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Social stress models in depression research : what do they tell us ?

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Abstract

There has been a recent surge of interest in the use of social stress models, especially social defeat. Such an interest lies both on the recognition that stressors of social origin play a major role in human psychopathologies and on the acknowledgement that natural and hence ethologically-based stress models bear important translational value. The use of the most recent technology has allowed the recognition of the mechanisms through which social defeat may have enduring psychoneuroendocrine effects, especially social avoidance and anhedonia, two behaviours relevant to human depression. Taken with the sensitivity of these behavioural outcomes to repeated antidepressant treatments, it has been proposed that the social defeat model might be an animal model of depression. The present survey is aimed at examining the limits of such an interpretation, focusing on methodological aspects and on the relevance of social defeat to the study of anxiety-related pathologies.

Keywords Social defeat - Social avoidance - Depression - Anxiety - Anhedonia - Food intake

Introduction

It is now half a century since acute/chronic stress has been used to model mood and anxiety disorders in laboratory animals. Such an extensive use stems from the early observations that stress may be a risk factor in the aetiology of depression and anxiety in some genetically and/or environmentally predisposed individuals. Initially, stress models that have been developed differed mainly with respect to their nature (metabolic, endocrine, physical and/or psychological). However, since the recognition that (i) the nature of the stressor impacts on defence systems through specific neurobiological circuits (Herman and Cullinan 1997; Ulrich-Lai and Herman 2009) that hence also differ in their specific relevance to human psychopathologies, and (ii) predictability and controllability of the stressor are key qualitative and quantitative variables in the psychoneuroendocrine responses to stress (Koolhaas et al. 2011), several stress models have progressively gained broad interest compared to others. In adolescent-to-adult animals (as opposed to animals subjected to stressors during their prenatal or immediate postnatal lives; Lupien et al. 2009), the chronic mild stress model consisting in the repeated application of several physical and psychological stressors over weeks (Willner 2005), the paw/tail shock model wherein uncontrollable electrical shocks are delivered acutely or repeatedly (Maier et al. 2006), and the chronic social stress (or social defeat) model based on the repeated subordination to an unfamiliar dominant in its own home territory (see below), are three illustrations of the aforementioned shift in the nature of the stressors used nowadays.

This publication will focus on several aspects of the social defeat model, highlighting our need to be cautious when labelling this paradigm as a "depression" model. By no means the items discussed below and their accompanying references are aimed at providing an extensive review on social defeat. Rather, the goal of the present publication is to draw attention to some of the limits of social defeat as a depression model, including through a consideration of practical issues that might bias the interpretation of social defeat outcomes. Readers wishing to gather detailed information on the psychoneuroendocrine consequences of social defeat stress are invited to consult different reviews published on that topic in animals and humans (Björkqvist, 2001; Buwalda et al. 2005; Huhman, 2006; Miczek et al. 2008; Nestler and Hyman 2010; Sachser et al. 2011; Shively and Willard, 2012).

Ethological validity of social stress models

Modelling human psychopathologies by means of laboratory animals requires several criteria, among which construct (i.e. causes of the disease), face (i.e. symptomatology of the disease), and predictive (i.e. therapy of the disease, albeit it mostly refers to the management of the symptoms rather than to its causes) validity criteria have been given priority (see Willner 1984 for the use of these criteria in the definition of animal models of depression). Because the precise aetiology of human psychopathologies is still unknown, establishing an appropriate construct is a difficult task. However, it is considered that one prerequisite (which is of course not sufficient *per se*) for such an establishment lies in the high ethological value of the model, assuming that defence reactions to that stressor, and their role in survival, lie on basic mechanisms that are present in all species. Indeed, social stress fulfils that demand because social (and territorial) relationships play through inter-individual communication and its consequences on the genome and the epigenome a major ecological role in animals and humans (Robinson et al. 2008). This is especially true for agonistic behaviours seen during social conflicts and their role in the genesis of hierarchy as to rank the access to food resources and sexual mating (Buwalda et al. 2005; Huhman 2006; Koolhaas et al. 2011; Shively and Willard 2012). In humans, stress is mainly of social origin (especially in those ranked low: Wood et al. 2012) and may happen throughout life, from school bullying to work harassment (Björkqvist 2001). Indeed, social stress is thought to have increasing consequences in our daily lives due to ever growing urban environments (Lederbogen et al. 2011). Although endowed with good translational validity, it should be also acknowledged that social stress in rodents cannot fully recapitulate the social stress symptomatology in humans. This is especially true for the subjective impacts of social stress, as illustrated by e.g. humiliation feelings or diminished self-esteem (Björkqvist 2001). Thus, in predisposed individuals, the negative consequences of social stress may be felt in a pathological manner due to an inappropriate perception of the consequences this conflict may objectively bear on one's position in the social hierarchy. In rats and mice, the species that are mostly used in stress research, innate strategies have evolved so that defeated animals adapt to their social rank, e.g. by showing submissive postures as to

avoid injuries that would, at best, forbid access to food and mating (Korte et al. 2005; Miczek et al. 2008). Although these animals may display behavioural and endocrine disturbances, we are far from modelling this subpopulation of human individuals suffering social stress due to public offences and/or to the intimate perception that their social rank is not the most appropriate one (Björkqvist, 2001; Huhman 2006).

Social stress models in laboratory rodents

Due to space limitations, focus will be drawn here on rats and mice notwithstanding the fact that social stress studies in other species, e.g. lizards (Summers et al 2003), Syrian hamsters (Huhman 2006), pigs (van der Staay et al. 2008) and non human primates (Fuchs and Flügge 2002; Shively and Willard 2012) have both provided evidence for inter-species constants and helped to gather crucial information on the psychoneuroendocrinology of the socially stressed individual.

Under laboratory settings, different paradigms have been used to study dominance-subordination relationships and/or to examine the consequences of social stress. Among these, one model that has provided important knowledge in the biological outcomes of social relationships lies in social instability triggered by daily rotations of male rats in cages housing female animals (Taylor et al. 1987; Mormède et al. 1990). Another model of interest refers to the "visible burrow system" wherein animal (i.e. rat) cohorts mixing males and females are housed in a burrow that somewhat mimics the natural environment. This burrow is made of Plexiglass as to allow the determination of the social position of each animal, the interactions between dominants and subordinates, and hence the consequences of these interactions on the psychoneuroendocrine status of each animal (Blanchard et al. 1990; Blanchard et al. 1995). A third model, which is the focus of the present survey, involves resident-intruder settings wherein the experimental animal is introduced in the cage of a resident (housed alone or with a female congener removed during the stress episode) that has been selected on the basis of its innate ability to aggress intruders (Avgustinovich et al. 1997; Buwalda et al. 2005; Miczek et al. 2008; Golden et al. 2011). This selection is made by choosing either the most aggressive congeners of the intruder or animals from aggressive strains. Repeated social defeat procedures have

long-lasting behavioural and autonomic consequences, some of which worsen with the number of defeat episodes, indicating sensitisation to the procedure, whilst others desensitise as a result of habituation (Tornatzky and Miczek 1994; Buwalda et al. 2005; Bhatnagar et al 2006; Dubreucq et al., 2012b). Of note is the observation that responses undergoing sensitisation take place although intruders progressively engage in rapid submissive postures with the number of episodes. Moreover, animals given the opportunity to flee the intruder during the stress episodes still display conditioned defeat postures (McCann and Huhman 2012). As initially developed in the late eighties and early nineties, most social stress studies use procedures wherein the physical interaction between the resident and the intruder is often preceded and/or followed by sensorial interaction phases (Tornatzky and Miczek 1994; Meerlo et al. 1996a; Avgustinovich et al. 1997; Koolhaas et al. 1997). During these sensorial phases, which are needed to observe strong anxiogenic consequences of social defeat (Miczek et al. 2008), the intruder is physically, but not sensorially, protected from the resident (container, grid). Social defeat bears a major drawback in that it is generally inefficient in female rodents due to the lack of aggressive interactions (but see Holly et al. 2012 for the potential use of lactating dams as residents). This is noteworthy given the high prevalence of depression - one pathology social stress is thought to model - in the human female population. Another potential drawback lies in the agonistic nature of this model. Thus, as opposed to stress models such as restraint or shock exposure in which the true psychoneuroendocrine impact of the stressor will be solely accounted for by the perception of that stressor by the individual, social stress lies first on the behaviour of the dominant animal. Beyond the need for aggressive dominants (see above), this model requires a quantification of the dyadic interactions between the resident and the intruder (Fernandez-Espejo and Mir, 1990; Miczek et al. 2001; Miczek et al. 2008). This step is important because resident animals show high variability with regard to their aggressiveness and their will to protect their environment. Unfortunately, numerous studies do not report on these interactions, either because too many confrontations are led simultaneously, thus hampering a detailed behavioural analysis or because this step is considered as an unessential step. However, quantifying these interactions, with at minimal the latency to the first attack, the number of attacks, and verifying that intruders behave in a submissive manner is a prerequisite for any dissection of the mechanisms through which

environmental or pharmacological treatments provided before or during the course of social stress may facilitate or worsen the course of adaptation. Thus, such a quantification allows to distinguish the effects these treatments bear on dyadic interactions (e.g. by altering the social behaviour of the intruder) from those interfering with the consequences of the stressor (see for illustration Berton et al. 1999).

Social defeat stress and social avoidance

Social stress has a major impact on several dimensions of emotionality. Among these, social avoidance of aggressive and non-aggressive congeners was already observed in socially stressed rats and mice more than 15 years ago (Meerlo et al. 1996b; Avgustinovich et al. 1997). The recent interest in that particular behaviour stems from mouse studies that have used social avoidance as an enduring marker of social defeat (Berton et al. 2006; Krishnan et al. 2007) to explore through genetic (including optogenetic) and viral approaches the identification of the neurobiological circuits responsible for such a behaviour (see below). Because social avoidance is observed in humans suffering depression (Trew 2011), this symptom is often referred to when arguing that the social defeat model is a model of depression (Nestler and Hyman 2010). However, social avoidance is also observed in patients suffering panic disorder, social phobia or post-traumatic stress disorder (PTSD; Pollack and Marzol 2000; Nestler and Hyman 2010), indicating that we should be cautious before providing a "human disease" label to a model that we should first consider as a tool to study social behaviour. Moreover, caution should be also exerted in interpreting social behaviour of defeated animals. This is especially important when decreased social interaction is used as an index of susceptibility to social defeat. Thus, it has been reported that mice submitted to repeated social defeat can be differentiated thereafter into two groups, so-called resilient and susceptible, on the basis of their social behaviour, their weight changes and their sucrose preference (Krishnan et al. 2007). In this study as in other relevant studies, social defeat is mostly assessed by measuring after the repeated stress period the propensity of each stressed mouse to explore a neutral zone hosting an unfamiliar mouse of the strain used to promote social defeat. However, as it stands, the failure of the so-called susceptible stressed mouse to express a

social interest for the unfamiliar mouse could be considered an adaptive process. Thus, would you establish a social contact with someone resembling one of your former aggressors? Certainly not. One obvious control experiment in the aforementioned social interaction test thus lies in the replacement of the mouse from the aggressive strain by an unstressed congener. When performed, this control experiment actually shows that social avoidance is a general phenomenon (Berton et al. 2006), thereby providing a particular translational interest with respect to human pathologies. Unfortunately, a significant number of studies using this social avoidance test does not actually perform this key control experiment. This missing information thus opens the possibility of selective decreases in social interactions with individuals that resemble the former aggressors, hence ruling out a general social withdrawal.

Social defeat stress and body weight/food intake

One classical response to stress in laboratory rodents is a reduction in the growth rate, a metabolic change mainly accounted for by decreased food intake contingent to the stress period (Koolhaas et al. 2011). Confirmingly, most social defeat studies have reported decreased body weights and/or body weight growth during and following acute/repeated social stress (Koolhaas et al. 1997; Buwalda et al. 2005; Korte et al. 2005). However, it is not unusual to observe the opposite trend (Bartolomucci et al. 2004; Foster et al. 2006; Moles et al. 2006; Dubreucq et al. 2012a,b). The bases for such differential effects of social defeat are unknown but the respective experimental settings are likely to play a role. This is illustrated by the observation that control animals to which are compared socially defeat animals may also display body weight decreases, albeit with lower amplitude (Krishnan et al. 2007; Chuang et al. 2010). Whether the social defeat-elicited decrease in body weight is a specific marker of susceptibility to the stressor is unlikely because stressed mice, whether subcategorised as susceptible or resilient responders, decrease their body weight during the repeated social stress period (Krishnan et al. 2007). It has been reported that such a decrease may indeed extend for a short period after the stress period in susceptible mice only (Krishnan et al. 2007). This is true if absolute body weight values are considered but the analysis of weight variations indicates that susceptible mice display an identical

body weight growth to that measured in control and resilient mice. This observation may be generalised to numerous social stress studies reporting enduring after effects of social stress on body weights, a statement contradicted by the analyses of body weight growth after stress (and which can be illustrated e.g. by the parallel slopes in growth rate in control animals and in animals previously exposed to repeated defeat). This indicates that social stress is not endowed with prominent consequences on body weight on stress cessation. Indeed, one study reported that repeated social defeat, which decreased body weight during its application, triggered thereafter a compensation-like increase in body weight (Chuang et al. 2010). As indicated above, repeated exposure to social stress has been also reported to increase body weight growth. This increase in the growth rate may be associated with hyperphagia (Foster et al. 2006; Moles et al. 2006) but this is not a general observation as repeated social stress may increase growth rate without altering food intake (Bartolomucci et al. 2004; Dubreucq et al. 2012b). In the latter case, it indicates that social stress may actually increase the caloric efficiency of the food ingested and promote caloric storage. This is confirmed by the finding that social stress is able to increase the weight of the white adipose tissue (Bartolomucci et al. 2004). It is interesting to note that in a rat study aimed at differentiating the effects of social defeat on food intakes during the light and dark phases, food intake increases during the inactive, but not the active, phase were observed (Bhatnagar et al. 2006). However, because rats consume most of their food during the dark/active phase, the aforementioned hyperphagia during the light phase was not sufficient to alter daily feeding rates. Beyond indicating that gross (i.e. once daily) analyses of food intakes may not be sufficient to examine the impact of social stress on caloric intake, this study reveals that social stress may disrupt the normal cycle of food intake. Thus, it may increase food intake at a time in the nycthemeral cycle during which the individuals should not normally store energy, thus mimicking the daily deregulated food consumption pattern that can be observed in several stress-related human pathologies where food craving is of major importance (Dallman et al. 2003). This is especially true if food bears a highly palatable value (see below). The finding that social stress may under certain circumstances increase food intake and/or over stimulate body weight growth (especially in subordinates: Bartolomucci et al. 2004) should thus be taken as evidence that social stress may not only model several dimensions of depression, but also anxiety (see below). The biological bases for

these stress-induced increases in body weight growth and/or food intake are likely to involve the metabolic actions of the hypothalamo-pituitary-adrenal axis (Dallman et al. 2003; Coccurello et al. 2009).

Social defeat stress and sweet preference

As for other stress models, sweet preference analyses are often included in the battery of tests aimed at delineating the behavioural consequences of social defeat. The main reason for such an inclusion lies on the consideration that the deregulation of hedonic processes, and hence anhedonia, is one of the two core symptoms, with depressed mood, that define major depression (American Psychiatric Association 2000). However, there are numerous limits that may confound the use of sweet preference as a depression-like measure in laboratory animals. First, this symptom is not observed exclusively in depressed patients as it is one of the negative symptoms of schizophrenia (American Psychiatric Association 2000). Second, although depressed people may actually down rate the hedonic value of pleasurable stimuli, such a relationship is not general because depression may also occur without changes in such ratings (Treadway and Zald 2011). Third, it is unknown whether depressed patients down rating the hedonic values of positive stimuli do so in a specific manner of whether this is simply the illustration of an overall emotional degradation (Treadway and Zald 2011; Salamone and Correa 2012). Fourth, most social defeat studies, if not all, rely on a classic procedure wherein animals are given a restricted/unrestricted choice between two bottles containing respectively water and the sweet (sucrose or saccharin) solution (Willner et al. 1987). The preference ratio for the sweet solution is thus based on the calculation of the passive consumption of each of these two solutions. However, this simple index does not discriminate between consummatory/appetitive (i.e. drive) processes and motivational/decisional (i.e. incentive) processes, the sensitivities of which are affected to different extents in depression (Treadway and Zald 2011; Salamone and Correa 2012). Accordingly, because the animals do not need to provide much efforts to drink pleasurable solutions, it is impossible to estimate the extents to which "liking" and "wanting" processes (i.e. processes with different neurobiological grounds, including with respect to their dependence on ventrostriatal dopaminergic

systems: Salamone and Correa 2012) are affected by the stressor. The use of passive consumption tests without operant protocols can thus lead to misleading conclusions, as nicely illustrated by Hayward et al. (2002) and Van Bokhoven et al. (2011). In the first study, mice lacking β-endorphin and enkephalin were reported to display decreased motivation to work to gather a sucrose-based chow, but actually failed to display differences with their wild-type congeners in a two-bottle sucrose preference test (Hayward et al. 2002). In the second study, which relates to the long-term (3 months) effects of repeated social defeat followed by individual housing, stressed rats displayed reduced anticipatory activity for a sucrose reward – such a reduction vanishing with an antidepressant treatment - but no change in passive sucrose preference, compared to the controls (Van Bokhoven et al. 2011). The possibility that sweet preference tests may indeed bear an underestimated "consummatory" dimension was already raised in the past in studies using the chronic mild stress protocol. Thus, it has been proposed that reduced sucrose consumption was mainly accounted for by the negative impact of that stressor on body weights (Forbes et al. 1996; but see Willner et al. 1996). Moreover, because sucrose bears a caloric impact, as opposed to e.g. saccharin, the use of a sweet solution as opposed to a sweetener solution may lead to divergent conclusions as to the hedonic consequences of stress (Dess 1992).

Beyond the aforementioned limits of two-bottle sucrose preference tests, it is interesting to observe that repeated social defeat, as other stressors, diminish sucrose preference in most studies (see Buwalda et al. 2005; Rygula et al. 2005; Krishnan et al. 2007; Becker et al. 2008; Miczek et al. 2008; Covington et al. 2010; Chaudhury et al. 2013). This is especially true in studies where social defeat stress had a negative impact on body weight growth and/or food intake. This response, which could be taken as an argument for the "depression" outcome of the social defeat model, may also partly depend on the experimental settings, including the time period (i.e. during or after the stress protocol) during which sucrose preference is measured, and the frequency and duration of the social defeat procedure (Rygula et al. 2005; Miczek et al. 2008; Miczek et al. 2011; Venzala et al. 2013). Thus, sweet preference may remain unaffected (Meerlo et al. 1996; Croft et al. 2005; Miczek et al. 2008; Hollis et al. 2010; Miczek et al. 2011) or may even, albeit in a minority of studies, be increased by repeated social defeat (Miczek et al. 2008; Dubreucq et al. 2012a,b). This last trend has been observed in

animals exposed to other stress models (Dess, 1992; Pecoraro et al. 2004; Willner 2005; Leigh Gibson 2006), indicating that particular experimental settings may favour the appearance of that stress response. Of relevance to the present issue is the observation that cannabinoid type-1 receptors located on serotonergic neurones might play a key role in the increased sucrose preference observed in socially defeated mice (Dubreucq et al. 2012b). Although this increase in sucrose preference and/or consumption is found in a minority of studies, it may be endowed with profound meanings. Thus, it may bear a human relevance as stressed humans displaying high circulating cortisol levels may respond to stress exposure by increased sweet consumption, as opposed to "low-cortisol" individuals (Newman et al. 2007). This observation is in keeping with both the impact of stress-elicited corticoid release on pleasure centres (Adam and Epel 2007; Coccurello et al. 2009) and the comfort food hypothesis (Dallman et al. 2003) which posits that such an increased consumption of carbohydrates in stressed individuals is intended at counteracting corticotropic hyperactivity. Whatever the causes, increased intake of sucrose should be considered as an active means to cope with the anxiogenic impact of stress. The report that social stress subordinates display an increased fat consumption when provided in the diet, compared to dominants (Moles et al. 2006), supports the finding that although stress may decrease the intake of standard food, it may well increase the consumption of fat- and carbohydrate-enriched palatable food (Dallman et al. 2003; Coccurello et al. 2009). Moreover, the observation that sucrose or saccharin availability during repeated stress attenuates several consequences of stress on the hypothalamo-pituitary-adrenal axis (Ulrich-Lai et al. 2007) supports the hypothesis that increased carbohydrate consumption should be viewed as a self-medication aimed at coping with stress. Because repeated social defeat bears positive and negative effects on the consumption of cocaine or alcohol depending on the frequency of stressor application (Miczek et al. 2008; Miczek et al. 2011), increased consumption of sucrose could reflect increased sensitivity of the reward circuits. If so, one would expect the generalisation of this increased consumption of sucrose to the consumption of other natural rewards, such as sex or voluntary wheel-running (Lett et al. 2002; Belke 2005; Greenwood et al. 2011). As sexual behaviour is concerned, repeated social defeats affect negatively sexual interest (Nocjar et al. 2012) and copulatory activity (Yoshimura and Kimura 1991). On the other hand, the finding that socially defeated mice increase their wheel-running activity

(Uchiumi et al. 2008) might be taken as a strong support for the hypothesis that social defeat might sensitise reward circuits. However, the observation that such an increase occurred when the aggressor was present (Uchiumi et al. 2008) rather indicates that wheel-running should be considered as a flight response to the anxiogenic stimulus. This hypothesis is reinforced by previous findings obtained using another stressor, i.e. inescapable foot shocks (Desan et al. 1988), and by our own recent experiments showing that repeated social defeat decreases markedly running activity on stress days in mice housed with running wheels, this decrease vanishing progressively after stress cessation (Dubreucq and Chaouloff, unpublished observations). Taken together, these results might indicate that the increased sucrose consumption observed in socially defeated animals results is merely a consequence of alterations in consumatory, rather than reward, processes in order to counteract social stress-induced anxiety (see thereafter).

Social defeat stress and anxiety

Social defeat bears anxiogenic consequences, as assessed by unconditioned anxiety tests (see Buwalda et al. 2005 and Miczek et al. 2008 for reviews). This finding indicates that social defeat cannot be considered a selective "depression model" but rather as an aversive stimulus with different emotional outcomes, including anxiety. This last finding is reinforced by the finding that acute social stress substitutes for the anxiogenic compound pentylenetetrazol in animals conditioned to discriminate this drug (Miczek et al. 2008). The observation that social stress increases anxiety may indicate that the latter belongs to a unique, and thus common, behavioural dimension to which belong other emotional consequences of social defeat, including e.g. socialisation, body weight growth, hedonia. However, one study reported that socially defeated mice classified as susceptible mice on the basis of their social behaviour, body weight growth and hedonic responses following repeated social defeat (see above) proved as anxious as their resilient congeners (Krishnan et al. 2007). This was true both immediately after the end of the social stress protocol and in the long-term, raising the hypothesis that social defeat might be considered first as an anxiogenic paradigm that with time passing triggers "depressogenic" mechanisms in some individuals. One question which remains open is whether in susceptible mice the

anxiety-triggering effect of social defeat plays a causal role in their so-called "depressive" profile. The answer to that question is of importance given that human depression may be a consequence of the inability to respond to repeated anxiogenic stimuli. One means to answer that question is to analyse whether the mechanisms regulating social behaviour in socially defeated animals impact on their anxiety profiles. Unfortunately, studies aimed at studying resilience to social avoidance in socially defeated mice did not address that particular issue (see below). One possibility to explore this link between anxiety and "depression-like" behaviours would lie in the use of factorial (principal component) analyses to examine whether and how the social withdrawal, anhedonic and anxiogenic responses to social defeat segregate among dependent and independent behavioural dimensions throughout the course of the repeated social defeat procedure. It could be argued here that such a quest is meaningless given that anxiety and depression share high comorbidity in humans. Although this is true in the clinics, and possibly in most - if not all - so-called animal models of depression, a time-dependent analysis of the consequences of social defeat on the aforementioned behavioural dimensions might still help us in further defining the outcomes of social defeat models and their significance. As far as therapeutics are concerned, this particular issue could be addressed by examining the short-term impacts of selective anxiolytic treatments, including on the concentrations of antidepressants (but see below) needed thereafter to act positively on the long-term.

In addition to its consequences on unconditioned anxiety, social defeat may also have a major impact on (conditioned) fear, amplifying progressively the cued fear response (as assessed by freezing behaviour) during recall sessions and affecting or not extinction responses (Narayanan et al. 2011; Dubreucq et al. 2012b). It is noteworthy that this observation, which is reminiscent of the conditioned fear response that is observed with other stressors (Izquierdo et al. 2006; Miracle et al. 2006), is independent from any impact of social defeat during the fear conditioning step of the procedure. Whether these results help us to define the emotional and cognitive profile of the socially stressed individual is unknown given that increased fear memory may be viewed as a reinforcement of an adaptive means to face danger.

Social defeat stress and "behavioural despair"

Animals exposed to forced swim or to tail suspension tests rapidly display passive behaviour, as illustrated by immobility (Porsolt et al. 1978; Cryan et al. 2002). Initially, it was assumed that these tests captured the "behavioural despair" of the animals (Porsolt el. 1978); however, due to its anthropomorphic connotation, reference to behavioural despair will be abandoned here at the profit of "immobility". Repeated social defeat has been shown either to leave intact or to increase the duration of immobility in the forced swimming test (Berton et al. 1998; Rygula et al. 2005; Krishnan et al. 2007; Becker et al. 2008; Hollis et al. 2010; Lehmann and Herkenham 2011; Venzala et al. 2013). What these observations tell us on the behavioural repertoire of socially defeated animals is difficult to ascertain. Thus, it is now more than 30 years since these tests have been validated for the screening of antidepressants (including with acute regimens that are ineffective in humans), this class of drugs promoting a decreased duration of immobility (Porsolt et al. 1978; Cryan et al. 2012). Unfortunately, on the basis of this result, it is sometimes inferred that endogenous or exogenous manipulations that trigger increases in immobility are depressogenic. Beyond the simple observation that the occurrence of depression is a long-lasting process in humans, as compared to the short duration of the forced swimming and tail suspension tests, the behavioural meaning of immobility in these tests is far from being univocal. Thus, stressed animals that increase their duration of immobility in inescapable environments may do so because they appreciate more rapidly than their control counterparts the inescapable outcome of the tests. Accordingly, increased immobility could illustrate increased adaptation rather than "depression-like" behaviour. In addition to this fundamental doubt, it should be reminded here that stress, including social defeat stress, bears autonomic consequences (e.g. on body temperature: Koolhaas et al. 1997; Buwalda et al. 2005; Koolhaas et al. 2011). Because water temperature has a major impact on the emotional outcome of the forced swimming test (Jefferys and Funder 1994; Bächli et al. 2008), social stress-elicited changes in the autonomic nervous system could bias the interpretation of the findings due to changes in the sensitivity of the body to water temperature.

Resilience to social defeat stress

Early studies have indicated that the genetic status of the individual and its own pre- and postnatal life experience with regard to stressful stimuli (partly through what is now referred to as epigenetic mechanisms) are main variables on which lie the amplitude and the direction of his psychoneuroendocrine responses to stress. This is especially true for social defeat, the behavioural, endocrine and/or metabolic consequences of which are sensitive both to the animal strain (Berton et al. 1998, 1999; Razzoli et al. 2011), and to the past experience of the animal with a former stressor (especially if this animal has a control over that previous stressor: Amat et al. 2010). Nowadays, the use of genetic tools allowing (i) to alter the expression of genes in discrete brain areas or in distinct cell populations, and (ii) to stimulate/inhibit through optogenetics the activity of selected cell groups in animals exposed to stress has provided a major breakthrough in the recognition of the mechanisms underlying resistance (resilience) to stress (Feder et al. 2009; Franklin et al. 2012). However, as stress elicits a vast array of responses which cannot be examined in a global manner (hence illustrating the fact that the expression "resilience to stress" is meaningless), studies aimed at studying resilience need as a prerequisite to define which particular stress response(s) will be investigated. As indicated above, the finding that social avoidance may display high inter-individual variability has led to studies aimed at defining by means of this behavioural screen the mechanisms responsible for the sensitivity/resilience to social defeat. Although such a quest has gathered important findings (see below), we still ignore the extent of the relationships, if any, between social avoidance (and sucrose preference, often taken as a concomitant measure thereof), anxiety, and the immediate and long-term neuroendocrine (e.g. corticotropic and sympathetic hyperactivities) and metabolic (e.g. food intake and body weight growth changes) impacts of social defeat (but see Blugeot et al. 2011). Studies aimed at examining the neurobiology of social avoidance behaviour have delineated the roles of e.g. brain-derived neurotrophic factor (Berton et al., 2006; Krishnan et al. 2007), ΔFosB (Vialou et al. 2010), extracellular signal-regulated kinase (Iniguez et al. 2010), and the glucocorticoid receptor (Barik et al. 2013) in mesocorticolimbic dopaminergic neurons or in accumbal dopaminoceptive neurons. These results, which highlight the important role played by mesocorticolimbic pathways in the consequences of social defeat on social interaction, have recently gained support from optogenetic findings revealing

that the mesocortical and the mesolimbic pathways have divergent impacts on this behaviour (Chaudhury et al. 2013). In addition to the ventral tegmental area, the origin of the mesocorticolimbic dopaminergic pathways, the dorsal raphe nuclei (Espallergues et al. 2012), one source of brain serotonergic fibers, and the medial prefrontal cortex (Covington et al. 2010) have been shown to be involved in the social interaction outcomes of social defeat. Whether these findings are accounted for by the key role played by the frontocortical innervation of the dorsal raphe in the controllability over stressors (Amat et al. 2005) remains to be established. Besides, evidence has been gathered for the importance of epigenetics and chromatin changes on susceptibility/resilience to social defeat, again as defined by social avoidance behaviour (Tsankova et al. 2006; Elliott et al. 2010). These studies may provide potential therapeutic targets for human suffering social stress disorders, including drugs targeting histone acetylation and methylation processes at the chromatin level (Tsankova et al. 2007). However, we cannot ignore the risk that these drugs might bear unwanted side-effects due to the contribution of these epigenetic mechanisms to a plethora of biological functions. Besides this set of studies aimed at deciphering the mechanisms leading to resilience, other studies have explored how environmental changes may affect the amplitude of the behavioural consequences of social defeat. It has been shown that housing mice in an enriched environment either before or after repeated social defeat may blunt social avoidance (Schloesser et al. 2010; Lehmann and Herkenham 2011), dentate gyrus neurogenesis playing a key role in the after effects of the environment enrichment (Schloesser et al. 2010). Taken together, all these stress-resilience studies actually point to a plethora of mechanisms through which social avoidance (and low sucrose preference) are triggered by social defeat in predisposed individuals. Clearly, future studies will be needed to provide a framework allowing to extrapolate these findings to pathologies evoked by stressors of different nature.

Antidepressants and social defeat stress

The identification of the drug class(es) endowed with protective effects in socially defeated animals is considered one necessary, albeit not sufficient, step in translating social defeat stress outcomes in rodents to human psychopathology (see above). Assuming that social defeat is a model of depression thus requires that clinically active antidepressants blunt several of its psychoneuroendocrine consequences (see below). However, translating animal models to human psychopathology is not a straightforward task, especially when focusing on depression models (Markou et al. 2009; Nestler and Hyman 2010). Such a difficulty finds its origin in (i) our limited knowledge of the etiology of disorders such as depression, (ii) the absence of depression-selective biomarkers, (iii) the recognition that depression-associated symptoms may only reflect comorbidity with other illnesses, such as anxiety, and (iv) the general acknowledgement that the so-called "depression" pathology is a multidimensional entity with distinct categories that still need to be identified, including at the biological level. The fact that there is no stress model that provides all the behavioural outcomes (i.e. symptoms) observed in clinical depression should be simply acknowledged as should be the fact that, as underlined above, stress does not necessarily trigger depression in humans. In keeping with these diagnosis limits, it is not surprising to consider that the simple use of a therapeutic class of drugs is certainly not sufficient to label an experimental animal paradigm a "model of human pathology". This is especially true for antidepressants and their use in animal models of stress. Thus, (i) there is not an all-or-none therapeutic difference between the positive effects of antidepressants, including those considered as standards in this therapeutic class, and those of placebos in depressed patients , (ii) antidepressants help to alleviate symptoms of depression rather than targeting specifically the causes of depression, (iii) this class of drugs are also effective against other pathologies, including anxiety, and (iv) one hallmark of antidepressant therapy lies in its efficacy in a majority of, but not in all, depressed patients, indicating that an adequate animal model of depression should at best include resistance to antidepressants in a significant fraction of the animal population tested. Although all these limits are generally taken into consideration, still it is sometimes considered that a stress model is a "depression-like" or a "depression" model if its consequences are counteracted by antidepressants. This of course holds true for numerous rodent stressors, including repeated social defeat. This "depression model" label stems from the observation that (i) part of the behavioural, neurochemical,

endocrine and/or metabolic consequences of social defeat are observed in depressed patients (see above), and (ii) the chronic, but not the acute, administration of antidepressants, such as the tricyclic imipramine or of the selective serotonin reuptake inhibitor fluoxetine diminish the amplitudes of these consequences (Kudryavtseva et al. 1991;Von Frijtag et al. 2002; Berton et al. 2006, Tsankova et al. 2006; Becker et al. 2008; Elliott et al. 2010; Blugeot et al. 2011; Espallergues et al. 2012). However, there is extensive evidence for the anxiolytic properties of tricyclics and selective serotonin reuptake inhibitors, thus opening the possibility that these drugs proved effective in the social defeat model by opposing anxiety. This possibility is reinforced by the finding that the antidepressants fluoxetine and venlafaxine may, under certain experimental conditions, blunt the anxiogenic effects of social defeat, as assessed by means of anxiety tests (Berton et al. 1999; Venzala et al. 2012). This result underlines the need for caution before labelling social defeat as a "depression" model sensitive to "antidepressants" as it may lead to the assumption that all drugs or manipulations that blunt social defeat consequences should be considered as "antidepressants".

Concluding remarks

As stated at its beginning, the goal of this communication was not intended at reviewing the scientific literature on the social defeat model but rather to examine the grounds on which lie its validity as a depression-model. The recent surge of interest in the social defeat model of stress has led investigators to acknowledge that natural and ethologically-based stressors might be endowed with translational outcomes that are essential to drive progress in our knowledge of the mechanisms underlying inadaptation to stress. The surge of studies devoted to the molecules, cells or brain circuits that are either affected by social defeat or that bear an impact on social defeat outcomes must be underlined here. However, at the present step, we should just consider that the social defeat model has allowed much progress to be made in the neurobiology of stress rather than trying to assign to this model a "human" value. Of course, pressures of different kinds lead us to link our research to public health

issues. However, such a link, if any, will bear more impact if we demonstrate that we have profound knowledge of what animal models can provide or not to this translational will. As mentioned above, the sole use of one or two different behavioural outcomes of social defeat as their sensitivities to drugs endowed with antidepressant properties should not be considered sufficient to label the social defeat model as a "depression" model. Indeed, on the basis of the clinical symptoms of PTSD and hence the psychoneuroendocrine criteria used to model such a pathology (Stam 2007; Siegmund and Wotjak 2007; Pitman et al. 2012), social defeat might well be considered an animal model of PTSD. The finding that one main characteristic of PTSD, namely increased startle amplitude (Stam 2007; Pitman et al. 2012), is observed in socially defeated animals (Pulliam et al. 2010) might reinforce the latter suggestion. However, the possibility remains that depression- and PTSD-related social avoidance behaviours do not belong to a unique dimension of emotionality, i.e. that these behaviours lie on different and thus specific brain circuitries. In other words, we should not consider social defeat responses as a whole but rather focus on each individual response *per se*. This line of reasoning, derived from that used in psychiatry genetics in the quest for the bases of "endophenotypes", as opposed to full syndromes, could help us to identify the translational value of each of these consequences of social defeat. Beyond this illustration of our need to avoid misleading anthropomorphic interpretations due to the diversity of social defeat responses, such a diversity leads to the following provocative question. Should we try to counteract all the effects of repeated social defeat? Shouldn't we consider that several responses of the socially defeated animal are adaptive in nature (Korte et al. 2005)? This may hold true for social interaction but also for other responses, including (unconditioned and conditioned) anxiety. Indeed, exposure to stress, with its potentially damaging consequences, might be considered as an event favouring adaptation, and hence resilience, to future stressors. It should be reminded here that the prevalence rates of human depression or PTSD are "relatively" low (up to 20 % and 8%, respectively), indicating that the vast majority of humans adapt adequately to depression- and PTSD-promoting events. These percentages are indeed much lower than those reported for susceptibility to social defeat (circa 55 %: Krishnan et al. 2007), questioning again the validity of the criteria chosen to label stressed mice as adapted or maladapted. Clearly, the definition of the boundary between adaptive and maladaptive responses to social defeat

will be a major challenge in the future. That challenge will surely require that we define which of the diverse responses to social defeat belong to common dimensions of emotionality and then, how each of these dimensions relate to adaptation, including toward other stressors. Although this quest might appear distant, at first glance, from translational issues, it is obvious that in the long-term that quest will translate in the clinics. This statement is supported by the recent proposal that human depression might has evolved as an adaptive process aimed at allowing the individual to concentrate on the means to solve his problems, including social ones (Andrews and Thomson 2009). According to this hypothesis, priority given to analytical "rumination" would hamper the desire to think and engage in other activities, including hedonic ones. In addition to this necessary quest for the definition of the adaptive vs maladaptive nature of social stress consequences, one other route of investigation will be to address the impacts of variables that have been shown to be of key importance in stressed (including socially stressed) humans. For example, that adolescence, regardless of gender, is one important life period during which stress, including social stress (e.g. bullying), has major health consequences (Björkqvist 2001; Paus et al. 2008), should be considered to a greater extent than it is nowadays.

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