PROBLEMS AND PARADIGMS

Stress-induced depression: Is social rank a predictive risk factor?

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Abstract

An intriguing question in the field of stress is what makes an individual more likely to be susceptible or resilient to stress-induced depression. Predisposition to stress susceptibility is believed to be influenced by genetic factors and early adversity. However, beyond genetics and life experiences, recent evidence has highlighted social rank as a key determinant of susceptibility to stress, underscoring dominant individuals as the vulnerable ones. This evidence is in conflict with epidemiological, clinical, and animal work pointing at a link between social subordination and depression. Here, we review and analyze rodent protocols addressing the relevance of social rank to predict vulnerability to chronic social stress. We also discuss whether a specific social status (i.e., dominance or subordination) is the appropriate predictor of vulnerability to develop stress-induced depression or rather, the loss of social rank and resources.

Keywords: Social hierarchy, Social defeat stress, Vulnerability, Metabolites, Nucleus accumbens, Depression.

Introduction

Although stress is a well-known major risk factor for the development of psychopathologies, extensive data from both animals and humans highlight the existence of major differences in individuals' susceptibility to stress [1–3]. This has been particularly well-documented in depression, with extensive evidence showing that, whereas some individuals display a high vulnerability following exposure to stress, others remain resilient to expected symptoms [3, 4]. In recent years, a great emphasis has been placed on the identification of risk factors and mechanisms involved in such differences in vulnerability to stress [5–8]. Increasing work involving the stratification of individuals as either vulnerable or resilient according to specific criteria (typically of behavioral nature) exhibited following stress exposure has allowed great progress [5, 6, 9–16]. However, a key challenge for the field is to identify risk factors and biomarkers for vulnerability to stress-induced depression, so that individual susceptibility can be identified *a priori*, i.e., before stress exposure. Identifying predictive factors would allow addressing the mechanisms that determine individual vulnerability to stress and to, eventually, develop preventive approaches for at risk individuals.

A great deal of work has highlighted the relevance of genetic factors [17, 18] and exposure to early life stress [19, 20] in the contribution to this neurobehavioral diversity. In addition, rodent [21–26] and human [27–32] studies have pointed out certain personality traits –particularly anxiety– [4] as key predictors of vulnerability to develop stress-induced depression. The predicting value of personality traits in this context might be due to the fact that they are, to a large extent, shaped by genetic factors [33–35], early life experiences [36–38], and their interaction [39, 40].

However, consistent observations over the past decades have documented substantial differences in the development of behavioral and neurobiological alterations following stress exposure at adulthood in genetically identical mice (inbred) exposed to equal husbandry and experimental conditions, and not submitted to early life adversity [5, 10, 41]. This somehow puzzling discovery has posed the question [5] as to whether the observed differences in stress effects represent random variability [42] or, instead, emerge from non-genetic pre-existing factors? In a recent study in C57BL/6J inbred mice, we have identified rank attained within a homecage social hierarchy as a strong predictor of the development of depression-like behaviors following exposure to chronic social defeat stress (CSDS), with dominant mice being the ones that showed susceptibility [43]. These data implies that social rank in pre-established hierarchies could emerge as a predictive risk factor, that can be identified non-invasively, of stress-induced depression-like behaviors. Importantly, the recognition of social status as a potentially key determinant of susceptibility and resilience to stress is in agreement with earlier work proposing strong links between social status, stress responsiveness, and depression [44, 45]. However,

underscoring dominant individuals as the vulnerable ones [43] is at odds with substantial literature establishing a link between social subordination and depression [44, 46, 47]. Therefore, in this review, after discussing the rationale for identifying non-invasively risk factors of stress susceptibility, we will re-open the debate as to whether a specific social status (i.e., dominance or subordination) predicts vulnerability to develop stress-induced depression or whether additional factors should be accounted for [48, 49].

Why segregating individuals for stress-susceptibility is crucial?

The existence of behavioral, physiological and neurobiological diversity in stress effects across individuals is becoming increasingly recognized [50]. Consequently, an important current trend in the field of psychiatric neuroscience is moving away from the traditional approach focusing on group effects. An increasing number of studies are implementing a *post hoc* stratification of individuals, as either vulnerable or resilient to stress [5, 9–15, 22, 51]. Typically, this approach compares findings from individuals that deviate on specific behavioral criteria from the values of the control group, with those that present values equivalent to controls and, therefore, treats the non-stressed group as 'uniform'.

Therefore, a critical point in this procedure is the definition of the behavioral criteria that will determine 'vulnerability' vs. 'resilience'. In the framework of rodent studies of depression, animals have been classified according to their differential performance in tests for anxiety-like behaviors [10], behavioral despair [22], anhedonia [41], and social exploration [5, 9–13, 15, 16, 43]. The latter parameter is the most widely used in recent years in the context of the standardized CSDS protocol in which stratification is performed by using a 'social interaction (SI) ratio'. This ratio is calculated as the time spent in the interaction zone when the target is present divided by the time spent in the interaction zone when the target is absent [5, 9, 13, 52]. An alternative index recently developed for the same purpose is a social avoidance score that integrates four parameters 1) the absolute time spent in the interaction zone when the target is present; 2) the absolute time spent in the corner zones when the target is present; 3) social interaction ratio and 4) corner zone ratio. [13, 43]. Accordingly, the so called 'susceptible' mice are those that show social interaction deficits, whereas mice defined as 'resilient' show social avoidance similar to undefeated mice (see next section for more details).

This segregation approach in rodent studies is allowing to make sense of the large variation frequently observed at the broader group level. Establishing separate groups of individuals is allowing a targeted approach to underscore physiological and neurobiological correlates of 'vulnerability' and 'resilience'. This approach in rodents complements human studies –that have mainly focused on neuroendocrine parameters– by enabling unprecedented progress on the identification of neural, molecular,

epigenetic, and hormonal responses that underlie individual differences in stress susceptibility [3, 53]. However, whereas these studies indicate that individual vulnerability to stress can be reflected *a posteriori* at the behavioral and biological levels, they do not provide insights on the origin of the identified differences and vulnerability. Thus, while the majority of these studies are generating major insights on the neurobiological processes that differ between individuals after stress exposure (i.e., *a posteriori*), they do not allow ascertaining if there are pre-existing differences that map on to the differential susceptibility.

Is there a good way to determine susceptibility to stress-induced depression?

As indicated above, being able to identify individuals at risk to develop depression and other psychopathologies before they are actually exposed to specific stressful events at adulthood is a critical step to interrogate the mechanisms that constitute *a priori* individual differences in susceptibility. The CSDS model, typically applied in the inbred C57BL/6 mouse strain, is increasingly considered to be particularly suitable to investigate key non-genetic factors involved in stress-induced depression-related behaviors [9, 54–56]. It presents strong face validity, as social defeat (e.g., bullying) is a major risk factor to developing depression in humans [57], and CSDS-induced depressive-related behavior is sensitive to chronic but not acute antidepressant treatment [55], as observed in humans. In this model, an experimental intruder mouse is physically defeated by an aggressive resident mouse for 5-10 min daily (and then housed, with sensory contact only, with the aggressor for the rest of the day) over 10 consecutive days. Typically, depression-like behaviors are indexed by a reduction in social interaction with an unfamiliar mouse in a test given 24 h after the last defeat session and profound anhedonia revealed by a decreased sucrose preference [5, 55]. These behavioral alterations are observed in the so called 'susceptible' mice, whereas mice defined as 'resilient' show social avoidance scores and sucrose preference similar to undefeated mice [5, 6, 10]. However, with a few exceptions including several tests for the purpose [10], the classification into susceptible or resilient individuals is typically done on the sole basis of a mice behavior in the social interaction test.

Despite substantial consensus about the relevance of social avoidance to model depressive-like states in rodents, some criticisms have been formulated regarding the validity of this parameter in the context of CSDS research [58, 59]. A major objection has been that the social avoidance displayed by defeated mice should not be interpreted as pathological but rather as an adaptive response. Specifically, this argument is formulated as follows: 'Would you establish social contact with someone resembling one of your former aggressors? Certainly not [58]'. Although this is certainly a legitimate concern given that most reports include avoidance testing towards an unfamiliar mouse from the same CD1 strain as the original aggressor, additional research has shown that social avoidance in this model

is generalizable to mice from other strains different to the aggressor's one, including experimental animals' (i.e., C57BL/6J) [55]. Importantly, social avoidance was also observed one month after CSDS, revealing the long-lasting impact of CSDS on this parameter [55]. These observations support the view that reducing the engagement, particularly if long-lasting, with a new unfamiliar mouse might not be a fully adaptive response [6]. In favor as well of the relevance of the CSDS model is that social avoidance in susceptible mice is reverted by chronic, but not acute antidepressant treatment [55], as observed for the effectiveness of antidepressants in humans. A second objection regarding the CSDS model is the fact that physical interactions during the defeat sessions are classically not analyzed and, hence, they cannot be discarded as potential contributors to inter-individual variability in brain and behavioral parameters observed after CSDS [43, 58, 59]. Another point to consider regarding the CSDS model of depression is the specifics of the formula used to calculate the 'social interaction (SI) ratio' broadly used to segregate defeated mice as either 'susceptible' or 'resilient' [5, 9, 13, 52] and whether or not a third category should be added for animals that do not avoid, but behave 'indiferent' to the social target [60]. Although alternative methods for segregating individuals could be implemented to strengthen the data (e.g., by performing cluster analyses on animal's performance on a variety of tasks [10] or by using a chronic unpredictable stressor (CUS) to assess individual differences in gene expressions and mood-related behavioral traits [22]), the *post-hoc* characterization of resilient versus susceptible mice to social defeat based on the SI ratio has enabled the identification of crucial cellular and molecular adaptions underlying susceptibility to develop depression-like behaviors [5, 52, 53, 55, 61].

Can we predict vulnerability versus resilience to stress-induced depression?

While there is now some evidence for neuronal [10–12, 14, 15] and physiological [5, 6, 9, 13] signatures of stress susceptibility mainly identified following stress exposure, a challenge in the field has been to predict stress susceptibility before exposure to stress. To date, three longitudinal studies have elegantly uncovered in stress-naïve mice predictive physiological and neurophysiological biomarkers for vulnerability to develop stress-induced depression (as assessed by decreases in social exploration of an unfamiliar male mouse) in the CSDS model.

One of the studies that recently succeeded in this task focused on the immune system [62]. Specifically, it pinpointed preexisting differences in the reactivity of the cytokine interleukin-6 (IL-6) elicited by a first stress exposure as a good predictor of stress susceptibility. Higher stimulated IL-6 levels in susceptible individuals were shown to predict and promote social defeat stress-induced vulnerability profile. The other two studies underscored specific neural circuit mechanisms underlying individual differences in vulnerability to stress [63]. The first of them [64] recorded local field potential (LFP) and single unit activity in the prefrontal cortex (PFC) and amygdala and explored the potential existence of

a ‘neural signature’ of stress vulnerability present before chronic stress exposure. They succeeded to find that, specifically, the change in PFC 2–7 Hz oscillatory power measured during a first stress session correlated with the degree of individual susceptibility observed across the same cohort of mice after chronic social defeat. The second neurophysiological study [63] focused in the nucleus accumbens (NAc), given the substantial evidence that link this brain region with the pathophysiology of depression, including data from the CSDS model in mice [65]. Its aim was to delineate a cell-type specific signature of stress susceptibility and resilience in NAc medium spiny neurons (MSNs). Using fiber photometry calcium imaging in awake behaving mice, the authors differentiated between MSNs showing predominant expression of either D1 or D2 dopamine receptors, as they show distinct changes in their activity following chronic social defeat stress. They found that D1-MSN, but not D2-MSN, activity prior to stress is a predictive marker of CSDS-induced susceptibility; i.e., resilient mice exhibited *a priori* increased baseline D1- MSN activity.

These studies contribute invaluable knowledge regarding pre-existing physiological and neurophysiological differences corresponding to variation in individuals’ susceptibility to chronic stress. They also provide biomarkers allowing the pre-identification of individuals at risk to develop stress-induced depression-like phenotypes, as well as those eventually resilient, paving the way to go deeper in the identification of molecular and cellular mechanisms conferring individual stress vulnerabilities, and eventually promote preventive treatments. However, their detection involves invasive approaches (i.e., acute social defeat stress and submandibular vein blood extraction [62], chronic intracerebral implantation of electrodes [64] or optic fibers [63]) that deter from their high-throughput and systematic use. It is noteworthy that these susceptibility signatures have been identified retrospectively, following CSDS. The ideal situation would be to stratify groups according to the basal level of the biomarker candidates before stress exposure [66] allowing to predict susceptibility to chronic stress at the behavioral level, perhaps emerging from mice social organization, such as pre-existing dominance hierarchies, as previously hypothesized [5, 6, 67].

Naturally established rank in a social hierarchy as predictor of susceptibility to chronic stress

Social hierarchy organization is ubiquitous in socially living species [68] and critically important for individuals’ health and well-being [44, 45, 69]. Laboratory mice form stable and linear hierarchies in homecage colonies that can be reliably detected using well-validated tests, such as the tube and urine marking tests and assessing agonistic confrontations [70, 71]. A recent study by Larrieu et al. [43] in C57BL/6J mice investigated the predictive power of hierarchical status to identify stress susceptibility to CSDS (**Figure 1A**). It found that defeated dominant animals display a susceptible phenotype (as

assessed through a social index score), while subordinate mice show a resilient phenotype. In this study [43], the hierarchy was established within a group of four homecage mates cohabitating for at least four weeks. The CSDS challenge was subsequently given to mice individually for 10 consecutive days, according to the standardized protocol by Golden et al. [9].

The finding that dominant males are the ones susceptible to CSDS [43] might appear paradoxical, as previous work in rodents had pointed at subordinate animals as the ones showing vulnerability to social defeat stress. However, important methodological differences between the studies reveal that the behavioral processes engaged by the different studies greatly differ. For example, vulnerability to develop anhedonia after chronic variable stress in rats was related to submissive behavior in a resident-intruder paradigm [72]. This characterization of social submissiveness clearly differ from the homecage rank established in the Larrieu et al. study in mice [43].

Issues related to how the dominance-submissive relationship is determined

Work in male Syrian hamsters has pointed out subordinates, but not dominants, as the ones more affected by social defeat experiences. Subordinates are the ones that specifically show 'conditioned defeat' following a brief social defeat stressor (3 agonistic encounters with 3 aggressive hamsters for 5 minutes), as evidenced by increased avoidance when subsequently exposed to a non-aggressive novel intruder [73, 74]. However, critical species-specific differences in social structure make difficult to compare stress procedures and outcomes between these two species. At difference to the Larrieu et al. [43] study that involved hierarchies naturally expressed within groups of mice in a homecage, dominance and subordination in the Syrian hamster studies is established in a series of resident-intruder encounters (**Figure 1B**). This difference is motivated by the fact Syrian hamsters are territorial and solitary rodents in the wild and, therefore, the establishment of a dominance-submissive relationship requires a resident and an intruder. Accordingly, rank selection in these two studies uses different criteria, hence potentially favoring a different definition of 'dominant' and 'subordinate' animals. In favor of this view is the fact that the duration of the dominance relationship is a key factor for dominant hamsters to show a differential conditioned defeat response, which they show following 14-day, but not only 1- or 7-day, dominance encounters [74]. Furthermore, the use of brief and acute social defeat encounters rather than CSDS might be not sufficient to produce susceptibility in dominant hamsters, as suggested by the fact that they initially do fight back the aggressor during the defeat session [73, 74]. This is in line with observations in rats indicating that intruders that fight aggressively against residents are the one less affected by defeat stress [75].

Another experimental model that has highlighted a particular vulnerability of subordinate animals is the one developed by Bartolomucci et al. [76] involving chronic psychosocial stress in male mice. In this protocol, mice are first individually housed for one week. Then, each resident receives an intruder with whom it will interact daily (5-10 min direct interaction, rest of the day through a partition in the same cage) for the upcoming 3 weeks. This model produces four categories of mice: resident dominant, resident subordinate, intruder dominant, and intruder subordinate [77] (**Figure 1C**). Rank leads to differences in body weight and locomotor activity; i.e., dominants show a decrease in body weight and hyperactivity, whereas subordinates show an increase and locomotor retardation. These neurobehavioral profiles have been interpreted as increased coping attempting by dominants and as helplessness and depressive-like behavior in subordinates [49]. However, again, direct comparison with the Larrieu et al. [43] study is difficult, given that as in the Syrian hamster studies discussed above, dominance hierarchy is also in this chronic psychosocial stress model forced and established through brief agonistic encounters under stressful external manipulations (i.e., the resident-intruder paradigm). On the contrary, in the Larrieu et al. [43] study dominance/subordination is established in a steady state condition within a group of four mice cohabiting in the same homecage for several weeks and, supposedly, leading to a more 'natural' social organization.

We should also note that another study in mice did not find a correlation between social rank assessed in the homecage and vulnerability to social defeat. However, at difference to Larrieu et al. [43] that exposed mice to a chronic social defeat immediately after group cohabitation, mice in the Lehmann et al. [78] study were 1) socially isolated during two weeks and 2) exposed to an acute social defeat stress. Such isolation procedure might have altered individuals' predispositions and, the use of acute social defeat rather than CSDS might be not sufficient to produce susceptibility in dominant mice.

Therefore, the finding that mice higher in rank in well-established homecage hierarchies are the ones vulnerable to show depressive-like behaviors following CSDS [43] is not contested by existing evidence. In fact, the vulnerability of dominant individuals to health problems [44, 79–82], including anhedonia and motor hyperactivity [49, 83], following chronic social defeat has been addressed by earlier studies. In our view, the findings in the Larrieu et al. [43] study might be revealing very important processes to understand vulnerability to develop depression. As CSDS was given immediately following group cohabitation, high social status of dominant mice was the one particularly challenged by the social defeat stress procedure. High rank mice go from a situation in which they have privileged ownership over the homecage territory and power in interactions with cagemates, to a chronic condition in which their territory is substantially reduced and they lose power. On the contrary, subordinate animals might be used to being defeated during their pre-established social hierarchy establishment, making

them more resilient to subsequent social defeat. Although it needs to be tested, such a possibility would imply that the resilience profile observed in subordinate animals after CSDS might be due to the habituation of a stressor (losing aggressive interaction) rather than the social rank *per se*. In addition, the new CSDS situation experienced by low rank mice might be even judged advantageous over their former group condition as, for most part of their days, they count with their own territory only briefly challenged by the aggressor. Previous work has revealed that social subordination might be adaptive during unstable social structure periods [49, 84] perhaps by exerting a sort of 'behavioral immunization' preventing the negative consequences of social defeat [49, 73, 85]. In aggreement with our reasoning here, resident male mice losing the territory ownership were shown to be more prone to develop immune system alterations compared to resident mice that maintained their high status [76].

Collectively, these observations are in line with the idea that dominant animals are the ones that suffer the greatest 'loss of social standing', and potentially resources, when exposed to repeated defeat, and suggest a causal link for defeat and rank loss, rather than social subordination, with depression [86–88].

Is it social rank or the loss of social rank that correlates with depression?

The conclusion from the previous section highlighting a higher risk to develop stress-induced depression for dominant animals might be surprising given the frequently reported link between reduced fitness and social subordination or low socio-economic status [44, 69, 89, 90]. Given that dominant individuals maintain power and typically have priority to resources [91], social subordination has been thought to be generally linked with impaired physical and mental health [46]. The field of evolutionary psychology, particularly the 'Social rank theory' of depression, has considered depression as an adaptive submissive response to a competitive loss, originally aimed at reducing risk of injury or death [92]. In the same vein, submissive behavior in humans has been associated with low self-esteem [46], and low self-esteem proposed to be both a symptom of depression [93] and a vulnerability factor for this condition [94].

However, the existence of a deterministic link between low self-esteem or submissiveness and depression has been also questioned. Supporting examples in primates include evidence in female cynomolgus monkeys that, although social subordination is stressful and depressive behavior is more common in socially subordinate monkeys, depressive behavior is not present in all subordinates [95, 96]. The nature of social interactions within the social organization might be critical i.e., the degree of stability and despotism of social hierarchies. Indeed, during social reorganization in baboons, dominant

individuals show the greatest psychological stress compared to their subordinates counterparts [44, 97, 98]. In outbred CD1 mice, dominants display lower corticosterone levels than subordinates, that are more physiologically stressed, in highly despotic social groups [99]. In contrast, dominant mice show greater plasma corticosterone than subordinates in pair-housed conditions [99]. Noteworthy, subordinates from social structures generated by the visible burrow system (VBS) in rats display a blunted corticosterone response to acute novel stressor following 14-day chronic social stress in the visible burrow system [100] suggesting that subordinates are more vulnerable to subsequent stressors than dominant rats. In humans, rates of depression and anxiety are higher in competitive rather than in gentle societies [101, 102]. In addition, evidence suggests that there might be an important difference between imposition of subordination or naturally occurring subordinate behavior. While the imposition of subordination frequently leads to impaired cognition function [103–105], predisposition toward subordination is not related to cognitive impairment [103] and may even be co-expressed with a higher capacity for cognitive performance [106]. Unwanted subordinate positions and striving to avoid inferiority in humans were shown to be significant predictors of depression [107]. Thus, depressive episodes in humans are typically triggered by perception of social defeat, major social loses and humiliations, i.e., rank losses [108–111]. Therefore, this combined evidence support the view that social defeat in dominant individuals is more pertinent to depression than perceptions of low rank *per se* [86–88] and suggests rank loss as a critical mediating factor.

This view is also reinforced by research in rodents. In pioneer work establishing the model of chronic social defeat, Willner et al. [83] showed that dominant rats within a pre-established homecage social hierarchy showed different behavioral alterations following chronic social defeat by another aggressive male, depending on whether or not they were defeated in those encounters. Only defeated ones lost dominance in their own homecage interactions, as well as a decrease in sucrose intake – indicative of anhedonia– relative to non-defeated dominant animals. These observations support the view that losing rank and power in dominant animals is closely linked to the development of depression-like symptoms. However, the study did not examine the impact of aggressive social defeat in subordinates precluding conclusions in this regard.

In addition, data from the chronic psychosocial stress model developed by Bartolomucci et al. [49, 76] indicates a differential impact of social defeat in mice that become subordinate depending on whether they were the resident or the intruder of the homecage in which animals newly cohabitate. Specifically, resident mice that become subordinate are the ones that showed a unique profile of physiological alterations including a substantial increase in body weight and a strong depression of immune functions. Therefore, it is not subordination by itself that is detrimental to health but a loss of a key

resource [49], a threat to power. In this paradigm, at difference to intruders, resident subordinates following defeat by an intruder lose a territory and power and, therefore, social defeat in both types of animals had a different motivation [49]. Similarly, alterations in immune function were also reported for dominant rats in semi-naturalistic colonies that lose their rank [81].

Beyond losing rank, loss in several domains (e.g., physical, financial, social) is central to stress-induction and a key feature of depression in humans. A recent study in rats has illustrated the strong impact of significant loss for the development of depression-like behaviors. Specifically, male rats that were removed from long-term access to a rewarding enriched environment showed increased passive coping in the forced swimming test, increased body weight gain associated with hyperpahgia, and HPA axis hyporeactivity [112]. In the same vein, aggression/dominance toward conspecifics is highly rewarding and can be see as a positive reinforcer under various contingencies [113, 114]. As such, a proportion of aggressive old-breeder CD1 mice display robust conditionned place preference to a C57Bl/6J intruder-paired context [114, 115]. Accordingly, vulnerability to CSDS observed in dominant mice [43] might be the result of a complex interaction between losing rank/power and losing reward.

Therefore, the reassessed literature supports the conclusion that losing rank and/or key resources and/or reward, rather than subordination *per se*, is particularly relevant for the development of chronic defeat stress-induced depressive behavior. This points at individuals in high dominance positions at particularly higher risk to stress-induced depression as they attain a superior rank and power that can be lost, supporting recent findings in mice with the CSDS model [43].

Outstanding questions

As indicated above, the summarized evidence points at rank loss as a critical mechanism in social defeat-induced depression and, therefore, suggests that dominant individuals are at a higher risk of developing depression-like behavior following chronic defeat stress. However, several important issues remain to be established.

The first ones are methodological. To what extent differences in methodology for assessing dominance-submissive relationships are critical to conclude about the vulnerability to stress linked to a particular social rank. Given that social behaviors depend on a range of interacting environmental, individual, and social factors [99], it would be important to assess vulnerability in social rank establishment through other models and procedures (e.g., [116–118]). In addition, in the CSDS model, it will be critical to establish whether there are detectable differences in the behavior of dominant and subordinate mice during social defeat. Most studies do not examine the quality of the defeat sessions

(e.g., latency to be attacked, duration of aggression received, duration of submission produced), and a note of caution has been voiced in this respect [58, 59, 119].

Another issue is whether the susceptibility to CSDS observed in dominant mice can be generalized to other non-social stress protocols, or whether the 'social' defeat component is the one that operates specifically to induce depression-like neurobehavioral changes in these mice. The social environment is known to be an important source and moderator of individuals' stress [45, 120]; would factors related to rank in social hierarchy be specifically sensitive to social stressors? To clarify this point, future work is needed to test whether dominant mice are more vulnerable to develop depression-like behaviors when exposed to physical, instead of social, stressors. Should that be confirmed, the interpretation of the findings by Larrieu et al. [43] should down-tone the relevance of losing social rank in favor of a particular vulnerability of dominant mice to loss of controllability in face of stressful situations. This view would be in line with the central role of lack of controllability for the development of depression proposed by Maier [121] and confirmed in depressed patients [122]. As such, while dominant animals can exert control over cagemates in a familiar context (e.g., homecage), the effect of stress uncontrollability reflected by CSDS or chronic physical stress on mood-related behaviors could be more sallient for dominant individuals than for subordinates.

A third relevant issue is the origin of social rank attainment. Genetic factors certainly contribute to behavioral differences in outbred populations [123]. Using selective breeding of outbred Sabra mice for dominant and submissive trait, a genetic component was revealed underlying the inheritance of these phenotypes [124, 117]. However, in inbred mice maintained under equivalent experimental and husbandry conditions, individual differences could be due to the exposure of differential factors during early development (e.g., differences in maternal care or in social interactions between siblings) or to specifics related to the social organization within the homecage. In fact social behaviors depend on a range of interacting environmental, individual and social factors [99]. There might be *a priori* differences that predispose individuals to attain a specific social rank order. For example, in the Larrieu et al. [43] study, dominant mice showed higher anxiety-trait levels towards the beginning of their group cohabitation (1 week) and, hence, several weeks before the rank was clearly established and stable. This higher basal anxiety in dominant mice is in line with strong evidence indicating that high trait anxiety (i.e., individuals with a predisposing temperament to respond anxiously across situations) is a risk factor for stress-induced depressive-like behaviors [4, 21–23, 125]. It is also, more broadly, consistent with several recent studies reporting a strong predictive power of the exploratory pattern displayed by animals when individually exposed to a novel environment (e.g., open field, elevated plus maze) [1, 24–26, 126]. In Kazlauckas et al. [126] for example, high exploratory mice are less anxious in

the light-dark test and the elevated plus maze, and show increased locomotion in an open field. In addition, low exploratory mice are more submissive in the resident/intruder test than high exploratory mice. Given the existing link between anxiety and social competition [127, 128], future studies should address the potential contribution of anxiety trait for rank-related susceptibility to stress.

A fourth issue is whether other non-invasive biomarkers could be identified as predictors for stress-induced depression. Importantly, the Larrieu et al. [43] study applied proton magnetic resonance spectroscopy (^{1}H-MRS) to compare the neurochemical and metabolic profile between controls and chronically defeated high and low rank mice in the NAc and the medial prefrontal cortex (mPFC). The metabolic profile revealed status-related differences in the NAc metabolic profile, both under basal conditions and following chronic social defeat, while no significant differences between groups were detected in the mPFC. In subordinates, but not dominants, levels of energy-related metabolites were increased after exposure to CSDS. Moreover, the study revealed key differences in the NAc levels of some of the metabolites (i.e., creatinine and phospho-creatinine, taurine and alanine) under basal conditions, suggesting that they could eventually be used as biomarkers for rank and stress-induced depression. Future studies should explore this promissing possibility.

Conclusions and outlook

The segregation of individuals presenting susceptibility to develop stress-induced psychopathologies has greatly facilitated progress on the identification of molecular and cellular mechanisms involved in vulnerability to stress. Emerging work is now focussing on the identification of biomarkers for vulnerability to develop stress-induced depression, and social rank has been identified in recent rodent work as a predictive behavioral risk factor. In light of these findings, we have re-opened here the debate as to whether a specific social status (dominant or subordinate) can be accounted for differential susceptibility to develop stress-induced depression. The revised literature led us to propose that losing rank/power/reward, and associated resources, is more salient for depression than social subordination *per se*. Therefore, this line of thinking implies that, indeed, dominant individuals (the ones sustaining higher rank and resources) are at higher risk of developing depression-like symptoms when confronted to chronic situations implying loss of rank and resources. However, should major resources being also taken out chronically, subordinates should as well reflect vulnerability to stress. Accordingly, although we cannot discard the existence of *a priori* differences that could predispose individuals to attain a specific social rank order, existing evidence indicate that beyond genetics, one of the key contributing sources to anxiety and stress vulnerability relies on the social architecture and nature of social interactions within the homecage. We expect that this insight will

greatly facilitate progress on the identification of the neurobiological mechanisms inherent to vulnerability to stress and those that foster resilience.

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Figure legends

Figure 1. Rodent protocols addressing the relevance of rank to predict vulnerability to chronic social stress. (A) Adapted from [43]. In the Larrieu et al. [43], 4 weeks after their arrival at 6 week-old, groups of 4 C57BL/6J mice per cage are segregated into two groups [i.e., dominant mice (Rank 1 and Rank 2; in green) and subordinate mice (Rank 3 and Rank 4); in red] using a social confrontation tube test. At 13 weeks of age, mice are subjected to a chronic social defeat stress for 10 days [9]. This protocol leads to 4 groups i.e., defeated dominants, defeated subordinates, non-stress dominants and non-stress subordinates. After the last session of stress, dominant and subordinate mice are tested for their social avoidance toward an unfamiliar CD1 mouse to determine resilience and susceptibility phenotype [43]. **(B)** Adapted from [73, 74]. In Morisson et al. [73, 74] a 3-4-month-old-resident Syrian hamster is individually housed for 1 week before undergoing a resident-intruder test consisting in puting another hamster from the same age labelled as intruder 'I' inside its homecage. After 10 minutes (for the day1) and 5 minutes (for the remaining days) of physical interaction, intruder hamster returns to its homecage for the rest of the day. In this phase called 'dominant-subordinate encounters' the same dyad of resident/intruder hamsters is used for 14 days to determine a stable dominant/subordinate relationship. Dominants (in green) and subordinates (in red) are then exposed to a social defeat training (3 times with 3 old aggressive hamsters for 5 minutes) 24 h after their final dominance encounter. After this, all animals are tested for conditioned defeat behavior consisting in a 5-minute social interaction test during which a younger non-aggressive intruder is placed in the subject's homecage. Submissive/defensive, aggressive and non-social behaviors are then quantified during the social interaction test. **(C)** Adapted from [49, 129]. In Bartolomucci et al. [49, 129], a 4-month-old-CD1-resident 'R' mouse is individually housed for 1 week before undergoing a resident-intruder test consisting in puting a younger (3-month-old) CD1 mouse labelled as intruder 'I' inside its homecage. Following 10 minutes of physical interaction, the resident is separated from the intruder by a perforating divider allowing sensorial interaction only for the rest of the day. The perforated divider is removed daily for a total of 21 days. In this protocol the same dyad of resident/intruder mice is used to determine a stable dominant/subordinate relationship seen after 2 days of sessions. This chronic psychosocial stress leads to 4 behavioral categories in CD1 mice i.e., resident dominants, resident subordinates, intruder dominants and intruder subordinates.