Reward Loss as Psychological Pain

Mauricio R. Papini*, Michael Wood, Alan M. Daniel, and Jacob N. Norris

Texas Christian University

Abstract

This article reviews research that suggests parallels between the mechanisms underlying physical pain and fear, and those underlying psychological pain derived from reward loss. Reward loss is a major source of emotional arousal and conflict that can be modeled in the laboratory in a preparation known as consummatory successive negative contrast (cSNC). In cSNC, a group of rats is exposed to a downshift in the incentive value of a sucrose solution that leads to a sharp suppression of consummatory behavior. Research reviewed in this article demonstrates that the opioid system is normally engaged in cSNC and that individual differences in sensitivity to opioid antagonists correlate with fast recovery (resilience) and slow recovery (vulnerability) from reward loss. The co-option of the opioid system into playing a role in adjustment to situations involving psychological pain may be an evolutionary adaptation unique to mammals.
Key words: Incentive contrast, Psychological pain, Reward loss, Consummatory successive negative contrast, Opioids, Individual differences.

Resumen

Pérdida de recompensa como dolor psicológico. Este artículo resume una serie de trabajos que sugieren un paralelo entre los mecanismos del dolor físico y el miedo, y los que subyacen al dolor psicológico derivado de la pérdida de incentivos. Los episodios de pérdida están vinculados con estados de activación emocional y conflicto que pueden modelarse en el laboratorio en una preparación conocida como contraste negativo sucesivo consumatorio (CSNc). En el CSNc, un grupo de ratas es expuesto a una devaluación en el valor de una solución de sacarosa que desencadena un proceso de supresión drástica de la conducta consumatoria. Aquí se presentan resultados que demuestran que el sistema opioide se activa normalmente durante el CSNc y que las diferencias individuales en la sensibilidad a antagonistas opioides se correlaciona con una recuperación rápida (elasticidad) o lenta (vulnerabilidad) de situaciones de pérdida. La co-opción del sistema opioide para que juegue un papel en el dolor psicológico podría ser una adaptación evolutiva única de los mamíferos.
Palabras clave: contraste de incentivo, dolor psicológico, pérdida de incentivos, contraste negativo sucesivo consumatorio, opioides, diferencias individuales.

* Correspondence concerning to this article should be addressed to the first author: Department of Psychology. Texas Christian University. Box 298920. Fort Worth, TX 76129, U.S.A. 817-257-6084. E-mail: m.papini@tcu.edu.The authors thank an anonymous reviewer for valuable suggestions.

Reward loss is a major source of emotional arousal and conflict in everyday life situations. This claim is validated by a variety of research data as much as by common experience. In the Social Readjustment Rating Scale, an instrument that has been used as a tool for ranking stressful life events, many of the top most stressful life events may be promoted by an experience of loss, including the death of a spouse, jail term, divorce, death of a family member, personal injury, being fired from work, and retirement (Scully, Tosi, & Banning, 2000). Clinical research shows that separation from or loss of a loved one are often followed by a variety of emotional and physical disorders, including disruption of autonomic function and sleep patterns, immunosuppression, and increased mortality (Bartrop, Luckhurst, Lazarus, Kiloh, & Peny, 1977; Hall & Irwin 2001; Rando, 1993; Stein & Trestman, 1990).

An episode involving a significant loss of loved ones or property is often embedded in a traumatic experience and may contribute to the development and severity of symptoms of posttraumatic stress disorder. This is an anxiety disorder characterized by increased arousal, intense fear, feelings of helplessness, persistent reexperiencing of the traumatic event, and impairment of social and occupational functioning. Posttraumatic stress disorder may be triggered by events such as military combat, violent personal attack, torture, earthquakes, serious accidents, or being diagnosed with a life-threatening disease (DSM-IV, 1994). After the attacks on the World Trade Center on September 11, 2001, greater demands for mental health services occurred among individuals who suffered personal loss (Galea, Ahem, Resnick, Kilpatrick, Bucuvalas, & Vlahov, 2002). Among Guatemalan refugees from a civil war living in Mexico, symptoms of anxiety and distress were significant in those who have witnessed the disappearence of others or the violent death of a family member or friend, even 20 years after the conflict (Sabian, Cardozo, Nackerud, Kaiser, & Varese, 2003). The consequences of loss episodes also tend to be more severe in persons who experienced previous traumatic events or were in psychiatric treatment at the time of the loss (Franklin, Young, & Zimmerman, 2002).

Several types of psychological treatments for recovery from traumatic events have been developed and evaluated (Bills, 2003), but their effectiveness remains a matter for study. One source of heretofore untapped information lies in the normal process of recovery. Although extremely traumatic events, such as the 1989 San Francisco earthquake, are typically followed by an increase in the use of mental services among those directly involved (Boscarino, Galea, Ahem, Resnick, & Vlahov, 2002), many persons recover spontaneously. There is an impressive capacity for recovery from loss and traumatic events that remains largely unexplored. Studies focusing on the notion of resilience have identified some protective factors that promote coping strategies (Bonanno, 2004). Resilience involves achieving positive outcomes in situations that pose serious threats to the individual (Masten, 2001). Often, such situations involve traumatic loss events.

However revealing, clinical research cannot identify causes, but only point to correlations. For example, depression and bereavement-related stress are positively correlated with impairment of immune function, but these may be «proxy measures for some other causal factor such as diet or other health behavior,» or, «conversely, it might also be argued that immune system changes cause symptoms of depression and stress»

(Hall & Irwin, 2001, p. 482). Animal models that permit careful manipulation of reward loss parameters can contribute significantly to an understanding of the interconnection of these factors. But animal models have a major drawback: They tend to simplify the situation. For example, it would be difficult to argue that any animal model can capture the complexity of human mourning for the loss of a spouse. Thus, animal models may be viewed as a compromise between simplicity (necessary for experimental analysis) and validity (ability of the model to connect in some fundamental way with the human problem of interest). A review of the literature on animal models of anxiety suggests that progress is hindered by the absence of models that specifically target loss-induced anxiety (Flaherty, 1991). For the most part, available models of stress and anxiety are based on the induction of fear either by the presentation of aversive events (e.g., shock-induced pain, discomfort induced by cold-water immersion, aggressive encounters with conspecifics), or by exposure to situations that engage species-typical tendencies (e.g., elevated plus maze tapping on the rat's fear of open spaces).

This review focuses attention on a model of loss-induced anxiety known as successive negative contrast (SNC). There are two varieties of SNC, one in which the target behavior involves instrumental searching for the appetitive reinforcer and is thus referred to as instrumental SNC (iSNC). In the other preparation, the target behavior involves direct consumption of the appetitive reinforcer and is thus referred to as consummatory SNC (cSNC). These two forms of contrast do not always yield the same results (e.g., Sastre, Lin, & Reilly, 2005). cSNC can be obtained in situations in which the same animals fail to exhibit iSNC, thus suggesting that the processes underlying cSNC are somehow more fundamental. Papini and Pellegrini (in press) suggested that the difference lies in the memory mechanisms engaged by these two situations. In iSNC, modulation of the target behavior requires cued-recall memory since the animal must retrieve key information about the degraded incentive before it comes into contact with it. In cSNC, however, the target behavior only requires recognition memory, activated by direct access to the devalued incentive. Thus, SNC can contribute to a better understanding of the mechanisms underlying adjustment to reward loss and its behavioral and physiological consequences, under the controlled conditions of the laboratory. Studies published since the original report of iSNC by Elliot (1928) indicate that SNC is accompanied by an emotional reaction, modulated by behavioral treatments thought to induce stress inoculation, influenced by pharmacological treatments that target systems known to be involved in anxiety, and disrupted by lesions in a variety of brain sites (Flaherty, 1982, 1996; Papini, 2003; Papini & Dudley, 1997). Overall, this evidence points to a fundamental similarity among the processes that characterize reward loss and those that characterize what may be called the pain-fear domain. Since the word «pain» has acquired a dual meaning in many languages, it seems appropriate to use the phrase «psychological pain» when referring to loss-induced anxiety (invoked by such words as frustration, anguish, grief, and disappointment), while leaving the phrase «physical pain» to the state induced by actual bodily damage (invoked by words like injury, harm, and wound). This review opens with an account of the central idea of this article, namely, that psychological and physical pains are controlled by similar neural mechanisms.

The Physical Pain = Psychological Pain Hypothesis

Following Gray's (1987) style, this hypothesis is presented in a strong form by including the «equal-to» symbol. In the current state of development, mechanistic similarities between psychological and physical pain are at the center of attention and constitute the focus of this review. As research progresses, attention will likely move toward a characterization of the differences between these two systems. Thus, the strong formulation presented here should be taken as a heuristic device designed to encourage the study of what appear to be striking similarities between the neural systems controlling psychological and physical pain.

Functional Similarities Between Fear and Frustration

The hypothesis that the brain systems controlling psychological and physical pain exhibit a striking degree of similarity was first advanced by Gray (1987), who labeled it the fear = frustration hypothesis. This basic idea had been noted before on the basis of purely behavioral evidence (e.g., Wagner, 1969). However, by the 1980s there was a considerable amount of convergent physiological data that provided a strong basis for Gray's formulation.

Gray argued that fear and frustration have similar emotional and motivational properties. A person's ability to distinguish between these internal states may be based more on «knowledge of the events leading up to or accompanying the physiological state we are in at the time,» than on an ability to distinguish the internal states directly (Gray, 1987, p. 174). Following Konorski's (1967) distinction between preparatory and consummatory conditioning, Gray (1987) suggested that both fear and frustration are preparatory emotional states activated by the experience of pain and surprising nonreward, respectively. The ability of stimuli to activate any of these states requires conditioning and, therefore, these are to be understood as conditioned internal states or responses. Following Amsel's (1992) frustration theory, and to be more precise, the equality should be expressed as «fear = secondary frustration,» where the latter refers to a conditioned internal state developed after a stimulus is paired with surprising nonreward. The analogy may be extended to the unconditioned states that give rise to these two conditioned internal states. This yields a «physical pain = primary frustration» hypothesis, since fear is typically caused by the administration of electric shocks that induce peripheral pain and secondary frustration by the surprising or unanticipated withdrawal or degradation of an appetitive reward (Papini, 2003). Several lines of research led to the fear = frustration hypothesis. In general, they demonstrate that operations involving pain and primary frustration lead to similar behavioral phenomena and are affected by similar physiological variables (see Papini & Dudley, 1997).

Three sources of classic behavioral evidence will be cited here. The first involves escape learning. Animals easily learn to escape from a location where they experience either electric shocks or surprising nonreward (see Campbell & Church, 1969). For example, Adelman and Maatsch (1956) tested rats in a runway with a modified goal box that allowed the animal to jump up and escape into another compartment. Rats

shifted from reward to nonreward learned to jump faster than animals given continuous reward or continuous nonreward. This phenomenon, known as escape from frustration, highlights the similarity between escape from physical pain and escape from surprising nonreward (Daly, 1974). The second source of behavioral evidence involves the potentiation of the startle reflex by stimuli paired with electric shock. The startle reflex is induced in rats by loud noises (i.e., rats crouch against the floor and remain motionless for a few seconds). The presentation of a signal for shock shortly before the loud noise facilitates the startle response (Brown, Kalish, & Farber, 1951). Similarly, a stimulus paired with surprising nonreward and later presented just before a loud noise acquires the ability to potentiate the ensuing startle reflex (Wagner, 1963). Third, inconsistent reinforcement, whether aversive or appetitive, increases resistance to extinction. Brown and Wagner (1964) demonstrated within a single experiment that both partial reinforcement and partial punishment increase resistance to extinction in rats. In their experiment, one group received continuous reinforcement, another partial reinforcement, and another partial punishment superimposed on a continuous reinforcement schedule. After training, independent groups were shifted to either extinction (i.e., no food present in any trial) or continuous punishment (i.e., shock delivered in every trial). The results revealed increased resistance to extinction and to punishment in animals previously experiencing either partial reinforcement or partial punishment. These three lines of behavioral evidence provide support for the functional similarity between fear and secondary frustration.

The fear = secondary frustration hypothesis is also supported by physiological evidence. One source of evidence is provided by the effects of benzodiazepine anxiolytics on performance in situations assessing fear (e.g., fear conditioning, fear-potentiated startle) and frustration (e.g., cSNC). Midazolam (1 mg/kg, i.p.) reduces fear-potentiated startle and diminishes freezing after contextual fear conditioning in rats (Santos, Gárgaro, Oliveira, Masson, & Brandão, 2005). Also in rats, midazolam (2 mg/kg, i.p.) attenuates cSNC when administered before the second postshift trial (Becker, 1986). Diazepam (2.5 mg/kg, i.p.) reduces fear-potentiated startle in rats (Davis, 1979), and it also eliminates cSNC in mice (4 mg/kg, i.p.; Mustaca, Bentosela, & Papini, 2000). Diazepam (30 μg/kg) infused into the amygdala, but not the hippocampus, also attenuates cSNC in rats (Liao & Chuang, 2003). These studies indicate that benzodiazepine anxiolytics attenuate both cSNC and fear conditioning.

A second source of physiological evidence for the fear = frustration hypothesis comes from brain lesion studies. For example, excitotoxic lesions caused by infusing kainic acid into the hippocampus impair both contextual and discrete-cue fear conditioning in rats, but have no effect on unconditioned fear induced in the light-dark test situation (Yin, Bardgett, & Csernansky, 2002). Similarly, ibotenic acid lesions of the hippocampus reduce iSNC (Flaherty, Coppotelli, Hsu, & Otto, 1998). Some conditioned fear responses are also reduced by bilateral electrolytic lesions to the nucleus accumbens, such as urination, vocalizations, and increased heart rate. Freezing and avoidance behaviors, however, remain intact (Antoniadis & McDonald, 2006). Similarly, bilateral electrolytic lesions of the nucleus accumbens delay or reduce iSNC (Leszczuk & Flaherty, 2000). Bilateral excitotoxic (ibotenic acid) lesions of the medial amygdala reduce unconditioned freezing to predator odors and increase contact with a cloth soaked with cat odors (Li,

Magliano, & Takahashi, 2004). In the same study, damage to the central amygdala had no effect on unconditioned fear, but it significantly reduced freezing to a context previously paired with shock. Similar lesions also affect cSNC. In one experiment, bilateral electrolytic lesions of the lateral, basolateral, and basomedial nuclei of the amygdala attenuated cSNC, but did not completely eliminate it (Becker, Jarvis, Wagner, & Flaherty, 1984). These studies indicate that the amygdala plays a complex role in aversive conditioning, whether related to fear or secondary frustration, affecting both memory and emotional processes. It should be noted that the same brain lesion may have complex effects in SNC situations. For example, hippocampal and accumbens lesions disrupt iSNC, but have no effects on cSNC (Flaherty *et al*., 1998; Leszczuk & Flaherty, 2000). These and other similar examples of dissociation between iSNC and cSNC suggest that these tasks may require different cognitive mechanisms (Papini & Pellegrini, in press). Despite these caveats, evidence supports the presence of some brain parallels among tasks based on the presentation of aversive events and tasks based on the withdrawal of appetitive events, as suggested by the fear = frustration hypothesis (Gray, 1987).

Role of the Opioid System in Psychological Pain

This extension of Gray's (1987) original hypothesis follows the analogy from the conditioned states to the respective unconditioned states that support them (Papini, 2003). Thus, fear is typically induced by administration of electric shocks that produce peripheral pain, whereas secondary frustration is the conditioned version of an unconditioned reaction to surprising nonreward. The experience of physical pain is usually subdivided into two components: sensory and hedonic (Price, 2000). There is no basis to postulate a sensory component for primary frustration because it is induced by the absence of an expected reward. Thus, whatever similarities are found among these internal states, they must correspond to the hedonic component, that is, the aversive internal state induced shortly after the presentation of a physically painful stimulus or the surprising omission of a reward.

A major neurochemical system involved in the hedonic aspects of physical pain is the opioid system. Opioids are a family of neuroactive peptides known as the β-endorphins, enkephalins, and dynorphins, whose precursors are under the direct control of the proopiomelanocortin gene, proenkephalin gene, and prodynorphin gene, respectively. These peptides act on a series of opioid receptors, also under direct genetic control. There are three major receptor classes, μ, δ, and κ, widely distributed throughout the central nervous system (Mansour, Fox, Akil, & Watson, 1995). Some additional receptors (known as opioid receptor-like receptors, ORL) exhibit a high degree of homology with the classic opioid receptors, but do not bind the typical ligands (Sim-Selley, Vogt, Childers, & Vogt, 2003). Their functional properties are poorly understood and thus they will not be considered in this article (Bodnar & Hadjimarkou, 2003).

The role of opioids in treating physical pain derived from wounds and surgery has been known for millennia. The medicinal value of opium may have been known to the Sumerians and Assyrians, about 4,000 years ago, and it is well described by some ancient Greeks like Theophrastus and Discorides, more than 2,000 years ago (Whitlock,

1987). Its active ingredient is morphine, isolated from poppy juice in the early 19th century and thereafter widely used by physicians to alleviate physical pain. The ability of morphine to modulate behavior and psychological states in a wide variety of situations with hedonic value has been uncovered by more recent experimental research (see Bodnar & Klein, 2005). Less well-understood is the role that the opioid system plays in psychological pain, but its effects are consistent with the physical pain = psychological pain hypothesis.

The effects of opioids on reward loss situations have been studied in some detail in the cSNC situation. In a series of experiments, Rowan and Flaherty (1987) reported that morphine has a small but reliable attenuating effect. Independent groups of rats were exposed to a downshift from 32% sucrose solution to 4% sucrose (32→4) or only to the 4% sucrose solution (4→4). In one experiment, independent groups of rats were injected (i.p.) with six doses of morphine before the second postshift trial, ranging between 0.5 and 16 mg/kg. The effective doses were 2, 4, and 8 mg/kg; these doses attenuated suppression induced by a 32→4 downshift in incentive, without affecting the drinking behavior of 4→4 unshifted controls. Lower doses had no effect, whereas the 16 mg/kg dose affected consummatory behavior in the unshifted (as well as downshifted) animals. An additional experiment indicated that the attenuating effect of morphine (4 mg/kg) on the second postshift trial was eliminated by the concurrent administration of naloxone (0.5 mg/kg). Morphine (4 and 8 mg/kg) also reduced cSNC when administered before the first postshift trial.

Mirroring the effects of the nonselective opioid receptor agonist morphine, the administration of the nonselective antagonist naloxone by itself enhances cSNC, lengthening the recovery period (Pellegrini, Wood, Daniel, & Papini, 2005). To appreciate the extent of the naloxone-induced suppression of consummatory behavior, rats received training under conditions that normally yield weaker evidence of contrast, such as a 32→6 downshift, rather than the usual 32→4 downshift (Pellegrini, Muzio, Mustaca, & Papini, 2004). This reduces any potential floor effect that may hinder chances of observing the suppressing effects of naloxone. Rats received the usual training protocol, but were injected with a dose of naloxone (2 mg/kg, i.p.) before the first and second postshift trials. A follow-up experiment demonstrated enhanced suppression in a group treated with naloxone relative to a saline control, after the more conventional 32→4 downshift (Pellegrini *et al.*, 2005).

The effects of naloxone suggest that incentive downshift engages the opioid system much as done by stimuli inflicting physical pain. However, because morphine and naloxone activate several types of opioid receptors, it is not possible to determine what branch of the opioid system mediates these effects. More importantly, these treatments do not speak to the possibility that different opioid subsystems modulate different aspects of the cSNC situation. cSNC is known to be a composite phenomenon in the sense that performance during the first versus second postshift trials depends on different mechanisms. For example, benzodiazepine anxiolytics reduce cSNC when administered before the second postshift trial, but not when administered before the first postshift trial (Flaherty, Clark, & Coppotelli, 1996; Flaherty, Grigson, & Rowan, 1986). Similarly, plasma corticosterone levels are significantly increased after the second postshift trial,

but not after the first postshift trial (Flaherty, Becker, & Pohorecky, 1985; Mitchell & Flaherty, 1998). Such a dissociability of performance is consistent with Amsel's (1992) frustration theory, elaborated on the basis of purely behavioral evidence. According to frustration theory, the surprising downshift of an incentive (whether in quality or quantity) induces an aversive internal state called primary frustration (R_F). Stimuli paired with such a state acquire the ability to elicit a conditioned expectancy of primary frustration in later trials, called secondary frustration (e_F). This theoretical framework was originally developed to account for instrumental learning phenomena (Amsel, 1992; Daly & Daly, 1982), but it can be directly applied to the cSNC effect (Papini, 2003; Wood, Daniel, & Papini, 2005), as shown in Figure 1 for two critical trials, the first and second postshift trials (usually trials 11 and 12).

According to frustration theory, suppression of consummatory behavior in the cSNC situation has two different sources. During the first postshift trial, when there is an expectancy violation (i.e., expecting a large reward than that encountered), the main source is R_F, that is, the aversive unconditioned state induced by surprising reward loss. But simultaneously, the animal learns to anticipate this internal state through a Pavlovian mechanism (see arrow connecting S to R_F). After a few drinking bouts, S acquires the ability to elicit e_F, that is, an expectation of primary frustration. During the second postshift trial, S has acquired the ability to elicit an expectancy of the large reward (because of preshift training) and also an expectancy of frustration (because of the first postshift trial). These opposing expectations create the conditions for an approach-avoidance conflict (Miller, 1944). The approach component of the conflict drives the rat to drink the downshifted solution, whereas the avoidance component drives the rat away from the sipper tube. It is during this stage that some drugs appear to be maximally effective, such as benzodiazepine anxiolytics, perhaps by reducing the strength of the avoidance component of the conflict, thus increasing consummatory behavior (Gray & McNaughton, 2000). Interestingly, in other experimental models of anxiety, such as the elevated plus maze, the anxiolytic effects of the benzodiazepine tranquilizer chlordiazepoxide appears to require normal activity of the μ and κ opioid subsystems, although not of the δ subsystem (e.g., Agmo & Belzung, 1998). These differential effects of the δ subsystem and the μ and κ subsystems are also evident in the cSNC situation.

The selective δ-opioid receptor agonist D-Ala2-,N-Me-Phe4,Gly-ol (DPDPE, 24 μg/kg, i.p.) also exhibits a differential effect on cSNC. DPDPE attenuated contrast when administered before the first postshift trial, but had no measurable effect when administered before the second postshift trial (Wood *et al.*, 2005). The differential nature of DPDPE's effects on 32→4 downshifted performance coupled with the absence of any evidence of an effect on 4→4 unshifted controls discards several potential explanations. Among these potential DPDPE effects that can be safely discarded are deflation of the incentive value of the larger reward (32% sucrose), facilitation of consummatory behavior, inflation of the incentive value of the smaller reward (4% sucrose), and interference with other responses induced by the 32→4 downshift. In the same vein, the pretrial administration of naltrindole (a selective δ-opioid receptor antagonist, 1 mg/kg, i.p.) increased cSNC on the first postshift trial, but failed to affect

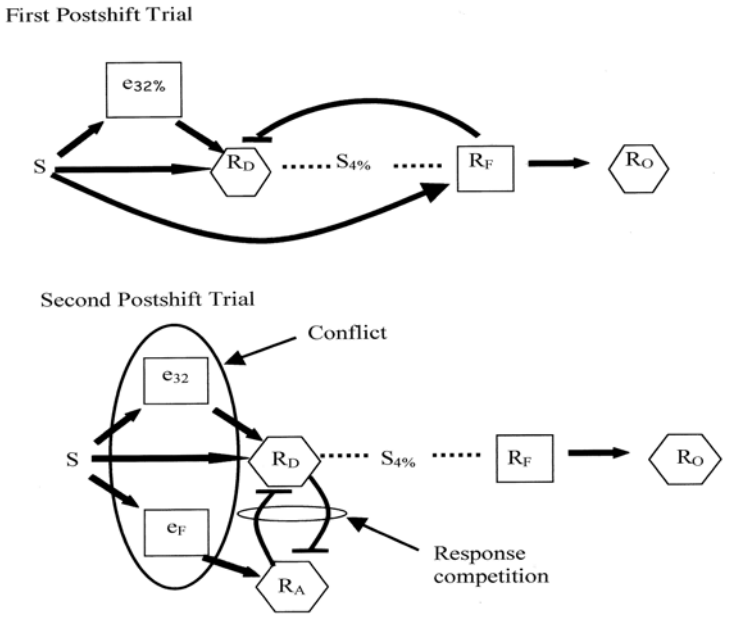

Figure 1. A model representing the cSNC effect based on Amsel's (1992) frustration theory. Only the two critical trials are represented here, the first and second postshift trials (usually trials 11 and 12). External stimuli (S and $S_{4\%}$) are unenclosed. Hexagons enclose responses (R_D: drinking, R_O: other responses; R_A: avoidance responses). Squares represent internal states ($e_{32\%}$: expectancy of the 32% solution; R_F: primary frustration; e_F: secondary frustration). Arrows and dashed arrows represent excitatory and inhibitory associations. Dashed lines represent transitions between states and events. Conflict and response competition are distinguished in terms of their covert and overt characteristics. The components of this model were derived entirely from behavioral studies.

cSNC when injected before the second postshift trial (Pellegrini *et al.*, 2005). These data indicate that the δ opioid system is engaged selectively during the initial exposure to incentive downshift, as seen in the first postshift trial of the cSNC preparation. Wood *et al.* (2005) suggested two possible loci for this action. The first possibility (see 1 in Figure 2), is that the δ subsystem attenuates the intensity of the unconditioned aversive state of primary frustration, thus reducing the initial reaction to surprising incentive loss. The second (see 2 in Figure 2), is that the δ subsystem disrupts the development of a Pavlovian association underlying secondary frustration. Choosing among these possibilities requires additional data. Whatever the case, it seems plausible that the effects of the nonselective agonists (morphine) and antagonists (naloxone) on the first postshift trial described previously are mediated by the action these drugs on the δ

subsystem.

Experiments with the κ-opioid receptor agonist U-50,488H also suggest a selective action on cSNC, but one that is opposite to that of DPDPE and morphine. In one experiment (Wood, Norris, & Papini, 2006), rats injected with U-50 (3 mg/kg, i.p.) after the first postshift trial exhibited a significant enhancement of cSNC on the following trials. This posttrial effect of U-50 is, in fact, analogous to that of corticosterone (3 mg/kg, s.c.; Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006). In both cases, the enhancing effects are interpreted as strengthening the aversive memory of the incentive downshift experience. The effects of U-50 and morphine on the second postshift trial suggest the hypothesis represented in Figure 2. According to this hypothesis, once secondary frustration is established, the μ and κ subsystems would exert opposing influences on its intensity. Whereas the former would attenuate the intensity of secondary frustration, the latter would increase it. The balance between these opposing influences may determine the speed of recovery and the degree of vulnerability and resilience in the face of reward loss.

All together, these findings suggest that μ and κ opioid receptors may have different functions during the early and later portions of the postshift phase. The involvement of the opioid system in cSNC has been identified using procedures other than through drug administration. In one such experiment (Pellegrini *et al.*, 2005), rats were exposed to the 32→4 incentive downshift procedure and their postshift behavior was classified as either fast-recovery or slow-recovery performance based on the consummatory behavior exhibited in the first and second postshift trials. In a subsequent activity test, slow-recovery rats showed greater sensitivity to naloxone (2 mg/kg, i.p.) than fast-recovery rats. Furthermore, a significant litter effect indicated that animals within the same litter were more likely to be classified within the same recovery group, either as slow- or fast-recovery animals. These results suggest that recovery from reward loss may be correlated with individual variation in opioid-receptor efficacy. Genetic variation of opioid receptors is known to occur in rodents and humans. Furthermore, different alleles for these receptors display differential efficacy in neuropeptide binding (Mayer & Höllt, 2001; Zimprich, Simon, & Höllt, 1995). Pellegrini *et al.* (2005) hypothesized that individual genetic differences in opioid-receptor efficacy contribute to the individual's ability to express resilience or vulnerability in the face of reward loss. Of course, the potential contribution of early experience and of gene-environment additive and interactive effects should also be acknowledged. These hypotheses remain to be tested.

Further support for the opioid involvement in cSNC using indirect methods comes from an experiment that compared the performance of rats in the hot plate test immediately after either the first or the second postshift trial (Mustaca & Papini, 2005). The reasoning behind this experiment was as follows. If cSNC normally engages the opioid system, then the 32→4 downshift should be equivalent to the administration of an opioid agonist. Thus, rats exposed to painful stimulation should exhibit reduced pain sensitivity (hypoalgesia). Pain sensitivity, assessed with the hot-plate test, was reduced immediately after the second postshift trial, but not after the first postshift trial. This differential effect provides an additional piece of evidence demonstrating that the

mechanisms underlying the initial response to incentive downshift are different from those implicated in the conflict phase.

Physical, Psychological, and Social Pain

An idea similar to that developed in the previous section has been pursued in the areas of reward loss and social exclusion with human subjects. This research is unique

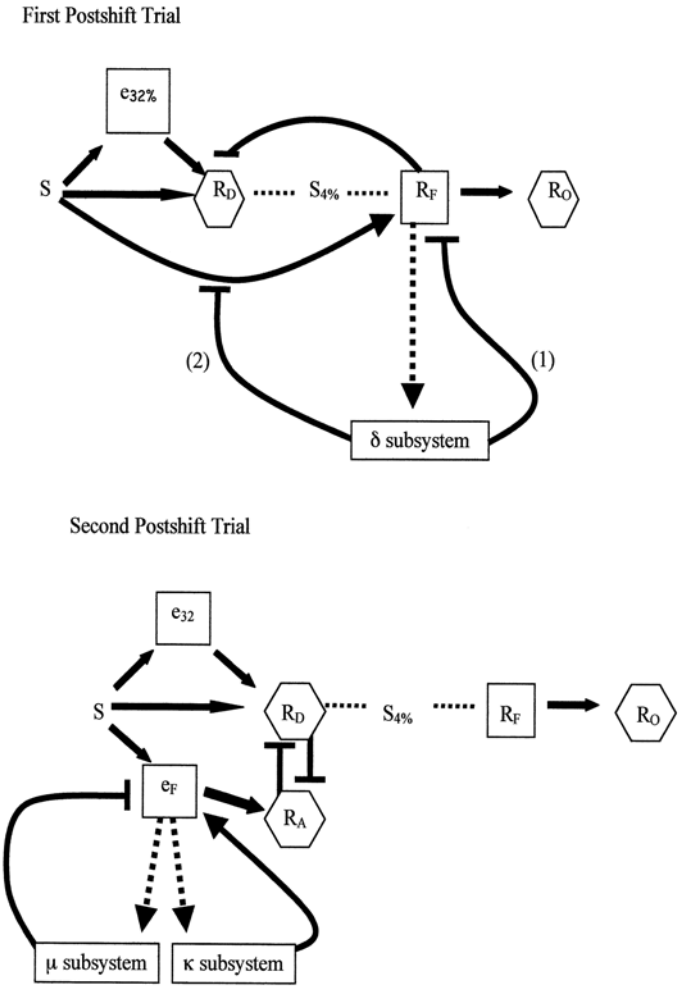

Figure 2. This figure represents the hypotheses derived from the study of the effects of opioid agonists and antagonists on cSNC. The functions of the various opioid subsystems are mapped and interpreted on the basis provided by Amsel's (1992) frustration theory. Dashed arrows represent hypothetical transitions between intervening variables (e.g., R_F and e_F) and the opioid subsystems. See legend to Figure 1 for a description of the components.

in that behavior in situations involving reward loss is correlated with brain activity assessed with techniques such as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging). These studies also point to an extensive overlap between the brain systems involved in physical and psychological pain. A brief summary of the brain system implicated in the processing of physical pain serves as a starting point.

In a review of PET and fMRI studies concerning the processing of physical pain signals, Chen (2001) outlined three stages, each implicating specific neuroanatomical structures. The first stage, called sensory transmission-discrimination stage, relates to the processing of signals carrying sensory information about physical pain and involves the brain stem, thalamus, primary somatosensory cortex, and secondary somatosensory cortex. The second stage, called affective-motivational stage, relates to the assignment of hedonic value to afferent information and involves the insular cortex, hypothalamus, amygdala, hippocampus, and cingulate cortex. Finally, the cognitive-evaluative stage frames the experience in a cognitive context and involves posterior parietal cortex, prefrontal cortex, supplementary motor cortex, and primary motor cortex. This general map of the physical pain system may be taken as a point of reference for comparing the results of studies involving either reward loss or social exclusion.

Participants who are dealing with tasks involving surprising reward loss exhibit increased activation in some of the same areas listed as part of the physical pain system. In one study (Abler, Henrik, & Erk, 2005), participants were asked to press a button for monetary reward on a series of trials, some of which were not rewarded despite correct responding, while their brain activity was being monitored using fMRI. Surprising nonreward was correlated with an increase in activity in the right insular cortex, the right ventral prefrontal cortical region, and the anterior cingulate cortex. As the authors noted, these are sites also involved in the processing of physical pain.

Extensive evidence supports the hypothesis that physical and social pains are controlled by a common set of brain structures (Eisenberger & Lieberman, 2004; MacDonald & Leary, 2005). In one study (Eisenberger, Lieberman, & Williams, 2003), participants were told that they were going to play a ball-tossing video game with two other players. In reality, a computer program controlled the other two players and was set to either include or exclude participants in the game. Simultaneously with the video game, the participants' brain was being scanned using fMRI. There were three phases in this study. First, participants were told that due to technical difficulties, they were not going to be included in the game. Second, participants were included in the ball-tossing game. Third, after receiving several throws, participants were excluded from the game for the rest of the session. The results were expressed in terms of brain activation in the third phase (exclusion) relative to the second phase (inclusion). Activation was significantly higher in two areas: the anterior cingulate cortex and the right ventral prefrontal cortex. These same cortical areas were previously shown to be active during moments of distress involving physical pain (see Panksepp, 1998).

Eisenberger and Lieberman (2004) suggested that physical and social pain overlap in neurocircuitry and computational processes in the anterior cingulate cortex, which acts as a portion of a larger mechanism they called the neural alarm system. This brain

system has a defensive-protective function. Considerable evidence indicates that the anterior cingulate cortex is a major component of the system that provides a hedonic tone to the experience of physical pain. For example, following cingulotomy (used as treatment for intractable chronic pain), patients report that they still feel the pain, but it no longer bothers them (Foltz & White, 1968). Several neuroimaging studies have identified involvement of the dorsal anterior cingulate cortex in the hedonic content of a physical pain experience (Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Tolle *et al.*, 1999; Peyron, Laurent, & Garcia-Larrea, 2000), whereas the sensory cortex and dorsal insula have been associated with the sensory-discrimination properties of physical pain (Peyron *et al.*, 2000). Finally, individuals with greater sensitivity to physical pain also show greater activity in the dorsal anterior cingulate cortex (Coghill, McHaffie, & Yen, 2003).

The role of the anterior cingulate cortex in social pain has also been documented in studies involving nonhuman animals. For example, distress vocalizations emitted by infant mammals separated from their mother are disrupted by lesions of the cingulate cortex (MacLean, 1993; Lauberbaum *et al.*, 2002). Ablation of the dorsal anterior cingulate cortex eliminates spontaneous production of distress vocalizations in squirrel monkeys (Kirzinger & Jurgens, 1982). Conversely, electrical stimulation of the same area induced distress vocalizations in macaques (Robinson, 1967; Smith, 1945), and decreased affiliative behavior, as if the need for social closeness were reduced (Hadland, Rushworth, Goffan, & Passingham, 2003; Ward, 1948).

Distress vocalizations are also produced by infant mammals in response to reward loss (see Papini & Dudley, 1997). However, two pieces of evidence remain for future analysis. First, the extent to which the anterior cingulate cortex is involved in iSNC and cSNC, and second, the extent to which the anterior cingulate mediates the effects of opioids described in the previous section. Whereas there is no information concerning these two hypotheses, the basis for a role of the cingulate cortex in the opioid-mediated effects on cSNC is provided by neurochemical studies. A variety of techniques used to determine the distribution of opioid receptors and mRNA expression of receptor genes indicate moderate to dense presence of opioid receptors across cortical areas, including the cingulate cortex (Mansour, Thompson, Akil, & Watson, 1993; Peckys & Landwehrmeyer, 1999; Vogt, Wiley, & Jensen, 1995). A potential role of the cingulate cortex in the cSNC phenomenon would indicate a common component integrating the effects of nociceptive stimulation with those involving fear, reward loss, and social exclusion.

Some Evolutionary Speculations

The connection between physical and psychological pain has been recognized for a long time, but only recently subjected to experimental study. Mowrer (1960) pointed out that administering an aversive reinforcer or withdrawing an appetitive reinforcer contingent upon some instrumental response tends to have the same functional effect, namely, to suppress behavior. These treatments are known as punishment and omission training, respectively. Since instrumental behavior always occurs in the presence of

some stimulus, Mowrer (1960) suggested that these stimuli induced internal mediational states with emotional content and called them fear (anticipation of physical pain) and disappointment (anticipation of reward loss). Mowrer's disappointment was the same conditioned state that Amsel (1958) had previously referred to as secondary or anticipatory frustration, to differentiate it from its unconditioned state, called primary frustration. Wagner (1969) further explored the parallels between punishment and omission training in a variety of experiments, using the concepts of fear and anticipatory frustration to integrate a variety of experimental results, including the results on partial reinforcement and partial punishment described above (Brown & Wagner, 1964). The literature was brought together by Gray's (1987) fear = frustration hypothesis, which, as described previously, raised the intriguing hypothesis that the same underlying circuit may explain the emotional state induced by signals of physical pain and primary frustration. However compelling, the evidence for a single circuit for both emotional states is incomplete at best, as shown by comparative research on learning. Describing this evidence requires a procedural clarification.

The hallmark of both fear and secondary frustration is their anticipatory nature, that is, the ability of stimuli paired with the corresponding unconditioned events (i.e., pain and primary frustration) to elicit a conditioned state that anticipates the goal event. This is what is typically measured in experiments in which some exteroceptive signals, such as situational cues, acquire control over behavior as a result of previous pairings with an unconditioned event. The cleanest way to illustrate the anticipatory nature of fear and secondary frustration is to measure behavior in the absence of any carry-over information from previous trials and before direct contact with the incentive (Couvillon, Brandon, Woodard, & Bitterman, 1980; Hull, 1952). One procedure that accomplishes this goal is to administer a single trial per day. With a 24-h intertrial interval, all the short-term effects of previous trials can be safely assumed to have decayed in time during the interval (e.g., Atkinson & Shiffrin, 1968; Hull, 1943; Roberts & Grant, 1976). Thus, any effect of training stimuli on behavior shows the power of situational cues to reactivate the memory of past outcomes (i.e., pain, primary frustration).

Some procedures used to study the acquisition of fear fit the requirement of 24-h long intertrial intervals, including passive avoidance and fear conditioning assessed via freezing (Bouton & Bolles, 1980; Randall & Riccio, 1969). Likewise, the original demonstrations of iSNC involved a single trial per day (Elliott, 1928; Crespi, 1942). Therefore, any explanation of these phenomena has to incorporate a mechanism for memory reactivation (i.e., cued recall) of fear or secondary frustration since these cannot be assumed to be aftereffects triggered by the presentation of shock or the omission of food, respectively, on the previous trial. This picture breaks down when analogous experiments are carried out with vertebrates other than mammals. As far as fear is concerned, available evidence indicates that goldfish acquire a two-way active avoidance response when training is administered at a rate of one trial per day (Portavella, Salas, Vargas, & Papini, 2003). Moreover, this type of avoidance learning depends on the medial pallium, an area of the fish telencephalon that contains structures homologous to the mammalian amygdala (Portavella, Torres, Salas, & Papini, 2004). Thus, goldfish have at least some of the components of the brain circuit responsible for fear conditioning.

However, experiments on iSNC, cSNC, and related effects in goldfish show no evidence of behavioral control that could be attributed to anticipatory frustration (Bitterman, 2000; Papini, 2002, 2003). In fact, nonmammalian vertebrates show a reversed SNC effect, that is, their behavior indicates discrimination of reward magnitudes, but the incentive downshift is followed by either a gradual change in behavior or no change at all (e.g., Papini, 1997; Papini, Muzio, & Segura, 1995). Thus, the brain circuit responsible for secondary frustration, as assessed in the SNC situation, appears to be unique to mammals.

Based on this evidence, Papini (2003) suggested that situations involving reward loss may lead to two separable forms of learning, called allocentric and egocentric. Allocentric learning refers to a mechanism that updates information about environmental changes and holds it either in working memory or in long-term memory. When pigeons, for example, received training with one trial per day and are exposed to a single incentive downshift transition (whether from a large to a small reward, or from a large reward to extinction), their behavior shows signs of adjustment to the new conditions, without any indication of contrast (Papini, 1997; Papini & Thomas, 1997). This outcome, common to all nonmammalian vertebrates studied thus far, and also to adult rats trained under some conditions (e.g., with anxiolytic treatment, Rosen & Tessel, 1970) and to preweanling rats (Chen, Gross, & Amsel, 1981), suggests that the allocentric learning circuit is phylogenetically ancient and was probably present in the earliest vertebrates (Papini, 2003). In contrast, egocentric learning refers to a mechanism that encodes information about the organism's own emotional reaction to environmental changes. Thus, in the reward loss situation, egocentric learning refers to secondary frustration, that is, the ability to anticipate the frustrative response that occurs when appetitive rewards are unexpectedly omitted.

Fear is also an example of egocentric learning involving the anticipation of pain. Thus, the presence of fear coupled with the absence of secondary frustration in fish (Papini, 2003) indicates that they cannot be under the control of the same circuit, as demanded by Gray's (1987) fear = frustration hypothesis. Furthermore, this dissociation requires an evolutionary explanation. Papini (2003) suggested that the circuit underlying secondary frustration evolved from the fear circuit by means of gene duplication and co-option, two processes that help explain the evolution of other phenotypic traits (Raff, 1996). The data reviewed in this article suggest a further elaboration of this evolutionary hypothesis. If it is assumed that the opioid system was originally devoted to providing physical pain and fear experiences with a hedonic tone, then it is possible that opioid mechanisms could be further modified and co-opted to produce a circuit devoted to psychological pain in primitive mammals or their ancestors. Since primitive mammals are generally solitary and exhibit limited social behavior (Eisenberg, 1981), it is possible that emotional states induced by social isolation and separation, including social anxiety, exclusion, and grief, may represent yet further elaboration and co-option of the neural system (including an opioid component) devoted to reward loss (Panksepp, 1998; Papini, 2003).

Problems for Future Research

Many sources of stress in real life involve personal loss. For all its importance, progress in understanding the consequences of reward loss has been hampered by a lack of adequate animal models. Such models are important because they permit a transition from the identification of potential factors, to the attribution of causal status to variables according to experimental outcomes. Moreover, potentially relevant animal models have been available for a long time, but their use in the laboratory has been mostly driven by basic theory. As a result, their potential connection to loss-induced anxiety has remained cryptic until recently. This is the situation with the SNC effect, originally discovered in 1928 by Elliott and used consistently during the past eight decades to study a variety of problems (Flaherty, 1996). The fear = secondary frustration hypothesis (Gray, 1987), and its logical extension to physical pain and primary frustration (Papini, 2003), have opened a conceptual door suggesting some counterintuitive proposals. However, many problems remain open for future analysis, including the following.

First, how extensive is the similarity between physical and psychological pain? The research reviewed in this paper points to parallels in the area of opioid function. However, the cannabinoid system, also involved in physical pain and in the hedonic evaluation of stimuli (e.g., Cota, Tschöp, Horvath, & Levine, 2006), provides an independent assessment of the similarity between physical and psychological pain. In one experiment (Genn, Tucci, Parikh, & File, 2004), cSNC was eliminated by the administration of the cannabinoid-receptor agonist CP 55,940 (5 μg/kg, i.p.) before the first and second postshift trials in rats. Systems affecting the hedonic value of events, such as the opioid and cannabinoid systems, are expected to modulate egocentric learning, that is, the organism's ability to learn about its own emotional evaluation of the situation.

The relationship between physical pain and the opioid system has also been characterized in terms of Solomon and Corbit's (1974) opponent-process theory. A similar opponent-process view would be consistent with the function of the opioid system sketched in Figure 2. The alternative possibility, suggested by the inhibitory arrows in the figure, may be phrased in terms of negative feedback functions, rather than opponent processes. A hallmark of opponent-process theory is that it accounts for the phenomenon of tolerance to shock-induced pain, a phenomenon known as conditioned analgesia (e.g., Ross & Randich, 1985). Data consistent with tolerance in the cSNC situation were reported in experiments involving the periodic administration of trials reinforced with the 32% sucrose solution and trials reinforced with distilled water. In such a situation, called partial reinforcement, a subsequent downshift to 4% sucrose is characterized by an attenuation of cSNC and a faster recovery of consummatory behavior (Pellegrini et al., 2004). The alleviating effects of partial reinforcement on cSNC are eliminated if the nonreinforced preshift trials are preceded by the administration of chlordiazepoxide (5 mg/kg, i.p.), or DPDPE (24 μg/kg, i.p.; Kamenetzki, Mustaca, & Papini, 2006; Pellegrini *et al.*, 2004; Wood *et al.*, 2005). In the cSNC situation, partial reinforcement may be conceptualized as a chronic exposure to psychological pain facilitating the development of tolerance against reward loss.

Pain tolerance may also be a dimension distinguishing acute from chronic forms

of physical pain, which have been shown to have different effects on some types of tasks (e.g., Moseley, Sim, Henry, & Souvlis, 2005). It could be argued that mood disorders such as depression may be thought of as examples of chronic psychological pain. In fact, there is some preliminary evidence of depression-like effects after incentive downshifts. For example, male rats exposed to incentive downshift and given posttrial access to a conspecific that they had defeated in a pretest encounter exhibit suppressed aggressive behavior (Mustaca, Martínez, & Papini, 2000). This effect, reminiscent of the disruptive effects of exposure to inescapable shock on aggressive behavior in the learned helplessness preparation with rats (Williams, 1982), remains to be fully explored.

Second, how is the loss event represented in the cSNC situation? In typical cSNC experiments, incentive downshift occurs only once, on the first postshift trial. The same downshifted solution continues to be presented during several subsequent postshift trials, but the downshift event is no longer a novel experience. The recovery of consummatory behavior may be conceptualized as resulting from this one-trial learning episode. The ensuing memory can be then studied using posttrial manipulations. Posttrial drug administration is an established approach to study mechanisms that modulate memory acquisition and consolidation (McGaugh, 2000). Using this approach, Bentosela *et al.* (2006) found that the administration of corticosterone (3 mg/kg, s.c.) immediately after the first postshift trial, but not 3 h after this trial, impaired recovery during the subsequent four daily trials. Unpublished data show that the selective κ-opioid receptor agonist U-50,488H (3 mg/kg, i.p.) administered after trial 11 also lengthens the recovery of consummatory suppression (Wood et al., 2006). One interpretation of these effects is that both corticosterone and U-50,488H strengthen the aversive memory of the loss event occurring just before. This approach can help characterize the process of memory consolidation that follows reward loss.

Third, is incentive contrast restricted to the loss of food rewards? Evidence suggests that the loss of many types of appetitive events induces similar processes. The concept of psychological pain provides a way of integrating these disparate lines of research that have progressed more or less independently from each other. As mentioned previously, social rejection activates some of the same brain areas that also regulate physical pain (Eisenberger & Lieberman, 2004). One of these areas, the right ventral prefrontal area, is also activated in human subjects during loss of monetary incentives (Abler *et al.*, 2005). There is an extensive literature on the consequences of mother-infant separation in primates that can be seen from the perspective of reward loss (see Papini & Dudley, 1997). The results of these experiments parallel clinical research on the consequences of separation and loss briefly mentioned above, going beyond in the area of gene expression and long-term consequences of early traumatic events (Champagne & Curley, 2005; Levine, 2005).

SNC can also be induced in aversive situations involving pain. For example, variations in the amount of time in the safe compartment during one-way avoidance training affect avoidance behavior in a manner analogous to that seen with the loss of appetitive incentives. In one experiment (Cándido, Maldonado, Mejías, & Catena, 1992), two groups of rats received one-way avoidance training in a shuttle box. The unshifted control group was kept in the safe compartment for 1 s after avoiding the shock throughout

training. The downshifted group was kept in the safe compartment for 30 s during a series of preshift sessions and then downshifted to 1 s of safety. Avoidance performance deteriorated significantly in the downshifted group relative to the unshifted control, thus demonstrating an incentive contrast effect in an aversive situation. Of course, the very presence of SNC suggests that the length of the safety period, an appetitive source of reinforcement, is one of the relevant incentives at work in one-way avoidance learning (fear reduction provides for another source of reinforcement; Kamin, 1956). Interestingly, subsequent research showed that whereas the benzodiazepine anxiolytic diazepam (1 mg/kg, i.p.) attenuated this contrast effect, the serotoninergic anxiolytic buspirone (0.5 and 0.75 mg/kg, i.p.) did not affect contrast, although it interfered with the development of the avoidance response (Torres, Morales, Cándido, & Maldonado, 1995). This is a pattern similar to that observed in cSNC with the same drugs (Flaherty, Grigson, Demetrikopoulos, Weaver, Krauss, & Roway, 1990; Mustaca *et al.*, 2000). The contrast procedure developed by Cándido and collaborators offers a unique opportunity to study the interaction of physical and psychological pain within the same training situation.

Fourth, what are the applied implications of this research? Whereas it may seem premature to extrapolate from a relatively limited amount of basic data collected mostly with rodents, to the complexities of human coping with psychological pain, one speculation may be offered as a working hypothesis in the area of risk assessment. A central argument of the present review is the notion that the opioid system, notoriously involved in the regulation of physical pain, also regulates adjustments to situations involving psychological pain, such as SNC. As mentioned previously, research on individual differences in the speed of recovery from incentive downshift also suggests that variations in the efficacy of some components of the opioid system may shed light on vulnerability and resilience in the face of traumatic events. Rats that exhibited slow recovery (vulnerability) of consummatory behavior after a 32→4 incentive downshift later exhibited greater sensitivity to naloxone in an activity test compared to fast recovery rats (resilience). Many factors can contribute to this pattern of results, including genetic variation and early experience. Although virtually nothing is known about the contribution of early experience to the development of cSNC (Fagen & Shoemaker, 1979), there is extensive documentation of genetic variation in opioid receptors (Mayer & Höllt, 2001; Zimprich, Simon, & Höllt, 1995). Opioid receptor polymorphisms are interesting because alleles differ in binding efficacy, thus providing information about the individual's level of opioid sensitivity (Ikeda, Ide, Han, Hayashida, Uhl, & Sora, 2005). The risk of development of addictive behavior and the analgesic power of opioids such as morphine may be derived from this information, allowing for clinical interventions. If endogenous opioid activation is one of the key factors determining recovery from reward loss, as it is argued in this paper, then knowing the specific alleles carried by an organism may provide information about the risk of vulnerability to traumatic loss events.

Whether the alternatives offered by this and the other suggestions developed in this section are viable remains to be determined by future research.

NOTES

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