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Impulsivity, Neural Deficits, and the Addictions: The “Oops” Factor in Relapse

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SUMMARY

Impulsive behaviors are observed in a wide range of psychiatric disorders, including substance use, bipolar, attention-deficit hyperactivity, antisocial and borderline personality, gambling, and eating disorders. The shared phenotype of impulsivity is thought to significantly contribute to both the etiology and perpetuation of these disorders. In this review, we focus upon the relevance of impulsivity to the addictive disorders, particularly substance use disorders. First, the literature supporting the presence of impulsive behaviors prior to the onset of drug use and addiction is discussed. The relevance of impulsivity to relapse is then presented, with a focus on three distinct neurocognitive constructs: automaticity, response inhibition, and decision making. Automaticity is a quickly occurring relapse process resulting from the learned habits induced by persistent drug use. Addicted persons with response inhibition deficits are unable to suppress these previously reinforced behaviors. Decision-making deficits contribute to relapse through a poorly considered assessment of the consequences of drug use. The brain regions associated with each model of impulsive behavior are described, and relevant neurobiologic disruptions in addicted subjects are discussed in the context of their specific neurocognitive deficit(s). Descriptive confusions in the terminology and confounds inherent in the study of impulsivity are described. Empirical

investigations documenting the hypothesized relationship between specific deficits in impulsive behaviors, coupled with their neurobiological correlates, and relapse should be the focus of future studies.

Keywords

Addictive disorders; impulsive behavior; substance use; automaticity

MECHANISMS OF RELAPSE: DEFICITS IN RESPONSE INHIBITION AND DECISION MAKING

Up to seventy-five percent of addicted patients relapse following treatment.^{1,2} Various causal factors have been posited to explain this high relapse rate, including self-efficacy, biased belief systems, current coping resources, and stressor intensity. Across theoretical models, multiple determinants of relapse include negative emotional states, interpersonal conflict, social pressure, and frustration or anger. Over the past two decades, neurobiologic influences on the addictive process and relapse have also become increasingly appreciated. This work has particularly focused upon the mesolimbic dopaminergic system, reward, and “craving.”^{3–7} Although this effort has resulted in an explosion in our understanding of the biological underpinnings of the addictive process, it has been of limited utility in providing new psychotherapeutic or pharmacologic treatment approaches to decrease relapse.

The impulsive relapse, in which the return to an addictive behavior occurs swiftly and often in the absence of a conscious awareness of craving, may be a key determinant of relapse in many patients. In this scenario, the return to drinking in an alcohol-addicted patient seems to come out of the blue and is unassociated with life stressors, cravings, or a determined plan to return to substance use. As described by Bill W. in the *Alcoholics Anonymous Big Book*, “I saw I could not have so much as one drink. ... Shortly afterward I came home drunk. ... Someone had pushed a drink my way, and I had taken it” (p. 5).⁸ It is only in retrospect that the addict recognizes he or she has impulsively relapsed, often acknowledging their transgression with an “oops!” (or a more powerful expression of disappointment, regret, and self-loathing). For example, we asked a group of 25 recently abstinent substance-dependent subjects to consider the timing, circumstances, and cognitive processes that occurred just prior to their most recent relapse (see Figure 1). The most critical item that distinguished between a “planned” from an “impulsive” relapse was the time from the initial decision to use to the time of actual use (the time required to obtain the drug was negligible). Approximately 40% of these subjects reported that the time from the initial decision to return to drug use to actual use was less than one hour, and 25% endorsed a return to use in less than one minute!⁹

Impulsive behaviors are observed in a wide range of psychiatric disorders, including substance use, bipolar, attention-deficit hyperactivity, antisocial and borderline personality, gambling, and eating disorders. Neuroimaging and preclinical studies suggest that impulsivity may share a common biological substrate that spans the spectrum of these associated psychiatric disorders [see Moeller et al.¹⁰]. Patients with impulsivity-related

disorders exhibit a consistent set of symptoms: an absence of planning, a disregard for consequences, a focus upon immediate gain, and an inability to inhibit maladaptive behaviors. In this review, we will focus on this broad concept of impulsivity (refined below) as a relevant process in both the etiology and perpetuation of addictive disorders. Although this behavioral concept likely pertains to all addictive disorders, including eating, gambling, and sexual addictions, we will use the substance use disorders as a template for this overview.

IMPULSIVE BEHAVIORS AS A RISK FACTOR FOR ADDICTIVE DISORDERS

Impulsive behaviors during childhood increase the risk for later substance use and abuse.^{11,12} For example, Caspi et al.¹³ identified a group of “undercontrolled” 3-year-old children who were impulsive, restless, and distractible. These children were then followed until they were 21 years old. Boys, but not girls, identified as under controlled at 3 years of age were almost three times more likely to exhibit alcohol-related problems upon follow-up than boys with a normal temperament. Wills et al.¹⁴ annually assessed drug use risk factors in several hundred children prior to any drug use. The temperamental variable of “self-control” was a prime domain of investigation. Self-control measured the ability of children to delay gratification and problem solve, as well as soothability and dependability; children with high self-control tended to approach a problem with a thoughtful plan of action, whereas children with low self-control were impatient, distractible, and prone to anger. Both “good control” and “poor control” in early childhood were significant mediators (in opposite directions) of later drug use.

Similarly, researchers at the University of Pittsburgh followed children from a young age until many experienced substance use problems. These investigators developed a construct of “neurobehavioral disinhibition,” which combined externalizing behavioral symptoms, decision-making, and negative emotion into a single factor score. This combination of traits was both highly heritable¹⁵ and predicted substance use disorders at 19 years of age.^{16,17} Similar predictive effects of disinhibitory traits upon early substance use, particularly in boys, have been reported by McGue et al.¹⁸ Children with a family history of substance abuse also have a higher incidence of impulsivity than low-risk children.¹⁹

Personality disorders associated with impulsivity, such as Antisocial Personality (or Conduct Disorder in adolescents) and Borderline Personality, are presumably reflective of trait behaviors that precede the development of substance use disorders. Persons with both of these personality disorders have extremely high rates of substance use pathology, with rates approaching or exceeding 50%. Most studies show that these personality traits and disorders precede the onset of substance use disorders (see review by Ottomanelli and Adinoff²⁰). Specific personality dimensions associated with impulsivity, including extroversion, sensation seeking and novelty seeking, differ across personality theory^{21–23} and self-report²⁴ measures (see review by Acton²⁵). Nevertheless, it is generally supported that personality characteristics associated with impulsivity are elevated in the addicted population.²⁶

The P300 evoked related potential (ERP) may offer a potential biologic marker of the disinhibited behaviors associated with an increased risk for substance use disorders. The

P300 ERP correlates with the attention devoted to a stimulus and the latency in attending to a stimulus (for reviews by Soltani and Knight,²⁷ Polich and Herbst²⁸). Several investigators have reported that the P300 is blunted in the children of parents with alcohol use disorders.^{29–31} Rather than predicting substance use per se, it appears that the P300 ERP may convey a non-specific marker for behavioral disinhibition.^{32–33} The increased maturation and expression of the dopaminergic system (associated with reward) relative to the serotonin system (associated with inhibition) during adolescence has also been associated with a heightened risk of substance abuse (and other impulsive behaviors) during this vulnerable period of life (see Chambers et al.¹² for review).

AUTOMATICITY, DISINHIBITION, AND DECISION MAKING

The previous section referred to impulsivity as a tendency to exhibit disinhibitory behaviors, evidenced by poor self-control, impatience, and poor planning. Impulsivity itself is a multidimensional concept,³⁴ consisting of traits such as acting without thinking (“motor impulsivity”), quick decision making (“cognitive impulsivity”), thinking about the present rather than the future (“nonplanning”), and difficulty in concentrating (“attentional impulsivity”).^{10,24,35–37} Others conceptualize impulsivity as an impairment in either facilitatory (increasing probability of action) or inhibitory (decreasing probability of action) processes³⁸ or the choosing of lesser immediate rewards over greater delayed rewards (temporal discounting).^{39,40}

Moeller has described the general concept of impulsivity as “... a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others” (p. 1784).¹⁰ This definition incorporates speed (“rapid”), the absence of forethought (“unplanned”), and quick decision-making (“without regard”). These are all relatively distinct cognitive and biobehavioral processes. The terminology used to describe specific aspects of impulsive cognitions and behaviors vary substantially between the developmental, social, cognitive, and biological scientists.

For clarity, we offer three relatively distinct “impulsive” processes. First, impulsivity may be the result of a “bad habit,” or an overlearned, routinized, and undesirable behavior that occurs in the presence of relevant cues. This relapse style has also been referred to as “automaticity.” A second impulsive process involves disinhibition. Disinhibition refers to the inability to suppress (or inhibit) previously reinforced behaviors that are no longer working to the person’s advantage. Both automaticity and disinhibition occur quickly—within seconds. The third impulsive process involves impaired decision making. Persons with impaired decision-making abilities assess the pros and cons of a situation and make a choice that does not maximize long-term survival. The decision-making process can take up to several minutes. Automaticity, disinhibition, and impaired decision making each involves distinct brain mechanisms.

Automaticity

In a seminal paper, Tiffany^{41,42} described a relapse process called “automaticity.” This process involves behaviors that are stereotyped (constant repetition of same behavior),

stimulus bound (associated with internal or external cues), effortless, and occur outside of conscious awareness. Thus, automaticity suggests a relative lack of control. Behaviorists refer to this process as habit learning (also called stimulus-response, procedural, or instrumental learning). Habit learning is defined as an over-learned sequence of behaviors that occur gradually through repetition, which develops in the presence of a salient (or meaningful and relevant) stimulus. Neurocognitive psychologists⁴³ have described automaticity as an attentional process called contention scheduling. Contention scheduling is an automatic selection process elicited through external stimuli involving little or no conscious awareness, and is used for handling routine behaviors that occur under familiar circumstances. Automaticity, habit learning, and contention scheduling all describe a neurocognitive process that occurs following constant repetition of a behavior. This repetition strengthens the neural associations between the stimulus and the response and results in the progressively smoother execution of an action.^{44,45} Interestingly, these automated behaviors are preserved even in amnesic patients who cannot recall learning the behavior.⁴⁶ In clinical terms, these behavioral sequences are repeated because in previously experienced situations, accompanied by similar internal and/or environmental cues, the same behavior has always been performed. This behavior was regularly rewarded, solidifying its expression.

Automaticity appears to be linked primarily to motor processes. Learning initially occurs through an associative process, whereby a new behavior is linked with reward (or punishment), arousal and emotional memories. This learning is called conditioned learning (e.g., Pavlov's dog) and is mediated, in part, by the mesolimbic dopaminergic pathway. This pathway originates in the midbrain ventral tegmental area (VTA) and terminates in the ventral striatum (nucleus accumbens), with glutamatergic connections to the amygdala [see Adinoff⁵ for review]. Over time and with repeated practice, however, conditioned learning shifts to more automatic processes.⁴⁷ These processes are then mediated by motor actions rather than emotional input and memory. As habit learning replaces conditioned learning, the anatomical focus shifts from the mesolimbic to the nigrostriatal dopaminergic pathway, which extends from the substantia nigra to the dorsal striatum.⁴⁸

From a clinical perspective, automaticity results in an addicted person who continues to use substances because "that is what I have always done." The alcoholic, when offered a drink, will accept it and drink it because that is the motor action most practiced and familiar when a drink is presented. As noted by Bill W. earlier, "Someone had pushed a drink my way ... and I had taken it" (p. 5).⁸ This fixed, automated, and ritualized behavior can only be overridden by a conscious effort and a desire not to use. The overlearned nature of these habits, unfortunately, make them very difficult to extinguish and they tend to persist even when the results become undesirable.^{49,50}

Disinhibition

Inhibitory control allows a previously potent, or practiced, response to be suppressed when the behavior is no longer to an organism's advantage. This control mechanism can be applied to both internal thoughts and behavioral acts. This inhibitory process is also referred to as supervisory attentional control, a top-down process in which attention is modulated by

inhibiting externally activated behaviors held in short-term memory (see van Zomeren and Brouwer⁵¹). (This top-down process is in contrast to the bottom-up process of automaticity or contention scheduling.) Thus, following the development of an overlearned behavior (i.e., habit learning), inhibitory control provides a mechanism to stop the automatic response.

“Disinhibition” refers to the inability to suppress (or inhibit) previously reinforced behaviors that are no longer adaptive for the individual. Problems with response inhibition may involve either thoughts (perceptual impulsiveness) or motor responses (motor impulsiveness).⁵² For example, a cocaine-addicted individual may be unable to suppress recurrent thoughts of using cocaine (perceptual impulsiveness) or the behavioral response triggered by cocaine-associated cues (motor impulsiveness).

Although the suppression of internal thoughts is difficult to assess in a laboratory setting, personality measures may offer insight into this process. We assessed personality traits in treatment-seeking, cocaine-addicted men ($n = 20$) and women ($n = 7$) without other active substance use disorders or lifetime Axis I (non-substance use) pathology [ages (mean $\pm$ SD) 39.4 ± 4.0 years old] and psychiatrically healthy matched male ($n = 14$) and female ($n = 12$) controls (34.9 ± 6.6 years old) using the Temperament and Character Inventory (TCI).⁵³ One measure associated with impulsive behaviors on the TCI is the Congruent Second Nature subscale. Subjects with lower scores in this domain believe that “their will power appears to be too weak to overcome many strong temptations,” whereas high scorers feel that their good habits allow them to “automatically act in accord with their long term values and goals.”⁵⁴ Cocaine-addicted subjects scored markedly lower (7.5 ± 2.6) relative to controls (11.2 ± 1.4) ($p < 0.0001$; see Figure 2). Thus, cocaine-addicted subjects with relatively recent cocaine use (two to four weeks abstinent) acknowledge that their “second nature” (or habit) is to use drugs and they question their inability to repel the force of these habits (i.e., they have poor response inhibition).

Given the inherent difficulty in measuring internal thought processes, research studies have focused on behavioral inhibition. Both animal and human studies have consistently supported an association between substance use disorders and reduced behavioral inhibition.^{55–60} Behavioral disinhibition is also observed in other psychiatric populations, such as Attention-Deficit-Hyperactivity Disorder (ADHD),^{61–63} Oppositional/Defiant Disorder, and Antisocial Personality Disorder (ASP), as well as in traumatic brain injury.^{64–66} Perhaps because of shared disinhibition, there is significant overlap between these disorders (particularly ASP and traumatic brain injury) and substance use disorders.

A number of neurocognitive paradigms demonstrate impaired behavioral inhibition in substance abusing populations, including the Stroop Color Word Task,⁶⁷ continuous performance tasks, Go/No-Go tasks, and the stop-signal task. The Go/No-Go task has a high frequency, rapidly presented Go signal alternating with a low frequency No-Go signal. The Go signal requires a motoric response, typically by pushing a button. The No-Go signal requires inhibition of this motoric response. In the Stop-Signal paradigm, the Stop signal occurs shortly following the Go signal, converting the Go signal *a posteriori* to a Stop (or no-go) signal.⁶⁸ Persons with poor inhibitory control are unable to withhold the pre-potent Go response when confronted with a Stop signal, and the Stop Signal task puts a higher load

on response inhibition relative to the Go/No-Go task. Kaufman et al.⁶⁹ have reported impaired inhibitory control on the Go/No-Go paradigm in subjects with active cocaine use relative to age-matched healthy controls. Hester and Garavan⁷⁰ further report that, relative to healthy controls, the magnitude of the cocaine users' impairment during a Go/No-Go task tends to increase proportionally with the demand on inhibitory control. Using the stop-signal task, Fillmore and colleagues^{58,71,72} have demonstrated reduced inhibitory control in cocaine-addicted subjects relative to healthy controls. Of particular importance was the finding that speed and accuracy of response to the Go signals, as opposed to the Stop signals, was not impaired in the patient group, thus revealing specific deficits in the inhibitory process.

Functional magnetic resonance imaging (fMRI) techniques have provided the spatial and temporal resolution necessary to explore the brain regions involved in inhibitory processes. This technique allows the blood flow in relatively circumscribed areas of the brain to be measured approximately every second, providing investigators the means to separate the neural response occurring during an appropriately inhibited motor response from a response that is not inhibited. Using fMRI techniques, Rubia et al.^{68,73,74} have described several brain regions that are activated during motor inhibition. This work shows activation of the mesial, medial, and inferior frontal and parietal cortices during inhibition (whether induced during the Go/No-Go or the Stop-Signal task), and specific activation in the anterior cingulate and inferior prefrontal cortex during the inhibition elicited in the Stop-Signal task. In the Go/No-Go study in cocaine-addicted subjects mentioned above, Kaufman et al.⁶⁹ found reduced activation of the anterior cingulate (and insular cortex) during inhibition in the cocaine-dependent subjects. Hester and Garavan have similarly reported that reduced anterior cingulate, as well as pre-supplementary motor and right superior frontal activation is associated with the inhibitory control deficit in subjects addicted to cocaine.⁷⁰ Furthermore, a heightened demand for inhibitory control was associated with increased anterior cingulate activation in the control, but not the cocaine, group. These findings suggest that the anterior cingulate, a brain region involved in emotional self-control, error detection, performance monitoring, and the adaptive response to changing conditions,⁷⁵ may show suboptimal activation in cocaine-addicted subjects under conditions requiring response inhibition.

The Stroop Color Word Task⁶⁷ requires subjects to read aloud words printed in incongruous colors (e.g., "yellow" printed in blue ink) under timed conditions. Thus, patients are required to inhibit the stronger tendency to state what the word says rather than its color. Individuals with prefrontal lesions perform significantly slower on this task and demonstrate a reduced ability to inhibit pre-potent responses.⁷⁶ In a group of cocaine-dependent and alcohol-dependent subjects, activation of the orbitofrontal cortex (assessed with positron emission tomography, or PET) during Stroop performance was associated with increased errors in the control population and decreased errors in the addicted group, suggesting that the OFC is not appropriately engaged in addicted subjects.⁷⁷ The orbitofrontal cortex is activated in situations that are unpredictable or uncertain, and can alter the reinforcement value of stimuli depending on recent experience (see below).

Finally, diffusion tensor imaging has demonstrated that reduced white matter integrity of the corpus callosum is related to impaired impulse control as assessed by a continuous

performance task and the Barrett Impulsivity Scale (BIS-11).⁷⁸ These findings suggest that disruptions in white matter connections between cortical brain regions may interfere with inhibitory processing following chronic cocaine use.

Decision Making

Decision making requires that internal states, sensory cues, and memories of past experiences are appropriately utilized to select the most advantageous response. As internal and external conditions are in constant flux, choosing the optimal strategy necessitates both flexibility and adaptation. The decision-making process involves two distinct features (see discussion in Bechara⁵²). First, the situation must include the evaluation of possible positive and negative outcomes. Second, the outcome must be uncertain and unpredictable. This is in contrast to response inhibition, which does not require an assessment of potential consequences as the outcome to any given choice is both certain and predictable. Although some have referred to impaired decision-making as “cognitive impulsiveness,”⁷⁹ decision-making requires that a response be temporally delayed. This delay allows time for reflection and planning prior to response selection. Thus, response inhibition must be sufficiently intact in order for decision making to occur.

Two broad categories of neurocognitive functioning are often considered in the assessment of decision-making, particularly in substance use disorders. The first process involves risk and delay. This process requires that the value of a reward or punishment, the time it takes before the selected outcome is experienced, and/or the likelihood of the outcome occurring must be weighted prior to making a decision (see discussion in Monterosso et al.⁸⁰). Long-term survival frequently requires the selection of choices with little chance of immediate payoffs but a high likelihood of long-term gains, or a high probability of small, instantaneous losses but a low likelihood of larger, more delayed losses, or a combination of both. The selection of smaller, immediate rewards with postponed but heightened punishments instead of early losses accompanied by larger, deferred rewards has been referred to as a “myopia for the future.”⁸¹ Thus, it is likely that the reader of this paper is successful in delaying gratification (having undergone a lengthy, low-reward/high-punishment education for the long-range goal of professional success), whereas the addicted subject with temporal myopia chooses the more proximal reward (or the relief of pain, anxiety, or craving) offered by a drug. This latter choice comes at the expense of neglecting the delayed and larger rewards provided by abstinence. In fact, one of the identifying features of addiction is the persistence of addictive behaviors despite the likelihood of negative long-term effects. Making a riskier choice may indicate a personality or cognitive style associated with increased sensation⁸² or novelty-seeking.⁸³ In these persons, rewards are more powerful than punishments. Alternately, a riskier choice may reflect the discounting of risk: punishments carry less weight than rewards.^{83,84}

Two common tests of delay and risk are the Delayed Discounting Procedure (DDP)⁸⁵ and the Gambling Task.⁸⁶ The DDP offers smaller-sooner rewards relative to larger-later rewards, typically using real or hypothetical money. For example, a subject may determine that \$1000 in one year is similar in value to \$5 immediately. The point at which a smaller-sooner reward equals a larger-later reward is called the indifference point. Using a series of

delays, an indifference curve can be plotted (see discussion in Bickel and Marsch⁴⁰). By comparing the indifference curves in substance abusing patients to those of healthy controls, a relative increase or decrease in perceived value versus temporal reinforcement can be determined between groups. A series of studies utilizing the DDP have demonstrated that persons addicted to cigarettes,^{85,87} opioids,^{88,89} and cocaine^{89,90} exhibit a rapid loss of subjective value for delayed outcomes relative to non-drug using comparison group (see review by Bickel and Marsch⁴⁰). Greater temporal discounting was also observed in problem drinkers relative to social drinkers⁹¹ and in heavy social and problem drinkers relative to light social drinkers.⁹¹

In the Gambling Task, subjects are offered four decks of cards. Two of the decks offer the possibility of large immediate rewards coupled with a risk of large punishments; the other two decks offer the possibility of small rewards with a risk of small punishments. Reward-punishment ratios are fixed so that selection from the first two decks will result in a net loss and selection from the last two decks will result in a net gain upon completion of the task. Optimal performance requires conservative choices (e.g., smaller rewards) to accumulate a larger payout upon task completion. A series of studies have shown that substance abuse patients perform more poorly on this task relative to controls; substance abusers are more likely to choose large immediate rewards despite the risk of higher losses, resulting in diminished net gains.⁹²⁻⁹⁹ Other groups, however, have not observed differences between substance use disordered patients and controls in Gambling Task performance.¹⁰⁰⁻¹⁰² In general, patients in the positive studies were typically studied shortly following active use and endorsed more than one drug of abuse. In contrast, the negative studies assessed abstinent, cocaine-addicted subjects. Other confounds may include the gender, intellectual abilities, and/or socioeconomic status of both the patient and control groups.

Response reversal, or set shifting, is the second major process involved in decision-making. Response reversal is required when response contingencies, such as the amount of reward, direction of reward (win or lose), or the time it takes to obtain a reward, are altered. When a response that previously produced a positive outcome suddenly becomes aversive, a reversal in cognitive and behavioral strategies is required to suppress the course of action that is now no longer appropriate. Thus, response reversal considers the positive and negative attributes of a potential response, followed by a decision to either maintain or change the present direction of responding. In laboratory tasks of response reversal, the directional salience is altered (i.e., stimuli that are initially rewarded become aversive) but the amount and probability of the rewards and punishments remain constant. The Wisconsin Card Sorting Test (WCST)¹⁰³ is a traditional test of response reversal. In contrast, the varying rewards and losses associated with any given stimulus in the DDP and Gambling Task are consistent throughout the task.

In the addicted subject, impaired response reversal becomes evident during the development of the addiction. Initially, a drug user will experience the substance as highly rewarding and without an associated downside. As drug use becomes progressively less pleasurable and accompanied by increasingly negative consequences, an intact response reversal process should dictate a change in behavior. The addict, however, will persist in using drugs. Thus, a

previously rewarded behavior is not adaptively reversed following a change in contingencies.

Both risk/delay and response reversal processes activate the OFC. The OFC assesses the internal and external environment and compares this experience to the expected milieu. If the expected milieu is, indeed, present, there is resonance and orbitofrontal activity is restrained. If an unexpected milieu is experienced, however, there is a “false” resonance, or mismatch, and the orbitofrontal cortex is activated.¹⁰⁴ Furthermore, the OFC plays an important role in the neural networks involved in positive reinforcement and has reciprocal connections with many brain regions that mediate reward.^{105,106}

Patients with lesions of the OFC make inappropriate decisions and are unable to process emotions appropriately, yet their global cognitive abilities (e.g., memory, learning, language, and attention) are often preserved. In general, these patients show a perseveration of non-advantageous behavior, with continued responding to stimuli that are no longer rewarding; a reversal of reinforcement contingencies does not reverse behavioral responses.¹⁰⁷ These patients may exhibit changes in personality, social behavior, and judgment characterized by irresponsibility and the repetition of inappropriate or self-destructive behaviors. In a seminal study by Bechara et al.,⁸⁶ patients with OFC lesions performed poorly on the Gambling Task but were not deficient in tasks of working memory. The reverse was seen in patients with dorsolateral prefrontal cortical lesions.

As might be expected, decision-making tasks requiring the selection of targets with varying salience (i.e., high vs. low monetary rewards, immediate vs. delayed gain, similar or dissimilar objects) appear to require processing by the OFC.^{108–112} With specific relevance to the tasks discussed above, the OFC is activated during the Gambling Task^{101,111,112} and a response reversal task.^{110,113} Several studies have indicated that OFC regional cerebral blood flow or energy utilization is decreased in cocaine, methamphetamine, and alcohol addicted subjects^{114–117} either at rest or following a saline infusion (see Figure 3). Low basal activity of the OFC may be related to the impaired decision-making observed in drug-addicted subjects. This is consistent with preclinical studies, in which OFC lesions decrease the time required to self-administer cocaine and lead to an erratic pattern of drug responding.¹¹⁸ Chronic experimenter-administered cocaine also produces a pattern of deficits on a reversal learning paradigm identical to those seen after lesions to the OFC.¹¹⁹ During administration of the Gambling Task in cocaine-addicted and control subjects, Bolla and colleagues¹⁰¹ reported increased right OFC activity in abstinent cocaine-dependent subjects relative to controls. Performance on the Gambling Task, however, was not significantly different between groups. Activation of the left OFC was significantly correlated with previous cocaine use. This work suggests abnormal OFC functioning despite similar performance measures, as well as a relationship between previous cocaine use and OFC activation.

Performance on decision-making tasks is also related to activity of the anterior cingulate and dorsolateral prefrontal cortex (DLPFC). Adinoff et al.¹⁰⁰ have reported that performance on the Gambling Task was positively correlated with basal activity (by SPLCT) of the anterior cingulate and DLPFC in both cocaine-addicted and healthy control subjects. Using a similar

paradigm. Tucker et al.¹⁰² also found a significant correlation between Gambling Task performance and anterior cingulate regional cerebral blood flow (rCBF) changes in cocaine-dependent subjects. Interestingly, however, the relationship was in the opposite direction as that reported by Adinoff et al.,¹⁰⁰ i.e., increased anterior cingulate rCBF was correlated with poorer Gambling Task performance. Differences between these two studies may be explained by the testing of recently using cocaine-addicted subjects (last use 4.6 ± 3.1 days prior to testing) in the Adinoff et al. study¹⁰⁰ vs. at least two weeks abstinence in the Tucker et al. study.¹⁰²

Using fMRI, Paulus et al.¹²⁰ demonstrated a relationship between anterior cingulate and DLPFC (among other regions) activity and outcome predictability during a two-choice decision task. This group has also shown blunted activation of the DLPFC, as well as the OFC, in methamphetamine-addicted subjects during this same decision-making task.¹²¹ Of particular interest is work by Volkow et al.^{115,122} demonstrating a positive correlation in both basal OFC and anterior cingulate energy utilization (by PET) with striatal D2 receptor number in cocaine-addicted subjects. This finding suggests a neurobiologic relationship between alterations in OFC and anterior cingulate functioning (relevant to decision making) and mesolimbic dopaminergic pathways (relevant to reward).

DESCRIPTIVE CONFUSION, CLINICAL IMPLICATIONS, AND FUTURE DIRECTIONS

Our review addresses a wide range of behaviors typically referred to as impulsivity. As discussed, however, these varied behaviors encompass discrete neurocognitive constructs and utilize distinct brain regions. Cognitive measures of these behaviors do not necessarily overlap^{87,123} and different measures (i.e., self-report questionnaires versus neurocognitive tasks) examining a single construct may not show a tight correlation.¹²⁴ Thus, significant confusion surrounding the exact meaning of “impulsivity” is evident. This is particularly problematic for those processes that occur extremely rapidly (automaticity and response inhibition) compared to those that require some delay (decision making). The use of “impulsivity” to describe both subsets of behavior portends difficulties among and across disciplines in the assessment and treatment of persons with these deficits. Therefore, it is critically important that any use of the term “impulsivity” be accompanied by a description of the specific neurocognitive process of-interest.

Furthermore, our use of automaticity, response inhibition, and decision making to describe impulsive behaviors is by no means a common conceptualization, and different approaches and definitions are likely seen both within and across disciplines and investigators. A neurocognitive psychologist, for example, may argue that our concept of response inhibition also overlaps with components of error-detection, distraction, delayed recovery, executive inhibition, motor inhibition, response retraction, response selection, decision making, or engagement of the inhibitory process. Finally, as the careful reader may have noted, there were no empirical studies of automaticity in addicted subjects. By definition, automatic behaviors require extended periods of practice and thus experimentally-derived behaviors are difficult to produce in the laboratory setting. The assessment of automatic drug use behaviors in the laboratory would be difficult, if not impossible, to deconvolve from the

affective and cognitive components of craving. It would also not be possible to compare automatic drug use behaviors to matched behaviors in control subjects.

The use of the cognitive tests may also have significant limitations in assessing impulsive behaviors in a clinically meaningful manner. For example, the use of monetary rewards in the DDP and Gambling Task may not have particular relevance to persons addicted to drugs. Bickel et al.⁸⁵ and Madden et al.¹²⁵ compared preferences for cigarettes (in nicotine dependent subjects) and heroin (in heroin dependent subjects) compared to monetary incentives in the DDP paradigm. These investigators found that drugs lose their delayed value more quickly than money does. The use of real versus simulated incentives may also yield different results. The ecological validity of cognitive tasks such as the Go-NoGo, Stop Signal Task, and response reversal task to the real world temptations of drug use may be limited.

Measures of these constructs may also vary with race, gender, intelligence, socioeconomic status, length of abstinence, drug of choice, the presence or absence of personality disorders, and other co-morbid conditions (i.e., gambling problems in a cocaine-addicted subject being tested with the Gambling Task). These potential confounds are often not taken into consideration when testing populations with impulsive disorders and/or control populations. However, all of these parameters cannot realistically be accounted for in any given study and therefore limit the generalizability of the findings.

Finally, despite the intuitive appeal of an association between automatic behaviors, deficits in response inhibition, and impaired decision making with a heightened risk for relapse, this relationship has yet to be demonstrated. Clearly, prospective studies assessing the relevance of impulsive behaviors and their associated neurobiologic disruptions with relapse risk are required prior to any definitive claims of impulse-induced relapse. In addition, it will be important to determine if the specific deficits are related to the subsequent relapse behavior. For example, the patient with response inhibition deficits and alterations in mesial prefrontal cortical functioning would be expected to relapse within seconds after being exposed to a drug. The drug-dependent patient with poor response reversal and low OFC perfusion would be hypothesized to relapse after several minutes of consideration. And the patient without impulsive behaviors might be presumed to relapse either after extensive planning and/or the intrusion of craving, anxiety, or stress. When the cognitive, behavioral, and biologic determinants of future relapse can be isolated, targeted psychosocial and pharmacological interventions can be utilized for directed treatment.

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FIGURE 1.

Time from initial decision to use of substance to actual use precipitating most recent relapse in abstinent substance dependent patients.

FIGURE 2.

Recently abstinent cocaine-addicted subjects reported significantly less Congruent Second Nature (from the Temperament and Character Inventory) than age-similar healthy controls. Low scores on Congruent Second Nature reflect one's sense that they will easily give into temptation out of habit.

FIGURE 3.

Cocaine-addicted abstinent subjects ($n = 55$) exhibit a decrease (blue) in the perfusion of the right and left orbitofrontal cortex relative to healthy controls ($n = 50$). (Coronal view at Talairach coordinate $y = 20$).