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Perspectives Emerging from Neuroscience on How People Become Addicted and What to Do about It

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This paper reviews the new ideas emerging from neuroscience regarding the question of why some people are compelled to use drugs. During the process of drug exposure, the brain's motivational system is changed in ways that co-opts the individual's motivational system. Changes in the brain's motivational structures along with changes in the brain's self-regulatory structures compel an individual to drug use. Ways to reverse those changes in an addicted brain have been identified, as have ways to enhance self-regulatory control. The information from neuroscience offers a new perspective on "loss of control" as well as offering implications for treatment.

KEYWORDS: genetics of addiction; neuroscience of addiction; incentive-salience; n-acetylcysteine; heart rate variability; kindling, self-regulation

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Several reasons exist for why social workers should be familiar with information emerging from neuroscience addressing the process of addiction. First, neuroscientists have attempted to make findings from their government-funded research available to the public. Social workers will probably receive inquiries from clients about the information they are hearing in the media. Second, findings from neuroscience have stimulated the development of new pharmaceutical interventions for treatment of addictions. Many clients will have questions about how these treatments work. Social workers should be prepared to answer their questions. Finally, the details from neuroscience validate the article of faith presented in Alcoholics Anonymous (A.A) about addiction being a physical condition and not a matter of choice. While A.A. explained alcoholism as an allergy to alcohol, through neuroscience, we have a better understanding of the nature of the physical processes removing choice from the process of addiction.

The focus on biology does remove the humanness and the individual variation from the process of addiction. Indeed, a reader of this paper stated: "There is something about reducing patients to biological beings, almost without unique qualities, that feels antithetical to social work practice." But, that is precisely why the neuroscience perspective offers a new perspective for social workers who are schooled in the importance of individual factors. Addiction involves fundamental brain structures that evolved long ago. In terms of the brain's structures involved in addiction, all mammals (rodents, people, primates) share motivational structures that function similarly. As with average body temperature and response to a cold virus, environmental factors such as culture and values do not affect these processes very much. Genetic differences, environmental opportunities for drug use, and stress exposure certainly influences one's risk for becoming addicted. However, once an individual has become substance dependent, the addictive phenomenon at the level of the brain with accompanying compelled behavior is the same for all

mammals. That is why addictions are so frightening. That is why it is useful to think of addiction as a disease. The automaticity of the reward-structure function dampens, even eclipses aspects of a person's cultural heritage, values, and humanness. These structures and their biochemistry are the strongest influences on an addict's behavior, an addict's desires, and an addict's thought processes. Knowledge of the biological underpinnings of addictions will hopefully render beginning practitioners much more respectful of the struggle their clients face and may also help clients appreciate why their compulsive drug use really is a disease. The neuroscience perspective on addiction does paint a bleak picture. However, social workers must remember that they have seen addicts recover. Here is where culture, values, and human connection can come into play.

This paper will review findings from neuroscience and related areas on the physical processes occurring as a person becomes addicted. In the latter half of the paper, research is discussed that offers suggestions for altering physical processes in ways that foster sobriety.

THE CHANGES IN FEELINGS AND BEHAVIOR MEDIATED BY DOPAMINE RELEASE

Early in the field, addiction was defined by the presence of withdrawal symptoms and by the build-up of tolerance to a drug. Modern ideas place greater emphasis on compulsion as the essential phenomenon in addiction (O'Brien, 2008), equating addiction with compulsive drug taking. Researchers have identified changes associated with the development of compulsion.

In 1987, Wise and Bozarth, neuroscientists, made the observation that all drugs resulting in compulsive use share the property of inducing release of dopamine by neurons whose cell bodies are located in the Ventral Tegmental Area (VTA) onto neurons in the shell of the Nucleus

Accumbens. Earlier work had shown that the presentation of natural reinforcers (food and sex) or cues indicating that natural reinforcers are available, also induce release of dopamine into the shell of the Nucleus Accumbens and forebrain structures (Dackis & O'Brien, 2005; Montague, Hyman, Cohen, 2004; Nestler, 2005). Dopamine connections from the VTA to the Nucleus Accumbens became known as the "reward circuitry," because animals exert effortful responding to achieve a surge in dopamine from the VTA. Moreover, these same structures had been identified as part of the circuitry for self-stimulation where animals would self-administer electrical impulses at seemingly endless rates (Berridge & Kringelbach, 2008; Peciña, Smith, Berridge, 2006; Robinson & Berridge, 1993; Wise & Rompre, 1989).

It was easy to move from the observation that animals would work for the release of dopamine into the Nucleus Accumbens, to the assumption that dopamine induced a state of pleasure in the animal. However, it just turned out not to be true. Kent Berridge's work on reward structures challenged the idea that dopamine mediated the subjective state of pleasure. Moreover, in discrediting the idea that dopamine release mediates a pleasurable state, Berridge and colleagues, along with others, have been able to elucidate those functions that reward structures (dopaminergic projections from the VTA) do subserve.

Several observations led Berridge and colleagues to abandon the idea that dopamine release mediates pleasure. First, it was noted that dopamine is released in the shell of the Nucleus Accumbens if an animal is subjected to shock or restraint as well as when exposed to cues signaling the availability of food and drugs (Faure, Reynolds, Richard, & Berridge, 2008; Pruessner, Champagne, Meaney, & Dagher, 2004; Salamone, Correa, Farrar, & Mingote, 2007). Second, dopamine continues to be released as an animal works for food and sex, but when the animal is eating or ejaculates, dopamine is no longer being released (Baldo & Kelley, 2007;

Berridge & Robinson, 1998). Thirdly, when researchers destroyed the VTA, the animal continued to display signs of enjoying food if passively fed, but the animal would not work for the food (Berridge and Robinson, 1998; Robinson & Berridge, 2008). These observations led to the notion that dopamine release was about "wanting" rather than "liking." Thus, the usual motivation for behavior (when people feel good they repeat their behavior) cannot explain addiction.

Subsequent work further refined the function of the reward circuits. When an animal experiences a surge of dopamine release from the VTA, the animal becomes alert, intensely aware, and is in a state of readiness to make associations between environmental cues and behavior: the animal is ready to learn. Further, those behaviors that lead to the dopamine surge will be repeated more avidly; that is, a compulsive behavior directed toward inducing more dopamine release is observed (Robinson & Berridge, 2008). Berridge and colleagues (Robinson & Berridge, 1993) refer to this component of dopaminergic function as "incentive salience". But, Robinson and Berridge (2008) caution that "incentive salience" is more than just learning. Many associations are learned (e.g., learning to tie a shoe to avoid tripping over a shoe lace) without resulting in compulsive behavior (Robinson & Berridge, 2008). Thus, learning alone cannot account for compulsion. However, even though incentive salience is more than learning, dopamine release does facilitate learning. The VTA sends dopaminergic projections to the hippocampus, an area involved in creating memories. Dopamine facilitates the changes in dendritic structure undergirding the creation of new memories (Lemon & Manahan-Vaughan, 2006).

Salmone and others have further refined the function of dopamine. Effortful responding seems to require dopamine. This conclusion rests on the following observations. When

dopamine function is inhibited, animals switch their preference to unpalatable foods that they do not have to work for as opposed to better-tasting food that requires effort to obtain. Animals whose levels of dopamine have been chemically depleted will actually consume more food that they do not have to work for than control animals (suggesting that dopamine is not affecting the pleasure associated with eating the food). Rather, without dopamine, the cost of putting in effort is just too great. To put it in colloquial terms, animals with inhibited dopamine tone are lazy and unmotivated (Font et al., 2008; Niv, Daw, Joel, & Dayan, 2007; Salamone & Correa, 2002; Salamone et al., 2007).

Berridge's recent research has identified brain structures and neurotransmitters that do mediate pleasure (Berridge, 2003; Berridge, 2007a; Berridge, 2007b; Berridge & Kringelbach, 2008; Berridge, Robinson, & Aldridge, 2009; Peciña, Smith, & Berridge, 2006). Berridge's operational definition of pleasure was particular facial gestures which accompany the eating of preferred foods. Through processes of injecting various neurotransmitters into various structures or destroying particular structures, and examining how these changes impacted signs of enjoyment, Berridge identified those brain structures involved in pleasure. The parabrachial area, certain parts of the Nucleus Accumbens in the rostral and dorsal one-quarter of the medial shell (Berridge & Kringelbach, 2008), and the Ventral Pallidum are critical structures for the experience of pleasure. The neurotransmitters identified as enhancing pleasure are cannabinoids, GABA, and opioids. Destruction of the ventral pallidum precludes signs of enjoyment (Berridge et al., 2009). Destruction of areas involved in working for rewards, does not impact signs of enjoyment (Robinson & Berridge, 1993). Thus, the bottom-line from Berridge and colleagues is that the "wanting" system is distinguishable from the "liking" system anatomically and chemically.

KINDLING AND ADDICTION

In addition to studies examining what happens in the brains of animals when they consume drugs that lead to compulsive use, researchers have also developed animal models for the process of becoming addicted. They wanted to test their assumption that a brain that had been exposed to an addicting drug, e.g., a stimulant such as amphetamine or cocaine, is different from the brain of a naïve animal. Consistent with the hypothesis, researchers noted that an animal given low doses of a stimulant drug over a series of days, will exhibit an increase in the amount of dopamine released from VTA neurons. Moreover, the behavioral response to the stimulant also augments over time. The same dose of stimulants will result in much more locomotion in a drug-experienced animal than in a naïve animal (Robinson & Berridge, 1993). In humans as well, repeated exposure to amphetamines results in sensitization of the response to the drug (Boileau et al., 2006; Leyton, 2007).

In seeking to explain the sensitization process to the stimulant, researchers analogized the process to a process called "kindling" which had been observed in animals subjected to electrical stimulation of the brain. If an animal is given a small dose of electrical stimulation over a series of days, the small dose will eventually elicit a seizure, although this dose would not be sufficient to elicit a seizure in a naïve animal (Post & Weiss, 1988). Borrowing the term from the electrical stimulation research, the terms "kindling" and "sensitization" became interchangeable when referring to a brain that had been subjected to repeated doses of an addicting chemical over time.

A kindled/sensitized animal exhibits changes in behavior in addition to just responding more strongly to an injection of the addicting drugs. Exposure to cues associated with drug

delivery, trigger release of dopamine from the VTA (Berridge & Robinson, 1998). Animals work assiduously for the delivery of their drug. Essentially, the action of the brain's motivational system gets hijacked by the drug. This capture of the brain's motivational system has many manifestations.

The VTA sends projections to many structures in the brain, including the Prefrontal Cortex (PFC). While parts of the PFC are involved in self-control and inhibiting strong impulses (to be discussed below), the PFC is also involved in planning for goal attainment and focusing attention in the face of distracting input. The VTA, through dopaminergic input, updates the PFC about the current value of rewards. The VTA, in a sense, informs the PFC about what thoughts should be brought to awareness (Montague et al., 2004).

When drug-associated cues trigger the release of dopamine from the VTA to the PFC, the thinking processes of the individual get captured in the service of obtaining more drug (Dackis & O'Brien, 2005). Distracting thoughts, perhaps about other goals, get gated out before reaching awareness. Thoughts and planning relevant to the goal of obtaining more drug become automatic. It just may not occur to the person to think about competing goals. Planning for more drug use dominates the individual's conscious awareness (Miller, 2000; Montague et al., 2004). Indeed, in addicted people, drug-associated imagery grabs attention. Their eyes move automatically to track the drug-associated images (Field, Mogg, & Bradley, 2006).

The VTA and the Nucleus Accumbens also projects to the anterior cingulate, an area in the PFC. Cues associated with drug use will trigger the release of dopamine in the anterior cingulate. The anterior cingulate is believed to mediate the subjective experience of craving. Once the anterior cingulate is activated, craving is experienced, which, of course, will bolster the urge for further drug-seeking (Dackis & O'Brien, 2005). Indeed, for addicts, cocaine-associated

drug paraphernalia or memories of use induce activity in the anterior cingulate (Childress et al., 1999; Kilts et al., 2001). Recent evidence suggests that an area adjacent to the cingulate, the insula, may also play a role in craving (Naqvi & Bechara, 2009).

During the process of kindling development, the Nucleus Accumbens plays a major role. With chronic use of a drug, the VTA augments release of dopamine to the dorsal striatum (a structure located above the Nucleus Accumbens and the VTA), where "must do" behavioral programs are activated (Belin & Everitt, 2008; Everitt et al., 2008; Everitt & Robbins, 2005; Volkow et al., 2006; Yin & Knowlton, 2006). Once the VTA is activated, drug-seeking behavioral programs become much more automatic, and the individual's behavioral routines for drug-seeking become activated.

Drugs that augment dopamine function increase motivation across a broad range of activity. When dopamine drugs are in the body, gusto for a wide variety of reinforcers is enhanced. Not only will an animal on a stimulant work harder for drug delivery, but the animal will work harder for food and sex as well (Berridge & Robinson, 1998; Berridge, 2007a; Nocjar & Panksepp, 2002; Robinson, & Berridge, 1993; 2008). When people are given dopamine enhancing drugs, they also display increased goal directed activity for a wide variety of reinforcers. Interestingly, for Parkinson's disease patients who are treated with dopamine-enhancing drugs, gambling and hyper-sexuality often emerge as problems (Bostwick, Hecksel, Stevens, Bower, & Ahlskog, 2009; Dood et al., 2005; Stamey & Jankovic, 2008). Then there are the long-term effects of having been exposed to stimulant drugs. Animals whose brains have been kindled with stimulants display greater release of dopamine to both stress and natural reinforcers. Moreover, exposure to a conditioned stimulus for a drug will induce working for a wide range of rewards (Berridge, et al., 2009). The animal findings are observed in people as

well. Bechara (2001; 2003) identified a subgroup of addicts who, when exposed to monetary rewards while sober, exhibit exaggerated autonomic responses (e.g., heart rate acceleration).

Volkow and colleagues (Goldstein & Volkow, 2002; Volkow, Fowler, Wang, 2004) have proffered the hypothesis that addicts have an impaired capacity for motivation to seek natural rewards (food, sex, etc.). They base this hypothesis on the lower level of activation of the anterior cingulate and PFC observed in addicts who may have been still in withdrawal, in response to erotic stimuli and other natural reinforcers (Aguilar de Arcos, Verdejo-Garcia, Peralta-Ramirez, Sanchez-Barrera, & Perez-García, 2005; Garavan et al., 2000). The idea that addicts are hypo-responsive to natural reinforcers contradicts the notion that sensitization to drugs creates a cross-sensitization to other stimuli that activate the VTA: stress, sex, food. It is possible that both phenomena are true. During withdrawal, addicts are depleted in their dopamine reserves (Knoblich et al., 1992; Leyton, 2007; Schulteis & Koob, 1996). With depleted dopamine reserves, cocaine addicts are less responsive to reward, even cocaine associated cues (Leyton, 2007). Dopamine depletion long after cocaine addicts have discontinued drug use is evidenced by the finding that visual responses controlled by dopamine are aberrant long after sobriety (Desai, Roy, Brown, & Smelson, 1997; Roy, Roy, Williams, Weinberger, & Smelson, 1997). Thus, until levels of dopamine are restored, some addicts in withdrawal may be hypo-responsive rather than hyper-responsive to natural rewards.

CHANGES IN AN ADDICTED BRAIN PREDISPOSING TO RELAPSE

The operational definition of a kindled/sensitized brain is that in response to a stimulant drug, an exaggerated release of dopamine from neurons in the VTA is observed. It is now appreciated

that many changes are evident in the brains of animals who have received low doses of stimulants (both passively or after lever-pressing) over a period of time (Kalivas, 2005).

Clinically, perhaps the most troubling aspect of addiction is that even after long periods of sobriety, people relapse. Researchers have modeled the phenomenon of relapse in animals. After kindling the brain with stimulants, researchers have extinguished lever-pressing for the drug by failing to provide the stimulant following lever-pressing. Animals whose drug-seeking has been extinguished, can once again be induced to lever-press for drugs through three procedures: (1) delivery of a priming dose of stimulant; (2) presentation of a cue, such as a light that was present when the animal learned to lever-press for the stimulant; or (3) exposure to a stressor such as shock (Kalivas, Volkow, Seamans, 2005). In examining the many changes in the brains of addicted animals, researchers have sought to identify two types of changes: those changes that sustain working for drug delivery; and those that reinstate working for drug delivery after extinction (Kalivas, 2005).

While we have focused on the dopaminergic system, cues associated with drug use become understood by higher structures in the brain, parts of the cortex. Then a signal is sent from the cortex to the motivational structures. At this point, glutamate, the brains primary excitatory neurotransmitter, comes into play. Studies blocking the delivery of glutamate (a neurotransmitter) to neurons in the core of the Nucleus Accumbens from neurons in the dorsomedial PFC suggest that glutamate is required for the reinstatement of drug-seeking after extinction (Cornish & Kalivas, 2000; Di Ciano & Everitt, 2001; Everitt & Robbins, 2005; Knacksted & Kalivas, 2009; McFarland, Lapish, & Kalivas, 2003). Moreover, it was noted that elevated levels of glutamate are released on the cells into the core of the Accumbens from neurons in the PFC in the brains of addicted animals (Kalivas et al., 2003).

Next, Kalivas and his colleagues wanted to identify the changes that might break the chains of an addicted animal. They knew, as indicated above, that high levels of glutamate delivered to the core of the Nucleus Accumbens are associated with drug reinstatement. But, what accounts for the elevated level of glutamate to the core of the Nucleus Accumbens in an addicted animal? Perhaps if the reasons for the enhanced glutamate could be found, something could be done to alter the addicted brain so drug relapse would not occur. In this regard, Kalivas and colleagues found that an exchanger protein that moves glutamate out of the cell while moving cysteine (an amino acid) into the cell operates slowly in addicted animals.

Kalivas' research does have practical implications. It has led to the discovery of genetic variations predisposing individuals to addiction to stimulants. Persons with particular variants of Homer proteins, associated with the level of the exchanger present in the brain, are more susceptible to addiction to cocaine (Dahl et al., 2005; Szumlinski, Ary, & Lominac, 2008). Moreover, delivery of a synthetic version of cysteine called N-acetylcysteine can induce the cysteine/glutamate exchanger protein to function more rapidly than it would in untreated addicted animals. Given the trigger of drug cues, less glutamate is released into the core of the Nucleus Accumbens, and drug-seeking-reinstatement is abrogated (Kalivas & Volkow, 2005; McFarland et al., 2003; Moussawi et al., 2009). In regard to people, N-acetylcysteine (which causes the cysteine/glutamate exchangers to function at a faster rate) has demonstrated efficacy in the treatment of compulsive gambling and cocaine addiction (Larow et al, 2006; Grant, Kim, & Odlaug, 2007). It reduces cravings to cocaine drug cues (LaRowe et al., 2007) and reduces impulses to gamble by 40% (Grant, et al., 2007).

Reasons exist for believing that N-aceytlcysteine will be a major improvement over past pharmacological interventions. Although drugs (naloxone, acamprosate, modafinil) are available

to reduce cravings given exposure to drug cues, the mechanism of action of these therapeutic drugs is to alter the general operation of the brain. While naloxone can reduce the craving for cocaine triggered by conditioned stimuli, naloxone also reduces desire for natural rewards, as well as inducing lethargy and cognitive slowing (Williams & Woods, 1999; Physician's Desk Reference, 1995, p. 967). Moreover, in animals, naloxone induces conditioned place aversion (Berridge & Robinson, 1998). Similarly, acamprosate, a drug which will reduce the expression of particular subunits of receptors for glutamate, will decrease glutamate signaling generally, although evidence for a major impact on reward system is scant (DeWitte, Littleton, Parot, & Koob, 2005). Modafinil similarly alters glutamate signaling (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005). In contrast, N-acetylcysteine intervenes in a targeted way to reverse alterations specific to a kindled brain.

N-acetylcysteine is sold in health food stores. It is used in the treatment of acetaminophen overdose, cystic fibrosis, and chronic obstructive lung disease. No major adverse effects have been noted, although transient nausea, vomiting, and flatulence have been observed (LaRowe et al., 2006). It will be interesting to observe whether N-acetylcysteine will become a major treatment for addiction.

CONTROL OVER MOTIVATIONAL STRUCTURES

Berridge and Kalivas have focused on changes in the reward structures in an addicted animal. Changes in reward structures can explain why there is a strong drive to seek a drug. In a sense

the addicted brain has learned too well (Hyman, 2005; Kelley, 2004). But, many believe that changes in the reward structures provide only half the story. Overwhelming compulsion arises from contributions of a more intense motivational system (strong impulse) along with a failure of brain structures to inhibit the dopaminergic motivational system (Jentsch & Taylor, 1999). When considering the factors that result in compulsive drug taking, attention to inhibitory control over impulses should be examined.

In the literature, problems with impulse control have been operationalized in various ways including repetitive behaviors, inability to delay gratification, inability to suppress strong initial impulses, lack of premeditation prior to action, insufficient sampling of relevant information prior to decision making, and resistance to extinction (Garavan, Kaufman, & Hester, 2008). As a group, substance abusers and gamblers have problems with impulse control. They prefer immediate, small rewards to larger, delayed rewards (Bechara, 2005; Coffey, Gudleski, Saladin, & Brady, 2003; Simon, Mendex, & Setlow, 2007). They think less before making decisions (Bechara, 2005; Bechara, Noel, & Crone, 2006) and perform more poorly on tests that require the blocking out of distractions (e.g., the Stroop test) (Crone, Cutshall, Recknor, Van den Wildenberg, & Bechara, 2003; Potenza et al., 2003). They are motorically hyperactive and have trouble inhibiting responses (Colzato, van den Wildenberg, & Hommel, 2007; Hester & Garavan, 2004; Garavan & Stout, 2005). They have trouble with tasks involving withholding a response to particular stimuli (Beveridge, Gill, Hanlon, & Porrino, 2008). They make riskier choices (Fishbein, 2005; Verdejo-García, Perales, & Perez-García, 2007). They fail to respond to feedback indicating they made a bad choice and display reduced awareness of having made errors (Garavan & Stout, 2005).

Researchers have identified brain structures and neurotransmitters involved in inhibiting impulses and behavior (Dalley, Cardinal, Robbins, 2004). Serotonin is believed to play a large role in inhibiting impulses (Brewer & Potenza, 2008; Bizot, Le Bihan, Puech, Hamon, & Thiébot, 1999). Areas in the PFC are believed to house structures allowing for executive function and self-regulation. With damage to the ventromedial PFC, a loss of self-directed behavior in favor of more automatic sensory-driven behavior ensues (Bechara, 2005).

Consistent with the poor performance on tasks requiring inhibitory control, substance abusers show deficiencies in the inhibitory systems which might counteract strong motivational impulses (Bechara, 2005; Garavan & Stout, 2005). Alcoholics who have a stronger family predisposition to alcoholism (early onsetters), have lower levels of serotonin metabolites in the cerebrospinal fluid (Fils-Aime et al.,1996). During tasks requiring inhibition and executive function, stimulant addicts display lower levels of metabolism and blood flow in the PFC (Beveridge, et al., 2008; Garavan & Stout, 2005). Lower levels of activation of areas in the PFC (ventromedial PFC, left posterior cingulate cortex, and the right striatum) during tasks requiring cognitive control, predict post-treatment abstention from cocaine (Brewer, Worhunksy, Carrol, Rounsaville & Potenza, 2008).

Presently, it is unclear whether problems with impulse control precede or follow exposure to drugs (Beveridge et al., 2008; Garavan et al., 2008). However, the finding that similar changes in PFC are observed in primates after drug exposure, suggest that chronic stimulant use can impair PFC function (Beveridge, et al., 2008). Ironically, the initial, short-term impact of stimulants improves impulse control (Fillmore, Rush, & Hays, 2005; Garavan et al., 2008; Wade, de Wit, & Richards, 2000), while resulting in impaired control with chronic use (Franklin et al., 2002). Regardless of the reason for poor executive control (also referred to as

self-regulation), strengthening self-regulatory control should be addressed in treatment as will be discussed in the final section of this paper.

PREDISPOSING FACTORS TO BECOMING ADDICTED

Genetic contributions account for 60% of the risk for substance abuse (Kreek, Bart et al., 2005; Kreek, Nielesen, et al., 2005). Identifying the gene variants and temperaments that place persons at higher risk for substance abuse is important for two reasons: First, once the function of the protein variant promoting addiction is elucidated, interventions to reduce the risk might be found; Second, prevention efforts can be developed that are particularly influential for persons with temperaments that place them at risk for drug abuse.

Compulsive drug use arises from contributions of a more intense motivational system along with a failure of structures in the PFC to inhibit the dopaminergic motivational system. Allelic variations (i.e., variation in the version of a gene that a person inherits) in genes specifying proteins functioning in the dopaminergic structures and genes specifying proteins whose functions are relevant to inhibitory structures, have been examined. Some of the allelic variants seem to be implicated in both the function of dopamine structures as well as a less inhibited temperament. While it is beyond the scope of this article to survey all of the genes identified as increasing the risk for addiction, some of the more prominent variations with clear relevance to dopaminergic reward structure or executive function are mentioned.

With regard to functions of the dopaminergic motivational structures, alleles of the dopamine 4 receptor, the dopamine 2 receptor, and the dopamine transporter predict substance abuse as well as Attention Deficit/Hyperactivity Disorder (Brewer & Portenza, 2008). In both

rodents and humans, hyperactivity and impulsivity increase the speed of developing compulsive drug use (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Boileau et al., 2006; Verdejo-García, Lawrence, & Clark, 2008). Poor impulse control at age 10 to 12 predicts drug use at age 19 (Tarter et al., 2003). Allelic variations in genes related to serotonin function have been studied with regard to impulsivity, but findings have been somewhat inconsistent (Kreek et al., 2005; Verdejo-García et al., 2008).

Volkow, the director of NIDAA, has focused on Type 2 dopamine receptors. Type 2 receptors for dopamine (D2R) are expressed in the Nucleus Accumbens and the Striatum (an area to which the N. Accumbens projects). With regard to function, D2R are found on the axons of dopamine neurons and decrease the probability of the neuron's firing. D2R are therefore probably inhibitory to the dopamine system (Goodman, 2008), although not always appreciated as such (Nader, Czoty, Gould, & Riddick, 2008; Volkow, Fowler, & Wang, 2004). The density of D2R observed in the striatum has significance for substance abuse. Those drug-naive persons with low density of D2R in the striatum experience cocaine more positively (Volkow et al., 2004; Volkow, Wang et al., 2002). This is consistent with animal findings. Rats that more avidly self-administer stimulants have lower D2R density in the Nucleus Accumbens (Dalley et al., 2007), as do monkeys (Nader, et al., 2006). D2R density also relates to temperament. In rats, those with low D2R density in the Nucleus Accumbens are more impulsive (Dalley et al., 2007). In humans, those who are at genetic risk for low D2R density are similarly more impulsive (Verdejo-García et al., 2008). For impulsive people, the Taq1 allele for the D2 receptor is less readily expressed and may therefore serve to identify those with lower D2R density (Pohjalainen et al, 1998). However, environmental influences can also influence the

density of the D2R in relevant structures. Stimulant drugs will lower D2R density (Dalley et al., 2007).

While D2R receptor density is relevant for the function of structures in the dopaminergic reward/motivation systems, D2R density is related to the function of brain structures involved in self-regulation as well (Volkow et al., 2004; Volkow et al., 1993).

Life experiences may also place individuals at risk for addiction. In the early work on kindling the brain in rodents, it was noted that extreme stressors can also result in an augmented release of dopamine released by neurons in the VTA onto neurons in the Nucleus Accumbens. Thus, previous exposure to strong stressors can kindle the brain and elevate the risk for becoming addicted, given drug consumption (Robinson & Berridge, 1993). Michael Meaney has focused on the impact of early maternal deprivation on the brain. Early maternal deprivation is associated with a stronger response to stress. Among those individuals with early maternal deprivation, more dopamine is released into the N. Accumbens when they are given a stressful task to perform (Pruessner et al., 2004). The brains of those animals experiencing early deprivation operate as if they were previously kindled. Thus, persons who were neglected or abused as children can be expected to be at risk as well. This prediction is consistent with findings in the literature indicating that child abuse does elevate the risk for addiction (Shipman & Taussiq, 2009).

How individuals developing addictions because of a genetic predisposition differ from addicts without a genetic predisposition, has been addressed in the literature on alcoholism. On average, alcoholics with a genetic pedagogy develop alcoholism much earlier in life. Often, they cannot identify a period in their lives when they drank in a controlled fashion. They display compulsion very soon after being introduced to alcohol (Littrell, 1991a). Evidence suggesting

that treatments should vary for those with a genetic predisposition versus those without has not emerged. But, certainly prevention efforts for the children of those addicts with a strong family history should be made.

IMPLICATIONS FOR TREATMENT

Addiction to drugs involves both triggering of craving and intense urges through the VTA along with a failure of inhibition of these impulses. In treating substance abusers, strategies should be developed to avoid triggering strong urges and craving. Since it may be impossible to totally avoid triggering urges, ways to self-regulate or inhibit these urges need to be developed. Thus, improving self-regulation is a goal of effective treatment.

Avoiding the Triggering of the VTA and Enhancing Coping When It Is Triggered

The animal research has identified reliable triggers to drug-seeking reinstatement. Stress, a small amount of the drug, and environmental cues previously associated with drug use, will trigger release of dopamine from the VTA and will initiate drug-seeking. The triggers for drug reinstatement in animals are mirrored in the relapse precipitants literature. Stressful events are the most frequent precipitant to relapse (Littrell, 1991b). Exposure to drug cues can precipitate relapse (Robinson & Berridge, 2008), and A.A. recommendations include the avoidance of "slippery places." A.A.'s acronym, HALT, admonishes that members should avoid being hungry, angry, lonely, or tired. At least for the hunger component, ghrelin, a hormone released during food deprivation, can activate the VTA (Abizaid et al., 2006; Cummings, Naleid, &

Lattemann, 2007; Jerlhag et al., 2007; Tessari et al., 2007). Moreover, glucose deprivation is associated with release of dopamine into the Nucleus Accumbens (Adler et al., 2000). Thus, neuroscience research suggests that A.A.'s admonition to avoid hunger is good advice.

During treatment, it is important to identify personal triggers. These triggers might be external cues (being with a former drug partner, returning to an old neighborhood, TV advertisements) or internal cues (experiencing urges, experiencing stress). When possible, triggers should be avoided. However, it may not always be possible to avoid all triggers. Then, the objective is to link coping skills to these triggers (Carroll & Onken, 2005).

While treatment involves developing awareness of triggers, it is important not to spend much time describing or remembering the triggers. Focusing on what Mischel and Ayduk (2004) refer to as the "hot" dimensions of urges and cues will activate the automatic, drug-seeking behavioral programs. Focusing on the "what to do instead" recruits more self-regulation and executive function. Walter Mischel and colleagues have studied the process of self-regulation in children. Mischel examined how some children were able to delay gratification, choosing to deny themselves an immediate delicious treat in order to eat a larger treat later. Those children who were able to restrain from eating a delicious treat immediately, employed distracters and spent *less* time attending to their eventual reward (eating the treat) (Metcalfe & Mischel, 1999). They avoided dwelling on the hot dimensions of eventual success and focused on cold distracters of "what to do right now". Extrapolating from these findings, focusing on what to do instead might be more successful than dwelling on urges.

A.A. has gainsaid the importance of a lack of willpower in explaining drug-seeking (Littrell, 1991b). A.A. seems to regard willpower as a trait with which one is born. Mischel and Ayduck (2004) view willpower as a coping skill. In addition to research on delay of

gratification, Mischel examined the behavior of children who were able to solve more math problems while resisting playing with an attractive toy. Those children who were better able to resist the toy did not differ in the number of times they gazed at the toy. Rather, they made more self-statements directing themselves back to the math problems. Consistent with the findings on delay of gratification, those children who were able to resist eating delicious food focused on the cold features of the candy bar (the slick wrapper) rather than imagining the hot features (delicious taste) of the candy bar (Metcalfe & Mischel, 1999). Additionally, if children were given a specific task to think about, they could better refrain from eating the delicious food (Littrell, 1991b; Mischel & Ayduck, 2004). This research has demonstrated that where a person focuses his/her attention is a modifiable skill. Since judicious focusing can function to delay gratification, modifying a person's attention patterns can bring about (in lay terms) an increase in willpower.

Ways to Increase Executive Control

The general issue of self-regulation has emerged as a focus of research in both neuroscience and social psychology. A recent October 2008 National Institute of Drug Abuse (NIDA) sponsored conference at Colombia University (Transdisciplinary Approaches to Mechanisms of Behavior Change in Alcohol: Connecting Basic Science Discoveries to Behavior Change Research), focused on the topic of self-regulation/executive control. When addressing the topic of self-regulation/executive control, the function of the PFC is relevant. By bringing in the function of the PFC, links to seemingly unrelated areas of research are introduced. Parasympathetic tone is linked to the function of the PFC and to self-regulation/executive control.

Parasympathetic Tone

Parasympathetic tone, measured by greater heart rate variability (HRV), has been a focus of attention in its own right (Porges, 2007; 2009). It helps to know a bit about the parasympathetic nervous system. Control over the heart and other organs is exercised by the autonomic nervous system. The autonomic nervous system has two branches: the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). The PNS decreases heart rate and increases heart rate variability (variability in the time elapsed between beats) to ensure better coordination with breathing. The SNS has the opposite effect (Porges, 2007; 2009).

It has long been known that greater heart rate variability is a protective factor against cardiovascular disease (Hayano et al., 1990; Hayano, Yasuma, Okada, Mukai, & Fujinami, 1996). In fact, the same areas of the brain mediating self-regulation/executive-control also regulate parasympathetic control over bodily functions (Ahern et al., 2001; Thayer, 2006; Thayer & Lane, 2000). Recent research connects greater heart rate variability with stronger PFC function and better executive control. Those individuals with greater heart rate variability are better able to take turns; to inhibit strong impulses; to cope with stressors; and to better focus attention (Allen, Matthews, & Kenyon, 2000; Fabes & Eisenberg, 1997; Hansen, Johnsen, & Thayer, 2003; Segerstrom & Solberg Nes, 2007). HRV also relates to self-regulation capacity in addicts. Those alcoholics who display greater increase in heart rate variability during exposure to drinking cues report stronger self-efficacy in refraining from drinking (Ingjaldsson, Laberg, & Thayer, 2003).

There is reason to believe that during the process of exerting self-regulation, that is, in activating relevant areas of the PFC, parasympathetic tone (as evidenced by greater HRV) increases as well. Segerstrom and Solberg Nes (2007) monitored heart rate variability as individuals performed a task requiring self-regulation. As persons successfully performed the task, their HRV increased. This contrasted with tasks during which the research-participant's self-esteem was threatened. During threats to self-esteem, HRV decreased.

Of course, if HRV reflects activity of brain areas related to executive control, strategies for enhancing HRV becomes relevant for treatment of substance abusers. While differences among people in heart rate variability are to some extent inherited (Smoller, et al., 2008), environmental factors can influence heart rate variability. Inexpensive biofeedback equipment has been successfully used to increase heart rate variability, which improved the lung function of patients with asthma (Lehrer et al., 2006; Lehrer, et al., 2003). No doubt, in the future, biofeedback for increasing heart rate variability will be evaluated in the treatment of addictions as well. Beyond biofeedback, aerobic exercise increases HRV, as does performance on tests requiring executive function (Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004).

There is also reason to believe that attending A.A. may increase heart rate variability and, by extension executive control. Oxytocin is a hormone released by the hypothalamus that enhances bonding both to offspring and sexual partners. Not only is oxytocin released during nursing and orgasm, but it is also released given social cues suggesting that a person is trusted and accepted by a group (Porges, 2007; Zak, Kurban, & Matzner, 2004). Interestingly, preliminary data suggest that oxytocin increases heart rate variability (Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008; Grippo, Carter, & Porges, 2007). A.A. attendance does decrease drug relapse (Littrell, 1991b). One mechanism of action might be

through an increase in oxytocin, which then improves executive control over behavior. The following chain of events occurs: Trust and bonding during A.A. meetings stimulates the release of oxytocin. The oxytocin induces greater activity in the PFC reflected in better impulse control and greater heart rate variability. With greater impulse control, a break is placed on the automatic urges to use emanating from activation of the motivational structures of the brain.

In the future, directing attention to deliberately strengthening HRV might improve outcomes in substance abuse treatment. Indeed, Alan Marlatt has shown that meditation was effective in reducing substance use after release from prison in Washington State (Simpson et al., 2007). Meditation changes breathing patterns in a manner similar to changes observed with biofeedback training done by Lehrer. Thus, there is strong reason for suspecting that meditation training can increase heart rate variability, as does biofeedback training. Thus, incorporating meditation into treatment programs may prove to be an effective strategy for increasing HRV which in turn will enhance self-regulation, which will decrease risk of relapse.

Self-regulation as a Limited Resource

Self-regulation (a term for executive control) has emerged as a focus of research in social psychology as well. This area of research is linked to research on HRV, but here researchers have been concerned with more deliberate efforts to self-regulate. As will be discussed, the research on self-regulation bolsters support for the HALT acronym from A.A. Some of the results of this research are detailed below because knowledge of the parameters governing the deliberate processes of self-regulation may allow for improved strategies for avoiding relapse.

Self-regulation entails a deliberate, conscious, and effortful process. Research suggests that capacity for self-regulation operates as a limited resource (Baumeister, Vohs, & Tice, 2007; Vohs & Baumeister, 2004). If you exert a great deal of effort focusing attention, delaying gratification, denying an urge, or making hard choices, the next urge is harder to deny and you become less efficient at focusing on the next task. For example, Baumeister and colleagues found that people who resisted eating freshly baked cookies were less productive in solving math problems than were people who had indulged (Schmeichel & Baumeister, 2004). Suppressing a forbidden thought weakens ability to stifle laughter afterward (Baumeister, Bratslavsky, Muraven, & Tice, 1998). On any given occasion, capacity for exercising self-regulation can be depleted.

One reason why self-regulation operates as a limited resource may involve glucose regulation. Exerting self-control consumes a great deal of glucose and persons who start out with high levels of blood glucose are better at exerting self-control (Gailliot, 2008). Consumption of a glucose drink can offset the depletion of the limited resource of self-control (Gailliot et al. 2007). Since sleep deprivation depletes brain glucose reserves, this might be the mechanism through which sleep deprivation leads to impaired impulse control (Gailliot, 2008). Thus, the research on self-regulation vindicates A.A.'s advice to avoid being hungry or tired. Either condition will vitiate the limited resource of self-regulatory capacity, making relapse in the face of temptations to use substances more likely.

Baumeister analogizes self-regulation with the operation of muscles in the body. Although on any given day self-control is a limited resource, in the long run, you can build capacity. Baumeister, Gailliot, DeWall & Oaten (2006) found that those persons randomly assigned to practice exhibiting self-control, were better at self-control a week later than those

with no prior practice. Executive control resources can be bolstered by positive moods and laughter (Tice, Baumeister, Shmueli, & Muraven, 2007). However, loud noises, crowds, frustrations, or being treated unfairly can vitiate self-control (Muraven & Baumeister, 2000). Thus, A.A.'s advice to avoid bad moods (e.g., anger and loneliness) is also supported because good moods foster self-regulation, whereas bad moods diminish regulatory capacity.

While self-regulation is a deliberate, effortful process, people may not always be aware of when their self-regulatory effort is declining (Segerstrom & Solberg Nes, 2007). However, decreases in heart rate variability may signal less activity in PFC mediating self-regulation. In the future, devices to measure HRV might be developed to warn addicts in recovery when self-regulation is flagging (Segerstrom & Solberg Nes, 2007). Within limits, given a warning, persons can consciously engage a greater level of self-regulation and overcome faltering efforts (Martijin, Tenbult, Merckelbach, Dreezens, & de Vries, 2002; Muraven & Slessareva, 2003). Thus, the research on self-regulation offers suggestions for heightening self-awareness of vulnerability to relapse so that prevention strategies (e.g., attending an A.A. meeting) can be engaged.

Making Coping Behaviors Automatic

Drug cues can activate the dopaminergic circuits and precipitate drug-seeking. Dopaminergic circuits activate the anterior cingulate and the behavioral routines for drug-seeking (believed to reside in the dorsal striatum) in a reflexive, automatic fashion (Belin & Everitt, 2008; Everitt & Robbins, 2005; Yin & Knowlton, 2006). Thoughts about protecting sobriety may not come into awareness. Once cued by environmental stimuli, drug-seeking is automatic. However, the fact

that many people are able to quit using drugs implies that it is possible to find ways to impede automatic behavioral routines. The hope is to find strategies for making behavioral routines for coping skills in the face of drug cues, just as automatic as those driving drug-seeking (Palfai, 2004; Palfai, 2006). Whereas the deliberate, conscious process of self-regulation as described by Baumeister operates as a limited resource, automatic routines may not operate as limited resources (Webb & Sheeran, 2003).

Research suggests ways to enhance the automaticity of sobriety-promoting behaviors. Bargh's work has focused on situational cues that can raise specific motivations in an individual's hierarchy of motivations (Bargh, Gollwitzer, Lee-Chai, Barndollar, & Trotschel, 2001). For example, by embedding the word "mastery" in a word list, subjects were primed to enhance their performance on a verbal task. The primed subjects actually performed better than those subjects not receiving the prime. Primes can activate goals and behavior to achieve a particular goal, even when the individual is not consciously aware of the cue that primes the motivated behavior (Aarts & Dijksterhuis, 2000; Bargh & Chartrand, 1999; Bargh et al., 2001). Applying this principle to preventing relapse, having many reminders of valuing sobriety (e.g., sobriety birthday chips in one's pocket) might prime executive control and behaviors which are incompatible with drug use (e.g., attending aftercare or A.A. meetings). Research suggests that when a goal is primed, the cognitive availability of means to alternative goals decline (Shah, Friedman, & Kruglanski, 2002). Thus, priming sobriety goals can attenuate drug-seeking goals.

Gollwitzer and colleagues have performed experiments to identify optimal strategies for increasing the automaticity of coping mechanisms. A process of identifying specific behavioral plans for reaching goals has been shown to be superior to merely identifying goals (Gollwitzer Fujita, & Oettingen, 2004). Describing situational cues beckoning one to go astray and

articulating behaviors to be implemented in the event of situational cues to stray (if-then plans) improves outcomes. Of course, generating many alternative coping behaviors, in case one fails, will enhance the probability of success. For relapse prevention then, the strategy is articulating specific behaviors to be implemented in tempting situations, including many alternative behaviors, and practicing them both in role play and in imagination. At the critical moment, the rehearsed coping mechanism should be automatic. These strategies improve self-confidence and persistence in reaching one's goal (Gollwitzer et al., 2004). In the course of treatment, social workers should be deliberate about incorporating specific plans to counter temptations to relapse into their work with clients.

CONCLUSION

As neuroscience has identified the mechanisms underpinning drug-seeking, clinical interventions have been suggested. Physical processes involved in better self-regulation have been identified. Treatments for enhancing self-regulation have been suggested. In the near future, more ways to treat addiction emerging from neuroscience research will most likely evolve. Moreover, many of the neuroscience findings have validated the wisdom of some central A.A. teachings and interventions that have long been utilized by social work clinicians in the field of addiction.

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