Neuroscience and Biobehavioral Reviews 48 (2015) 53–69

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Behavioral neuroscience of psychological pain

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ARTICLE INFO

Article history:
Received 23 June 2014
Received in revised form 3 September 2014
Accepted 14 November 2014
Available online 25 November 2014

Keywords:
Psychological pain
Physical pain
Reward loss
Reward omission
Reward devaluation
Appetitive extinction
Successive negative contrast
Frustration
Opioid receptors
Anterior cingulate cortex
Roman high- and low-avoidance strains

ABSTRACT

Pain is a common word used to refer to a wide range of physical and mental states sharing hedonic aversive value. Three types of pain are distinguished in this article: Physical pain, an aversive state related to actual or potential injury and disease; social pain, an aversive emotion associated to social exclusion; and psychological pain, a negative emotion induced by incentive loss. This review centers on psychological pain as studied in nonhuman animals. After covering issues of terminology, the article briefly discusses the daily-life significance of psychological pain and then centers on a discussion of the results originating from two procedures involving incentive loss: successive negative contrast—the unexpected devaluation of a reward—and appetitive extinction—the unexpected omission of a reward. The evidence reviewed points to substantial commonalities, but also some differences and interactions between physical and psychological pains. This evidence is discussed in relation to behavioral, pharmacological, neurobiological, and genetic factors that contribute to the multidimensional experience of psychological pain.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2014.11.012
0149-7634/

1. Introduction: problem and terminology

In English and other languages, "pain" has both a physical dimension (e.g., discomfort caused by injury or disease) and a psychological dimension (e.g., suffering caused by grief or disappointment; Eisenberger and Lieberman, 2004). The identification of these two sources of aversive emotion with the same word, "pain," suggests that there might be important underlying commonalities in the brain mechanisms underlying these two dimensions of pain. In this article, we will argue that there is evidence of an extensive common ground, but also that important differences are starting to emerge.

This paper centers on psychological pain, but relations to both physical and social pains are pointed out as required by the argument. This review sets out to achieve three goals. First, to identify common themes, concepts, and outcomes among lines of research that have proceeded largely independently. This also requires a relatively homogeneous terminology to avoid unwanted semantic confusion. Second, to show the substantial overlap in the neurobiological basis of these types of pain despite the seemingly different procedures used to induce them. Although not phrased in terms of "pain," functional and neurobiological connections between physical and psychological pains have been recognized since the 1960s in terms of common outcomes in situations involving fear conditioning and frustrative nonreward (Gray, 1975, 1987; Wagner, 1966, 1969). Finally, the last aim of this review is to identify areas in which systematic research could have a significant impact in our understanding of psychological pain.

As in any emergent area of research, bringing together domains that have been treated separately in the past creates terminological confusion. To complicate matters further, many of the technical words used in descriptions of this type of research are also of common usage and therefore have less precise semantic limits. It is also important to recognize that many of the relevant concepts can be characterized either as intervening variables (Tolman, 1938) or hypothetical constructs (MacCorquodale and Meehl, 1948), that is, *unobservable variables* postulated theoretically to account for empirical evidence, but with the implication of mapping to a lower level of analysis (e.g., brain circuitry). Table 1 provides a list of the key concepts used in this article and their definition.

Three types of pain have been distinguished in the recent literature. Research described by the word "pain" that is connected to physical injury, disease, or intense discomfort is referred to as physical pain. *Physical pain* is a multidimensional experience that incorporates the sensory and emotional consequences that follow the administration of nociceptive stimuli (Pace et al., 2006). Laboratory studies have induced physical pain with a variety of procedures, including electric shock delivered peripherally (to the animal's feet, cheeks, legs, etc.), gastric discomfort induced by toxins (e.g., lithium chloride), peripheral nerve ligation (e.g., sciatic nerve), subcutaneous administration of chemical substances causing irritation or inflammation (e.g., formalin), and similar procedures. Organisms come to anticipate such aversive internal states, even with minimal exposure, by associating them with preceding stimuli (i.e., signals or conditioned stimuli, CSs). CSs of physical pain induce a variety of conditioned responses such as freezing, escape, rejection, and avoidance, assumed to reflect internal states usually referred to as *fear* (Whalen and Phelps, 2009) or *disgust* (Reilly and Schachtman, 2009), depending on the type of pain that induced the association (e.g., intense discomfort, sickness).

A second type of pain has been called social pain. *Social pain* is triggered by rejection, exclusion, separation, or loss events involving conspecifics (Eisenberger and Lieberman, 2004; MacDonald and Jensen-Campbell, 2011). A distinction between actual and anticipated states can also be drawn in the case of social pain.

Table 1
Definitions of key terms used in this article.

Psychological concept	Definition
Fear	Aversive state induced by *anticipated* physical pain
Incentive	An organism's expectation of an appetitive outcome
Reward devaluation	Presentation of an appetitive outcome of lower incentive value (in quality or magnitude) than that predicted by current stimuli (e.g., successive negative contrast)
Reward loss	A negative discrepancy between expected and obtained rewards. Two major instances are reviewed in this article: reward devaluation and reward omission
Reward omission	Absence of an appetitive outcome in the presence of stimuli previously associated with its presentation (e.g., appetitive extinction)
Physical pain	A multidimensional aversive state induced by *actual* disease or body injury, or by sensory signals associated to injury (e.g., electric shock)
Primary frustration	Aversive state induced by *actual* reward omission or devaluation in quality or magnitude
Psychological pain	Aversive state induced by *actual* or *anticipated* reward omission or devaluation in a nonsocial context
Secondary frustration	Aversive state induced by *anticipated* reward omission or devaluation in quality or magnitude
Social pain	Aversive state induced by *actual* exclusion or separation in a social context

Note: Some of these definitions may be more restrictive than in the common usage; they are intended to reflect how these terms are defined in the research reviewed in this article. Some key references: Amsel (1992), Logan (1960), MacDonald and Jensen-Campbell (2011), Pace et al. (2006) and Papini et al. (2006).

The terminology is complicated because social life, especially in humans, distinguishes many types of situations that might induce such an aversive state. This could be illustrated using social rejection. Whereas the actual emotion may be described in terms of feelings of *personal rejection*, the anticipated form may be described in terms of *social threat* (MacDonald and Leary, 2005). Thus, it seems plausible that a person who has felt rejected in a certain type of situation (e.g., a party with a specific group of friends) may later avoid confronting a similar situation. Much of the recent research on social pain with human participants is based on traditional methods of experimental social psychology occasionally combined with brain imaging techniques. A close analog in nonhuman animals would be research on mother–infant separation as studied in nonhuman primates and other animals (Maestripieri, 2003). Such studies have provided important information on the impact of rejection, exclusion, separation, and incentive loss. The research on mother–infant separation usually focuses on the immediate consequences and the long-term effects of early experience (Suomi, 2006), rather than the anticipatory effects.

A third type of pain, the one central to the present review article, can be called psychological. *Psychological pain* refers to the aversive emotional consequences of exposure to a reward loss event, relative to what was expected (Papini et al., 2006). Three types of reward loss events are distinguished: reward devaluation (reduced, but non-zero outcome), reward omission (complete outcome removal), and response-reward barrier (obstruction). This review centers on the first two since little research has been done with the obstruction procedure (for an example with human babies, see Kramer and Rosenblum, 1970). A major distinction between physical and psychological pains is the lack of a sensory component to psychological pain. The detection of a significant negative discrepancy between expected and actual rewards triggering a reaction of psychological pain is not a singular sensory event, but a comparison between actual and anticipated (i.e., retrieved from memory) incentive values. The distinction between psychological and social pain is less precise. Psychological pain has been typically studied in nonsocial

situations in which the incentives are, for example, different types or quantities of food, fluids, or access to safe locations. However, keeping these two types of pain separate assumes a fundamental difference between social and nonsocial incentives that does not seem entirely justifiable on empirical grounds (e.g., Domjan, 2005; Hoppitt and Laland, 2008). A similar distinction between actual and anticipated responses has been made in an area of research traditionally known as frustrative nonreward (Amsel, 1992). Frustration, also called disappointment (Flaherty, 1996; Spence, 1956), is an internal emotional state induced by the unexpected devaluation, omission, or inaccessibility of a reward. When this emotion is triggered in the actual situation of reward devaluation or omission it is called *primary frustration*, whereas when the emotion is anticipated based on CSs of reward devaluation or omission is called *secondary frustration*. Situations triggering frustration can involve conflict, aggressive behavior, escape responses, stress, emotional activation, depression symptoms, and a variety of additional consequences (Huston et al., 2013; Papini and Dudley, 1997).

2. Daily-life significance

Most organisms exhibit behavioral flexibility at the service of obtaining biologically relevant rewards, such as food, shelter, and sex mates. The absence or failure to attain these rewards can threaten reproductive success. This selective pressure has led to the evolution of many different modes of adjustment to reward omission and devaluation Papini (2014). In mammals (Papini, 2002, 2006), these adjustment strategies involve powerful emotional responses that result in the breakdown of an attachment to a resource or associated site (i.e., incentive disengagement) and a redirection of behavior to other sources of reward (Papini, 2003).

Situations associated with reward loss are also a major source of emotional arousal and conflict in humans. This claim is validated by a variety of research sources showing that the devaluation or omission of rewards increases the risk for the onset of depression, anxiety, stress, and related disorders (Huston et al., 2013). In the Social Readjustment Rating Scale, an instrument that has been used for five decades as a tool for ranking stressful life events, many of the top most stressful life events may be promoted by an experience of incentive loss, including the death of a spouse, jail term, divorce, death of a family member, personal injury, being fired from work, and retirement (Scully et al., 2000). A study of stressful events that actually occurred over the past year in a representative national sample of 3400 individuals indicated that six of the top ten most common items involved financial- and work-related loss events (Hobson and Delunas, 2001).

Clinical research shows that separation from or loss of a loved one is often followed by a variety of emotional and physical disorders, including disruption of autonomic function and sleep patterns, immunosuppression, and increased mortality (Bartrop et al., 1977; Hall and Irwin, 2001; Rando, 1993; Stein and Trestman, 1990). Divorce or parental separation can also have a variety of health-related consequences for children, including increased risk of cardiovascular disease (McEwen, 2003). Children who experience parental divorce also tend to exhibit deregulation of the hypothalamic-pituitary-adrenal axis as young adults. In one study (Kraft and Luecken, 2009), exposure to a stressful task (a public speech) was associated with lower cortisol levels in young adults who had experienced parental divorce early in life when compared to an equivalent sample with intact parental marriage.

In some cases, an episode involving a significant loss of loved ones or property is embedded in a traumatic experience and may contribute to the development and severity of symptoms of posttraumatic stress disorder—an anxiety disorder characterized by persistent symptoms, such as, recurrent traumatic memories, avoidance of trauma-related thoughts or people, persistent negative emotions related to the traumatic event, hypervigilance, and occupational and social impairments, among others (American Psychiatric Association, 2013). Posttraumatic stress disorder may be triggered by direct exposure (or indirectly by learning of traumatic events suffered by a close relative or friend) to events such as military combat, violent personal attack, torture, earthquakes, serious accidents, or being diagnosed with a life-threatening disease. Chronic stress associated with prolonged reward loss has also been linked to a higher risk for the onset of major depressive disorder and a higher severity of depressive symptoms (Carvalho et al., 2011; Hammen, 2005; Kessler, 1997; Mazure, 1998).

The relevance of psychological pain for daily-life wellbeing and health stimulates the development of animal models of reward loss. Animal models of human psychopathological disorders have both advantages and limitations (Carroll and Overmier, 2001). The main advantage lies in the ability of controled research to pinpoint the causal factors leading to states of psychological pain, especially in connection with underlying brain mechanisms. This has been extensively studied in situations involving physical pain and fear, both conditioned and unconditioned, as these situations are clearly connected to stress and anxiety. However, relatively little attention has been paid to the contribution of reward devaluation and omission to psychopathological disorders such as anxiety and depression (e.g., Kumar et al., 2013). The main limitation of animal models of psychological pain is the relative simplicity of the experimental tests. Thus, whereas it is hoped that these animal models will tell us something about the consequences of traumatic events of significance in human life, such as those mentioned in the Social Readjustment Rating Scale (e.g., death of a close relative, divorce, illness, or unemployment; Scully et al., 2000), modeling such events in great detail with rodents is virtually impossible. Moreover, as with any type of animal model, extrapolation to humans requires that the mechanisms are demonstrably homologous from an evolutionary perspective. Homology of behavioral mechanisms requires similarities across various levels of analysis, including psychological, neurobiological (brain circuits), neurochemical (synaptic transmission), and cell-molecular (Papini, 2002, 2003). The rest of the paper reviews the available evidence with these advantages and limitations in mind.

3. Comparative studies of psychological pain

3.1. What procedures can be used to study psychological pain?

Although experimental preparations for the study of psychological pain have existed for a long time, they have traditionally been viewed in connection to learning and cognitive processes, rather than in terms of emotion (e.g., Delamater, 2004; Hull, 1952). We suggest here that these training protocols include the necessary conditions to induce psychological pain related to reward downshifts (devaluation or omission), as defined above (see Table 1). Consider the following two procedures extensively cited in this article: successive negative contrast and appetitive extinction.

3.1.1. Successive negative contrast (SNC)

In SNC, following acquisition with a large reward, animals are downshifted to a small reward and their performance is compared to that of unshifted controls always exposed to the small reward. Downshifted animals exhibit a transient reduction in response strength relative to unshifted controls. SNC has been traditionally considered in discussions of animal models of anxiety (Flaherty, 1996; Gray, 1987). There are two basic procedures to study SNC. One procedure involves instrumental behavior (iSNC), that is, behavior that reflects the effect in anticipation of the goal event.

In his classic demonstration, Elliott (1928) administered one trial per day to two groups of rats in a complex maze. One group rapidly learned to locate a highly palatable cereal mixture, whereas the other learned to locate a less valuable sunflower seed reward. When the groups had demonstrated a substantial reduction in errors, the reward was unexpectedly devalued from cereal to sunflower seeds in one group, while remaining unchanged in the group that had started with sunflower seeds. Elliott found that such a qualitative reward downshift led to a rapid deterioration of behavior. Similar effects were subsequently shown with downshifts in reward magnitude (Crespi, 1942). Second, a procedure that involves consummatory behavior (cSNC), that is, changes in the consumption of the reward. In another classic demonstration, Tinklepaugh (1928) trained monkeys to expect either a highly prized piece of banana or a less preferable, but usually acceptable leaf of lettuce; monkeys could observe the experimenter hiding the reward underneath one of two cups. Choice was allowed after a short retention interval. In occasional probe trials, the banana was switched for lettuce during the interval and outside the monkey's view. Monkeys refused to consume the lettuce on these trials, exhibiting emotional behavior toward the experimenter (see also Watanabe, 1996). More recently, cSNC has become a major source of data in connection with reward devaluation thanks to the systematic work on its pharmacology and neurobiology by Flaherty and colleagues (Flaherty, 1996).

For psychological pain to be activated and have measurable behavioral and physiological effects in these and similar situations, the degree of disparity between the reward magnitudes or qualities before and after the downshift must reach a threshold. Thus, although an animal may be able to detect the difference between two incentive values, the disparity in a downshift situation may not be sufficient to trigger a state of psychological pain. In the SNC situation, the size of the disparity between the preshift and postshift rewards is analogous to the intensity of pain (e.g., shock amperage) in a physical pain situation. Just as there is a shock magnitude above which fear conditioning is detected in terms of freezing (e.g., Boyd, 1981; Cordero et al., 1998), there is also a reward disparity above which SNC is detected (for iSNC: Di Lollo and Beez, 1966; Gonzalez et al., 1962; for cSNC: Papini and Pellegrini, 2006).

To illustrate this "threshold assumption," consider the following example. Administration of the stress hormone corticosterone immediately *after* the first exposure to a 32-to-4% sucrose devaluation retarded the subsequent recovery from the downshift compared to vehicle-treated rats (Bentosela et al., 2006). Such enhancing effect of corticosterone on the memory of the reward devaluation event is not present after an 8-to-4% sucrose downshift (Ruetti et al., 2009). Thus, the magnitude of the incentive disparity determines whether animals would associate the downshift event with negative affective value, as indexed in terms of effects of postsession corticosterone administration. Therefore, reward devaluation is necessary, but not sufficient to induce psychological pain.

3.1.2. Appetitive extinction

Appetitive extinction involves a downshift from a period of reinforcement to one of nonreinforcement. Reward omission may lead to an initial increase in response strength followed invariably by a reduction in response strength. In appetitive extinction, the unexpected omission of a reward can be a frustrating experience that triggers a variety of behaviors, including an initial increase in response strength (the extinction burst or spike), aggression, agitation, ultrasonic vocalizations, anxiety-like responses, escape, immobilization, alternative responses to the reward, and search behavior, among others (Huston et al., 2013; Papini and Dudley, 1997). Four types of extinction procedures have been used as animal models of incentive loss. First, the appetitive extinction of anticipatory behavior acquired either under instrumental or Pavlovian conditioning procedures, usually rewarded with food pellets. In the autoshaping situation, for example, rats exposed to Pavlovian pairings between presentations of a lever followed by food delivery acquire lever-pressing responses that then extinguish when food is withheld. In this situation, early extinction trials are characterized by an extinction spike (Thomas and Papini, 2001). Second, the extinction of appetitive consummatory behavior acquired by simple exposure to the reward (typically sucrose solutions) has also served as a model to study incentive loss, especially in relation to drug effects (Flaherty, 1996; Kamenetzky et al., 2009; Norris et al., 2008). Third, in escape conditioning situations (e.g., Morris water maze, Barnes maze) the animal learns to find a goal or safe location, such as a submerged platform or an escape box (Morris, 1981; Vargas-López et al., 2011). These tasks have a negative reinforcement component (i.e., escaping from the water or lighted surface), but they also have a reward component (i.e., safety time in the platform or in the escape box). After the animal has learned the task, extinction trials can be introduced in which the goal is removed. The behavioral consequences of escape extinction are measured in terms of immobility (Huston et al., 2009) or search behavior (Vargas-López et al., 2011). Fourth, animals also learn to escape a location in which a reward has failed to occur—a phenomenon traditionally called escape from frustration (Daly, 1974). Such escape responses can be assessed by measuring entries and time spent in the withdrawal chamber (Huston et al., 2012), the latency to escape (Norris et al., 2009), or by calculating the average distance away from the food tray in a runway (Komorowski et al., 2012).

SNC and appetitive extinction provide a valid ground to test the notion that reward loss induces psychological pain, although they have been traditionally conceptualized in learning-cognitive terms. The emotional side of both paradigms is highlighted by a variety of consequences (Papini and Dudley, 1997), but the next section centers on experiments demonstrating these paradigms' connection to the stress response.

3.1.3. SNC, appetitive extinction, and emotional stress

cSNC is accompanied by activation of the hypothalamic-pituitary-adrenal axis. Two key stress hormones, the adrenocorticotropic hormone (ACTH; secreted by the pituitary gland) and corticosterone (secreted by the adrenal cortex), are elevated in plasma in animals that had experienced reward devaluation. For example, rats exposed to cSNC exhibit increased corticosterone release after the first devaluation session and also before and after the second devaluation session (Flaherty et al., 1985; Mitchell and Flaherty, 1998; Pecoraro et al., 2009). Levels of ACTH were also elevated after both the first and second 32-to-4% sucrose devaluation sessions (Pecoraro et al., 2009). Rats exposed to reward devaluation also exhibited an increase in body temperature; such change was attenuated by adrenalectomy supplemented by a low-release corticosterone replacement (Pecoraro et al., 2007). Adrenalectomy generally reduced sucrose intake both before and after a 32-to-4% sucrose downshift in a 4-arm maze, but replacing corticosterone levels progressively led to sucrose intake levels similar to those of sham animals (Pecoraro et al., 2005). Rats are known to increase their response variability during reward downshift (Pecoraro et al., 1999; Pellegrini and Mustaca, 2000), an effect that seems to depend on normal levels of circulating corticosterone. In the 4-arm maze, for example, this increased activity observed in sham animals after reward devaluation was not paralleled in adrenalectomized rats (Pecoraro et al., 2005). Thus, reward devaluation induces hypothalamic-pituitary-adrenal activation associated to a reorganization of appetitive behavior.

Appetitive extinction is also known to induce emotional stress (Coover et al., 1971; Davis et al., 1976; Kawasaki and Iwasaki, 1997; Romero et al., 1995). For example, rats downshifted from

acquisition to extinction in a lever-pressing situation exhibited an increase in plasma levels of ACTH and corticosterone (Coe et al., 1983). Rats also showed faster extinction in a runway situation after acquisition with a large reward than with a small reward, and this was accompanied by higher corticosterone release (Kawasaki and Iwasaki, 1997). Similar glucocorticoid elevation has been reported in other mammalian species exposed to appetitive extinction (Carbonaro et al., 1992; Dantzer et al., 1980; Lyons et al., 2000). Extinction is also sensitive to adrenalectomy, which deprives the animal of glucocorticoids. The extinction spike is eliminated in adrenalectomized rats (Thomas and Papini, 2001). Interestingly, pigs exposed to partial reinforcement actually showed a reduction in corticosterone concentration after extended training (Dantzer et al., 1987). This result is analogous to the attenuation of the cSNC effect by partial reinforcement during preshift sessions (Cuenya et al., 2012; Pellegrini et al., 2004), an effect that occurs in the anxiety-prone Roman low-avoidance rat strain (Cuenya et al., 2012) and is eliminated by the administration of chlordiazepoxide (a benzodiazepine anxiolytic) before each nonreinforced preshift session (Pellegrini et al., 2004).

These results highlight the potential of situations involving reward loss to induce not only new learning, but also changes in behavior and hypothalamic-pituitary-adrenal axis activation that can be best conceptualized as emotional. The next section asks whether a more clear connection between reward loss and pain systems can be established.

3.2. Why "psychological pain"?

Although the word "pain" is ambiguous in common usage (Eisenberger and Lieberman, 2004), it has traditionally implied physical pain in the realm of scientific research, whether in terms of sensory or affective processes. So, why invoke the concept of pain in relation to reward loss? Adopting a new terminology often points to connections between fields that have developed independently, thus suggesting novel experimental tests and implications. But the new terminology must be justifiable. The key finding that led Papini et al. (2006) to suggest the idea of psychological pain in animal research was the discovery that endogenous opioids, known mainly for their ability to reduce physical pain (e.g., Simons et al., 2014), are normally released during an episode of incentive loss, in the absence of any actual or potential tissue damage (Pellegrini et al., 2005). Cannabinoid receptors are also involved in the regulation of physical pain (Anand et al., 2009; Pertwee, 2000) and, therefore, are expected to influence psychological pain, as the review below will show.

3.2.1. Role of opioid and cannabinoid receptors

A series of pharmacological experiments connected opioid and cannabinoid receptors with incentive loss (Papini, 2009; Papini and Ortega, 2011). For example, the nonselective opioid-receptor agonist morphine reduces the cSNC effect (Rowan and Flaherty, 1987), whereas the nonselective antagonist naloxone enhances the cSNC effect (Daniel et al., 2009; Pellegrini et al., 2005). Both of these effects are observed whether the drug is administered before the first or the second downshift session. Interestingly, selective opioid-receptor compounds can have effects on either the initial reaction to the downshift or after the animal has had some experience with the downshifted reward. For example, the delta opioid-receptor agonist DPDPE [D-Penicillamine(2,5)-enkephalin] and antagonist naltrindole reduced and enhanced the cSNC effect, respectively, when administered before the first downshift session, but had no effects when administered before the second downshift session (Pellegrini et al., 2005; Wood et al., 2005). Conversely, the kappa opioid-receptor agonist U50,488H modulates the cSNC effect when administered before the second downshift session, but has no effects when administered before the first downshift session (Wood et al., 2008). Such session selectivity is consistent with models that distinguish between the initial response to incentive loss (analogous to a Pavlovian unconditioned response) and the response resulting from learning about the new reward conditions (analogous to a conditioned response), such as Amsel's (1992) frustration theory and Flaherty's (1996) multistage model. Moreover, posttraining opioid administration, designed to influence memory consolidation, has no effect either on cSNC or on appetitive extinction situations (Daniel et al., 2009; Wood et al., 2008). Thus, opioid modulation of reward loss does not appear to depend on memory processes.

Similarly, cannabinoid receptor agonists can influence the response to reward devaluation. Low (5 μg/kg) and high (40 μg/kg) doses of CP-55,940 blocked cSNC when administered before the first 32-to-4% sucrose devaluation session, whereas only the lower dose abolished this effect when administered before the second devaluation session (Genn et al., 2004). Of the two doses of CP-55,940, it is the low one that yielded interesting results; the cSNC effect was eliminated by an increase in consummatory behavior in downshifted animals, relative to vehicle controls. WIN 55-212,2, a cannabinoid-receptor agonist, administered into the basolateral amygdala prevented the enhancing effect of a stressful experience (elevated platform test) on the iSNC effect, without affecting the reaction to reward devaluation (Ramot and Akirav, 2012). This pattern is consistent with the results reviewed above for opioid agonists and suggests that both opioid and cannabinoid receptors modulate the intensity of the response to an episode involving reward loss.

Appetitive extinction is also sensitive to treatments with nonselective opioid-receptor compounds. For example, Molinengo (1964) reported that morphine significantly increased responding during extinction after training with a fixed-ratio 3 schedule of food reward. Similarly, Le Moal et al. (1979) showed that the peripheral injection of alpha and gamma endorphins, two endogenous opioid peptides, retarded extinction of an appetitively motivated behavior (alley running for water reward). Conversely, the nonselective opioid-receptor antagonist naloxone increased extinction rate after acquisition with either food or sucrose pellets, without affecting instrumental behavior during acquisition, at least at low doses (Norris et al., 2009). As mentioned above, naloxone also disrupted escape from a site paired with appetitive extinction (Norris et al., 2009).

The effects of opioid blockage on cSNC and appetitive extinction suggest that reward loss can induce a compensatory response based on the release of endogenous opioids. Such compensatory response normally attenuates the behavioral impact of psychological pain. Antagonists generally act by blocking a receptor without having intrinsic activity, that is, the ability to activate the receptor (Nestler et al., 2009). When this endogenous response is prevented by naloxone, incentive loss has a more pronounced suppressive effect on appetitive behavior, whether instrumental or consummatory. This regulatory influence is also significant in that it was not anticipated by theories based on behavioral data (e.g., Amsel, 1992; Capaldi, 1994; Daly and Daly, 1982; Flaherty, 1996), but is reminiscent of the regulatory effects of opioid blockage in situations involving physical pain (e.g., Harris and Westbrook, 1994; Krank et al., 1981).

Extinction can also be influenced by cannabinoids, although the evidence is mixed. Irritable aggression arising from physical pain or frustration can be increased by administration of cannabis extract. Boshka et al. (1966) administered 5 mg/kg of delta-9-tetrahydrocannabinol (THC) to rats undergoing withdrawal from morphine and observed an increase in fighting behavior in comparison to vehicle-treated animals. THC also facilitated extinction of running behavior in a T-maze (Gonzalez et al., 1971). In this

vein, Drewnowski and Gray (1975) suggested that THC might block frustrative nonreward, abolishing the usually greater resistance to extinction observed after partial reinforcement, than after continuous reinforcement, when administered only during acquisition sessions (see Mason, 1983).

The research reviewed in this section first suggested framing the outcome of experiments involving SNC and appetitive extinction in terms of psychological pain. The classic connection between physical pain, opioids, and cannabinoids, combined with the newly discovered role these receptors play in situations involving reward loss suggested the idea (Papini et al., 2006). Contact between these two classes of pain must be made at the level of the affective, rather than sensory, aspects of pain. Consistent with this conclusion is a link between reward loss and neurochemical systems known to be involved in depression and anxiety, as shown in the next section.

3.2.2. Anxiolytics and antidepressants

In addition to the opioid and the cannabinoid systems, several other neurotransmitters have been implicated in psychological pain. cSNC and iSNC are reduced or abolished by the acute administration of benzodiazepine anxiolytics (see Flaherty, 1996), including chlordiazepoxide (Flaherty and Driscoll, 1980; Flaherty et al., 1990b; Freet et al., 2006; Ortega et al., 2014a; Pellegrini et al., 2004; Rosen and Tessel, 1970; Vogel and Principi, 1971), midazolam (Becker, 1986; Flaherty and Driscoll, 1980), flurazepam (Flaherty et al., 1992), and diazepam (Morales et al., 1992; Mustaca et al., 2000). Barbiturates also reduce cSNC when administered before either the first or second downshift session, as well as in the iSNC situation (Flaherty and Cheke, 1982; Flaherty and Driscoll, 1980; Rosen et al., 1967). Unlike barbiturates, the effects of benzodiazepines on cSNC tend to be selective for the second downshift session (Grigson and Flaherty, 1991; Ortega et al., 2014a), although effects on both first and second downshift sessions have also been reported (Genn et al., 2004). Ethanol also reduces cSNC when administered before the second downshift session (Becker and Flaherty, 1982, 1983; Flaherty et al., 1994)

This session specificity is similar to that described above for selective opioid-receptor compounds. In these cases, the implication is that the neurochemical systems engaged by these drugs are activated only after the animal has acquired some experience with the downshifted solution. Consistent with this view, both chlordiazepoxide and ethanol are effective on the first downshift session after repeated downshift experience (Flaherty et al., 1996; Kamenetzky et al., 2008). Moreover, chlordiazepoxide and diazepam are also effective when the session is longer than the typical 5 min used in most experiments (Flaherty et al., 1986; Mustaca et al., 2000). Benzodiazepines are allosteric neuromodulators acting on the gamma-aminobutyric acid receptor type A ($GABA_A$) only when the endogenous ligand is present (Jones-Davis et al., 2005). Flaherty (1996) suggested that GABA receptors become involved only when search behavior induced by the downshift fails to locate the more preferred reward, a process that would usually take approximately 5 min. Flaherty (1996, pp. 96–97) cited the results of an unpublished experiment involving intraventricular infusions of muscimol, a GABA-receptor agonist, together with systemic administration of chlordiazepoxide before the first downshift session. With muscimol activating GABA receptors, chlordiazepoxide did reduce the cSNC effect during the first downshift session.

Not all anxiolytics reduce the effects of reward devaluation. Acute and chronic administration of serotoninergic anxiolytics has uncovered no measurable effects. For example, pretrial treatment with the serotoninergic drugs buspirone and gepirone produced no detectable effects on the cSNC situation (Flaherty et al., 1990a). Buspirone also failed to reduce SNC in the one-way active avoidance situation (Torres et al., 1995). These two papers also showed that both cSNC and SNC in one-way avoidance were reduced by treatment with benzodiazepine anxiolytics.

Whereas serotoninergic anxiolytics produce a diversity of effects by acting as partial agonists/antagonists of the serotonin-1A receptors, antidepressants consistently increase serotonin brain levels by blocking the reuptake mechanism (Nutt et al., 1999). The latter drugs have yielded some measurable effects on reward devaluation. Pretraining administration of the serotonin-reuptake inhibitor antidepressants fluoxetine and citalopram (5 days of treatment; Nikiforuk and Popik, 2009), and the tricyclic antidepressant clomipramine (postnatal day 8–21; Ruetti et al., 2013) attenuated the impact of a 32-to-4% sucrose downshift. Ruetti et al.'s experiment showed that neonatal treatment with clomipramine attenuated the cSNC effect in adult rats.

Appetitive and aversive extinction have also been extensively characterized from a pharmacological perspective, showing their sensitivity to both GABAergic anxiolytics and serotoninergic antidepressants. Unlike SNC, instrumental and consummatory extinction procedures seem to be differentially affected by anxiolytic drugs. Barbiturates, benzodiazepines, and ethanol increase resistance to instrumental extinction in food-reinforced tasks (see Mason, 1983), whereas they facilitate consummatory extinction (Kamenetzky et al., 2009). However, this is not always the case for pharmacological treatments. For example, opioid blockage with naloxone enhances instrumental extinction of food-reinforced lever pressing (Norris et al., 2009) and it also enhances consummatory extinction after access to sucrose solution (Norris et al., 2008). This congruent result across instrumental and consummatory paradigms makes sense on the view that endogenous opioids modulate the intensity of psychological pain (see Section 3.2.1). Thus, just as with peripheral pain and fear (e.g., Fanselow, 1981), opioid blockage makes the extinction experience more intense thus facilitating the disruption of approach behavior. However, by the same token, drugs that reduce one type of extinction should also reduce the other, but that appears not to be the case for anxiolytics. The reasons for anxiolytics to have opposite effects on instrumental and consummatory extinction remain to be determined.

A series of pharmacological studies suggest that appetitive extinction is affected by repeated administration of antidepressants. On this basis, Huston et al. (2013) suggested that some extinction procedures are valid animal models of depression. For example, Huston et al. (2012) trained rats to press a lever for food in a Skinner box and then introduced a withdrawal compartment during extinction sessions. They found that the tricyclic antidepressant imipramine and the selective serotonin reuptake inhibitor citalopram significantly attenuated the "avoidance from extinction" tendency characterizing behavior during extinction trials, reducing the number of entries, time spent, rearing, and biting behaviors registered in the withdrawal compartment. Both drugs also influenced rearing, run time, distance to the goal, total distance moved, grooming, and quiescence registered during the extinction of food-reinforced runway behavior (Topic et al., 2012). Clomipramine and citalopram significantly decreased the distance from a pellet feeder located in an elongated Skinner box in which a cued fixed-time food-delivery schedule was first trained and then extinguished (Komorowski et al., 2012). Interestingly, extinction measured by immobility after escape training in the Morris water maze (escape from a water pool onto a safety platform) was attenuated by desipramine (Schulz et al., 2007). These results suggest that depression-like behaviors induced during extinction of positively and negatively reinforced tasks are modulated by treatment with antidepressants.

It is assumed here that anxiety and depression symptoms such as those instigated by SNC and appetitive extinction in nonhuman animals have a human counterpart in the comorbidity typically found between anxiety disorders and depression (e.g., Kleiman

Table 2
Memory processes related to reward loss.

Drug function	Egocentric memory	Allocentric memory
Enhancement of consolidation/retrieval	Suppress approach behavior (Corticosterone, D-cycloserine)	Increase approach behavior (?)
Interference with consolidation/retrieval	Increase approach behavior (?)	Suppress approach behavior (Chlordiazepoxide)

Note: Only drugs that failed to induce conditioned taste aversion are cited here. Key references: Bentosela et al. (2006), Norris et al. (2011), Ortega et al. (2014a) and Ruetti et al. (2009).

and Riskind, 2012) and their relationship with physical pain (e.g., Castillo et al., 2013; Ligthart et al., 2013). We suggest these are aspects of the same underlying dimension of psychological pain. But in addition to their direct influence on behavior, states of psychological pain can be sufficiently powerful to induce the consolidation of emotional memories. Moreover, the consolidation of new memories can have important implications for the process of recovery from reward loss.

3.2.3. Memory modulators

Papini (2003) argued that situations involving reward loss, whether in terms of devaluation (SNC) or omission (appetitive extinction), may induce the consolidation of two different types of memories. First, the downshift in incentive conditions may promote, if significant enough, the acquisition of an emotional memory encoding the organism's reaction to the loss. This was called *egocentric memory* since it contains information about the organism's emotional state—an internal event. Second, interaction with the new incentive conditions may promote the acquisition of a cognitive memory about the properties of the new reward. This was called *allocentric memory* because it contains information about the new reward—an external event. When reactivated, these memories tend to have opposing effects on behavior (Table 2). For example, in the cSNC situation, consolidating or retrieving the egocentric memory would promote suppression of consummatory behavior and, of course, failing to consolidate/retrieve such a memory would promote enhancement of consummatory behavior. Notice, however, that the two memories are theoretically established in rapid succession and without a clear boundary. After the organism detects a significant downshift (Papini and Pellegrini, 2006), the emotional response is recruited and egocentric memory is hypothesized to become encoded; but soon after, as it interacts with the new incentive conditions, the organism will automatically learn about them, thus encoding the allocentric memory. Whereas egocentric memory is hypothesized to promote withdrawal, rejection, and avoidance of the goal, thus extending the effects of reward loss, allocentric memory is hypothesized to promote approach to the goal, thus facilitating recovery from reward loss (Abler et al., 2005; Papini, 2003; Papini et al., 2006).

Perhaps the simplest approach to drug screening for memory effects is to administer the drug immediately after training (i.e., posttraining drug administration). This strategy, successfully used to identify neurochemical systems involved in fear conditioning (e.g., McGaugh, 2000), has one important caveat for situations involving appetitive rewards. Drugs that induce aversive posteffects may support conditioned taste aversion. Whether the drug is presented after a reward, as in the SNC situation, or after signals previously associated with a reward, as in extinction, its posteffects can act as aversive unconditioned stimuli in typical Pavlovian conditioning fashion, much as, for example, lithium chloride does in conditioned taste aversion experiments (Reilly and Schachtman, 2009). Thus, a drug might suppress approach behavior to sucrose not because it modulates egocentric memory consolidation, but because it supports a conditioned aversion to sucrose. This option can be tested directly using the training parameters of the reward-downshift situation, but in the absence of a reward downshift. The performance of these animals can then be compared to that of an explicitly unpaired control for nonassociative effects (e.g., sensitization) exposed to the same individual events, but with a temporal delay between reward and drug administration.

Several drugs have been studied using this general approach. Some have proven ineffective. Opioids fall into this category. Whereas, as shown above, pretraining opioid blockage affects cSNC and appetitive extinction, posttraining opioid blockage does not seem to affect memory processes associated with incentive loss. This was shown in experiments in which either the nonselective antagonist naloxone or the selective delta-receptor antagonist naltrindole was administered immediately after the first session of the downshift in the cSNC situation or the first session of appetitive extinction (Daniel et al., 2009). The selective delta-receptor agonist DPDPE also failed to modulate the cSNC effect when administered after the first downshift session. The selective kappa-receptor agonist U50,488H did enhance consummatory suppression when administered immediately after the first downshift session in a dose-dependent manner, but apparently via conditioned taste aversion (Wood et al., 2008). A similar outcome was obtained in the cSNC situation after systemic administration of the protein-synthesis inhibitor anisomycin, which induced a strong conditioned taste aversion (Ortega et al., 2014b).

Although the lack of posttraining effects of opioid blockage must be taken with caution, the possibility that opioid receptors are not involved in memory consolidation in psychological pain situations must be considered (Papini, 2009). We have emphasized parallels between physical and psychological pains in this article, but the role of opioid receptors in memory processes might be a property distinguishing between these two types of pain. In physical pain situations involving electric shock administration and fear, posttraining opioid blockage is known to enhance memory consolidation (Gold, 2008; McGaugh and Roozendaal, 2008). For example, Izquierdo and Dias (1983) administered endorphin (agonist) or naloxone (antagonist) immediately after training rats in a step-down passive avoidance task, and reported interference and enhancement of retention 24 h later, respectively. The importance of the connection between opioid receptors and memory in reward-loss situations warrants further study.

Two memory-enhancing drugs that have passed the conditioned taste aversion filter and still enhanced cSNC when administered after the first downshift session are corticosterone and D-cycloserine. Corticosterone, a stress hormone released from the adrenal cortex, leads to several peripheral and central effects, including enhancing aversive memories in posttraining administration experiments (Gold, 2008; McGaugh and Roozendaal, 2008). These memory-enhancing effects of glucocorticoids are mediated by noradrenergic activity in the basolateral nucleus of the amygdala (McReynolds et al., 2010; Roozendaal et al., 2006), also known to be involved in cSNC (Becker et al., 1984). When administered immediately (but not 3 h) after the first downshift session, corticosterone enhanced the cSNC effect in subsequent sessions (Bentosela et al., 2006). This effect was quite specific to a relatively large disparity between the pre- and postshift sucrose concentrations in the cSNC situation. It failed to occur after an 8-to-4% sucrose downshift, in 4% sucrose unshifted controls, or in an anticipatory negative contrast situation involving 4% and 32% sucrose rewards (Ruetti et al., 2009).

Analogous results were obtained with D-cycloserine, a partial agonist of the N-methyl-D-aspartate (NMDA) glutamate receptor. There is strong evidence that the NMDA receptor is involved in memory consolidation (Morris, 2013). D-Cycloserine binds to

the glycine site of the NMDA receptor and displays lower binding affinity than the endogenous ligand. Thus, D-cycloserine's ability to agonize depends on the extracellular availability of glycine (Hood et al., 1989). Its partial agonist status notwithstanding, D-cycloserine has been shown to selectively enhance extinction learning after fear conditioning (e.g., Ledgerwood et al., 2003). There is also evidence that NMDA receptors may mediate some behavioral effects induced by glucocorticoids. For example, restraint stress in mice exposed to neuropathic pain induces allodynia, a pain-like response to a stimulus that would not normally cause that response (plantar stimulation with von Frey filaments in the hind feet of mice); allodynia is eliminated by blockage of either corticosterone receptors or NMDA receptors, thus implicating a common cascade (Alexander et al., 2009). Results such as these suggest that the effects of corticosterone on cSNC may be mediated by NMDA receptors. Consistent with this hypothesis, Norris et al. (2011) observed a retardation of recovery from reward devaluation after posttraining D-cycloserine administration. D-cycloserine did not affect unshifted controls and did not support conditioned taste aversion; however, when administered immediately after the first 32-to-4% sucrose downshift session, the cSNC effect lasted longer than in saline controls. D-cycloserine achieved this effect by causing suppression of consummatory behavior during the initial portion of each session, when animals do not normally exhibit a cSNC effect. This was interpreted as facilitating the retrieval of the egocentric memory of the downshift. Interestingly, D-cycloserine had no effect when administered after a 32-to-6% sucrose downshift, supporting again the threshold assumption (see above). Just as D-cycloserine enhanced the cSNC effect, it also accelerated appetitive extinction. In one experiment, Shaw et al. (2009) trained mice in a fixed-ratio 5 schedule before downshifting them to extinction. D-cycloserine administered immediately after each extinction session facilitated extinction performance. However, there was a difference between these two D-cycloserine studies. Whereas D-cycloserine had an effect in the early portion of a consummatory session in the cSNC situation (Norris et al., 2011), D-cycloserine did not disrupt spontaneous recovery of responding during the early portion of the subsequent session in appetitive extinction (Shaw et al., 2009).

Whereas pretraining administration of chlordiazepoxide (before first, second, or both downshift sessions) can reduce cSNC, chlordiazepoxide administration after the first or second downshift session actually enhances the cSNC effect on subsequent sessions (Ortega et al., 2014a). Posttraining chlordiazepoxide did not support taste aversion learning, was specific of the reward downshift experience, and it was reduced by delayed administration. Because chlordiazepoxide is known to interfere with memory consolidation (e.g., Ghoneim, 1992), the effects of posttraining administration were interpreted in terms of an interference with memory consolidation of the experience with the downshifted reward or allocentric memory.

As revealing as they are, these experiments tell us nothing about the locus of action of these memory modulators. One approach is to target specific brain sites for physiological manipulations while animals are experiencing reward loss. This has been done using the iSNC paradigm, in the runway, with a 10-to-1 pellet downshift, and targeting the amygdala. In one experiment, Salinas et al. (1993) infused lidocaine in several amygdala locations immediately after the first downshift session. Lidocaine is a sodium-channel blocker that produces a reversible inactivation of neural activity. While both lidocaine and vehicle rats exhibited comparable response latencies on the first downshift session, lidocaine-treated animals recovered faster in the following sessions. This suggests that the amygdala is broadly involved in egocentric memory. However, the diffuse distribution of the reversible lesions prevents identifying the exact location of the effect and the general inactivation produced by lidocaine does not allow an identification of the neurotransmitter systems involved. In another experiment using the same procedure, Salinas and McGaugh (1996) implanted cannulae in the amygdala, but infused bicuculline, a $GABA_A$-receptor antagonist, immediately after the first downshift session. Bicuculline enhanced the iSNC effect, suggesting that $GABA_A$ receptors are involved in either the attenuation of the frustrative state induced by the downshift, or the encoding of the allocentric memory of the new reward conditions. Interfering with allocentric memory would enhance the iSNC effect (see Table 2). Consistent with this result, the infusion of the $GABA_A$ agonist diazepam in the amygdala reduced the cSNC effect (Liao and Chuang, 2003). Further research in the same behavioral paradigm, but with more restricted neurotoxic lesions uncovered differential effects. Whereas lesions of the central nucleus of the amygdala enhanced the iSNC effect, lesions of the basolateral nucleus reduced the iSNC effect (Salinas et al., 1996). Interestingly, none of the two lesions affected the initial response to the downshift, as it is the case after systemic treatment with benzodiazepine anxiolytics (see references above). Two conclusions can be derived from these data. First, different amygdala sites may exert opposite effects on recovery from the iSNC effect, and second, $GABA_A$ receptors in the amygdala are involved in the modulation of the response to reward devaluation.

The brain tends to have redundant representations for some memory traces, a fact suggesting that targeting specific brain sites for microinfusion or lesions may not provide a full view of the memory circuit involved in reward loss. To narrow the possibilities of potential brain locations responsible for memory consolidation in reward-loss situations, one may use molecular techniques as tools. Pecoraro and Dallman (2005) assessed levels of c-Fos (a protein expressed in neurons immediately after depolarization) following the first or the second session of a 32-to-4% sucrose downshift. A large number of brain locations exhibited activation after the first downshift session, including the ACC, insular cortex, nucleus accumbens, and medial amygdala. However, none of these areas showed activation after the second downshift session. In another study involving cSNC (Glueck et al., 2014), rats exposed to either 32-to-4% sucrose downshift or unshifted controls were sacrificed after either the first or second downshift session and their brains prepared for measuring expression levels of phosphorylated cyclic adenosine monophosphate response element-binding protein (pCREB). Whereas c-Fos provides information of neural activity, pCREB is thought to more specifically assess sites of synaptic plasticity (Sakamoto et al., 2011). Compared to unshifted controls, downshifted rats exhibited higher pCREB levels after the first downshift session (when the memory is being encoded) than after the second downshift session in areas including the dorsomedial striatum, the prelimbic cortex, the anterior cingulate cortex, and the central nucleus of the amygdala. Some of these areas overlap with fear memory circuitry derived from shock-induced physical pain (e.g., Helmstetter et al., 2008; Kim and Jung, 2006; Levenson et al., 2009). These results are consistent with the role of the central nucleus of the amygdala in the iSNC described above, but suggest that additional areas may be involved. Targeted microinfusions and lesions in these areas may provide a more complete view of the circuitry underlying the egocentric and allocentric memories involved in reward loss.

3.3. What new research was suggested by psychological pain?

Since the original reports by Elliott (1928) and Tinklepaugh (1928), SNC has significantly contributed to our understanding of the mechanisms underlying adjustment to incentive loss and its behavioral and physiological consequences. 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 some limbic structures like the amygdala (Flaherty, 1996; Papini, 2003, 2009; Papini and Dudley, 1997). What new insights were gained by conceptualizing SNC and analogous situations in terms of psychological pain?

Recent research points to a connection between physical and psychological pain that was directly suggested by this new framework. Using the cSNC preparation, Mustaca and Papini (2005) reported that rats exposed to the hot plate test (which measures pain sensitivity) exhibited hypoalgesia immediately after the second session of a 32-to-4% sucrose downshift, but not after the first downshift session. This is yet further evidence that the initial and subsequent exposure to the devalued incentive activate different brain processes. Although it is still unclear whether downshift-induced hypoalgesia is mediated by opioid receptors, it is tempting to hypothesize based on evidence reviewed above that the release of endogenous opioids during conflict is directly responsible for this reduction in pain sensitivity. The facts reviewed thus far suggest that this instance of session selectivity may be mediated by kappa (and perhaps mu) receptors, but not by delta opioid receptors (Wood et al., 2005, 2008).

The experiment described above illustrated the modulation of physical pain (hot plate) by psychological pain (cSNC), but is psychological pain modulated by physical pain? A series of experiments explored this question by inducing physical pain via the formalin test and then testing its effects on cSNC (Ortega et al., 2011a). In these experiments, physical pain was induced by a subcutaneous injection of formalin in a hind paw. Such treatment induces pain, but the animal continues to behave almost normally, except for an occasional licking of the irritated foot. In one experiment, pain induction before the first and second downshift sessions resulted in enhanced consummatory suppression in the 32-to-4% sucrose condition, but no detectable effect in unshifted, 4% sucrose controls. Thus, the effect was selective to the group that experienced reward devaluation. In another experiment, peripheral pain was administered before the first downshift session to a group that experienced a 16-to-4% sucrose devaluation. Although this disparity is below the threshold, usually yielding no evidence of a cSNC effect (e.g., Papini and Pellegrini, 2006), as it was the case in this experiment, the addition of peripheral pain produced a significant degree of consummatory suppression. Interestingly, there was no evidence that the formalin test acted by enhancing memory consolidation. When formalin was administered immediately *after* the first downshift session, recovery of consummatory behavior proceeded as in saline-control animals (Ortega et al., 2011a). This evidence points to a motivational/emotional effect of peripheral pain on the cSNC effect (i.e., a nonassociative effect), rather than one mediated by memory processes.

One possibility is that independent sources of pain (e.g., peripheral pain and reward devaluation) summate to enhance each other. The strength of the resulting emotional state could have effects that neither of the individual states would produce, facilitating the retrieval of aversive memories and influencing aversively motivated behavior (Ortega et al., 2013). To test this aversive summation hypothesis using only sources of psychological pain, animals were exposed to restraint stress for 1 h before either the first or the second reward devaluation session (Ortega et al., 2013). In both cases, restraint stress selectively enhanced consummatory suppression in 32-to-4% sucrose animals, without affecting the behavior of 4% sucrose controls. As an additional control, restraint stress had no effect on animals that had exhibited cSNC, but had recovered from the effects of reward devaluation at the time of the restraint test. Restraint stress also affected instrumental behavior. In the same series of experiments, animals received 8 trials of escape training in the Barnes maze on Day 1 and were exposed to extinction of escape behavior for an additional 8 trials on Day 2. Restraint stress did not affect the initial response to the correct hole in extinction, but it significantly enhanced the approach to other holes in the maze. Interestingly, when restraint stress was administered a day after extinction, it reduced approach to the goal hole. The authors suggested that the aversive state induced by restraint facilitated the retrieval of the extinction memory, thus reducing the amount of spontaneous recovery.

There are also parallels between physical and psychological pain in the area of emotional self-medication. For example, neuropathic pain induced by sciatic nerve ligation led to enhanced self-administration of (R,S)-AM1241, a CB2 cannabinoid-receptor agonist, in rats (Gutierrez et al., 2011). Moreover, rats exposed to inescapable shocks consumed ethanol (an anxiolytic drug) more than water, and more than rats exposed to avoidable shocks (Anisman and Waller, 1974). These results suggest that a similar type of self-medication should be demonstrable in rats exposed to loss-induced anxiety, such as appetitive extinction.

This notion was tested in experiments with Roman high- and Roman low-avoidance rat strains (RHA, RLA), which exhibit, respectively, low and high sensitivity to reward loss events (see section 3.5). Using a consummatory extinction paradigm, Manzo et al. (2014) observed that RLA rats, but not RHA rats, increased consumption of ethanol immediately after the initial extinction sessions. Such enhanced voluntary consumption of ethanol was not observed after acquisition sessions with 22% sucrose; moreover, enhanced consumption was not observed in control groups given access to water after each session, whether in acquisition or extinction. Similar results were obtained using an instrumental extinction paradigm. This effect was extended to unselected Wistar rats using a cSNC paradigm, with postsession oral consumption of ethanol or chlordiazepoxide (Manzo et al., 2015). Further studies should explore the role of psychological pain as a precipitant agent in the intake of potentially addictive substances.

Experiments manipulating reward omission or devaluation in conjunction with other sources of aversive emotion (e.g., hot plate, formalin test, restraint stress) or in relation to regulatory behaviors (e.g., self-medication) were suggested by a characterization of situations involving incentive loss in terms of psychological pain. These experiments provide a new set of phenomena for neurobiological analysis.

3.4. What is the role of the ACC in psychological and physical pain?

Conceptualizing reward omission and devaluation as psychological pain suggests that the literature on physical pain may be a guide for neurobiological analysis. The distinction between affective and sensory aspects of physical pain is important because there is no simple sensory process underlying psychological pain. Therefore, common ground between physical and psychological pain would have to be found in the affective domain, including emotional memory. There are a number of candidate brain areas that could underlie an emotional/affective function common to both physical and psychological pain (Abler et al., 2005; Eisenberger and Lieberman, 2004; Gray and McNaughton, 2000; Papini et al., 2006; Ruetti and Justel, 2010). We focus here on the ACC as an example of the type of problems raised by an attempt to identify the neural substrate of pain processes.

3.4.1. ACC and physical pain

Neural imaging studies with human participants implicate the anterior cingulate cortex (ACC) in situations involving incentive loss (Abler et al., 2005) and social exclusion (Eisenberger and Lieberman, 2004), as well as in relation to physical pain and fear (Peyron et al., 2000; Zhou et al., 2012). However, neuroimaging

studies tell us little about the actual function of an area that happens to be active during a specific task. Is the activated area having an excitatory, inhibitory, or modulatory function on the final output? Lesion studies with nonhuman animals can help fill the gap. Although evidence suggests that the ACC processes pain affect (Rainville et al., 1997), there has been a paucity of basic research exploring the neural mechanisms underlying affective/motivational nociceptive processing (Borszcz and Streltov, 2000). Additional behavioral paradigms, such as the place escape/avoidance test (LaBuda and Fuchs, 2000), have permitted the separate assessment of pain affect and pain sensitivity, and have led to the examination of the underlying neuroanatomical and neurochemical processes involved in modulating pain affect (Fuchs et al., 2014). For example, electrolytic lesions of the ACC differentially alter mechanical hypersensitivity and escape/avoidance behavior (LaGraize et al., 2004). Connections between the ACC and the periaqueductal gray indicate that ACC activity might initiate a compensatory cascade at the level of the periaqueductal gray. Focal electrical stimulation of the ACC has been shown to inhibit the response of dorsal horn neurons to mechanical stimulation (Senapati et al., 2005) and also to reduce escape/avoidance behavior (LaBuda and Fuchs, 2005). However, lesions of the ventro-lateral periaqueductal gray significantly attenuate the effects of ACC stimulation (LaBuda and Fuchs, 2005).

It is possible that one mechanism of action by which the ACC selectively modulates the affective properties of physical pain is via mu opioid receptors. The ACC has a high density of opioid receptors (Kujirai et al., 1991; Lewis et al., 1983; Mansour et al., 1987, 1995), and the ACC mu opioid-receptor system activity during sustained pain is negatively correlated with McGill Pain Questionnaire affective scores (Zubieta et al., 2001) and the Positive and Negative Affectivity Scale (Zubieta et al., 2003). This hypothesis was tested in an animal model of neuropathic pain determining the mechanical paw-withdrawal threshold and the development of escape/avoidance behavior in the same animals (LaGraize et al., 2006). Morphine microinfusion into the ACC produced a selective decrease in escape/avoidance to mechanical stimulation of the hyperalgesic paw (an indication of pain affect), but no change of mechanical paw withdrawal threshold (pain sensitivity). Thus, the ACC is involved in the modulation of the affective properties of physical pain.

3.4.2. ACC and psychological pain

These results led to the hypothesis that the ACC should also be involved in modulating the adjustment to incentive loss. Previous research indicated that extensive lesions of the ACC eliminated the iSNC effect (Gurowitz et al., 1970), so one would predict similar results for the cSNC situation. Moreover, if disrupting activity in the ACC resulted in a reduction of the affective components of physical pain, then lesions of the ACC should also lead to a reduction of the cSNC effect, just as it was the case for the iSNC effect. Indeed, ACC lesions proved to play a very specific role in the cSNC effect, although it was not what was predicted. Instead of eliminating the cSNC effect, ACC lesions actually enhanced it, disrupting selectively the recovery process initiated during the second downshift session (Ortega et al., 2011b). Interestingly, ACC lesions did not affect preshift performance, the behavior of animals exposed to unshifted reward conditions, or the behavior of downshifted rats during the first downshift session. When within-session data were analyzed, animals with ACC damage exhibited increased suppression during the early portion of the second (and subsequent) downshift session, although not during the first downshift session. One interpretation of this early-session effect is that the retrieval of information of the downshift event consolidated after the first downshift session (see Bentosela et al., 2006; Norris et al., 2011) was facilitated by the ACC lesion. This implies that the function of the ACC is to attenuate the response to reward devaluation. In its absence (due to the lesion), such regulation is removed thus resulting in a stronger negative response to the downshift event. Whether such regulation is mediated by opioidergic neurons influencing downstream processing (e.g., amygdala?) remains to be determined.

These results introduced two reasons for pausing. First, similar ACC lesions reduced physical pain in the escape/avoidance situation (LaGraize et al., 2004), but they enhanced psychological pain in the cSNC situation (Ortega et al., 2011b). Before accepting the possibility that this area may have opposite functions in these two types of pain, we need to question the interpretation of the results. One interpretation that could explain both effects is based on the hypothesis that the ACC plays a role in the update of allocentric memory (Abler et al., 2005; Papini, 2003). As mentioned above, allocentric memory refers to the encoding of events related to changes in the environment and it is contrasted with egocentric memory, which encodes information about emotional reactions of the organism to changes in the environment (Papini, 2003). Thus, the effect of ACC lesions in the cSNC situation may be understood in terms of a disruption of allocentric memory. Such disruption of memory update would cause the animal to compare the current incentive with the preshift incentive, rather than with the new devalued incentive, thus prolonging the cSNC effect. Similarly, the ACC lesion would interfere with the encoding of response-outcome contingencies in the escape/avoidance situation, thus leading to a learning deficit. There is independent evidence suggesting that ACC lesions interfere with the development of incentive expectancies (McKee et al., 2010; Newman and McGaughy, 2011). For example, microinfusions of the N-methyl-D-aspartate receptor antagonist AP5 into the ACC disrupt the acquisition of lever-pressing behavior, but have no effect once the behavior is acquired (McKee et al., 2010).

The second reason for pausing is the conflicting results between iSNC and cSNC experiments with similar lesions—while disturbing, they are not surprising. Similar dissociations between these two procedures have been observed with lesions of the hippocampus (Flaherty et al., 1998), nucleus accumbens (Leszczuk and Flaherty, 2000), and gustatory thalamus (Sastre and Reilly, 2006). Whereas hippocampal and accumbens lesions disrupted iSNC and had no detectable effects for cSNC, the opposite was the case for gustatory thalamus lesions. Besides these conflicting results, the different lesion techniques used in the early study by Gurowitz et al. (1970) and in Ortega et al. (2011b) study (aspiration and electrolytic, respectively) are known to have different activation profiles in the brain (Glenn et al., 2005). For example, c-Fos activation after aspiration lesions of the perirhinal cortex, but not after similar electrolytic lesions, affect the dentate gyrus; since iSNC, but not cSNC, is known to depend on an intact hippocampus (e.g., Flaherty et al., 1998), the discrepancy could be caused by the differential remote effects of these two types of lesions.

The role of the ACC in social pain has also been documented in studies involving nonhuman animals, although their potential connection to memory processes is unclear. For example, distress vocalizations emitted by infant mammals separated from their mother are disrupted by lesions of the cingulate cortex (Lauberbaum et al., 2002; MacLean, 1993). Ablation of the dorsal ACC eliminates spontaneous production of distress vocalizations in squirrel monkeys (Kirzinger and Jürgens, 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 et al., 2003; Ward, 1948).

The conclusion from this section is that the ACC is an important component of the circuit underlying psychological pain. It is possible that it plays a significant role in memory update processes related to recovery from an episode of incentive loss.

3.5. What are the genetic correlates of psychological pain?

In the animal laboratory, it has been repeatedly shown that unexpected reward devaluation or omission triggers physiological, cognitive, and behavioral states that seem to depend on the activation of brain circuits also involved in physical pain, stress, fear, and anxiety (Flaherty, 1996; Gray, 1987; Papini et al., 2006). Although this hypothesis has been supported by behavioral, pharmacological, hormonal, and neuroanatomical evidence (Papini et al., 2006), only a few studies have systematically explored the genetic basis of individual differences in psychological pain (Torres and Sabariego, 2014). There are well-defined individual differences in recovery from reward devaluation (S. Papini et al., 2014) that respond to selective breeding (Flaherty et al., 1994; Ortega et al., 2014c). But the bulk of information comes from established strains. Animals selectively bred for extreme divergence in avoidance learning, which also led to differences in anxiety or emotional reactivity, have been recently used to this aim: the Roman high- and low-avoidance (RHA, RLA) rat strains. These strains have been selected from a Wistar parental stock since the 1960s for good (RHA) and poor (RLA) ability to acquire a two-way active avoidance response (Driscoll and Bättig, 1982). The reproduction and maintenance of these strains has continued since 1993 at the Autonomous University of Barcelona (Spain), leading to inbred varieties called RHA-I and RLA-I. Evidence shows that as a result of this psychogenetic selection both outbred and inbred strains differ in their emotional reactivity in a variety of situations. RLA rats show a more pronounced response when exposed to anxiety tests related to conflict, novelty, and innate fear stimuli (Driscoll et al., 2009). By contrast, RHA rats show lower rates of anxiety in novel situations and a greater tendency to sensation seeking, drug self-administration, impulsivity, active coping in stressful environments, and resistance to stress-induced depression (Giorgi et al., 2007; Manzo et al., 2012; Moreno et al., 2010; Piras et al., 2010, 2014; Steimer and Driscoll, 2005).

Recent studies have extended the behavioral phenotyping of Roman rats to psychological pain, showing the behavioral resistance of the RHA-I strain to an experience involving reward devaluation or omission. For example, an impairment of the anticipatory response of running (iSNC) was not observed in RHA-I (as opposed to RLA rats) when animals were downshifted from 12 pellets to 2 pellets in the goal box of a runway (Rosas et al., 2007). Similar results were obtained by decreasing the time spent in the safe compartment (from 30 s to 1 s) in a one-way active avoidance task (Torres et al., 2005). Wistar and RLA-I rats showed an impairment of the avoidance response that was not observed in RHA-I rats. Roman strain differences were also found in the cSNC situation. Compared to RLA-I rats, RHA-I rats showed faster recovery from the consummatory suppression induced by a 22-to-4% sucrose downshifting (Gómez et al., 2009a).

Strain differences were also observed during appetitive extinction in the runway. RHA-I rats exhibited a slower extinction rate (i.e., higher resistance to extinction) compared to RLA-I and Wistar rats (Gómez et al., 2009b). Similar results were obtained by Coppens et al. (2013) in an operant chamber in which the schedule of reinforcement was changed from a fixed-ratio 1 schedule to a variable interval 15-s schedule, followed by an extinction phase. Other behavioral effects related to reward devaluation and omission that have been shown in RLA-I rats, also failed to occur in RHA-I rats, including the partial reinforcement extinction effect (Gómez et al., 2008) and the partial reinforcement contrast effect (Cuenya et al., 2012). Both phenomena are experimental examples of response-outcome uncertainty during acquisition (e.g., partial reinforcement) that results in an increased, rather than decreased, behavioral persistence during the subsequent omission or devaluation of the reward (Pellegrini et al., 2004).

Roman rat strains have also been used to explore the genetic basis of vulnerability/reactivity to reward loss. Given that the RHA-I strain shows remarkable resilience in a variety of procedures involving reward devaluation and omission, compared to the RLA-I strain and nonselected Wistar rats, these animals can shed light on the genetic predisposition to endure (RHA-I) or succumb (RLA-I) to psychological pain. Recent studies have identified molecular pathways that could play a role in complex behavioral traits known to be divergent in Roman rats (Fernández-Teruel et al., 2002; Sabariego et al., 2011). In this vein, Sabariego et al. (2013) exposed Roman rats to reward devaluation in the goal box of a straight alley and observed an iSNC effect in RLA-I rats, but not in RHA-I rats. This behavioral divergence was accompanied by differences in the hippocampal expression of genes such as TAAR2, THAP1, PKD2L1, and NANOS, which have been related to schizophrenia, depression, anxiety, and drug addiction.

4. Further comments

The body of work reviewed here makes it clear that, although there are a number of common themes, concepts, and outcomes along different lines of "pain" research, there are also potentially important differences allowing psychological pain and physical pain to be dissociated experimentally. An important difference is the lack of a sensory peripheral mechanism associated with psychological pain, as it is the case for physical pain. Therefore, the research aiming at their interactions reviewed in this article has focused on affective central processes. Fig. 1 provides a summary of the common and divergent aspects of psychological and physical pain discussed in this article.

Additional evidence suggests a greater degree of specificity in underlying neural mechanisms associated with processing physical pain versus social pain (Wager et al., 2013). Brain imaging techniques provide a unique view of the awake, functioning human brain, but they also pose potentially serious problems of interpretation. For example, the fact that a particular brain area (e.g., ACC) is activated during an experience of physical pain does not imply that knowing that this area is currently active means that the individual must be experiencing pain (Iannetti et al., 2013). This is because many other states can also activate the same brain areas. It is rarely the case that a particular brain area is exclusively dedicated to processing of only one type of psychologically meaningful information. Most commonly, specific brain sites participate in a variety of psychological functions. Common activation patterns in fMRI studies may be produced by different sets of neurons located in the same region subserving different functions, thus giving the impression that, for example, two types of pain involve the activation of the same region (Wager et al., 2013). This could be the result of the low resolution of current imaging techniques. For example, using gene-expression profiling in the central nucleus of the amygdala, Purgert et al. (2012) observed that different neuronal populations were activated by signals for shock (fear inducing) and signals for food omission (frustration inducing). Moreover, as pointed out above, the fact that a region shows activation during a specific task does not say much about the type of influence it has on behavior. Suppose, for example, that X and Y both show above threshold activation during a task involving psychological pain, does that imply that both contribute to enhance the behavioral output? Lesion experiments may show that whereas one up-regulates behavior, the other down-regulates it, although both would become active during the task. This scenario could realistically materialize in an experiment in which the role of the insular cortex and the ACC are simultaneously assessed during the cSNC task. Different experiments, with somewhat different methodologies, but testing a 32-to-4% sucrose downshift

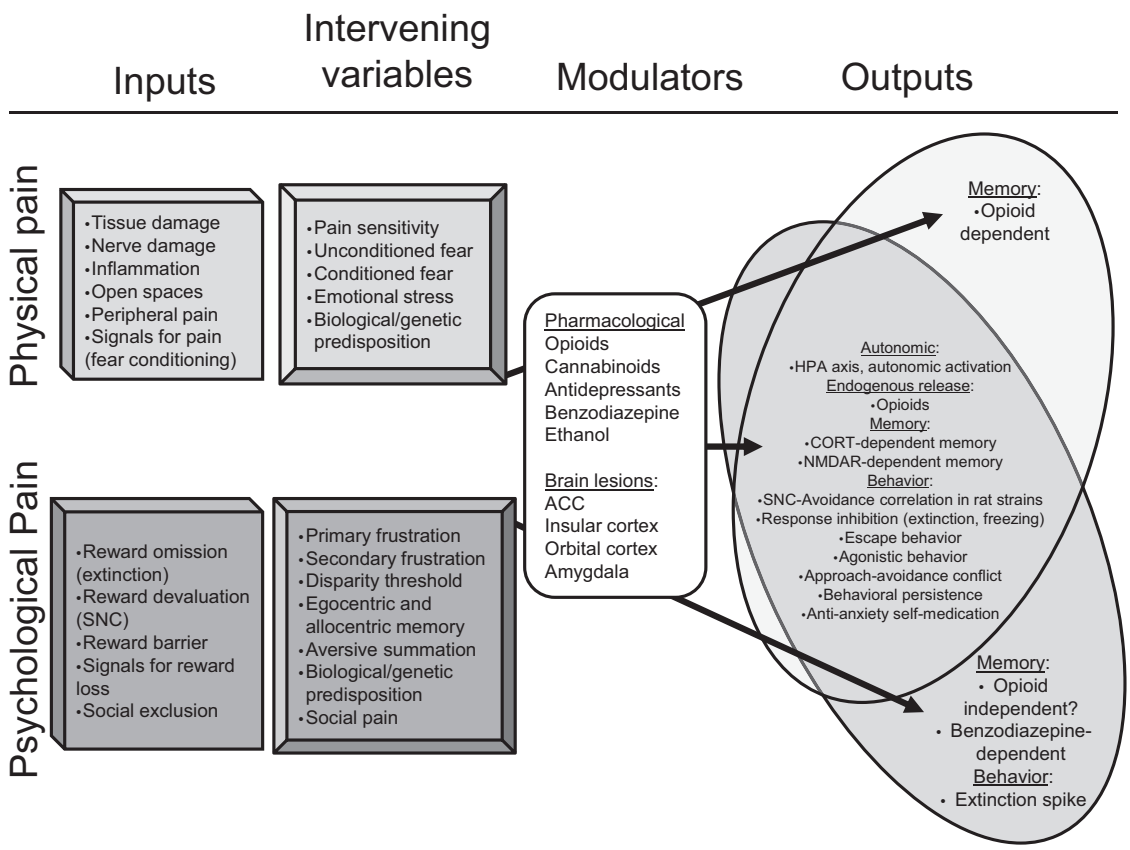

Fig. 1. A visual representation of some of the common and divergent aspects of psychological and physical pain discussed in this article. Following a parsimonious approach and for simplicity, social pain is considered here a special case of psychological pain. ACC, anterior cingulate cortex; HPA, hypothalamic-pituitary-adrenal axis; NMDA:,N-methyl-D-aspartate receptors; SNC, successive negative contrast.

have shown that whereas lesions of the insular cortex eliminate the cSNC effect, lesions of the ACC enhance it (Lin et al., 2009; Ortega et al., 2011b). Although brain imaging data are valuable, they are no substitute for other approaches, including lesions, microinfusions, gene-expression patterns, and behavioral manipulations.

The subjective experience of different types of emotion merits also some comments. The overlap in brain mechanisms of physical and psychological pain suggested that there is something fundamentally similar among these psychological states (e.g., Eisenberger et al., 2003). Iannetti et al. (2013, p. 375) claimed that the perceptions of "painful and non-painful sensations as well as between the experience of physical and social pain," are easily distinguishable, a claim that runs counter to the connections between pain/fear and frustration that led Gray (e.g., 1987) to suggest the "fear = frustration" hypothesis. We cited above these ideas as providing the initial recognition of the common ground between different types of pain and it may be appropriate to briefly consider their empirical origins. A series of studies published in the 1920s and 1930s suggested that participants injected with adrenalin, a drug causing sympathetic activation, could experience either positive or negative emotions depending on their initial state (see Schachter and Singer, 1979). Based on these data, Schachter and Singer (1962) designed a study in which participants injected with adrenalin were placed in a room together with a confederate instructed to engage either in positive (euphoria) or negative (anger) emotional displays. Later, participants reported emotional states consistent with the displays of the confederate, especially when the instructions received were misleading relative to the nature of the procedure. Schachter and Singer (1962) suggested that the emotional states induced by sympathetic activation were differentiated mainly on the basis of cognitive information about the triggering events. Thus, as Gray (1987, p. 174) put it, once an aversive emotional state is detected, labeling it as fear or frustration requires knowledge of "whether this turmoil was evoked by the sight of a snake or by a broken date." The notion that emotional states of equivalent hedonic value are difficult to differentiate is consistent with the aversive summation hypothesis described above in relation to experiments demonstrating the joined influence on behavior of separate sources of pain (e.g., Ortega et al., 2013). Similarly, the specificity of some treatments, including post-training corticosterone administration (Bentosela et al., 2006), to the reward loss condition (i.e., effects after 32-to-4% sucrose downshift, but not in the 4% sucrose unshifted control), is also consistent with the notion that exogenous activation works best in coincidence with an emotionally arousing experience (see Singer, 1963). It would be instructive to run experiments similar to the adrenalin studies described above, but correlating subjective reports with brain imaging data.

Another potential difference warranting further scrutiny relates to the role of opioid receptors in memory processes triggered by events involving physical or psychological pain (Papini, 2009). As noted above, there is evidence, albeit not extensive, that postsession opioid administration modulate consolidation after passive avoidance training (Izquierdo and Dias, 1983), but not after cSNC or appetitive extinction (Daniel et al., 2009). Interestingly, whereas the effect of postsession naloxone on passive avoidance is mediated by β-noradrenergic receptors in the amygdala (McGaugh et al., 1988), there is no evidence that such receptors affect the cSNC effect (see Flaherty, 1996). If the mechanisms underlying the encoding of reward-loss memories evolved by co-option from pain-fear memory mechanisms, as suggested by Papini (2003)

based on comparative evidence, then the homology may be only partial, not including opioid and adrenergic receptors.

Studies on physical pain in humans are usually dichotomized into acute and chronic pain (Cousins and Power, 1999) based on the etiology and temporal properties of the pain condition, with different symptom clusters associated with acute and chronic pain patients (Fishbain et al., 2014). Although acute physical pain can have important psychological implications, it is relatively well managed using pharmacological and non-pharmacological approaches (Cousins and Power, 1999). However, chronic physical pain can have long-term consequences beyond the obvious negative emotional implications (Apkarian et al., 2009; Fishbain, 1997; Gatchel et al., 2007). Animal models of reward loss can reproduce acute effects, as done in the cSNC and appetitive extinction situations reviewed in this article, but studies on chronic psychological pain show a more complex pattern of results. For example, reward uncertainty induced by extensive exposure to partial reinforcement training can have negative consequences even after hundreds of trials, suggesting lack of tolerance to surprising reward omission after chronic exposure (Ludvigson et al., 1979). However, extensive exposure to partial reinforcement can also reduce the disrupting effects of surprising reward omissions or devaluations (Cuenya et al., 2012; Pellegrini et al., 2004; Ross, 1964). Similarly, an isolated experience of appetitive extinction may have transient effects on behavior, but multiple extinction events can induce depression-like symptoms in biologically predisposed animals (Huston et al., 2013). Therefore, the issue of modeling chronic psychological pain in animals remains open for development.

It is also clear that psychological and physical pains are controlled by similar neural mechanisms that need to be studied in greater detail. Although the components of the neural circuit underlying the processing of psychological and physical pains remains to be fully identified, it is likely that the system encompasses the body-self neuromatrix that has been proposed to engage perceptual, behavioral, and homeostatic systems in response to injury and chronic stress (Melzack, 2001). Examining the complex interaction of different forms of "pain" will most certainly increase our understanding of how biological and psychological mechanisms contribute to the onset and maintenance of several psychological phenomena not obviously related. In addition to theoretical issues in learning theory, brain function, and evolution (Amsel, 1992; Bitterman, 1975; Gray and McNaughton, 2000), research on psychological pain may be relevant to the study of anxiety disorders (Papini et al., 2006), depression (Huston et al., 2013), chronic pain (Gatchel et al., 2007), addictive behavior (Manzo et al., 2014), and obesity (Adam and Epel, 2007), to name but a few. This review provides impetus for exploring these connections.

Acknowledgements

This paper was partially supported by grants from the TCU/Research and Creative Activities Fund, TCU/Invests in Scholarship, and Science and Engineering Research Center grants (USA) to MRP, and from Junta de Andalucía (HUM-642 and BIO-302), Ministerio de Ciencia e Innovación (PSI2010-15787 and PSI2009-10532), and Fundació la MARATÓ TV3 (092630/31) (Spain) to CT. The authors thank two anonymous reviewers, Ivan Annicchiarico, and Santiago Papini for useful comments on an earlier version of the article.

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