TITLE:

The Hippocampus in Stress Susceptibility and Resilience: Reviewing Molecular and Functional Markers

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1. Introduction

Exposure to chronic stress has been linked to the development of psychopathologies such as depression (Schmidt et al., 2008) and post-traumatic stress disorder (PTSD (Davidson and Baum, 1986)). It has been reported that approximately 50-60% of Americans will have experienced a traumatic stressor in their lifetime (Ozer et al., 2003). However, following highly stressful events or traumas healthy functioning can persist in a subset of individuals and is termed resilience (Bonanno, 2004). In fact, in groups of individuals who have experienced similar traumas or tragic events, only 10-30% develop PTSD or depression. (Bonanno et al., 2006; Bonanno et al., 2002; Deshields et al., 2006; Lewis et al., 2019; Zisook et al., 1997). Resilience is not merely a lack of susceptibility but is fostered by active coping processes (Charney, 2004; Friedman et al., 2014; Krishnan et al., 2007; Russo et al., 2012). Contrasting the biological differences between individuals who are either susceptible or resilient to stress is a powerful approach to reveal underlying biological mechanisms, which can be targeted for the development of novel therapies.

Apart from its roles in learning and memory (Squire, 1992), the hippocampus emerges as a highly studied brain region that is differentially affected in those that are susceptible or resilient to stress. Its functions, such as the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Jacobson and Sapolsky, 1991) and neurogenesis (Mahar et al., 2014), have been implicated in the etiology and treatment of depression, respectively. Hippocampal shrinkage is a feature common to depression (Gurvits et al., 1996; McEwen and Sapolsky, 1995; Smith, 2005; Videbech and Ravnkilde, 2004) and PTSD (Logue et al., 2018). Smaller hippocampal volume also confers an increased risk of PTSD (Gilbertson et al., 2002) and depression (Chen et al., 2010; Rao et al., 2010). Given the role of the hippocampus in the processing and storage of information, it may contribute to the biased processing of negatively valanced information that has been described in

the cognitive theory of depression by Dr. Aaron Beck (Beck, 1967, 2008). Taken together, the hippocampus presents as critical to the understanding of the cellular and cognitive mechanisms of stress susceptibility and resilience.

Animal studies provide the flexibility required for examining the role of the hippocampus in stress susceptibility and resilience. It is timely to review these findings with a focus on those that have specifically examined animals that are susceptible and/or resilient to stress (i.e., we have not included those looking at the general effects of stress compared to control groups). Although the majority of studies report findings in mice, we did not discriminate based on rodent species, and included studies with rats and hamsters that met criteria. We first review three commonly used animal models that allow researchers to separately study stress susceptibility and resilience. We then focus on studies that employ these models and highlight hippocampal molecular and functional markers mediating susceptibility and resilience.

2. Animal models for studying stress susceptibility and resilience

2.1: Chronic social defeat stress (CSDS):

CSDS is a social stressor incorporating the importance of territorial relationships to both animals and humans (Malatynska and Knapp, 2005; Robinson et al., 2008). Using a resident-intruder paradigm, male rodents are introduced into the home cage of an aggressor and experience attacks for a limited period (Berton et al., 2006). The aggressor is usually an older rodent of an aggressive strain (e.g., retired breeders of the CD1 strain for defeating C57BL/6 mice). During social defeat, intruder rodents will assume a submissive, supine posture, emit frequent distress calls, and express freezing behavior. In addition to physical attacks, CSDS also consists of emotional stress from cohousing with the aggressor for hours or the remainder of the day through a perforated partition to prevent further attacks. The daily attacks/cohousing procedure is repeated

across several consecutive days with different aggressors to avoid habituation. CSDS susceptible animals have been shown to express social avoidance (Krishnan et al., 2007), behavioral despair (Iniguez et al., 2016; Iniguez et al., 2018), abnormal circadian rhythms (Wells et al., 2017), anhedonia (i.e., a decrease in the ability to experience pleasure from positive stimuli), a greater preference for drugs of addiction, and weight loss (Krishnan et al., 2007).

Several reasons make CSDS a highly popular model for studying stress susceptibility. CSDS paradigms have been successfully adapted to various rodent species including mice (Berton et al., 2006), rats (Miczek, 1979), hamsters (McCann and Huhman, 2012), and voles (Smith et al., 2013). Habituation to stressors can be avoided by using different aggressors in each day of defeat. Depression-like symptoms in susceptible mice can also be reversed following the administration of chronic, not acute, tricyclic or selective serotonin reuptake inhibitor (SSRI) antidepressants (Tsankova et al., 2006), which mirrors the human condition where weeks are needed for these medications to show an amelioration in symptoms. Ketamine, a fast-acting antidepressant, also ameliorates social avoidance in this model (Donahue et al., 2014). Apart from using CSDS to model depression, CSDS can also recapitulate characteristics common to PTSD (Berton et al., 2006) and anxiety (Rodgers and Cole, 1993). Importantly, the use of social subordination as a stressor is ethologically relevant for social animals like rodents and humans. Drawbacks to the use of the CSDS model include controlling the level of injury between animals, difficulties in keeping the intensity of the stressor consistent as it depends upon the action of the aggressor, and the lack of aggressive interactions with female or adolescent subjects. In recent years the latter issue has been circumvented with protocols adapted for females (for a review see (Lopez and Bagot, 2021)), such as vicarious social defeat, wherein female rodents witness the attacks of an aggressor towards a male conspecific (Iniguez et al., 2018). Another variation of CSDS termed accelerated social

defeat primes aggressors with the brief introduction of an adult mouse into their home cage, then subsequently replaces this adult with an adolescent. Primed aggressors will then defeat adolescent mice (Vassilev et al., 2021).

Criteria for defining susceptibility and resilience: The social interaction test is conventionally used to determine susceptibility to CSDS via the expression of social avoidance (Golden et al., 2011). Approximately 90% of CSDS studies define susceptibility according to the social interaction test. In this test, animals are allowed to explore an arena containing a social target that is novel, but of the same strain as the aggressors encountered in CSDS. Susceptible animals are those who spend more time distanced from the social target, while resilient animals maintain levels of social interaction that are comparable to non-stressed controls. This is calculated through a social interaction ratio, which compares the time spent in the area immediately surrounding the social target when the animal is present versus absent. Susceptible animals are those with interaction ratios less than 1 who actively avoid the social target (Berton et al., 2006; Krishnan et al., 2007). However, only using performance in a social interaction test to divide stressed animals into susceptible and resilient groups may be insufficient. For instance, mice exhibiting social avoidance after CSDS may not express other stress-related psychopathologies such as anhedonia (Alves-Dos-Santos et al., 2020; Smith et al., 2013), another commonly used criteria for stress susceptibility. Avoidance after CSDS is also specific to the aggressive strain and is not a generalized social impairment (Ayash et al., 2019; Venzala et al., 2012). Moreover, performance in the social interaction test after CSDS has been attributed to innate behavioral traits that are independent from social avoidance, such as changes in exploratory behaviors (Milic et al., 2021) and inhibitory learning (Dulka et al., 2015; Meduri et al., 2013; Milic et al., 2021). The contribution of these behavioral traits to stress susceptibility remains poorly understood.

2.2: Chronic mild stress (CMS):

CMS exposes rats (Willner et al., 1987) or mice (Monleon et al., 1995) to a variety of mild socio-environmental stressors over several weeks. An example of a CMS protocol used in mice includes periods of food and water deprivation, overnight illumination, cage tilt, soiled cage, intermittent sound, and stroboscopic illumination scheduled over 3 weeks (Monleon et al., 1995). Popular variations of CMS include chronic unpredictable mild stress (CUMS), unpredictable chronic mild stress (UCMS), and the chronic unpredictable stress (CUS) models. Although these variations emphasize the uncertainty of the stressor schedule, it is important to note that a fixed schedule is rarely used in CMS models (Willner, 2017a). Stress-induced psychopathologies that have been observed following CMS include anhedonia (Willner et al., 1992), decreased sexual and aggressive behavior (D'Aquila et al., 1994), disturbances in sleep patterns (Cheeta et al., 1997; Gorka et al., 1996; Moreau et al., 1995), and weight loss (Muscat and Willner, 1992; Willner et al., 1996).

The advantages to the CMS model lie in its parallels to depression. Firstly, following CMS more self-stimulation of the ventral tegmentum (a region mediating rewarding experiences) is required to elicit reward (Moreau et al., 1992), which serves as a representation of anhedonia. Secondly, the hedonic effects are reversed by chronic (3-5 week) treatment with tricyclic antidepressants (Muscat et al., 1990; Muscat et al., 1988; Sampson et al., 1991; Willner et al., 1987), atypical antidepressants (Muscat et al., 1992), and ketamine (Franceschelli et al., 2015; Garcia et al., 2009). Lastly, CMS is regarded as a realistic model of depression as the mild nature of the encountered stressors are thought to parallel the intensity of the daily challenges that people face (Willner et al., 1992). Although issues with the establishment of CMS procedures and the replication of results have been noted by some groups, recent findings support a high reliability of

this model in different laboratories (Willner, 2017b). However, the labour-intensive and time-consuming nature of the associated procedures can serve as obstacles for researchers.

Criteria for defining susceptibility and resilience: The presence of anhedonia is commonly employed as the defining criteria for CMS susceptibility (Strekalova et al., 2022). Anhedonia is evaluated through the sucrose preference test (SPT (Liu et al., 2018c)) where it is characterized as a loss in preference for sucrose over regular drinking water.

2.3: Models from selective breeding:

Selective breeding for the presence of genetic traits that favour the expression of susceptibility or resilience is another method for studying stress susceptibility in mice (Touma et al., 2008) and rats (for review, see Table 1 in (Wegener et al., 2012)). This is generally achieved by first introducing the animals to a stressor and later testing for behavioral representations of a depression-like behavior. Animals exhibiting behaviors that are in accordance with high levels of susceptibility are selected and bred together, while those with high resilience are bred in separate litters. The resulting offspring undergo the same stressor along with the selective breeding process and this is repeated for 5-30 generations. In most cases, inbreeding is avoided for the first 5 generations. The populations of animals generated will then descend from lines that were either susceptible or resilient to a particular or several measures of depression-like behaviors.

Selective breeding models are rooted in the fact that genetic predispositions influence whether an individual is likely to develop vulnerability to depression (Englund and Klein, 1990; Gershon et al., 1976; McGuffin et al., 1991; Weissman et al., 1984) and thus demonstrate construct validity. Markers for stress susceptibility could be validated in selective breeding models before stress exposure, an advantage when compared to CSDS and CMS as changes in markers could also be a stress response. However, care should be taken to incorporate environmental stress

exposure in genetic models of depression to better represent the human experience which is not strictly based on genetics.

Criteria for defining susceptibility and resilience: Various laboratories have successfully bred populations of rodents for the study of stress susceptibility. For instance, Sprague Dawley (SD) rats have been bred based on the expression of learned helplessness (LH), a behavior which manifests as the failure to escape repeated aversive shocks (Vollmayr and Gass, 2013). Following the 29th generation a strain exhibiting a LH phenotype without exposure to uncontrollable shock and another strain of congenitally non-LH rats emerge (Vollmayr and Henn, 2001). Using the forced swim test (FST), with rodents swim in an inescapable cylinder filled with water where greater immobility time marks susceptibility (Brenes Saenz et al., 2006), SD rats have been bred into Swim Low-Active and Swim High-Active strains, which at the 5th generation show immobile and active struggling behaviors in the test, respectively (Scott et al., 1996). Wistar Kyoto (WKY) rats were also separately bred into WKY most immobile and WKY least immobile strains according to their performances in FST, with differences in immobility being apparent following even the 1st generation (Will et al., 2003). Similar approaches have been used for selectively breeding CD1 mice into helpless and non-helpless lines with differences in immobility time that reach 40-fold by the 10th generation (El Yacoubi et al., 2003), and 6th generation Swiss mice into lines that are either susceptible or resilient to swim-stress induced analgesia (Panocka et al., 1986). There are also strains that were not originally bred for their reactivity to stress but have been shown to be useful for modeling. For instance, breeding SD rats according to their sensitivity to a cholinesterase inhibitor has developed the 26th generation Flinders Sensitive (FSL) and Flinders Resistant lines (FRL, (Overstreet, 1986)). Apart from their lower sensitivity to cholinergic agents, FRL rats are markedly more resilient to stress in the FST than FSL rats (Wegener et al., 2012).

Using animal models of stress has identified various molecular markers implicated in stress susceptibility and resilience. Hippocampal molecular markers including epigenetic mechanisms that affect gene expression, individual molecular, neuroinflammatory and hormonal markers, and neurogenesis, are reviewed below.

3. Molecular hippocampal markers for stress susceptibility and resilience

3.1: Epigenetic markers

Epigenetic mechanisms including DNA methylation, histone modification, and noncoding RNAs regulate gene expression and protein synthesis. These mechanisms contribute to the impact of gene and environment interaction on stress susceptibility. For instance, differences in maternal care could modify the histone marks and methylation pattern of the promotor of glucocorticoid receptors (GRs) in the rat hippocampus to regulate stress responses in offspring (Szyf et al., 2005). Differences in histone marks have also been observed in the ventral hippocampus (VH) between rats that are susceptible and resilient to CSDS (Kenworthy et al., 2014). In the mouse model of CSDS, a greater expression of the DNA methylation enzyme DNA methyltransferase 3α (DNMT3a) was found in newly born and maturing neurons in the dentate gyrus (DG) of resilient mice (Hammels et al., 2015). Moreover, the number of DNMT3a-positive DG neurons correlated with the interaction time in a social interaction test and with sucrose intake in the SPT. Environmental enrichment, which enhances stress resilience (Schloesser et al., 2010), also can modify the transcriptional and methylation pattern of gene expression in the DG (Zhang et al., 2018a). Stress susceptibility can be modified by targeting these epigenetic changes. Karnib et al (2019) examined the pro-resilient effect of lactate following CSDS and showed that susceptible

mice had lower expression of class I histone deacetylase (HDAC 2 and 3) than resilient animals in the hippocampus. Lactate rescued the change in HDAC levels along with social deficits and anxiety. Inhibition of HDACs with the compound CI-994 promoted resilience. These findings are in parallel to the pro-resilient effect of direct dorsal hippocampal (DH) injection of HDAC inhibitor MS-275 or LMK-235 in stressed mice (Covington et al., 2011; Higuchi et al., 2016).

Noncoding RNA is another epigenetic mechanism that has been implicated in the hippocampal regulation of stress susceptibility. Noncoding RNAs such as microRNAs (miRNA) bind to mRNA to regulate translation. Comparing the levels of miRNA between susceptible and resilient animals have revealed some miRNA species that could regulate stress reactivity. For instance, in the hippocampus of rats that are susceptible to CMS, Zurawek et al (2016) have shown a decrease in miR-16 levels at 7 weeks of CMS when compared to control and resilient rats. Manipulating miRNA levels in the hippocampus can also affect stress susceptibility. Direct hippocampal injection of Lethal-7 miRNA reduced stress susceptibility in the tail suspension test (TST), where susceptibility is characterized by a longer immobility time when animals are hung from their tails, and FST (Bahi and Dreyer, 2018). Chronic ultra-mild stress, a modified version of CMS, reduced the hippocampal levels of miR-124 (Higuchi et al., 2016). Overexpressing miR-124 in the DH was sufficient to confer the resiliency. Moreover, mice become susceptible to a milder stress paradigm after DH inhibition of miR-124. Curiously, the opposing effect of miR-124 on stress susceptibility was observed in rats. miR-124 levels were upregulated in the rat hippocampus after a 21-day exposure to CSDS (Bahi et al., 2014). This increase in miR-124 is causally linked to stress susceptibility since overexpressing miR-124 in the rat hippocampus exacerbated susceptibility. Whether these conflicting data are due to differences in the species of animals and stress paradigms used in these studies remains unclear.

3.2: Signaling markers

3.2.1: BDNF: Hippocampal brain-derived neurotrophic factor (BDNF) has been implicated as a resilience factor. BDNF deficiency has been associated with a higher susceptibility to CMS in male but not in female mice (Advani et al., 2009). Rats susceptible to CMS or inescapable foot shocks have lower BDNF in the DH compared to resilient rats (Taliaz et al., 2011; Yang et al., 2015). BDNF overexpression in the DH also prevented anhedonia in adult male rats stressed by CMS (Taliaz et al., 2011), while its knockdown in dorsal DG or ventral subiculum reduced sucrose preference in both young and adult rats (Taliaz et al., 2010) . In the VH, elevated BDNF mRNA expression was found in the CA3 region of rats resilient to CMS compared to control and susceptible animals (Bergström et al., 2008). Notably, BDNF is required for the impact of exercise on facilitating hippocampal neurogenesis (Liu and Nusslock, 2018), which mediates the behavioral effects of some antidepressants (Mateus-Pinheiro et al., 2013; Santarelli et al., 2003).

BDNF is also an important player for other pro-resilience markers. Branched-chain amino acids (BCAA) such as leucine, isoleucine and valine, enhanced stress resilience when administered before social defeat (Nasrallah et al., 2019). The pro-resilience effect of BCAA is associated with an upregulation of hippocampal BDNF and can be blocked by inhibiting tyrosine receptor kinase B (TrkB), a receptor binding BDNF. BDNF is also related to the pro-resilience effect of interleukin 4 (IL4), an anti-inflammatory cytokine. Mice that are susceptible and resilient to CMS have lower and higher hippocampal expression of IL4, respectively (Zhang et al., 2021a). In addition, while knocking down IL4 enhanced stress susceptibility, mice become resilient to CMS after hippocampal overexpression of IL4. Interestingly, the pro-resilience effect of IL4 is mediated by BDNF and the activation of pro-neurogenic signals in microglia.

3.2.2: GSK-3β and β-catenin: Glycogen synthase kinase-3β (GSK-3β) and β-catenin are major players in the Wnt signaling pathway. GSK-3β normally acts to phosphorylate β-catenin, leading to its destabilization and degradation by proteosomes (Gould et al., 2008; Wada, 2009). GSK-3β is inactivated when phosphorylated by protein kinase B (AKT). As a result, β-catenin is stabilized and migrates to the nucleus to mediate the transcription of several genes including those that are implicated as stress resilience factors, such as BDNF (Wada, 2009). The AKT/GSK-3β/β-catenin pathway notably shows altered signaling in correlation with enhanced fear memory in genetically susceptible B6N mice (Dahlhoff et al., 2010). Stress susceptible B6N mice showed lower phosphorylated GSK-3β and β-catenin expression in the hippocampus. Since phosphorylated GSK-3β is inactive, these findings support a link between GSK-3β activity and stress susceptibility. To prevent the inactivation of GSK-3β, a GSK3 knockin mouse with deficient phosphorylation of the serine inhibitory phosphorylation sites can be used (McManus et al., 2005). Such GSK3 knockin mice showed greater susceptibility in terms of enhanced escape failures following escapable and inescapable foot shocks, immobility in FST and TST, increased anxiety in an elevated plus maze, and increased freezing in contextual and cue fear conditioning (Polter et al., 2010). A reduction in the inhibitory phosphorylation of GSK-3β and decreased AKT activity in the cortex and hippocampus were associated with vulnerability to LH. Finally, lentiviral overexpression of GSK-3β in the DG increased sensitivity to CMS as measured by susceptible behaviors in the FST, TST, and SPT (Zhang et al., 2013). Enhanced apoptosis in the hippocampus was also seen with GSK-3β overexpression.

β-catenin has been shown to increase stress resilience. Transgenic mice with β-catenin overexpression displayed less immobility in FST (Gould et al., 2007). Overexpressing β-catenin in the nucleus accumbens (NAc), a region implicated in rewarding experiences, and the VH also

enhanced stress resilience (Dias et al., 2014; Vidal et al., 2019). Notably, overexpressing and knocking down β-catenin in glutamate/aspartate transporter-expressing stem cells and astrocytes in the hippocampus could enhance and reduce stress resilience, respectively (Vidal et al., 2019). These hippocampal effects of β-catenin are likely related to neurogenesis, since enhancing β-catenin signals from overexpression was associated with increased neurogenesis.

3.2.3: CREB: cAMP response element binding protein (CREB) is a transcription factor known to regulate the expression of thousands of genes and is a factor that has been implicated in the pathophysiology of stress-related mood disorders such as depression and PTSD. Mice with hippocampal CREB knockdown exposed to UCMS showed a resilience to weight loss and hypothermia, both being physiological stress responses. (Manners et al., 2019). CREB activation may be related to neuroinflammation. UCMS in wildtype animals caused an increase in the expression of various factors associated with inflammation and the immune system, including toll-like receptor 1 (TLR1). Conversely, the upregulation in TLR1 expression was abolished in stressed animals lacking hippocampal CREB. Results from mice that were stressed by social stress are less consistent, as CREB was upregulated in the hippocampus after CSDS (Li et al., 2019). However, mice that were susceptible to CSDS showed a lower phosphorylated CREB/CREB ratio than resilient and control mice (Jianhua et al., 2017). Contradicting findings concerning the impact of CREB on stress vulnerability may be dependent upon the hippocampal region studied. Overexpression of CREB in the DG, but not CA1, can reduce immobility time in the FST following inescapable foot shocks (Chen et al., 2001). Similarly, CMS has been shown to reduce CREB in the DG but not in the CA regions (Gronli et al., 2006).

3.3: Neuroinflammatory markers

Various findings have shown that stress-related psychopathologies, including depression (Brites and Fernandes, 2015; Kim et al., 2016) and PTSD (Zass et al., 2017) are closely associated with neuroinflammatory signaling. In the hippocampus, chronic stress activates toll-like receptor 4, which subsequently activates GSK-3β and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB (Cheng et al., 2016)), a transcription factor regulating innate immunity (Silverman and Maniatis, 2001). The expression of pro-inflammatory cytokines, such as interleukin 1β (IL-1β), interleukin 6 and tumor necrosis factor α (Cheng et al., 2016), is also induced. Differences in cytokines and pro-inflammatory signaling have been found between animals with different stress susceptibilities. For instance, comparing between mouse strains that are less (C57BL/6 mice) and more susceptible (BALB/c) to stress, Sathyanesan et al (2017) have found increased expression of various pro-inflammatory cytokine genes in the hippocampus of BALB/c mice. In addition, BALB/c female mice also expressed more NF-κB mRNA than C57BL/6 female mice after chronic stress in the hippocampus (McWhirt et al., 2019). Using a hamster model of CMS, Avolio et al (2017) found a higher hippocampal expression of NF-κB and IL-1β (and interleukin 10) in resilient hamsters when compared to susceptible hamsters.

The hippocampus has a high density of microglia (Lawson et al., 1990). Microglial overactivation has been associated with the development of psychiatric disorders in humans and susceptibility in chronic stress models (Wang et al., 2018; Woelfer et al., 2019). Studying CX3CR1 knockout (KO) mice with deficient microglia function has demonstrated a decrease in hippocampal microglia along with resilience to CUS (Rimmerman et al., 2017). Resilient CX3CR1 KO mice also showed a reduction in the transcription of major histocompatibility complex I and downstream interferons. Notably, the activation of hippocampal microglia is not always associated

with stress susceptibility. As mentioned earlier, IL4 activates pro-neurogenic signals, such as BDNF, in microglia to enhance stress resilience (Zhang et al., 2021a). Microglia could therefore be differentially programmed to induce susceptibility and resilience in response to chronic stressors.

Interestingly, recent work focused on the concept that exposure to innate immune activation, or immune preconditioning, may be neuroprotective and confer tolerance to the effects of hyperactive immune functions, thus reducing the severity of associated disorders. This was explored using lipopolysaccharide (LPS), an innate immune enhancer, which is believed to have anti-inflammatory effects that promote its neuroprotective function (Marsh et al., 2009; Schaafsma et al., 2015). Administration of a systemic LPS injection prior to CSDS protected against susceptibility as measured by the social interaction test, TST, and FST (Gu et al., 2021). The results were further supported by the presence of an anti-inflammatory phenotype in the hippocampus and prefrontal cortex (PFC), which dictates cognitive processes including working memory, planning, decision making and goal-oriented behavior (Kesner and Churchwell, 2011).

Neuroinflammation is also related to the impact of miRNA in regulating stress susceptibility. Knocking down miR-155 in mice reduced susceptibility to the FST and TST, as well as the expression of inflammatory markers in the mouse hippocampus (Fonken et al., 2016). In rats exposed to CSDS, susceptible animals have shown greater VH expression of miR-30e-3p, while resilient rats have higher miR-455-3p expression (Pearson-Leary et al., 2017). Interestingly, these changes in miRNA expression were associated with increased inflammatory markers, greater blood-brain barrier permeability, increased blood vessel density and enhanced FosB/ΔFosB expression in the VH, not the DH, of susceptible rats. Greater neuroinflammation likely underlies the observed vascular remodeling and in the VH it acted to increase susceptibility to CSDS, while

resilience is promoted by its decrease. In a follow up study, fecal transplant from susceptible to non-stressed rats was sufficient to increase immobility in FST and enhance the number of microglia in the VH (Pearson-Leary et al., 2020). Thus, changes in miRNA expression along with the importance of the gut microbiome and neuroinflammation of the VH may work in tandem to mediate stress susceptibility.

3.4: Hormonal markers

Hyperactivity of the HPA axis is a well-documented finding in both clinical research of depressed patients (Schatzberg, 2015; Schuhmacher et al., 2013) and animal models of social stress (Keeney et al., 2006; Pich et al., 1993; Razzoli et al., 2009). The HPA axis is controlled by negative feedback mechanisms involving the GR, which upon activation (by cortisol in mammals and corticosterone in rodents) homodimerizes and translocates to the nucleus where it acts as a transcription factor. Mice resilient to CSDS show elevated GR protein expression and translocation in the hippocampus (Han et al., 2017). Another CSDS study found decreased hippocampal GR expression in susceptible mice, which was rescued by ketamine (Wang et al., 2019). This indicates that the decreased expression and nuclear translocation of GR in the hippocampus are features common to CSDS susceptibility and potentially lead to a less effective shutdown of HPA axis activity by the hippocampus.

Further differences in the expression of receptors that are central to the regulation of HPA axis activity have been identified in the hippocampus and vary with stress vulnerability. In a variation of the CSDS protocol, hippocampal expression of the corticotropin-releasing factor receptor 1 mRNA in resilient animals was elevated when compared to controls (Gururajan et al., 2019). Mice resilient to CSDS also show greater hippocampal mineralocorticoid receptor (MR) expression in comparison to susceptible and control mice (Schmidt et al., 2010). The latter finding

corroborates clinical observations where single-nucleotide polymorphisms (SNP) associated with increased MR expression appeared to protect against depression in women as they correlated with higher optimistic scores, lower hopelessness and rumination scores, and a lower risk for depression (Klok et al., 2011). Interestingly, individuals who are carriers of a SNP associated with increased MR expression and function show a higher incidence in switching from a hippocampal-dependent cognitive strategy to a striatum-dependent habit strategy when solving a memory task under stress (Wirz et al., 2017). It has been speculated that such a switch from a cognitive to a habitual brain system could be adaptive and serve to cope with stress (Vogel et al., 2016). The utilization of a habitual response allows for the quick retrieval of previously reinforced behaviors that are well-learned. Habitual brain systems are also less impacted by stress in comparison to the hippocampus and PFC. Additionally, a habitual strategy is less demanding than other memory systems, which allows cognitive resources to be distributed to other brain regions for stress coping. Such findings suggest that an MR-mediated weakening of hippocampal function may serve to enhance resilience by promoting stress coping.

Apart from corticosterone, sex steroid hormones such as estrogen and progesterone have also been implicated in stress resilience and susceptibility of female animals. Using a LH model, 17β estradiol has been shown to enhance the resilience of ovariectomized female rats to inescapable foot shocks (Bredemann and McMahon, 2014). Before 17β estradiol treatment, susceptible female rats displayed reduced hippocampal long-term potentiation (LTP) compared to resilient rats. Interestingly, 17β estradiol enhances stress resilience and rescues LTP deficits. However, stress susceptibility can also be enhanced by sex hormones. Hokenson et al (2021) have shown that when female mice have elevated estradiol levels in early-proestrus, they are more susceptible to developing stress-induced spatial memory impairments compared to mice at low

estradiol stages. In adolescent female mice that are resilient to developing anxiety from a food restriction stress, progesterone treatment exacerbated the impact of stress and was postulated to be due to changes in the expression of α4 GABAA receptor subunits in hippocampal pyramidal neurons (Wable et al., 2015). More work is needed to apprehend how hippocampal stress mechanisms are influenced by sex steroid hormone dynamics.

3.5: Neurogenesis

Neurogenesis is an extensively examined cellular process of the hippocampus that has been implicated in brain development and in higher order brain functions such as learning and memory. Although it continues to be debated whether neurogenesis is greatly attenuated or even absent after brain development in humans, a strong interest in studying neurogenesis remains in the field of stress. Hippocampal neurogenesis is inhibited by stress (Mirescu and Gould, 2006), induced by antidepressants (Malberg et al., 2000) and plays a crucial role in their therapeutic effect in both stress-naïve (Santarelli et al., 2003) and stressed animals (Perera et al., 2011; Schloesser et al., 2010) (see (Planchez et al., 2020) for a review).

Several studies have examined the impact of stress on neurogenesis in animals with different behavioral responses to stress and found that newborn neurons support resilience. Chronic stressors such as CMS (Jayatissa et al., 2010), inescapable foot shocks (Vollmayr et al., 2003) and CSDS (Lagace et al., 2010; Yap et al., 2006) reduce hippocampal neurogenesis. Snyder et al (2011) developed the GFAP-Tk mouse, a transgenic animal which allows for the inhibition of adult neurogenesis by valganciclovir. These mice showed enhanced latency to feed in an anxiogenic environment as measured by the novelty-suppressed feeding test, reduced latency of immobility in the FST, and decreased sucrose preference. Ablation of neurogenesis in GFAP-Tk mice (Snyder et al., 2011) or via X-ray irradiation (Tsai et al., 2015) further enhances stress-

induced corticosterone release, suggesting that stress acts to suppress neurogenesis in rodents to enhance susceptibility. A study of mice adrenalectomized prior to CSDS found enhanced resiliency and increased neurogenesis, further supporting the relationship between neurogenesis and corticosterone (Lehmann et al., 2013). The protective effect of an adrenalectomy was abolished in mice that lacked hippocampal neurogenesis.

In terms of mechanism, Anacker et al. (2018) have demonstrated that neurogenesis may act to confer resilience via the inhibition of DG neuronal activity. Using *in vivo* calcium imaging, they identified ventral DG neurons that were preferentially active during attacks in the CSDS model. Increasing neurogenesis using designer receptors exclusively activated by designer drugs (DREADDs) acted to enhance resilience by diminishing the activity of the DG, while reducing the activity of newborn neurons increased susceptibility. Thus, adult newborn neurons may confer resilience via the inhibition of mature granule cells in the ventral DG.

Curiously, evidence exists suggesting that neurogenesis is also required for stress susceptibility. Through bromodeoxyuridine labelling, an increase in the number of newly born DG cells following CSDS was found in susceptible mice compared to resilients and controls (Lagace et al., 2010). Using X-ray radiation to ablate newborn DG cells prior to stress reduces the expression of social avoidance affiliated with susceptibility to CSDS. In support of these findings, a transgenic mouse model where newly born neurons can be selectively inhibited shows a promotion in CSDS resilience (Kirshenbaum et al., 2014). This remained true in adolescent mice, but not adults, indicating that newborn cells in adolescence hold a more pivotal role in the determination of behavioral stress response. How neurogenesis plays opposing roles in stress susceptibility in these different studies remains unclear. As suggested in (Lagace et al., 2010), one possibility is that neurogenesis is a plastic process that is crucial for the neuroadaptation after stress

and antidepressant treatments. Depending on the type of stimuli that triggers neurogenesis, blocking neurogenesis could result in either an enhancement or a reduction in stress responses. Precise methods of targeting neurogenesis, for example using GFAP-Tk mice, have the potential to provide a more thorough understanding of the mechanisms through which stress responsiveness is regulated by neurogenesis.

We have described the contributions of specific hippocampal molecular markers to the expression of stress susceptibility and resilience. The presence of these molecular markers not only reveals the biological complexity of stress susceptibility and resilience, but also suggests more molecules are at play in determining individual differences in stress responses. Together with the advancement of technology, these molecules have been examined at the level of the transcriptome, proteome, and metabolome in the hippocampus of animals that are susceptible and/or resilient to chronic stress. Below, we summarize findings from omics studies.

3.6: Screening for hippocampal markers of stress susceptibility and resilience with -omics studies

3.6.1: Transcriptomic studies: Many studies have compared hippocampal transcriptomes between stress susceptible and stress resilient rodents using microarrays or RNA sequencing (see Table 1). While most of these studies examined the transcriptome of the whole hippocampus, some of them focused on the VH (Bagot et al., 2016), the hippocampal region that has been implicated for emotion regulation (Fanselow and Dong, 2010). Subregions such as the DG were also targeted (Nasca et al., 2019). In addition, non-hippocampal regions such as the PFC, amygdala, NAc, and raphe nucleus (i.e., the main source of serotonergic input to the hippocampus) were included in

some of these studies (Bagot et al., 2016; Kanarik et al., 2011). Most of these transcriptome studies examined animals that were susceptible or resilient to CMS and CSDS. However, selectively bred lines that show differences in stress-induced analgesia (Lisowski et al., 2011) and mouse strains that are known to have different stress reactivities (Malki et al., 2015) were also used. In most of these studies, stress susceptibility was represented by the expression of anhedonia, behavioral despair, or social avoidance. However, in a transcriptome study that examined 28 BXD recombinant inbred strains from the Jackson laboratory (Jung et al., 2017), latency to locate a platform in the Morris water maze was used to define stress resilient and susceptible animals as those with high and low spatial memory performance respectively. Apart from one study where tissue from male and female animals were mixed (Malki et al., 2015), all these studies were performed in adult male animals. In more recent studies, transcriptome of alternative splice events (Jung et al., 2017) and noncoding RNAs (Roy et al., 2018) that are related to stress susceptibility were also examined. Some transcriptional changes between susceptible and resilient animals were also confirmed by polymerase chain reaction (Bergström et al., 2007; Lisowski et al., 2011).

These transcriptome studies revealed tens to hundreds of differentially regulated genes (DEGs) in susceptible and resilient animals. While susceptible and resilient animals shared some common DEGs, animals from these groups also expressed DEGs that were exclusive to their group. Most transcriptome studies revealed more DEGs in resilient than susceptible animals in the hippocampus (Bagot et al., 2016; Bergström et al., 2007; Kanarik et al., 2011; Lisowski et al., 2011; Nasca et al., 2019; Pitychoutis et al., 2014). These findings support the notion that resilience is not a lack of stress susceptibility but an active process that could be orchestrated by distinct transcriptional changes.

To understand the functional significance of transcriptomes that are differentially regulated in animals with different stress susceptibilities, various tools for the functional annotation of DEGs and their roles in physiological processes have been used. Using these tools revealed biological processes that are highly regulated by DEGs in animals with different stress susceptibilities. One of these processes is immune system function. Some DEGs in Swiss-Webster mice with a high reactivity to swim stress-induced analgesia constructed an interaction network for inflammatory/immune response (Lisowski et al., 2013). DEGs in BALB/c mice, which exhibit higher stress reactivity than C57BL/6 mice, revealed a network that was centered on the NF-κB complex (Malki et al., 2015), which modulates proinflammatory cytokine release (see ***3.3: Neuroinflammatory markers***). NFκB signaling was also implicated in the susceptibility to CSDS (Bagot et al., 2016). In BXD inbred strains showing lower spatial memory performance in the Morris water maze after CMS, DEGs that were related to chemokine and cytokine signaling pathways were upregulated (Jung et al., 2017). While these findings suggest an association between neuroinflammation and stress susceptibility, immune response-related genes were downregulated in rats that were susceptible to CMS (Bergström et al., 2007). Another set of processes that were commonly observed in these transcriptome studies were related to cell proliferation and cell death. Compared to resilient rats, DEGs that were related to cellular growth and apoptosis were down- and up-regulated in rats that were susceptible to CMS, respectively (Bergström et al., 2007). There were also clusters of DEGs in Swiss-Webster mice with low reactivity to swim stress-induced analgesia that were involved in apoptosis and neurogenesis. Apoptosis-related DEGs were also found in mice that exhibited a high reactivity to stress (Malki et al., 2015) and low spatial memory performance in a water maze after stress (Jung et al., 2017). Together, these findings strongly support the involvement of neuroinflammation and neurogenesis

in the pathogenesis and treatment of depression, respectively. Other cellular processes that were implicated in stress susceptibility and resilience by these transcriptome studies included cell-cell signaling, metabolic processes, neurotransmitters level, and synaptic transmission (Bagot et al., 2016; Jung et al., 2017; Lisowski et al., 2013; Lisowski et al., 2011; Pitychoutis et al., 2014; Roy et al., 2018).

Among different DEGs, some of them are known as ‘node’ or ‘hub’ genes that affect the expression of multiple genes (Long et al., 2021). These genes may be important molecular targets that regulate gene networks in stress susceptibility. For instance, node genes that are highly connected to inflammatory response networks such as Atx1, GH, Cebpb, and Hspa8 were up regulated in stress susceptible mice (Lisowski et al., 2013). Using Weighted Gene Coexpression Network Analysis on BALB/c (more stress sensitive) and C57/BL6 mice (less stress sensitive), Malki et al (2015) identified a stress related gene network that centered on CREB1. Interestingly, searching for upstream regulators of DEGs that were related to the impairment of spatial learning caused by CMS also pointed to the CREB1 regulator (Jung et al., 2017). Overexpressing hub genes such as Dkkl1, Neurod2, or Sdk1 in the VH was sufficient to promote susceptibility (Bagot et al., 2016).

Finally, apart from protein coding RNAs, long noncoding RNAs (lncRNAs) in the hippocampus could also determine susceptibility in a LH model (Roy et al., 2018). More differentially regulated lncRNAs were found in LH than in non-LH mice. Differentially regulated lncRNAs in LH mice were functionally clustered towards cellular endocytosis, RNA transport and mRNA surveillance. However, lncRNAs that were upregulated in non-LH mice were closely related to neurotrophin signaling.

3.6.2: Proteomic studies: Hippocampal proteomic changes that are related to stress susceptibility and resilience have been extensively investigated in the last decade (see Table 2). Using 2-dimensional difference gel electrophoresis or liquid chromatography to separate protein species and to confirm the identity of these proteins by mass spectrometry, various differentially regulated proteins (DEPs) in animals with different stress susceptibilities were identified. Most of these studies were performed in rats. Apart from CMS, social isolation (Filipovic et al., 2020; Peric et al., 2021) and CSDS (Hamilton et al., 2020) were used as stressors in these studies. While most studies examined proteome in the whole hippocampus, targeted proteomic changes in the VH were also examined (Bisgaard et al., 2007; Hamilton et al., 2020; Zhang et al., 2021b). Finally, all proteomic studies were performed in male animals only.

Alterations in hippocampal DEPs that are related to neurotransmission or metabolic pathways are two major biological changes that are related to stress susceptibility and resilience. Henningsen et al (2012) showed that compared to rats that are susceptible to CMS, resilient rats had a downregulation in the expression of alpha-synuclein and synaptogyrin-1 along with an increase in adaptor-related protein complex 3 within the hippocampal CA regions. All of which are implicated in the regulation of vesicle density at synaptic terminals (Di Rosa et al., 2003; Nakatsu et al., 2004; Nemani et al., 2010; Sugita et al., 1999). Levels of α-SNAP and β-SNAP were also upregulated in the VH of CMS susceptible rats (Bisgaard et al., 2007). Fewer DEPs that were related to exocytosis, transmembrane and vesicle-mediated transport were found in resilient rats when compared to rats that were susceptible to CMS (Zhang et al., 2021b). Finally, Filipovic et al (2020) found many down regulated cytosolic proteins that were related to vesicle-mediated transport in the hippocampus of rats resilient to social isolation.

To further examine changes in synaptic proteins between animals with different stress susceptibilities, techniques of subcellular fractionation were used to isolated proteins that were enriched in synapses and postsynaptic membranes. Peric et al (2021) found that susceptible rats have more DEPs that were related to synaptic vesicular transport upregulated than resilient rats. Han et al (2015) found that in lysates that were enriched by postsynaptic density proteins, rats that were susceptible to CMS showed an increase in N-methyl-D-aspartate subtype of glutamate receptor (NMDAR)-related downstream signals including densin-180, neurogranin and a small GTPase Rab5c. Notably, both densin-180 (Carlisle et al., 2011) and neurogranin (Zhong and Gerges, 2010) have been implicated in synaptic plasticity. However, upregulation of proteins for neurotransmitter release, such as synapsin-1, syntaxin-1, Munc18-1, SNAP25 and VAMP2, were found in the hippocampus of resilient rats (Zhou et al., 2015). Additionally, resilient animals demonstrated a decrease in the expression of Rab3a, a regulator of Ca^{2+}-dependent exocytosis. Synaptic vesicular proteins were shown to be downregulated in rats that were susceptible to CUMS (Zhang et al., 2018b). Although these findings strongly suggest that proteins for vesicular transport in synapses are differentially expressed between stress susceptible and resilient animals, upregulation of synaptic proteins was found in both animal groups. How these proteomic changes affect synaptic function and plasticity in these animals remains unclear.

Lastly, DEPs in regulating metabolic processes are another group of hippocampal proteins that are implicated in stress susceptibility and resilience. CMS resilient rats had various proteins for oxidative phosphorylation upregulated (e.g., COX5A, NDUFB7, NDUFS8, COX5B, and UQCRB, (Henningsen et al., 2012)), suggesting that enhanced oxidative phosphorylation acts as an adaptation to chronic stress in resilience. Xie et al (2018a) showed that half of the hippocampal DEPs in susceptible and resilient mice were mitochondrial proteins, with many of these proteins

linked to oxidative phosphorylation. Tang et al (2019) also showed that 1/3 of DEPs identified in susceptible and resilient rats were related to metabolic processes. In rats resilient to social isolation, Filipovic et al (2020) observed a downregulation of proteins that were related to glycolysis but an upregulation of proteins for tricarboxylic acid cycle and oxidative phosphorylation. Resilient rats also showed a decline in the expression of a mitochondrial glutamate carrier and transport-involved protein, suggesting a reduced transport demand. Finally, Zhang et al (2021b) found that stress resilient rats exhibited upregulated proteins that are associated with mitochondrion organization in the VH.

3.6.3: Metabolomic studies: Apart from proteomic changes, various studies have attempted to examine changes in metabolome of animal models of depression. Many of these metabolites are neurotransmitters that determine the activity and function of the brain. Changes in metabolic pathways are likely crucial for determining individual differences in stress susceptibility. Most of these metabolomic studies (Table 3) have used mass spectrometry technology that is coupled with liquid (Dulka et al., 2017; McGowan et al., 2018; Zhang et al., 2019a) or gas chromatography (Hamilton et al., 2020; Liu et al., 2018b; Yang et al., 2019; Zhang et al., 2018b). In addition, nuclear magnetic resonance (NMR) spectrometry has been used for analyzing metabolites (Akimoto et al., 2019; Prabhu et al., 2019). Finally, metabolite levels could be investigated in vivo in stressed animals using magnetic resonance spectroscopy (Magalhaes et al., 2019). For a review of metabolite changes in depressed patients and various animal models of depression, readers could consult the online database MENDA (Metabolite network of depression database (Pu et al., 2021)).

Amino acids belong to the major type of metabolites that are altered in rodents with different stress susceptibilities. Amino acids such as alanine, GABA (γ aminobutyric acid),

glutamate, and glutamine are crucial metabolites for protein synthesis and glucose metabolism. GABA and glutamate are also major inhibitory and excitatory neurotransmitters, respectively. Levels of these amino acids are sensitive to chronic stress. For instance, GABA and glutamate have been shown to be increased (Liu et al., 2018b; Magalhaes et al., 2019; Yang et al., 2019), decreased (Liu et al., 2018b), not altered (Akimoto et al., 2019; Zhang et al., 2019a; Zhang et al., 2018b), or differentially regulated (Dulka et al., 2017; Hamilton et al., 2020; Liu et al., 2018b; Prabhu et al., 2019) in stress susceptible animals. Factors underlying the conflicting changes in GABA and glutamate in these studies may be related to differences in tissue preparation, quantification methods, and the type of stressors used. For instance, Liu et al (Liu et al., 2018b) compared metabolites between rats that were susceptible to different chronic stressors and revealed that while hippocampal levels of glutamate were increased in rats that were susceptible to chronic restraint and CSDS, glutamate levels were reduced in the hippocampus of rats that were susceptible to CMS and LH. Similarly, hippocampal GABA levels were increased by chronic restraint and CSDS but decreased by LH in susceptible rats. Another factor that may affect the change in metabolite levels is the hippocampal region used in the study. While most of these studies examined the levels of metabolites in the whole hippocampus, GABA levels have been shown to be higher (Dulka et al., 2017) and lower (Hamilton et al., 2020) in the DH and VH, respectively, in CSD susceptible mice. These findings suggest that stress susceptibility and resilience can be regulated by hippocampal levels of these amino acids and can have differing effects depending on subregion. In addition, the effects of these metabolic changes may be partly related to alterations in neuronal excitability due to the perturbation of GABA and/or glutamate levels in the hippocampus.

Tryptophan is another amino acid that is highly implicated in depression. Not only tryptophan is a precursor of serotonin, but its metabolites such as kynurenic acid have also been suggested to contribute to the pathophysiology of depression (Erabi et al., 2020; Liu et al., 2018a; Ogyu et al., 2018; Tanaka et al., 2020). Mice that were susceptible to CSDS showed lower hippocampal levels of kynurenic acid than control mice (Xu et al., 2019). Susceptible animals also showed lower levels of kynurenine aminotransferase I and II, which are enzymes responsible for the conversion of kynurenine to kynurenic acid. Further studies are needed to confirm whether a lower hippocampal level of kynurenic acid is responsible for enhancing stress susceptibility.

Lactate, a compound whose levels are increased by exercise, was shown to enhance stress resilience. When treated with lactate 4 hours prior to each episode of CSDS, a pro-resilience effect was observed (Karnib et al., 2019). Metabolomic studies have revealed a decrease in lactate in the VH of susceptible mice when compared to resilient mice (Hamilton et al., 2020). However, examining lactate in the DH between susceptible and resilient mice revealed no change (Dulka et al., 2017; Prabhu et al., 2019). These findings suggest that there are DH and VH differences in the impact of lactate on stress susceptibility.

Finally, emerging findings have revealed changes in molecules for lipid synthesis in animals with different stress susceptibilities. For instance, hippocampal levels of arachidonic acid, glycerol, and O-phosphorylethanolamine in rats susceptible to CSDS were higher than control rats (Liu et al., 2018b; Yang et al., 2019). However, VH levels of ethanolamine in susceptible mice were lower than resilient mice (Hamilton et al., 2020). More lipidomic analyses are needed to reveal the contribution of different lipid species to stress susceptibility.

Findings from omics studies show that differences in stress susceptibility are related to disturbances in hippocampal immune function, neurotransmission, neurogenesis, and metabolism. Causal roles of the hippocampus in regulating stress susceptibility could be revealed by examining the direct impact of manipulating the expression of these genes and proteins on stress susceptibility. Some differentially regulated genes, proteins, and metabolites found in the hippocampus were not observed in other regions implicated in stress vulnerability such as the NAc and PFC (Bagot et al., 2016; McGowan et al., 2018), suggesting these unique genes and cellular processes may exclusively regulate stress responses through the hippocampus. However, findings from different labs reveal a low percentage of overlapping DEGs and DEPs. Factors that may reduce the percentage of overlapping genes include the use of different detection methods (e.g. different microarrays), animal strains, stressors, and study designs. Indeed, more overlapping genes were found when similar study designs (comparing stressed animals vs. controls in (Bagot et al., 2016) and (Bergström et al., 2007)) and strains (looking at C57BL/6 mice in (Bagot et al., 2016) and (Nasca et al., 2019)) were used. Finally, the expression of DEGs is also highly dynamic. Bagot et al (2016) found more DEGs in susceptible and resilient mice 4 weeks versus 2 days post-stress. Interestingly, only ~20% of DEGs in stressed mice were overlapping between these two time points. It must be acknowledged that the rarity of similar target genes being reported by different groups raises the possibility that some of these DEGs may have little to do with differences in stress susceptibility. Nonetheless, their identification is not futile, but instead provides clues as to which biological pathways warrant further investigation.

As a neural hub for information processing and storage, the hippocampus could contribute to stress susceptibility and resilience through the processing of stress- or trauma-related information. Changes in functional markers, such as the neurotransmission and neural activity of the hippocampus, could have a major impact on information processing and storage. These markers are summarized below.

4. Functional hippocampal markers for stress susceptibility and resilience

4.1: Neurotransmission

4.1.1: Glutamatergic transmission: Glutamate is the primary excitatory neurotransmitter in the hippocampus. Differences in glutamate synapses between stress susceptible and resilient animals have been found at the anatomical and functional levels. Synaptic spines are postsynaptic compartments of glutamate synapses. Spine density is notably sensitive to chronic stress exposure, with CSDS profoundly diminishing spine density within the CA3, DG, and PFC of susceptible mice (Qu et al., 2018). However, the opposite is observed in the NAc and ventral tegmental area, which show increased spine density with susceptibility. Spine loss in mice that are susceptible to LPS-induced inflammation (Zhang et al., 2014) and LH (Shirayama et al., 2015) is rescued by the TrkB receptor agonist 7,8-dihydroxyflavon, which also produced an antidepressant effect. Consequentially, diminished CA3 and DG spine density along with a reduction in hippocampal BDNF signaling (as described in *3.2.1: BDNF*) may be factors crucial to the determination of stress susceptibility. Taken together, these findings suggest that a loss of hippocampal spines could increase stress susceptibility.

Differences in glutamate receptor expression and function have also been identified in animals with different stress susceptibilities. A study of mice exposed to CSDS found susceptible animals displayed higher protein expression of the NMDAR and α-amino-3-hydroxy-5-methyl-4-

isoxazolepropionic acid receptor (AMPAR) subunits, GluN2A and GluA1 respectively, in comparison to resilient mice (Xu et al., 2019). Further study of the CSDS model implicated NMDARs outside of synapses as important to the expression of resilience versus susceptibility (Tse et al., 2019). Following CSDS, hippocampal NMDAR function was compared at the synaptic and extrasynaptic locations. Lower CA1 extrasynaptic NMDAR function was found in susceptible mice compared to control and resilient animals, while no changes in synaptic NMDAR function was observed. Increasing extrasynaptic NMDAR function promoted resilience, which was achieved through either N-acetylcysteine, to increase extrasynaptic glutamate release via astrocytic transporters, or NMDAR agonist bound gold-coated nanoparticles that are too large to enter synapses. Hippocampal extrasynaptic NMDAR function may therefore serve as a potential therapeutic target promoting resilience.

A role for hippocampal metabotropic glutamate receptors (mGluRs) in stress vulnerability has also emerged, particularly regarding mGluR5 and mGluR2. SD rats that are susceptible to an acute elevated platform stress or CMS have increased expression of mGluR5 (Sun et al., 2017). The observed increase in mGluR5 appears to be mediated by GR and cannabinoid receptor 1 (CB1), as hippocampal injections of either a GR antagonist or a CB1 agonist normalized mGluR5 expression and ameliorated anhedonia. In addition, stress susceptibility was affected by manipulating the hippocampal levels of Homer 1 (Wagner et al., 2015), a scaffolding protein that links mGluR5 with downstream signaling. In identifying susceptible mice based on their performance in the FST, SPT, and coat-state rating scale following CMS, it was found that such animals exhibited lower hippocampal mGluR2 expression than resilient mice (Nasca et al., 2015). This suggests that susceptibility might be related to mGluR5 overexpression and diminished mGluR2 levels in the hippocampus.

4.1.2: GABAergic transmission: A decrease in GABA levels in the hippocampus has been implicated in stress vulnerability. Ardi et al (2016) found that SD rats pre-exposed to stress as juveniles had enhanced expression of stress-related symptoms as adults after an underwater trauma. Notably, they also found that rats who were unaffected or resilient to these stressors had higher expressions of both the α1 and α2 subunit of $GABA_A$ receptors in the VH. In a follow up study (Ardi et al., 2019), apart from confirming the increased α1 subunit expression in the VH of resilient rats, it was found that this increase was occluded by environmental enrichment, a pro-resilient treatment. These findings support a pro-resilient role for the $GABA_A$ receptor in the VH.

Particular isoforms of $GABA_B$ receptor subunits were found to differentially regulate the susceptibility to CSDS (O'Leary et al., 2014). O'Leary et al exposed mice deficient in either $GABA_{B(1a)}$ or $GABA_{B(1b)}$ to CSDS. Susceptibility was greater in $GABA_{B(1a)}^{-/-}$ mice, while $GABA_{B(1b)}^{-/-}$ presented as resilient to anhedonia and social avoidance. These results were further corroborated through the study of the Helpless H/Rouen mouse, a genetic model of depression showing longer immobility in the TST, which was found to have increased mRNA expression of $GABA_{B(1b)}$ in the DG, CA1, and CA3. The mechanistic consequences of differential isoform expression remain unclear, but it is known that $GABA_{B(1a)}$ is preferentially expressed in development and influences presynaptic inhibition as it is localized to glutamatergic terminals in dendrites. $GABA_{B(1b)}$ is expressed in the adult brain and impacts postsynaptic inhibition (Cryan and Kaupmann, 2005; Gassmann and Bettler, 2012). While more needs to be understood about the role of both isoforms, it is conceivable that stress-induced changes in their expression would impact local hippocampal circuitry and may have large scale implications on signaling.

4.1.3: Cholinergic transmission: Hyperactive cholinergic systems have been implicated in the regulation of mood disorders, including depression (Dulawa and Janowsky, 2019). In a mouse

study, an acute elevation of acetylcholine concentration in the hippocampus through the local injection of the acetylcholinesterase (AChE) inhibitor physostigmine induced increased immobility in the TST (Mineur et al., 2013). In further support of their findings, a knockdown of AChE in the hippocampus using shRNA induced susceptibility in several tests including TST and FST. Additionally, mice with hippocampal AChE knockdown displayed a higher susceptibility to CSDS, which was rescued by the overexpression of AChE. In addition, knocking down α7 nicotinic acetylcholine receptors in the hippocampus reduced immobility time in both FST and TST (Mineur et al., 2018). As we have mentioned earlier, screening of rats for their reactivity to an AChE inhibitor has led to the discovery of stress susceptible FSL and stress resilience FRL lines (Overstreet, 1986).

Hyperactive cholinergic systems in the hippocampus may enhance stress susceptibility through miR-132. AChE mRNA is a target of miR-132, which can downregulate AChE levels (Shaked et al., 2009). Stress transiently increases AChE mRNA levels (Kaufer et al., 1998), which in turn increases the levels of miR-132 in the hippocampus. Enhanced miR-132 is responsible for suppressing AChE levels to enhance cholinergic function. Notably, Shaltiel et al (2013) found that stress-induced impairment of cognitive function in mice with hippocampal AChE downregulation can be rescued by reducing miR-132 expression, suggesting a direct impact of miR-132 in stress susceptibility.

4.1.4: Serotonergic transmission: Chronic stress has been shown to reduce the levels of the 5HT1A receptor in the hippocampus (Watanabe et al., 1993). Maintaining a high level of hippocampal 5HT1A receptor has also been associated with stress resilience. For instance, in the dorsal CA1 region, 5HT1A receptor binding in FSL rats was lower than resilient FRL rats (Nishi et al., 2009). In male wild house mice that were selectively bred for high and low aggression,

Veenema et al (2003) found that mice that were highly aggressive displayed more resilient phenotypes, such as active coping, when compared to lowly aggressive mice. These resilient mice also show higher 5HT1A receptor binding in the CA1 and DG compared to susceptible mice. In addition, hippocampal 5HT1A receptor activity was reduced in β-catenin KO mice, which exhibited enhanced stress susceptibility (Garro-Martinez et al., 2020). Comparing to rats that were susceptible to CMS, resilient rats showed a higher expression of 5HT1A receptor in the dorsal, but not ventral, CA1, CA2, and CA3 regions (Zurawek et al., 2019). These increases in 5HT1A receptors in resilient rats a were associated with a decrease in DH levels of miR-18a-5p, a miRNA that decreases the expression of 5HT1A receptors in cultured hippocampal neurons. In adult offspring from prenatally stressed dams that were separated into anhedonic and non-anhedonic groups by SPT, anhedonic rats show a higher ratio of 5HIAA/5HT in the VH. In addition, 5HT levels in non-anhedonic rats were higher than controls (Jimenez Vasquez et al., 2020).

4.2: Hippocampal activity and engrams

4.2.1: Hippocampal activity: Enhanced hippocampal activity has been associated with the vulnerability to depression. Imaging studies revealed increased hippocampal response to sad faces (Fu et al., 2004) and stronger hippocampus-amygdala connectivity during negative information encoding (Hamilton and Gotlib, 2008) in depressed patients. Recently, Mary et al. (2020) examined the suppression of intrusive memories in individuals exhibiting susceptibility and resilience to the 2018 Paris terrorist attack. They observed that dorsolateral PFC top-down inhibition of a neutral memory remained intact in controls and subjects who were resilient to the trauma. However, such top-down suppression of the hippocampus was not seen in PTSD patients, suggesting the importance of memory suppression in the hippocampus for stress resilience.

Animal research corroborates clinical findings and demonstrating that enhanced hippocampal activity is related to stress susceptibility. A lower expression of the immediate early genes Arc and Egr1 were uncovered in the VH of mice resilient to CSDS (Bagot et al., 2015). In comparison to susceptible mice, resilient mice also presented with higher optogenetically-induced paired pulse responses in the NAc from the VH suggesting reduced glutamate release from VH afferents. In further support of the role of VH activity in stress susceptibility, optogenetic induction of long-term depression (LTD) in the VH-NAc pathway promoted resilience, while acute stimulation of this pathway induced social avoidance. Another study employed machine learning to identify functional networks that are related to CSDS vulnerability (Hultman et al., 2018). Oscillations from the PFC and NAc to the VH were enhanced in acute exposure to a CD1 aggressor in susceptible mice before and after CSDS. This increased activity remained consistent across various models of depression including the overexpression of the depression-related hub gene Sdk1 in the VH, chronic injection of the cytokine interferon α, and early life stress from maternal separation.

Enhanced hippocampal activity in stress susceptible mice could be due to a reduction in GABAergic inhibition. Chronic stress reduced more somatostatin, neuropeptide Y, and calretinin immunoreactive interneurons in the ventral CA1 region of susceptible rats than in resilient rats (Czeh et al., 2015). It was found that GAD65$^{-/-}$ mice, with reduced levels of the neurotransmitter GABA and interneuron marker neuropeptide Y in the hippocampus, presented with an increased susceptibility to stress-induced seizures in an open field (Qi et al., 2018). However, the activity of hippocampal parvalbumin-expressing interneurons is related to stress susceptibility. In the DG, parvalbumin-expressing interneurons have high levels of p11, a protein that has been implicated in depression (Egeland et al., 2010). Chemogenetic activation and inhibition of parvalbumin-

expressing interneurons in the DG promoted susceptibility and resilience to CSDS, respectively (Medrihan et al., 2020).

4.2.2: Hippocampal engrams: Hippocampal activity along with its implications in the formation and recall of neutral and negative memories are factors that vary with stress vulnerability. Recently our group has used TetTag mice to examine the reactivation of CA1 neurons following CSDS exposure (Zhang et al., 2019b). TetTag mice express transgenes for the cFos promoter-driven expression of tetracycline-controlled transactivator (tTA) and tetracycline operator (tetO)-driven expression of the reporter protein β-galactosidase (LacZ) (Reijmers et al., 2007). Tagging of activated neurons can be initiated when TetTag mice are taken off doxycycline-containing food (Dox off). During Dox off, tTA expressed from activated neurons can be freely bound to tetO to induce LacZ expression. Using this technique enabled us to identify engram cells, which are the ensemble of neurons that are activated with an experience and later reactivated when that memory is retrieved (Tonegawa et al., 2015). Briefly, we labeled engram cells during the first 2 episodes of social defeat by LacZ. These LacZ expressing neurons are negative memory engram cells that are related to the defeat experience. After we separated stressed mice into susceptible and resilient groups by a social interaction test, we reactivated these negative memory engram cells with a reminder episode of defeat to induce cFos expression. Neurons that expressed both LacZ and cFos were reactivated negative memory engram cells. In comparison to control and resilient mice, susceptible mice displayed a higher proportion of reactivated CA1 negative memory engram cells in both the DH and VH. Activity of these CA1 engrams cells was causally related to the expression of social avoidance. Optogenetic inhibition of negative memory engram cells in the DH suppressed the expression of social avoidance. Moreover, chemogenetic activation of these engram cells enhanced the susceptibility of mice that were stressed by a subthreshold protocol of

social defeat (2 episodes of defeat vs. 8 episodes of defeat in regular CSDS). Engram cells representing a neutral context also showed increased reactivation in the ventral, not dorsal, CA1 in susceptible mice. In essence, with susceptibility there is greater activity of negative memory engrams in the CA1 region of the DH and VH.

These results are in line with the theory that neurons with increased excitability are preferentially allocated to engrams. Direct evidence for this phenomenon was first observed in the lateral amygdala (Han et al., 2007), but also appears to extend to the memory encoding mechanisms of the CA1 (Cai et al., 2016; Cohen et al., 2017; Epsztein et al., 2011; Rickgauer et al., 2014). Enhancements in spatial and contextual memory have been shown following increases in a small and random population of DH neurons (Brightwell et al., 2007; Park et al., 2016; Sekeres et al., 2012). Along the same lines, CA1 pyramidal neurons with greater excitability are more likely to become place cells (Cohen et al., 2017; Epsztein et al., 2011) and excitation of silent pyramidal neurons can bias them towards becoming place cells (Lee et al., 2012; Rickgauer et al., 2014). Speculating on the consequences of increased hippocampal activity in susceptibility, it is possible that such a phenomenon would promote the storage and reactivation of negative memories in susceptible animals. In other words, a greater memory for the chronic stressor endured may underlie susceptibility. This would mirror a consistent cognitive symptom of clinical depression—a negative memory bias or an easier recall of negative compared to positive life events (Disner et al., 2011).

The increased activity of the hippocampus and the facilitated reactivation of hippocampal engram cells both support the contribution of enhanced hippocampus-dependent memory to stress susceptibility. Indeed, the several hippocampal signaling markers we reviewed in this article that regulate stress susceptibility and resilience are tightly involved in synaptic plasticity, a cellular

mechanism for learning and memory. While BDNF and CREB are known for their roles in LTP (Barco et al., 2002; Lu et al., 2008), GSK-3β is crucial for LTD formation (Peineau et al., 2007). The facilitation of hippocampal LTP may be a mechanism for enhancing engram cell activity in susceptible mice. Additionally, recent findings suggested that stress-related memory in susceptible mice can also be generalized. Lesuis et al (2021) suggested that fear generalization caused by corticosterone is causally related to increased activity of DG engram cells. Overgeneral autobiographic memory is commonly observed in patients with mood disorders (Williams et al., 2007). Recent work has hypothesized that CSDS mice resilient to social avoidance learn to associate an aggressor strain with trauma in a specific context or with specific cues, but can relearn this association, while susceptible animals instead maintain a generalized avoidance (Ayash et al., 2020). The flexibility of relearning and diverting cognitive resources from an aversive experience by the hippocampus may be an important coping mechanism. Neurogenesis is crucial for signal discrimination and pattern separation (Sahay et al., 2011). Reduced neurogenesis in stress susceptible animals may also facilitate the reactivation of negative memory engram cells due to poor discrimination. Taken together, the increased engram cell activity in susceptibility may be the result of generalized negative memory and poor discrimination, which could precipitate negative affect and cognitive symptoms. Future studies should examine if stress resilience is associated with a reduction in negative memory generalization. In addition, the effect of enhancing hippocampal neurogenesis on the reactivation of negative memory engram cells in susceptible animals should be studied.

5. Concluding remarks and future directions

We have reviewed many molecular and functional markers in the hippocampus that regulate stress susceptibility and resilience. Markers that lead to neuroinflammation, hyperactivity,

and impaired neurogenesis in the hippocampus are strongly associated with stress susceptibility. Some of these markers are exclusive to the hippocampus (Bagot et al., 2016; Hamilton et al., 2020; Kanarik et al., 2011; Lisowski et al., 2011). Manipulating many of these markers alone is sufficient to regulate stress vulnerability. We also reviewed some seemingly contradictory findings related to these markers, which can be due to the animal model used in these studies and the hippocampal region targeted. While further studies are needed to parse out the mechanisms, these findings strongly suggest a pivotal role of the hippocampus in determining the sensitivity to developing susceptibility following stress.

In parallel to the functional role of the hippocampus in learning and memory, many hippocampal factors for stress susceptibility and resilience are related to information processing in this region. Candidate genes and proteins that are differentially regulated in susceptible and resilient animals are tightly related to vesicular transport and synaptic transmission. Metabolomic findings also revealed differences in the hippocampal levels of glutamate and GABA, both being neurotransmitters crucial for determining neuronal excitability, in animals with different stress susceptibilities. Mechanisms for determining stress susceptibility are closely related to those for synaptic plasticity and memory engrams (Lesuis et al., 2021; Zhang et al., 2019b). Emerging evidence suggests that stress susceptibility could be related to the altered processing and storage of stress-related information. For instance, an innate increase in conditioning learning could enhance stress susceptibility (Milic et al., 2021; Shumake et al., 2005). While inhibiting hippocampal negative memory engrams reduces stress susceptibility (Zhang et al., 2019b), activating hippocampal positive memory engrams facilitates neurogenesis and produces an antidepressant effect (Ramirez et al., 2015). This is supported by findings in humans which demonstrate that weakening hippocampal activity through a MR-mediated mechanism may be

responsible for switching from a hippocampal-dependent cognitive strategy to a striatum-dependent habit strategy to enhance stress coping (Wirz et al., 2017). Similarly, weakening hippocampal activity by prefrontal inputs (Mary et al., 2020) or neurogenesis (Anacker et al., 2018) enhances stress resilience. Moreover, deficits in the ability to forget have been suggested to mediate the negative bias in depression (Hertel and Gerstle, 2003; Xie et al., 2018b). Future studies could investigate whether the forgetting mechanisms in the hippocampus (Akers et al., 2014; Migues et al., 2016) can be harnessed to enhance stress resilience. These findings are in parallel to the increased hippocampal activity seen in depressed patients when processing negative stimuli (Fu et al., 2004; Hamilton and Gotlib, 2008). Animal research provides the opportunity to target hippocampal hyperactivity in the treatment of cognitive biases common to depression or persistent trauma-related memory seen in PTSD. While these approaches remain experimental, future use of brain stimulations altering hippocampal activity, such as through deep brain or transcranial stimulation, could be a promising therapeutic avenue.

As a broader note, the categorization of stressed animals into resilient or susceptible groups and its implications need to be reflected upon. There is currently no unified definition of the criteria for susceptibility. This is problematic as the way different groups delineate a pathological versus an adaptive response to stress can greatly alter the conclusions drawn from a study. Moreover, the mechanisms governing distinct behaviors, such as stress-induced anhedonia versus social avoidance may be (and are likely) different. This brings us to question why these behavioral manifestations of maladaptive stress response are conflated under the same umbrella term. To better reflect such nuances perhaps we could be more intentional with the vernacular used and begin adopting terms which are precise, such as anhedonia-resilient or social interaction-susceptible, when reporting findings. A consensus on the minimum set of requirements for

susceptibility through a unified methodology can also be established. If implemented, result reproducibility and data comparison across laboratories would be increased, aiding in the identification of hippocampal markers of susceptibility. As previously noted, susceptibility following CSDS and CMS are primarily evaluated through the social interaction test and SPT, respectively. Susceptibility can be better defined by considering findings from these conventional tests in conjunction with additional tests for related pathological behavior. This practice has already been employed by some groups who define CSDS susceptibility based on the presence of both social avoidance and anhedonia (Alves-Dos-Santos et al., 2020; Athria et al., 2021; He et al., 2021) or susceptible behavior in 3 out of 5 behavioral tests (Li et al., 2021).

We also recommend implementing several measures in the future investigation of the hippocampal role in stress susceptibility. While most studies have focused on the role of the hippocampus in the expression of susceptibility, *how* stress-related information is processed by the hippocampus has been scarcely examined. Longitudinal designs are needed to examine the impact of chronic stress on hippocampal activity, for example using calcium imaging or functional magnetic resonance imaging. This provides a distinct advantage over techniques that look at a snapshot of hippocampal activity at a singular timepoint, with longitudinal studies instead allowing for the trajectory of hippocampal impairments to be evaluated. For example, functional changes predating stress or changes marking the onset of impairment could be more readily identified. Although changes in the VH have been commonly observed between stress susceptible and resilient animals, the DH is also crucial for regulating stress reactivity. Manipulating miRNAs (Higuchi et al., 2016), BDNF (Taliaz et al., 2011), or NMDAR (Tse et al., 2019; Zhang et al., 2019b) in the DH alone enhances stress resilience. The DH is crucial for the formation and retrieval of contextual fear memory (2018). In addition, the DH connects to the lateral septum and

retrosplenial cortex, both being brain regions that have been implicated in the regulation of stress susceptibility (Harro et al., 2014; Mirrione et al., 2014; Miyagi et al., 2020). The DH network, including the medial septum and supramammillary nucleus that project to the whole hippocampus, could affect the VH in the regulation of stress susceptibility. Thus, examining both the DH and VH is crucial to have a more complete picture of the hippocampal role in stress susceptibility. Finally, the inclusion of female animals is needed to investigate the role of sex-related factors such as sex steroid hormones in the hippocampal regulation of stress susceptibility. Female cohorts are often considered to be susceptible and are contrasted to resilient males, but few make the distinction between susceptible *and* resilient females. This is likely due to the difficulty in adapting chronic stress models to be applicable to both sexes. However, with the advent of new stress approaches that are female-specific (Lopez and Bagot, 2021), studies examining susceptible and resilient female populations may become more commonplace.

Information gathered from studying animal models of stress susceptibility and resilience have advanced our understanding of the hippocampal processes that are underlie these opposing responses to stress. Translating these findings into applicable therapies remains the challenge but is more attainable as knowledge in the field becomes abundant.

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7. Appendix

AChE	Acetylcholinesterase
AKT	Protein kinase B
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BCAA	Branched-chain amino acids
BDNF	Brain-derived neurotrophic factor
CB1	Cannabinoid receptor 1
CMS	Chronic mild stress
CREB	cAMP response element binding protein
CSDS	Chronic social defeat stress
CUMS	Chronic unpredictable mild stress
CUS	Chronic unpredictable stress
DEGs	Differentially regulated genes
DEPs	Differentially regulated proteins
DG	Dentate gyrus
DH	Dorsal hippocampus
DNMT3a	DNA methyltransferase 3α
Dox	Doxycycline
DREADD	Designer receptors exclusively activated by designer drugs
GABA	γ aminobutyric acid
GR	Glucocorticoid receptor
GSK-3β	Glycogen synthase kinase-3β
FRL	Flinders resistant line
FSL	Flinders sensitive line
FST	Forced swim test
HDAC	Histone deacetylase
HPA axis	Hypothalamic-pituitary-adrenal axis
IL-1β	Interleukin 1β
IL4	Interleukin 4
KO	Knockout
LacZ	β-galactosidase
LH	Learned helplessness
lncRNAs	Long noncoding RNAs
LPS	Lipopolysaccharide
LTD	Long-term depression
LTP	Long-term potentiation
MENDA	Metabolite network of depression database
mGluR	Metabotropic glutamate receptor
miRNA	microRNA
MR	Mineralocorticoid receptor
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDAR	N-methyl-D-aspartate subtype of glutamate receptor
NMR	Nuclear magnetic resonance
NAc	Nucleus accumbens
PFC	Prefrontal cortex

PTSD	Posttraumatic stress disorder
SD	Sprague Dawley
SNP	Single-nucleotide polymorphism
SPT	Sucrose preference test
SSRI	Selective serotonin reuptake inhibitor
tetO	Tetracycline operator
tTA	Tetracycline-controlled transactivator
TLR1	Toll-like receptor 1
TrkB	Tyrosine receptor kinase B
TST	Tail suspension test
UCMS	Unpredictable chronic mild stress
VH	Ventral hippocampus
WKY rats	Wistar Kyoto rats

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