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Risky Business: Emotion, Decision-Making, and Addiction

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Although metabolic abnormalities in the orbitofrontal cortex have been observed in substance dependent individuals (SDI) for several years, very little attention was paid to the role of this brain region in addiction. However, patients with damage to the ventromedial (VM) sector of the prefrontal cortex and SDI show similar behaviors. (1) They often deny, or they are not aware, that they have a problem. (2) When faced with a choice to pursue a course of action that brings an immediate reward at the risk of incurring future negative consequences, they choose the immediate reward and ignore the future consequences. Studies of patients with bilateral lesions of the VM prefrontal cortex support the view that the process of decision-making depends in many important ways on neural substrates that regulate homeostasis, emotion, and feeling. Parallel lines of study have revealed that VM cortex dysfunction is also evident in subgroups of individuals who are addicted to substances. Thus, understanding the neural mechanisms of decision-making has direct implications for understanding disorders of addiction and pathological gambling, and the switch from a controlled to uncontrolled and compulsive behavior. On the clinical front, the approach to treat addictive disorders has been dominated by a diagnostic system that focuses on behaviors, physical symptoms, or choice of drugs. The article emphasizes the concept of using neurocognitive criteria for subtyping addictive disorders. This is a significant paradigm shift with significant implications for guiding diagnosis and treatment. Using neurocognitive criteria could lead to more accurate subtyping of addictive disorders, and perhaps serve as a guide for more specific, and potentially more successful, behavioral and pharmacological interventions.

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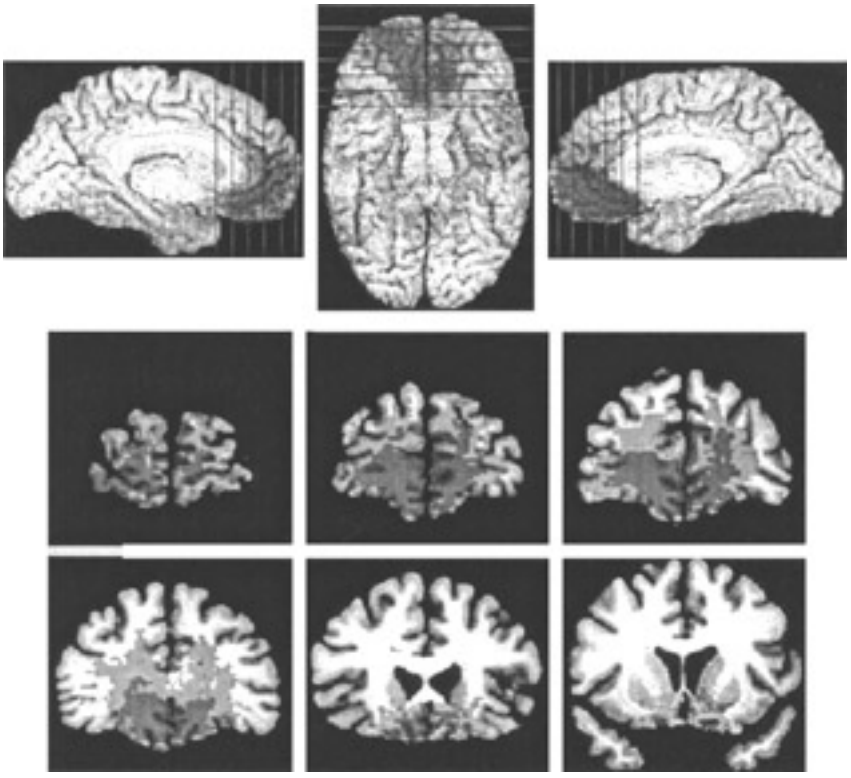
INTRODUCTION

One of the first and most famous cases of the so-called "frontal lobe syndrome" was the patient Phineas Gage, described by Harlow (Harlow, 1848, 1868). Phineas Gage was a railroad construction worker, and survived an explosion that blasted an iron-tamping bar through the front of his head. Before the accident, Gage was a man of normal intelligence, energetic and persistent in executing his plans of operation. He was responsible, sociable, and popular among peers and friends. After the accident, his medical recovery was remarkable. He survived the accident with normal intelligence, memory, speech, sensation, and movement. However, his behavior changed completely. He became irresponsible, untrustworthy, and impatient of restraint or advice when it conflicted with his desires. Using modern neuroimaging techniques, Damasio and colleagues have reconstituted the accident by relying on measurements taken from Gage's skull (Damasio, Grabowski, Frank, Galburda, & Damasio, 1994). The key finding of this neuroimaging study was that the most likely placement of Gage's lesion included the Ventromedial (VM) region of the prefrontal cortex, bilaterally. The VM sector includes both the gyrus rectus and mesial half of the orbital gyri, as well as the inferior half of the medial prefrontal surface, from its most caudal aspect to its most rostral in the frontal pole. Mesial sectors of areas 10 and 11, areas 12, 13, and 25, and subgenual sectors of areas 24 and 32 of Brodmann are included in this sector, as is the white matter subjacent to all of these areas (H. Damasio, 1995).

The case of Phineas Gage paved the way for the notion that the frontal lobes were linked to social conduct, judgement, decision-making, and personality. A number of instances similar to the case of Phineas Gage have since appeared in the literature (Ackerly & Benton, 1948; Brickner, 1932; Welt, 1888). Interestingly, all these cases received little attention for many years. The revival of interest in various aspects of the "frontal lobe syndrome" was triggered in part by the patient described by Eslinger and Damasio (Eslinger & Damasio, 1985), a modern counterpart to Phineas Gage. Over the years, we have studied numerous patients with this type of lesion (Figure 1). Such pa-

Figure 1
Overlap of Lesions in a Group of VM Patients.



From Bechara, Damasio, & Damasio, 2000.

tients with damage to the VM prefrontal cortex develop severe impairments in personal and social decision-making, in spite of otherwise largely preserved intellectual abilities. These patients had normal intelligence and creativity before their brain damage. After the damage, they begin to have difficulties planning their workday and future, and difficulties in choosing friends, partners, and activities. The actions they elect to pursue often lead to losses in diverse areas, e.g., financial, social standing, family and friends. The choices they make are no longer advantageous, and are remarkably different from the kinds of

choices they were known to make in the pre-morbid period. These patients often decide against their best interests. They are unable to learn from previous mistakes as reflected by repeated engagement in decisions that lead to negative consequences. In striking contrast to this real-life decision-making impairment, problem-solving abilities in laboratory settings remain largely normal. As noted, the patients have normal intellect, as measured by a variety of conventional neuropsychological tests (Bechara, Damasio, Tranel, & Anderson, 1998; Damasio, 1994; Damasio, Tranel, & Damasio, 1990; Eslinger & Damasio, 1985).

For many years, the condition of these patients has posed a challenge. However, while these VM patients were intact on nearly all-neuropsychological tests, the patients did have a compromised ability to express emotion and to experience feelings in appropriate situations. In other words, despite normal intellect, there were abnormalities in emotion and feeling, along with the abnormalities in decision-making. Based on these observations, the *somatic marker hypothesis* was proposed (Damasio, 1994; Damasio, Tranel, & Damasio, 1991).

THE SOMATIC MARKER HYPOTHESIS OF DECISION-MAKING AND ITS RELEVANCE TO MECHANISMS OF ADDICTION

Primary inducers are stimuli or conditioned stimuli that are innately set as pleasurable or aversive, and when they are present in the immediate environment, they automatically elicit a somatic response. Somatic refers to the Greek work "Soma," (i.e., body). Thus, we use the term somatic state to refer to the physiological changes that occur in the body in response to an emotionally charged stimulus that is present in the environment, or to a thought (memory) that has some emotional significance. Thus the gain or loss of a certain amount of money can automatically induce a somatic response, and so does the presence of a drug in the case of a drug addict. These are examples of primary inducers. We find that the amygdala is a critical substrate in this system (Bechara, Damasio, Damasio, & Lee, 1999).

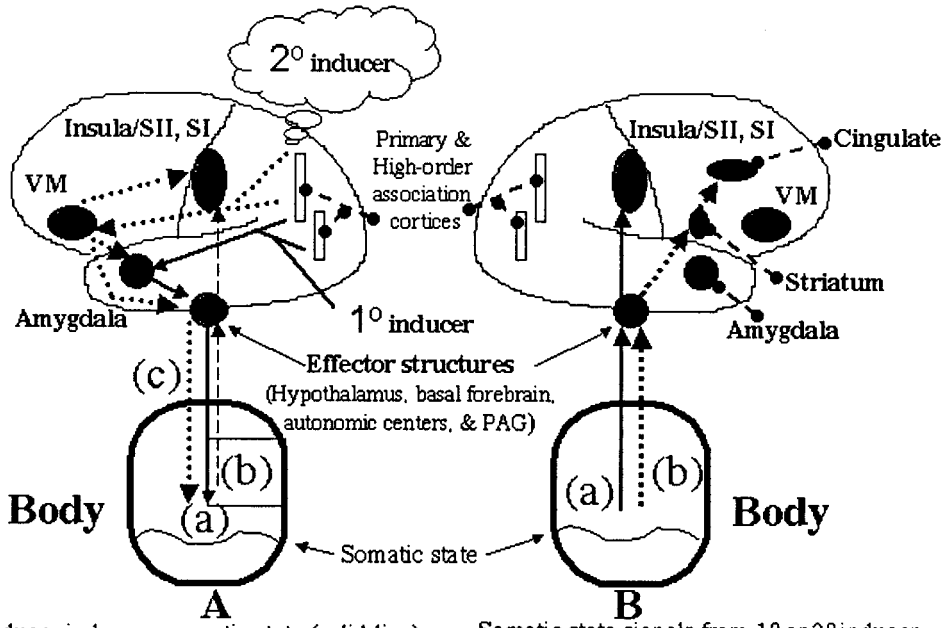
Secondary inducers are entities generated by recall or by thought, and when they are brought to memory they elicit a somatic response

(A. R. Damasio, 1995). Evoking an emotion from the recall or thought about a previous emotional experience is an example of a secondary inducer. The "thought" of gaining or losing a certain amount of money can trigger a somatic response, and so does the "thought" of taking a drug in the case of a drug addict. These are also examples of secondary inducers. The VM cortex is a critical substrate in the system necessary for activating somatic states from "thoughts" about rewarding or punishing events that are not currently present in the immediate environment (Bechara et al., 1999).

Once somatic states from primary inducers are induced, signals from these somatic states are relayed to the brain. Representations of these signals can remain covert at the level of the brainstem, or can reach the parietal cortices (insula/SII, SI) and posterior cingulate cortices and be perceived as a feeling (Damasio et al., 2000; Maddock, 1999). When we process a secondary inducer, i.e. recall an event associated with a feeling, we may re-enact the somatic state characteristic of the feeling. The VM cortex is a *trigger* structure for somatic states from secondary inducers (Figure 2).

Decision-making is a complex process that sometimes involves a conflict between a primary inducer (e.g., a drug that is present right in front of the subject), and a secondary inducer (e.g., thoughts of negative consequences associated with prior drug use). Sometimes, the conflict could be between only secondary inducers (e.g., one thought in mind about the reward from taking the drug and another thought about the negative consequences). Regardless of how somatic states are triggered, once somatic states induced by primary and/or secondary inducers are enacted in the body, an overall or a sum of all these somatic states, which is either positive or negative, is formed. This overall somatic state provides signals to the brain that participate in two functions. (a) In one, it provides a substrate for feeling the overall emotional state, possibly via the insular/SII, SI cortices. (b) In the other, it provides a substrate for biasing the decision to select a response (Damasio, 1996). This biasing effect may occur covertly at the level of the striatum; i.e., the person acts without conscious decisions to act. The biasing effect may also occur overtly at the level of the lateral orbitofrontal cortex and anterior cingulate; i.e., when the person focuses on a thought or a plan of action and have a conscious control of the action.

Figure 2
A Schematic Model of Somatic State Activation and Decision-Making



(a) A 1° inducer induces a somatic state (solid line).
(b) Somatic state signals generate representations in brainstem and insular/SII, SI cortex, which can be perceived as a feeling (dashed line).
(c) Images associated with the 1° inducer can now induce a somatic state, i.e., a 2° inducer (dotted line).

Somatic state signals from 1° or 2° inducer are relayed back to the brain. These somatic signals participate in two operations:
(a) feeling the emotional state (solid line).
(b) biasing the decision to select a response (dotted line).

From Bechara et al., 2002.

TESTING THE SOMATIC MARKER HYPOTHESIS: THE GAMBLING TASK AND VM PATIENTS

The first challenge in studying the decision-making in VM patients was the ability to detect and measure in the laboratory the decision-making impairment that these VM patients have in real-life. We overcame this challenge by developing a card task, which became known as "the gambling task" (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Tranel, & Damasio, 2000). The task is carried out in real-time and it resembles real-world contingencies. It factors reward and punishment (i.e., winning and losing money) in such a way that it creates a conflict between an immediate, luring reward and a delayed, probabilistic punishment. Therefore, the task engages the subject in a quest to make advantageous choices. As in real-life choices, the task offers choices that may be risky, and there is no obvious explanation of how, when, or what to choose. Each choice is full of uncertainty because a precise calculation or prediction of the outcome of a given choice is not possible.

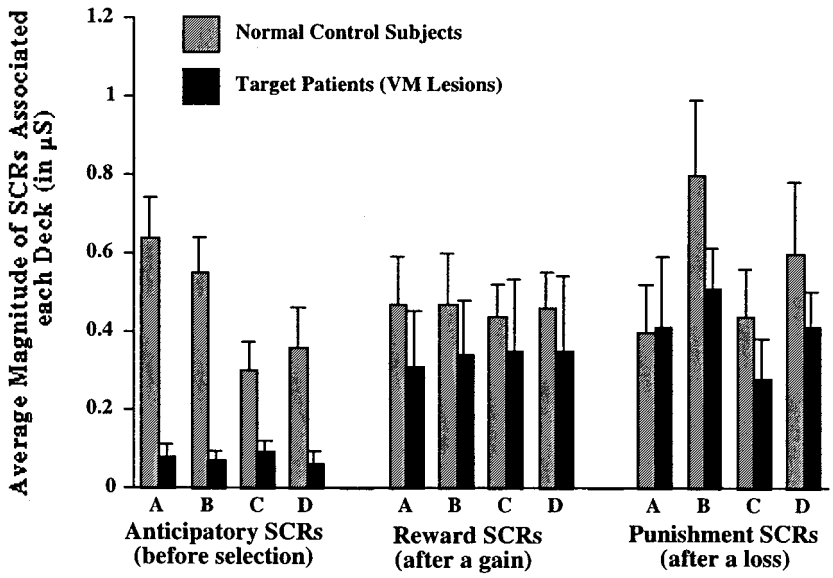
The task involves 4 decks of cards. The goal in the task is to maximize profit on a loan of play money. Subjects are required to make a series of 100 card selections; however, they are not told ahead of time how many card selections they are going to make. Subjects can select one card at a time from any deck they choose, and they are absolutely free to switch from any deck to another at any time, and as often as they wish. However, the subject's decision to select from one deck versus another is largely influenced by various schedules of immediate reward and future punishment. These schedules are pre-programmed and known to the examiner, but not to the subject. The detail of these schedules and the procedure to administer the task are published elsewhere (Bechara et al., 1994; Bechara, Tranel et al., 2000). Briefly, most every time the subject selects a card from deck A or deck B, the subject gets $100. Most every time the subject selects deck C or deck D, the subject gets $50. However, in each of the 4 decks, subjects encounter unpredictable punishments or money loss. The punishment is set to be higher in the high paying decks A and B, and lower in the low paying decks C and D. If 10 cards were picked from deck A or B over the course of trials, one earns $1000. However, in those 10 card picks there are unpredictable punishments in the amount of $1250. On the other hand, every 10 cards from deck C or D earn only $500, but only

cost $250 in punishment. In essence, decks A and B are disadvantageous because they cost more in the long run; i.e., they result in losing $250 for every 10 cards selected. Decks C and D are advantageous because they result in an overall gain in the long-term; i.e., they result in winning $250 for every 10 cards selected.

We investigated the performance of normal controls and VM patients on this task. We also compared their performance to brain-damaged patients (with lesions outside the target areas; i.e., the occipital or lateral temporal cortex). We found that normal controls learned to avoid the bad decks A and B, and selected more cards from the good decks C and D. The same was true for controls with lesions in the occipital or lateral temporal cortex. In contrast, VM patients failed to avoid the bad decks A and B, and selected fewer cards from the good decks C and D. Thus, from these results we suggested that the VM patients' performance profile is comparable to their real-life inability to decide advantageously in situations involving choosing between immediate vs. delayed reward or punishment. This is especially true in personal and social matters, a domain for which in life, as in the task, an exact calculation of the future outcomes is not possible and choices must often be based on approximations, hunches, and guesses (Bechara et al., 1994). Based on these behavioral results, we asked the following questions: Why do these patients have this "myopia" for the future? Why can they not "foresee the future"?

To answer these questions, we added a psychophysiological measure while playing the gambling task. The goal was to assess somatic state activation when making decisions during the gambling task. We studied 2 groups: normal subjects and VM patients. We had them perform the gambling task while we recorded their skin conductance response (SCR) activity (Bechara, Tranel, Damasio, & Damasio, 1996). Both normal controls and VM patients generated SCRs after they had picked the card and were told that they won or lost money. The most important difference, however, was that normal controls, as they became experienced with the task, they began to generate SCRs prior to the selection of any cards; i.e., during the time when they were pondering from which deck to choose. These anticipatory SCRs were more pronounced before picking a card from the risky decks (A and B) when compared to the safe decks (C and D). VM patients entirely failed to generate any *SCRs* before picking a card (Figure 3). These results provide strong support for the notion that decision-making is

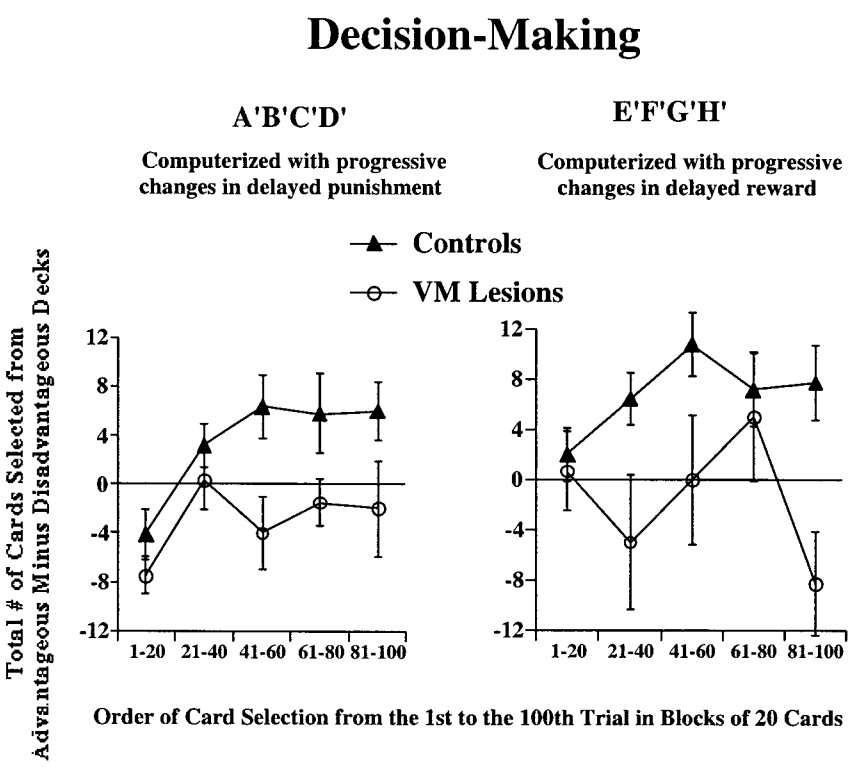
Figure 3
Means ± s.e.m. of the Magnitudes of Anticipatory, Reward, and Punishment SCRs Generated by Normal Controls and Target Patients (VM lesions) Averaged Across All Cards Selected from a Given Deck



guided by emotional signals (or somatic states), which are generated in anticipation of future events.

Would increases in the magnitude or frequency of future consequences ameliorate the decision-making deficit in VM patients and shift their behavior in the advantageous direction (Bechara, Tranel et al.)? To answer this question, we introduced two types of manipulations. In one, as in the original gambling task described above, we progressively increased the magnitude or frequency of delayed punishment as more cards were selected from the disadvantageous decks. In another, a variant version of the gambling task, we reversed the order of reward and punishment, so that the advantageous decks yielded high immediate punishment but even higher future reward. The disadvantageous decks yielded low immediate punishment but even lower future reward. In this variant task, we progressively decreased the magnitude or frequency of reward in the disadvantageous decks. Both ma-

Figure 4
Net Scores ((C' + D') − (A' + B') or (E' + G') − (F' + H')) of Cards Selected by Each Group Across Different Blocks Expressed as Mean ± s.e.m. (Positive net scores reflect advantageous performance while negative net scores reflect disadvantageous performance.)



From Bechara et al., 2000.

nipulations failed to shift the behavior of VM patients away from the disadvantageous decks (Figure 4). These results suggest that VM patients are insensitive to future consequences, positive or negative, and are primarily guided by immediate prospects. This "myopia for the future" in VM patients persists in the face of severe adverse consequences; i.e., rising future punishment or declining future reward.

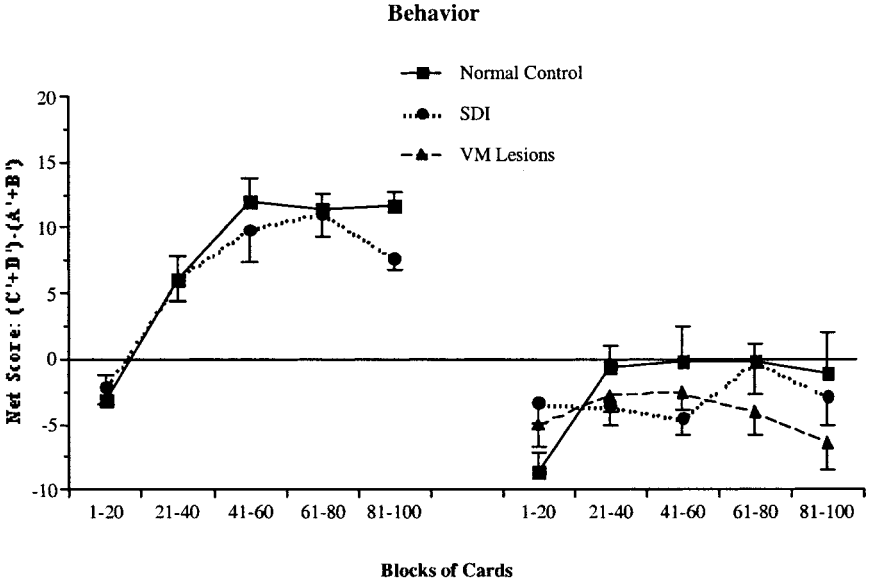
DECISION-MAKING AND ADDICTIVE DISORDERS: FINDINGS IN SUBSTANCE DEPENDENT INDIVIDUALS (SDI)

Although orbitofrontal cortex abnormalities have been observed in SDI for several years (Childress et al., 1999; London, Ernst, Grant, Bonson, & Weinstein, 2000; Stapleton et al., 1995; Volkow & Fowler, 2000; Volkow et al., 1991), very little attention was paid to the role of the prefrontal cortex in addiction. However, VM patients and substance dependent individuals (SDI) show similar behaviors. (1) They often deny, or they are not aware, that they have a problem. (2) When faced with a choice to pursue a course of action that brings an immediate reward, at the risk of incurring future negative consequences, including the loss of reputation, job, home, and family, they choose the immediate reward and ignore the future consequences. Because of this "myopia" for future consequences seen in VM patients and SDI, the first attempt to establish a link between the two using strategies applied to the study decision-making in neurological patients was conducted by Grant and colleagues, who investigated the mechanisms of decision-making in cocaine addicts using the GT paradigm (Bartzokis et al., 2000; Grant, Contoreggi, & London, 1997, 2000; Grant, Bonson, Contoreggi, & London, 1999). Since then, several groups have used similar strategies and found a relationship between substance abuse and poor decision-making (Mazas, Finn, & Steinmetz, 2000; Petry, Bickel, & Arnett, 1998; Rogers, Everitt et al., 1999). We have also used strategies applied to the study of decision-making in neurological patients and investigated the mechanisms of decision-making and somatic state activation in SDI. Studies have shown that the abnormal mechanisms of processing drug reward in SDI generalize to other rewards, including monetary reward (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Breiter & Rosen, 1999). Therefore, we predicted that the abnormalities of SDI in processing somatic states would apply not only to drugs, but also to reward in general, such as the monetary reward used in the GT paradigm.

Behavioral and Neuropsychological Findings

We conducted experiments where we tested three groups of subjects: SDI, normal controls, and VM patients. All SDI met the DSM-IV

Figure 5
The Net Scores ((C' + D') − (A' + B')) of Cards Selected by Nonimpaired (left panel) and Impaired (right panel) Subgroups Across Different Blocks Expressed as Mean + s.e.m. (Positive net scores reflect advantageous [nonimpaired] performance while negative net scores reflect disadvantageous [impaired] performance.)



From Bechara & Damasio, 2002.

criteria for dependence, with either alcohol or stimulants (methamphetamine or cocaine) as the primary substance of choice (Bechara & Damasio, 2002; Bechara, Dolan et al. 2002). The results revealed a significant impairment in the performance of SDI relative to normal controls. A significantly high proportion of SDI (63% versus only 27% of normal controls) performed within the range of the VM patients, while the rest performed within the range of normal controls. Using the maximum score achieved by any of the VM patients as a cut-off score for impaired performance (below the cut-off score) and non-impaired performance (above the cut-off score), Figure 5 reveals that the majority of normal controls and a minority of SDI performed

Table 1
Spearman Rank Correlations of Factors Unique to Substance Abuse and Decision-Making Performance

	Spearman R	*p-level*
Drug of Choice	0.13	0.4
Years of Abuse	0.13	0.4
Duration of Abstinence	0.12	0.5
Times in Treatment	0.07	0.6
Holding Employment	0.36	0.02
Prediction Index	0.43	0.006

Note: Prediction Index = duration of abstinence in days × employment years of abuse × times in treatment.

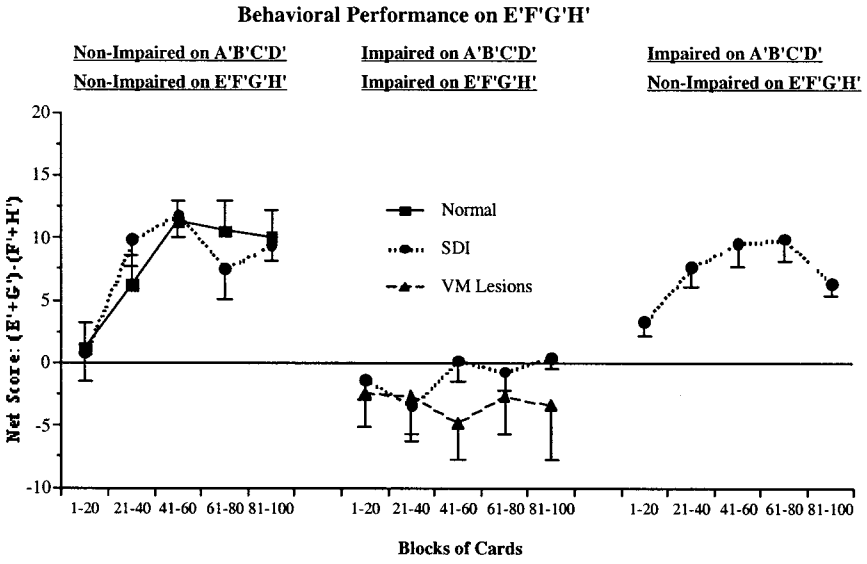
advantageously. Conversely, a majority of SDI, all VM patients, and a minority of normal controls performed disadvantageously.

General demographic factors such as age, sex, and level of education could not explain these differences in performance. As well, differences in performance were not explained by intelligence (IQ), memory, or performance on standard executive function/frontal lobe tests. Performance on the gambling task was best predicted by a combination of factors, including duration of abstinence, years of abuse, relapses and times in treatment, and the ability to hold gainful employment (Table 1) (Bechara, Dolan et al., 2001).

Interestingly, the ability to maintain gainful employment, despite a drug or alcohol habit, was the best predictor of performance. This is not surprising in light of the fact that VM patients are unable to hold gainful employment. This real-life behavior of SDI suggests that some of them continue to seek substances despite losing their jobs and suffering other adverse consequences, and this behavior is reflected by a severe impairment in performance on the gambling task. On the other hand, the other SDI, who also met the criteria for dependence, have not lost their jobs, and this behavior is reflected by normal performance on the gambling task.

When looking at the results from the variant version of the gambling task, with a progressive decrease in the magnitude and frequency of reward in the disadvantageous decks, a different picture emerged. Using the data from VM patients to establish cut-off score for impaired

Figure 6
Net Scores of Performance on the Variant Gambling Task (E'F'G'H') (Groups are divided according to nonimpaired or impaired behavioral performance on both the original [A'B'C'D'] and variant [E'F'G'H'] versions of the GT. The criteria for impaired or nonimpaired performance are based on cut off scores between the performance of normal controls and patients with VM lesions. For the original task, the impaired net score is < 10. For the variant task, the impaired score is < 8. Data are presented as means + s.e.m.)



From Bechara et al., 2002.

and non-impaired performance as indicated earlier, the SDI who were not impaired on the original GT were also not impaired on the variant GT. Those who were impaired on the original GT were now divided on the variant GT: (1) Some SDI were like VM patients, in that they failed to shift their behavior away from the bad decks, i.e., decks with declining future reward. (2) The remaining SDI were opposite to VM patients, in that they quickly shifted away from choices with declining future reward (bad decks) and pursued choices with high immediate punishment but progressively rising delayed reward (good decks) (Figure 6).

Psychophysiological Findings

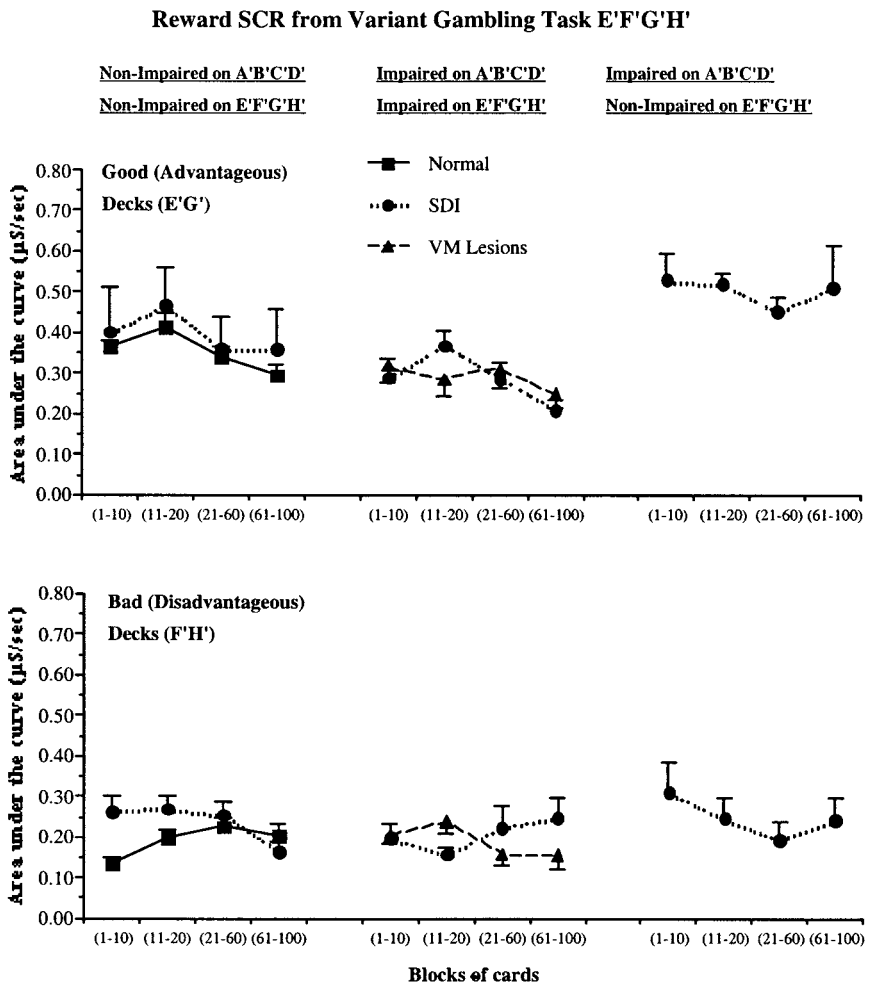
Measuring SCR activity of subjects after receiving reward (Reward SCRs), and before making a choice (Anticipatory SCRs), revealed additional clues. The reward SCRs from the non-impaired SDI on the original GT were like normal controls. Those from the impaired group on the original GT mirrored the behavioral results of the variant GT. The impaired SDI on the variant GT had reward SCRs that were no different from VM patients and normal controls. The non-impaired SDI on the variant GT had significantly higher reward SCRs in relation to the good decks (those with the highest amounts of reward) and lower reward SCRs in relation to the bad decks, relative to controls and VM patients (Figure 7).

The anticipatory SCRs from the non-impaired SDI on the original GT were like normal controls. Those from the impaired group on the original GT mirrored the behavioral results of the variant GT. The impaired SDI on the variant GT had defective anticipatory SCRs like VM patients. Most intriguing, the non-impaired SDI on the variant GT showed a significant rise in anticipatory SCRs in relation to decks yielding a gradual rise in delayed reward, and they showed a significant decline in anticipatory SCRs in relation to decks yielding a gradual decline in delayed reward (Figure 8).

In relation to punishment and its anticipation, the punishment and anticipatory SCRs from the non-impaired SDI on the original GT were like normal controls. Those from SDI who were impaired on both tasks were identical to VM patients; i.e., normal punishment SCRs and defective anticipatory SCRs. SDI who were impaired on the original GT and non-impaired on the variant GT had abnormal anticipatory SCRs (albeit not as defective as VM patients) and slightly lower than normal punishment SCRs (Bechara, Dolan, & Hindes, 2002).

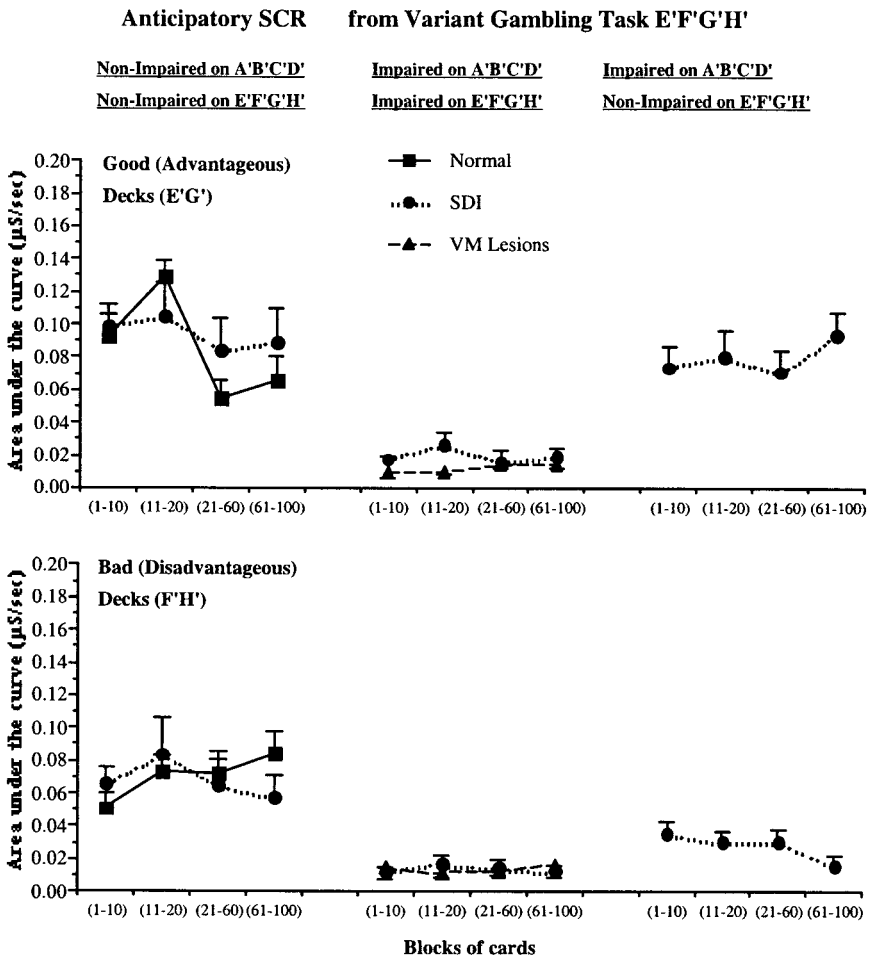
These results suggest that at least a sub-population of SDI is hypersensitive to reward, so that the presence or the prospect of receiving reward dominates their choice and behavior. Thus, there are 3 sub-groups of SDI. In one sub-group, the decision-making impairment is more consistent with a hypersensitivity to reward explanation. We still do not completely understand the pathophysiology underlying this hypersensitivity to reward, but it likely goes beyond the VM prefrontal region and involves abnormalities in a fronto-parietal (insular and SII cortex) neural system. In another subgroup, the decision-making im-

Figure 7
Reward SCR from the Variant Gambling Task (E'F'G'H') (Groups are divided according to nonimpaired or impaired behavioral performance on both the original [A'B'C'D'] and variant [E'F'G'H'] Versions of the GT. The upper panel presents data from reward received in the Good [Advantageous] decks. The lower panel presents data from reward received in the Bad (Disadvantageous) decks. Data are presented as means + s.e.m.)



From Bechara et al., 2002.

Figure 8
Anticipatory SCR from the Variant GT (E'F'G'H') (Groups are divided according to nonimpaired or impaired behavioral performance on both the original [A'B'C'D'] and variant [E'F'G'H'] versions of the task. The upper panel presents anticipatory SCR in relation to the Good [Advantageous] decks. The lower panel presents anticipatory SCR in relation to the Bad [Disadvantageous] decks. Data are presented as means + s.e.m.)



From Bechara et al., 2002.

pairment is more consistent with insensitivity to future consequences, positive or negative. The impairment in this group is indistinguishable from VM patients, and thus is likely linked to a damaged or hypoactive VM cortex. There is one subgroup that appears normal and shows no signs of impairments with the GT paradigm.

DISCUSSION

Several models of addiction suggested that addiction might be related to two processes (Everitt et al., 1999; Jentsch & Taylor, 1999; Koob, 1999). One process relates to abnormal activity in the extended amygdala system, thereby resulting in exaggerated processing of the incentive values of drug-related stimuli. The other process relates to abnormal activity of the prefrontal cortex system necessary for inhibiting the substance-seeking action associated with immediate reward. Decision-making mediated by the VM cortex is only one of those mechanisms that help control the person behavior in relation to potentially rewarding actions that later lead to negative consequences. However, there are several other prefrontal mechanisms for impulsiveness or response inhibition that are important for behavioral control that could be impaired in SDI and also pathological gamblers, and which are not detected by the GT paradigm. What are these mechanisms?

We argue that decision-making and impulsiveness may be separate both cognitively and anatomically. In addition, evidence suggests that there are several different mechanisms of impulsiveness or response inhibition. Impulsiveness is fundamentally different from decision-making in the following way: decision-making as exemplified in the GT paradigm involves a dilemma that requires a solution; i.e., there is no easy answer. A real life example would be a person who finds a briefcase with $100,000 in it in a dark alley. The person may deliberate on whether to keep or return the money, and there may not be one easy answer. A deficit in decision-making as measured by the GT can arise from a dysfunction in the VM cortex, especially the anterior sector of the VM cortex; i.e., towards the frontal pole, or just anterior to Brodmann area 25 (Bechara et al., 1998). Area 25 is considered a part of the anterior cingulate and it is thought to carry a different function as described below. We consider that the behavioral economic con-

structs on discounting (Ainslie, 2000; Green, Fristoe, & Myerson, 1994; Green, Fry, & Myerson, 1994; Kirby & Herrnstein, 1995) that have been applied to addiction research (Heyman, 1996; Petry et al., 1998; Vuchinich & Tucker, 1988) as consistent with this type of deficit in behavioral control. In all these instances, the behaviors involve evaluation of several competing options, outcomes, and strategies as in the GT, and there is a steeper discounting of the future in various populations of substance addicts relative to controls. The use of another decision-making instrument, the "betting task" that is similar, but not identical, to the GT has also yielded concordant findings to those of the GT in patients with orbitoforntal cortex damage as well as populations of substance abuse (Rahman, Sahakian, Rudolph, Rogers, & Robbins, 2001; Rogers, Everitt et al., 1999; Rogers, Owen et al., 1999), suggesting that the two tasks may tax the same decision-making function. The study of Monterosso and colleagues in cocaine addicts has specifically addressed this issue, and it has shown a significant correlation between performance on the GT, the "betting task," and tasks of delayed discounting (Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001), thus supporting the notion that these three sets of tasks may engage a common mechanism of decision-making.

On the other hand, impulse control as measured by various neuropsychological tasks does not present a dilemma. It is simply a learned inhibition that has one correct solution, which is to inhibit the prepotent response. A real-life example would be the same person finding a pile of money spread out on a table inside a bank. In this case, a person sees the money and does nothing! A normal person does not stand and ponder whether to grab the money and run away. Any impulse to have access to this amount of money is simply inhibited. If the person cannot help it and unwillingly reaches for the money and takes it, then this is a sign of a dis-inhibited behavior or poor impulse control. (In the event that the person may be desperate and may willingly consider robbing the bank, then the whole evaluation process of whether to rob the bank or not, and the consequences of robbing the bank, will invoke the process of decision-making.) An addict or a pathological gambler may have abnormalities in one or both types of mechanisms. For instance, the choice between another gamble and the family pressure not to gamble presents a dilemma to a pathological gambler, and the advantageous choice is dependent on intact mechanisms of decision-making. However, the ability to put a stop and quit a

gambling activity inside a casino after losing a certain amount of money is more dependent on mechanisms of response inhibition and the ability to control the impulse of wanting to do one more gamble. A pathological gambler inside a casino who involuntarily loses control over this ability to resist and put a stop to one more gamble is a sign of defective mechanisms in response inhibition and impulse control. Recently, Petry has conducted a study involving the assessment of three measures of impulsivity (impulse control, novelty seeking, and time orientation), and also the assessment of gambling task performance in populations of pathological gambling substance abusers, non-pathological gambling substance abusers, and controls (Petry, 2001). The results were intriguing: substance abuse and pathological gambling exerted additive effects on the impulse control and time orientation, but not novelty-seeking factors. Most important, the study shows that performance on the GT did not correlate with any of the impulsivity measures, but the presence of both pathological gambling and substance abuse exerted additive effects on shifting GT performance in the disadvantageous direction (Petry, 2001). These findings support the notion that although pathological gamblers and substance abusers may have decision-making impairments as measured by the GT, these deficits may not relate directly to deficits in impulsiveness as measured by a variety of personality scales (Petry, 2001), thus suggesting that the two functions (decision-making and impulsiveness) may be processed by separate mechanisms in the brain.

Evidence reveals that there are several sub-types of mechanisms involved in inhibitory control that can be measured by different tasks and attributed to different neural regions:

(a) Cognitive flexibility or perceptual impulsiveness: This simply reflects an inability to inhibit a recurrent thought held in working memory. The inhibition of a thought of wanting to take drugs or wanting to gamble is one example. Perseveration on the Wisconsin Card Sorting Task (WCST) and inability to shift attentional sets (ID-ED shift) are laboratory measures of this type of deficit in impulse control (Dias, Robbins, & Roberts, 1996; Dias, Robbins, & Roberts, 1997; Milner, 1963). The lateral frontal and anterior insular cortices appear critical for this type of impulsiveness. Studies have linked performance on the WCST task to the lateral orbital and frontal cortices in functional neuroimaging (Konishi et al., 1999; Lombardi et al., 1999) as well as lesion (Anderson, Damasio, Jones, & Tranel, 1991; Milner, 1963) studies. In humans, it has been shown that attention set shifting (shift atten-

tion from one perceptual dimension of a complex visual stimulus to another) is selectively impaired following lateral prefrontal cortex lesions (Owen et al., 1993; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991).

(b) Behavioral flexibility or motor impulsiveness: Motor impulsiveness reflects an inability to inhibit a pre-potent motor response. Although the anterior cingulate is critical for this mechanism of motor impulse control, functional neuroimaging and lesion studies suggest that there may be two different types of behavioral flexibility or motor impulsiveness:

(i) Non-affective flexibility or motor impulsiveness of non-affective nature: This reflects an inability to inhibit a pre-potent response that is non-affective. Controlling habit responses and rituals that some addicts engage in before the steps leading to drug taking is one example. The Stroop test, in which the subject must name the print color of a word and inhibit the stronger tendency to read the name of a color itself, provides a laboratory measure of this type of deficits in impulse control. The supracallosal sector of the anterior cingulate (also named cognitive component of the anterior anterior cingulate [Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995]) appears critical for this type of impulsiveness. Functional neuroimaging studies have revealed activation in the *supracallosal* sector of the anterior cingulate in association with performance on the Stroop (Carter et al., 1998; Frith, Friston, Liddle, & Frackowiak, 1991; Garavan, Ross, & Stein, 1999; Pardo, Pardo, Janer, & Raichle, 1990).

(ii) Affective flexibility or motor impulsiveness of affective nature: This reflects an inability to inhibit a pre-potent response that is affective, i.e., a pre-potent rewarded response. When an addict sees a drug, or a pathological gambler sees a gamble, and involuntarily reach for it, even when they don't want to (i.e., they could not help it), is one example of this type of deficit. Go/no Go tasks, delayed alternation, and reversal learning are prime examples of paradigms that measure this type of behavioral control. The subgenual sector of the anterior cingulate (also named visceral/affective component of the anterior cingulate (Bush et al., 2000; Devinsky et al., 1995)) appears critical for this type of impulsiveness. In humans, it has been shown that impairments at reversal learning of previously rewarded responses are more associated with damage involving the subgenual sector of the anterior cingulate (Owen et al., 1991; Rolls, Hornak, Wade, & McGrath, 1994).

It is very important to realize that although these different cogni-

tive and behavioral mechanisms can be dissociated under controlled experimental conditions, they are all inter-related and act together in a functioning brain. Injuries or diseases that affect a single or a combination of any of these mechanisms will have a devastating impact on judgment, decision-making, and the whole social and real-life behavior of the affected individual.

Finally, a strong argument has been put forward regarding the importance of basing certain pathological gambling studies on studies of substance dependence and looking for similarities and differences (Potenza & Wilber, 2001). Perhaps pathological gambling can serve as an informative model for substance dependence since it represents a similar addictive disorder, but it does not carry the confounding issue of exogenous drug effects on brain substrates (Potenza & Wilber, 2001). However, when studying the cognitive and behavioral mechanisms underlying pathological gambling and/or substance abuse, it is important to consider the real-life behavior of affected individuals and not simply rely on laboratory derived measures. For example, Cavedini et al. (Cavedini et al., 2001) and Petry (Petry, 2001) have shown that pathological gamblers perform poorly on the GT relative to controls. In contrast, Cremer von Schinkel (Cremer von Schinkel, 2001) has presented evidence that there is no difference in performance on the GT between controls and pathological gamblers. How can we reconcile these differences?

In a previous study of SDI, we found that the ability to maintain gainful employment, despite a drug or alcohol habit, was a good predictor of performance on the GT (Bechara, Dolan et al., 2001). This is not surprising in light of the fact that VM patients are unable to hold gainful employment. Factors other than employment are also characteristics of VM patients, such as destruction of family life and loss of friends. However, we did not assess these factors in SDI, and it would be interesting to find out whether they would be good predictors of performance on the GT. This real-life behavior of SDI suggests that some SDI continue to seek substances despite losing their jobs and suffering other adverse consequences. This group of SDI appears to have the most severe impairment in decision-making, as reflected by their scores on the GT. On the other hand, SDI who meet the criteria for dependence, but have not lost their jobs do not show clear evidence of suffering severe adverse consequences (in social or real-life) that perhaps outweigh the reward of substance use. Interestingly, this

sub-group of SDI does not show impairment in decision-making on laboratory tasks. Thus decision-making represents a balance between the reward of the substance and the punishment of the consequences. Consequently, substance abuse may not be always associated with deficits in decision-making; i.e., when the delayed punishment in real-life does not outweigh the immediate reward, then seeking the reward may not necessarily reflect a dysfunction in the mechanisms of decision-making. Rather, a poor decision-making is when the individual continues or escalates the use of substances in the face of rising adverse consequences. Thus, seeking the reward of a substance may not represent a problem unless it leads to some sort of social, physical, or psychological harm. For instance, we seek the reward of food, but such a behavior is not considered addictive or problematic unless the eating behavior begins to incur adverse social, health, or psychological consequences. The same logic should apply to pathological gambling. Individuals who meet the criteria for pathological gambling, who gamble but do not encounter significant social, health, or psychological harm may not necessarily suffer from decision-making deficits that can be detected by laboratory instruments such as the GT. In contrast, pathological gamblers who continue to gamble in spite of rising harm to their social standing, health, or psychological state in real-life are more likely to show signs of decision-making deficits in laboratory settings. Empirical data that support or refute this notion is not available at this stage. However, the notion presents a testable hypothesis that can be addressed in future studies of pathological gambling.

CONCLUSIONS AND IMPLICATIONS FOR PROGNOSIS AND REHABILITATION STRATEGIES

Beside decision-making, the prefrontal cortex hosts three other mechanisms for response inhibition and impulsiveness, which are not detected by the gambling task, and which could be impaired in SDI and pathological gamblers. We believe that dysfunction of one or more of these mechanisms constitute one of the principal mechanisms responsible for the switch from a controlled to uncontrolled and compulsive behavior. The neurocognitive strategies for studying decision-making in VM patients and SDI should also apply to the mechanisms underlying pathological gambling. Characterization of SDI (and pathological

gamblers) on the basis of neurocognitive criteria has strong implications for prognosis and rehabilitation. Those who do not show signs of prefrontal impairment may have the best prognosis. Indeed, there are individuals who decide at some point, for one reason or another, that they must quit their addiction and they do! These individuals (whether SDI or pathological gamblers) who have considerably greater control of their behavior may represent those with less severe prefrontal impairment. Individuals who are similar to VM patients we predict would have the worst prognosis. Such individuals would be predicted to repeatedly engage in problematic behaviors, make mistakes of a similar nature one after another, and never shift their behavior towards long-term thinking and avoiding future negative consequences on their own. Individuals who show only signs of hypersensitivity to reward we would predict to fall somewhere in between. We speculate that the weakness of these individuals and their loss of behavioral control are precipitated primarily in the presence of reward or irresistible cue. In other words, they may have the cognitive capacity to learn to stay way from the situations that make them vulnerable to succumbing to their addiction.

We have begun pharmacological research aimed at understanding prefrontal cortical neurochemical differences that mediate in SDI their decision-making impairment and loss of behavioral control. We studied normal subjects under a serotonin manipulation with either: (1) a placebo (Vitamin C); (2) a selective serotonin reuptake inhibitor (fluvoxamine); and, (3) a serotonin 5HT2A receptor antagonist (cyproheptadine) with H1 histamine receptor antagonist properties. We studied other normal subjects under a dopamine manipulation involving the use of either: (1) a placebo; (2) a psychostimulant (dextroamphetamine) resulting in a net increase in dopaminergic neurotransmission; and, (3) a dopamine D2-like receptor antagonist (haloperidol). For each drug condition, the subjects were tested with a different version of the gambling task (GT) for assessing decision-making, with the order of the 3 drug conditions counterbalanced within each group. The blockade of both dopamine and serotonin interfered with the selection of advantageous choices, but the dopamine effect seemed restricted to the earlier part of the GT, when decisions are still guided by covert knowledge. The stimulation of both dopamine and serotonin improved the selection of advantageous choices, but only in specific parts of the task. Serotonin improved only the latter part of the task,

when decisions are guided by conscious knowledge of which choices are good or bad. By contrast, dopamine improved only the early part of the task when guidance is covert. The results suggest that covert biasing of decisions might be dopaminergic, whereas overt biasing might be serotonergic (Bechara, Damasio, & Damasio, 2001). We note that ondansetron, a serotonin antagonist (5HT3 antagonist), was successful in treating patients with early-onset alcoholism, presumably by ameliorating an underlying serotonergic abnormality (Johnson et al., 2000). On face value, this effect may be inconsistent with the findings that serotonin agonists improved decision-making. However, the findings do implicate the serotonergic system in this complex process and highlight further the notion that pharmacological systems may interact in complex ways to facilitate or ameliorate addictive disorders.

Together, these findings have implications for the treatment of addictive disorders in that more than one neurotransmitter system may be involved in the addictive process, and thus different aspects of the addictive process may respond preferentially to different pharmacological treatments. Most importantly, optimal treatment strategies are likely to involve a combination of specific pharmacological and behavioral interventions. That is, we hypothesize that poor prefrontal mechanisms of decision-making in SDI are in part related to learning in the presence of neurochemical abnormalities that modulate nonconscious (e.g., at the level of the striatum) or conscious (e.g., at the level of the cortex) decisions. Thus, individuals with addictive disorders often must "re-learn" how to think and behave in particular situations related to drugs or gambling in the context of neural systems "normalized" with medications. Thus, re-learning (i.e., rehabilitation) in the presence of normal pharmacology (i.e., drug treatment) will likely represent the most effective way to restore advantageous decisions in an addicted individual. Further studies are needed to confirm these hypotheses, and to determine which treatment strategies will work best for specific groups of individuals with addictive disorders.

In essence, the approach to treat addictive disorders has been dominated by a diagnostic system that focuses on behaviors, physical symptoms, or choice of drugs. We emphasize the use of neurocognitive criteria for subtyping addictive disorders. This is a significant paradigm shift with significant implications for guiding diagnosis and treatment. The use of neurocognitive criteria has the potential to lead to more accurate subtyping of addictive disorders, and serve as a guide

for the development and testing of more specific and successful behavioral and pharmacological interventions.

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