalova et al., 2009; Mata et al., 2012; Xu et al., 2013) have identified important distinctions between the two measures (e.g., differences in pay-off structures, learning requirements, and amount of ambiguity). It is possible that detection of associations between striatal DA signaling and *IGT performance* requires provocation of the system. As previously described, findings from gambling studies have given little indication of associations between IGT scores and striatal D2 BP_{ND}, but showed positive associations between gambling and phasic DA release induced by either risk-based tasks or AMPH (Boileau et al., 2013a; Joutsa et al., 2012; Linnet et al., 2010a; 2012; Peterson et al., 2010).

Our results showing that risky decision-making was associated with greater right, but not left VS DA release, correspond with prior evidence that decision-making engages a predominantly right-lateralized neural network (Bechara 2005; Ernst et al., 2002; Mohr, Biele, Heekeren 2010). In one study, disruption of the right PFC by low-frequency repetitive transcranial magnetic stimulation induced risk-taking behavior (Knoch et al., 2006). There is evidence that IGT performance, in particular, is dependent on right hemispheric lateralization, especially in men (van den Bos, Homberg, de Visser 2013). Better performance is associated with greater right-sided activation in the mOFC/VMPFC, DLPFC, ACC, insula, and caudate nucleus (Bolla et al., 2003; Ernst et al., 2002). Patients with damage to the DLPFC or parietal cortex perform poorly, primarily when damage is on the right side (Bechara 2005; Clark et al., 2003). Right ventral striatal (RVS) DA release during IGT performance has been positively correlated with both gambling high and symptom severity (Joutsa et al., 2012). Dopamine release induced by gambling (Joutsa et al., 2012) and unpredictable reward tasks (Martin-Soelch et al., 2011) has also been reported to be lateralized to the right striatum in healthy controls.

In addition to our findings showing that risky decision-making predicted RVS DA response to AMPH, we observed positive associations between risk-taking and DA release in the RdCN. These findings are consistent with evidence of heightened dorsal striatal DA responses to oral AMPH in persons with gambling disorder (Boileau et al., 2013a). Preclinical findings suggest that the dorsal striatum mediates important aspects of decision-making, such as selection of outcomes based on expected reward value (Balleine, Delgado, Hikosaka 2007). Dorsal striatal DA circuits have been shown to be involved in behavioral flexibility (Darvas and Palmiter 2011) and risk-taking in rodents (Palm et al., 2014; Simon et al., 2011). Robust activation of this region has also been demonstrated during voluntary risk-taking in humans (Hsu et al., 2005; Rao et al., 2008). Interestingly, Acheson et al. (2009) reported that

individuals with a family history of alcoholism showed significantly more activation in the left caudate nucleus (CN) during IGT performance than individuals without such history in spite of a lack of behavioral differences between groups. These findings suggested that task-related alterations in DA function in the CN may contribute to risks for substance abuse. Positive associations have also been found between subjective AMPH sensitization and caudate nucleus activation during reward anticipation (O'Daly et al., 2014).

Several limitations of this study should be noted. First, although it is tempting to speculate that the relationship we observed between risky decision-making and DA release varies along a continuum that reflects increasing risks for psychopathology, extrapolation is limited by the lack of real world deficits in our sample. Subjects did not meet criteria for a DSM-IV Axis I disorder. They were mostly low to moderate drinkers with limited exposure to illicit drugs. We did not observe associations between quantity/frequency of substance use and IGT scores. Since we did not do a comprehensive assessment of risky behaviors other than substance use (e.g., risky sexual practices, driving, internet activities, or gambling), we are unable to determine whether risk-taking behavior was expressed in other maladaptive ways. It is also possible in any studies using human laboratory tasks that findings may not generalize to the “real world.” Nevertheless, an important strength of our study is the lack of confounding effects of psychopathology and/or heavy alcohol or drug use on the neural parameters of interest. Given the established ecological validity of the IGT (Dunn, Dalgleish, Lawrence 2006), we suggest that the linear association that we observed between risky decision-making and DA release may have emerged even stronger in a more clinically diverse group. However, the prior evidence showing that associations between DA release and IGT performance may be represented by a quadratic relationship in gambling disorder (Linnet et al., 2012) leaves open the possibility that our findings may also represent only the descending limb of an inverted U-shaped curve.

Inherent limitations of the neuroimaging and behavioral methods in the present study also constrain the conclusions. Although the findings implicate VS DA function in human decision-making, the specific aspect of DA neurotransmission that may be responsible for the findings remains elusive. Individual differences in BP_{ND} could be the result of differences in the affinity or density of D2/3 receptors or extracellular levels of endogenous DA. Due to the potential carryover effects of AMPH, the saline scan was always conducted before the AMPH scan. An acknowledged limitation of these methods is that extraneous variables associated with order, such as anticipatory anxiety, might also influence DA release. Our group (Oswald et al., 2014) and others (Volkow et al., 1994) have previously observed associations between baseline anxiety and stimulant-induced DA release. Nevertheless, no differences were observed in analog ratings of anxiety prior to each of the scans (data not shown), suggesting a lack of order effects related to this variable. There is also currently no evidence of diurnal variation in basal levels of endogenous DA. An alternative to the present design would have been to counterbalance the order of the two drug conditions by administering them on different days. However, we believe that this alternative design would have compromised experimental control over confounding variables between sessions, as well as increasing the likelihood that some subjects might not complete both scans. An additional limitation in the interpretation of findings concerns a lack of clarity about the specific components of decision-making that are being measured by

the IGT. Although our secondary findings suggest that RVS DA responses to AMPH were more closely linked to decision-making under risk than to decision-making under ambiguity, this hypothesis merits further investigation. Additionally, we cannot draw definitive conclusions about whether hyperresponsivity of the VS DA system reflects enhanced sensitivity to reward or reduced sensitivity to loss, either of which could potentially drive the behavior of risky-decision-makers. Finally, given that this was a correlational study, it is possible that some other variable that co-varies with decision-making was responsible for the findings.

Our findings contribute to the growing body of translational research that is helping to expand knowledge about the neurobiology of human decision-making. The findings are consistent with notions that deficits in decision-making can be linked, at least in part, to the function of mesolimbic DA circuits. We suggest that understanding of normative decision-making processes and their neural bases is fundamental to understanding what “goes wrong” in psychopathological conditions. The challenge for future studies will be to work towards establishing an integrative framework, perhaps using dual radiotracer approaches that allow evaluation of detailed associations between neurotransmitter systems (Potenza and Brody 2013), to explore the involvement of mesocortical DA pathways and interrelationships between VS and PFC DA systems. Additional research is also needed to tease apart the various components of risk-taking and to evaluate the clinical implications of the findings, particularly with respect to addictive behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Coronal images of BP_{ND} (saline minus amphetamine BP_{ND}) of the lowest (Panel A) and highest (C) quartiles of the IGT net scores with MRI image showing anatomical details of the coronal images. Right ventral striatum (RVS) is indicated by arrows.

Fig. 2.
Relationship between amphetamine-induced right ventral striatal (RVS) dopamine release and total net scores on the Iowa Gambling Task (IGT), adjusted for gender and perceived stress.

Fig.3.

Relationship between amphetamine-induced right dorsal caudate nucleus (RdCN) dopamine release and total net scores on the IOWA Gambling Task (IGT), adjusted for gender and perceived stress.

Table 1Sample characteristics^a

	Total	Male n=27	Female n=18	p-value
Race, no. (%)				0.224 ^b
Asian	4(8.9)	4(8.9)	0(0.0)	
Black	16(35.6)	8(17.8)	8(17.8)	
White	20(44.4)	13(28.9)	7(15.6)	
Other	5(11.1)	2(4.4)	3(6.7)	
Age, years	22.7 (3.0)	22.6(2.9)	22.8(3.2)	0.836
Education, years	15.2 (2.1)	14.8 (2.0)	15.7 (2.4)	0.147
BMI	23.8(2.7)	23.7(2.9)	24.0(2.6)	0.731
Drinks per week, no.	1.7(2.7)	2.0(3.2)	1.2(1.4)	0.825 ^c
BDI (range 0–63)	2.0(2.4)	2.1(2.6)	1.9(2.2)	0.924 ^c
PSS (range 0–40)	9.4 (5.2)	9.2 (5.4)	9.7 (4.9)	0.754
IGT Net Score	16.9(27.3)	21.3(26.8)	10.2(27.3)	0.183
IGT Money Won/Lost (\$)	–445.4(1265)	–217.2(1302)	–787.8(1161)	0.140

^aValues represent means (SD) except where otherwise indicated. Gender differences were compared by t-test except where otherwise indicate;^bFisher's exact test;^cWilcoxon-Mann-Whitney test.

BDI=Beck Depression Inventory, PSS=Perceived Stress Scale, IGT=IOWA Gambling Task. Range for BDI and PSS indicates the possible range of scores on these measures.

Table 2[¹¹C]Raclopride binding potentials during saline and amphetamine PET scans^a

Region	Saline	Amphetamine	Difference (%)	p-value
Left Ventral Striatum	3.05± 0.33	2.70 ± 0.28	11.74 ± 6.40	< 0.0001
Right Ventral Striatum	2.93± 0.31	2.55 ± 0.32	12.77 ± 9.01	< 0.0001
Left Dorsal Putamen	4.17 ± 0.38	3.40 ± 0.31	18.22 ± 5.73	< 0.0001
Right Dorsal Putamen	4.10 ± 0.36	3.36 ± 0.29	17.87 ± 5.69	< 0.0001
Left Dorsal Caudate Nucleus	3.50 ± 0.34	3.17 ± 0.31	7.90 ± 6.92	< 0.0001
Right Dorsal Caudate Nucleus	3.39 ± 0.34	3.10 ± 0.33	8.55 ± 7.40	< 0.0001

^aValues represent means and standard deviations

Post-hoc regression slopes between IOWA Gambling task measures and dopamine release in the left and right ventral striatum^a

Table 3

Response Variable	DA Release in LVS				DA Release in RVS			
Explanatory Variable	Beta	Std. Err.	t stat ^b	p	Beta	Std. Err.	t stat ^b	P
IGT Net score	-.0008	.037	-0.02	.98	-.124	.045	-2.73	.009
IGT Money Won/Lost	-.0003	.0008	-0.34	.73	-.0028	.0010	-2.89	.006

^aRepeated measures linear mixed models with adjustment for gender and perceived stress.

^bDegrees of freedom=41.

IGT=IOWA Gambling Task, DA=dopamine, LVS=left ventral striatum, RVS=right ventral striatum.

Table 4

Post-Hoc regression slopes between money won/lost on the IOWA Gambling Task and dorsal striatal dopamine release^a

Region	Beta	Std. Err.	t stat. ^b	p
Left Dorsal Caudate Nucleus	-.00046	.00081	-0.57	.58
Left Dorsal Putamen	-.00025	.00067	-0.38	.71
Right Dorsal Caudate Nucleus	-.00222	.00083	-2.67	.011
Right Dorsal Putamen	-.00037	.00066	-0.56	.58

^aRepeated measures linear mixed model with adjustment for gender and perceived stress; dopamine release is the response variable, amount of money won/lost on the IOWA Gambling Task is the explanatory variable.

^bDegrees of freedom = 41.