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Review article

Hormones and behavior and the integration of brain-body science☆

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ABSTRACT

The investigation of hormones, brain function and behavior over the past 50 years has played a major role in elucidating how the brain and body communicate reciprocally via hormones and other mediators and how this impacts brain and body health both positively and negatively. This is illustrated here for the hippocampus, a uniquely sensitive and vulnerable brain region, study of which as a hormone target has provided a gateway into the rest of the brain. Hormone actions on the brain and hormones generated within the brain are now recognized to include not only steroid hormones but also metabolic hormones and chemical signals from bone and muscle. Moreover, steroid hormones, and some metabolic hormones, and their receptors, are generated by the brain for specific functions that synergize with effects of those circulating hormones. Hormone actions in hippocampus have revealed its capacity, and that of other brain regions, for adaptive plasticity, loss of which needs external intervention in, for example, mood disorders. Early life experiences as well as in utero and transgenerational effects are now appreciated for their lasting effects at the level of gene expression affecting the capacity for adaptive plasticity. Moreover sex differences are recognized as affecting the whole brain via both genetic and epigenetic mechanisms. The demonstrated plasticity of a healthy brain gives hope that interventions throughout the life course can ameliorate negative effects by reactivating that plasticity and the underlying epigenetic activity to produce compensatory changes in the brain with more positive consequences for the body.

1. Introduction

Because of the increasing attention to "brain health" (https://brainhealth.nia.nih.gov/), it is timely for the 50th Anniversary of *Hormones and Behavior* to have a review summarizing how the study and application of integrated brain-body science has evolved to a great extent from the study of hormone effects on behavior and behavioral effects on hormone secretion. This began with the pioneering work of hormone behaviorists like Young, Beach and Lehrman (e.g., see Young et al., 1964) and neuroendocrinologists like Harris, Scharrer, Guillemin, Schally and Vale (for review and one point-of-view see McEwen et al., 2015b). As information expands, we tend to be caught in silos of knowledge. Indeed, the traditional view of medicine has been to ignore the brain above the hypothalamus and pituitary, while psychiatry, neurology and neuroscience, traditionally, have largely ignored the influence of the body on the brain, However, it is now quite evident that brain and body communicate reciprocally via hormones and other mediators and in ways that promote brain and body health but which can also accelerate disease processes when dysregulated. For example, physical activity stimulates neurogenesis in the dentate gyrus and depends upon circulating IGF-1 from the liver (Trejo et al., 2001), among other neural and systemic signals; yet the brain can become resistant to insulin and leptin and this can lead to depression and later dementia along with systemic disorders such as Type 2 diabetes and cardiovascular disease (Biessels and Reagan, 2015; Rasgon and McEwen, 2016), In this short review I shall recount phases of discovery and concepts, albeit from the point of view of my laboratory and like-minded colleagues, that have been reviewed in more detail elsewhere (https://www.sciencedirect.com/journal/frontiers-in-neuroendocrinology/vol/49). Our work began with the hippocampus as a uniquely sensitive and vulnerable brain region that has acted as a gateway to the rest of the brain. This review will also emphasize recent findings and novel concepts that have grown out of this research path.

2. Hormone actions in the hypothalamus and hippocampus provided a gateway to the rest of the brain

After the discovery of estrogen receptors in the hypothalamus with its implications for sexual behavior and neuroendocrine function (Pfaff, 1980), the serendipitous discovery of adrenal steroid receptors in the hippocampal formation provided a gateway to identifying hormone receptors and hormone actions throughout the brain with implications for influences upon cognitive function, mood and neurological processes (McEwen et al., 2015b).

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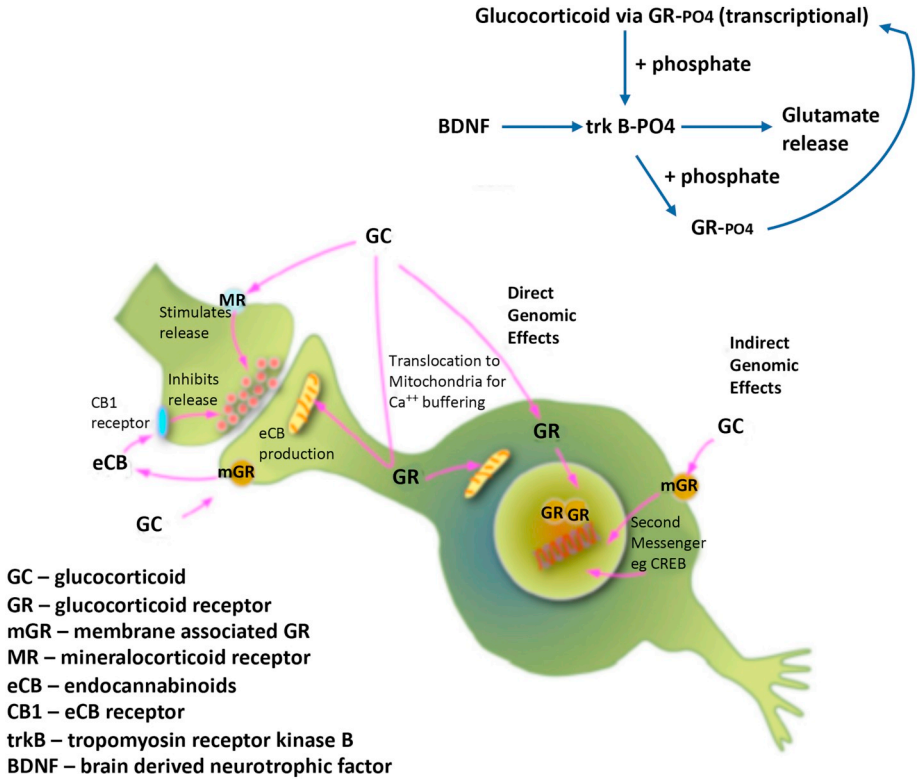

Fig. 1. Glucocorticoids produce direct and indirect genomic actions as well as nongenomic signaling actions via glucocorticoid (GR) and mineralocorticoid (MR) receptors. These involve not only direct and indirect genomic actions, but also direct stimulation of glutamate release and stimulation of endocannabinoid production, which then feed back on glutamate and GABA release and actions in mitochondria to affect Ca++ buffering and free radical formation (Popoli et al., 2012) (Upper Right). As shown in the article by Arango-Lievano et al. (2015), BDNF, in the presence of glucocorticoids, phosphorylates the GR at sites that facilitate its translocation to the cell nucleus for transcriptional actions; this effect is synergistic with the ability of glucocorticoids to activate, via a genomic mechanism, the phosphorylation of the Trk B receptor independently of BDNF, thus creating a positive feedback loop. From (McEwen et al., 2015a, 2015b) with permission.

In the case of steroid hormone, not only were the receptors found in the cell nucleus with implications for gene regulation, receptors were also found with higher resolution methods in synapses, mitochondria and glial cells (e.g., see Milner et al., 2001) that indicated both indirect effects on gene expression as well as cellular signaling processes that regulate second messenger formation and cytoskeletal polymerization leading for example to synapse formation (see Fig. 1).

Indeed, one of the features of the brain that emerged from these findings is the dynamic nature of the healthy brain, referred to as "adaptive plasticity", with synapse turnover, dendrite shrinkage and growth and dentate gyrus neurogenesis, all regulated by circulating hormones along with endogenous growth factors and excitatory amino acid neurotransmitters (McEwen et al., 2015a). Excessive stimulation by excitatory amino acids in the presence of glucocorticoids, however, causes permanent damage as is the case with stroke, seizures and head trauma (Sapolsky, 1992), as well as involvement in the progression of Alzheimer's pathology (Pereira et al., 2017) and major depressive illness (Nasca et al., 2013).

A more subtle form of impaired brain health is loss of plasticity in the aftermath of stressful experiences, in which structural change produced by those experiences cause the brain to "get stuck" and not adapt when conditions improve. Such is the case with shrinkage of the hippocampus in major depression and overactivity of the amygdala in anxiety disorders and depression where external behavioral and/or pharmacological intervention are required (Sheline et al., 2019).

Table 1
Cellular mechanisms of adaptive plasticity: from nucleus to cell surface.

Nuclear pores – NUP62 – nuclear-cytoplasmic communication
Required for dendritic remodeling in CA3 neurons (Kinoshita et al., 2014)
Cytoskeleton: Actin polymerization/depolymerization
Dendrite length and branching changes within hours during hibernation and arousal (Arendt et al., 2003; Magarinos et al., 2006)
Estradiol activates actin polymerization as part of synapse formation (Yuen et al., 2011)
Cell surface: PSA-NCAM – limits and facilitates pasticity
Removal of PSA causes uncontrolled growth of CA3 dendrites and increases vulnerability to (McCall et al., 2013)

Recognizing adaptive plasticity of the adult as well as developing brain has led to more in depth knowledge of cellular mechanisms from the cell nucleus to the cell surface (see Table 1). Besides actin polymerization leading to estrogen-induced synapse formation in hippocampus (Fig. 2), cytoskeletal depolymerization and polymerization is a feature not only of stress-induced shrinkage of dendrites in hippocampus and post-stress recovery, but also of rapid shrinkage of dendrite in hibernation and rapid recovery when the animal is aroused. Pores in the cell nucleus that allow two-way communication between the cytoplasm and genes in the nucleus contain at least one protein, Nup62, that is required for dendrite recovery after stress-induced shrinkage. And a cell surface molecular called PSA-NCAM is not only required for dendrite plasticity in hippocampus but also limits the dendrite regrowth that occurs after stress-induced shrinkage (Table 1).

Endocannabinoids are among the neurally-derived molecules that modulate stress-induced remodeling in amygdala and hippocampus. They are formed and released post-synaptically and act pre-synaptically to inhibit either glutamate or GABA release and glucocorticoids stimulate their formation and release (Balsevich et al., 2017). Blockade of CB1 receptors during stress increases the stress-induced remodeling, whereas the inactivation or knock-out of the degradative enzyme, FAAH, markedly blunts the effects of stressors in the amygdala (Hill et al., 2013; Hill and Lee, 2016).

Another revelation due in part to the study of hormone action in the brain is the recognition of the role of mitochondria with their own genetic information and ability to respond to hormones like estradiol and glucocorticoids (Du et al., 2009; Nilsen et al., 2007; Picard and McEwen, 2018). Mitochondria generate free radicals and excess free radicals increase inflammatory tone; yet, their normal function is providing energy and carefully modulating free radical tone in the spirit of allostasis (see below) (Picard et al., 2017). Mitochondria generate mitokines that communicate with each other and with the cell nucleus (for review see Picard and McEwen, 2018).

The brain uses mitochondria to generate and use steroid hormones and it also expresses other hormones normally associated with the body. Besides progesterone generation by Schwann cells and oligodendrocytes

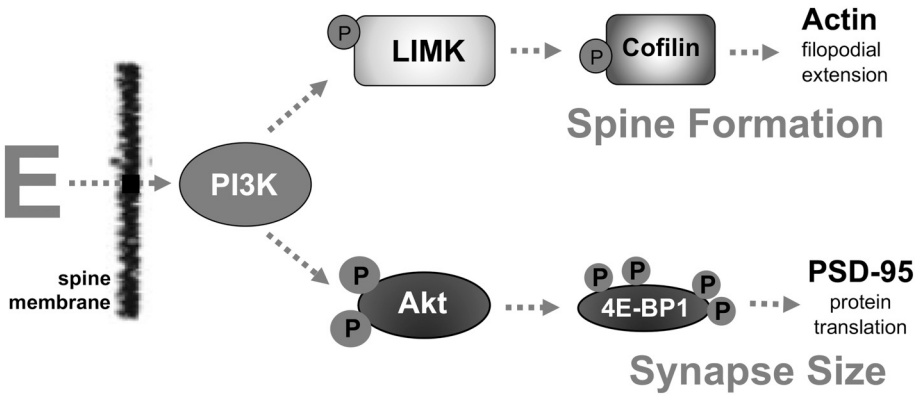

Fig. 2. Non-genomic estradiol action: synapse formation. Estradiol activates LIMK-1 to promote actin polymerization and PI3kinase to activate translation of PSD95 mRNA. In the male hippocampus, androgens generate synapses and do so genomically at least in part via nuclear AR (Romeo et al., 2005; Yuen et al., 2011).

Table 2
Systemic protein/peptide hormones expressed and/or acting in hippocampus.

Insulin – acts in hippocampus with neuroprotective and pro-cognitive effects different from promoting glucose transport (Biessels and Reagan, 2015)
IGF-1 – acts in hippocampus and required for exercise-induced neurogenesis (Trejo et al., 2001)
Leptin –acts in hippocampus on cognitive function, neurogenesis, neuroprotection and is also expressed in hippocampus (McGregor and Harvey, 2018; Yook et al., 2019)
Growth hormone –acts in hippocampus and expressed in hippocampus and responds to experience, aging and sex hormones; implicated in cognitive function and neuroprotection (Aramburo et al., 2014; Donahue et al., 2006)
Ghrelin – acts in hippocampus but does not appear to be expressed in brain; it has neuroprotective and pro-cognitive effects including neurogenesis in hippocampus (Buntwal et al., 2019). Yet prolonged exposure to ghrelin has negative effects related to fear memory (Yousufzai et al., 2018).
Prolactin – acts in hippocampus and may be expressed there; affects neurogenesis, increases synaptogenesis and neuronal plasticity, promotes consolidates memory and acts as a neuronal protector against excitotoxicity (Carretero et al., 2019).

Note: Resistance to these hormones results in pathophysiology as well as vulnerability to damage.

(Schumacher et al., 2012), the brain is capable of making estradiol and also androgens. Estradiol production "on demand" from cholesterol via aromatization in an ischemic brain has been documented (Hojo et al., 2003), and knocking out aromatase in brain exacerbates the damaging effects of ischemia (McCullough et al., 2003). Furthermore, after ovariectomy estrogen level are detectable after 3 weeks of gonadectomy in the male or female amygdala and in the female prefrontal cortex but not in hippocampus, suggesting a local source (Barker and Galea, 2009). For androgens, the ability of exercise to stimulate neurogenesis in male rat hippocampus is dependent on extra-gonadal production of dihydrotestosterone (Okamoto et al., 2012). The brain also has the capacity to generate neuroactive steroids such as A-ring reduced metabolites of progesterone that are allosteric modulators of the GABAa receptor that mediate its anaesthetic and sedative effects (Baulieu and Robel, 1990; Gee et al., 1987).

Systemic hormones also act via receptors expressed in hippocampus and some are also expressed there and have neuroprotective and pro-cognitive effects on neuroplasticity. Leptin and growth hormone act in hippocampus and are also expressed in hippocampus (Table 2). Ghrelin acts in hippocampus as does prolactin via receptors expressed there and they do not appear to be expressed in that brain region; likewise, insulin and insulin-like growth factor (IGF-1) also act in hippocampus to promote plasticity and protect against damage (Table 2). Moreover, factors from bone and muscle have effects on neural activity and adaptive plasticity, thus broadening what must be considered as systemic influences on the nervous system (Khrimian et al., 2017; Moon and van Praag, 2014).

3. Protection and damage – allostasis and allostatic load - biphasic actions under rubric of "stress"

Because some of the mediators that affect brain and body are linked to negative as well as positive actions, another outcome of this line of research has led to the concepts of allostasis and allostatic load that have broadened the definition of "stress" (McEwen, 1998; McEwen and Gianaros, 2011; McEwen and Stellar, 1993). We know that "homeostasis" means the physiological state which the body maintains to keep us alive - that is, body temperature and pH within a narrow range and adequate oxygen supply. In order to maintain homeostasis, our body activates hormone secretion and turns on our autonomic and central nervous system (we call these "mediators" like cortisol, adrenalin, the immune system and metabolism) to help us adapt, for example, when we get out of bed in the morning, walk up a flight of stairs, have a conversation. These systems are also turned on when we are surprised by something unexpected, or get into an argument, or run to catch a train. Some of these experiences we may refer to as "stressful" but other we do not. So using the word stress does not really recognize all of the underlying biology. The "mediators" help us adapt as long as they are turned on in a balanced way when we need them and then turned off again when the challenge is over. When that does not happen, they can cause unhealthy changes in brain and body. This is also the case when the "mediators" are not produced in an orchestrated and balanced manner – for example, too much or too little cortisol or an elevated or too low blood pressure. When this happens and continues over weeks and months, we call it "allostatic load" to refer to the wear and tear on the body that results from the chronic overuse and imbalance of the "mediators". Accumulation of abdominal fat is an example as is the development of chronic hypertension both of which can be called "allostatic overload" when they lead to disease (McEwen and Wingfield, 2003). Note, however, that we are talking, not about one mediator, like cortisol, but a host of mediators that are all released in allostasis in a coordinated manner to help us adapt but which can also cause damage when overused and dysregulated as described above.

4. Epigenetics, genetics and the individual: example of sex differences

Thus experiences of the life course that are mediated in part via hormones help to create each individual and do so epigenetically, as seen for example in differences among identical twins (Fraga et al., 2005) (see Box 1). Yet, the genome sets the limits on what is possible and sex differences are a complex example of the interaction between those genetic influences of the X and Y chromosome and mitochondrial DNA inherited primarily via the mother. As already noted, the entire brain has receptors for sex hormones, both genomic and non-genomic, and is able to generate sex hormones for local use. Three examples of sex differences in relation to stressful experiences illustrate the

Box 1
Epigenetics.

"Epigenetics" originally meant the emergence of developmentally-programmed characteristics as a fertilized egg develops into a living organism characteristic of that species (Waddington, 1942). This is programmed into each species, but the individual characteristics are influenced by experiences, and that is where the modern use of "epigenetics" comes from. An example of this is a pair of identical twins with genes that predispose them to schizophrenia or bipolar illness. Even with the same DNA, the probability that one twin will develop the disease when the other twin gets it is only in the range of 40–60%, which leave plenty of room for experiences and other environmental factors to either prevent of precipitate the disorder. As an indicator of this, the methylation patterns of DNA diverge as identical twins grow older (Fraga et al., 2005). Thus, "epigenetics", now meaning "above the genome", that is, not changing the genetic code, replaces and makes unnecessary the old question: "which is more important, genes or environment?". The CpG methylation of DNA is now a well-known form of epigenetic modification (Szyf et al., 2008).

But there are other mechanisms that include histone modifications that repress or activate chromatin unfolding (Allfrey, 1970) and the actions of non-coding RNA's (Mehler, 2008), as well as transposons and retrotransposons (Griffiths and Hunter, 2014; Hunter et al., 2015) and RNA editing (Mehler and Mattick, 2007). The repressive H3K9me3 histone mark is induced by acute stress in hippocampus of naïve rodents and is chronically turned on by early life stress (ELS) and then, in those ELS mice, turned off by acute stress. Although the meaning of this is unclear, it should be noted that the H3K9me3 mark represses DNA that includes transposon-like elements as well as non-coding regulatory RNA's that may have important functions in gene regulation and gene stability, particularly in hippocampus that may be unique within the brain (Hunter et al., 2015; Hunter et al., 2012).

divergence of response due to genetic/epigenetic sex. First, exposure of male and female rats to restraint plus intermittent tail shock has opposite effects on classical eyeblink conditioning, inhibiting it in females and enhancing it in males; in females, this effect is abolished by ovariectomy and is therefore estradiol dependent (Shors et al., 2001; Wood and Shors, 1998). A morphological correlate of this in the hippocampus is the finding that acute stress inhibits estradiol-depending spine formation in CA1 neurons of the hippocampus, whereas the same acute stressors enhance spine density in male CA1 neurons, possibly by increasing testosterone secretion (Shors et al., 2001) upon which spine formation in the male CA1 is dependent (Leranth et al., 2003). Neonatal masculinizaton of females made them respond positively, like genetic males, to the shock stressor (Shors, 2016) Moreover, in females, depending on reproductive status and previous experience, the negative stress effect was epigenetically altered, e.g., it was absent in mothers and virgin females with experience with infants (Shors, 2016).

Second, in the hippocampus of male rats, 21 days of chronic restraint stress (CRS) causes apical dendrites of CA3 neurons to retract and a loss of ~30% of the parvalbumin (PARV)-containing neurons in the dentate gyrus; these changes do not occur following CRS in female rats (Galea et al., 1997; Milner et al., 2013). Moreover, female and male rats show effects in the opposite direction of chronic stress on hippocampal dependent memory, with males showing impairment and females showing enhancement or no effect (Bowman et al., 2003; Luine et al., 1996; Luine et al., 1994). At the level of gene expression, using RNA sequencing of ribosome-bound mRNA from hippocampal CA3 neurons, we found remarkable sex differences and discovered that female mice displayed greater gene expression activation after acute stress than males (Marrocco et al., 2017). Moreover, genes that were common to males and females in response to acute stress tended to go in the opposite direction, with the exception of the immediate early gene, c-fos, which was increased in both sexes by acute stress (see Fig. 3).

Moreover, having even one copy of the Met allele in BDNF Val66Met mice, both sexes show a pre-stressed translational phenotype that was not evident in mice with the BDNF Val/Val genotype where the same genes were activated by an acute stressor. Behaviourally, only heterozygous BDNF Val66Met females exhibit spatial memory impairment, regardless of acute stress. Interestingly, this effect is not observed in ovariectomized heterozygous BDNF Val66Met females, suggesting that circulating ovarian hormones induce cognitive impairment in Met carriers. Cognitive deficits were not observed in males of either genotype. Thus, in a brain region not normally associated with sex differences, this work sheds light on ways that genes, environment and sex interact to affect the transcriptome's response to a stressor (Marrocco et al., 2017).

Third, males and females differ in response to stress in the medial prefrontal cortex – males show stress-induced shrinkage of dendrites that project cortically whereas females do not show that change but, rather, show stress-induced expansion of dendrites that project to the amygdala but only when there was estradiol in the circulation after ovariectomy (Shansky et al., 2010). These differences may underlie sex differences in how male and female rats learn and extinguish fear conditioning even though the outcome is similar (Gruene et al., 2015). The degree to which these differences are genetically, hormonally or experientially determined is not yet known.

5. Lasting epigenetic effects of early life adversity

Early life experiences are particularly potent in setting the direction of the life course and increase the risk, in humans, of depression, substance abuse and suboptimal cognitive development later in life but also allostasis and the propensity to develop allostatic load and overload in such disorders as cardiovascular disease and diabetes (Felitti et al., 1998; McEwen and McEwen, 2017). Moreover, adverse early life experience in infancy and childhood involving poverty, abuse and neglect, affect how genes are expressed and determine how well brain regions such as the hippocampus, amygdala and prefrontal cortex develop and function during childhood into young adulthood. (McEwen and McEwen, 2017; McEwen and Gregerson, 2019) Animal models are useful, and, for the brain, the hippocampus, once again, provides a glimpse into what happens at the level of gene expression. As noted earlier, CA3 neurons that are crucially involved in cognitive function and mood regulation as well as activation of glucocorticoid (CORT) secretion exhibit structural and functional changes after early-life stress (ELS) as well as after chronic stress in adulthood. Exposed to a protocol of chronic ELS induced by limited bedding and nesting material followed by acute-swim stress (AS) in adulthood, mice with a history of ELS display a blunted CORT response to AS, despite exhibiting activation of immediate early genes after stress similar to that found in control mice (Marrocco et al., 2019). Yet acute stress increases the expression of the repressive histone H3 lysine 9 tri-methylation (H3K9me3) in hippocampal fields of control mice, including the CA3 pyramidal neurons. Yet, ELS mice showed persistently increased expression of H3K9me3 histone mark in the CA3 subfield at baseline that was subsequently decreased following AS. **See** BOX 1. Using translating ribosome affinity purification (TRAP) method to isolate CA3 translating mRNAs, we found that expression of genes of the epigenetic gene family, GABA/glutamate family, and glucocorticoid receptors binding genes were decreased transiently in control mice by AS but showed a persistent reduction in ELS mice and no response to an AS challenge. A stringent filtering of genes affected by AS in control and ELS mice revealed a remarkable decrease in gene expression change in ELS mice elicited by acute stress compared to control. Fig. 4. Thus, ELS programs a restricted translational response to stress in stress-sensitive CA3 neurons leading to persistent changes in gene expression, some of which mimic the transient effects of AS in control mice, while leaving in operation the immediate

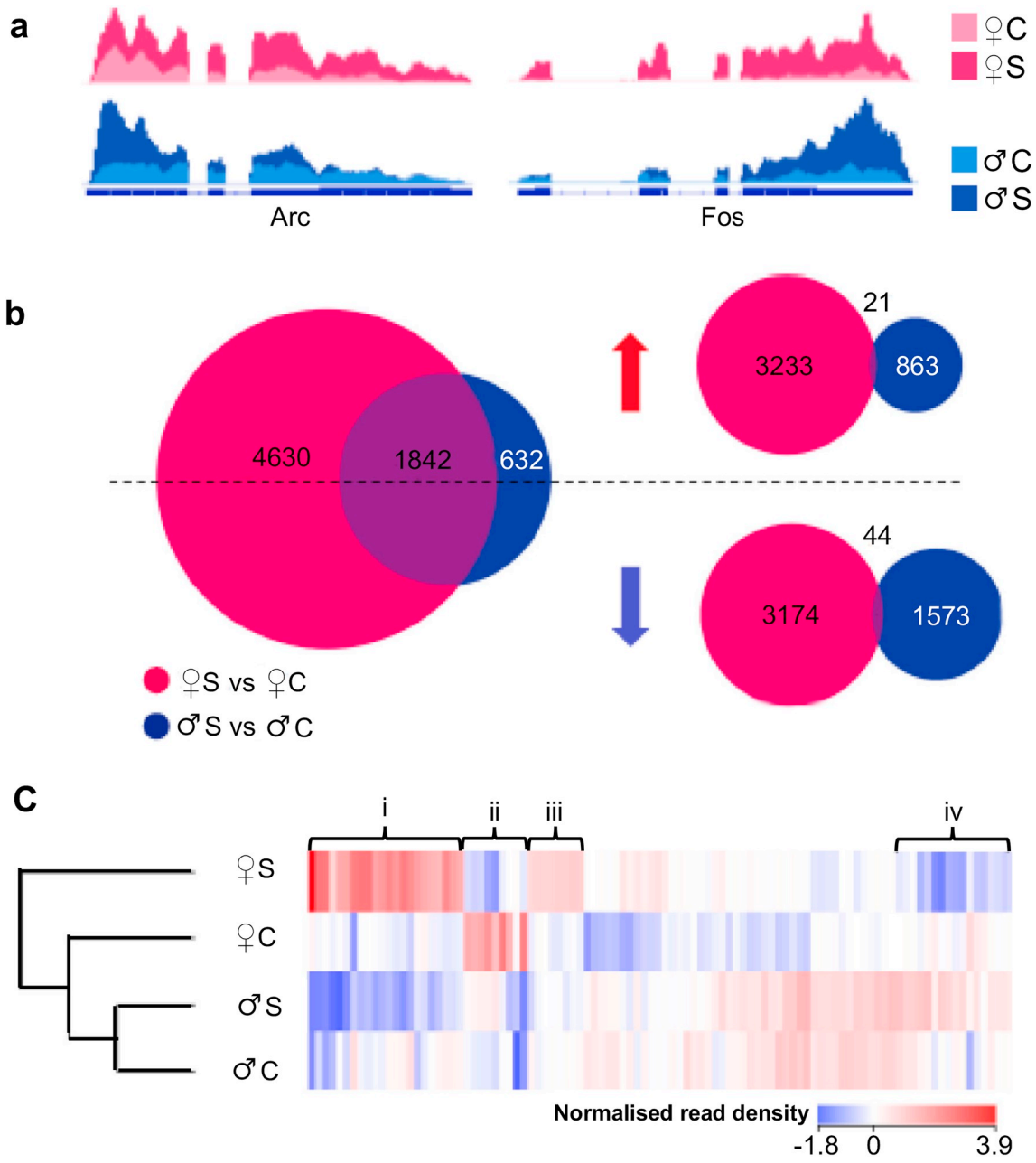

Fig. 3. Acute stress affects CA3 neurons in a sex-dependent manner and alters a greater number of genes in females than in males. A histogram of mapped reads showing expression of Arc and Fos, as genes representative of the immediate early gene transcription (IEG) cascade. Blue line represents the introns (thin) and exons (thick). Shaded areas indicate the number of normalized reads for female controls (light pink), stressed female (dark pink), male controls (light blue), and stressed male (dark blue). As expected, acute stress increases IEG expression in both males and females. b (Left) Venn diagram depicting the number of genes altered by acute stress in females (pink circle), males (blue circle), and in both sexes (purple overlap) (Z-score < 0.001; absolute fold change > 1.5). (Right) Venn diagrams are broken into up-regulated (red arrow) and down-regulated (blue arrow) genes. c Heat map representing the normalized read density of the 100 genes with the highest variance across all groups. Genes were clustered based on similar expression profile: (i) Genes up-regulated by stress in females and down-regulated by stress in males; (ii) Genes down-regulated by stress in females and unaffected by stress in males;(iii) Genes up-regulated by stress in females and unaltered by stress in males; (iv) Genes down-regulated by stress in females and up-regulated by stress in males. C control, S stressed (Marrocco et al., 2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

early gene response to AS (Marrocco et al., 2019).

While sex differences have so far not been studied in this model after ELS, based upon the discussion above it is very likely that the response of CA3 neurons will be quite different in females. Moreover, transgenerational transmission either by behavior (O'Donnell and Meaney, 2017) or modifications of the germline DNA or epigenetic changes in the fetus during pregnancy in the case of obesity are now recognized (Bohacek and Mansuy, 2015; Donkin et al., 2016; Kral et al., 2006).

6. Putting it all together

The unfolding of individuality within what the genetic endowment allows has led to a new view of the epigenetic changes over the life course that determine trajectories of health and disease. The plasticity of the brain offers opportunities for changing the trajectory (Halfon et al., 2014). Indeed, we cannot "roll back the clock" and truly "reverse" the effects of experiences, positive or negative. Rather, we must think of "recovery" and "redirection" and "resilience", rather than "reversal". We

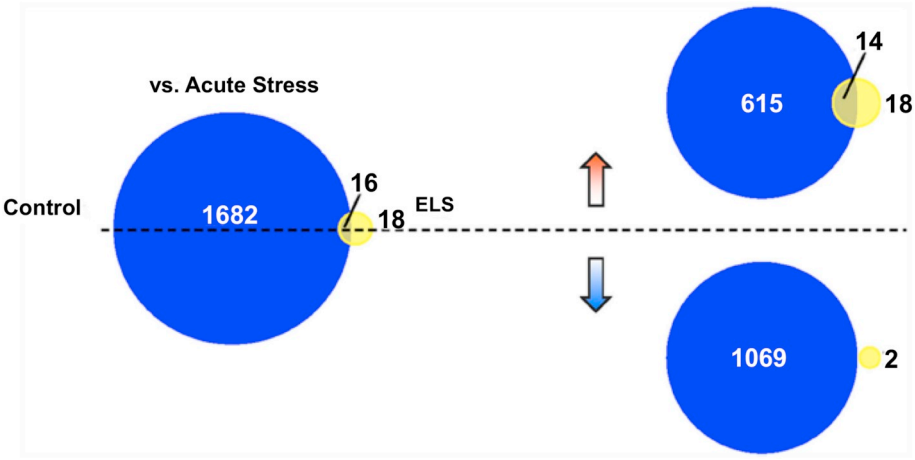

Fig. 4. Translational repression in ELS mice following AS. Venn diagram depicting the number of genes altered in stressed control mice vs. unstressed control mice (dark blue), stressed ELS mice vs. unstressed ELS mice (yellow), and in both comparisons (yellow-blue overlap; $p < .05$). AS induces a markedly limited gene expression change in ELS mice relative to control mice. We found that AS induces 1698 genes in control mice and 34 genes in ELS mice, with 16 genes common to both comparisons. Separating these AS-regulated genes based on the direction of their fold change revealed that AS upregulates 629 genes in control mice and 32 genes in ELS mice, with 14 genes commonly upregulated in both comparisons. In addition, 1069 genes are downregulated in control mice and two genes downregulated in ELS mice by AS, with no genes common to both comparisons. ELS, early life stress; AS, acute stress (Marrocco et al., 2019). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

therefore think about "changing trajectories" of function resulting in compensatory changes in the brain and body over the life course. One example of this is the remarkable differences in the qualitative nature of gene expression in hippocampus after a bolus of corticosterone compared to the effects of a novel acute forced swim (FST) in naïve rats compared to FST effects in animals that were chronically restrained (CRS) before or FST in animals that had recovered after CRS. Each treatment group showed acute stress largely unique gene expression responses, indicating that the brain is continually changing with experience. Nevertheless, there is a set of genes that was always activated by FST (e.g., immediately early genes) (Gray et al., 2014).

Given the potency of early life experiences, both positive and negative, and the substantial sex difference that exist at the level of gene expression and brain circuitry, interventions that change the trajectory of behavior and physiology should recognize these powerful influences and take advantage of windows of opportunity when the likelihood of change is increased (Halfon et al., 2014). Very early childhood is one obvious window, along with pregnancy for the mother and her partner and programs like the Nurse-Family Partnership focus on that phase of the lifecourse, with good success (https://www.nursefamilypartnership.org/). Adolescence is another window of opportunity when hormones and brain circuits are changing an amenable to interventions that build bonds with parents and develop skills for coping with bullying and other forms of resilience with adversity (Brody et al., 2017a; Brody et al., 2017b).

7. Conclusion

Due in large part to studies of hormones, brain function and behavior, it is now quite evident that brain and body communicate reciprocally via hormones and other mediators and in ways that promote brain and body health but which can also accelerate disease processes when the mediators of allostasis are dysregulated. Hormone actions on the brain and within the brain now involve not only steroid hormones but also metabolic hormones and chemical signals from bone and muscle. Early life experiences as well as in utero and transgenerational effects are now being elucidated and appreciated for their power at the level of gene expression, and sex differences are recognized as affecting the whole brain via both genetic and epigenetic mechanisms. The demonstrated plasticity of a healthy brain gives hope that interventions throughout the life course can ameliorate negative effects by reactivating that plasticity and the underlying epigenetic activity that produces compensatory changes in the brain with more positive consequences for the body.

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