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Decision-making and neuroendocrine responses in pathological gamblers

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Abstract

Recent neuropsychological research indicates that patients with pathological gambling (PG) exhibit deficits in laboratory tasks of decision-making which are suggested to be associated with neurochemical alterations within the prefrontal cortex. Some studies also revealed that hypothalamic–pituitary–adrenal axis activity in gamblers is altered. To date, very little is known about the relationship between decision-making and neuroendocrine parameters. Therefore, we examined patients with PG (n = 22) and healthy comparison subjects (n = 19) with a laboratory task of decision-making (Game of Dice Task) and sampled salivary cortisol and alpha-amylase (sAA) concentrations before and in the course of task performance. Results showed that the PG patients' neuroendocrine responses were comparable to those of the healthy subjects, even though the patients had severe decision-making deficits. Within both groups, there were no changes in cortisol and sAA responses. However, correlations and a subgroup analysis for sAA revealed that only those patients who showed less disadvantageous decision-making patterns had an increase of sAA during the task. Accordingly, the increase of sAA – as an indirect marker of sympathetic nervous system activity – in those patients with less severe decision-making deficits could reflect the use of somatic markers biasing the decision-making process.

Keywords: Decision-making; Pathological gambling; Cortisol; Alpha-amylase

1. Introduction

Pathological gambling (PG) is classified as impulse-control disorder according to DSM-IV (American Psychiatric Association, 1994) with parallels to compulsive disorders and substance addiction. Pathological gamblers tend to make risky decisions in the context of their maladaptive gambling behavior (e.g. gambling for high stakes) which normally leads to disastrous consequences within the familial, social and economic realms. Despite this apparent deficit in everyday decision-making, only a few studies investigated decision-making abilities from a neuropsychological perspective in pathological gamblers. One of those studies is that of Cavedini et al. (2002), which examined decision-making under ambiguous conditions in pathological gamblers using the Iowa Gambling Task (Bechara et al., 2000a,b). In this task, rules are not explicit and subjects have to learn to avoid disadvantageous alternatives (which are associated with high losses of fictitious money long-term) by using feedback from previous trials. The observed pattern of patients' deficits on this task looks similar to decision-making impairments in a wide range of patient groups with psychiatric

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and neurological disorders (e.g. Bechara et al., 2001b; Bechara, 2004; for a review see Dunn et al., 2006).

Due to the fact that in everyday life and also in gambling situations in the casino, the rules for punishment and reinforcement are often explicit (e.g. probabilities for winning and losing in roulette are easy to calculate), we studied decision-making deficits of pathological gamblers in a task with explicit rules for gains and losses — the Game of Dice Task (GDT; see description below and Brand et al., 2005b). Compared with healthy individuals, pathological gamblers showed impaired decision-making on the GDT, that is, they chose the alternatives with high but improbable gains leading to high losses more frequently than the advantageous alternatives (which lead to small gains more likely than to losses). Both kinds of decision-making deficits in PG patients were assumed to be associated with neurochemical alterations within the orbitofrontal and/or dorsolateral prefrontal cortex. In line with this interpretation, some studies demonstrated that PG patients have multiple transmitter dysfunctions comprising particularly dopaminergic alterations, but also changes in the serotonergic and adrenergic systems (Comings et al., 1996; Bergh et al., 1997; Comings, 1998; Gerra et al., 1999; Potenza, 2001; Ibanez et al., 2003). Additionally, some studies revealed changes in hypothalamic–pituitary–adrenal (HPA) axis activity resulting in increased secretion of stress-related glucocorticoid hormones in gamblers — in particular an increased cortisol response due to real life gambling situations involving the gambler's own money compared with a control condition without financial stakes (Meyer et al., 2000; Meyer et al., 2004; Krueger et al., 2005). In a recent study Meyer et al. (2004) also compared neuroendocrine measures of problem gamblers with those of non-problem gamblers in an experimental real life gambling situation for the gamblers' own money and a control condition without stakes. In both groups cortisol levels were transiently increased at the beginning of the experimental condition. Moreover, heart rate as well as norepinephrine and dopamine levels was higher in problem gamblers than in non-problem gamblers during the experimental session. Although classification criteria for problem and non-problem gamblers were not mentioned by the authors, one could assume that PG patients experience stress while gambling, possibly due to financial risk-taking, high winning expectancies or fear of losing money that might be related to decision-making dysfunctions.

Alternatively, an enhanced HPA activity in PG patients might be a reflection of their prefrontal dysfunction. The prefrontal cortex has a high density of glucocorticoid receptors and is not only a major target of glucocorticoid action in the human brain (Lupien and Lepage, 2001) but also is critically involved in HPA regulation as demonstrated in lesion studies in rats (Diorio et al., 1993) as well as in correlational studies in humans using structural (Wolf et al., 2002) or functional MRI (Wang et al., 2005).

However, to the authors' knowledge, to date no studies directly investigated the relationship between performance on a decision-making task and neuroendocrine responses in PG within a well-controlled laboratory setting. With healthy subjects only one study analyzed the potential association between decision-making on the Iowa Gambling Task and HPA activity (van Honk et al., 2003). The authors found that within their group of young adults those with low basal cortisol levels showed more disadvantageous patterns of decision-making on the Iowa Gambling Task compared with subjects with high basal cortisol levels. Van Honk and colleagues suggested that low levels of cortisol are linked to decreased punishment sensitivity and increased reward dependency resulting in disadvantageous decision-making. The results of van Honk et al. might also be interpreted in the context of previous findings indicating that several cognitive functions seem to benefit from glucocorticoid secretion (overview in Erickson et al., 2003). For instance, it is well known that a certain concentration of cortisol is necessary for optimal memory performance (Erickson et al., 2003; Andreano and Cahill, 2006). Other cognitive functions, such as specific working memory and attention processes, also most likely profit from an (at least moderate) increase of cortisol levels (Born et al., 1989; Lupien and Lepage, 2001; al'Absi et al., 2002). These results potentially suggest that an increased HPA activity may mobilize cognitive and behavioral resources leading to better decision-making performance. However, other studies reported negative effects of glucocorticoids on cognitive processes (Wolkowitz et al., 2004; Gold et al., 2005; MacLullich et al., 2005), indicating that high levels of cortisol might disrupt performances on memory and other neuropsychological functions. In summary, whether or not decision-making processes are influenced by the glucocorticoid level is still a topic of debate.

Concerning decision-making in patients with PG, results from previous studies can be summarized as follows: patients with PG show (1) decision-making deficits in real life as well as in laboratory gambling tasks and (2) enhanced cortisol concentrations during a real life gambling situation than in a control condition without financial stakes (although the cortisol level was

not significantly higher compared with that in healthy subjects; c.f. Meyer et al., 2004). Furthermore, there is some evidence for a relationship between basal cortisol levels and decision-making in a laboratory situation in normal individuals. The aim of the current study was to directly investigate the potential relationship between decision-making deficits and neuroendocrine reactivity in PG patients. We assume that pathological gamblers show alterations in neuroendocrine activity throughout a decision-making task with explicit rules – the GDT – compared with healthy subjects. For this purpose we studied salivary cortisol levels before and after performing this gambling task. As an additional salivary stress marker, the enzyme salivary alpha-amylase (sAA) was assessed. The release of sAA is under adrenergic control and therefore this enzyme has been suggested to be an indirect salivary marker of sympathetic nervous system activity. In addition, some but not all studies observed a correlation between amylase and plasma adrenalin (Chatterton et al., 1996; Nater et al., 2005; Nater et al., 2006; van Stegeren et al., 2006).

2. Participants and methods

2.1. Participants

We examined a total of 23 male patients with PG according to ICD-10 (World Health Organization, 1994) and DSM-IV (American Psychiatric Association, 1994) criteria.

One patient was excluded from the analyses because his amylase baseline level was more than three standard deviations above the mean values of the study samples. Accordingly, a total of 22 male patients were included in the data analyses. In addition, a group of 19 male healthy comparison subjects (CS) was included in the study. The participants are a subgroup of patients and healthy subjects who were investigated with the GDT and a neuropsychological test battery in the course of a previous study (Brand et al., 2005b). Pathological gamblers were inpatients from the Sociopsychosomatic Clinic Wigbertshoehe, Germany, where they received psychotherapeutic interventions to treat their gambling problems for 7.56 (S.D. = 3.62) weeks on average. Mean duration of illness was 12.22 (S.D. = 7.26) years at examination time. None of the PG patients and comparison subjects had a diagnosis of alcoholism or other substance addiction except for nicotine (19 PG patients and 17 CS were regular cigarette smokers). Two patients had mild depression (no axis I diagnosis according to DSM-IV) medicated with tricyclic antidepressants in one patient and with a selective serotonin reuptake inhibitor in the other patient. History of neurological and/or psychiatric disease was an exclusion criterion.

All participants were informed about the procedure, took part voluntarily and gave written consent before the examination. No financial compensation was given to the subjects. The groups were matched regarding age, education and intelligence (measured using the German intelligence test battery Leistungs-Prüfsystem; Sturm et al., 1993; see Table 1).

2.2. Methods

2.2.1. Decision-making under risk

The computerized GDT was used to investigate decision-making under risk (for a detailed task description see Brand et al., 2005a). In the GDT, subjects are asked to maximize a fictitious starting capital (1000 €) within 18 dice throws. Before each throw, subjects have to guess which number or combination of numbers will be thrown next. Therefore subjects have to choose one out of four different alternatives: a single number, or combinations of two, of three, or of four numbers. Each alternative is associated with specific fictive gains/losses in accordance with the probability of occurrence of choice: 1000 € gain/loss for the choice of a single number (with a winning probability of 1/6), 500 € gain/loss for two numbers (winning probability of 2/6), 200 € gain to/loss for three numbers (winning probability 3/6), and 100 € gain/loss for four numbers (winning probability 4/6). The rules of winning and losing are explicitly described and stable during the whole procedure. After the dice have been thrown, it is indicated on the screen whether the subject chose correctly, and the amount of money won or lost is presented and added to/subtracted from the balance. To

Table 1
Age, education and intelligence of the pathological gambler (PG) patients and the controls (CS)

	PG	CS	*t*	*df*	*P*
	n=22	*n*=19			
Mean age in years (S.D.)	40.45 (9.41)	42.89 (14.18)	−0.66	39	0.52
Mean education in years (S.D.)	9.55 (0.74)	9.79 (1.55)	−0.63	24.94	0.54
Mean intelligence, LPS (S.D.)	109.48 (12.19)	112.38 (8.33)	−0.82	35	0.42

T-tests for independent samples did not reveal any differences between groups.
S.D. = standard deviation.
LPS = Leistungs-Prüfsystem.

analyze decision-making, choosing one single number or a combination of two numbers was evaluated as disadvantageous because winning probability is less than 50% and losses are high. Choosing combinations of three or four numbers was valued as advantageous because winning probabilities are 50% or higher.

2.2.2. Design and procedure

Salivary samples to analyze cortisol and sAA concentration were taken four times during the examination procedure (see Fig. 1). The first sample (baseline at t_0) was taken after an acclimatization period of about 20 min, in which the subjects were introduced to the examiner and started with an easy neuropsychological test (DemTect; Kessler et al., 2000) to exclude patients with striking cognitive deficits. After collection of the first sample, the subjects performed the GDT, which took approximately 10 min. After finishing the GDT, subjects were asked to rate their subjective stress level and excitement on a virtual scale from zero ("not excited/not stressed at all") to ten ("very excited/very stressed"). Thereafter, the next sample was taken (t_1). Subsequently, the subjects did another task, the Knowledge Test, as a filler task, because cortisol responses have a latency of about 15–20 min after the beginning of the stressful task (see Kudielka et al., 2004). This task is like a quiz in which easy questions concerning different topics like policy, sports and culture are presented together with four answering alternatives. The difficulties of the questions could be chosen freely by the subjects. Behavioral results of this task support its use as a filler task. No differences between both groups concerning the choices of difficulty in this task occurred (all $P>0.16$) as well as no differences in the number of questions answered correctly in each category (all $P>0.21$). The whole task took 10 min again and afterwards the third saliva sample was given by the subjects (t_2). Before the last sample was taken ([t_3], 30 min after the baseline), subjects were given the German version of the Sensation Seeking Scale V (original version, Zuckerman et al., 1964), which also took about 10 min. The groups' scores in this scale did not differ significantly (total score: PG: mean=18.59, S.D.= 5.80; CS: mean=18.26, S.D.=3.91; $t=2.14$, $df=36.98$, $P=0.83$).

2.2.3. Endocrine measures

Salivary cortisol and sAA levels were assessed out of unstimulated saliva samples obtained using Salivette collection devices (Sarstedt, Nuembrecht, Germany). For determination of cortisol and sAA, samples were sent to the laboratory of Prof. Kirschbaum in Duesseldorf, Germany. Free cortisol levels were measured using a commercially available immunoassay (IBL, Hamburg, Germany). Inter- and intra-assay variations were below 10%. For sAA a quantitative enzyme kinetic method was used as described in details elsewhere (van Stegeren et al., 2006).

3. Results

3.1. Decision-making

In the GDT, patients chose the disadvantageous alternatives significantly more frequently than the CS did (PG: median=10, range=1–18; CS: median=1, range=0–13; $U=46.50$, $P<0.001$). No significant difference between PG and CS groups emerged in the comparison of subjective stress experience ratings after the end of the GDT (PG: mean=4.73, S.D.=2.73; CS: mean=3.73, S.D.=2.05; $t=1.20$, $df=39$, $P=0.24$).

3.2. Endocrine measures

3.2.1. Salivary cortisol

In an analysis of variance with repeated measurements (MANOVA) with "points in time" as the within-

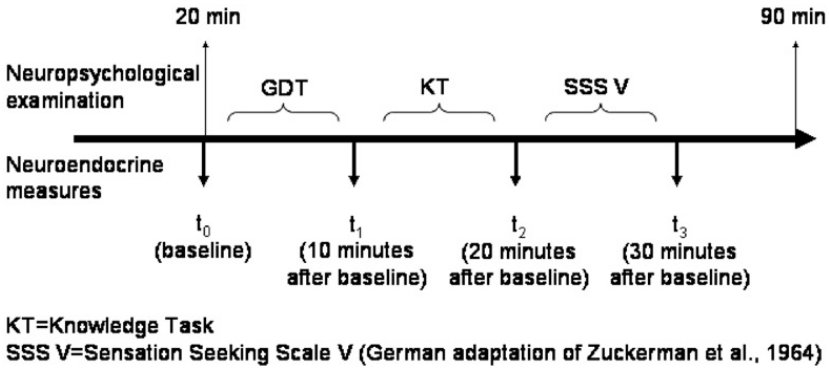

Fig. 1. Course of examination and points in time of neuroendocrine measurements (t_0 to t_3).

Table 2
Cortisol scores (nmol/l) for all points in time within the PG and CS groups

	PG	CS	*t*	*df*	*P*
	Mean (S.D.)	Mean (S.D.)			
t_0	9.89 (8.63)	6.24 (4.76)	1.64	39	0.11
t_1	8.86 (6.82)	7.73 (6.64)	0.54	39	0.59
t_2	9.28 (7.25)	7.0 (6.88)	1.03	39	0.31
t_3	7.92 (4.61)	6.59 (5.34)	0.86	39	0.40

T-tests for independent samples did not indicate any difference between groups.
S.D. = standard deviation.
df = degrees of freedom.

subject factor and "group" as the between-subjects factor, no significant main effect for "point in time" ($F=0.79$, $df=3$, $P=0.50$) and no interaction of "group"×"point in time" ($F=1.20$, $df=3$, $P=0.31$) were revealed. The absence of an interaction between "group" and "point in time" indicates that cortisol profiles of both groups did not differ from each other. Single comparisons are summarized in Table 2. They demonstrate that PG patients did not differ in their cortisol levels from the CS at any of the four points in time of measurement.

To determine a possible relationship between HPA activity and decision-making on the GDT, correlations were calculated (see Table 3). Two indices were used: the baseline measure and a delta response (or increase) measure. For the response measure the baseline cortisol level was subtracted from the cortisol level at t_2 (20 min after the start of the GDT). As mentioned in Section 2, this point in time was chosen to reflect the fact that cortisol levels rise in response to stress with a delay of 15–20 min. However, no significant association between the baseline or the response cortisol measure and GDT performance was detected. This was the case for the PG as well as for the CS group (see Table 3 for ρ and P scores).

Within the PG group, subjective stress experience ratings neither correlated with cortisol levels at baseline ($r=0.30$, $P=0.18$), nor with the crucial delta-score for cortisol changes ($r=0.02$, $P=0.92$). In contrast, within the CS group cortisol baseline-scores were significantly correlated with subjective stress ratings ($r=0.57$, $P=0.03$), but stress experience was not correlated with the delta-score for cortisol alterations ($r=-0.16$, $P=0.57$).

3.2.2. Salivary alpha-amylase

To analyze the profile of sAA levels, a MANOVA with "point in time" as the within-subject factor and "group" as the between-subjects factor was conducted. In an analogous manner to the results of cortisol release, no significant main effect ($F=1.21$, $df=3$, $P=0.31$) and no interaction "group"×"point in time" ($F=1.10$, $df=3$, $P=0.37$) was revealed (for single comparison see Table 4).

On a descriptive level the CS group appeared to respond with an increase in sAA levels to the GDT (increase from t_0 to t_1), but this increase was not significant, even in an exploratory *t*-test for dependent samples for the CS group only ($t=-1.35$, $df=18$, $P=0.19$). The patient group did not show an increase of sAA following the GDT even at a descriptive level, but appeared to show a response to the filler task (increase from t_1 to t_2), which however also remained non-significant in an exploratory *t*-test ($t=-1.93$, $df=21$, $P=0.07$). However, behavior in the filler task (choice of degree of difficulty) and sAA alteration from t_1 to t_2 was not correlated within the two groups (all $P>0.19$).

To determine a possible relationship between sAA activity and decision-making on the GDT, correlations were calculated (see also Table 3). Two indices for sAA were used: the baseline measure and a delta response measure. For the latter, the baseline sAA level was subtracted from the sAA at t_1 (directly after the end of the GDT; see Fig. 1). This point in time was chosen in order to reflect the fast reactivity of sAA in response to stress (see Nater et al., 2006).

In contrast to the cortisol results, the number of disadvantageous choices correlated significantly with the delta-score for sAA alterations ($\rho=-0.46$, $P=0.03$) within the PG group. For the CS, the delta-score for the sAA response was not correlated with the total number of selections of disadvantageous alternatives on the GDT ($\rho=0.04$, $P=0.89$).

In both groups the total number of disadvantageous choices on the GDT did not correlate with sAA levels at

Table 3
Spearman correlations of relevant cortisol and sAA scores with the total number of disadvantageous choices in the GDT in both groups

	Cortisol baseline		Cortisol increase at t_2+20		Amylase baseline		Amylase increase at t_1+10	
	PG	CS	PG	CS	PG	CS	PG	CS
Total number/disadvantageous choices	0.113	0.291	−0.070	−0.218	0.284	0.381	−0.463 *	0.035

* $P<0.05$.

baseline (PG: $\rho=0.28$, $P=0.20$; CS: $\rho=0.38$, $P=0.10$). Neither in the CS nor in the PG group did significant correlations between subjective stress experience rating and sAA baseline or sAA changes emerge (all $P>0.62$).

3.2.3. Subgroup analysis

We further conducted an additional subgroup analysis by splitting the PG group with the median of total number of disadvantageous choices on the GDT. Group 1 contains those subjects who chose disadvantageous alternatives fewer than 10 times ($n=9$), whereas group 2 consists of subjects who chose disadvantageous alternatives 10 times or more ($n=13$).

Subjects from groups 1 and 2 did not differ in their cortisol baseline and in the relevant delta-score for changes at t_2 (cortisol baseline: group 1: mean=9.52, S.D.=5.37; group 2: mean=10.15, S.D.=10.54; $t=-0.16$, $df=20$, $P=0.87$; cortisol changes: group 1: mean=−0.30, S.D.=3.18; group 2: mean=0.90, S.D.=4.08; $t=-0.74$, $df=20$, $P=0.47$). No significant differences between groups 1 and 2 were observed concerning sAA baseline (group 1: mean=70.89, S.D.=48.21; group 2: mean=120.07, S.D.=82.29; $t=-1.38$, $df=20$, $P=0.18$). However, both groups differed significantly in their delta-scores for sAA alterations at t_1 (group 1: mean=18.85, S.D.=12.08; group 2: mean=−11.19, S.D.=−33.78; $t=2.95$, $df=16.02$, $P<0.01$; see Fig. 2). Due to small sample sizes after splitting the PG, effect sizes (d-scores) for the difference in sAA changes at t_1 were calculated. The effect size of $d=0.98$ supports the result from the t-test and suggests a strong difference between the two subgroups of patients.

This result indicates that those subjects who decided less disadvantageously on the GDT show an increase of sAA from the baseline until the end of the GDT. In contrast, those patients who preferred the disadvantageous alternatives seem to show on average a decrease of sAA from baseline until the end of the GDT. To confirm this interpretation, we tested whether subjects' sAA alterations differed significantly from zero (no difference from zero indicates no sAA changes from baseline to t_1). Those subjects who chose the disadvantageous alternatives less frequently (group 1) showed a significant sAA increase at t_1 (test-score=0, $t=4.68$, $df=8$, $P<0.01$). The subjects who selected the disadvantageous alternatives most often (group 2) showed no significant increase or decrease at t_1 (test-score=0, $t=-1.19$, $df=12$, $P=0.26$). Additionally, the CS did not generate a significant increase or decrease of delta-score for t_1 (mean=13.32, S.D.=43.08; test-score=0, $t=1.35$, $df=18$, $P=0.19$).

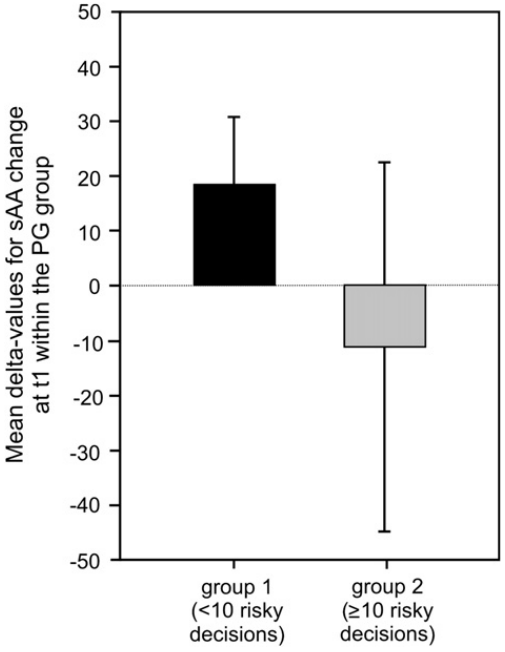

Fig. 2. Results of subgroup analysis for sAA alterations at t_1 (compared with baseline measurements of sAA, data in U/ml). Group 1 includes patients who chose disadvantageous alternatives in the GDT fewer than 10 times. Group 2 includes patients who chose disadvantageous alternative 10 or more times. A t-test for independent samples revealed a significant difference between groups for amylase alterations at t_1 (group 1: mean=18.85, S.D.=12.08; group 2: mean=−11.19, S.D.=−33.78; $t=2.95$, $df=16.02$, $P<0.01$).

Table 4
Scores of sAA (U/ml) for all points in time within the PG and CS

	PG	CS	t	df	P
	Mean (S.D.)	Mean (S.D.)			
t_0	102.82 (72.15)	102.14 (52.49)	0.03	39	0.57
t_1	103.92 (57.40)	115.46 (74.71)	−0.56	39	0.72
t_2	120.04 (75.85)	109.65 (71.46)	0.45	39	0.58
t_3	105.5 (61.10)	112.03 (72.96)	−0.31	39	0.88

T-tests for independent samples did not reveal any difference between groups.
S.D. = standard deviation.
T-tests for independent samples did not reveal any difference between groups.
df = degrees of freedom.

4. Discussion

Our results showed that PG patients chose disadvantageous alternatives more frequently than healthy subjects in a decision-making task with explicit rules for gains and losses (as described in the previous publication by Brand et al., 2005b). In the present report we describe the neuroendocrine responses observed in patients with PG while they performed the GDT. Two

main observations became apparent, which will be discussed in turn. Firstly, the salivary neuroendocrine stress markers (cortisol and sAA) assessed before and after GDT performance did not differ between the patients and the healthy subjects. Also no significant changes over time (increase or decrease) occurred. Secondly, while the conducted group comparisons failed to find any significant differences, one interesting association was detected in the correlative within-group analysis. Here, a correlation within the PG group between GDT performance and the sAA response (delta alteration between baseline [t_0] and post-task samples [t_1]) was observed. Thus a stronger response of the sympathetic nervous system was associated with less disadvantageous choices within the patient group. This association was supported by the subgroup analysis comparing patients with high frequency of disadvantageous choices with patients with lower frequency of disadvantageous decisions. Here, only those patients who decided advantageously generated a significant sAA increase.

With respect to the first main finding – the absent cortisol and sAA response to the task – it appears obvious to conclude that the task did not induce stress. This assumption is supported by the subjective stress ratings. Neither group indicated feeling stressed after GDT performance (mean subjective stress ratings indicate a moderate level of excitement). The absent cortisol response to the GDT in the comparison group is in line with a recent meta-analysis of Dickerson and Kemeny (2004). The authors concluded that only those tasks which present a social-evaluative threat to the subject's self and which are experienced as uncontrolled evoked a robust cortisol response. In the GDT, subjects are not – or minimally – exposed to social evaluation and they have some degree of control over the consequences within the GDT by determining the amount of fictitious money they bet on more or less risky options. However, the fact that the patient group did not show a cortisol or sAA response to the task and also did not differ in their subjective stress ratings is interesting by itself, even though the patients had severe deficits on the GDT. This indicates that the gambling task conducted in the laboratory was not more exciting or more stressful for the patients compared to healthy subjects. One reason for the missing differences between and within groups might lie in the fact that the GDT is a laboratory task without having the features of real gambling in a casino (e.g. no real money). Meyer et al. (2000), Meyer et al. (2004) and Krueger et al. (2005) demonstrated cortisol increases in gamblers in a real life gambling situation exclusively when participants played with their own money. Moreover, sympathetic nervous system activation (but not HPA activation) during gambling was higher in problem gamblers compared with non-problem gamblers (Meyer et al., 2004). In our experimental laboratory study the absence of financial stakes might result in less arousal and excitement compared to field studies. However, further research is needed in order to show whether or not patients with PG show increased cortisol responses that are correlated with deficits in a standardized decision-making task when financial incentives are offered. Additionally, it is so far unclear whether or not endocrine responses beyond cortisol release are associated with decision-making deficits in PG.

Another interesting aspect of this study is the result from the cortisol baseline comparisons because, until now, only very few studies have examined basal cortisol activity in PG patients and these provided inconsistent results (Ramirez et al., 1988; Roy et al., 1988; Schmitt et al., 1998). In their recent study, Meyer et al. (2004) also analyzed cortisol baseline values in healthy subjects and in blackjack gamblers in a real life gambling situation and found no differences. In line with Meyer and colleagues, we did not find differences between our two groups, indicating that PG patients show no cortisol alterations per se. Given the result that pathological gambling behavior seems to be relatively unaffected by cortisol responses in gambling situations, the significance of cortisol measures in investigating biological correlates of PG appears to be limited. Nevertheless, some caution is appropriate because we did not study basal cortisol levels in PG patients for a longer period of time and with measures more suited for the characterization of basal HPA activity (e.g. cortisol day profiles, cortisol awakening response, 12 or 24 h urinary measures). In addition, one has to keep in mind that our patients received psychotherapeutic intervention and stopped gambling for at least 4 weeks prior to the investigation. Accordingly, the lack of cortisol responses on the gambling task applied could also result from the psychotherapeutic treatments and the gambling abstinence. This topic could be addressed in future studies on potential biological markers of PG and successful recovery from gambling.

In the context of neuroendocrine responses and decision-making van Honk et al. (2003) are to the best of our knowledge so far the only ones who studied the relationship between basal cortisol and decision-making on the Iowa Gambling Task. They found that young healthy adults with low cortisol levels (measured prior to task performance) showed the most disadvantageous behavioral patterns on the Iowa Gambling Task. No

such relationship was found in our study with the GDT. Differences in the tasks used as well as the cortisol sampling points in time might be able to explain these discrepancies, but it appears that future research in this area is needed.

There is some evidence that endocrine changes might influence prefrontal cortex functioning (inhibitory control, attention and planning processes) negatively in humans (Lupien et al., 1999; Young et al., 1999; Gold et al., 2002) as well as in animals (Lyons et al., 2000) and vice versa. In our previous report we assumed that decision-making deficits in PG patients were probably linked to neurochemical dysfunctions primarily within the dorsolateral prefrontal cortex as well as within the ventral part of the prefrontal cortex (see Brand et al., 2005b; for a discussion of possible serotonergic alterations in PG associated with dysfunctional orbitofrontal cortex see Cavedini et al., 2002). We found that decision-making deficits do not seem to be associated with neuroendocrine alterations within PG patients, so that we speculate that possible prefrontal dysfunctions in PG are not due to neuroendocrine changes or vice versa. In this context, it has to be considered that only high stress levels of glucocorticoids lead to changes in prefrontal functioning (e.g. Roelofs et al., 2005). In animal studies, such strong HPA activations are often induced by highly aversive physical stressors, such as forced swimming tests or noise exposure (e.g. Arnsten and Goldman-Rakic, 1998; Johnson et al., 2006) and in humans by acute psychosocial stressors (Kirschbaum and Hellhammer, 1999; Dickerson and Kemeny, 2004; Roelofs et al., 2005). In contrast, in our study, the PG patients did not show a hyperactivity of the HPA axis following the experimental task; however, this was a decision-making task most likely only minimally accompanied by social stress responses (see discussion of this topic above). Further studies should directly investigate other potential neurochemical alterations possibly associated with decision-making deficits using functional imaging techniques (e.g., raclopride positron emission tomography) or other neurobiological techniques (e.g., measuring metabolites of the dopamine or serotonin system).

As mentioned above, we did not reveal any differences between and within both groups in sAA activity. Nevertheless, in the PG group, the correlation analysis with the sAA response indicates a relationship between decision-making on the GDT and adrenergic activity.

The enzyme sAA is mainly synthesized by the parotid glands and is suggested to respond to physical as well as to psychological acute and chronic stressors (e.g. Chatterton et al., 1996; Bosch et al., 2003; Nater et al., 2005; Nater et al., 2006; van Stegeren et al., 2006). Amylase is often interpreted as a marker for sympathetic nervous system activity (Chatterton et al., 1997; Chatterton et al., 2000; Skosnik et al., 2000; Xiao et al., 2000; Morrison et al., 2003; van Stegeren et al., 2006). The sympathetic nervous system might be involved in generating and processing of somatic markers (e.g., biasing signals from the body) that can guide decisions (Bechara et al., 2000a, 2001a,b; Bechara and Damasio, 2005; Dunn et al., 2006; but see also O'Carroll and Papps, 2003). Damasio (1996) argues that somatic markers are mediated by the release of neurotransmitters of all major neurotransmitter systems (e.g. dopamine, serotonin, acetylcholine and noradrenalin). However, somatic markers activity during decision-making processes is often indirectly measured by skin conductance responses reflecting emotional reactivity. An increase of skin conductance response in the anticipatory phase, that is, before choosing disadvantageous alternatives on the Iowa Gambling Task, was observed in the majority of healthy subjects and was associated with good task performance (e.g. Denburg et al., 2006). By contrast, patients with ventromedial prefrontal lesions and those with lesions of the amygdalae, who exhibit decision-making deficits, did not show anticipatory skin conductance responses (Bechara et al., 1996; Bechara et al., 1999). Nevertheless, it is discussed controversially whether skin conductance responses are a valid index for somatic marker activity (see Tomb et al., 2002; Crone and van der Molen, 2004). Beyond skin conductance responses, little is known about the relationship between other physiological measures – for example neuroendocrine responses – and somatic markers, although such a relationship was postulated by Damasio and co-workers (e.g. Damasio, 1994, 1996; Dunn et al., 2006).

In the present study, PG patients who chose disadvantageous alternatives did not show significant sAA increases during the task, whereas those patients who behaved less disadvantageously showed a significant increase in sAA release at that point. Accordingly, one can speculate that our results on the relation between sAA and GDT performance indicate differential activation/generation of somatic markers in PG patients. In those subjects who preferred the disadvantageous alternatives it could be that somatic markers were not generated or did not bias decisions resulting in a high frequency of disadvantageous choices. In those subjects who behaved advantageously, somatic markers – reflected in higher levels of sAA release – could prevent subjects from choosing the risky alternatives.

Even though healthy subjects in the present study showed an increase of sAA directly after finishing the GDT on a descriptive level, the increase was not significant, most likely due to high variances. However, no association between the sAA response and GDT performance occurred within the comparison group, which at least in part might be secondary to a ceiling effect in performance in this group. In contrast to the Iowa Gambling Task the GDT used in the current study provides participants with explicit rules and thus can be performed with a "cognitive approach", which might not only rely on somatic markers (Brand et al., 2006). Interestingly, the associations in the patient group could suggest that those patients showing less disadvantageous behavior might do so because of implicit somatic signals rather than using explicit probabilistic rules to generate an advantageous strategy for decisions. Nevertheless, due to the fact that no direct (somatic) markers for sympathetic nervous system activity or catecholamine activity were assessed, findings have to be treated carefully and the interpretations are preliminary. Moreover, further investigations are needed to clarify the influence of former gambling experiences in the context of somatic marker generation both in healthy subjects as well as in PG patients. It might be that healthy subjects differ in somatic marker generation in gambling-like situations, possibly due to missing gambling experiences.

In sum, while the current study observed clear decision-making deficits in PG patients in a laboratory gambling task, the used salivary markers did not provide evidence for a neuroendocrine response to this task. Future studies are needed in order to investigate whether or not similar associations can be observed in real life gambling situations and to determine if other neurotransmitters are involved in decision-making processes. Moreover, the relevance of our findings for therapeutic interventions remains to be investigated.

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