



Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences

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Abstract

Some substance dependent individuals (SDI) suffer from a decision-making impairment akin to that seen in neurological patients with lesions of the ventromedial (VM) prefrontal cortex. The somatic-marker hypothesis posits that decision-making is a process that depends on emotion and that deficits in emotional signaling will lead to poor decision-making. In this study, we tested the hypothesis that SDI who perform disadvantageously on a decision-making instrument, the gambling task (GT), have a deficit in the somatic signals that help guide their decision in the advantageous direction. Since deficits in decision-making/somatic markers can also result from dysfunctional amygdala, we asked indirectly (i.e. via tests sensitive to VM or amygdala dysfunction) whether such a deficit in SDI is restricted to VM dysfunction or includes the amygdala. Using the GT, and skin conductance response (SCR) as an index of somatic state activation, we studied groups of SDI ($n = 46$), normal controls ($n = 49$), and VM patients ($n = 10$). A subgroup of SDI showed defective performance on the GT coupled with impaired anticipatory SCR, but normal SCR to punishment, and normal acquisition of conditioned SCR to an aversive loud sound. This supports the hypothesis that the poor decision-making in some SDI is associated with defective somatic state activation that is linked to a dysfunctional VM cortex. Thus, the dysfunctional VM cortex underlying the “myopia” for the future in some SDI may be one of the principle mechanisms underlying the transition from casual substance taking to compulsive and uncontrollable behavior. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Some substance dependent individuals (SDI) and patients with bilateral VM prefrontal cortex (VM) lesions show similar behaviors in real-life in that they prefer choices that bring immediate benefit, even if these choices were coupled with negative future consequences (e.g. loss of jobs, home, family and friends). The “gambling task” (GT), which simulates real-life decisions in the way it factors reward, punishment, and uncertainty of outcomes, has been shown to be sensitive to the decision-making impairment of VM patients [3,5,6,11]. Several studies have also shown that SDI perform on the GT in a manner similar to what is seen in VM patients [10,26,37,41]. Concordant findings have also been reported with the use of decision-making instruments similar, but not identical, to the GT [43]. Several studies have revealed abnormal activity in the orbitofrontal region of cocaine [36,45,48,49] and alcohol [32,48] abusers. These findings

suggest that dysfunctional VM cortices could underlie the decision-making impairment, at least in a subgroup of SDI [10,25]. Impaired decision-making could be one of the critical mechanisms underlying the transition from casual to compulsive and uncontrollable substance taking.

Impaired decision-making in VM patients has been explained on the basis of the somatic marker hypothesis, which posits that decision-making is closely dependent on normal emotion processes [18]. Bilateral damage of VM cortices would preclude the use of somatic signals necessary to guide the decision-making process in an advantageous direction [7,12]. On the other hand, the somatic marker hypothesis also proposes that decision-making is not mediated by the VM cortex alone, but arises from large-scale systems that include other cortical and subcortical components. Such structures include the amygdala, the insular/somatosensory (SII, SI) cortices, and the peripheral nervous system [4,18]. In this study, we asked whether such a decision-making deficit in SDI is consistent with a VM dysfunction. In previous studies, we used the skin conductance response (SCR) as an index of somatic state activation. Patients with

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VM lesions did not generate anticipatory SCR when making decisions in the GT [7,12]. However, VM patients did generate SCR to punishment (loss of money in the GT) [5]. Furthermore, VM patients, particularly those with anterior lesions that spare the posterior aspect of the VM region, were able to acquire conditioned SCR to stimuli paired with aversive noise [5]. Thus, we tested the hypothesis that addiction to substances may be associated with malfunction of VM cortices, and predicted that SDI would show the same profile of behavioral and physiological impairments as VM patients.

2. Methods

2.1. Subjects

Normal control subjects were selected from the Normal Control Subject List of the University of Iowa's Division of Behavioral Neurology and Cognitive Neuroscience. These subjects are initially recruited through local advertisement. The selection criteria of normal subjects include the absence of a history of mental retardation, learning disability, psychiatric disorder, substance abuse, neurological disorder, or systemic disease that may affect the central nervous system, based on clinical interviews conducted with these subjects before their induction. All normal control subjects were paid for their participation.

SDI were brought for testing shortly before their completion of a drug rehabilitation treatment at the Mid-Eastern Center for Chemical Abuse (MECCA). All SDI were paid for their participation in gift certificates at an hourly rate that was identical to that of normal controls. The selection criteria for SDI were, (1) meeting the DSM-IV criteria for substance dependence; (2) absence of psychosis; (3) no documented head injury or seizure disorder.

Patients with VM lesions were selected from the Patient Registry of the University of Iowa's Division of Behavioral Neurology and Cognitive Neuroscience. All VM patients had undergone basic neuropsychological [46] and neuroanatomical characterization [19–21]. The selection of VM patients conformed to an absence of a history of mental retardation, learning disability, psychiatric disorder, substance abuse, and presence of a stable and chronic lesion (at least 3 months post onset), with bilateral involvement of VM cortices.

All subjects were adults (>18 years old) and provided informed consent that was approved by the appropriate human subject committees at the University of Iowa. The demographic data on the three groups are presented in Table 1.

2.2. Testing procedures

The SDI underwent some additional test procedures that were not conducted in normal control subjects.

Table 1
Demographics of subjects who participated in the study

	SDI	Normal	VM Lesions
Total <i>n</i>	46	49	10
Age (years): mean \pm S.D.	33.5 \pm 10.6	38.6 \pm 10.1	44.9 \pm 14.9
Gender (M/F)	21 (M)/25 (F)	21 (M)/28 (F)	5 (M)/5 (F)
Education (years): mean \pm S.D.	12.5 \pm 2.4	15.5 \pm 2.1	11.7 \pm 2.9

2.2.1. Tests conducted with SDI

Testing consisted of two–three sessions of 3–5 h each. After screening, qualified participants were interviewed to assess the presence of psychiatric disease. This was followed by the administration of neuropsychological tests, and then experimental tasks. The procedure for testing was as follows.

2.2.1.1. Identification of the SDI. In this study, the majority of SDI consisted of inpatients that had been admitted to MECCA for detoxification and treatment. A few SDI were brought from the Chemical Dependency Center at the University of Iowa. All SDI had experienced serious substance abuse problems in the past that had required professional intervention, which was the reason for their treatment. The duration of abstinence from substance use was known in these participants based on their length of stay at MECCA or Chemical Dependency Center. Each SDI was tested at the end-stage of their treatment, i.e. shortly before their dismissal. The time varied among individuals, but the minimum period of abstinence from any substance use was 15 days. Thus, at the time of their testing, the SDI were no longer in acute withdrawal or taking any medications to control withdrawal (e.g. benzodiazepines). Urinalyses and breathalyzers tests were not conducted on these SDI immediately before testing because they were routinely checked at MECCA or Chemical Dependency Center before they were brought for testing. Thus, the use of substances sometimes after being checked for recent substance use and before our tests is highly unlikely, knowing the environment in the Iowa City area, although this possibility cannot be ruled out. The primary drug of choice, the duration of abstinence, the number of times in treatment, and the total number of years of abuse were obtained from verbal reports and available information from MECCA or Chemical Dependency Center, as shown in Table 2.

2.2.1.2. Diagnosing the SDI. The Structured Clinical Interview for DSM-IV (SCID-IV) was used to assign Axis I diagnoses (including alcohol and other drug abuse and/or dependence). SDI whose preponderant use was alcohol or stimulant drugs were identified through verbal report. The results showing primary drug of choice are presented in Table 2. We used a comprehensive self-report version of the SCID [23], which covers fewer areas of psychopathology, and thus, requires a shorter time for administration. The

Table 2
Drug histories of SDI who participated in the study

	SDI	
	Non-impaired	Impaired
Drug of choice		
Alcohol (<i>n</i>)	5	12
Cocaine/crack (<i>n</i>)	7	7
Metamphetamine (<i>n</i>)	2	6
Abstinence in days: mean \pm S.D.	284.0 \pm 617.4	108.7 \pm 219.0
Times in treatment: mean \pm S.D.	4.3 \pm 2.5	4.6 \pm 2.9
Years of abuse: mean \pm S.D.	11.9 \pm 10.8	10.6 \pm 7.7

areas of co-morbid psychopathologies that we probed with the SCID were:

- (a) *Psychoses*: SDI who met the criteria for psychoses were excluded from the study.
- (b) *Current major depressive episode (MDE)*: We assigned either a score of 1 (i.e. present) or 0 (i.e. absent).
- (c) *A history of MDE or major depressive disorder*: We assigned either a score of 1 (i.e. present) or 0 (i.e. absent).
- (d) *Current anxiety disorder including panic, Agoraphobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social phobia, or any specific phobia*: We assigned scores of 0 (i.e. absent), 1 (i.e. 1 anxiety disorder is present), or 2 (i.e. 2 anxiety disorders or more are present).
- (e) *A history of anxiety disorder*: We assigned scores of 0 (i.e. absent), 1 (i.e. 1 anxiety disorder was present), or 2 (i.e. 2 anxiety disorders or more were present).
- (f) *Other diagnoses*: This included current or a history of attention deficit and hyperactivity disorder (ADHD), Anorexia Nervosa, or Bulimia Nervosa. We assigned a score of 0 (i.e. absent), 1 (i.e. one disorder is present), or 2 (i.e. >1 disorder is present).

2.2.1.3. Co-morbid psychopathology score. In order to obtain an index of the co-morbid psychopathologies present in an individual subject, we obtained the sum of scores from the psychopathologies listed above for each participant. SDI with co-morbid psychopathology score >3 were excluded from the study.

We further assessed and probed in more detail in SDI the presence of antisocial personality disorder. For this purpose, we used the Hare psychopathy checklist-revised (PCL-R). Upon its completion, each individual receives a total score (PCLTOT) and two factor scores. The first factor (PCLFAC1) reflects the interpersonal and affective disturbances characteristic of the prototypical psychopath, including callousness and selfishness. The second factor (PCLFAC2) measures impulsive and socially deviant behavior, which involves an unstable and antisocial lifestyle. Total scores on the PCL-R range from 0 to 40; a score of 30 or more warrants the diagnosis of psychopathy [30].

We also probed in this group of SDI other psychological measures related to mood, such as depression and anxiety. We used the Beck depression inventory (BDI) to assess the level of depression and the Beck anxiety inventory (BAI) to assess the level of anxiety.

2.2.1.4. Neuropsychological tests to assess basic cognitive functioning in both SDI and normal control groups. We conducted two sets of neuropsychological tests. One set was aimed at measuring basic neuropsychological profiles. The other set was aimed at measuring executive/frontal lobe functions:

- (a) *Basic neuropsychology*: This included the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III). It consists of a battery of tests designed to measure verbal intelligence (VIQ) and performance intelligence (PIQ). An overall measure of intelligence (IQ) is a combination of the two measures, the full scale IQ (FSIQ). In normal controls, instead of obtaining WAIS-III (VIQ, PIQ, FSIQ) data, we used the Wide Range Achievement Test-III-Reading sub-test (WRAT-III) [33], which gives reliable estimate of VIQ.

We also included the Benton visual retention test (BVRT) [44], which tests visual perception, visual memory, and visual-constructive abilities. We used the Rey auditory verbal learning test (RAVLT), which consists of five learning trials of a list of 15 words. Thirty-minute recall and recognition tasks assess anterograde verbal memory.

- (b) *Executive function/frontal tests*: This included the STROOP, the Wisconsin card sorting test (WCST), and the Tower of Hanoi (TOH-computerized version). These tasks have been shown to be a useful measure in assessing executive/frontal lobe functions [24]. Data from the STROOP test and TOH were not collected in normal control subjects.

2.2.1.5. Experimental tasks for assessing decision-making in both SDI and normal control groups. We used a computerized version of the GT and monitored the subjects' SCR activity as described elsewhere in more detail [8,11].

- (a) *Gambling task*: The task involves four decks of cards called A', B', C', and D'. In two decks (A' and B'), choosing a card is followed by a high gain of money, but at unpredictable points, the selection of a card is followed by a high penalty, so that in the long run, these decks are disadvantageous. In the other two decks (C' and D'), the immediate gain is smaller, but the future loss is also smaller, so that in the long run, these decks are advantageous. More specifically, the schedules of reward and punishment are structured in such a way that the discrepancy between reward and punishment in the disadvantageous decks (A' and B') is rendered larger in the negative direction. That is, the net difference between

reward and punishment in each block of 10 cards was set up in such a way that this difference in decks A' and B' increased in the negative direction across each block (i.e. towards larger loss). By contrast, this discrepancy between reward and punishment in the advantageous decks (C' and D') is rendered larger in the positive direction, i.e. this difference in decks C' and D' increased in the positive direction across each block (i.e. towards larger gain). The total number of trials was set at 100 card selections. To score the performance of the subject on the GT, the number of cards picked from decks A' and B' are added in each block of 20 cards, and the number of cards picked from decks C' and D' are added separately in each block of 20 cards. A net score is then obtained by subtracting the total number of cards selected from advantageous minus disadvantageous decks $((C' + D') - (A' + B'))$ for each block of 20 cards.

- (b) *SCR recording*: An automated and computerized method for collecting, measuring, and analyzing SCR data was described in a previous study [5]. For this study, we measured two types of SCR generated during the task: (1) *punishment SCR*, which are generated *after* turning a card for which there is a reward immediately followed by a penalty. (2) *Anticipatory SCR*, which are generated *prior* to turning a card from any given deck, i.e. during the time period the subject ponders from which deck to choose. The time windows for the punishment SCR are the 5 s immediately *after* the click of a card. SCR generated during the end of the 5 s window (i.e. after finding out the outcome of the selection) and before the next click of a card are considered anticipatory SCR. The inter-trial interval is set at 6 s, i.e. a subject cannot make a second response before the expiry of the 6 s. However, because of deliberation time, the average of the real inter-trial interval is about 10 s [5]. The current procedure of scoring these SCR is automated and has been described previously [5]. The SCR data were acquired through an MP100WS system (BIOPAC Systems, Inc.) at a rate of 100 samples per second. The data were stored on a Macintosh computer, and they were analyzed using AcqKnowledge III software for the MP100WS system. Quantification of the SCR wave involved initial elimination of the down drift in the SCR wave using the function "difference", followed by a visual inspection of the wave for experimental artifacts. We measured the "area under the curve" in the 5 s time window *after* selecting a card for punishment SCR), and the time window, between the end of the 5 s after clicking a card and *before* the next click of a card, for anticipatory SCR.

For punishment SCR, the time interval is always 5 s. Therefore, we divided each area under the curve measurement by 5, and then the area measurements per second ($\mu\text{S/s}$) from the good (advantageous) versus bad (disadvantageous) decks were averaged. For anticipatory SCR, the time interval varies from trial to trial, but on average it is also about 5 s. Therefore, each area

measurement from an individual trial was divided by its correspondent time interval. The area measurement per second ($\mu\text{S/s}$) was then obtained. The area measurements per second ($\mu\text{S/s}$) from anticipatory SCR from the good (advantageous) versus bad (disadvantageous) decks were averaged.

- (c) *SCR conditioning with a loud sound*: As a further test of whether impaired SDI showed impairment consistent with VM or amygdala dysfunction, we collected conditioning data from SDI chosen at random (four males and four females) from this impaired subgroup. We compared the results to an equal number of subjects chosen at random from the non-impaired controls (also four males and four females).

We used color slides (blue) as the conditioned stimulus (CS), an aversive loud white noise sound (103 db) as the unconditioned stimulus (US), and electrodermal activity (SCR) as the dependent measure of autonomic conditioning. Each experiment involved, (1) a habituation phase where four color stimuli (blue, red, green, and orange) were presented twice each without the US on a computer screen. (2) A conditioning phase in which the blue slides were followed by the US. (3) An extinction phase in which blue slides were repeatedly presented without the US. In the conditioning phase, the US followed 10 presentations of the blue slides, and it did not follow other 8 presentations of blue slides. The eight blue slides that were not followed by the US served as test conditioned stimuli (CS). The blue slides were mixed with 10 red slides. There were one green and two orange slides as well. All the slides were presented in a pseudo-random order. Each slide appeared for 3 s on the screen, followed by a 10 s inter-trial interval of blank screen. The computer automatically triggered the loud noise, through a white noise generator. The loud noise was delivered through a headphone placed over the ears of the subject. When a blue slide followed by the US appeared, the white noise was triggered at time 2 s and remained on for 2 s, i.e. 1 s after the slide disappeared. The extinction phase consisted of the presentation of the blue slide six times and the red slides three times. The quantification of the conditioning SCR involved elimination of the down drift in the SCR wave using the function "difference", and measurement of the "area under the curve" in the 6 s time window since the appearance of the slide.

To score the habituation phase, we subtracted the average SCR of the red slides from those of the blue slides. For the acquisition phase, we subtracted the average SCR of the red slides from those of the test blue slides (CS), i.e. the blue slides that were not followed by the US. Because of the habituation effect of SCR, we divided the conditioning phase into two blocks: acquisition 1 included the first four test blue slides (CS), five blue slides followed by US, and five red slides. Acquisition 2 included the latter four test blue slides (CS), five blue slides followed by US, and five red slides. In the extinction phase, we subtracted the average SCR of the three red slides from those of the last three blue slides.

The green and orange slides served as memory tools to test whether the subject was paying attention during the conditioning experiment. We asked each subject to recall how many different colors they saw (a score of 0.5 for correct answer), to name the colors (0.5 for correct answer), how many different colors were followed by the white noise (0.5 for correct answer), and to name the color followed by the white noise (2.5 for correct answer). Any subject with a recall score of zero was excluded from the analyses of the conditioning SCR results.

3. Results

3.1. Initial analyses

All statistical analyses of the data presented below were conducted using the software STATISTICA 4.1 for the MacIntosh of Statsoft Inc. The results concerning demographic factors, drug histories, psychological and neuropsychological measures confirm previously published results [8]. Specifically, although our population samples included groups with some differences in age and education, we found no relationship between these demographic factors and performance on the GT. Differences in performance

related to primary drug of choice, years of abuse, duration of abstinence, or times of relapse were not found. Differences in performance based on IQ, memory, or performance on standard executive function/frontal lobe tests were not found. The significance of similar findings were addressed and discussed in more detail in a previous report [8]. For the current study, because of the lack of significant differences in performance on the GT among the sample of SDI with different forms of dependencies, and demographics, the impact of these individual factors on decision-making was not entered in our analyses.

3.2. Neuropsychological and personality measures

Data from the different groups of participating subjects are shown in Table 3. There were no outstanding differences among the groups in terms of scores on basic neuropsychological tests of IQ and memory. There were some group differences in performance on the WCST. The mean of perseverative errors of the SDI group was higher than that of either controls or VM patients. Table 3 reveals that the average PCLTOT of the SDI group was far below the threshold score of 30 for psychopathy. The SDI had low co-morbid psychopathology scores given a possible maximum score of 8. The BDI scores from the SDI group were higher than

Table 3
Neuropsychological data of subjects who participated in the study

	SDI	Normal	VM Lesions
Basic neuropsychology			
WAIS-III			
VIQ (mean \pm S.D.)	103.0 \pm 13.9	103.2 \pm 8.0	102.4 \pm 15.5
PIQ (mean \pm S.D.)	102.6 \pm 13.2	–	97.4 \pm 16.1
FSIQ (mean \pm S.D.)	102.8 \pm 13.0	–	100.0 \pm 13.5
BVRT			
Correct (mean \pm S.D.)	6.8 \pm 2.6	8.3 \pm 1.3	7.0 \pm 1.7
Errors (mean \pm S.D.)	3.3 \pm 2.3	2.1 \pm 1.7	4.5 \pm 2.7
RAVLT			
Trials 1–5 (mean \pm S.D.)	51.6 \pm 9.3	53.7 \pm 7.6	45.9 \pm 13.5
Thirty minute recall (mean \pm S.D.)	11.1 \pm 2.3	11.5 \pm 2.4	8.0 \pm 5.1
Executive function/frontal			
STROOP			
Interference (mean \pm S.D.)	48.3 \pm 7.0	–	52.0 \pm 15.8
WCST			
Perseverative errors (mean \pm S.D.)	12.5 \pm 7.1	6.4 \pm 2.8	9.6 \pm 5.4
Categories (mean \pm S.D.)	5.2 \pm 1.6	6.0 \pm 0	5.9 \pm 0.3
Tower of Hanoi			
Trial 4 (mean \pm S.D.)	74.0 \pm 35.0	–	79.1 \pm 30.2
Personality measures			
Psychopathy			
PCLFAC1 (mean \pm S.D.)	3.7 \pm 3.6	–	–
PCLFAC2 (mean \pm S.D.)	6.0 \pm 3.7	–	–
PCLTOT (mean \pm S.D.)	12.0 \pm 7.8	–	–
BDI (mean \pm S.D.)	9.9 \pm 8.2	3.3 \pm 2.7	8.1 \pm 8.7
BAI (mean \pm S.D.)	8.5 \pm 6.8	–	–
Co-morbid psychopathology (mean \pm S.D.)	1.0 \pm 1.1	–	–

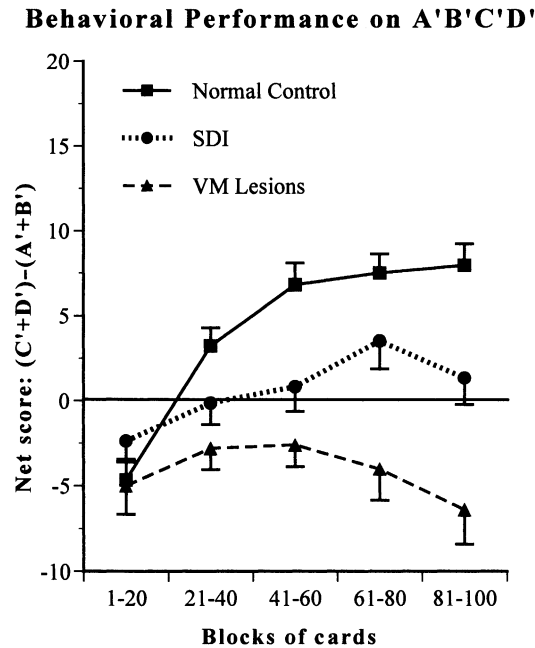


Fig. 1. Relative to normal control subjects, substance dependent individuals (SDI) were impaired in their performance on the GT, but the impairment was not as severe as that seen in VM patients. The figure shows net scores $((C' + D') - (A' + B'))$ of cards selected by each group across different blocks expressed as mean \pm S.E.M. Positive net scores reflect advantageous performance while negative net scores reflect disadvantageous performance.

controls; but they were not significantly different from VM patients.

3.3. Behavioral performance

We subdivided the 100 card selections into five blocks of 20 cards each. For each block, we counted the number of selections from decks A' and B' (disadvantageous) and the number of selections from decks C' and D' (advantageous), and then derived the net score for that block $((C' + D') - (A' + B'))$. Fig. 1 represents the net scores (total number of cards selected from advantageous minus disadvantageous decks) as a function of group and block. As the task progressed, normal controls gradually shifted their preference towards the good decks (C' and D'), and away from the bad decks (A' and B'), as reflected by the shift of the net scores towards positive. Fig. 1 reveals that in contrast to normal control subjects, VM patients failed to demonstrate a shift in behavior; they tended to select more cards from the disadvantageous decks. The SDI group fell in between the control and VM lesion groups. They were not as impaired as the VM patients, but they performed significantly poorer than normal controls.

A 3(group) \times 5(block) ANOVA on the net scores revealed a significant main effect of group ($F_{2,102} = 12.6$, $P < 0.001$), block ($F_{4,408} = 6.9$, $P < 0.001$), and interaction of group and block ($F_{8,408} = 3.7$, $P < 0.001$). Post

hoc Newman–Keuls test comparing the net scores from the control, SDI, and VM groups confirmed that normal controls had significantly higher scores than SDI ($P < 0.03$), and VM patients ($P < 0.001$). The scores from SDI were also significantly higher than the net scores from VM patients ($P < 0.01$).

3.3.1. Anticipatory SCR

We had complete physiological data from 31 normal control subjects, and from 39 SDI. The drop in number was due to (1) collecting behavioral data in some subjects without physiological recording, and (2) failure of some subjects to generate SCR to orienting stimuli such as loud sound, deep breath, and a cough.

Fig. 2 shows the average anticipatory SCR associated with the advantageous (good) or disadvantageous (bad) decks for normal control, SDI, and patients with VM lesions. Anticipatory SCR develop over time as a result of experience with different decks [12]. Because of the variance of SCR measures and the fewer responses in relation to specific decks during later trials, we averaged the anticipatory SCR associated with the advantageous or disadvantageous decks in the first two blocks of 10 cards each, and the second two blocks of 40 cards each.

Concordant with the behavioral results, the SDI as a group generated lower anticipatory SCR than normal controls, but higher than VM patients. A 3(groups) \times 2(disadvantageous versus advantageous decks) \times 4(blocks) ANOVA on the anticipatory SCR revealed a significant main effect of groups ($F_{2,77} = 6.4$, $P < 0.01$), of decks ($F_{1,77} = 9.6$, $P < 0.01$), and of blocks ($F_{3,231} = 5.1$, $P < 0.01$). The analysis also revealed a trend towards significant interaction of groups with decks with blocks ($F_{6,231} = 2.15$, $P < 0.05$).

For the disadvantageous decks (Fig. 2, upper panel), post hoc Newman–Keuls test revealed that the anticipatory SCR from normal control subjects were significantly higher than those from SDI ($P < 0.01$). For the advantageous decks (Fig. 2, lower panel), Newman–Keuls test did not reveal any significant difference between normal control and SDI ($P > 0.1$). However, for both the disadvantageous and advantageous decks, both the normal control and SDI groups were significantly higher than the VM lesion group ($P < 0.01$).

3.4. Further analyses of gambling task performance

In previous studies, we determined from normal distribution plots of normal controls and VM lesions the threshold for impaired performance on the GT. All VM patients fell at the lower end of the distribution curve of the normal control group. Specifically, the maximum net score of selected cards achieved by any of the VM patients who participated in the study was < 10 cards [8]. Based on this criterion, the net scores from SDI and control groups showed that most normal controls performed advantageously (i.e. a net score ≥ 10), but some (37%) showed performance within the range of VM patients (i.e. a net score < 10). Fewer SDI performed

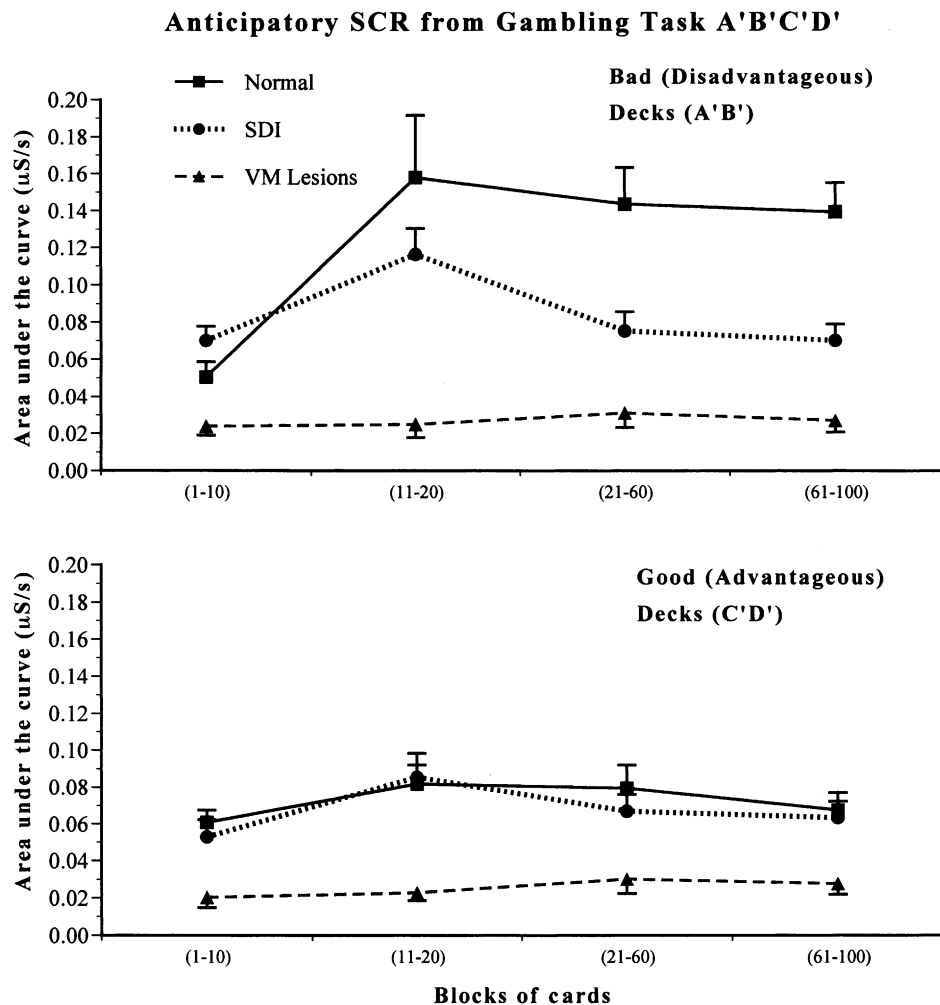


Fig. 2. Anticipatory SCRs are presented as the mean \pm S.E.M. of the average area under the curve of responses generated prior to selecting cards from the disadvantageous decks (decks A' and B') or the advantageous decks (decks C' and D').

advantageously, and a substantial number (63%) performed disadvantageously within the range of VM patients. Table 4 shows the proportion of impaired or non-impaired controls versus SDI on the GT. The high proportion of SDI (relative to controls) who performed within the range of VM patients (i.e. a net score <10) was statistically significant.

We pursued further behavioral and SCR analyses of subjects with impaired or non-impaired performance on the GT, and with complete SCR data, in order to obtain a further characterization of the decision-making impairment in the different subgroups of SDI. Thus, the following analyses were conducted on 31 normal control subjects and 39 SDI.

Table 4

Proportion of normal control subjects and SDI who were non-impaired or impaired on the gambling task with decks A'B'C'D'

	Non-impaired	Impaired
SDI (%)	37 ($n = 17$)	63 ($n = 29$)
Normal control (%)	63 ($n = 31$)	37 ($n = 18$)

Chi-square = 6.6, $P < 0.01$.

Table 5 reveals that there were no differences in the demographics and drug histories of the impaired and non-impaired subgroups.

With the exception of a significantly higher PCL-R scores from impaired relative to non-impaired SDI, there were no other differences on other psychological and neuropsychological measures among the impaired and non-impaired subgroups (Table 6).

Table 5

The t -tests comparing mean demographic differences between impaired and non-impaired subjects on the gambling task (A'B'C'D')

	SDI		Normal	
	t -value	P -value (two-tailed)	t -value	P -value (two-tailed)
Age	0.04	0.9	-1.02	0.3
Education	0.67	0.5	0.78	0.4
Abstinence	1.30	0.2	—	—
Times in treatment	-0.35	0.7	—	—
Years of abuse	0.42	0.7	—	—

Table 6

The *t*-tests comparing mean neuropsychology score differences between impaired and non-impaired subjects on the gambling task (A'B'C'D')

	SDI		Normal	
	<i>t</i> -value	<i>P</i> -value (two-tailed)	<i>t</i> -value	<i>P</i> -value (two-tailed)
Basic neuropsychology				
WAIS-III				
VIQ	1.70	0.1	0.46	0.6
PIQ	0.52	0.6	–	–
FSIQ	1.45	0.2	–	–
BVRT				
Correct	1.74	0.1	1.04	0.3
Errors	–0.64	0.5	–0.97	0.3
RAVLT				
Trial 1–5	–1.09	0.3	0.33	0.7
Thirty minute recall	–0.49	0.6	–0.03	0.9
Executive function/frontal				
STROOP				
Interference	0.89	0.4	–	–
WCST				
Perseverative errors	1.37	0.2	0.24	0.8
Categories	–0.33	0.7	0	1
Tower of Hanoi				
Trial 4	0.80	0.4	–	–
Personality measures				
Psychopathy				
PCLFAC1	2.10	0.05	–	–
PCLFAC2	1.86	0.07	–	–
PCLTOT	2.22	0.03	–	–
BDI	–1.21	0.2	1.21	0.2
BAI	–1.07	0.3	–	–
Co-morbid psychopathology	0.19	0.9	–	–

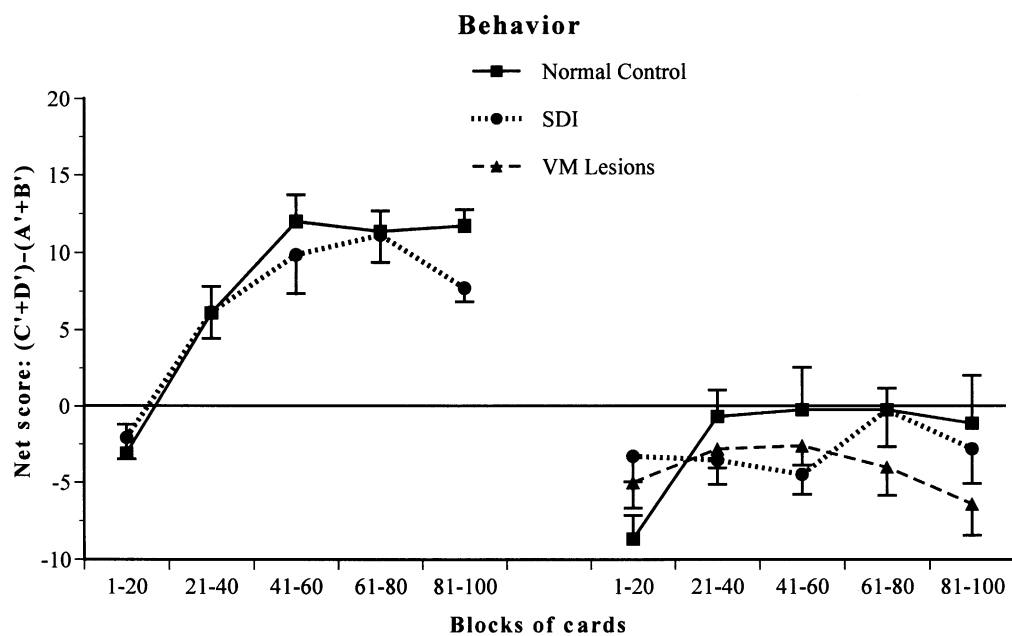


Fig. 3. The net scores $((C' + D') - (A' + B'))$ of cards selected by non-impaired (left panel) and impaired (right panel) sub-groups across different blocks expressed as mean \pm S.E.M. Positive net scores reflect advantageous (non-impaired) performance while negative net scores reflect disadvantageous (impaired) performance.

3.5. Behavior

Because of the heterogeneity of the groups in terms of performance on the GT, we divided the groups with complete SCR data into non-impaired (an advantageous performance above that of VM patients) and impaired (a disadvantageous performance within the range of VM patients) subgroups using the net score of 10 as a cut-off criterion. The net score of 10 represents the highest possible score achieved by any of the VM patients who participated in the study. Twenty-two normal controls and fourteen SDI fitted the criterion of “non-impaired”. Nine normal controls and twenty-five SDI fitted the criterion of “impaired” as their performance on the GT fell within the range of the ten VM patients who participated in the study.

In order not to undermine the power of statistical analyses by dichotomizing the distribution of each group into “impaired” and “non-impaired” subgroups, we performed

an ANOVA on the data keeping the dependent measures as continuous distributions. A 3(groups) \times 5(blocks) ANOVA on the net scores from the GT revealed a significant main effect of groups ($F_{2,77} = 11.6$, $P < 0.001$), of blocks ($F_{4,308} = 6.7$, $P < 0.001$), and an interaction of groups with blocks ($F_{8,308} = 3.0$, $P < 0.003$). An ANOVA using five groups (dichotomized distributions) yielded similar results except with more significant P -values (groups: $P < 0.001$; blocks: $P < 0.001$; interaction: $P < 0.001$). Fig. 3 presents the data in terms of “impaired” and “non-impaired” groups as explained earlier. Newman–Keuls test revealed that “non-impaired” controls or SDI had significantly higher scores than the “impaired” controls, SDI, or VM lesions ($P < 0.01$). There was no difference between the net scores from normal controls and SDI in the non-impaired subgroup (Fig. 3; left) ($P > 0.1$). Similarly, there was no difference between the net scores from normal controls, SDI, and VM lesions in the impaired subgroup (Fig. 3; right) ($P > 0.1$).

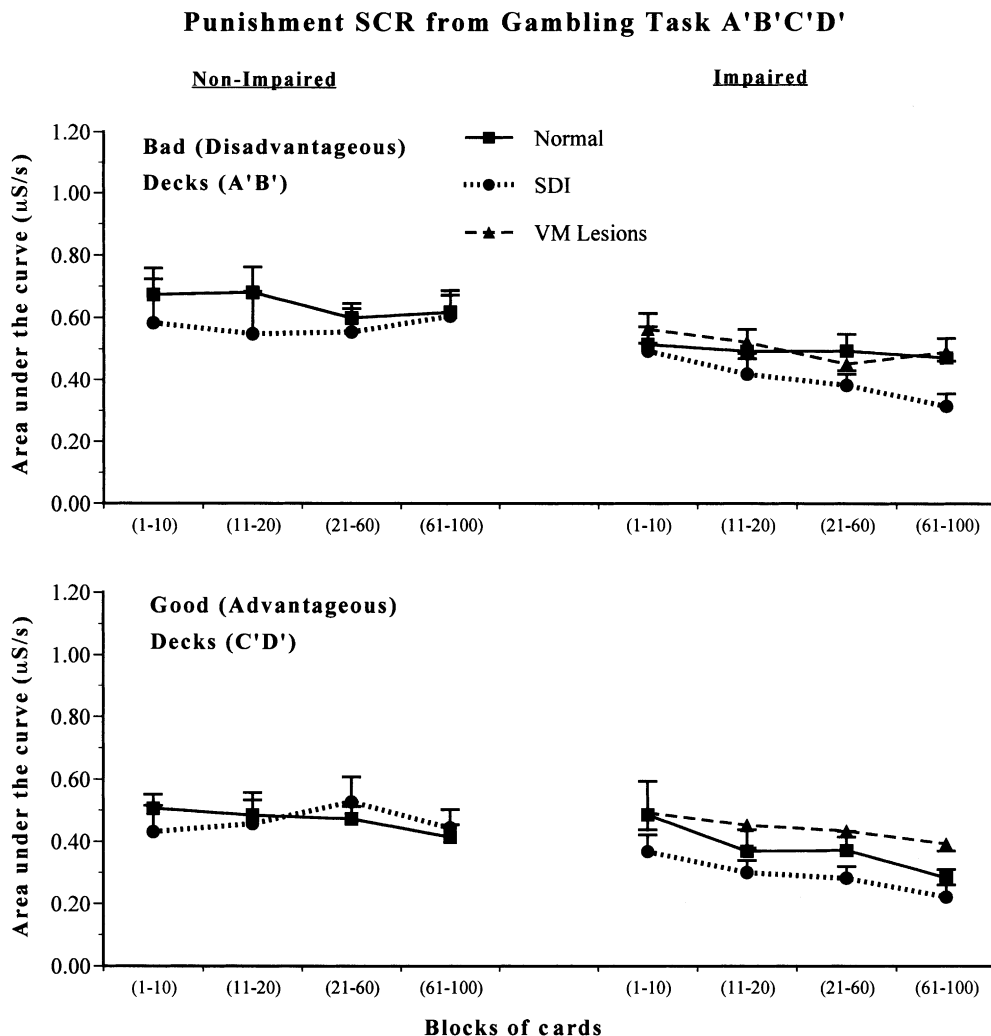


Fig. 4. Punishment SCR from normal control subjects and substance dependent individuals (SDI) divided according to behavioral performance (impaired or non-impaired) on the GT. Punishment SCR are presented as the mean \pm S.E.M. of the average area under the curve of responses generated after selecting cards for which there was a penalty from the disadvantageous or advantageous decks.

3.5.1. Punishment SCR

As for the behavioral data, we conducted an ANOVA on punishment SCR from three groups (controls, SDI, and VM) (i.e. non-dichotomized groups of impaired and non-impaired) in order to apply a more stringent analysis. In Fig. 4, we presented the data in terms of “impaired” or “non-impaired” subgroups. A 3(groups) \times 2(disadvantageous versus advantageous decks) \times 4(blocks) ANOVA on the punishment SCR revealed a significant main effect of groups ($F_{2,77} = 4.1$, $P < 0.02$), of decks ($F_{1,77} = 17.3$, $P < 0.001$), and a significant main effect of blocks ($F_{3,231} = 2.8$, $P < 0.04$). There were no significant interactions. An ANOVA using five groups (dichotomized distributions) yielded similar results (groups: $P < 0.001$; decks: $P < 0.001$; blocks: $P < 0.05$; interactions: non-significant).

Fig. 4 shows the punishment SCR from the three groups divided into “impaired” and “non-impaired” subgroups. In the “non-impaired” subgroups (left panels), Newman–Keuls

test revealed no difference between the punishment SCR from normal controls and SDI in either the bad (top panel) or good (bottom panel) decks ($P > 0.1$). Similarly, in the “impaired” subgroups (right panels), there was no difference between the punishment SCR from normal controls, SDI, and VM patients in either the bad or good decks ($P > 0.1$).

Fig. 4 shows that the means of punishment SCR from the “non-impaired” subgroups (controls and SDI; left panels) are slightly higher than those in the “impaired” subgroups (controls, SDI, and VM; right panels). Newman–Keuls test revealed that for the bad decks (top panel) this difference was most significant in the 4th block of trials ($P = 0.01$). For the good decks (bottom panel), the difference was non-significant for the most part ($P > 0.1$), but it did reach a significant level ($P = 0.02$) when comparing measures in the 4th block between the non-impaired subgroups (controls or SDI) and the impaired subgroups (only SDI).

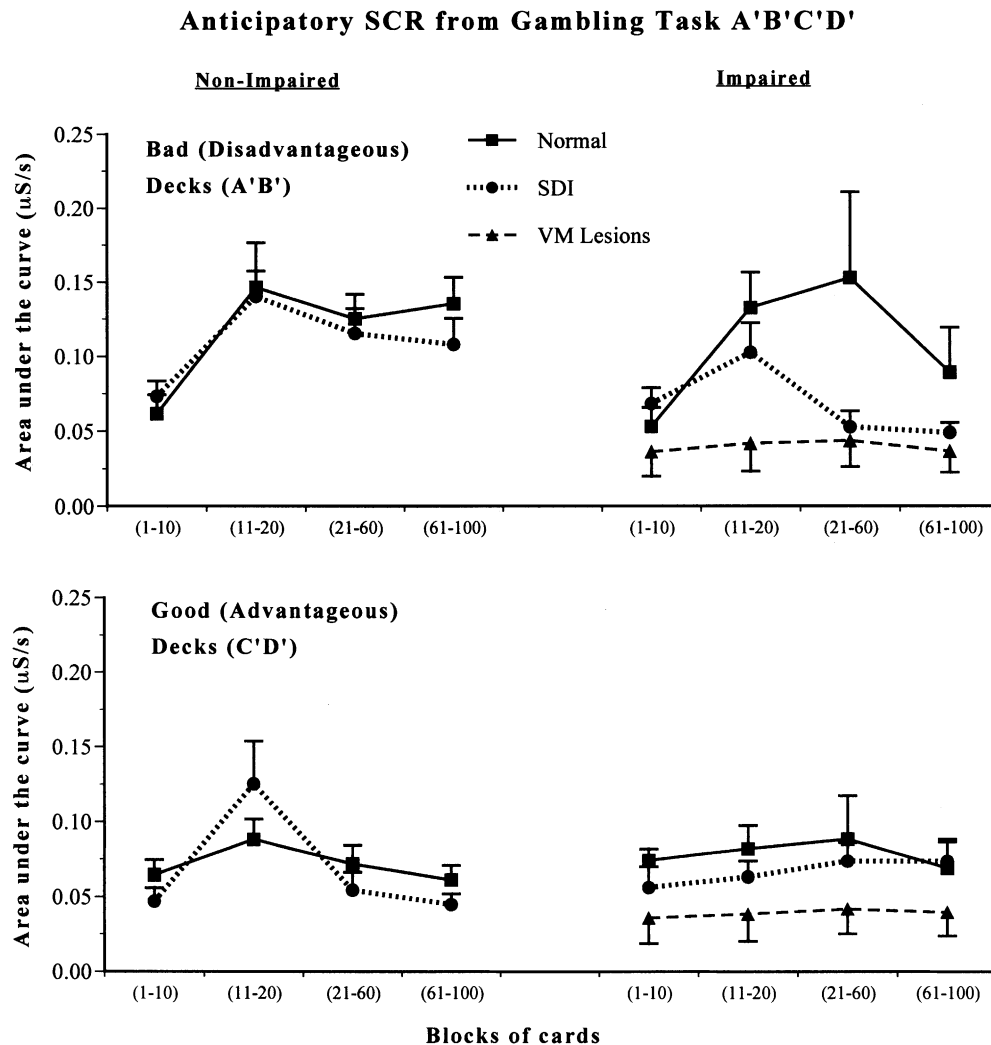


Fig. 5. Anticipatory SCR from normal control subjects and substance dependent individuals (SDI) divided according to behavioral performance (impaired or non-impaired) on the GT. Anticipatory SCR are presented as the mean \pm S.E.M. of the average area under the curve of responses generated before selecting cards from the disadvantageous or advantageous decks.

3.5.2. Anticipatory SCR

As before, we conducted an ANOVA on anticipatory SCR from three groups (controls, SDI, and VM) (non-dichotomized groups). We presented the data in Fig. 5 in terms of “non-impaired” or “impaired” subgroups. A $3(\text{groups}) \times 2(\text{disadvantageous versus advantageous decks}) \times 4(\text{blocks})$ ANOVA on the anticipatory SCR revealed a significant main effect of groups ($F_{2,77} = 6.4$, $P < 0.003$), of decks ($F_{1,77} = 9.6$, $P < 0.003$), and of blocks ($F_{3,231} = 5.1$, $P < 0.002$). There were significant interactions of groups with decks ($F_{2,77} = 3.9$, $P < 0.03$), and interactions of groups with decks with blocks ($F_{6,231} = 2.1$, $P < 0.05$). An ANOVA using five groups (dichotomized distributions) yielded similar results (groups: $P < 0.008$; decks: $P < 0.001$; blocks: $P < 0.001$; groups \times decks: $P < 0.004$; groups \times decks \times blocks: $P < 0.003$).

Fig. 5 reveals that in the “non-impaired” subgroups (controls and SDI; left), there was no difference between the anticipatory SCR from controls and SDI in either the bad or good decks (Newman–Keuls $P > 0.1$). In the “impaired” subgroups (controls, SDI, and VM; right), Newman–Keuls test revealed that the anticipatory SCR of control subjects were significantly higher than VM lesions in both the bad decks (top panel) ($P < 0.01$) and good decks (bottom panel) ($P = 0.03$). The SDI groups were slightly different. The anticipatory SCR of normal subjects were higher than SDI in the bad decks ($P < 0.01$), but not the good decks ($P > 0.1$). The difference between SDI and VM lesions was not significant in the bad decks ($P = 0.09$) or the good decks ($P = 0.06$).

3.6. Conditioning SCR

One control subject (male) was excluded from the analysis because upon debriefing, he had a recall score of zero, indicating lack of attention during the experiment, so we were left with eight SDI and seven normal controls whose recall score was a minimum of 2.5.

Fig. 6 shows the magnitude of SCR during habituation, acquisition of conditioning, and extinction. Both normal controls and SDI acquired the conditioning, albeit the conditioning in SDI appears weaker. A $2(\text{groups}) \times 4(\text{conditioning phases})$ ANOVA on the average SCR from the CS (blue) minus unpaired (red) slides did not reveal a significant main effect of groups ($F_{1,13} = 0.14$, $P > 0.1$), or an interaction of groups and conditioning phases ($F_{3,39} = 0.5$, $P > 0.1$). However, the ANOVA did reveal a significant main effect of conditioning phases ($F_{3,39} = 4.6$, $P < 0.01$). Post hoc Newman–Keuls test confirmed that the conditioned SCR during the early (acquisition 1) or later (acquisition 2) half of the conditioning phase were significantly higher than habituation ($P < 0.01$ and 0.04 , respectively). The difference between habituation and extinction was not significant. Although a visual inspection of the figure shows that the SCR from SDI were lower than normal controls during

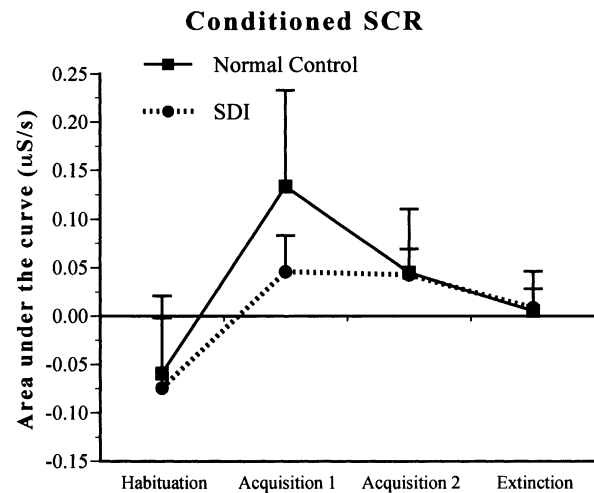


Fig. 6. Differential SCR conditioning with an aversive noise expressed as the mean \pm S.E.M. of the average SCR generated after the CS (a test blue slide) minus the average of SCR generated after the unpaired slide (red slide). For each subject, a differential score was obtained for the habituation phase, acquisition 1 (acquisition phase including the first five presentations of the CS and unpaired stimulus), acquisition 2 (acquisition phase including the latter five presentations of the CS and unpaired stimulus), and extinction phase. A difference score of zero indicates no differential conditioning.

acquisition 1, a t -test of this data point in the figure was not significant.

4. Discussion

One subgroup of SDI was indistinguishable from normal controls on the behavioral and psychophysiological measures of decision-making used in this study. Another subgroup of SDI showed impaired performance on the GT coupled with impaired anticipatory SCR. Even normal control subjects who performed disadvantageously on the GT acquired anticipatory SCR. The anticipatory SCR of impaired SDI resembled those of VM patients.

This impaired subgroup of SDI generated SCR to punishment, and acquired conditioned SCR to aversive noise, albeit the magnitude of these responses was slightly reduced. The difference between VM and amygdala lesions is that VM patients generate punishment SCR, whereas amygdala patients do not [5]. Furthermore, VM patients (those with lesions that spare the posterior and basal forebrain region) acquire conditioned SCR, whereas amygdala patients do not [5]. The results obtained from at least a subgroup of SDI are more consistent with VM malfunction, thus supporting our primary hypothesis that drug addiction may be associated with malfunction of VM cortices. This is consistent with recent findings showing impairment on the GT in cocaine [2,8,26], opiate [41], and alcohol [37] abusers. It is also consistent with studies showing impaired performance of stimulant and opiate abusers on other decision-making

tasks, e.g. the “betting task” [43]. These results are also in accord with functional neuroimaging studies that revealed abnormal activity in VM cortices of cocaine [36,45,48,49] and alcohol [32,48] abusers.

A malfunctioning VM cortex does not fully explain the loss of control over drug taking in all SDI. First, only a subgroup of SDI was severely impaired on the GT. Second, the physiological results in the impaired subgroup of SDI support a pattern that includes, but does not appear restricted to VM dysfunction. Most relevant in this respect is that the punishment and conditioned SCR in impaired SDI were below normal, with variations such that some SCR were normal and others were severely impaired. These results raise the possibility that the decision-making impairment in SDI may extend beyond the VM cortex to include other components of a neural system for decision-making/somatic markers, namely the amygdala.

Did the VM dysfunction in SDI develop as a result of chronic use of substances or it existed as a developmental predisposing factor to addiction in certain individuals? This question cannot be addressed directly in the current study. However, we believe that a developmental VM dysfunction alone does not lead to substance use, but it presents a phenotypic characteristic of certain subjects that may succumb to substance dependence. Individuals with developmentally abnormal function in the cortical mechanisms critical for decision-making, response inhibition, and the control of behavior are more susceptible to pursuing actions that are rewarding in the short term, even when these actions lead to deleterious consequences in the long term. This is consistent with genetic studies revealing that certain genes (e.g. the serotonin transporter gene) contribute to the vulnerability of individuals carrying them to multiple drug addictions. There is a wealth of clinical evidence indicating that impairments in real-life decisions related to anti-social, impulsive, and aggressive behaviors are associated with reduced central serotonin metabolites [35,47]. A combination of predisposing factors and environmental conditions can influence the specificity of an addiction. For instance, depending on which reward stimulus the individual is repeatedly exposed to (e.g. drugs, alcohol, gamble, etc.); these exposures then induce neural and physiological changes that become specifically evoked by subsequent exposure to cues of the same reward. Chronic exposure to certain substances (e.g. *metamphetamine*) can in turn produce neurotoxicity in the cortical systems of decision-making and behavioral control, thus exacerbating the “myopia” for the future and the addiction to substances.

However, substance addiction could also be acquired through faulty learning in individuals whom otherwise have intact mechanisms of decision-making and behavioral control. For example, growing up in an environment where the use of substances is encouraged, or at least the use of substances is not met with negative consequences; the continuous use of substances would not be marked with negative somatic states signaling future consequences. In this

instance the use of substances is sustained through faulty learning (receiving reward without future punishment) and not necessarily abnormal decision-making. However, the fundamental difference between these individuals and those with developmental abnormalities in decision-making and behavioral control functions is the following: in individuals with intact mechanisms of decision-making, it is possible to reverse the faulty learning and break the habit of substance use once the behavior (i.e. substance use) begins to be met with severe punishment, unless the abuse has been so chronic to the extent of inducing neurotoxicity in the cortical mechanisms subserving decision-making and behavioral control. In contrast, individuals with abnormal mechanisms of decision-making would be like the VM patients characterized by a severe myopia for the future and complete failure to learn from repeated mistakes.

Why did some normal control subjects perform poorly on the gambling, and are they prone to substance dependence? Among the subgroup of normal controls who performed poorly, the variance in anticipatory SCR was high, with some individuals having defective anticipatory SCR similar to VM patients and some having anticipatory SCR similar to normal controls. Based on our observations, most of the normal subjects who perform poorly on the GT, but they generate anticipatory SCR, describe themselves as high-risk takers, thrill seekers, or gamblers in real-life. Even if the choices made by such individuals on the GT may look similar to the choices made by VM patients, a major difference remains. These normal control subjects generate anticipatory SCR before attempting a risky choice (i.e. selection from disadvantageous decks), whereas VM patients do not. Thus, there is a physiological distinction between the disadvantageous behavior of certain normal individuals and the disadvantageous behavior of SDI or VM lesions. It is important to realize here that the generation of anticipatory SCR help bias or modulate the selection of actions, and thus, shift behavioral responses in a certain direction. However, these SCR (or somatic states) do not trigger or cause the behavioral response, so that the somatic state signal (indexed by anticipatory SCR) can always be overridden by conscious deliberation. The issue of risk-taking versus poor decision-making has been addressed in previous studies [38,43]; all indicate that taking a risk is not the same as having poor judgment and impaired decision-making. On the other hand, it remains a possibility that normal controls with poor performance on the GT, coupled with defective anticipatory SCR, may represent a population with an abnormal decision-making system, who are at a high risk of becoming addicted to substances.

Studies have shown a high correlation between antisocial personality disorder (ASPD) and substance dependence [15–17,22,40]. Could the deficits identified in SDI be related to psychopathy? This question becomes more pertinent in light of recent studies in alcohol abusers showing that ASPD contributed significantly to impaired performance on the GT [37]. Although we have shown that impairment on the

GT can be associated with dependence on substances alone, independent of co-morbid psychopathologies [8], the presence of ASPD can indeed explain the poor decision-making and the persistent substance use of SDI. Our current results confirm this to some extent in that the PCL-R scores from the impaired subgroup of SDI were significantly higher in comparison to the non-impaired subgroup. However, several studies have established a link between psychopathy and structural abnormalities in the prefrontal cortex [42]. Therefore, our findings suggest that the defective neural mechanism of decision-making associated with a malfunctioning VM cortex is one phenotype of the personality traits of ASPD.

The triggering of a negative somatic state, such as fear, from thoughts about negative future consequences is one mechanism of behavioral control, which help a person refrain from expressing an action. Activity within this high-order (i.e. conscious thoughts) system serves to control and modulate the behavioral and somatic response triggered by immediate drug cues. If the system for processing somatic states from thoughts about a possible encounter of severe punishment were hypoactive, then the negative somatic state induced by these thoughts would be weak. If the system for processing somatic states from thoughts related to drug reward were hyperactive, then the positive somatic state induced by these thoughts would be strong. In either case, the end-result is a shift in the choice of behavior towards the immediate outcome, i.e. seeking the immediate reward and ignoring the delayed punishment. The anticipatory SCR during the GT reflect somatic responses induced by thoughts about possible punishment when choosing a particular deck. The finding of impaired anticipatory SCR in some SDI suggests a hypo-functioning VM cortex-insular/SII, SI cortex system in relation to thoughts about future punishment. Indeed, abnormal blood flow in the orbitofrontal and insular cortices has been detected in SDI performing the GT [28]. However, there is also evidence for a hyper-functioning VM cortex-insular/SII, SI system in relation to thoughts about drug reward. In cocaine abusers, functional neuroimaging studies have shown that the orbitofrontal cortex and both the left and right insula were activated during the mental imagery of a cocaine experience [51]. Activation in orbitofrontal and insular cortices was also observed in cocaine addicts exposed to pictures of drug paraphernalia that remind them of drug experiences [14,27,36,48]. Both lines of evidence support a common behavioral outcome related to an increase in the value of immediate drug reward, and a decrease in the value of future punishment.

The critical question that remains un-addressed: what about the SDI who performed normally on the GT?

A subgroup of SDI showed a normal behavioral performance on the GT, and no signs of SCR impairment. It is possible that a severe decision-making deficit in this subgroup of SDI is precipitated only when these subjects are exposed to drug/alcohol related cues. All our experiments were conducted in abstinent SDI, and the non-impaired SDI

might well become impaired on the GT when tested in the presence of substance-related cues. A second possibility is alluded to earlier that the dichotomy between impaired and non-impaired SDI may reflect a critical distinction between two types of addicts: those with a normal VM function who can overcome their addiction when the costs of their actions are raised. The others with VM dysfunction who are unable to quit no matter how high the costs of their actions become. A third possibility is that there are other mechanisms undetected by the GT, which lead to loss of behavioral control over substance taking. Decision-making as measured by the GT and the constructs on discounting [1,29,34], which have been applied to addiction research [31,41,50], rely on mechanisms for evaluating immediate against future consequences. Recent findings in cocaine addicts showing a significant correlation between performance on the GT, the “betting task” [43], and tasks of delayed discounting [39] support this notion. However, there are several other behavioral mechanisms of impulsiveness and response inhibition that can be measured by different tasks and attributed to different neural regions and may not be detected by the GT [9]. Defects in these behavioral control mechanisms may be expressed in several forms of impulsive or disinhibited behaviors, and thus, independently contribute to the loss of behavioral control over substance taking.

Finally, it is important to note that we have shown that the decision-making impairment in VM patients is characterized by insensitivity to future consequences, positive and negative, such that their behavior is always guided by immediate contingency [8]. It remains possible that the underlying mechanism of the decision-making impairment in SDI is different from VM patients, so that they could be hypersensitive to reward, and the presence or the prospect of receiving reward dominates their behavior. The rationale for this hypersensitivity to reward hypothesis comes from several studies in SDI that revealed altered function of the orbitofrontal cortex [36,48]. During drug craving (i.e. when thoughts about drugs and the expectation of drug reward are intense), numerous studies have shown hyper-activation of the orbitofrontal cortex [13,14,27,36,48,51]. Longer periods of detoxification and the absence of craving were associated with hypo-activation of the orbitofrontal cortex [48]. Too much activation of the orbitofrontal cortex could render this region dysfunctional, i.e. functionally equivalent to a VM lesion, thus precipitating a decision-making impairment. However, the underlying mechanism for this dysfunction in SDI is obviously different from VM patients. In this case, hyperactivity of the orbitofrontal cortex may relate to a body state that gives rise to a conscious feeling of craving and an intense drive to seek drug reward. This strong body state would then preclude somatic signals related to future punishment from exerting any bias on choice and on behavior [4]. As such, the individual would behave, like the VM patient, as she is oblivious to the future consequences of their actions. Thus, the following study [9] was an attempt to address this issue and test this hypothesis.

Acknowledgements

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