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Review

REVIEW

Making Sense of Rodent Models of Anhedonia

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Abstract

A markedly reduced interest or pleasure in activities previously considered pleasurable is a main symptom in mood disorder and psychosis and is often present in other psychiatric disorders and neurodegenerative diseases. This condition can be labeled as "anhedonia," although in its most rigorous connotation the term refers to the lost capacity to feel pleasure that is one aspect of the complex phenomenon of processing and responding to reward. The responses to rewarding stimuli are relatively easy to study in rodents, and the experimental conditions that consistently and persistently impair these responses are used to model anhedonia. To this end, long-term exposure to environmental aversive conditions is primarily used, and the resulting deficits in reward responses are often accompanied by other deficits that are mainly reminiscent of clinical depressive symptoms. The different components of impaired reward responses induced by environmental aversive events can be assessed by different tests or protocols that require different degrees of time allocation, technical resources, and equipment. Rodent models of anhedonia are valuable tools in the study of the neurobiological mechanisms underpinning impaired behavioral responses and in the screening and characterization of drugs that may reverse these behavioral deficits. In particular, the antianhedonic or promotivational effects are relevant features in the spectrum of activities of drugs used in mood disorders or psychosis. Thus, more than the model, it is the choice of tests that is crucial since it influences which facets of anhedonia will be detected and should be tuned to the purpose of the study.

Keywords: hedonic response, intracranial self stimulation, motivation, self administration, stress

Introduction

Anhedonia is listed in the DSM-5 (American Psychiatric Association, 2013) among the main schizophrenia negative symptoms, and it is defined as "the decreased ability to experience pleasure from positive stimuli or a degradation in the recollection of pleasure previously experienced." Similar concepts—loss of interest or pleasure, not feeling any enjoyment in activities that were previously considered pleasurable—are also reported among the main symptoms and criteria for the diagnosis of major depressive disorder (DSM-5, American Psychiatric Association, 2013). These symptoms are often associated with "social withdrawal." The condition of anhedonia, that is, in its stricter connotation, the loss of feeling pleasure, is the disruption of just one facet in a complex reward-processing phenomenon that encompasses pleasure expectation, reward evaluation, determination of the effort necessary to obtain it, and planning and deciding the appropriate strategy to repeat the pleasurable experience. A deficit in any of these aspects in the reward process may result in behaviors that could be interpreted as "anhedonia." For instance, the expression "a degradation in the recollection of pleasure previously experienced" refers to pleasure-triggered cognitive processes codified in brain areas and by mechanisms very likely different from those underpinning pleasure perception (Der-Avakian and Markou, 2012), and this is true either for the recollection of a previous pleasurable experience or for its degradation. Thus, although several authors strongly sustain that the definition of anhedonia should be restricted to a well-defined neurobiological construct (Berridge and Robinson, 2003; Smith et al., 2011; Der-Avakian and Markou, 2012),

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the term is often used both in the clinical evaluation of patients and in basic science experimental contexts in a broader connotation.

Anhedonia can be studied in its different aspects in humans and in nonhuman animals, ranging from different mammalian species, even productive animals (Figueroa et al., 2015), to zebrafish, the new promising, complementary model organism (Fontana et al., 2018). However, rodents are still the species most commonly used (Ellenbroek and Youn, 2016). Rewards of a different nature can be used to examine and experimentally dissect in its components the response to rewarding stimuli. Food is a stimulus very frequently used, since it is fairly easy to manipulate and the confounding variables can be identified and controlled with reasonable effort. Thus, this review will focus on rodent models and responses in different tests mainly to food stimuli.

Taste Hedonic and Food Intake

In animal studies, the most frequently used approach to evaluate the competence to experience pleasure is the sucrose preference test (Figueroa et al., 2015; Willner, 2017a), while the pattern of orofacial taste responses elicited by the consumption of palatable foods, including sucrose, is used as an index of the hedonic value of gustatory stimuli (Grill and Norgren, 1978). There is general agreement that pleasure perception is mainly mediated by μ-opiod (MOR) and endocannabinoid receptor stimulation in different brain areas, whereas the information encoded in mesolimbic dopamine neurons plays a central role in reward motivational value and motivational salience (Hajnal and Norgren, 2005). In striatal areas, MOR stimulation is considered to confer hedonic value in rodents and/or humans to different rewarding stimuli, including opiate drugs, palatable food, social interaction, music/art, sex, humor, and monetary gain (Haber and Knutson, 2010; Ikemoto, 2010), whereas a phasic increase in extraneuronal dopamine is believed to confer incentive salience to pleasurable stimuli (Berridge, 2007). That is, in striatal areas a single pleasurable stimulus may activate at the same time 2 distinct neurotransmitter systems with distinct yet concurrent influence on the development of the hedonic response. Morphine and opioid peptides have potent stimulatory effects on food intake (Morley et al., 1983; Hoebel, 1985; Reid, 1985) and opioid peptides are remarkably effective at driving food intake and/or enhancing taste hedonics from specific subcortical sites, notably the nucleus accumbens (NAc), the central nucleus of the amygdala, and the ventral pallidum (Baldo and Kelley, 2007; Smith and Berridge, 2007). Experiments using caloric and noncaloric palatable foods led to the conclusion that the hyperphagia induced by MOR stimulation in the NAc is independent of the caloric value of tastants and is associated with the suppression of satiety signals inhibiting food intake (Katsuura et al., 2011). Thus, a theory that has received considerable support through the years is that opioids specifically regulate palatability, that is, the pleasurable or "hedonic" aspects of food stimuli (Berridge, 1996).

Gustative and Hedonic Pathways

In rodents, the first central gustatory relay is the nucleus of the solitary tract that projects rostrally to the pontine parabrachial nuclei (PBN) (Lundy and Norgren, 2004). From the PBN, 2 gustatory pathways arise: the first projects to the ventroposteromedial thalamic nucleus (the thalamic taste area), which in turn sends efferents to the primary gustatory cortex, and represents the sensory pathway for taste (Lundy and Norgren, 2004). The second, the hedonic pathway, distributes widely in the hypothalamus and the ventral forebrain including the amygdala and the bed nucleus of the stria terminalis (Lundy and Norgren, 2004), and in turn these PBN target areas send axons to the shell portion of the NAc (NAcS) and the ventral tegmental area (VTA) (Lundy and Norgren, 2004). Thus, PBN is not merely a sensory relay station, but it also plays an important role in integrating various ascending and descending inputs (Hajnal and Norgren, 2005). Interestingly, MORs are already involved in pleasure perception after palatable food consumption at the level of the PBN (Wilson et al., 2003).

Early seminal studies have demonstrated that the gustatory value (i.e., the palatability) of sucrose, or glucose, is concentration dependent (Davis, 1973) and food deprivation dependent (Booth, 1972). Thus, both the increased sweetness and the caloric deficit increase the hedonic value of a palatable food. However, experiments carried out in chronically decerebrate rats outline a substantial difference between these 2 factors. Chronically decerebrate rats, in which neural connections between the forebrain and the brainstem are severed, maintain only the progressive strengthening of the gustatory response to increasing concentrations of sugar (Kaplan et al., 2000; Lundy and Norgren, 2004). The absence of food deprivation-induced increase in gustatory value in the decerebrate animal preparation (Kaplan et al., 2000) suggests the existence of an interplay between the PBN and the forebrain in mediating this effect in intact animals. Thus, the pure perception of the gustatory value of a palatable food seems to be restricted to the condition of non-food deprivation, as fasting superimposes a modulation of palatability at the forebrain level. From this perspective, the clear-cut distinction between feeling pleasure ("hedonic responses") and pleasure expectation, reward evaluation, and determination of the effort necessary to obtain it can only be hypothesized and tested in rigorous experimental settings, but it is probably quite blurred in a "real life" context.

Dopaminergic Signaling and Hedonic Motivation

Consumption of palatable foods, including sucrose, increases extraneuronal dopamine levels in the NAc, and this effect is concentration dependent for sucrose solutions (Hajnal et al., 2004). The PBN plays a central role in the control of NAc dopamine levels via its extensive connections to the ventral forebrain, and specific lesions in the PBN hedonic pathway abolish the sucrose-induced increase of dopamine levels in the NAc (Hajnal and Norgren, 2005). Although the role of dopamine in reward remains controversial (Salamone, 2003), dopaminergic activity, particularly in the mesolimbic system, does increase when normally preferred stimuli are encountered (Wise, 2002). Thus, phasic increases in extraneuronal dopamine levels in the NAcS are used as an index of the reward value of a sucrose stimulus. Such transient increases in extraneuronal dopamine modify dopaminergic signaling in striatal areas as essentially they stimulate the low-affinity dopamine D_1 receptors, while the high-affinity dopamine D_2 receptors are already stimulated by basal levels of extraneuronal dopamine (Nakanishi et al., 2014). Palatable food consumption-induced increase in extraneuronal dopamine levels in the NAcS confers incentive salience to the food stimulus (Berridge, 2007). This phasic increase in NAcS dopamine levels is associated in rats with consistent dopamine D1 receptor-sustained modifications in the phosphorylation pattern of some cAMP-dependent protein kinase (PKA) substrates such as the dopamine and cAMP-regulated phosphoprotein of Mr 32 000 (DARPP-32) (Rauggi et al., 2005; Danielli et al., 2010). In particular,

modifications in the phosphorylation levels of the Thr34 residue of DARPP-32 consistently correlate with phasic modifications in NAcS extraneuronal dopamine levels (Danielli et al., 2010). Similarly to what was reported for NAcS dopamine levels, modifications in the phosphorylation levels of Thr34 DARPP-32 in response to palatable food consumption are blunted in rats exposed to a chronic unavoidable stress paradigm that induces a condition of "motivational anhedonia," detected as a reduced performance in sucrose self-administration protocols (Marchese et al., 2013; Scheggi et al., 2017b). Moreover, the modifications in the phosphorylation levels of Thr34 DARPP-32 in response to palatable food consumption and the motivation to operate in sucrose self-administration schedules show slightly, yet consistently, distinct patterns according to the feeding condition of the animal (Danielli et al., 2010; Scheggi et al., 2013, 2018). In the medium spiny neurons of striatal areas, dopamine D_1 receptors are predominantly coexpressed with MORs (Chartoff and Connery, 2014), and while MORs are coupled with a $G_{i/o}$ protein and inhibit adenylyl cyclase activity, the dopamine D_1 receptor activates the PKA signaling cascade through a G_s protein. The transduction systems of the 2 receptors are then in functional competition in the neurons where they are coexpressed, yet they may also concur to elicit common effects (Scheggi et al, 2009). In fact, in neurons of the cortex and striatum that express both receptors, the MOR can form stable heteromeric complexes with the dopamine D_1 receptor (Juhasz et al., 2008). Moreover, in mice acute MOR receptor stimulation elicits the formation of a β-arrestin2-mediated signaling complex that results in activation of dopamine D_1 receptor signaling in the NAc (Urs et al., 2011). A condition of mild food deprivation in rats increases the levels of β-arrestin2-dependent heteromeric complexes of MOR-dopamine D_1 receptors in the NAcS, and in food-deprived rats the observed sucrose-induced increase in dopamine D_1 receptor signaling is β-arrestin2-dependent in this area (Scheggi et al., 2017a). The observation that a mild food deprivation induces a β-arrestin2-mediated increase in dopamine D_1 receptor signaling upon MOR stimulation by endogenous opioid peptides released in response to sucrose highlights how complex the interplay can be between the neuronal systems that subserve the different components of the reward response and that can be differently affected in conditions of broadly defined "anhedonia." Thus, a cautious approach is probably warranted when studying the phenomenon of anhedonia and the neurobiological systems underpinning its behavioral manifestations in animal models.

Models and Tests

An animal model of a psychiatric disorder can be defined as a construct that, inducing abnormal animal behaviors, aims to reproduce relevant phenotypic aspects of mental disorders. In particular, according to the National Institute of Mental Health Research Domain Criteria initiative that encourages the identification and treatment of specific behavioral symptoms (Insel et al., 2010), animal models should be developed and used to assess specific behavioral domains more than an entire psychiatric syndrome (Der Avakian and Pizzagalli, 2018; Slattery and Cryan, 2017), and "positive valence systems" is the domain that includes dimensions of reward processing (Cuthbert and Insel, 2013). However, with regard to animal models of depression, the term "model" is often employed to describe the methods used to assess depressive-like behaviors (tests) as well as the protocols that induce the depressive-like phenotype. The distinction between a "model" and a "test" is an important one as the "model" is the complex phenotypic construct that can only be revealed by "tests" of depressive-like responses (van der Staay, 2006; Cryan and Slattery, 2007; Cryan and Sweeney, 2011; Kara and Einat, 2013; Belzung, 2014; Slattery and Cryan, 2017). On the other hand, a test employed outside the context of a model, that is, in a "normal" animal, is of limited value as it assesses the normal behavioral repertoire of the species, or strain, in response to the challenge (represented by the specific test applied) (Belzung, 2014). Since the risk of developing a depressive disorder consistently increases in subjects exposed to repeated adverse life events (DSM-5, American Psychiatric Association, 2013), animal models based on chronic exposure to stress protocols are widely used to study the behavioral and neurobiological modifications that develop under these conditions, in the assumption that these may be a correlate of the human disorder (Slattery and Cryan, 2017). In addition to stress models that relay on environmental stressors and have been defined "exteroceptive," "interoceptive" stress models are also used that involve detection of "stressors" (proinflammatory mediators) from the internal environment (Sawchenko et al., 2000; Stepanichev et al., 2014).

Tests are then used to assess the validity of the model and the potential effect of a treatment. The two key domains usually tested in animal models of depression are reactivity to aversive stimuli (behavioral despair, hopelessness, or helplessness) and anhedonia (Figure 1). Several models of depression based on repeated stress exposure, including the chronic unpredictable mild stress (CMS), social defeat, and early-life stress protocols (Bolton et al., 2018), can induce a condition of "anhedonia," even though not all of these models, or not consistently, also induce behavioral despair (reviewed in Duman, 2010). In these models, face validity is provided by the development of depressive-like behaviors following a long-term exposure to stressors that is reminiscent of the chronic course of depression and by the findings that long-term but not acute antidepressant administration usually relieves anhedonia (Papp et al., 1996). Behavioral despair is primarily assayed in rodents by exposure to inescapable stressors, such as those used in the tail-suspension test (TST) in mice or forced-swimming test (FST) in mice and rats, and it is quantified as the proportion of time spent performing escape-related behaviors relative to time spent immobile, which is interpreted as a sign of behavioral despair or passivity (Porsolt et al., 1977; Steru et al., 1985). Reward-related measures are often used in animal models of depression since anhedonia, in its broad definition, is a core symptom of depression that can be assessed in rodents. In fact, rodents attribute hedonic value to a variety of stimuli that are also endowed with hedonic value for human beings, such as palatable foods (mainly sweets, e.g., sucrose or saccharin), social and sexual interactions, and drugs of abuse, and they will actively work to obtain these stimuli. These behavioral responses to reward are impaired in rodents by exposure to chronic stress protocols, and they should be rescued by established or novel clinically useful antidepressant and/or antianhedonic treatments. Different approaches can be used to measure hedonic responses in rodents, from the largely used and relatively simple-to-perform sucrose preference test to the more technically and time-demanding, and invasive intracranial self-stimulation (ICSS) protocol, and the behavioral modifications observed are in general responsive to antidepressant treatments (Willner et al., 1987; Zacharko and Anisman, 1991). However, one must keep in mind that sucrose preference test, ICSS, and other tests, for example, the conditioned place preference (CPP) test, measure the behavioral response of the animal to a reward, and the interest in reward and the levels of consummatory pleasure can only be inferred from such response.

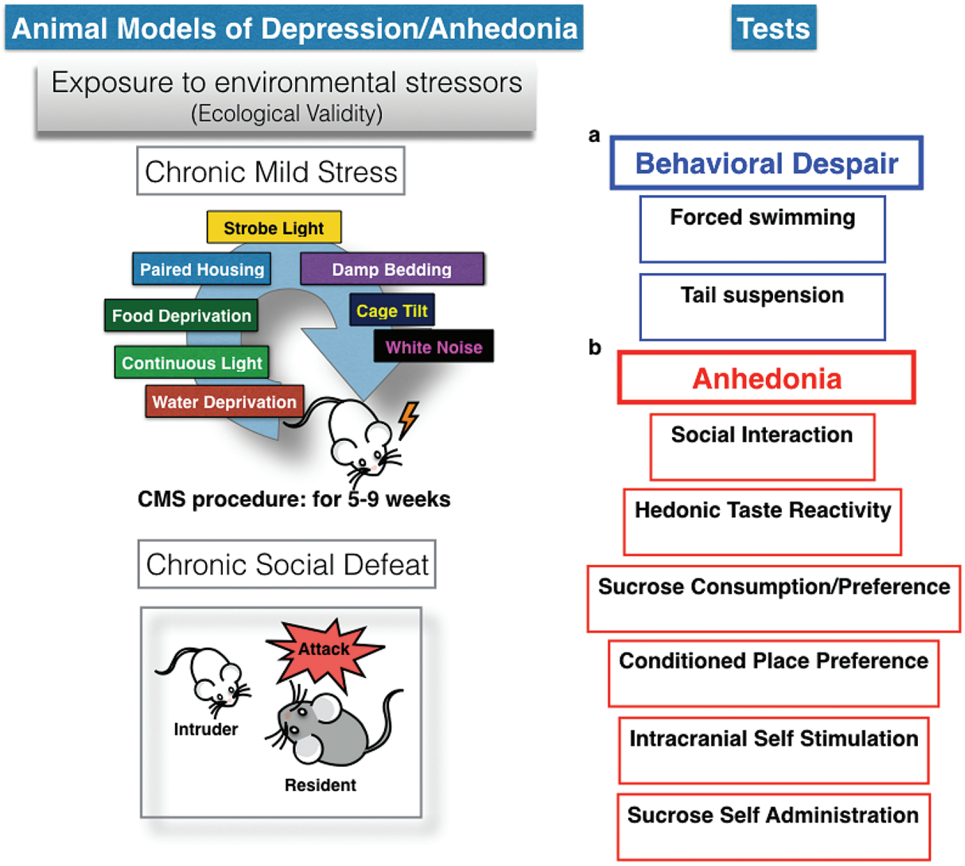

Figure 1. Rodent models of depression/anhedonia and behavioral tests used to evaluate reactivity toward aversive (a) and positive stimuli (b). The figure represents 2 of the most commonly used models that induce depressive- and anhedonic-like behaviors in rodents (chronic mild stress and chronic social defeat) and the behavioral tests primarily applied to these models to evaluate the reactivity toward aversive (a, behavioral despair) and rewarding stimuli (b, anhedonia). The chronic mild stress model of depression relies on a series of mild physical stressors that are presented in an unpredictable sequence for 5 to 9 weeks. The chronic social defeat model relies on an innate social behavior in adult male rodents that show a strong motivation to defend their territory (resident) against an unfamiliar male (intruder). The stronger resident predictably defeats the intruder and a stable dominant/subordinate relationship is formed. In the chronic protocol, the intruder is periodically subordinated by the territorially aggressive resident over a couple to several weeks.

Models

The Chronic Mild Stress Model

The CMS model derives from the studies published in the early 1980s by Katz and colleagues, in which rats were exposed to a sequence of different severe stressors, and stress effects were assessed using as readouts changes in open field behavior that were specifically reversed by repeated treatment with antidepressant drugs (Katz et al., 1981). Moreover, rats exposed to this stress protocol did not increase their fluid consumption when saccharin or sucrose was added to the drinking water, suggesting that this might indicate a decreased perceived hedonic value of the sweet solution (Katz, 1982). This hypothesis was then supported by the demonstration that exposure to uncontrollable foot-shocks elicits a decrease in ICSS behavior in mice, suggesting disturbances of motivational/reward processes that could be blunted by antidepressant administration (Zacharko and Anisman, 1991). These results stimulated the development of a model of stress-induced anhedonia. The model that was developed and validated uses stressors that can be defined as mild compared with the severe stressors used in the Katz studies and that have an ecological validity, representing possible environmental adverse situations (Willner, 2017a). The intense impact of the protocol on behavior derives from the exposure to an unremitting and unpredictable sequence of mild stressors that continues over several (5–9) weeks (Willner, 2017a). Rodents exposed to this protocol develop a pattern of behavioral modifications that may be considered as correlates of clinical symptoms of depression, in particular a decreased response to rewards (Figure 1). The CMS protocol has been adapted to mice (Monleon et al., 1995) and is today widely used in this species (Willner, 2017a). In the original version of the model, reward sensitivity is assessed by repeated tests before and during stress exposure in which the animal is given access to a palatable sweet solution (consumption test), or has the choice between a sweet solution and water (preference test). Consumption of, or preference for, the sweet reward decreases with exposure to the CMS protocol, but it can be restored to normal levels by long-term administration of different classes of antidepressant drugs (Willner, 2017a). The rationale for considering the CMS-induced decrease in sucrose intake or preference as a sign of anhedonia is based on the assumptions that consumption of a palatable sweet solution can be considered an index of the sensitivity to reward and that CMS exposure has a pervasive effect on the sensitivity to reward, rather than a selective effect on the response to sweets. This latter assumption is supported by the findings that CMS exposure also increases the threshold for ICSS in the VTA (Moreau et al., 1992) and impairs the development of CPP for different natural or pharmacological reinforcers (Papp et al.,

1991). However, a criticism to the first assumption is that anhedonic depressed patients may sometimes evaluate sweet tastes as less pleasant (e.g., Steiner et al., 1993), but more often the response to sweet tastes is not affected in depressed patients (e.g., Dichter et al., 2010). Since its first description, the CMS model has become one of the most frequently utilized models of depression and anhedonia. However, today many research teams use protocols of chronic exposure to sequences of mild stressors that differ, slightly or substantially, from the classical protocol and are labeled chronic unpredictable stress, unpredictable chronic stress, CMS, unpredictable chronic mild stress, and chronic varied or variate stress. A recent review shows that different names of the model do not strictly relate to the severity of the stressors used or predictability of the stressors (Willner, 2017a), and they usually yield similar results than the original protocol.

Despite its use in laboratories around the world and the recognition of its validity, the CMS model is often criticized for the lack of reproducibility of its effects. However, results from a recent survey of a large sample of users indicate that the CMS model is regarded as "generally reliable within, and robust across laboratories" (Willner, 2017b). The reliability of the model seems to be mainly influenced by few factors that should be carefully considered when planning to use it: the individual differences in the vulnerability to stressors, within and between rodent populations; the stressors used, which should be sufficiently intense to induce a stress response and sufficiently variable in their patterns of presentation to prevent the development of habituation; and the use of good laboratory practices, which are crucial when the sucrose test is the main outcome measure (Willner, 2017b). Individual differences in susceptibility to CMS in relation to strain differences have been demonstrated in mice between the more resilient DBA/2 and C57BL/6 and the more susceptible BALB/c strains (Griffiths et al., 1992; Farley et al., 2012). In rats, increased susceptibility to CMS has been reported for the Flinders Sensitive Line or Wistar-Kyoto strains (Pucilowski et al., 1993). Moreover, different susceptibility to CMS has also been reported among outbred Wistar rats from different suppliers (Theilmann et al., 2016). The variability in susceptibility to CMS within populations of animals of the same strain is usually regarded as a problem. However, the possibility to identify subgroups of CMS-susceptible and CMS-resilient rats or mice can be considered as an advantage since it allows the study of the neurobiological mechanisms underlying stress susceptibility and resilience (e.g., Couch et al., 2013; Nieto-Gonzalez et al., 2015; Rossetti et al., 2016).

Social Defeat or Social Stress

Animal models of social defeat stress have been developed based on the behavioral response of adult male rodents (residents) that show a strong motivation to defend their territory against unfamiliar males (intruders), such that a stronger resident-animal predictably defeats the intruder animal (Olivier and Mos, 1992). Thus, the experimental animal (the intruder) exposed to an ethological stressor, the aggressive socially dominant resident, develops specific behavioral modifications (mainly submissive behaviors) that are reminiscent of symptoms, such as anhedonia, social avoidance, despair, and anxiety, common to a number of psychiatric disorders including depression, posttraumatic stress disorder, and psychosis. The classical resident-intruder paradigm is based on dyadic agonistic encounters between adult male conspecifics and usually consists of a phase of physical contact during which the intruder is placed in the cage of the aggressive resident and exposed to its attacks, and a phase of sensory contact during which the intruder is in visual, auditory, and olfactory contact with the dominant resident, but it is protected from physical contact, to maintain a condition of psychological stress. Social defeat is defined as the intruder displaying submission signs (upright and sidewise posture, avoidance, fleeing, and freezing behavior) for a defined amount of time and the resident showing aggressive behavior (attack, escalated fight, chasing, rushing, and biting) (Kudryavtseva et al., 1991). Usually the physical interaction between the aggressive resident and the intruder lasts for a fixed period of time, or until defeat is observed, whichever presents first, when the experimenter intervenes to prevent severe physical injuries immediately after observing the established defeat criteria (Tornatzky and Miczek, 1993; Berton et al., 2006). The resident-intruder test is the classical paradigm of acute social stress and the model of social defeat is the chronic extension of this test. Exposure to social conflict in chronic protocols typically lasts from 10 (Berton et al., 2006) to 40 days (Bartolomucci et al., 2001). The most frequently used resident-intruder protocols are the chronic psychosocial stress model (Bartolomucci et al., 2001) and the chronic social defeat stress model (Berton et al., 2006), and, despite some differences in the experimental procedures, both protocols result in "social defeat." A different model that uses the resident-intruder protocol is the social defeat-induced persistent stress paradigm that consists of a short exposure to social defeat (5 encounters) followed by long-term exposure (2–3 months) to social isolation, a subthreshold stressor (Von Frijtag et al., 2000). The social defeat-induced persistent stress model is characterized by a long-lasting, anhedonic-like phenotype with social withdrawal and impaired processing of reward stimuli (Riga et al., 2015). In the social defeat model, animals show marked individual differences in their susceptibility or resilience to develop anhedonic-like behavior after chronic defeat (Der-Avakian et al., 2014), and these differences are more common in this model compared with the CMS model. The tests used to assess the behavioral consequences of chronic social defeat explore the domains of social behaviors (social avoidance), anhedonia, and reactivity toward aversive stimuli (Figure 1).

Immune-Mediated Models

An intricate interplay exists between the brain and the immune system and bi-directional communications between these apparently distinct systems have been implicated in the regulation of mood (Dantzer et al., 2008; Stepanichev et al., 2014). Depressed patients show increased levels of inflammatory markers in the periphery and brain, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α and T-cell activation markers (Dowlati et al., 2010; Maes, 2011). On the other hand, several inflammatory diseases or medical conditions that lead to chronic inflammation (e.g., cardiovascular diseases and type 2 diabetes) have a high co-morbidity with depression (Benton et al., 2007), and patients who undergo immunotherapy with interferon-alpha have an increased risk for developing depressive symptoms (Raison et al., 2006; Udina et al., 2012). Evidence indicates that stressors can activate the immune-inflammatory system and social experiences modulate such activation, exacerbating or reducing proinflammatory responses and mood disorders (Dantzer et al., 2008; Stepanichev et al., 2014). These data encouraged preclinical studies to investigate whether in stress-induced animal models of depression/anhedonia increases in immune-inflammatory system activation markers accompanied the development of behavioral impairments and whether

induction of an immuno-inflammatory response resulted in development of anhedonia and depressive-like behaviors. In different animal models of depression, inflammation and cell-mediated immune activation accompany the development of depressive-like behavioral responses, and antidepressant drugs that positively affect behavior also affect different markers of immuno-inflammation (Maes, 2011). In rats, exposure to the CMS protocol is accompanied by increased expression of pro-inflammatory cytokines IL-1β, IL-6, and markers and mediators of microglia activation, paralleled by a reduction of transforming growth factor-β expression (Rossetti et al., 2016). The significance of these results is supported by the selective increase in immuno-inflammatory markers in rats showing reduced sucrose intake in the sucrose consumption test, but not in resilient animals (Rossetti et al., 2016). A recent study in mice shows that exposure to a chronic social stress protocol activates the immune-inflammatory system in the periphery and in the VTA-NAc dopaminergic pathway, reducing mesolimbic dopaminergic transmission (Bergamini et al., 2018). At the behavioral level, defeated mice show a decrease in operant responding for sucrose in tests validated as sensitive assays for NAc dopaminergic activity, thus suggesting a possible mechanism for a causal correlation between immuno-inflammatory activation and anhedonic-like behaviors (Bergamini et al., 2018). Recent clinical and preclinical studies suggest that vulnerability to increased immune-inflammatory stimuli after a significant stress could be related to impaired integrity of the brain blood barrier around the NAc and may represent the link between stress exposure and development of depressive symptoms (Cooper et al., 2018).

In rodents, immune activation elicited by immune challenges, for example with the peripheral induction of cytokines by administration of bacterial lipopolysaccharide (LPS), induces an increase in proinflammatory cytokines also in the brain in regions such as the hippocampus and prefrontal cortex (Dantzer et al., 2008; Stepanichev et al., 2014; Jaehne et al., 2015), accompanied by a behavioral syndrome with a distinct time course that includes depression-like traits. In the first hours after the challenge, animals show what is defined "sickness behavior," characterized by fever, reduced food and water intake, reduction of locomotor and exploratory activity, and decreased social interaction (Dantzer et al., 2008; Stepanichev et al., 2014). Then, when the sickness behavior wanes, animals show a depressive-like phenotype, with anhedonia and behavioral despair (Dantzer et al., 2008; Painsipp et al., 2011; Jaehne et al., 2015). The observations that repeated antidepressant treatments attenuate some of the behavioral effects of immune challenge, such as decreased preference for sweet solutions and social interactions and decreased reactivity to aversive stimuli (Dantzer et al., 2008; Stepanichev et al., 2014), support the validity of immune-mediated models. Moreover, some second-generation antipsychotic drugs have been tested for their potential effects on LPS-induced neuroinflammation and behavioral impairments with conflicting results. The repeated administration of quetiapine or its metabolite norquetiapine before the LPS challenge induces a favorable balance in the levels of some pro- and antiinflammatory cytokines in the periphery and brain 4 hours after the challenge. However, this effect is not observed at 24 hours, when a lack of activity was also observed on LPS-induced decreased preference for a sweet solution (Jaehne et al., 2015).

An important bias in these experimental models is the occurrence of cytokine-induced sickness behavior that is characterized by a behavioral repertoire partially superimposable to depressive-like behaviors. The reduced food intake also causes decreased consumption of palatable foods that mimics anhedonia, while the reduced motor activity mimics the increase in immobility in tests of behavioral despair, such as the forced swimming and tail suspension tests (Dantzer et al., 2008). Thus, in these models specific depressive-like behavioral responses should be observed in immune-stimulated rodents independently of sickness-related impairments in performance, and this involves an accurate choice of doses and time intervals for the assessments. In mice, a dissociation between nonspecific, sickness-induced decreases in locomotor activity and food and water intake and, respectively, depressive-like behavioral responses in the FST and TST and in the sucrose preference test has been demonstrated by testing animals at the peak of the sickness syndrome (6 hours) and at 24 hours, when sickness was expected to be minimal (Frenois et al., 2007). Moreover, in rats, the administration of the proinflammatory cytokine IL-1β impairs effort-related choice behavior at doses that do not reduce food intake or affect preference for the highly palatable pellets and do not increase core body temperature (Nunes et al., 2014). These results indicate that carefully designed experimental models are useful tools to investigate the possible role of proinflammatory cytokines in different aspects of anhedonia, consummatory or motivational, such as anergia and fatigue.

Responses to LPS challenge are influenced by several factors. A recognized factor is the genetic background, as Fawn-Hooded rats, that show some of the behavioral traits of a depressive-like phenotype are more sensitive than Sprague-Dawley rats to IL-1β -induced immobility in the FST (Dantzer et al., 2008) and different mouse strains show different vulnerability to immune challenge (Painsipp et al., 2011; Stepanichev et al., 2014). The psychosocial context is another relevant factor in modulating responses to immune activation, and thus housing (single vs group housing) or sex may influence the effects observed (Frenois et al., 2007; Painsipp et al., 2011; Stepanichev et al., 2014). Another variable that influences responses to immuno-challenge is the age of animals. Inconsistent results have been reported on long-term behavioral consequences of immuno-challenges performed prenatally or at early stages of postnatal development (Stepanichev et al., 2014), while aging is associated with increased immune system activation, with an enhanced production of proinflammatory cytokines in the brain. Aged mice respond to LPS challenge with a higher brain inflammatory response accompanied by a more severe sickness behavior and depressive-like behavior compared with younger adults (Godbout et al., 2008).

Tests

Reactivity Toward Aversive Stimuli: Behavioral Despair

The FST and TST were developed, and are still frequently used, to test the efficacy of antidepressant drugs on the behavioral despair induced by acute exposure to the test itself (Porsolt et al., 1977; Steru et al., 1985). In these tests, behavioral despair is defined as increased immobility or decreased latency to immobility. The tests can also be used to assess the reactivity toward aversive stimuli in models of depression/anhedonia. Increased immobility in the FST has been reported following CMS, immune-mediated models, or acute and chronic social defeat in rats (Rygula et al., 2005; Becker et al., 2008). In mice, however, effects of social defeat exposure on the FST and TST are not consistently found (Kinsey et al., 2007; Krishnan et al., 2007). The FST, which measures the immobility that a rodent displays when immersed in a beaker filled with water from where no escape is possible, was introduced for screening

compounds with potential antidepressant activity (Porsolt et al., 1977). The FST has become a popular test frequently used for identifying potential antidepressant compounds and assessing the induction of a depressive phenotype in chronic models, with the anthropomorphical assumption that immobility in the test represents a facet of depression. However, when using and interpreting the FST, we should also remember that a switch from active to passive behavior in response to the acute stressor (forced swim) is the expression of an adaptive response, based on learning processes, that increases the chances of survival (Molendijk and de Kloet, 2015; Olney et al., 2018).

Tests for the Assessment of Anhedonia

As highlighted in the Introduction, the reward process involves multiple components that can be dissected experimentally, but are likely intermingled in real life situations: (1) the sensory detection of the stimulus, (2) the affective hedonic reaction, pleasure itself (liking), (3) the motivation to obtain the reward and work for it (wanting or incentive salience), and (4) the reward-related learning processes. In many studies of chronic stress models, the consumption of, and/or preference for, sweet solutions is used as a measure of gustatory hedonic behavior in rodents. Such tests, initially used in the CMS model, were then applied to the chronic social stress models (Rygula et al., 2005). Social defeat induces anhedonia, assessed as sucrose preference, only after long-term exposure (10 days or longer) (Yu et al., 2011), but not after a single defeat episode (Razzoli et al., 2011) or a shorter exposure (Von Frijtag et al., 2002), similar to what was observed in the CMS model, where anhedonia is usually evident after 3 to 4 weeks of stress exposure (Willner, 2017a). In immune-mediated models, such as those induced by LPS or IL administration, the development of anhedonia is often assessed by measuring the consumption or preference for sweet solutions (Stepanichev et al., 2014), but protocols probing motivational effort-related aspects of anhedonia for sweet rewards have also been successfully used (Nunes et al., 2014).

Social Interaction Test

Social motivation is a powerful drive of human behavior, and the disruption of social motivational mechanisms can represent a primary deficit (Chevallier et al., 2012). Accordingly, the Autism Spectrum Disorder can be regarded as an extreme case of early-onset diminished social motivation, or social reward deficit (social anhedonia) (DSM-5, American Psychiatric Association, 2013). Among social behaviors, sexual activity is highly rewarding for humans and animals (Trezza et al., 2011) since it induces a condition of well-being, pleasure, motivation, and associative learning (Berridge and Kringelbach 2008); a decrease in sexual drive is often seen in depressed patients. Like humans, mice and rats are social species and display a wide repertoire of social behaviors, engaging in reciprocal social interactions, parenting and mating behaviors, social play among juveniles, scent marking and aggressive behaviors, and behavioral assays have been developed to assess the aspects of sociability in rodents (Trezza et al., 2011). Diverse place conditioning paradigms are available that rely on the rewarding nature of social interactions, such as CPP induced by social play behaviors in juvenile animals, pup interactions in postpartum dams, interactions with conspecific in adult rodents, and sexual behavior (Trezza et al., 2011). However, the test most commonly used to assess impairments in social reward processing is the social interaction test (Figure 2d). In rodent models, stress-exposed animals spend significantly less time in proximity to a social target compared with control animals in a social interaction test (Berton et al., 2006), and the response to this test is used to distinguish susceptible from resilient animals. However, although chronic exposure to social defeat stress quite consistently results in social avoidance or decreased social approach in a variety of tests to measure social behavior (see Hammels et al., 2015), the influence of CMS or other chronic unavoidable stress protocols on social

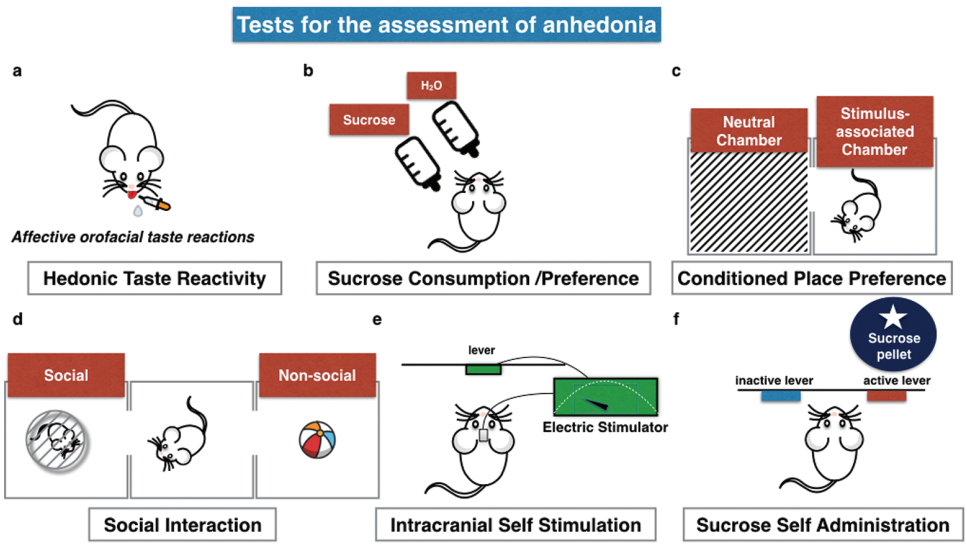

Figure 2. Schematic representation of some of the behavioral tests used to assess deficits in the responses to reward in rodents. In the hedonic taste reactivity test (a), affective reactions to a palatable sucrose solution are measured. In the sucrose consumption or preference test (b), the choice between a sweet solution and water is determined. In the conditioned place preference protocol (c), the preference for the chamber where the rewarding stimulus was previously presented compared with the neutral chamber is evaluated. In the social interaction test (d), the amount of time spent in proximity to a social compared with an inanimate target is determined. In the intracranial self stimulation protocol (e), the operant behavior that allows animals to self-stimulate specific regions in the brain reward circuitry by pressing a lever or turn a wheel is evaluated. In the sucrose self-administration protocol (g), the operant behavior that allows animals to self-administer a palatable food by pressing a lever is evaluated.

behavior is less consistent and has been explored to a lesser extent (D'Aquila et al., 1994). Conversely, social deficits characterize the behavioral phenotype of immune-mediated models (Stepanichev et al., 2014). The test has also been used to evaluate the ability of an intra VTA acute or short-term optogenetic stimulation to change the condition of susceptibility to resilience in mice, thus elucidating cellular mechanisms and neural circuits specifically involved in determining individual reactivity to a chronic social stress (Chaudhury et al., 2013; Friedman et al., 2014). A decrease in sexual activity, or sexual drive, has also been described in rodents after exposure to CMS (D'Aquila et al., 1994; Grønli et al., 2005). Moreover, impairments in sexual behavior are considered an index of anhedonia in other animal models of depression, such as the Flinders Sensitive rats (Ferreira-Nuño et al., 2002).

Female Urine Sniffing Test

The female urine sniffing test is a nonoperant protocol that measures reward-seeking behavior in rodents and is based on the interest in pheromonal odors from the opposite sex (Makelsman et al., 2010). In mammals, sexual activity is a primary stimulus and sexual behavior-associated chemosensory cues play a crucial role in social communication and in orienting behavior and affecting physiology. The rewarding value of sniffing estrus female urine by male rodents is supported by the ultrasonic vocalizations emitted in the presence of females or elicited by exposure to urinary pheromones (Wysocki et al., 1982). The test has 3 phases: a 3-minute exposure to a cotton tip dipped in sterile water; a 45-minute interval (no cotton tip is presented); and a 3-minute exposure to a cotton tip dipped in fresh urine collected from estrus females of the same strain. Sniffing duration is measured during exposure to water and female urine exposure (Malkesman et al., 2010). Exposure to female urine is accompanied by emission of ultrasonic vocalizations and increased dopamine levels in the NAc compared with levels during water exposure, supporting the rewarding value of the chemosensory cue (Malkesman et al., 2010). The tests has been validated in different strains of mice and in rats, and exposure to different stress models reduces the duration of female urine sniffing (Malkesman et al., 2010).

The advantages of the test are that it is simple and not time consuming. Moreover, it allows the evaluation of spontaneous reward-seeking behaviors and is not affected by possible impairments in taste, motor activity, or learning and memory processes. The limitations of the female urine sniffing test are that the response can be affected by pharmacological or genetic manipulations that impair olfactory system functions, or the sex hormone system may be dysfunctional in the model animal. Estrus female pheromonal odors also represent a social stimulus and a more general decrease in social motivation reduces female urine sniffing (Wersinger et al. 2004). Finally, the test has been developed for male rodents and has not yet been adapted to female testing.

Hedonic Taste Reactivity

Anhedonia, in its most narrow meaning, is considered to reflect a condition of reduced liking that can be regarded as the affective expression of pleasure in response to a sensory reward (Figure 2a). Liking reactions to sweet taste can be measured in rodents since they show affective facial expressions of taste pleasure ("liking") (Berridge, 1996). After consumption of a sweet solution (generally a sucrose solution), facial expressions, and patterns of licking are recorded in rats or mice and affective responses are scored. Hedonic responses include rhythmic midline and lateral tongue protrusions and paw licks. On the other hand, gapes, head shakes, face washes, forelimb flails, and chin rubs observed after exposure to unpleasant tastants are considered aversive responses, while passive dripping of solution out of the mouth, ordinary grooming, and rhythmic mouth movements are neutral responses. The licking behavior is also considered an index of hedonic response to reward, as the size of licking bouts is positively related to the palatability of the solution (Berridge, 2000). In an individual animal, totals of affective reactions are calculated for hedonic vs aversive categories by adding all response scores within an affective category (hedonic, aversive, and neutral). To examine the hedonic sensitivity to sensory rewards, the taste reactivity (TR) test is employed, which is considered to measure the hedonic value attributed to stimuli. In the TR test, a solution is presented to the animal and the oral facial reactions to that tastant are assumed to reflect its palatability. Palatable sucrose solutions elicit hedonic TR behaviors (rhythmic and lateral tongue protrusions), whereas aversive quinine solutions elicit aversive TR behaviors (e.g., gapes). Hedonic-appetitive and aversive taste reactions are highly conserved, and similar oral facial affective responses are seen in human infants, adult primates, and rodents. The TR test has been originally developed for rats by Grill and Norgren (Grill and Norgren, 1978) and the complete procedure is detailed in (Wilmouth and Spear, 2009). The hedonic TR test has also been used to identify and characterize the hedonic "hot spots," mainly in the NAc and ventral pallidum, where local microinfusions of opioid agonists or manipulations of the endocannabinoid system increase liking reactions and/or food consumption (Richard et al., 2013). On the other hand, the hedonic TR test is seldom used as readout of anhedonia in animal models, since it is hardly affected by pharmacological manipulations, in particular of the dopaminergic system (Berridge and Robinson, 1998; Berridge, 2000; Pardo et al., 2015) or by exposure to anhedonia-inducing protocols. However, we observed a reduction in hedonic TR responses in "anhedonic" cocaine-sensitized rats (Scheggi et al., 2011) and in rats exposed to a 21-day chronic unavoidable stress protocol (Gambarana et al., 2003); both these chronic conditions are characterized by low baseline dopamine levels and blunted dopaminergic response to sucrose in the NAcS. Another reason for a limited interest in the use of this test in the characterization of animal models or in the study of the response to antianhedonic treatments is that clinical evidence suggests that "taste anhedonia" does not play a relevant role in the reduced positive affect reactivity of depressed or psychotic patients.

Sucrose Consumption/Preference Test

The consumption of, or the preference for, palatable sweet solutions, sucrose or saccharin, is the most frequently used test to measure sensitivity to reward in rodents. Animals can choose between a palatable sweet solution and plain water (Figure 2b). Thus, the decreased consumption of, or preference for, palatable solutions that can be observed after CMS or chronic social defeat exposure is considered to reflect a condition of "hedonic deficit," or anhedonia (Willner, 1997; Slattery et al., 2007; Krishnan and Nestler, 2011). This test is considered as a readout of liking because the decrease in sucrose consumption is not related to the caloric content and does not reflect a general decrease in consummatory behavior (Willner, 1997). Sucrose intake is correctly calculated as the amount of consumed sucrose in milligrams per gram body weight, while the preference for sucrose is calculated as the percentage of consumed sucrose solution over the total amount of liquid intake and is a more reliable measure of the animal response to a sweet solution. The criterion for

anhedonia in the sucrose preference test is usually a preference for sucrose <65%, based on studies that demonstrate that mice and rats with a sucrose preference <65% also showed increased threshold for ICSS (Moreau et al., 1992), decreased latency and increased duration of REM sleep (Cheeta et al., 1997), reduction of sexual activity (D'Aquila et al., 1994), and alterations of circadian rhythms (Solberg et al., 1999). Thus, the criterion for anhedonia measured as a decrease in sucrose preference (consummatory anhedonia) is typically fulfilled by rodents that also show behavioral and physiological modifications that can be considered as correlates of symptoms and signs of depression and contribute to define a depressive-like syndrome. Mice and rats that reach this criterion are considered anhedonic and sensitive to the stress model. The animals exposed to the stress model that show a sucrose preference >65% are considered non-anhedonic and resilient to the stress.

The advantages of the test, which explain its popularity in laboratories throughout the world, are that it is not technically demanding or time-consuming, and possible modifications in motility, anxiety, and learning induced by the exposure to one of the stress models do not significantly affect the response in the test. The disadvantages are the variability in the results obtained in different laboratories, or the low reproducibility in the same laboratory, often related to low adherence to good laboratory practices (size of the bottles, accuracy in removing and placing again the bottles in the cage, frequency of switching position of the bottles, etc.) (Strekalova et al., 2004). Moreover, a recent study demonstrated that the standard practice of handling mice by their tails, as opposed to tunnel handling, decreases responses to reward in terms of sucrose consumption and licking bouts (Clarkson et al., 2018). Thus, careful attention to details should be paid when performing the sucrose test, and one should be aware that even common laboratory practices can influence the affective state of experimental animals and their responses to the test. Important factors that can influence the test outcome are the duration of the test, food and water deprivation, and concentration of the sucrose solution. Factors not strictly related to the hedonic state (e.g., interindividual differences in the pattern and amount of liquid intake, neophobia in animals naive to sucrose) are more likely to influence sucrose intake when the test lasts only a few hours, while they have a lesser impact in a 24-hour test. Circadian pattern in fluid and calories intake will also have a lesser impact on a 24-hour test. Food and water deprivation represents an acute stressor that affects the test, and when applied for many hours (e.g., 24 hours), it adds to the purely hedonic nature of the sucrose solution a caloric value. Thus, food and water deprivation, albeit frequently used, may represent a confounding factor (Strekalova et al., 2004). The concentration of sucrose solutions also represents a relevant variable as a U-shaped curve is often observed in rodent preference for sweet solutions (Willner, 2017b). Exposure to stressors reduces in rodents the consumption of diluted sucrose solutions, while it increases consumption of concentrated solutions (Willner, 1997). Similar results have also been obtained in pigs exposed to repeated social or restraint stress, suggesting conserved stress influences on consummatory hedonic responses (Figueroa et al., 2015). Furthermore, a sucrose solution has a caloric content, and with increasing sucrose concentration the likelihood of metabolic influence on intake increases. Thus, a 1% sucrose solution is often used, especially in 24-hour tests, as its consumption is more sensitive to stress exposure and less sensitive to motivational manipulations, such as food deprivation, than the consumption of more concentrated solutions. The caloric content of the sweet solution influences the assessment of consummatory anhedonia as exposure to a stress protocol does not reliably affect intake or preference for a sweet solution when a noncaloric saccharin solution (0.1% saccharin) is used, and the effect of stress exposure on saccharin intake appears to be dependent upon the duration of water deprivation that preceded the test (e.g., Harris et al., 1997; Grønli et al., 2005). Another possible factor that may influence the test outcome is that a loss in body weight can be observed in rodents exposed to a chronic stress protocol (more often in the CMS than in the social defeat model). A reduction in body weight is accompanied by a reduction in caloric needs that will affect sucrose intake. Sucrose intake is then more reliably calculated as the amount of consumed sucrose per gram body weight. Rodents may also show a side preference in drinking behavior that can affect the test outcome (Strekalova et al., 2004). For this reason, the position of the water and sucrose solution bottles is switched during the test. However, a frequent switch of the bottles may represent a subtle stressor for the animals and may increase the error in measuring the amounts consumed since few drops may be lost at every change of position (Strekalova et al., 2004).

Conditioned Place Preference

The CPP protocol evaluates the preference of an animal between 2 distinct environments: one where a stimulus was previously presented and the other where it was not (Bardo and Bevins, 2000) (Figure 2c). The protocol is based on classical (Pavlovian) conditioning, as neutral environmental cues (conditioned stimuli) can evoke approach behavior when they are repeatedly paired to a rewarding stimulus (unconditioned stimulus). CPP can be induced by natural rewarding stimuli (e.g., food or positive social interactions) or by psychoactive drugs, and it is often used as a first step in the assessment of the abuse liability of a compound. In experimental models of anhedonia, the preference for the environment paired with a reward (often a palatable food) can be evaluated. The CPP apparatus has 2 chambers with distinctive features (color and pattern of the wall, floor characteristics) separated by a small intermediate area. Rodents are exposed for several days to the freely available palatable food in one chamber, alternated with exposure to the other empty chamber. On the test day, they are free to explore the whole apparatus and are tested for side preference in the absence of the reward (Figure 2). Animals not exposed to a stress model show an increased preference for the environment where a reward was received (paired with the reward), while stressed animals show a reduced or abolished preference. This effect can be reversed by long-term antidepressant administration, as originally shown by Willner and colleagues in the CMS model (Papp et al., 1991). Although this protocol was suggested to assess the incentive motivation to obtain a reward, the interpretation that the performance of stressed animals in the CPP may result from a failure in reward reinforcement learning has also been proposed (Huston et al., 2013). CPP can also be induced by positive social interactions, such as sexual behavior, social play, or maternal behavior (Trezza et al., 2011). Social-CPP (SCPP) has been used to assess social anhedonia in a genetic model, the Disrupted-in-schizophrenia-1-Q31L mutant mouse, that shows decreases in monoamines content, in levels of β-arrestin-1,2 and CREB, and in spine density in the NAc (Lipina et al, 2013). Pair-bonding among cagemates is rewarding in adult mice that acquire SCPP, but not in mutant mice that have deficits in social hedonic responses. Interestingly, bupropion repeated treatment eases the anhedonic behaviors in Disrupted-in-schizophrenia-1-Q31L mutant mice, allowing SCPP acquisition, while desipramine and fluoxetine administration do not (Lipina et al, 2013).

These results support the role of the mesolimbic dopaminergic system in social rewards processing (Lipina et al, 2013). However, protocols based on social rewards are less frequently used when characterizing a model of anhedonia or studying the efficacy of a treatment. Psychoactive drugs induce CPP, but in the context of anhedonia models the results reported are quite variable, as they are influenced by the class of the drug used, the dose and pattern of administration, the species, and the construct of the model.

Intracranial Self-Stimulation

ICSS is an operant procedure in which rodents can self-stimulate specific brain regions in the reward circuitry (e.g., posterior lateral hypothalamus, medial forebrain bundle, VTA) through chronically implanted electrodes. Animals learn to press a lever or turn a wheel to receive the electrical stimulation (Figure 2e), and acquisition of the task is almost immediate in normal animals. Responding in ICSS protocols is sensitive to manipulations that affect reward, as the stimulation threshold is reduced in conditions that facilitate reward and is increased in conditions characterized by anhedonia, such as withdrawal from drugs of abuse or depression models. In particular, in the CMS model, an increased ICSS threshold and a reversal of this effect by antidepressant treatment has been described in rats (Moreau et al., 1992), albeit not all the studies successfully reproduced these results (Nielsen et al., 2000). In the social defeat model, susceptible rats show increased ICSS threshold immediately after defeat, and this increase continues throughout the stress protocol and can be still observed 3 weeks after the end of stress exposure (Der-Avakian et al., 2014). In contrast, resilient rats show an immediate increase in ICSS threshold, but the threshold quickly returns to baseline despite chronic exposure to social defeat (Der-Avakian et al., 2014). Moreover, only in subgroups of susceptible rats did the ICSS threshold return to baseline after repeated antidepressant treatments (Der-Avakian et al., 2014). Exposure of mice to a chronic social defeat protocol elicits an increase in ICSS threshold that is maintained during social stress exposure and persists for 5 days after the end of the stress protocol (Donahue et al., 2014). The same study also showed that mice overexpressing ΔFosB in striatal dopamine D_1 receptors expressing medium spiny neurons that are less susceptible to the effects of chronic social stress exposure on social avoidance are also less vulnerable to stress effect on ICSS thresholds (Donahue et al., 2014). The acute administration of ketamine to susceptible mice positively affects social avoidance but not the increase in ICSS threshold, suggesting that distinct neural circuits are involved in the regulation of distinct behavioral responses (Donahue et al., 2014).

A relevant advantage of ICSS compared with food self-administration is that responding is not influenced by satiation or stress-induced anxiety, and the response rate increases with the intensity of the stimulation, usually in terms of increase in the frequency (Hz) of the stimulus. Moreover, in well-trained animals, the stimulation threshold is quite constant and allows longitudinal evaluations of the effects of exposure to long-term stressors and/or treatments (Carlezon and Chartoff, 2007). The distinct responses on ICSS protocols of susceptible and resilient animals underscore the almost unique advantage of this procedure that allows the longitudinal study of the development of anhedonia, its consolidation only in susceptible populations, and the possible effects of treatments (Der-Avakian et al., 2014). Moreover, performance in ICSS protocols is considered a measure of motivation but also of the rewarding value of a stimulus, and for this reason it is still regarded as the gold standard assay to determine the abuse liability of a compound (Rizvi et al., 2016). The disadvantages are that the ICSS procedure is invasive and technically demanding, and it is not a reasonable first choice in screening studies of new molecules with potential antidepressant and/or antianhedonic effects. Moreover, performance in ICSS protocols is influenced by possible impairments in motor activity, learning, and memory processes.

Self-Administration

Several protocols have been developed to study motivational processes in animal models by examining behaviors aimed at obtaining natural rewards, such as food. The motivation to obtain a reward can be determined, for example, by protocols that measure how eagerly the animal runs for the reward in a runway (Ghiglieri et al., 1997; Pecina et al., 2003; Grappi et al., 2011) or by food self-administration protocols, as rodents can be trained to operate, usually to press a lever, to self-administer a palatable food (Figure 2). The palatable food is often sucrose, and even rats that are not food deprived can be easily trained to operate for it. In self-administration protocols, the schedule used to assess the motivation to work for a natural (or a drug) reward is commonly the progressive ratio (PR) schedule (Hodos, 1961) where increasing effort is required to obtain the reward as the ratio requirement progressively increases, and the last ratio completed is the breaking point. The breaking point measures the effort the animal is willing to exert to obtain the reinforcing stimulus and is then considered an index of motivation, or of the perceived reinforcing value of the stimulus. Thus, a decrease in breaking point may be regarded as a core symptom in animal models of anhedonia, although this decrease is not reliably observed in all the models. Reductions in breakpoints for sucrose have been reported in a genetic animal model of depression, the congenital learned helpless rat (Vollmayr et al., 2004), in a chronic unavoidable stress protocol in rats (Marchese et al., 2013; Scheggi et al., 2016), and in rats and mice exposed to chronic social defeat (Bergamini et al., 2016; Spierling et al., 2017). This index of reduced motivation for a natural reward can be restored to control values by treatments endowed with antidepressant and/or promotivational activity, for example, lithium, clozapine, aripiprazole, and lamotrigine (Marchese et al., 2013; Scheggi et al., 2015, 2017b; Scheggi, Pelliccia, De Montis and Gambarana, unpublished data). Conversely, exposure to the CMS model does not usually affect sucrose breaking point.

Possible confounding factors can affect response in the PR schedule; for example, satiety may reduce the motivation to work for further calories, the progressively increasing response requirement causes increasing time intervals between reward availability and may induce decreased breakpoints, overtraining may switch the goal-directed behavior into a habit that is no longer sensitive to the value of the reward (Balleine and Dickinson, 1998), or a reduced locomotor performance may nonspecifically impair responding. Moreover, it is still a debated issue what the breaking point actually measures since it is difficult to dissociate the motivational from the hedonic aspects of responding in a PR schedule as the manipulations used to modulate 1 of the 2 aspects of the reinforcer (e.g., food deprivation to increase motivation and different sucrose concentrations to vary the hedonic properties) actually affect both. Since motivation translates into action whereas the hedonic experience of the stimulus does not require action, operating for reward in a PR schedule is largely regarded as a measure of motivation. As previously noted, we tend to infer "liking" from a choice the animal makes or from the willingness to operate to obtain a stimulus, but we do not have a direct measure of it. Similarly, we do

not know whether a stimulus does or does not retain hedonic properties for the animal that stops responding in the PR schedule (Der-Avakian et al., 2016; Kissileff and Herzog, 2018). Thus, as suggested in the Introduction, the 2 aspects that sustain behavioral responses toward primary rewards are closely intertwined. Of relevance for these responses, in medium spiny neurons of the NAcS, a similar, strict relationship seems to link the opioid and dopaminergic transmissions. Limitations to the use of self-administration protocols are the time required for training the animals, which may encompass some weeks, and the dependence on conserved competence to perform required responding and learn the tasks.

Effort-Related Choice Behavior Tasks

Motivation has an activation component that plays a crucial role in the adaptive response of an organism to different impediments that are obstacles to the attainment of relevant stimuli. Symptoms related to impaired behavioral activation and effort-related motivational aspects (e.g., anergia, fatigue, lassitude, loss of energy, and psychomotor retardation) are present in different psychiatric and nonpsychiatric disorders, including depression, schizophrenia, and parkinsonism (Salamone et al., 2007). In animals, effort-based decisions and energy allocation in goal-directed actions are based on evaluation of effort-related costs and motivational value of the stimulus (Salamone and Correa, 2012). The mesolimbic dopamine system plays a crucial role in the neural circuitry that mediates behavioral activation and effort-related processes (Salamone et al., 1997, 2007; Salamone and Correa, 2012).

To study effort-related choice behavior (or effort-related, or effort-based decision-making) in experimental animals, several protocols have been developed based on the possibility for the animal to choose between a high-valued reward requiring a high-effort instrumental response and a lo-valued reward requiring a low effort (Salamone et al., 2007, 2016). The degree of effort requirement that favors the choice of the smaller reward is related to the level of motivation/energy of the animal, and decreased motivation is measured as reduced willingness to work for greater rewards compared with control animals. The FR5/chow-feeding protocol is an operant task where rats can choose between lever pressing in a FR5 schedule to obtain a palatable food (high-carbohydrate pellets) or approaching and consuming a freely available but less preferred food (standard laboratory chow) (Salamone, 1991). In this task, rats usually obtain most of their food by lever pressing in the FR5 schedule and consume only little amounts of standard chow. Another protocol is the T-maze barrier choice task (Salamone et al., 1994), where animals can choose between the 2 arms that contain different densities of reward (e.g., different number of food pellets, or some pellets vs no pellet) and different effort requirements, usually the access to the higher reinforcer density arm is hindered by a barrier. A third protocol is the PR/chow-feeding concurrent choice task that takes advantage of effort discounting procedures: rats can choose between lever pressing in a PR schedule to obtain the palatable high-carbohydrate pellets or approaching and consuming the freely available but less preferred standard food (Randall et al., 2012). Behavioral responses in these tasks are extremely sensitive to decreases in dopaminergic transmission such that administration of low doses of dopamine antagonists or reductions in accumbens dopamine levels significantly shift the choice behavior increasing selection of the low-effort/low-reward choices (Salamone, 1991; Salamone et al., 2007, 2016).

These effort-related choice protocols are used to assess impairments in motivational activation in models of depression/anhedonia and to test the possible positive effect of different treatments. Deficits in effort-related decision-making have been observed in an immune-mediated model induced by IL-1β administration (Nunes et al., 2014) and are elicited by acute stress exposure (Shafiei et al., 2012). Administration of tetrabenazine, an inhibitor of the vesicular monoamines transporter type-2 that at low doses mainly depletes dopamine in striatal areas, selectively shifts choice behavior in a FR5/chow-feeding task (Nunes et al., 2013), in a T-maze barrier choice task (Yohn et al., 2015), and in a PR/chow-feeding choice procedure (Salamone et al., 2012). Moreover, tetrabenazine administration decreased accumbal extracellular dopamine levels and dopaminergic signaling mediated by dopamine D_1 and D_2 receptors in terms of phosphoThr-34 and phosphoThr75-DARPP-32 levels (Nunes et al., 2013). In line with these results, administration of bupropion, a catecholamine uptake blocker that increases extracellular dopamine and norepinephrine levels, reverses the impairments in effort-related behavior induced by tetrabenazine administration (Nunes et al., 2013). In depressed patients, deficits in effort-related motivational aspects are relevant symptoms often resistant to antidepressant treatments (Fava et al., 2014). For these reasons, tests of effort-related decision-making have been translated to human studies in the effort expenditure for rewards task (Treadway et al., 2009) and, when applied to populations of depressed individuals (Treadway et al., 2012; Yang et al., 2014) or psychotic patients with a preponderance of negative symptoms (Gold et al., 2015), demonstrated decreased preference for the higher reward requiring high effort.

Translational Tasks to Assess Reward-Related Process

Translational tasks have been developed to evaluate different aspects of anhedonia (reward learning, motivation, reward valuation, and affect) in humans and experimental animals. The goal is to obtain preclinical tests as identical as possible to the clinical tests to reliably predict clinical outcomes and facilitate the development of effective treatments for reward-related symptoms. Thus, although it is possible to develop and use translational behavioral assessments, this is not an easy task and some relevant aspects should be carefully considered, as discussed by Der-Avakian and Pizzagalli (2018). In particular, challenging issues that should be considered are: (i) the inherent differences between the brief instructions given before the test to a human subject and the long training necessary in animals; (ii) the quality of the reinforcers (usually extrinsic reinforcers are used in humans, e.g., monetary rewards, while intrinsic reinforcers are used in animals, e. g., food); (iii) the stimuli chosen that should be selected based on the most acute sensory modalities of the species, and thus often differ between human and animals. Moreover, the validity of the behavioral task is increased when biological or physiological assessments are performed during the test (Der-Avakian and Pizzagalli, 2018), although it is extremely difficult to use imaging techniques in a performing animal, and the invasive biological and physiological procedures used in animals cannot be used in humans. Another relevant aspect of translational tasks is the evaluation of the effects of pharmacological manipulations on the response to the test. Drug administration should be carefully planned to be analogous in humans and nonhuman animals, in terms of doses, timing, and route of administration, considering the pharmacokinetic characteristics of the compound in the diverse species (Der-Avakian and Pizzagalli, 2018).

Translational behavioral tests developed for use in humans and rodents include: (1) probabilistic reward learning tasks, in which the subject should learn that a behavioral response results in reward delivery with a certain probability and then adapt behavior to maximize future rewards, for example, the Probabilistic Reward Task (PRT), developed for human use (Pizzagalli et al., 2005) and then for rodent use (Der-Avakian et al., 2013); (2) tests for the assessment of motivated behaviors where PR protocols and effort-related choice tasks have been translated from rodents for the use in human subjects; (3) tasks that assess the evaluation of rewards, such as the outcome devaluation task; and (4) tests that assess the affective condition of the subject, for example, the affective tone discrimination task, where the presence of a negative bias in emotional processing is examined (Der-Avakian and Pizzagalli, 2018). In some of these tasks (e.g., PRT, PR protocol, effort-related tasks), differences between the performance of control subjects and depressed and/or anhedonic subjects have been demonstrated both in humans and rodents (Der-Avakian and Pizzagalli, 2018). In some cases, the expected responses to pharmacological manipulations have been observed, for example, in the PRT and effort-related choice task, psychostimulant administration increases response bias and the choice for the high-effort/high-reward option, respectively, in rodents (Der-Avakian et al., 2013) and humans (Wardle et al., 2011).

Thus, translational analogous tasks that investigate in humans and experimental animals different aspects of anhedonia are important tools to develop potential treatments for the impaired reward processing. Moreover, their results can be analyzed by computational models, which allow the identification of neurobiological distinct subtypes within the heterogeneous symptom domain of anhedonia and can usher in targeted treatment approaches (Cooper et al., 2018). In fact, computational psychiatry is based on the idea that behavioral manifestations of clinical symptoms can be operationalized in terms of computational components allowing an objective assessment of clinical behaviors. Computational methods such as modeling and translational assessments can be applied to make inferences regarding mechanisms that underpin the observed behavior in groups of psychiatric patients and reduce subjective interpretations of behavioral responses to reward, both in experimental animals and humans (Cooper et al., 2018; Der-Avakian and Pizzagalli, 2018).

Advantages and Disadvantages of Rodent Models of Anhedonia

The CMS model is based on stressful environmental conditions that aim to reproduce stressors that can negatively impact human life and is defined as one of the most valid animal models of depression. The model, or models since many variants of the original one are used, is best characterized for inducing long-lasting impairments in reactivity to aversive stimuli (behavioral despair) and to reward (mainly assessed with the sucrose preference test, with the previous described limitations). The limitations of the model are that it is time consuming and laborious, and these factors may underlay the low reproducibility across different laboratories that has been reported, along with the experience of the experimenters, the severity of the applied stressors, and the conditions chosen for the evaluation tests (e.g., the concentration of sweet solution utilized in the sucrose preference test). Variability in vulnerability to the stressors between mice and rat strains and within the same strain have been consistently found. However, this disadvantage could actually allow the selection of subgroups of susceptible and resilient animals to study the neurobiological mechanisms of susceptibility and resiliency.

Models based on chronic social stress induce a decrease in social behaviors in defeated rodents with social avoidance and responses to rewarding stimuli, and an increase in anxiety-like behaviors. The impairments induced by chronic social defeat on reward responses are observed in rats and mice, for example, on ICSS, supporting the validity of this protocol to induce anhedonia in different species. On the other hand, the effects on reactivity towards aversive stimuli (behavioral despair) are less consistently observed; thus, these models are useful tools when "anhedonia" is the focus of the study and responses to social or nonsocial rewards can be evaluated. The effects of repeated treatments on the consequences of chronic defeat can be studied in these models. A disadvantage of these models is that they are not acute models and protocols may last several weeks (as for the CMS), with continued repeated exposure to social conflict or subthreshold stressors. Moreover, exposure to social stress models selects susceptible and resilient animals in a rodent population, more often and with a greater percentage of resilient animals than observed in the CMS model. This can be seen as an advantage of the model, since it is closer to the human condition where individual vulnerability interacts with adverse social environment to elicit depression onset and offers the possibility to investigate neurobiological characteristics of resilient animals.

Immune-mediated models, as well as studies of immune responses in exogenous stressors-induced models, can be used to verify whether activation of brain proinflammatory cytokine signaling represents the final common pathway for the various conditions that lead to a depressive-like phenotype. If this were proven to be the case, then these models can allow the identification of the molecular mechanisms that underlie the association between inflammation and depression and may suggest targets for the development of new antidepressant drugs. A limitation of the immune-mediated models is that while repeated preventive treatments can be used (Jaehne et al., 2015), the relatively short duration of the behavioral deficits after the challenge and waning of the sickness syndrome hinders long-term treatments. Although a long-lasting, anhedonic-like phenotype can be induced in mice, it is dependent on the strain, social environment, and probably sex (Painsipp et al., 2011), thus limiting the possible applications of the model. Therefore, the use of exogenous stressor-induced models to investigate immune responses and their role in anhedonic/depressive like phenotype may offer a more flexible choice of the species, strain, sex, and environmental variables.

Conclusions

Animal models of mood disorders are valuable tools that allow the study of their neurobiological underpinnings and the search of possible predictors of treatment outcome. This is particularly true for anhedonia since the presence of unremitting reduced responses to positive stimuli correlates in patients with poor treatment response (Uher et al., 2012), while early improvements in positive affect predict a positive treatment outcome and discriminates between treatment responders and nonresponders (Geschwind et al., 2011). Exposure to anhedonia models induces in rodents a collection of symptoms or behaviors, some unrelated to impaired reward responses (e.g., behavioral despair) and several concerning the domain of processing and responding to reward. Tests that tap into different observable

constructs of reward responses are available and validated, so we can examine the different steps, from the affective response to a sensory stimulus to the effort that the animal is willing to exert for a larger reward. Similar tests and tasks have been developed, or are under development, for clinical studies of impaired reward responses in patients. The progressive development of translational assessment tasks allows to integrate the application of computational methods to identify different behavioral profiles within a heterogeneous symptom domain (Cooper et al., 2018). However, although it is possible to dissect the different components of the complex responses to a rewarding stimulus in an experimental set up, this can be difficult in real life situations, both in animals and humans. Moreover, one caveat to the translation of preclinical to clinical studies in the field of anhedonia is that the response to primary rewards (e.g., food) is examined when testing anhedonia in animal models, whereas studies in humans primarily use secondary rewards (e.g., money). Evidence indicates that the neurobiological response to a primary reward may not completely overlap with the response to a secondary reward (Sescousse et al., 2013).

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Statement of Interest

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