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From serendipity to clinical relevance: How clinical psychology and neuroscience converged to illuminate psychoneuroendocrinology

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A tribute to Dirk Hellhammer.

ABSTRACT

Dirk Hellhammer and his colleagues have played a major role in creating the field of psychoneuroendocrinology from their roots in psychology. In this review, using examples from the history of the McEwen laboratory and neuroscience and neuroendocrinology colleagues, I summarize my own perspective as to how the fields of neuroscience and neuroendocrinology have contributed to psychoneuroendocrinology and how they converged with the contributions from Dirk Hellhammer and his colleagues.

1. Introduction

The field of psychoneuroendocrinology has matured and flourished as an amalgam of neuroscience, neuroendocrinology and endocrinology, immunology and psychology. Dirk Hellhammer' remarkable contributions and that of his many successful trainees have converged with the research interests of my laboratory – he from clinical psychology and my laboratory from cell biology, neuroscience and neuroendocrinology. Here I summarize my own path that has led to this convergence and, in so doing, provide an overview of some molecular as well as behavioral and physiological aspect of stress psychoneuroendocrinology and the key role of glucocorticoids.

2. From cell biology to neuroendocrinology

A chemistry major at Oberlin College, I came to The Rockefeller University for graduate study. Because of my experience investigating fatty acid oxidation by mitochondria (Fritz and Mc, 1959), I was fascinated by oxidative metabolism and oxidative phosphorylation by mitochondria, and I joined the laboratory of Alfred Mirsky and Vincent Allfrey, to study the question of how the cell nucleus obtains the ATP to make RNA. What I found in my Ph.D. thesis research is that there is another terminal oxidase, involving cytochrome b5 located in the nuclear envelope, that is less sensitive to carbon monoxide than the cytochome c of the mitochondria (McEwen et al., 1963a, b; McEwen et al., 1963c, 1964).

While working in the Allfrey-Mirsky laboratory, I was imbued with Mirsky's fascination with environmental control of gene expression and the Waddington concept of epigenetics (Waddington, 1942), together with Allfrey's pioneering work on the modification of histones as the start of the current blossoming of what is now called epigenetics (Allfrey, 1977; Maze et al., 2013; Moberg, 2012). These have had a powerful effect on my own science, and, indeed, when I returned to Rockefeller in 1966, it was the Mirsky and Allfrey influence that led me to study steroid hormone receptors in the brain because of the realization, at that time, that steroid hormones regulate gene expression in liver and uterus, for example. Very little was known about the brain in that regard.

The Rockefeller environment that I entered in 1966 was much different than the one I left in early 1964, because of the addition, not only of Neal Miller, but also Carl Pfaffmann (both physiological psychologists), George Miller and William Estes (cognitive psychologists), and Peter Marler and Donald Griffin (animal behaviorists). This constituted the Behavioral Sciences Program that, for a number of years, had a field program in Africa and connections with the New York Zoological Society. Many current leaders in behavioral neuroscience received training in this Program. For me, a number of younger colleagues, notably, my contemporaries, Donald Pfaff and Fernando Nottebohm, created an exciting environment where synthesis and cross-talk began between animal behavior and physiological psychology. A common denominator among us was the action of hormones, primarily sex hormones for Pfaff and Nottebohm.

Because of Neal Miller's interest in and development of "behavioral medicine", the topic of stress and stress hormones was one that I addressed, and our discovery of adrenal steroid receptors in the hippocampus in 1968 opened the path to the eventual realization in the latter part of the 20th century and beginning of the new millenium that circulating hormones of the gonads, adrenal cortex, thyroid gland and also

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the metabolic system affect many, if not most, areas of the brain, including those involved in higher cognitive function (McEwen, 2007). This provides a link, at least in retrospect, to what was in 1966 called cognitive psychology and which now includes not only cognitive neuroscience, but also the burgeoning field of social neuroscience. I say this because the circulating hormones are controlled, in part, by the social environment - and, besides the hypothalamus, they affect the areas of the brain involved in cognitive, social and emotional processes (McEwen et al., 2015b)! How this came about takes us into the realm of epigenetics.

3. 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 characteristics of each individual 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 or 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 *per se*, and it 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) and RNA editing (Mehler and Mattick, 2007). This leads to a discussion of how steroid hormones affect the brain.

4. Steroid hormone actions in hippocampus and beyond

It was the pioneering Allfrey/Mirsky work on epigenetic actions on gene expression via histones that led me to look for cell nuclear receptors, first in hypothalamus for estrogens (Zigmond and McEwen, 1970) and then in hippocampus for glucocorticoids (McEwen et al., 1968). (I had learned about the hippocampus as a postdoctoral fellow in Goteborg Sweden in 1964–66 in the Institute of Neurobiology headed by Holger Hyden). By administering ^{3}H corticosterone into adrenalectomized rats, we discovered receptors for adrenal steroids in the hippocampal formation of the rat and, later, the rhesus monkey (Gerlach and McEwen, 1972; Gerlach et al., 1976; McEwen and Plapinger, 1970; McEwen et al., 1968). Other studies revealed such receptors in the hippocampal homolog in other species including birds (Dickens et al., 2009; McEwen, 1976).

While there was very little interest in 1968 in epigenetics in the brain, the hippocampus has since become a "gateway" into learning how stress hormones, and also sex, thyroid and metabolic hormones like insulin, enter the brain, bind to receptors and act epigenetically to positively regulate structure and function not only in hippocampus but also throughout many part of the brain, affecting behavior and the ability to function in daily life (McEwen et al., 2015b).

In fact, the hippocampus was the subject of the Nobel Prize to UK-based researcher Prof John O'Keefe and Norwegian scientists, May-Britt Moser and Edvard Moser in 2014 as the "GPS" of the brain. Indeed the hippocampus is important for episodic and spatial memory and is now also recognized for its role in mood regulation. For spatial memory, for example, the hippocampus becomes active in London cab drivers during functional MRI imaging when they remember a route from one place to another (Maguire et al., 1997). The hippocampus is also important for food caching behavior in squirrels and birds (Biegler et al., 2001; Burger et al., 2013; Clayton, 2001). And the hippocampus is also "the canary in the coal mine" as far as conditions such as ischemia and seizures that cause brain damage as well as brain aging (Sapolsky, 1992). Last but not least, the hippocampus responds to sex hormones with effects on spatial memory and other functions (Sandstrom and Williams, 2001).

As a postdoctoral fellow in my laboratory, Ron de Kloet found that synthetic glucocorticoids like dexamethasone (DEX) are actively excluded from the brain (DeKloet et al., 1975) and, in his subsequent career, he showed that this is due to the "multi-drug resistance p glycoprotein"(Karssen et al., 2001). Indeed, DEX is a very potent inhibitor of inflammation and immune function and stimulates of liver glucose metabolism (hence the name "glucocorticoid"). We now know that synthetic glucocorticoids like DEX, when given to quell inflammation can shut off for a while the ability to secrete ACTH and make cortisol; and when DEX treatment is terminated the body and brain become deficient in cortisol and this results in terrible mood swings and metabolic and immune disruption (Judd et al., 2014).

Work by Hans Reul and Ron de Kloet demonstrated that there are two types of adrenal steroid receptors, mineralocorticoid (Type 1 or MR, not activated by DEX) and glucocorticoid (Type 2 or GR), in hippocampus and other brain regions (Reul and DeKloet, 1985). This was further elaborated by immunocytochemical mapping of the receptors (Ahima et al., 1991; Ahima and Harlan, 1990). Studies in our laboratory as well as by Diamond and by Joëls have shown biphasic effects mediated by MR and GR (Diamond et al., 1992; Joels, 2006; Pavlides et al., 1995). Ultradian fluctuations of glucocorticoids drive GR activation and reactivation, while MR occupancy for nuclear activation is more constant and promotes excitability (Stavreva et al., 2009).

Another important advance was made by Robert Sapolsky who found that, over the lifespan of a rat, that the cortisol equivalent in the rat, corticosterone, gradually cause a "wear and tear" on the hippocampus which impairs not only memory and mood but also the ability to shut off the production of its glucocorticoids (Sapolsky, 1992). This effect is more evident in animals and also people who have experienced toxic stress. The "glucocorticoid-cascade hypothesis of stress and aging", as it is called, was one of the bases for the concept of allostatic load and overload. Sapolsky also did seminal work on dominant and subordinate baboons in Africa and laid the groundwork for how income, education and human social hierarchies impact physical and mental health. His books "Why Zebra's Don't Get Ulcers", "A Primate's Memoir" and "Behave", and writings in the Wall Street Journal have made him an important figure for public awareness of behavioral science, along with his popularity as a teacher at Stanford University. While Robert Sapolsky's findings emphasized the role of glucocorticoids in neural damage and systemic pathophysiology, there was another side to the story, namely, the role of glucocorticoids and other hormones in adaptive plasticity of the adult as well as developing brain.

5. Plasticity of the brain

Long regarded as a rather static and unchanging organ, except for electrophysiological responsivity, such as long-term potentiation (Bliss and Lomo, 1973), the brain was finally recognized as capable of undergoing rewiring after brain damage (Parnavelas et al., 1974) and also able to grow and change as seen by dendritic branching, angiogenesis and glial cell proliferation during cumulated experience (Bennett et al., 1964; Greenough and Volkmar, 1973). More specific physiological changes in synaptic connectivity were also recognized in relation to hormone action in the spinal cord (Arnold and Breedlove, 1985), and in environmentally directed plasticity of the adult songbird brain (DeVoogd and Nottebohm, 1981). Seasonally varying neurogenesis in restricted areas of the adult songbird brain is recognized as part of this plasticity (Nottebohm, 2002). Indeed, adult neurogenesis in the adult

mammalian brain was initially described (Altman and Das, 1965; Kaplan and Bell, 1983) and then suppressed (Kaplan, 2001), only to be rediscovered in the dentate gyrus of the hippocampus (Cameron and Gould, 1994; Gould and McEwen, 1993) in the context of studies of neuron cell death and actions of adrenal steroids and excitatory amino acids in relation to stress. Neurogenesis in the dentate gyrus has gone on to become a huge topic related to effects of stress (Gould et al., 1997), exercise (van Praag et al., 1999), enriched environment (Kempermann et al., 1997), antidepressants (Duman et al., 1997) and learning and memory (Leuner et al., 2006). More than neurogenesis, structural plasticity includes dendrite remodeling, synapse formation and synaptic pruning. Chronic stress causes shrinkage of dendrites in the CA3 region of the hippocampus (McEwen, 2016) and in the medial prefrontal cortex (McEwen and Morrison, 2013), with expansion of dendrites in the basolateral amygdala and orbitofrontal cortex (Chattarji et al., 2015; Liston et al., 2006; Vyas et al., 2002).

In the human brain regular exercise increases the volume of the hippocampus in elderly subjects (Erickson et al., 2011), and a recent study shows how the brain architecture of a mother is sculpted during pregnancy as part of the formation of attachment to the child (Hoekzema et al., 2017). Moreover, a s's brain develop with enhanced size and connections of sensory and motor control regions of the cerebral cortex (Merzenich, 1998). Furthermore, various types of mindfulness and meditation interventions are reported to sculpt the cerebral cortex in specific ways.(Valk et al., 2017).

6. Behavioral medicine, allostasis and allostatic load

One step closer to my convergence with Dirk Hellhammer, my work on adrenal steroid hormone effects on the hippocampus and other limbic system brain areas attracted the attention of Eliot Stellar and colleagues at Penn. Because of Stellar, I was drawn into a MacArthur Foundation Network on Health and Behavior, together with Judith Rodin at Yale and others from many universities, and this experience broadened my perspective to learn about and include many aspects of translational behavioral science and behavioral medicine. The Health and Behavior Network also was the basis of the subsequent MacArthur Foundation Research Network on Socioeconomic Status (SES) and Health, where concepts of social neuroscience and behavioral medicine, were either applied and/or developed under the leadership of Nancy Adler, UCSF. They are helping to elucidate how SES "gets under the skin" and affects health of human populations (http://www.macses.ucsf.edu/). It was out of these two networks that the notion of "allostatic load" was born, and out of which began my involvement in better understanding stress effects upon the human brain and body.

Jerome Kagan has noted that the word "stress" is used so much in different ways so as to be ambiguous and almost meaningless; and he suggested that the word "stress" be used only in the cases where an event poses a serious threat to someone's well-being (Kagan, 2016). There are other uses of the word "stress". For starters, "good stress" involves taking a chance on something one wants, like interviewing for a job or admission to school, or giving a talk before strangers, and feeling rewarded when we are successful. (A negative experience in a job or school interview is not "good" stress, however, but may be tolerable!) "Tolerable stress" means that something bad happens, like losing a job or death of a loved one, or being unsuccessful in a job or school interview, but with personal resources, including good self esteem and locus of control, and support systems one is able to weather the storm. "Toxic stress" means what Kagan refers to, that is, something bad happens but one lacks the internal personal resources and/or external support systems, and feels a lack of control. As a result, one may sleep poorly and adopt other health damaging behaviors and may develop mental and physical health problems over time as a result of allostatic overload, as explained below.

Putting these three forms of "stress" into a biological and behavioral context, 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, or 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 others we do not. So using the word stress does not really recognize all of the underlying biology, including the health-promoting and health-damaging behaviors that also activate and sometimes dysregulate these mediators. The mediators, themselves, operate non-linearly and influence each other, so that abnormal activity of one mediator perturbs and distorts the rest of the network.

In 1988, Peter Sterling and Joseph Eyer published a paper on the concept of allostasis as applied to the cardiovascular system (Sterling and Eyer, 1988). Thanks to Eliot Stellar, I met Sterling and heard him speak. As my role in the network developed, Stellar and I wrote a paper that broadened the allostasis concept beyond the cardiovascular system and introduced the notion of cumulative change as a result of excessive or dysregulated allostasis (McEwen and Stellar, 1993) that was ultimately named "allostatic load" (McEwen, 1998). The MacArthur Network "morphed" into the MacArthur Research Network on Socioeconomic Status and Health that continued the development and validation of allostatic load with the important role of Teresa Seeman from UCLA (McEwen and Seeman, 1999; Seeman et al., 2010a, 2010b; Wiley et al., 2016). The basic concept behind allostatic load is an outgrowth of Robert Sapolsky's "glucocorticoid cascade hypothesis" of stress and aging (Sapolsky et al., 1986) that was broadened to encompass not only glucocorticoids and catecholamines but also other interacting mediators of adaptation. Allostasis and allostatic load acknowledge the central role of the brain in response to stress and the resulting health-promoting and health-damaging behaviors (Fig. 1).

The "mediators" of allostasis 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.

One more development of the allostatic load concept was contributed by a field biologist, John Wingfield, who pointed out that animals in the wild are continually searching for calories to stay alive while we humans, at least in affluent societies, are oversupplied with calories (McEwen and Wingfield, 2003). Moreover, Wingfield pointed out that forms of what we might call "allostatic load" are important adaptive features in bears putting on body fat for the winter, during which they burn it off. Yet, bears in a zoo can develop obesity associated with cardiovascular disease out of over-feeding, boredom and lack of physical activity.

This led to Wingfield's suggestion that "allostatic overload" might apply to those most negative aspects of dysregulated allostasis (McEwen and Wingfield, 2003, 2010). Yet, migrating salmon and marsupial mice experience "allostatic overload" that eliminates part of the population in order to provide resources to the next generation (Carruth et al., 2002; Poskitt et al., 1984). An example of allostatic overload in humans is when hypertension leads to coronary artery blockade, and abdominal fat contributes chemicals that accelerate the coronary artery blockade. Note, however, that we are not talking about just one mediator, like cortisol, but rather a host of mediators that are all released in allostasis in a coordinated manner to promote adaptation but which can also

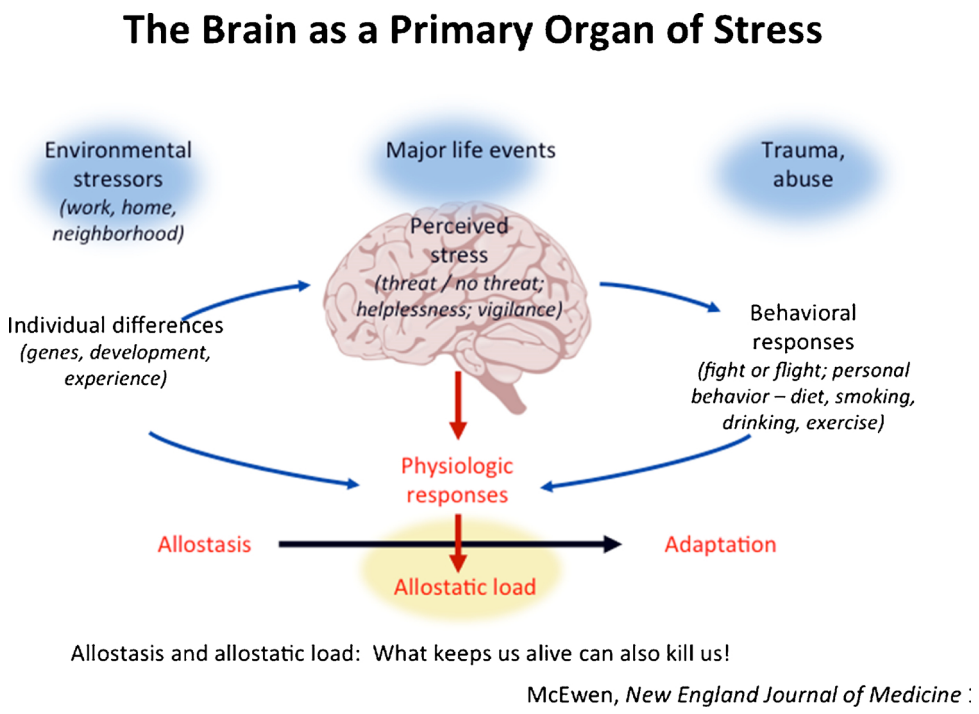

Fig. 1. The brain as the primary organ of stress and response to stress (redrawn from (McEwen, 1998).

cause damage when overused and dysregulated as described above. Because cortisol is well known in relation to stress and is an essential component of multiple physiological adaptive processes, this is where our interests converged with those of Dirk Hellhammer and his colleagues.

7. Convergence with Dirk Hellhammmer and the Trier Group

Cortisol is a component of the measurement of allostatic load, and single measurements of cortisol are virtually meaningless because of its moment-to-moment fluctuations. With Clemens Kirschbaum and other colleagues, Dirk Hellhammer introduced salivary cortisol (and later hair cortisol) and the Trier Social Stress Test (TSST), all of which have been adopted and used worldwide (Kirschbaum et al., 1993). Salivary samples can be taken repeatedly and do not involve the stress of blood sampling; moreover, salivary cortisol reflects free cortisol that is presumably active.

One series of papers of particular importance to me concerned salivary cortisol responses to repeated TSST exposure, in which a subset of men failed to habituate their cortisol elevation and produced higher cortisol levels and showed evidence of lower self-esteem (Kirschbaum et al., 1995). This example led to a figure in my 1998 New England Journal of Medicine paper defining allostatic load as one way that the stress response can lead to allostatic load, namely, by not habituating to repeated exposure to the same stressor (McEwen, 1998). Fig. 2. Indeed, new work emphasizes that low child and adult SES are associated with significantly slower recovery rate of the HPA response compared with high child and adult SES (Le-Scherban et al., 2018).

Moreover, led by Jens Pruessner, who went from Trier to McGill for some years, the Hellhammer team further explored the self esteem linkage and showed an association with a smaller hippocampus (Pruessner et al., 2005, 1999). The implications of this are very Important because low self esteem/locus of control and a smaller hippocampus are associated with increased risk for PTSD (Pitman et al., 2006) as well as major depression (Sheline, 2003). The relationship of self esteem and locus of control to hippocampal volume as been further amplified in relation to poverty (Wang et al., 2016), PTSD (Agroskin et al., 2014) and genetic vs environmental influences based on twin studies (Kubarych et al., 2012). This has implications for interventions during “windows of opportunity” based upon our increasing knowledge of brain plasticity. Recent work shows, for example, that intervention with African-American adolescents at age 11 and their caregivers to improve self-regulation and self-esteem/locus of control prevents a decline in hippocampal and amygdala volume as measured at age 25 that occurs without such an intervention due to poverty and racial discrimination among other stressors, (Brody et al., 2017).

8. The variety of roles of the HPA axis

As this work progressed, the Hellhammer group recognized and summarized physiological and psychological factors that influence variability in the HPA response (Hellhammer et al., 2009). Mechanistically, contributing factors include the balance of hypothalamic releasing factors, the 11HSD 1 and 2 enzymes that metabolize glucocorticoids, variation in corticosteroid binding globulin levels, effects of the innervation of the adrenal cortex by the splanchnic nerve, modulating effects of sex hormones and sex differences, along with level and activity of mineralocorticoid (MR) and glucocorticoid (GR) receptors and their allelic variants (Judd et al., 2014; McEwen, 2007; van Rossum et al., 2006). It is also noteworthy that MR and GR have both genomic and rapid non-genomic effects (Joels, 2006; McEwen, 2015; McEwen et al., 2015a). These factors help determine differences between cortisol levels measure in blood, saliva and urine (Hellhammer et al., 2009).

8.1. Hair cortisol

The emergence of cortisol in hair, pioneered by Kirschbaum KirKi (Kirschbaum et al., 2009), as a more integrated, longer-term measure of HPA activity has added to the ways of assessing effects of cumulative stress as well as chronic circadian disruption. One surprising result is the report that severe burnout characterized by exhaustion and reduced work efficiency is reported to be associated with hypercortisolism, as assessed by hair cortisol and reported and discussed by former Hellhammer trainees (Penz et al., 2018; Rohleder, 2018). For post-traumatic stress disorder (PTSD), hair cortisol measures have facilitated a more sophisticated modeling of the complex changes occurring after

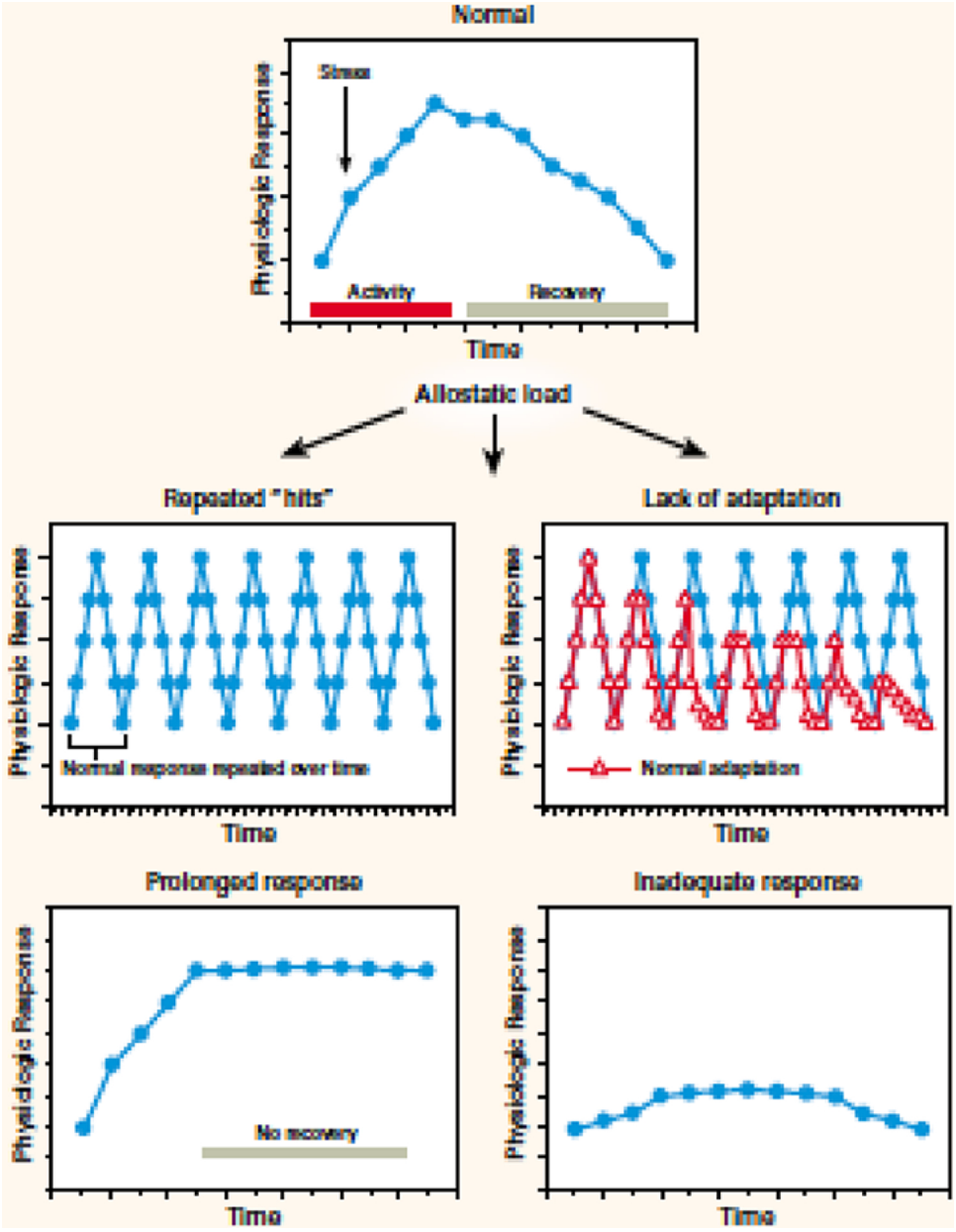

Fig. 2. Three Types of Allostatic Load.
The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load: repeated "hits" from multiplestressors; lack of adaptation; prolonged response due to delayed shutdown; and inadequate response that leads to compensatoryhyperactivity of other mediators (e.g., inadequate secretion of glucocorticoids, resulting in increased concentrations of cytokines that are normally counterregulated by glucocorticoids). From (McEwen, 1998).

trauma in which both cortisol elevation and reduction are reported (Steudte-Schmiedgen et al., 2016).

8.2. Too much cortisol or cortisol at the wrong time

Examples include a flat diurnal rhythm (see below) and Cushing's Disease when excess cortisol is produced by a pituitary gland tumor (Bas-Hoogendam et al., 2015; Starkman et al., 2003; van der Werff et al., 2015; Young et al., 1994)! Furthermore, acutely, a glucocorticoid elevation preceeding an inflammatory challenge exacerbates the inflammatory response, even though the inflammatory response triggers a counter-regulatory anti-inflammatory HPA response (Frank et al., 2016; Sorrells et al., 2009; Sorrells and Sapolsky, 2007).

8.3. Systemic metabolic actions of glucocorticoids

Moreover, as implied by the name "glucocorticoid", adrenalectomized animals respond to sucrose ingestion by normalizing hypothalamic expression of corticotropin-releasing-factor messenger ribonucleic acid and energy balance; this indicates that there is a glucocorticoid-systemic metabolic-brain axis that is independent of the stress axis mediated by neural actions of glucocorticoids; this has led to a new view of why we eat "comfort foods" when under stress (Dallman, 2003; Laugero et al., 2001)

8.4. Essential physiological role of glucocorticoids – circadian and immunity

We often forget that the cortisol response is not the "bad guy", as it is often implied by its elevation in the context of a bad experience;

rather, cortisol, which keeps us alive under those adverse circumstances, has a normal physiological role not only helping us adapt to stressors but also coordinating our metabolism with our daily activity and sleep patterns (McEwen et al., 1993). For example, diurnal and ultradian fluctuations of cortisol promote the formation and elimination of synapses in the brain and this helps us learn and adapt (Liston et al., 2013; Liston and Gan, 2011).

It should also be remembered that the circadian variation of cortisol determines the efficacy of the stress response, as shown by the Dallman laboratory; that is, a flat cortisol rhythm leads to a sluggish turn-on and turn-off of the HPA response, while a normal diurnal variation facilitates efficient allostasis (Akana et al., 1988; Jacobson et al., 1988).

Moreover, the diurnal early morning rise of cortisol, as well as an acute stress response activates adaptive immune function so that one can fight an infection or repair a wound, even though chronic stress has the opposite effect and suppresses inflammation and adaptive immune function (Dhabhar and McEwen, 1999). Beside cortisol and adrenalin involvement in this important adaptive function, key biochemicals of the immune system are also necessary and, together, they help immune cells "go to their battle stations" where they are needed! (Dhabhar et al., 2012). As exemplified by the concepts of allostasis and allostatic load, the body's response is like an orchestra involving many players that need to work in harmony!

8.5. Glucocorticoids and immune-related cells in the brain

Glucocorticoids regulate microglial function in the brain. Microglia express glucocorticoid receptors (GR) and also mineralocorticoid receptors (MR) that are the primary steroid hormone regulators of microglial inflammatory activity (Sierra et al., 2008). The down-regulation of steroid hormone receptors after LPS challenge may serve as a prerequisite to suppressing the anti-inflammatory actions of endogenous steroid hormones on the immune system, and contribute to a sustained activation of microglia (Sierra et al., 2008).

8.6. Variety of glucocorticoids actions over the life course

Finally, glucocorticoids do not play the same role across the life course but rather serve different functions, starting with their role in "wakening" of the amygdala in neonatal life (Moriceau and Sullivan, 2004) and continuing to their role in promoting ponderal growth in adolescence (Romeo et al., 2006) and their influence on the vulnerability of the adolescent brain to stressful experiences (Pattwell et al., 2011, 2016; Romeo, 2017) as well as the age-accelerating role of excess cortisol in aging (Lupien et al., 1998; Sapolsky et al., 1986).

9. Diagnosis and interventions

How can this information be used for better diagnosis and treatment of stress-related disorders? Besides the HPA axis, the Hellhammer group recognizes that there are other mediators of allostasis including other hormones, the immune system and the autonomic nervous system. Moreover, behavioral assessments and functional and structural imaging of the brain can also add useful information, in order to develop better psychosocial interventions in addition to pharmacological therapy. They have developed "neuropattern" as a diagnostic tool, which is defined as follows: "Neuropatterns are conceptualized endophenotypes of the activity and reactivity status of neurobiological interfaces, which participate in the crosstalk between the brain and peripheral organs under stressful conditions" (Hellhammer et al., 2012, 2018; Hero et al., 2012).

As to why this is so timely and important, the diversity of individual differences in behavioral and physiological responses within broad designations of "stress", "burnout", "PTSD" or "depression", means that no single behavioral or biological marker will be sufficient for diagnosis of stress-related disorders and discovery of effective treatments. Rather, a combination of measures from diverse methodologies is a key feature of Neuropattern, Allostatic Load, and RDoC. RDoC from the National Institutes of Mental Health has the same goals and uses different levels or units of analysis (molecular, circuit, behavior and symptom levels) to define constructs that are presumed to underlie core symptoms of mental disorders (Casey et al., 2013). For depression, for example, functional imaging of the brain identifies "biotypes" and is helpful in narrowing down a diagnosis (Drysdale et al., 2017). A future research direction might therefore address whether "Neuropattern" in combination with functional imaging and other systemic and neural biomarkers might narrow the possibilities of diagnosis and improve the effectiveness of treatments for stress-related disorders. Furthermore, and very important to keep in mind, the allostatic load/overload model and its measurement and analysis (Seeman et al., 2010a; Wiley et al., 2016) provides biomarkers for determining multisystem dysregulation of the cumulative effects of a stressful lifestyle that results in multimorbidity of brain and systemic disorders, including such co-morbidities of depression with diabetes and/or cardiovascular disease (Tomasdottir et al., 2015).

10. Conclusions

The convergence of research described herein has revolved around the many functions of glucocorticoids in organismal physiology, the multiple mechanisms by which these actions occur, and the multiple interactions between neural and body systems involving glucocorticoids, at least in part, along with the interacting mediators of allostasis. The Trier group, led by Dirk Hellhammer and his many outstanding colleagues, has led the way not only in non-invasive measurement of free cortisol in relation to psychophysiological challenges but also the dysregulation of these in conditions such as low self esteem and burnout along with sex differences and the influence of gonadal hormone variations. This is now being integrated with discoveries as to how cortisol interacts with other mediators of allostasis and contributes to brain-body interactions by regulating structural and functional plasticity of the brain via epigenetic mechanisms.

Conflict of interest

None.

References

Agroskin, D., Klackl, J., Jonas, E., 2014. The self-liking brain: a VBM study on the structural substrate of self-esteem. PLoS One 9 e86430.
Ahima, R.S., Harlan, R.E., 1990. Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. Neuroscience 39, 579–604.
Ahima, R., Krozowski, Z., Harlan, R., 1991. Type I corticosteroid receptor-like immunoreactivity in the rat CNS: distribution and regulation by corticosteroids. J. Comp. Neurol. 313, 522–538.
Akana, S.F., Jacobson, L., Cascio, C.S., Shinsako, J., Dallman, M.F., 1988. Constant corticosterone replacement normalizes basal adrenocorticotropin (ACTH) but permits sustained ACTH hypersecretion after stress in adrenalectomized rats. Endocrinology 122, 1337–1342.
Allfrey, V.G., 1970. Changes in chromosomal proteins at times of gene activation. Fed. Proc. 29, 1447–1460.
Allfrey, V.G., 1977. Post-synthetic modifications of histone strucure. A mechanism for the control of chromosome structure by the modulation of DNA-histone interactions. Chromatin and Chromosome Structure. Academic Press, New York, pp. 167–199.
Altman, J., Das, G.D., 1965. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J. Comp. Neurol. 124, 319–336.
Arnold, A., Breedlove, S., 1985. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. Horm.Behav. 19, 469–498.
Bas-Hoogendam, J.M., Andela, C.D., van der Werff, S.J., Pannekoek, J.N., van Steenbergen, H., et al., 2015. Altered neural processing of emotional faces in remitted Cushing's disease. Psychoneuroendocrinology 59, 134–146.
Bennett, E., Diamond, M., Krech, D., Rosenzweig, M., 1964. Chemical and anatomical plasticity of brain. Science 146, 610–619.
Biegler, R., McGregor, A., Krebs, J.R., Healy, S.D., 2001. A larger hippocampus is associated with longer-lasting spatial memory. Proc. Natl. Acad. Sci. U. S. A. 98, 6941–6944.
Bliss, T.V.P., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the

dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiology 232, 331–356.
Brody, G.H., Gray, J.C., Yu, T., Barton, A.W., Beach, S.R., et al., 2017. Protective prevention effects on the association of poverty with brain development. JAMA Pediatrics 171, 46–52.
Burger, D.K., Saucier, J.M., Iwaniuk, A.N., Saucier, D.M., 2013. Seasonal and sex differences in the hippocampus of a wild rodent. Behav. Brain Res. 236, 131–138.
Cameron, H.A., Gould, E., 1994. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience 61, 203–209.
Carruth, L.L., Jones, R.E., Norris, D.O., 2002. Cortisol and pacific salmon: a New look at the role of stress hormones in olfaction and home-stream migration. Integr. Comp. Biol 42, 574–581.
Casey, B.J., Craddock, N., Cuthbert, B.N., Hyman, S.E., Lee, F.S., Ressler, K.J., 2013. DSM-5 and RDoC: progress in psychiatry research? Nat. Rev. Neurosci. 14, 810–814.
Chattarji, S., Tomar, A., Suvrathan, A., Ghosh, S., Rahman, M.M., 2015. Neighborhood matters: divergent patterns of stress-induced plasticity across the brain. Nat. Neurosci. 18, 1364–1375.
Clayton, N.S., 2001. Hippocampal growth and maintenance depend on food-caching experience in juvenile mountain chickadees (Poecile gambeli). Behav. Neurosci. 115, 614–625.
Dallman, M.F., 2003. Chronic stress and obesity: a new view of' comfort food'. Proc. Natl. Acad. Sci. U. S. A. 100, 11696–11701.
DeKloet, E.R., Wallach, G., McEwen, B.S., 1975. Differences in corticosterone and dexamethasone binding to rat brain and pituitary. Endocrinology 96, 598–609.
DeVoogd, T., Nottebohm, F., 1981. Gonadal hormones induce dendritic growth in the adult avian brain. Science 214, 202–204.
Dhabhar, F., McEwen, B., 1999. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc. Natl. Acad. Sci. U. S. A. 96, 1059–1064.
Dhabhar, F.S., Malarkey, W.B., Neri, E., McEwen, B.S., 2012. Stress-induced redistribution of immune cells-from barracks to boulevards to battlefields: a tale of three hormones - Curt Richter Award Winner. Psychoneuroendocrinology 37, 1345–1368.
Diamond, D.M., Bennett, M.C., Fleshner, M., Rose, G.M., 1992. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus 2, 421–430.
Dickens, M., Romero, L.M., Cyr, N.E., Dunn, I.C., Meddle, S.L., 2009. Chronic stress alters glucocorticoid receptor and mineralocorticoid receptor mRNA expression in the European starling (Sturnus vulgaris) brain. J. Neuroendocrinol. 21, 832–840.
Drysdale, A.T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., et al., 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat. Med. 23, 28–38.
Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., et al., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U. S. A. 108, 3017–3022.
Fraga, M.F., Ballestar, E., Paz, M.F., Ropero, S., Setien, F., et al., 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proc. Natl. Acad. Sci. U. S. A. 102, 10604–10609.
Frank, M.G., Weber, M.D., Watkins, L.R., Maier, S.F., 2016. Stress-induced neuroinflammatory priming: a liability factor in the etiology of psychiatric disorders. Neurobiol. Stress 4, 62–70.
Fritz, I.B., Mc, E.B., 1959. Effects of carnitine on fatty-acid oxidation by muscle. Science 129, 334–335.
Gerlach, J., McEwen, B.S., 1972. Rat brain binds adrenal steroid hormone: radioautography of hippocampus with corticosterone. Science 175, 1133–1136.
Gerlach, J., McEwen, B.S., Pfaff, D.W., Moskovitz, S., Ferin, M., et al., 1976. Cells in regions of rhesus monkey brain and pituitary retain radioactive estradiol, corticosterone and cortisol differently. Brain Res. 103, 603–612.
Gould, E., McEwen, B.S., 1993. Neuronal birth and death. Curr. Opin. Neurobiol. 3, 676–682.
Gould, E., McEwen, B.S., Tanapat, P., Galea, L.A.M., Fuchs, E., 1997. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J. Neurosci. 17, 2492–2498.
Greenough, W.T., Volkmar, F.R., 1973. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Exp. Neurol. 40, 491–504.
Griffiths, B.B., Hunter, R.G., 2014. Neuroepigenetics of stress. Neuroscience 275, 420–435.
Hellhammer, D.H., Wust, S., Kudielka, B.M., 2009. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology 34, 163–171.
Hellhammer, D., Hero, T., Gerhards, F., Hellhammer, J., 2012. Neuropattern: a new translational tool to detect and treat stress pathology I. Strategical consideration. Stress 15, 479–487.
Hellhammer, D., Meinlschmidt, G., Pruessner, J.C., 2018. Conceptual endophenotypes: a strategy to advance the impact of psychoneuroendocrinology in precision medicine. Psychoneuroendocrinology 89, 147–160.
Hero, T., Gerhards, F., Thiart, H., Hellhammer, D.H., Linden, M., 2012. Neuropattern: a new translational tool to detect and treat stress pathology. II. The Teltow study. Stress 15, 488–494.
Hoekzema, E., Barba-Muller, E., Pozzobon, C., Picado, M., Lucco, F., et al., 2017. Pregnancy leads to long-lasting changes in human brain structure. Nat. Neurosci. 20, 287–296.
Jacobson, L., Akana, S.F., Cascio, C.S., Shinsako, J., Dallman, M.F., 1988. Circadian variations in plasma corticosterone permit normal termination of adrenocorticotropin responses to stress. Endocrinology 122, 1343–1348.
Joels, M., 2006. Corticosteroid effects in the brain: U-shape it. Trends Pharmacol. Sci. 27, 244–250.
Judd, L.L., Schettler, P.J., Brown, E.S., Wolkowitz, O.M., Sternberg, E.M., et al., 2014. Adverse consequences of glucocorticoid medication: psychological, cognitive, and behavioral effects. Am. J. Psychiatry 171, 1045–1151.
Kagan, J., 2016. An overly permissive extension. Persp. Psychol. Sci. 11, 442–450.
Kaplan, M.S., 2001. Environment complexity stimulates visual cortex neurogenesis: death of a dogma and a research career. Trends Neurosci. 24, 617–620.
Kaplan, M.S., Bell, D.H., 1983. Neuronal proliferation in the 9-month-old rodent-radioautographic study of granule cells in the hippocampus. Exp. Brain Res. 52, 1–5.
Karssen, A.M., Meijer, O.C., van der Sandt, I.C.J., Lucassen, P.J., de Lange, E.C.M., et al., 2001. Multidrug resistance P-glycoprotein hampers the access of cortisol but not of corticosterone to mouse and human brain. Endocrinology 142, 2686–2694.
Kempermann, G., Kuhn, H.G., Gage, F.H., 1997. More hippocampal neurons in adult mice living in an enriched environment. Nature 586, 493–495.
Kirschbaum, C., Pirke, K.-M., Hellhammer, D.H., 1993. The 'Trier social stress test' - a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81.
Kirschbaum, C., Prussner, J.C., Stone, A.A., Federenko, I., Gaab, J., et al., 1995. Persistent High cortisol responses to repeated psychological stress in a subpopulation of healthy men. Psychosomatic Med. 57, 468–474.
Kirschbaum, C., Tietze, A., Skoluda, N., Dettenborn, L., 2009. Hair as a retrospective calendar of cortisol production - increased cortisol incorporation into hair in the third trimester of pregnancy. Psychoneuroendocrinology 34, 32–37.
Kubarych, T.S., Prom-Wormley, E.C., Franz, C.E., Panizzon, M.S., Dale, A.M., et al., 2012. A multivariate twin study of hippocampal volume, self-esteem and well-being in middle-aged men. Genes, Brain, Behav. 11, 539–544.
Laugero, K.D., Bell, M.E., Bhatnagar, S., Soriano, L., Dallman, M.F., 2001. Sucrose ingestion normalizes central expression of corticotropin-releasing-factor messenger ribonucleic acid and energy balance in adrenalectomized rats: a glucocorticoid-metabolic-brain axis? Endocrinology 142, 2796–2804.
Le-Scherban, F., Brenner, A.B., Hicken, M.T., Needham, B.L., Seeman, T., et al., 2018. Child and adult socioeconomic Status and the cortisol response to acute stress: evidence from the multi-ethnic study of atherosclerosis. Psychosom Med. 80, 184–192.
Leuner, B., Gould, E., Shors, T.J., 2006. Is there a link between adult neurogenesis and learning? Hippocampus 26, 216–224.
Liston, C., Gan, W.B., 2011. Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. Proc. Natl. Acad. Sci. U. S. A. 108, 16074–16079.
Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., et al., 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. 26, 7870–7874.
Liston, C., Cichon, J.M., Jeanneteau, F., Jia, Z., Chao, M.V., Gan, W.B., 2013. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. Nat. Neurosci. 16, 698–705.
Lupien, S.J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., et al., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat. Neurosci. 1, 69–73.
Maguire, E.A., Frackowiak, R.S.J., Frith, C.D., 1997. Recalling routes around London: activation of the right hippocampus in taxi drivers. J. Neurosci 17, 7103–7110.
Maze, I., Noh, K.M., Allis, C.D., 2013. Histone regulation in the CNS: basic principles of epigenetic plasticity. Neuropsychopharmacology 38, 3–22.
McEwen, B.S., 1976. Steroid hormone receptors in developing and mature brain tissue. In: Snyder, S., McEwen, B.S. (Eds.), Neurotransmitters, Hormones and Receptors: Novel Approaches. Society of Neuroscience, pp. 50–66.
McEwen, B.S., 1998. Protective and damaging effects of stress mediators. New. Engl. J. Med. 338, 171–179.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol. Rev. 87, 873–904.
McEwen, B.S., 2015. Preserving neuroplasticity: role of glucocorticoids and neurotrophins via phosphorylation. Proc. Natl. Acad. Sci. U. S. A. 112, 15544–15545.
McEwen, B.S., 2016. Stress-induced remodeling of hippocampal CA3 pyramidal neurons. Brain Res. 1645, 50–54.
McEwen, B.S., Morrison, J.H., 2013. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life Course. Neuron 79, 16–29.
McEwen, B.S., Plapinger, L., 1970. Association of corticosterone-1,2 3H with macromolecules extracted from brain cell nuclei. Nature 226, 263–264.
McEwen, B.S., Seeman, T., 1999. Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. Ann. N.Y. Acad. Sci. 896, 30–47.
McEwen, B.S., Stellar, E., 1993. Stress and the individual. Mechanisms leading to disease. Arch. Intern. Med. 153, 2093–2101.
McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. Horm. & Behav. 43, 2–15.
McEwen, B.S., Wingfield, J.C., 2010. What is in a name? Integrating homeostasis, allostasis and stress. Horm. Behav. 57, 105–111.
McEwen, B.S., Allfrey, V., Mirsky, A., 1963a. Studies of energy-yielding reactions in thymus nuclei. I. Comparison of nuclear and mitochondrial phosphorylation. J. Biol. Chem. 238, 758–766.
McEwen, B.S., Allfrey, V., Mirsky, A., 1963b. Studies on energy-yielding reactions in thymus nuclei. II. Pathways of aerobic carbohydrate catabolism. J. Biol. Chem. 238, 2571–2578.
McEwen, B.S., Allfrey, V., Mirsky, A., 1963c. Studies on energy-yielding reactions in thymus nuclei. III. Participation of glycolysis and the citric acid in nuclear adenosine triphosphate synthesis. J. Biol. Chem. 238, 2579–2586.
McEwen, B.S., Allfrey, V., Mirsky, A., 1964. Dependence of RNA synthesis in isolated thymus nuclei on glycolysis, oxidative carbohydrate catabolism and a type of "oxidative" phosphorylation. Biochim. Biophys. Acta 91, 23–28.
McEwen, B.S., Weiss, J., Schwartz, L., 1968. Selective retention of corticosterone by

limbic structures in rat brain. Nature 220, 911–912.
McEwen, B.S., Sakai, R.R., Spencer, R.L., 1993. Adrenal steroid effects on the brain: versatile hormones with good and bad effects. In: Schulkin, J. (Ed.), Hormonally-Induced Changes in Mind and Brain. Academic Press, San Diego, pp. 157–189.
McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., et al., 2015a. Mechanisms of stress in the brain. Nat. Neurosci. 18, 1353–1363.
McEwen, B.S., Gray, J.D., Nasca, C., 2015b. 60 YEARS OF NEUROENDOCRINOLOGY: redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. J. Endocrinol. 226, T67–T83.
Mehler, M.F., 2008. Epigenetic principles and mechanisms underlying nervous system functions in health and disease. Prog. Neurobiol. 86, 305–341.
Mehler, M.F., Mattick, J.S., 2007. Noncoding RNAs and RNA editing in brain development, functional diversification, and neurological disease. Physiol. Rev. 87, 799–823.
Merzenich, M., 1998. Long-term change of mind. Science 282, 1062–1063.
Moberg, C., 2012. Entering an Unseen World: A Founding Laboratory and Origins of Modern Cell Biology 1910–1974. The Rockefeller University Press, New York, NY.
Moriceau, S., Sullivan, R.M., 2004. Corticosterone influences on mammalian neonatal sensitive-period learning. Behav. Neurosci. 118, 274–281.
Nottebohm, F., 2002. Why are some neurons replaced in adult brain? J. Neurosci. 22, 624–628.
Parnavelas, J., Lynch, G., Brecha, N., Cotman, C., GLobus, A., 1974. Spine loss and regrowth in hippocampus following deafferentation. Nature 248, 71–73.
Pattwell, S.S., Bath, K.G., Casey, B.J., Ninan, I., Lee, F.S., 2011. Selective early-acquired fear memories undergo temporary suppression during adolescence. Proc. Natl. Acad. Sci. U. S. A. 108, 1182–1187.
Pattwell, S.S., Liston, C., Jing, D., Ninan, I., Yang, R.R., et al., 2016. Dynamic changes in neural circuitry during adolescence are associated with persistent attenuation of fear memories. Nat. Commun. 7, 11475.
Pavlides, C., Watanabe, Y., Magarinos, A.M., McEwen, B.S., 1995. Opposing role of adrenal steroid type I and type II receptors in hippocampal long-term potentiation. Neuroscience 68, 387–394.
Penz, M., Stalder, T., Miller, R., Ludwig, V.M., Kanthak, M.K., Kirschbaum, C., 2018. Hair cortisol as a biological marker for burnout symptomatology. Psychoneuroendocrinology 87, 218–221.
Pitman, R.K., Gilbertson, M.W., Gurvits, T.V., May, F.S., Lasko, N.B., et al., 2006. Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. Ann. N. Y. Acad. Sci. 1071, 242–254.
Poskitt, D.C., Barnett, J., Duffey, K., Lee, A.K., Kimpton, W.G., Muller, H.K., 1984. Stress related involution of lymphoid tissues in Australian marsupial mice. Immunobiology 166, 286–295.
Pruessner, J.C., Hellhammer, D.H., Kirschbaum, C., 1999. Low self-esteem, induced failure and the adrenocortical stress response. Personality Individ. Differences 27, 477–489.
Pruessner, J.C., Baldwin, M.W., Dedovic, K., Renwick, R.M., Mahani, N.K., Lord, C., et al., 2005. Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. NeuroImage 28, 815–826.
Reul, J.M., DeKloet, E.R., 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology 117, 2505–2511.
Rohleder, N., 2018. Burnout, hair cortisol, and timing: hyper- or hypocortisolism? Psychoneuroendocrinology 87, 215–217.
Romeo, R.D., 2017. The impact of stress on the structure of the adolescent brain: implications for adolescent mental health. Brain Res. 1654, 185–191.
Romeo, R.D., Bellani, R., Karatsoreos, I.N., Chhua, N., Vernov, M., et al., 2006. Stress history and pubertal development interact to shape hypothalamic-pituitary-adrenal axis plasticity. Endocrinology 147, 1664–1674.
Sandstrom, N.J., Williams, C.L., 2001. Memory retention is modulated by acute estradiol and progesterone replacement. Behav. Neurosci. 115, 384–393.
Sapolsky, R., 1992. Stress, the Aging Brain and the Mechanisms of Neuron Death. Cambridge MIT Press 1: 423.
Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986. the neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr.Rev. 7, 284–301.
Seeman, T., Epel, E., Gruenewald, T., Karlamangla, A., McEwen, B.S., 2010a. Socio-economic differentials in peripheral biology: cumulative allostatic load. Ann. N. Y. Acad. Sci. 1186, 223–239.
Seeman, T., Gruenewald, T., Karlamangla, A., Sidney, S., Liu, K., et al., 2010b. Modeling multisystem biological risk in young adults: the coronary artery risk development in Young adults study. Am. J. Hum. Biol 22, 463–472.
Sheline, Y.I., 2003. Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiat. 54, 338–352.
Sierra, A., Gottfried-Blackmore, A., Milner, T.A., McEwen, B.S., Bulloch, K., 2008. Steroid hormone receptor expression and function in microglia. Glia 56, 659–674.
Sorrells, S.F., Sapolsky, R.M., 2007. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav. Immun. 21, 259–272.
Sorrells, S.F., Caso, J.R., Munhoz, C.D., Sapolsky, R.M., 2009. The stressed CNS: when glucocorticoids aggravate inflammation. Neuron 64, 33–39.
Starkman, M.N., Giordani, B., Gebarski, S.S., Schteingart, D.E., 2003. Improvement in learning associated with increase in hippocampal formation volume. Biol. Psychiat. 53, 233–238.
Stavreva, D.A., Wiench, M., John, S., Conway-Campbell, B.L., McKenna, M.A., et al., 2009. Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. Nat. Cell Biol. 11, 1093–1102.
Sterling, P., Eyer, J., 1988. Allostasis: a New paradigm to explain arousal pathology. In: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition and Health. John Wiley & Sons, New York, pp. 629–649.
Steudte-Schmiedgen, S., Kirschbaum, C., Alexander, N., Stalder, T., 2016. An integrative model linking traumatization, cortisol dysregulation and posttraumatic stress disorder: insight from recent hair cortisol findings. Neurosci. Biobehav. Rev. 69, 124–135.
Szyf, M., McGowan, P., Meaney, M.J., 2008. The social environment and the epigenome. Environ. Mol. Mutagen. 49, 46–60.
Tomasdottir, M.O., Sigurdsson, J.A., Petursson, H., Kirkengen, A.L., Krokstad, S., et al., 2015. Self reported childhood difficulties, adult multimorbidity and allostatic load. A Cross-sectional analysis of the Norwegian HUNT study. PLoS One 10 e0130591.
Valk, S.L., Bernhardt, B.C., Trautwein, F.M., Bockler, A., Kanske, P., et al., 2017. Structural plasticity of the social brain: differential change after socio-affective and cognitive mental training. Sci. Adv. 3 e1700489.
van der Werff, S.J., Pannekoek, J.N., Andela, C.D., Meijer, O.C., van Buchem, M.A., et al., 2015. Resting-State functional connectivity in patients with Long-term remission of Cushing's disease. Neuropsychopharmacology 40, 1888–1898.
van Praag, H., Kempermann, G., Gage, F.H., 1999. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. 2, 266–270.
van Rossum, E.F.C., Binder, E.B., Majer, M., Koper, J.W., Ising, M., et al., 2006. Polymorphisms of the glucocorticoid receptor gene and major depression. Biol. Psychiat. 59, 681–688.
Vyas, A., Mitra, R., Rao, B.S.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. 22, 6810–6818.
Waddington, C.H., 1942. The epigenotype. Endeavoour 1, 18–20.
Wang, Y., Zhang, L., Kong, X., Hong, Y., Cheon, B., Liu, J., 2016. Pathway to neural resilience: self-esteem buffers against deleterious effects of poverty on the hippocampus. Hum. Brain Mapp. 37, 3757–3766.
Wiley, J.F., Gruenewald, T.L., Karlamangla, A.S., Seeman, T.E., 2016. Modeling multisystem physiological dysregulation. Psychosom Med. 78, 290–301.
Young, E.A., Haskett, R.F., Grunhaus, L., Pande, A., Weinberg, M., et al., 1994. Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. Arch Gen. Psychiatry 51, 701–707.
Zigmond, R., McEwen, B.S., 1970. Selective retention of oestradiol by cell nuclei in specific brain regions of the ovariectomized rats. J. Neurochem 17, 889–899.