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Sexual trauma and the female brain

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ABSTRACT

Sexual aggression and violence against women (VAM) are not only social problems; they are mental health problems. Women who experience sexual trauma often express disruptions in emotional and cognitive processes, some of which lead to depression and post-traumatic stress disorder (PTSD). Animal models of neurogenesis and learning suggest that social yet aggressive interactions between a pubescent female and an adult male can disrupt processes of learning related to maternal care, which in turn reduce survival of new neurons in the female hippocampus. Mental and Physical (MAP) Training is a novel clinical intervention that was translated from neurogenesis research. The intervention, which combines meditation and aerobic exercise, is currently being used to help women learn to recover from traumatic life experiences, especially those related to sexual violence and abuse.

1. Introduction: sexual violence and trauma in women

1.1. Prevalence rates of trauma exposure in women

Sexual violence and aggression are some of the most stressful of all human life experiences. Women are most often the victims, although a great number of men have had similarly aversive encounters. It was recently estimated that more than 30% of women worldwide experience physical or sexual violence (World Health Organization, 2013), with similar estimates (27%) in the United States (Kessler, 2000). Exact statistics are difficult to obtain because many women do not report the event, nor do many seek medical assistance afterwards. Sexual assaults are most often inflicted on the young with the majority of rapes occurring before the age of 18 (Tjaden and Thoennes, 1998). These early life experiences have devastating and lasting repercussions for normal healthy development in both boys and girls (De Bellis and Thomas, 2003; De Bellis et al., 2013; Toth and Cicchetti, 2013), not to mention the fact that women who are sexually assaulted in childhood are twice as likely to be sexually assaulted as adults (Sarkar and Sarkar, 2005). In this review, we limit our discussion to sexual trauma adolescents and/or adults with related references to similar ages in animal models of stress and aggression (Shors, 2016; Shors et al., 2016) because antecedent events and consequences of abuse in childhood can be quite different from those during puberty and adulthood.

Sexual aggression and violent experiences are as a rule traumatic for the individual and therefore considered "traumatic" life events. Whether they necessarily result in long-lasting symptomatology or mental illness is an important question to answer and in clinical terms is often a matter of nomenclature. The Diagnostic Statistical Manual of Mental Disorders (DSM-5) defines trauma as "an event or events that involved actual or threatened death, serious injury or sexual violation to the self or a close other." However, this definition does not necessarily specify the features that make a sexual event traumatic. As outlined by Green (1990) and analyzed by McNally (2005), trauma can be defined in at least three ways: (1) the nature of the event itself, (2) the person's subjective experience of it, and (3) the physical and emotional response to it. In

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this review, we do not attempt to delineate traumatic events from non-traumatic yet stressful ones because much of our review relies on the literature from animal models of stress and sexual aggression, wherein the subjective experiences and interpretations of trauma cannot be ascertained. Nonetheless, it is presumed that the vast majority of sexually aggressive experiences are traumatic.

A variety of terms are used to refer to sexual violence against women (VAW). The word "rape" refers to vaginal penetration with force or threat, whereas the word "sexual assault" includes sexual coercion and touching behaviors, which can occur while a victim is incapacitated. The term "sexual violence" is more inclusive still, including acts that do not necessarily involve touch, but are nonetheless harmful, often psychologically so, such as stalking behaviors. Of the seemingly infinite sources of trauma, sexual assault is the most likely to induce post-traumatic stress disorder (PTSD) (e.g., Kessler, 2000; Ozer et al., 2003), a form of mental illness characterized by abnormal responses of fear, helplessness and horror during the traumatic event, followed by months and sometimes years of symptoms which include re-experiencing the trauma, avoiding reminders of the trauma, and hyperarousal, along with negative cognition and mood (American Psychiatric Association, 2013). As discussed, the definition of trauma can be debated and therefore the criteria necessary for a diagnosis of PTSD is likewise debatable and under some scrutiny, especially with the advent of the newly adopted R-DOC (The National Institute of Mental Health, 2013). R-DOC attempts to remedy the categorical approach to diagnosis with more continuous and mechanistic analyses from laboratory and clinical studies. Nonetheless, the risk of developing PTSD in women, as defined by various editions of the DSM, is approximately twice as high as that in men (e.g., Breslau, 2009; Kessler et al., 1995; Kilpatrick et al., 2013). Statistics further indicate that women are more than four times as likely as men to experience sexual assault and nine times as likely to experience rape (Kessler, 2000). Given these two sets of statistics, it is no surprise that PTSD is common among women. In what follows, we discuss the psychological and neuroanatomical changes that can occur in women as a result of sexual trauma, followed by a review of animal studies that model the effects of sexual aggression on processes of learning and neurogenesis in the female brain, including changes in the survival of new neurons in the hippocampus. We end with the description of an intervention that was inspired by studies on neurogenesis and designed to reduce ruminations about the past, especially in women who have suffered psychological and/or physical abuse.

1.2. Psychological consequences of trauma in women

It is long appreciated that women are more likely than men to experience symptoms of PTSD but the reasons for these differences are not easily explained. Initially, the sex difference was explained by exposure to differing types of trauma: war more often for men and sexual violence for women. However, more recent studies have compared PTSD diagnosis in men and women who have experienced similar types of trauma, such as those related to natural disasters or terrorism; irrespective of trauma type, sex differences persist (Kessler, 2000). Studies also have compared the incidence of PTSD in men versus women who were sexually abused but not raped. Women who experience sexual assault other than rape are more than twice as likely as men to develop PTSD, though men who are raped are more likely than women to develop PTSD. But because many more women than men are raped, the incidence of PTSD as a consequence of rape is still higher in women. Differences in trauma type and severity of experience may partially account for the high incidence of PTSD in women who have been sexually victimized but these relationships are not necessarily categorical or linear (Tolin and Foa, 2006). Aside from type and severity of trauma, psychological changes that occur within an individual during and after assault are meaningful and can differ between the sexes. For example, victims of sexual or physical assault often report negative thoughts about the self, including self-blame and shame, while viewing the world as bleak and from a negative perspective (Beck et al., 2015; Foa et al., 1999b). Believing that the world is "*completely dangerous*" or that one is "*entirely incompetent*" undoubtedly influences the likelihood that the individual will go on to develop symptomatology consistent with PTSD (Foa et al., 1999b). In addition, victims of trauma frequently overgeneralize, associating the horror and fear from the precipitating event with similar events in the past, as well as projecting that fear into the present and future context (Rubin, 2014).

Many studies of trauma focus on "positive" responses to trauma, meaning those responses that increase in magnitude as a result of the experience, such as startle, blood pressure, heart rate and emotional volatility. However, in many cases, the individual finds him or herself incapacitated in a state referred to as "tonic immobility," which is an involuntary response to inescapable threat. This response occurs in response to many types of threat (Fiszman et al., 2008), but it is common in women who are victims of sexual assault (Kalaf et al., 2015). This state can persist for days and weeks after the event and may be considered part of a larger set of symptoms reflected by disorganization, during which the person may be unable or unwilling to discuss or reveal the details of the traumatic event. It is presumed that some of the immobility and confusion arises because the victim cannot or has yet to incorporate the memory of the traumatic event into her existing autobiographical representations (i.e. her life story). These mental disruptions in everyday lived experience can be further exacerbated by the emergence of ruminations, whereby an individual spends an inordinate amount of time rehearsing the memory of the event and the conditions associated with it, even blaming herself for its occurrence (e.g., Frazier et al., 2005).

1.3. Memory for sexual trauma in women

It is often assumed that the memory for a traumatic event becomes distorted or degraded through psychological disassociation at the time of trauma or generally repressed and therefore resistant to retrieval. Such distortions would suggest that the central and peripheral nervous systems failed to process the experience as a whole at the time of the trauma (van der Kolk, 2000). However, much of the data with respect to trauma indicates that memories during the experience are encoded well and not necessarily via different mechanisms than other types of memory (McNally, 2005). Nonetheless, negative cognitions that arise later in women who experienced a traumatic event are often influenced by memories of the trauma, which then become integrated into her present life. These cognitions in turn influence memories related to the self in the recent and distant past, though this happens to varying degrees within trauma-exposed individuals (Boals and Rubin, 2011; Brewin, 2011). Moreover, the trauma memory can contain a high degree of sensory detail, which contributes to a fragmented and disjointed story upon recall. This constellation of memories continues to impact the person, oftentimes contributing to the maintenance of PTSD-related symptoms (Brewin, 2011). Some studies indicate that memories with negative content are stronger than positive ones (Kensinger and Corkin, 2003; Mickley and Kensinger, 2008), which are further influenced by changes in attentional processes and arousal levels during encoding (Boals and Rubin, 2011; Everaert and Koster, 2015; Kensinger and Corkin, 2004). The relationship between arousal and memory, although well established in principle, is complex because it depends on the interactions among degrees of arousal and stimulus properties surrounding the learning experience at the time of trauma, not to

mention sex differences in the stress response itself (Shors, 2006). Some of these variables can be controlled in laboratory studies, but obviously cannot be assessed while women experience sexual violence and trauma. As a result, many of the hypotheses and conclusions we consider here are based on data that are correlational at best, while being indirect and retrospective for the most part.

As noted, some studies suggest that memories for trauma are altered in women with PTSD, which might contribute to trauma-related cognitive symptoms (Bremner et al., 2000). Assuming that they are altered, *how* they act to maintain PTSD symptoms is unclear. Some have suggested that the persistence of PTSD symptoms is driven more by an inability to forget the trauma, rather than difficulty remembering important parts of the event, as previously thought (Berntsen and Rubin, 2014). In addition, the person may engage in maladaptive thoughts including involuntary, intrusive memories about the self, particularly those of negative content (Rubin et al., 2008). In either case, many symptoms reflect cognitive processes that are related to the rehearsal and/or suppression of newly acquired memories and because these types of memories are most often autobiographical in nature, they likely engage brain regions that are used for these same processes. The hippocampus is the brain structure most associated with the acquisition of autobiographical memories as well as the recollection of recently acquired declarative memories (Squire et al., 2015). Neuronal activity within the hippocampus is necessary for the acquisition of aversive trace memories, which are memories that require the association of a neutral stimulus with an aversive event that occurs later in time (Beylin et al., 2001; Moyer et al., 1990). The hippocampus is likewise necessary for and/or involved in the acquisition and shorter-term retrieval (weeks) of contextual memories, those memories that associate a traumatic or stressful event with personal time and space (Corcoran et al., 2005; Kim and Fanselow, 1992) and is thereby activated while humans learn context-specific associations (Alvarez et al., 2008; Bechara et al., 1995). Even during the execution of processes that do not depend on the hippocampus itself, such as extinction, hippocampal neurons remain engaged. For example, one study reported that the retention of extinguished fear related to an increase in the BOLD fMRI response in the human hippocampus (Milad et al., 2007). Other studies suggest that state-dependent fear is mediated by inhibitory activity within the hippocampus (Jovasevic et al., 2015). It is important to reiterate the fact that the hippocampus is active during most and probably all learning experiences, even when it is not necessary for the ongoing process to occur. Obviously, the hippocampus cannot "know" beforehand what type of learning process will be dependent on its activity and therefore, the structure as a whole must process all (or nearly all) incoming experiential information in anticipation of using it for future thoughts, behaviors and learning processes. In this way, the hippocampus resembles a "real-time" learning machine that processes information in the present, including associations with the present context (space and time), and further associating that information with previously-encoded experiences from the past, which are together used to predict the future. Some consider these memorial thought processes similar in concept to those associated with mental time travel. Some but not all studies support the hypothesis that mental time travel depends on changes in activity within the hippocampal formation (Bartsch et al., 2010; Nyberg et al., 2010).

1.4. Stress and learning in the hippocampus

In addition to learning, the hippocampus is involved in the modulation of learning by stressful life experience and under some conditions, is necessary for that modulation to occur (Bangasser and Shors, 2007; Shors, 2016). In one set of studies, female rodents were exposed to an acute stressful event that was known to disrupt their ability to learn a new association 24 hours later. When neurons within the hippocampus were lesioned with an excitotoxin, females learned well, as if the stressful event had not occurred. Therefore, under these conditions, the hippocampus is necessary to alter learning in females after a stressful event and in general, is an important structure to consider when trying to understand adaptive and pathological learned responses as a result of stressful and traumatic life events. Aside from the above-mentioned study (Bangasser and Shors, 2007), most studies connecting the hippocampus to stress and processes of learning have been conducted in male subjects despite known sex differences in these responses. For example, exposure to the stressful event that impairs learning in females actually enhances learning in males. This enhanced response still depends on the hippocampus, as well as structures not critically engaged in females. For example, the bed nucleus of the stria terminalis is necessary for enhancing learning in males after stress while the prefrontal cortex (prelimbic region) is necessary to suppress learning in females after stress (Maeng and Shors, 2013). Therefore, these particular sex differences in the stress response and learning depend on different brain circuits (Shors, 2016; Wood and Shors, 1998). The mechanisms within the circuits whereby males and females differ are less well described. Recent work by Oberlander and Woolley demonstrated that male and female rats utilize different presynaptic and postsynaptic mechanisms that influence excitatory synaptic activity in CA1 pyramidal cells of the hippocampus, both of which ultimately serve to increase synaptic potentiation in this brain region (2016). Some have suggested that the presence of estrogens might facilitate the extinction of fear in females by enhancing NMDA receptor function in pyramidal cells of the hippocampus and increasing mechanisms of plasticity such as long term potentiation (LTP) (Smith and McMahon, 2005; Smith et al., 2009). In other studies, acute stressful experience reduced the presence of dendritic spines in the female hippocampus, which was dependent on the presence of estrogens and induced via NMDA receptor activation. These same spines are involved in associative learning, again via NMDA receptor activation (Leuner and Shors, 2013; Shors et al., 2004). Therefore, one might propose that exposure to a stressful and traumatic event reduces the availability of synapse formation in the hippocampus and because these synapses are used in the learning process, learning itself becomes disrupted. These changes in synapse formation may further interact with sex differences in learning. For example, male and female rats utilize different strategies for spatial navigation, which likely recruit different brain structures and appear to differentially recruit newly generated neurons in the hippocampus (Epp et al., 2013; Williams et al., 1990). Sex differences in performance are likewise evident during fear and operant conditioning procedures (Dalla and Shors, 2009; Maren et al., 1994; Shors, 2016). For example, Maren et al. (1994) reported that female rodents did not express as much fear conditioning as males did. In subsequent studies, Barker and Galea (2010) reported that sex differences in conditioned fear could be modified by gonadectomy. Females that were ovariectomized expressed more fear to the context, performing similarly to intact males.

Sexual activity in and of itself can alter plasticity in the hippocampus. Adult male rats produced more newly-generated cells in the dentate gyrus of the hippocampus when exposed to a sexually-receptive female once as well as over the course of 14–28 consecutive days (Glasper and Gould, 2013; Leuner et al., 2010). Interestingly, male rats that were exposed to an acute mating experience released more of the stress hormone corticosterone from their adrenal glands while possessing a greater density of spines in the hippocampus (Leuner et al., 2010). Elevated glucocorticoids concentrations are most often associated with a decrease in

neurogenesis and spine density (e.g., Mirescu and Gould, 2006; Schoenfeld and Gould, 2012; Shors et al., 2007). Leuner and colleagues posit that the hedonic value of the sexual experience overrides potential deleterious effects of elevated glucocorticoids on dendritic growth and neurogenesis. Partner familiarity during sexual experience also appears to influence cell production. Males produced more new neurons when paired with a familiar than with an unfamiliar female (Spritzer et al., 2016). These data suggest that familiarly may interact with sexual experience to modulate neurogenesis through changes in cell production. These studies were conducted in male rats and therefore it is not clear how sexual experience would impact the female brain and whether it would be different from that which happens in the male brain. Still, a few studies have investigated neurogenesis in the female hippocampus and olfactory bulb, in order to attempt to understand how physiological systems regulate the female brain and mediate social and reproductive behavior. Shingo et al. reported that prolactin mediates the growth of interneurons in the olfactory bulb of pregnant female rats (but not cells in the dentate gyrus) (2003). Additionally, male pheromones have been shown to stimulate prolactin-mediated neuronal proliferation in the female olfactory bulb and hippocampus, and these newly generated cells might be implicated in the mating behavior (Mak et al., 2007) as well as maternal behavior (Larsen et al., 2008).

Sex differences in the human stress response are less commonly reported than in animal models and the results that do exist are less conclusive. Because lesions and other obstructive approaches are not possible, most findings are correlational in nature. In one study, women with PTSD expressed more conditioned fear when compared to similar responses in men with PTSD (Inslicht et al., 2013). In another, women with PTSD expressed more extinction recall along with less BOLD activation in the anterior cingulate cortex (ACC) when compared to similar responses in men with PTSD (Shvil et al., 2014). Interestingly, sex differences did not emerge in humans who experienced trauma but were not diagnosed with PTSD. Albeit interesting, these neuroimaging findings do not explain why PTSD is more prevalent in women or why women are especially vulnerable to stressful life experience. One might wonder if they ever could. The "explanations" for sex differences in PTSD likely lie within dynamic interactions among stress responses that occur during the trauma, which are modulated at the time of trauma by ongoing hormonal systems to impact engaged brain circuits related to learning and memory in the future. With respect to neurogenesis, new neurons are continuously being produced while some are dying and others are being rescued from death. Meanwhile, hormonal concentrations are always changing. Therefore, correlations among behavioral processes and hormones and levels of proliferation and/or survival can only go so far in revealing their function. It is also unlikely that these new neurons have one specific role in a process. After all, the new cells are part of a complex integrated circuit of neuronal processes and electrical activities. We do not demand that synapses, for example, participate in one or even a few processes of learning or other similar psychological constructs. We should not feel compelled to make similar demands of newly-generated neurons.

2. Trauma in the female hippocampus

2.1. Deficits in brain structure and function associated with trauma exposure

Sexual trauma early in life can be detrimental to brain structure and function. For example, a few studies have reported that women with a history of sexual abuse in childhood had smaller hippocampi when assessed with magnetic resonance imaging (MRI) (e.g., Bremner et al., 2003; Stein et al., 1997). Another reported similar effects in women with a history of childhood trauma, especially if they did not respond to the trauma with dissociative identity disorder (DID; e.g., Chalavi et al., 2015). With DID, individuals develop different alters (or persons), usually as a result of sexual trauma during childhood. It was thus proposed that dissociation during trauma and the different alters that emerged were adaptive, preventing the deficits in brain function in those victims who had developed a means of mental escape. It is important to note, however, that volume changes do not necessarily predict the risk of developing PTSD (Bonne et al., 2001) and these changes, when they do occur, are not necessarily unique to sexual violence, i.e. they do not predict whether the trauma involved interpersonal violence or not (Fennema-Notestine et al., 2002; Landré et al., 2010). A number of studies have suggested that a decrease in hippocampal volume reflects a decrease in neurogenesis (e.g., Stockmeier et al., 2004) but the exact cellular mechanisms underlying changes in hippocampal volume in humans remains unclear (Czéh and Lucassen, 2007). Given neurogenesis cannot be assessed in the living human brain, it is not possible to verify these hypotheses. Some have suggested, with good reason, that volume differences can preexist and therefore predict vulnerability to trauma rather than the consequence of it (Gilbertson et al., 2002; Pitman, 2001). In general, there are many discrepancies in human MRI studies and as such, we are not claiming or in any way implying that sexual abuse necessarily reduces the hippocampal volume of men and women who experience symptoms of PTSD (Patel et al., 2012). Indeed, one study reported more blood flow in the right hippocampus of women with abuse-related PTSD while they participated in an emotional Stroop task (color naming of assault-related words) when compared to similar responses in women who did not have PTSD (Bremner et al., 2004). And of course, the hippocampus, when it is involved, does not act alone. Trauma-related changes have been observed in the amygdala (Fonzo et al., 2010), insula (Bruce et al., 2012; Simmons et al., 2008) and medial prefrontal cortex, in the latter case to fearful faces (Bryant et al., 2008).

Most studies do not compare the responses in women who experienced trauma with PTSD to those without PTSD, making it difficult to tease apart the effects of trauma exposure versus those related and/or including symptoms of PTSD. But a few have. Namely, one study reported that women with PTSD expressed less connectivity between the amygdala and prefrontal cortex compared to trauma-exposed women without PTSD (Stevens et al., 2013). In another, exposure to a trauma memory increased functional connectivity among the right hippocampus and right amygdala, left hippocampus and striatum and dorsal cingulate cortex, and right hippocampus and striatum and orbitofrontal cortex, as assessed through fMRI (Cisler et al., 2014). Other studies compare men to women. Felmingham et al. (2010) reported that women with or without PTSD expressed greater brainstem and amygdala activation in response to fearful faces when compared to similar measures in men with PTSD. Exposure to the same fearful stimuli enhanced activity in the hippocampi of men with PTSD more than in other groups or the other sex. Exactly what these findings tell us about the female brain (or the male brain for that matter) after trauma remains to be determined.

3. Modeling sexual trauma

3.1. Sexual Conspecific Aggressive Response (SCAR) model

Very few studies have examined the effects of sexual trauma in women and none have done so during the experience, for obvious reasons. This is an instance wherein animal models become impor-

tant and arguably imperative. To meet the need, we developed an animal model of sexual aggression known as SCAR, which stands for Sexual Conspecific Aggressive Response (Shors et al., 2016). This model is the first that we know of that examines the impact of sexual aggression on neurogenesis and processes of learning and memory in females. During each SCAR episode, a sexually-experienced adult male is placed in a cage with a pubescent female rat for 30 min. The social interaction is quite aggressive. During an interaction, the adult male continuously chased the female around the cage, sniffing and tracking her ano-genital region while attempting to and oftentimes pinning her down (Fig. 1A–C). These behaviors were apparently stressful for the female, because her corticosterone concentrations were significantly elevated (Fig. 1D). As a result of the interactions, the female did not learn well. As a measure of associative learning, we first examined performance during trace eyeblink conditioning. During the training, the animal is presented with an auditory stimulus as the conditioned stimulus (CS), which is followed by a trace interval of 500 ms and then an unconditioned stimulus of an eyelid stimulation. The animal learns to associate the two stimuli across the temporal gap. This type of learning is dependent on the hippocampus as well as the presence of neurogenesis in the dentate gyrus of the hippocampus (Beylin et al., 2001; Shors et al., 2001). The performance deficit in response to SCAR resembles the response that has been observed after exposure to more traditional laboratory stressors such as swim stress (Shors et al., 2016; Wood and Shors, 1998), as well as the response in an adult female after one encounter with an adult male (Leuner and Shors, 2006). But perhaps more importantly, exposure to the adult male disrupted maternal behavior in the young female. Each day after being exposed to the adult male, the young female was given the opportunity to care for another female's offspring throughout the rest of the day and night. During these interactions and compared to females that were not exposed to the adult male, the SCAR females expressed very few maternal caring behaviors and those that were expressed did not emerge for nearly a week (Fig. 1H; Shors et al., 2016). These results suggest that stressful and presumably sexually aggressive interactions with an adult male can disrupt processes that relate to the care and survival of offspring. This finding, in general, is not necessarily unprecedented. Female nonhuman primates that experience early abuse are reportedly less likely to protect themselves and their offspring from dangerous life-threatening conditions (Suomi, 1991; van der Kolk, 2000). The potential mechanisms that could lead to these disruptions in caring behaviors are many. We discuss one here, that of neurogenesis.

3.2. Neurogenesis and learning

Thousands of new neurons are produced each day in a "normal" healthy brain (Gould et al., 1999). Many of these cells are produced in a part of the hippocampus known as the dentate gyrus, whose primary neuronal phenotype is the granule neuron. These newly generated granule neurons are especially responsive to environmental conditions that humans experience. For example, male rodents that are higher in a social dominance hierarchy produce more new cells than males lower in the hierarchy (Kozorovitskiy and Gould, 2004). Also, males that develop psychological control over a stressful event produce more new neurons than males without the ability to control the same stressor (Shors et al., 2007). But these new cells, even when they are produced, do not all survive. Indeed, as many as half of the new cells die within just a few weeks (Leuner et al., 2004). However, many of these cells can be rescued from death if animals engage in an effortful learning experience. In 1999, Drs. Gould and Shors reported that new neurons in the rat hippocampus survived after experiencing a new learning opportunity and that once present, they were involved in learning (Gould et al., 1999; Shors et al., 2001). The types of learning that can keep new neurons alive include trace conditioning and spatial maze learning; even learning a new physical skill can rescue new neurons from death (Curlik et al., 2013; Shors et al., 2002). But these positive effects of learning on neurogenesis depend on two conditions. First, learning itself must occur. Animals that are trained but do not learn do not retain more neurons than animals that are not trained. Second, the training experience must be effortful for the individual animal. Animals that learn very quickly either because of inherent ability or task demands do not retain more cells than animals that are not trained. But those that require more trials of training to learn and/or are trained on tasks that require effort retain more of the new cells (Waddell et al., 2011). Therefore, learning enhances the survival of new neurons in the adult hippocampus, as long as learning occurs and it occurs with some effort (Shors, 2014).

Females are fortunate to have the opportunity to learn one set of new and effortful behaviors in their lifetime – those related to caring for offspring during motherhood. Indeed, hippocampal plasticity in female rats is dependent on cyclical gonadal hormones and is also influenced by experiences of pregnancy and motherhood (Galea et al., 2014, 2013; Leuner and Gould, 2010). Hippocampal neurogenesis is also influenced by the stage of reproductive experience. For example, Pawluski and Galea reported that dams produced fewer new neurons regardless of the number of pups they birthed, but those that birthed multiple pups retained more new cells later in the postpartum period (Pawluski and Galea, 2007). The authors posit that changes in hormone levels over the postpartum period regulate these changes in cell proliferation and survival. Although some might argue that many maternal behaviors are "innate," a large number of them are acquired over time, requiring practice and increasing skill to master. Upon giving birth, a young female rodent may initially ignore her offspring but soon learns to feed them and keep them warm (Seip and Morrell, 2008). She also learns to retrieve them when they stray from the larger group, a behavior facilitated by ultrasonic calls made by the pups themselves. The expression of these maternal behaviors increases over days, at least as assessed in laboratory studies. As noted, even virgin female rats learn these behaviors, if given enough time and opportunity. Moreoever, learning these behaviors can protect females from some of the negative consequences of stressful life experience. In one study, females that were taking care of their offspring and then exposed to a stressful event did not express learning deficits that are typically expressed in females not caring for young (Leuner and Shors, 2006; Maeng and Shors, 2012). Moreover, these protective effects were similarly evident in virgin females that learned to care for another female's offspring. However and as discussed, females that were exposed to a sexually-experienced adult male during puberty expressed few maternal behaviors, even with weeks of exposure to offspring. In these same studies, females that did learn to care for offspring (though the process of maternal sensitization) retained more newly-generated cells in their hippocampus than females that were not exposed to offspring at all. The cells were approximately one week of age when the two groups (SCAR and no SCAR) were exposed to offspring and approximately three weeks of age when they were examined (Fig. 1E–I). Therefore, the cells were "new" but already present when the females were first exposed to the offspring and would have differentiated into neurons by the time the female had learned to care for the offspring. These data suggest that maternal caring behavior and the learning that occurs along with it, may be sufficient to keep newly generated cells alive. In contrast, exposure to a sexually-experienced adult male reduced the expression of these behaviors in the young female and they tended to retain fewer of the new cells. It was also reported that pup exposure itself, increases neurogenesis in the dentate gyrus

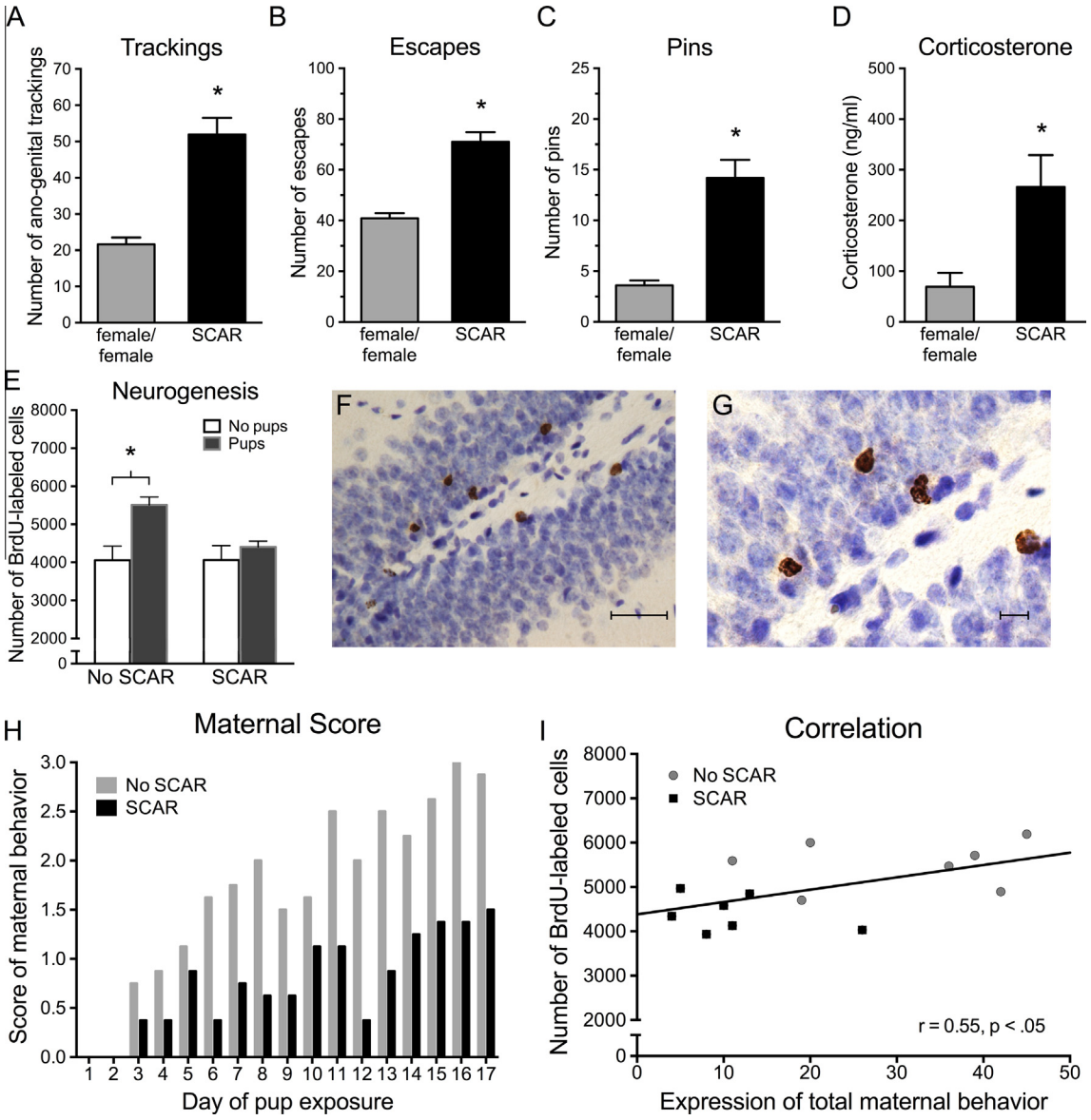

Fig. 1. During a 30-min interaction between the adult male and the pubescent female, the following behaviors were recorded: (A) the number of anogenital trackings, (B) number of escape behaviors, and (C) the number of times the pubescent female was pinned down by the adult. All were significantly greater when the pubescent female was paired with the adult male (SCAR) than when paired with an adult female (female/female). (D) Corticosterone concentrations were significantly elevated in pubescent females thirty minutes after they were exposed to the adult male when compared to concentrations in pubescent females when paired with an adult female. (E) Pubescent females were injected once with bromodeoxyuridine (BrdU) and sacrificed 21 days later. Females exposed to pups, but not to the adult male, retained more new cells than females not exposed to pups. (F and G) Representative photomicrographs of the granule cell layer (in the dentate gyrus of the hippocampus) show cells stained with cresyl violet and new cells, which are brown and labeled with BrdU. Scales bars for the photomicrographs are 0.05 mm and 0.01 mm respectively. (H) Four days after BrdU injection, pups were placed in the female's cage and maternal behaviors were recorded daily for 17 days. For each day of pup exposure, maternal behaviors—licking, retrieving and pup grouping—were tallied for a potential total score of 3. Pubescent females exposed to the adult male (SCAR) were less likely to express maternal behaviors. (I) The scores for maternal behavior were summed and compared to the number of BrdU-labeled cells in the dentate gyrus. The expression of maternal behavior was associated with an increase in the number of new cells. The vast majority of these cells will have differentiated into neurons, suggesting that learning maternal behaviors may increase neurogenesis in the female hippocampus (Shors et al., 2016).

(Ruscio et al., 2008). Voles exposed to foster pups for 20 min expressed an increase in cell proliferation and survival in the hippocampus compared to voles not exposed to pups.

In addition to neurogenesis, maternal behavior has beneficial effects on the stress response in the offspring. Sullivan and colleagues have conducted numerous studies investigating how female rats who are mothers serve as social buffers to stress for their pups, by suppressing HPA axis activation and corticosterone release in the pups, as well as amygdala-dependent fear learning (Moriceau and Sullivan, 2006; Sullivan and Perry, 2015). With respect to aggression, there are several animal models that resemble the SCAR model. Cooke and colleagues have developed an animal model of juvenile social subjugation in rats in order to understand why girls are more vulnerable than boys are to the effects of abuse. 28-day old male and female rats were exposed to an aggressive male daily for 10 min a day for 10 days. Female rats were more affected by the experience that males were; they displayed heightened corticosterone levels, performed poorly on a forced swim test, and showed less investigatory behavior in a test of social interaction (Weathington et al., 2013, 2012). Thus, the experience appears to elicit depressive and anxiety-like behaviors in the young females. Similarly, Huhman and colleagues have

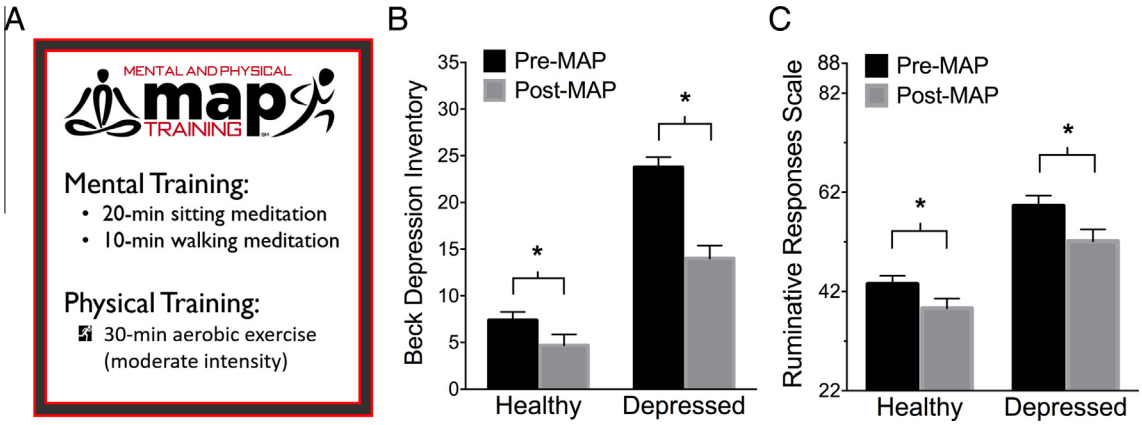

Fig. 2. (A) MAP Training is a clinical intervention that combines mental training with meditation and physical training with aerobic exercise (Shors et al., 2014). It was provided twice a week for 8 weeks to individuals with or without clinical symptoms of major depressive disorder (MDD) (Alderman et al., 2016). As expected, the scores on Beck Depression Inventory (BDI) were elevated prior to MAP Training, as was rumination as assessed with the Rumination Responses Scale (RRS). After MAP Training, symptoms of depression (B) and rumination (C) were significantly reduced in depressed individuals and healthy controls.

developed an animal model of social aggression in adult male Syrian hamsters (termed "conditioned defeat"). They identified different neural circuits underlying aggressive and submissive behaviors, which include the basolateral amygdala, ventral hippocampus and nucleus accumbens. In this model, the basolateral amygdala is necessary for the acquisition of conditioned defeat (Luckett et al., 2012; Markham et al., 2010). While animal models of social stress help to elucidate the neural circuits underlying aggressive behaviors, most examine male animals. Thus, we do not know whether the neural circuits involved in and necessary for expressing these behaviors are different in females, or how the brains of females, often those subject to aggression, are shaped by these behaviors.

These aforementioned laboratory studies along with the animal model of SCAR may have implications for women who experience sexual aggression and violence in their lives, but they are in no way definitive. Females of mammalian species have been experiencing sexual aggression for eons and as disturbing as the statistics are, most females learn to care for their young. Moreover, the SCAR studies were conducted under controlled laboratory conditions in rodent models, whereas women living under sexually-charged conditions produce a multitude of personal responses that cannot be captured in an animal model, not to mention their access to social and cultural antidotes that can alter outcomes in other and presumably more positive ways. These laboratory findings rather point to some of the neurobiological and behavioral changes that can occur when a female mammal experiences the stress of sexual aggression during puberty and young adulthood. They also present a new and potentially useful model for understanding the consequences of sexual aggression in women, more of which are needed in research environments (Jordan et al., 2010).

The data just discussed indicate that motherhood and the expression of maternal caring behaviors can have a positive impact on behaviors related to learning and measures of brain plasticity such as neurogenesis. Most human studies tend to focus on negative consequences of motherhood, such as the increased incidence of depressive and anxiety-related symptoms before and after giving birth (Altshuler et al., 2000). One study reported that new mothers with depression expressed less corticolimbic activation to infant-related stimuli than mothers who were not depressed (e.g., Swain et al., 2014), whereas another suggested that prenatal health concerns can manifest as emotional and behavioral problems in the offspring (Leis et al., 2014). Other studies suggest that children born to women with PTSD are more likely to experience trauma themselves (Roberts et al., 2012). But we also know that motherhood can confer protection from stress. Again in laboratory animals, females that were already caring for their young were resistant to the negative effects of stress on learning (Leuner and Shors, 2006), an effect that appears to extend well beyond weaning (Maeng and Shors, 2012; Shors, 2016). To our knowledge, there are few if any studies that assess women who experience sexual trauma before versus after they become mothers. This is understandable; many women who experience intimate partner violence while pregnant or lactating do not report the trauma because they want to protect their child and/or keep the family intact (Lévesque and Chamberland, 2015).

4. Learning to recover from sexual trauma

Many studies report that stress can reduce neurogenesis (Brummelte and Galea, 2010; Gould et al., 1997; Mirescu and Gould, 2006). These findings inspired us to develop a clinical intervention that would theoretically increase neurogenesis in women after trauma (Curlik and Shors, 2013; Shors et al., 2014). The intervention is known as MAP Training because it combines mental and physical training (see Fig. 2). It is well-established that physical training with aerobic exercise produces more new neurons in the hippocampus and as discussed, mental training that engages effortful learning processes keeps many of those new cells alive (Gould et al., 1999; Shors, 2014; van Praag, 2008). We hypothesized that the combination of these two activities – mental and physical training – would be an effective intervention for humans. For the mental training component, we chose meditation because it is effortful to practice and is associated with learning how to be present in this moment of time. It has also been associated with increases in hippocampal volume, which may reflect an increase in neurogenesis (Holzel et al., 2012). The physical training component consists of aerobic exercise, which is known to increase the production of new neurons in animal models with corresponding increases in hippocampal volume in humans (Erickson et al., 2014, 2011). However, neurogenesis cannot be directly assessed in living humans, and therefore we do not know whether more new neurons are made or rescued by MAP Training. Rather we emphasize that MAP Training was "inspired" by the discovery of neurogenesis in the hippocampus and its relationship to aerobic exercise and learning. Nonetheless, neurogenesis does occur in humans and therefore, there is reason to hypothesize that decreases in neurogenesis occur during and after a traumatic experience in women. Moreover, these decreases may be ameliorated

by an increase in neurogenesis as a result of positive lifestyle behaviors such as aerobic exercise and meditation, as well as learning experiences related to motherhood (Fig. 3).

Rumination about the past is a potential ramification of sexual trauma and abuse. During these thought processes, which are disruptive to many, an individual finds it difficult to concentrate on the present and make predictions about the future. Ruminative thoughts are especially evident in women who suffer from stress-related illnesses such as depression and PTSD (Mezo and Baker, 2012; Nolen-Hoeksema et al., 2008; Spasojević and Alloy, 2001). Despite a growing appreciation for their presence, we know less about how to reduce them. Most studies indicate that exposure therapy, during which the individual is exposed to stimuli related to the trauma, is effective in some individuals (Foa et al., 2002, 1999a; Resick et al., 2002). As discussed, ruminations are typically composed of autobiographical memories from the past and it is likely that those memories interfere with the "normal" processing capacity of the hippocampus. Indeed, people with depression who were high ruminators expressed less hippocampal activation to loss events with corresponding deficits in functional hippocampal connectivity (Hach et al., 2014; Johnston et al., 2015). Based on these and other findings, we have proposed that a person can learn to *not* attend to ruminative thoughts by engaging in the clinical intervention that combines "mental" and "physical" training, known as MAP Training. During the mental training component, participants engage in a form of meditation known as focused-attention (FA) meditation, during which a person sits in complete silence while learning to focus attention on the breath. The person is instructed to count each breath and when the counting becomes disrupted by intervening thoughts, he or she is instructed to return their attention to the breath and begin counting again at the number one. During this process, the individual acquires new skills that allow him or her to recognize when the interruption has occurred and thereby learns more about how personal thoughts about the past and future arise and dissipate. With practice, a person also learns to recognize and decouple ruminative thoughts about the past from current thoughts about the self in the present. After 30 min of meditation training, participants are supervised through 30 min of physical training. During this component, participants engage in aerobic exercise, practiced at a moderate intensity on a treadmill or cyclometer. After the aerobic exercise, the session is complete. Participants engage in two sessions of MAP Training each week for eight weeks.

Women and men who suffer from depression are more likely to ruminate about the past (Nolen-Hoeksema et al., 2008). To test whether MAP Training would reduce depression and/or ruminations, we provided 8 weeks of MAP Training (twice a week) to clinically depressed ($n = 22$) and otherwise healthy individuals ($n = 30$) (Alderman et al., 2016). After eight weeks, individuals with major depressive disorder (MDD) reported significant decreases in depressive symptoms, marked by a 40% reduction in scores on the Beck Depression Inventory (BDI-II). Even otherwise healthy individuals reported significantly fewer symptoms of depression (Fig. 2A–B). Although women reported a greater number of depressive symptoms before MAP Training, both sexes responded positively to the intervention, reporting fewer ruminations and depression symptoms. In another clinical study more relevant to the current review, we tested the effects of MAP Training in a small group of young mothers who were recently homeless, experiencing trauma and violence while living on the streets (Shors et al., 2014). After eight weeks of MAP Training, the women reported fewer ruminative thoughts about the past and fewer symptoms of depression, when compared to other women in the same community who did not receive MAP Training (Shors et al., 2014). Their anxiety levels, which were elevated before training, were also significantly reduced, as assessed with Beck Anxiety Inventory. All of the participants were mothers to small children and infants and therefore, we were able to assess their feelings about being a mother ("Being a Mother Scale"). The young mothers reported having fewer misgivings and anxiety about becoming or being mothers after the intervention was complete (unpublished data from the Being a Mother Scale).

At this point, we do not know the neurobiological mechanisms that underlie these MAP-induced changes in affect although we have documented some interesting relationships. For example, event-related potentials (ERPs) were recorded from the scalp while individuals engaged in a task that requires inhibitory control. The amplitude of an ERP response reflects the potential voltage of large groups of neurons firing in synchrony, as they are time-locked to stimuli delivered during the behavioral task. Before MAP Training, degree of rumination negatively correlated with the amplitude of late-onset ERPs (Alderman et al., 2015, 2016). In other words, individuals who ruminated more had a less robust ERP response during behavioral tests that require cognitive control. After MAP Training, the correlation was no longer significant. Therefore, individuals who responded to MAP Training with less rumination also expressed more synchronized brain activity while engaging in cognitive control processes. Although intriguing, we do not know whether this relationship is causal or exactly where in the brain these responses originate. These particular ERP responses reflect changes in synchronized neuronal activity in prefrontal, parietal and cingulate cortices, which likely interact with those in the hippocampus. As discussed, MAP Training was inspired by studies on neurogenesis in the hippocampus but we cannot prove that neurogenesis is increased. Therefore we do not claim that the positive effects are directly attributable to this phenomenon. Rather these data suggest that MAP Training is effective because it reduces the repetitive rehearsal of memories from the past, especially when those memories are depressing and disturbing to relive. We suggest that this intervention will prove especially effective in reduc-

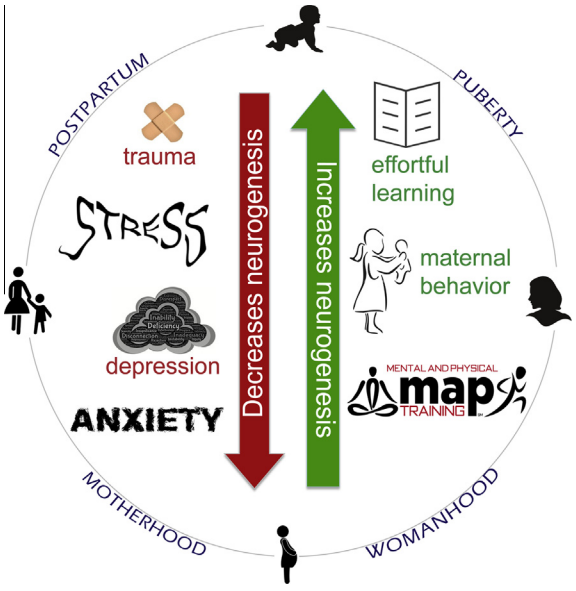

Fig. 3. This is an extrapolated depiction of how various stimuli affect human neurogenesis in the hippocampus. Based on animal studies, long and short-term stressors as well as induced states of depression and anxiety decrease the number of new cells in the hippocampus. However, exercise, effortful learning, and maternal behavior all increase neurogenesis in animal models. Given the research on animal neurogenesis, we hypothesize that the human equivalent of these experiences will have similar effects on neurogenesis. MAP Training was inspired by these animal neurogenesis studies to improve brain health, potentially by a hippocampal-dependent mechanism.

ing ruminations that can arise in women as a result of sexual violence and trauma.

5. Conclusion

Nearly one in three women experience sexual violence in their lives (Kessler, 2000; World Health Organization, 2013). Most of these events occur in adolescents and young adults. In the United States, one in five university women experience an incident of sexual violence while in college, most often in their freshman and sophomore years (Sinozich and Langton, 2014). Twenty percent of women who experience these kinds of traumas go on to develop symptoms of PTSD, according to the National Co-Morbidity Study (Breslau, 2009), along with feelings of depression, hopelessness and suicidal ideation (Danielson et al., 2009; McCauley et al., 2009; Wilsnack et al., 1997). Because prevalence rates of mood and anxiety disorders are consistently higher in women than in men (Kessler, 2003; Steel et al., 2014) and women are more likely to be victims of sexual trauma, it is presumed that these experiences initiate or minimally exacerbate the symptoms of existing psychological disorders. As if the statistics were not dire enough, sexual trauma enhances all-cause mortalities, including risks of cancer, heart disease, stroke and diabetes (van der Kolk, 2000). Therefore, it is imperative that we address this problem and that we do so on several fronts. First, as neuroscientists, we must develop and adopt appropriate animal models, like the SCAR model described here and others discussed. These models will provide scientists with the means and perhaps incentive to investigate how these aggressive and emotional experiences, in particular, change the female brain. On other fronts, we must increase awareness and prevention. Along those lines, a nationwide study on sexual violence on college campuses recently galvanized support and recognition at the institutional level, with appropriate responses for victims of sexual violence (Cantor and Fisher, 2015). These efforts include education about the behaviors, which constitute violence against women. These positive moves notwithstanding, we must face the fact that sexual violence and aggression between humans is not likely to disappear and therefore, we must develop effective interventions, specifically designed to help women learn to recover from the stress of sexual violence in their lives.

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