

Can I Get a Witness? Using Vicarious Defeat Stress to Study Mood-Related Illnesses in Traditionally Understudied Populations

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ABSTRACT

The chronic social defeat stress model has been instrumental in shaping our understanding of neurobiology relevant to affect-related illnesses, including major depressive disorder. However, the classic chronic social defeat stress procedure is limited by its exclusive application to adult male rodents. We have recently developed a novel vicarious social defeat stress procedure wherein one mouse witnesses the physical defeat bout of a conspecific from the safety of an adjacent compartment. This witness mouse develops a similar behavioral phenotype to that of the mouse that physically experiences social defeat stress, modeling multiple aspects of major depressive disorder. Importantly, this new procedure allows researchers to perform vicarious social defeat stress in males or females and in juvenile mice, which typically are excluded from classic social defeat experiments. Here we discuss several recent advances made using this procedure and how its application provides a new preclinical approach to study the neurobiology of psychological stress-induced phenotypes.

Keywords: Adolescent, Animal model, Anxiety, Depression, Female, Psychological stress, Social defeat, Witness defeat

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Depression is among the most prevalent mental illnesses, with 3.6% of the global population suffering from mood-related disorders (1), and depression is currently the leading worldwide cause of disability (2). Although there is a strong genetic component to major depressive disorder (MDD) and other psychiatric illnesses, the effects of individual genes and polymorphisms are weak, suggesting a strong environmental contribution to the manifestation of these diseases (3,4). A variety of environmental factors can increase risk for MDD, and exposure to stress, both chronic and traumatic, is associated with a higher incidence of mood disorders, including MDD (5–7). Because of the connection between exposure to stress and affective illnesses, an array of procedures expose rodents to stress to model aspects of mood-related symptoms (8,9).

Chronic social defeat stress (CSDS) is a widely adopted preclinical stress procedure that produces a persistent suite of behavioral changes (10) including deficits in social interaction (SI) and preference for rewarding stimuli like sucrose, while decreasing body weight (11,12). CSDS-induced behavioral alterations can be reversed by long-term (>10 days), but not short-term, exposure to traditional antidepressant drugs (11,13–16) as well as by short-term administration of the rapidly acting antidepressant drug ketamine (17–19). Moreover, CSDS produces a subgroup of resilient animals (~30%) that fail to develop these behavioral deficits after stress (10–12), providing face validity to the model because not all people exposed to stress develop mood disorders. Therefore,

CSDS has been used to study resilience to the effects of stress on mood. Resilience is an active process involving changes in gene expression, neuronal activity, and neurotransmitter function in multiple brain regions that can be targeted for novel therapeutics (20–22). Thus, CSDS is a valid and productive model for the study of resilience and susceptibility to stress-induced affective illnesses in adult male patients. However, stress exposure and mood disorders are not limited to adult males in human populations.

Women in the United States are twice as likely as men to be diagnosed with MDD (23). Although cultural pressures and perceived norms likely contribute to this disparity, depression in women is higher than in men across the world (24,25), indicating that cultural biases are unlikely to be the only factor in this difference. Moreover, both human and animal studies have revealed sex differences in brain regions and molecular pathways central to mood disorders (26–28). This suggests that physiological distinctions between the sexes drive differences in stress responses and/or the manifestation of affective illnesses. In addition, exposure to trauma or chronic stress can also occur in childhood and adolescence, and there are clear links between exposure to trauma at an early age and mood disorders occurring soon after or much later in life (29–31). Although women and young populations are particularly vulnerable to stress-induced mood disorders, most preclinical mechanistic studies of these diseases have exclusively involved adult male animals. While CSDS has been a valuable

model, its reliance on adult male territorial aggression prevents its application to these understudied populations, and new models are needed to expand the impact of mechanistic studies. In this review, we discuss a novel vicarious defeat stress (VDS) procedure wherein one mouse witnesses the physical defeat bout of a conspecific from the safety of an adjacent compartment and the potential impact of this new model on our understanding of mood disorders across all affected populations.

OVERVIEW OF CSDS AND VDS

Procedures

Although CSDS has been used across several animal species, this review focuses on findings from the mouse procedure introduced by Berton *et al.* (11). We focus on this version of CSDS because it serves as the basis for VDS and allows for straightforward comparison of the effects of each stressor (32). In CSDS, a male C57BL/6 intruder mouse intrudes into the home cage of a larger retired breeder male CD-1 resident mouse for 10 minutes per day for a total of 10 days. During this time, the resident repeatedly confronts and overpowers the intruder. At the end of this interaction, the resident and intruder are separated by a perforated divider, allowing visual, olfactory, and auditory interaction without further physical defeat for 24 hours. The intruder is exposed to a novel aggressor each day, and then typically single housed. Within 24 hours of the last social defeat session, CSDS-susceptible mice display aberrant mood- and reward-related behaviors (10–12).

VDS (sometimes called emotional or witness social defeat stress) uses a similar protocol (Figure 1) wherein a CD-1 resident mouse physically defeats a C57BL/6 intruder. However, a separate experimental VDS mouse is placed on the other side

of the perforated divider during this encounter, allowing visual, olfactory, and auditory perception of the confrontation (33). The VDS mouse is then housed (separated by a divider) with an aggressor CD-1 for 24 hours, and the process is repeated for 10 days. Behavioral effects of VDS begin as early as 24 hours after witnessing the last defeat, though some effects can take several weeks to emerge (32,34–36). While specific effects are immediately evident, others develop over time (i.e., incubate), such as decreases of sucrose preference or social avoidance. The mechanisms behind this incubation period are unknown, but multiple circuits are likely involved. An interesting possibility is that the delayed emergence of VDS-induced social avoidance (37) and/or anhedonia-like behavior (32) may represent resilience processes tapering off, leading to the emergence of latent behavioral effects (38,39).

Behavioral Effects of Male CSDS and VDS

Social Interaction. Mice exposed to CSDS typically spend less time interacting with a novel social target (11,12,40). This is considered a maladaptive response modeling social withdrawal relevant to many mood disorders because defeated mice avoid SIs with all mice, including those derived from their own background (11). Long-term, but not short-term, treatment with traditional antidepressants reverses this phenotype (11,15), as does a single injection of the rapidly acting antidepressant ketamine (17,41). This behavioral test is also used to differentiate defeated mice into subgroups based on their resilience to CSDS. Mice that spend more time interacting with a social target are termed “resilient,” while those spending less time with the social target are called “susceptible” (12). Similarly, VDS in adult male mice decreases SI both 24 hours and 30 days after the last stress session (32,37). Although significant, the decrease in SI is lower in magnitude after VDS than

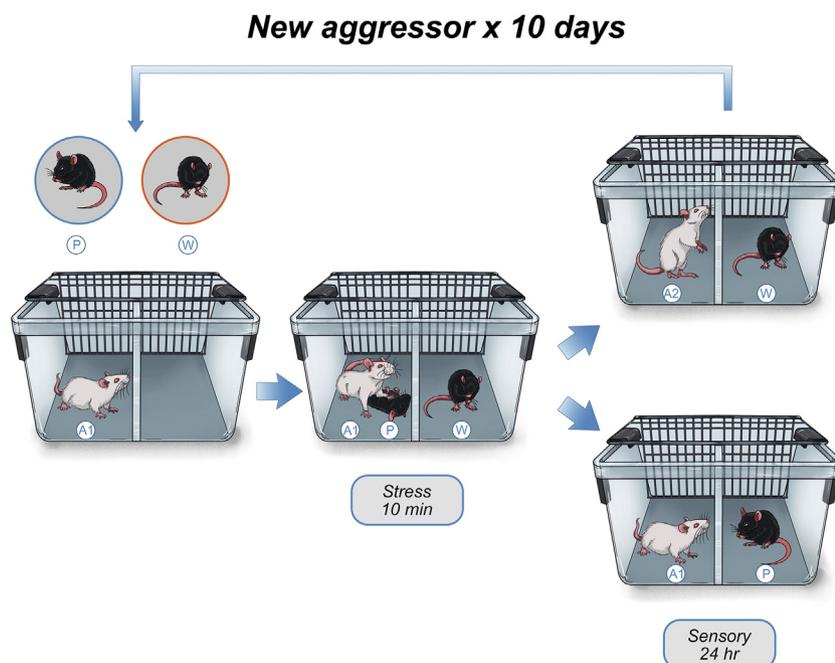


Figure 1. Vicarious social defeat stress procedure. The adult male C57BL/6 physical target intruder mouse (P) is placed into the divided cage with a resident adult male retired breeder CD1 aggressor mouse (A1), while the witness intruder mouse (W) is placed across the divider. Critically, the witness mouse can be either sex and adolescent or adult. After a 10-minute stress interaction involving physical aggression of the resident (A1) against the physical target (P), the witness mouse (W) is moved to a new cage, where it is housed across a divider from a different resident male retired breeder CD1 aggressor mouse (A2), while the physical target intruder mouse (P) is placed across the divider from the original aggressor mouse (A1), and the mice are cohoused for 24 hours. This process then repeats for a total of 10 consecutive days.

Table 1. Short-term Behavioral and Physiological Outcomes to VDS and CSDS in Male Rodents

| Behavioral/Physiological Syndrome | VDS | | CSDS | | |
|-----------------------------------|----------|-----------|-------------|-----------|-----------|
| | Observer | Reference | Susceptible | Resilient | Reference |
| Social Interaction | ↓ | (32) | ↓ | = | (12) |
| Forced Swim Test (Immobility) | ↑ | (32) | = | = | (12) |
| Anxiogenic Behavior | ↑ | (32) | ↑ | ↑ | (12) |
| Sucrose Preference | ↓ | (32) | ↓ | = | (12) |
| Drug Reward Sensitivity | ↑ | (67) | ↑ | = | (12) |
| Memory Performance | ↓ | (108) | ↓ | = | (43) |
| Locomotor Activity | = | (32) | = | = | (12) |
| Weight Change | ↓ | (32) | ↓ | = | (12) |
| Serum Corticosterone | ↑ | (32) | ↑ | ↑ | (37) |
| Stress-Induced Polydipsia | ↑ | (108) | ↑ | ↑ | (12) |
| Proinflammatory Markers | ↑ | (37) | ↑ | ↑ | (37) |
| Cardiovascular-Related Factors | ↑ | (93) | = | ↑ | (12) |

↑, significantly higher; ↓, significantly lower; =, no change from control; CSDS, chronic social defeat stress; VDS, vicarious social defeat stress.

CSDS (41), precluding the differentiation of resilient versus susceptible phenotypes using SI ratios. Importantly, while SI is used to categorize mice as susceptible or resilient to CSDS, resilient mice are not equivalent to nonstressed control mice. Resilient mice display differences in other behavioral end points (Table 1), neuronal activity (42), and gene expression (12,43) from control mice—demonstrating that stress exposure impacts them, albeit differently from SI behavior specifically.

Forced Swim Test. This test is a model for studying despair (44,45) and involves placing mice into water in an inescapable situation. Short-term treatment with virtually all antidepressants increases the time spent struggling and decreases time spent immobile. Surprisingly, CSDS does not reliably influence immobility in forced swim test (12,46–49), and in studies dividing mice into CSDS-susceptible and CSDS-resilient categories, no group differences are seen (12). This finding underscores the necessity for a multifaceted approach to assessing mood in rodent models. By contrast, VDS increases total immobility in adult male mice within 24 hours of the last stress session, persisting up to 30 days later (32). Similarly, VDS increases forced swim test immobility in male rats (34), a behavioral response that is prevented by prior exercise exposure (50), highlighting how naturalistic experiences, in addition to pharmacological treatments, reverse VDS-induced behavioral end points.

Elevated Plus Maze. The elevated plus maze test is a putative measure of anxiety-like behavior (51). Mice initially prefer the safety of the closed arms but will eventually explore the open arms of the elevated plus maze. Anxiolytic drugs decrease the latency to enter and total time spent in the open arms. CSDS increases time spent in the closed arms of the maze in both CSDS-susceptible and -resilient mice (52), and this effect persists up to 30 days after the last defeat session (12,32). Similarly, VDS in adult male mice increases closed-arm time within 24 hours of the last VDS session and persists for at least 1 month (32).

Natural Reward. The sucrose preference test assesses hedonic response to natural rewards, allowing a mouse to

choose to drink either water or a sweet sucrose solution. Typically, rodents exposed to CSDS consume less sucrose than unstressed control mice, suggesting anhedonia (12,46,53–58), with some exceptions (59). Initial studies found that while VDS-exposed adult male mice do not initially show decreases in sucrose preference, an anhedonia-like response is apparent 30 days after the last VDS session (32). However, a recent report found that VDS decreases sucrose preference at both early and late time points (36).

Drug Responses. Conditioned place preference is used to assess hedonic responses to drugs (60). Conditioned place preference for cocaine is increased following CSDS in mice (12,61–63) and rats (64), and the same is true of alcohol and benzodiazepines (61,65), suggesting increased sensitivity to the rewarding effects of drugs. However, the effect of VDS on conditioned place preference has not been elucidated and should be tested. Mice exposed to CSDS voluntarily consume more alcohol (66) and morphine (67) and may self-administer more cocaine, but this effect is variable between studies (59,68). Similarly, VDS increases voluntary consumption of morphine (67). The effect of CSDS on drug self-administration has been well described in rats (69). Defeated rats self-administer cocaine more readily (70,71) and will work harder for cocaine (72,73). Furthermore, CSDS can reinstate drug-seeking behavior after extinction (74,75), mimicking stress-induced drug seeking in human addicts. The contrast between CSDS-induced decrease in sucrose preference with this increase in drug preference/seeking suggests complex effects of CSDS on the brain circuitry underlying reward processing.

Neurobiological Effects of CSDS on Reward-Related Circuitry

Changes in the function of reward-related circuitry, specifically the nucleus accumbens (NAc) and ventral tegmental area (VTA), underlie behavioral responses to CSDS. Altered activity of NAc-projecting VTA dopamine (DA) neurons or of their target medium spiny neurons (MSNs) in NAc is necessary and sufficient to produce CSDS-associated behavioral effects (76). Since direct modulation of these neurons can promote and

prevent CSDS behavioral phenotypes, these data indicate that CSDS alters the physiology of these neurons to produce depressive-like behavior. However, the underlying neurobiological changes that promote these effects are not understood. Recent efforts have sought to link molecular and cellular changes in the reward circuitry to depressive-like behavior [reviewed by Fox and Lobo (76)], and here we highlight key neurobiological changes in the NAc and VTA after CSDS.

Nucleus Accumbens. Brain-derived neurotrophic factor (BDNF) levels in the NAc are increased following CSDS, and knockout of VTA BDNF reversed both CSDS-induced BDNF increases in the NAc and social avoidance (11), consistent with BDNF release from DA neuron terminals (77). Furthermore, the increase in NAc BDNF was limited to mice exhibiting social avoidance, as resilient mice displayed NAc BDNF levels equivalent to control mice (12). These data implicated BDNF in the NAc as a key biological substrate for CSDS (78,79). Other neuropeptides, kinases, transcription factors, and epigenetic modifiers (76) have also been implicated in NAc-mediated CSDS effects, and whole genome gene expression and epigenetic studies indicate that CSDS induces differential expression of hundreds or even thousands of genes (7), suggesting myriad players in NAc-associated stress phenotypes.

Many of the molecules implicated in these studies are involved in synapse structure and function, and indeed, CSDS changes the synaptic morphology of NAc MSNs. CSDS-susceptible mice had increased MSN dendritic spine density compared with control or CSDS-resilient mice (80,81). Analysis of single spine dynamics support changes in functional glutamatergic input onto NAc MSNs, although more prominent changes were observed in resilient compared to susceptible mice (82). Critically, there seem to be opposing adaptations induced in DA receptor D₁- versus D₂-containing MSNs, as CSDS-susceptible mice display decreased and increased excitatory input to D1-MSNs and D2-MSNs, respectively (83). Consistent with the activity findings, D1-MSNs in CSDS-susceptible mice exhibit decreased dendritic length, with no change in dendritic spine density, following CSDS (84–86), suggesting that stress-induced increases in spine density are driven by D2-MSNs. Moreover, altering cytoskeletal signaling dynamics is sufficient to prevent changes in spine plasticity and to reverse social-avoidance phenotypes (81,84). These data suggest that altered NAc connectivity is critical for CSDS effects, consistent with the NAc's role as a key integrator of cortical and limbic signals.

Ventral Tegmental Area. Activity of VTA DA neurons is increased in CSDS-susceptible (but not CSDS-resilient) mice, and optogenetic activation or inhibition of these neurons is sufficient to promote susceptibility and resilience to CSDS, respectively (12,87,88). Moreover, these effects are driven specifically by VTA DA neurons that project to the NAc (and not the prefrontal cortex), suggesting that cell type-specific adaptations are also critical in the VTA (87). In contrast to the NAc, the underlying signaling and molecular mechanisms have been understudied in the VTA. VTA BDNF plays a critical role in CSDS phenotypes, as VTA BDNF knockout prevents CSDS susceptibility (11), and modulation of kinases associated with neurotrophic factor signaling in the VTA has been linked to

CSDS responses (89–91), but molecular mechanisms of CSDS responses in the VTA remain an ongoing research focus for many groups.

Neurobiological Effects of VDS in Adult Male Mice

In comparison to the numerous studies elucidating the neurobiological underpinnings of traditional CSDS, less is known about the mediators of VDS. Notably, studies have yet to determine whether increased VTA DA neuronal activity and output to the NAc are necessary for VDS susceptibility, highlighting the critical need for electrophysiological and optogenetic studies in this area. However, VDS and CSDS similarly decreased the number of Fos-positive cells in the striatum and dorsal hippocampus (67). In contrast, regulation of another immediate early gene, Δ FosB, was more complex, as both VDS and CSDS increased the number of Δ FosB-positive cells in the dorsal hippocampus, but only CSDS increased Δ FosB-positive cells in the prefrontal cortex and dorsal and ventral striatum (67). While tentative, these data suggest that VDS and CSDS may rely on overlapping, but not identical, circuits and mechanisms.

To compare mechanisms contributing to CSDS versus VDS, gene expression changes in the VTA induced by VDS were examined (32). RNA-sequencing showed considerable overlap between CSDS and VDS with 312 and 349 transcripts similarly upregulated and downregulated, respectively (32). One of these transcripts was SGK1 (serum- and glucocorticoid-regulated kinase 1), which was increased in the VTA following CSDS and VDS in a follow-up study (67). We observed that transcription of ERK2 (extracellular signal-regulated kinase 2) is increased and Δ FosB decreased in NAc following both VDS and CSDS (92). However, we noted differences between the models in this study as well, as CSDS induced an increase in NAc dendritic spine density, consistent with previous studies, while no change in spine density was observed in mice exposed to VDS (92). Overall, the mechanisms supporting VDS phenotypes are largely unexplored, and given the results suggesting potential divergence from CSDS studies, identification and characterization of the molecular and cellular changes induced in the reward circuitry by VDS should become an active area of study.

Use of VDS Where Physical Stress Could Serve as a Confound

Multiple advantages to VDS allow completion of studies that are not compatible with CSDS. While established CSDS protocols attempt to minimize serious injury to the stressed mouse (10), aggression-mediated wounding is unavoidable. Wounding is not correlated with susceptibility to CSDS (12,37), thus disconnecting physical injury with behavioral adaptations to stress such as social avoidance. However, this wounding (and subsequent pain and inflammation) is a biological difference that is not typically controlled for, adding a caveat to many studies, particularly those investigating the role of inflammatory signaling. Therefore, studies investigating inflammatory mechanisms contributing to depressive-like phenotypes have recently utilized VDS to avoid confound of physical injury. For example, Hodes *et al.* found that interleukin-6 was increased in mice following their first

Vicarious Stress as a Model for the Study of Depression

exposure to CSDS, an effect that predicted their susceptibility to CSDS at the 11-day time point (37). However, this increase in interleukin-6 was also observed following VDS, indicating the interleukin-6 increase was not due to an acute injury response, but the psychological stress induced in both models. Moreover, bone marrow chimeras from VDS were sufficient to induce susceptibility, indicating that witnessing CSDS produced a peripheral immunogenic response that induced social avoidance. In this case, VDS and CSDS produced similar inflammatory responses. However, a recent study comparing CSDS and VDS in rats observed differences between the two models (93). Here, increased peripheral inflammation (via blood cytokine levels) was evident in CSDS, but not VDS, rats re-exposed to the stress context, despite both CSDS and VDS rats exhibiting increased mean arterial pressure and heart rate and increased epinephrine and corticosterone levels.

A related promising avenue for VDS studies is in modeling comorbidity of depression with pain disorders, which are also often linked to inflammation. Traditional CSDS promotes hyperalgesia and changes in nociception and pain sensitivity (94–96) and exacerbates postsurgical pain (97). VDS models might be beneficial in pain studies as they lack any potential confound of pain or inflammation induced by physical insult. A similar approach has been used recently, wherein mice that repeatedly witnessed foot-shock stress developed hyperalgesia and long-lasting pain sensitivity in a variety of nociception tests (mechanical, thermal, chemical) (98). VDS offers the additional benefit of utilizing an ethologically relevant stressor to potentially sensitize or promote pain sensitivity and hyperalgesia.

Another benefit of VDS is the ability to evaluate intake of drugs of abuse during stress exposure. These studies can be completed using traditional CSDS models, but caution must be taken that drug intake does not interfere with the subsequent physical defeat and escape behavior. Additionally, assessment of operant drug intake, typically via intravenous self-administration, is difficult to assess during CSDS owing to potential damage to the catheter/harness. Thus, VDS offers the potential benefit of investigating drug intake both during and following social stress. Given the consistent findings that repeated social stress sensitizes poststress drug responses (69), delineating the role of these processes during stress and whether access to drugs during stress affects the development of depressive-like behaviors are fertile grounds for study. Likewise, VDS would confer a similar benefit to studies attempting to record *in vivo* electrophysiological, imaging, or microdialysis measurements by allowing measurements to be taken from harnessed animals during a stress session.

Importantly, VDS could be beneficial in evaluating the connection between stress and opioid use disorders. Since most stress models involve physical insult that could result in pain, it may be difficult to separate the analgesic from rewarding aspects of opioid intake following stress. We took advantage of this approach recently, as we determined whether voluntary morphine consumption was altered following CSDS and VDS (67). We found that morphine preference and intake were similarly increased in CSDS- and VDS-exposed mice, suggesting that vicarious stress was sufficient to promote increased morphine reward. This encourages use of the VDS procedure for examining stress mechanisms that

alter opioid reward and intake, which may help inform our understanding of risk factors for opioid addiction without the confound of analgesia.

Use of VDS in Populations Typically Excluded From CSDS

Traditional CSDS is mostly limited to male subjects, since male and female rodents typically do not attack female conspecifics—some exceptions include Syrian hamsters, prairie voles, and California mice (99–103). In mice, researchers have encouraged physical aggressive behavior from a male resident to a female intruder by stimulating the ventromedial hypothalamus of male resident aggressors or by spraying male urine onto the female intruder (104,105). While such studies have demonstrated that CSDS female mice display a depressive-like phenotype, these approaches induce artificial stress situations, since in mice male-to-female aggression is unlikely under normal circumstances. Consequently, the female CSDS model may display low external and ethological validity for the study of stress-induced disorders. Critically, VDS can be applied to vulnerable populations that are traditionally excluded from CSDS studies, under ethologically relevant conditions. A growing body of work indicates that witnessing social-related stressors induces depression-related outcomes in male and female mice (41) when observed/experienced at different stages of development (92,106,107) as well as across species (108–111).

Female Rodents. Female C57BL/6 mice that have experienced VDS display behavioral and physiologic outcomes indicative of a depressive-like phenotype: decreased sucrose preference (anhedonia), lower sociability, and increased immobility in the tail suspension test (despair), along with increases in plasma corticosterone (hypothalamic-pituitary-adrenal axis activation) and decreased body weight (41). Short-term administration of ketamine reverses VDS-induced reductions in sociability, providing pharmacological validity to this model and offering a platform for future studies to screen for novel therapeutic agents. More recently, a complementary behavioral and physiologic profile has been reported in female Sprague Dawley rats witnessing male-to-male social aggression. Here, VDS-exposed female rats exhibited a depressive- and anxiogenic-like behavioral profile, along with a sensitized plasma corticosterone, epinephrine, and proinflammatory cytokine response (112). Additionally, this study demonstrates that VDS increases heart rate and blood pressure, as well as corticotropin-releasing factor protein and interleukin-1 β within the central amygdala, highlighting a potential biological mechanism by which psychological stress precipitates the development of depression-related behavior in the female population. This study also found that ovarian hormones are necessary for the development of the VDS-induced outcomes, although they occur in any stage of the estrous cycle (112). Collectively, these behavioral, pharmacological, cardiac, and neurobiological indices provide strong evidence of the translational validity of VDS for the study of sex differences in mood-related illnesses.

Younger Rodents. Male juvenile rodents display neurobehavioral alterations after CSDS exposure (58,113,114), a depressive-like phenotype that is sustained in later adulthood

Table 2. Behavioral and Physiological Responses to VDS

| Species/ Strain | Sex | Age | Stress Protocol | Behavioral Findings | Physiological Response | Reference |
|--|-----------------------|---------------------------|---|--|--|-----------|
| C57BL/6 Mice | Male | Adult (8 wk old) | VDS or CSDS: 10-min episodes/10 days | VDS and CSDS mediated depressive/anxiety-like behaviors 24 h after stress exposure (SI, FST, SPT, EPM). Both stressors decreased SI 1 mo later. Fluoxetine (20 mg/kg) reversed SI deficits after 30, but not 1, days of antidepressant exposure. | VDS and CSDS increased plasma CORT, decreased body weight, and dysregulated gene expression in the ventral tegmental area. | (32) |
| C57BL/6 Mice | Male | Adolescent (PD 35) | VDS or CSDS: 10-min episodes/10 days | VDS and CSDS decreased sociability (SI) 24 h after last stress exposure. | Adolescent VDS and CSDS increased nucleus accumbens spine density and decreased ERK2 and Δ FosB mRNA. CSDS increased pERK2 and Δ FosB protein. Both VDS and CSDS decreased pCREB protein within this brain region. | (92) |
| | | Adult (8 wk old) | VDS or CSDS: 10-min episodes/10 days | VDS and CSDS decreased sociability (SI) 24 h after last stress exposure. | Adult CSDS increased nucleus accumbens spine density. Both VDS and CSDS increased ERK2, while decreasing Δ FosB mRNA. Only CSDS increased pERK2 protein in nucleus accumbens. | |
| CD45.1+/ CD45.2+ C57BL/6 Mice | Male | Adult (7–8 wk old) | VDS: 10-min episodes/10 days | VDS decreased sociability (SI) 30 days post-VDS. | Increases in IL-6 30 days after VDS. | (37) |
| Sprague Dawley Rats | Male | Adult (225–250 g) | VDS or CSDS: 30-min/day (across 3 separate episodes)/7 days | Depressive/anxiety-like phenotype (OFT, LDB, EPM, FST) and memory impairment (RAWM) seen up to 8 days after VDS or CSDS exposure. Group housing (social buffering) ameliorated CSDS-induced alterations in LDB performance. | Both VDS and CSDS decreased body weight gain and increased water intake 24 h after stress exposure. Both stressors increased plasma CORT and decreased adrenal/thymus weight up to 9 days after VDS or CSDS. Group housing also prevented CSDS- and VDS-induced decreases in thymus weight. | (108) |
| Sprague Dawley Rats | Male | Adult (225–250 g) | VDS or CSDS: 30 min/day (across 3 separate episodes)/7 days | Depressive/anxiety-like behaviors (LDB, EPM, OFT, FST) and memory impairment (RAWM) seen up to 6 wk after VDS. | None reported. | (34) |
| Sprague Dawley Rats | Male | Adult (225–250 g) | VDS or CSDS: 30 min/day (across 3 separate episodes)/7 days | Depressive/anxiety-like phenotype (LDB, EPM, OFT, FST) along with memory impairment (RAWM) seen up to 1 wk after VDS. Fourteen days of exercise before VDS exposure prevented the development of the depressive/anxiety-like phenotype. | VDS increased plasma CORT 1 wk poststress. | (50) |
| Sprague Dawley Rats | Male and Female | Periadolescent (PD 21) | VDS (of mother): 30 min/day (across 3 separate episodes)/7 days | Despair-like behavior (FST), without changes in anxiogenic- like behavior (EPM, OF) or memory performance (RAWM) seen 1 mo after viewing their mother be socially defeated. | Periadolescent exposure to maternal VDS did not alter weight, food intake, or water intake in adulthood (PD 60). | (106) |
| Sprague Dawley Rats | Male | Adult (225–250 g) | VDS or CSDS: 15-min episodes/5 days | Depressive-like behavior (SPT) seen in VDS, but not CSDS, rats. | Both VDS and CSDS increased heart rate and mean arterial pressure. Both stressors also increased plasma CORT and epinephrine. Only CSDS increased plasma inflammatory-related proteins. | (93) |

Vicarious Stress as a Model for the Study of Depression

Table 2. Continued

| Species/ Strain | Sex | Age | Stress Protocol | Behavioral Findings | Physiological Response | Reference |
|---------------------------|--------|--------------------------|---|---|---|-----------|
| Sprague Dawley Rats | Female | Adult (175–200 g) | VDS: 15-min episodes/5 days | VDS mediated depressive/anxiety- like phenotype (FST, SPT, stress-evoked burying behavior). | VDS increased heart rate and mean arterial pressure. VDS elevated plasma CORT, epinephrine, and inflammatory-related proteins, along with corticotropin releasing factor and IL-1 β protein in the central amygdala. | (112) |
| C57BL/6 Mice | Female | Adult (8 wk old) | VDS: 10-min episodes/10 days | VDS-mediated depressive-like behavior (SI, SPT, TST). Short-term ketamine exposure (20 mg/kg) reversed VDS-induced SI deficits. | VDS increased plasma CORT and decreased body weight. | (41) |
| C57BL/6 Mice | Male | Adolescent (PD 28) | VDS or CSDS: 15-min episodes/10 randomized defeats within 1 wk | Only CSDS reduced sociability (SI). Social buffering ameliorated, but did not reverse, the CSDS- induced avoidance. Social buffering increased general locomotor activity in juvenile VDS mice. | Juvenile VDS and CSDS decreased body weight under grouped, but not isolated, housing conditions. | (114) |
| C57BL/6 Mice | Female | Adult (8 wk pregnant) | VDS (of male partner): 5- min episodes/17 days | Witnessing the defeat bout of a male partner, during pregnancy, induced anhedonia-like behavior (SPT). VDS-exposed female mice further display anxiety-like behavior (EPM, LDB) 21 days postlactation. | Five wk after VDS (of male partner), females display alterations in miR-206-3p and BDNF protein levels in the hippocampus, medial prefrontal cortex, and amygdala. | (35) |
| C57BL/6 Mice | Male | Adolescent (PD 49) | VDS or CSDS: 10-min episodes/10 days | VDS and CSDS mediated depressive-like behavior (SI, FST, SPT) up to 6 days after stress exposure; fasudil (10 mg/ kg) before each stress exposure normalized immobility behavior (FST) in CSDS, but not VDS, mice. | Juvenile CSDS increased body weight during stress exposure. One month after CSDS or VDS, plasma chemokines (CXCL16) were decreased. | (36) |

BDNF, brain-derived neurotrophic factor; CORT, corticosterone; CSDS, chronic social defeat stress; EPM, elevated plus maze; FST, forced swim test; IL, interleukin; LDB, light/dark box; mRNA, messenger RNA; OFT, open field test; pCREB, phosphorylated CREB; PD, postnatal day; pERK2, phosphorylated ERK2; RAWM, radial arm water maze; SI, social interaction; SPT, sucrose preference test; TST, tail suspension test; VDS, vicarious social defeat stress.

(115), but less is known about the effects of VDS on affect-related behavior within adolescent or younger populations. We demonstrated that male C57BL/6 adolescent mice exposed to VDS during postnatal days 35 to 44 had decreased social behavior (92), a depression-related end point that social buffering ameliorates (114). Furthermore, CSDS and VDS mediate unique alterations in NAc ERK2, Δ FosB, and CREB signaling as a function of age (92). Interestingly, CSDS and VDS similarly decrease NAc Δ FosB gene expression in adolescent and adult mice. In contrast, when compared to age-matched control mice, CSDS and VDS increase NAc ERK2 gene expression in adult mice, but decrease their expression in adolescents. These findings highlight similar neurobiological effects induced by both stress models, while displaying differential age-dependent effects in NAc messenger RNA expression. Further, CSDS and VDS reduced NAc-CREB phosphorylation in adolescent but not adult mice. Because adolescence is a period of increased synaptic plasticity and alterations in ERK2, Δ FosB, and CREB influence spine plasticity, we further evaluated total spine densities within this brain region. VDS increased spine density in the adolescent, but not adult, NAc of male mice, suggesting that

juvenile populations are more sensitive to the detrimental effects of psychological stress. This age-dependent alteration in NAc spines is intriguing, since the first episode of MDD is most commonly reported in adolescence (116), thus highlighting the strength and applicability of the VDS model for the study of juvenile affect-related illnesses. Moreover, VDS allows the inclusion of younger experimental populations to examine the long-term effects of witnessing parental maltreatment (106), a psychological stressor frequently reported in the pediatric population (117).

CONCLUSIONS

Procedures using social stress to model aspects of affective illnesses are providing critical insights into the neurobiology of depression and anxiety disorders. Most rodent studies using social stress have relied on territorial aggression, necessitating a focus on adult male subjects. Here, we demonstrated that models using vicarious stress are adaptable to underrepresented populations and remove confounds caused by physical interactions, such as pain and inflammatory responses. The

behavioral and neurobiological sequelae of VDS and physical CSDS are similar but not identical (Table 2). VDS primarily alters behavioral end points that are associated with despair, anhedonia, and sociability while not consistently altering anxiogenic-like behavior. Collectively, this profile not only lends validity to vicarious stress models but also allows the dissection of cellular and behavioral responses specific to either physical or psychosocial stress. We anticipate that vicarious models will continue to grow in popularity as they are further refined and characterized and that they will contribute to our developing understanding and potential treatment of stress-related psychiatric disorders in all populations at all ages.

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Vicarious Stress as a Model for the Study of Depression

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Vicarious Stress as a Model for the Study of Depression

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