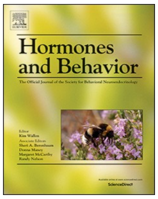
Hormones and Behavior 122 (2020) 104742

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh



Review article

An updated field guide for snark hunting: Comparative contributions to behavioral neuroendocrinology in the era of model organisms[☆]

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ARTICLE INFO

Keywords:
Comparative
Social brain network
Sexual differentiation
Context-dependency

ABSTRACT

Studying neuroendocrine behavioral regulatory mechanisms in a variety of species across vertebrate groups is critical for determining how they work in natural contexts, how they evolved, and ultimately what can be generalized from them, potentially even to humans. All of the above are difficult, at best, if work within our field is exclusively done in traditional laboratory organisms. The importance of comparative approaches for understanding the relationships between hormones and behavior has been recognized and advocated for since our field's inception through a series of papers centered upon a poetic metaphor of Snarks and Boojums, all of which have articulated the benefits that come from studying a diverse range of species and the risks associated with a narrow focus on “model organisms.” This mini-review follows in the footsteps of those powerful arguments, highlighting some of the comparative work since the latest interactions of the metaphor that has shaped how we think about three major conceptual frameworks within our field, two of them formalized – the Organization/Activation Model of sexual differentiation and the Social Brain Network - and one, context-dependency, that is generally associated with virtually all modern understandings of how hormones affect behavior. Comparative approaches are broadly defined as those in which the study of mechanism is placed within natural and/or evolutionary contexts, whether they directly compare different species or not. Studies are discussed in relation to how they have either extended or challenged generalities associated with the frameworks, how they have shaped subsequent work in model organisms to further elucidate neuroendocrine behavioral regulatory mechanisms, and how they have stimulated work to determine if and when similar mechanisms influence behavior in our own species.

1. Introduction

Years prior to the first edition of Hormones and Behavior that we are celebrating in this special issue, Frank Beach wrote an article in which he articulated his concern that scientists interested in the mechanisms of animal behavior, including that of humans, were losing sight of the very essence of behavior. The reason for his concern was the increasingly narrow focus on Norway rats that accompanied the rise of Behaviorism. The Snark was, in Beach's poetic metaphor, becoming a Boojum. For those unfamiliar with the poem by Lewis Carol, in it a hunting party sets out after Snark (presumably a genus), most species of which are quite safe to hunt, save the Boojum, the very sight of which will make a hunter vanish. According to Beach, in sighting the Norway rat and becoming mesmerized by the ease with which it could be studied in the lab, scientists studying natural behavior had begun to disappear.

But even as he worried about the channelization of work on the mechanisms of behavior into lab rats, he did see hope in the growing field of neuroethology, which was focusing on studies of behavior in naturalistic and evolutionary contexts. Indeed, Beach was prescient in foreseeing a vibrant study of animal behavior if the fields of Comparative Psychology and Neuroethology could merge, which has, to some degree, happened in the modern era of Behavioral Neuroscience, in which our own field, Behavioral Neuroendocrinology, is embedded. As we now (I hope) hammer home to our students, to understand the fundamental neuroendocrine mechanisms at the heart of behavior we need to determine if and how hormones work across a range of species. The similarities, of course, represent those fundamental operating principles that are likely widespread in the animal kingdom, either because they have been directly passed down by ancestral species or because they offer a common means, perhaps rooted in deep gene homologies, to solve similar problems when they arise in different groups of animals. And the disparities in how hormones work across organisms demonstrate the range of possibilities that exist within

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[☆] This paper belongs to special issue VSI: 50th Anniversary of H&B.

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https://doi.org/10.1016/j.yhbeh.2020.104742
Received 8 December 2019; Received in revised form 7 March 2020; Accepted 10 March 2020

nature to solve problems, and sometimes highlight the limits of initially oversimplified theories of hormone actions. Such disparate findings therefore open the door to future discoveries about the very essence of animal behavior, which many of us believe is rooted, at least in part, within the mechanisms under study in our labs.

Indeed, it was clear nearly 30 years ago that such integration had kept us all, as Beach feared we otherwise might, from disappearing, as was eloquently pointed out in “Has the Snark Become a Boojum,” Elizabeth Adkins-Regan's response to Beach's original paper (Adkins-Regan, 1990). In that now classic article, Adkins-Regan highlighted some of the diverse species that scientists interested in behavioral neuroendocrinology have studied since Beach. She also articulated many of the most compelling reasons for using comparative approaches and documented exemplars of the advances that have come from them. Several of the reasons she championed are worth repeating, or at least paraphrasing, for the sake of brevity: for the “sheer love of the species” or because the animal is “unusual” in some way; to determine how an organism has solved a unique environmental problem; to test the generalizability of what has been found in one organism, or group of organisms; to test specific hypotheses, perhaps about how hormones should affect behavior in particular ecological contexts or in relation to other effects the hormone has on physiology; to determine when particular hormone mechanisms evolved through phylogenetic analyses, and to determine if similar ecological or social conditions led distantly related organisms to solve the challenges of their environments through the convergent evolution of similar mechanisms. While not all of the studies she cites used truly comparative methods – the direct comparison of neuroendocrine mechanisms across species – they are all comparative at heart, having been designed and interpreted in the context of a broad body of work across species. However, I would argue (and believe that Adkins-Regin might agree), that the most powerful of the studies she cited, and of those discussed in this paper, are the hypothesis-driven ones that compared hormone regulatory mechanisms in closely related species that face different social/ecological challenges to understand why they evolved and the natural contexts in which they operate today.

Despite such strong arguments for comparative approaches and clear evidence of their power, Beach's concerns from over 50 years ago remain relevant in today's world of “model organisms,” themselves all potential Boojums. Indeed, Phelps et al. (2010) reconsidered the Boojum metaphor in light of that issue, noting the inability of a limited number of “model organisms” to represent the range of human conations, the impossibility, as Adkins-Regan had also noted, generalizing from studies in a few, often distantly related species, and the inability to determine the mechanisms that give rise to intraspecific variability from work in inbred laboratory animals.

Additionally, there is a problem with the Boojum metaphor itself that we should consider as comparative neuroendocrinologists. That is, who among us wants to only hunt Snark if they provide, as described in the poem, “a meager and hollow meal,” even if they do, as noted by Phelps et al., at least pair well with greens? Thankfully, the broad range of work reviewed by Adkins-Regan and the vole work synthesized by Phelps et al. have made it clear that the hunters in Carol's party were mistaken, and that some species of Snark, if chosen, for example, to explore a new type of hormone mechanism, test novel contexts in which a hormone might work, or asses the limits of established models of hormone action, can provide quite substantial meals. Nonetheless, while it is important to study a range of species to identify common operating principles, or “Rules of Life,” per the language of the National Science Foundation, if care is not taken when choosing a species, or the endeavor is purely descriptive, those efforts *can* result in meager outcomes, in terms of jobs, grants, publications and/or promotions. This is particularly true in an age when it is possible to measure and manipulate neuroendocrine regulatory mechanisms with the precision that work in “model organisms” has made possible. Thus, even the most comparative-minded among us should recognize, and appreciate, that somewhere along the way technology made it possible to successfully hunt Boojums, which proved to be exciting and fruitful, and that the study of behavior did not, as a result, completely disappear. Further, the technical advances developed in fruit flies, nematodes, zebrafish and laboratory mice, in particular, have so greatly increased the precision with which we can identify and manipulate individual neurons within circuits that control behavior, including those upon which hormones act, that studies lacking such precision will, like it or not, have less and less impact moving forward. But thanks to the work of many of those cited in this article, we are now begging to adapt the technologies developed in those species into more and more organisms operating in the “real world,” with all of their genetic diversity, unique ecological and social contexts, life-history transitions, and different degrees of phylogenetic relatedness. In so doing, we will avoid an increasingly narrow focus on a small number of “model organisms” from which it is difficult to generalize, and work in species currently given that label will be considered alongside work in many others, each in the context of their own unique evolutionary heritage. Scientists like Katz (2016) have pushed us to move in that direction, even advocating that we drop the label “model organism” altogether (hence my use of scare quotes throughout). And such arguments are not occurring within a vacuum - the National Science Foundation, at least, is promoting the growth of such work through initiatives like EDGE and NeuroNex, which fund research that will develop advanced technologies in species that are not typically considered “model organisms.” As a result of such development, comparative approaches will undoubtedly make greater and greater contributions to our understanding of hormone – behavior relationships in the future. However, this presumes that we will not reduce all of the species in which such technologies are developed into “model organisms” with the inherent problems of domestication and loss of genetic diversity that often arise from the husbandry associated with such technological development and which make generalizations difficult. Further, it presumes that we will avoid becoming overly reliant upon standardized laboratory testing procedures that often accompany attempts to scale up work in “model organisms,” but which can lose touch with the natural contexts in which hormones work within an animal's unique life-history. Thus, there should always be special place for field work, which represents the gold standard for studying hormone mechanisms in natural contexts, particularly for studies that find creative ways to employ advanced technologies in those conditions.

Working off the modified metaphor that we should balance traditional Snark hunting with efforts to go after Boojum, dangerous as it may be, I will briefly highlight some of the major contributions that comparative studies have made to our field, avoiding those highlighted by Adkins-Regan (1990) or Phelps et al. (2010) in their iterations of the poetic metaphor. I will also discuss how comparative approaches have often informed subsequent studies in traditional lab animals to elucidate mechanism with greater precision and/or in humans to see if and how those mechanisms translate to our own species. I will close by discussing studies conceptualized within a comparative framework in which technologies developed in “model organisms” are being deployed in species not traditionally given that label. Such studies are making it possible to identify and manipulate neuroendocrine regulatory mechanisms “in the real world,” by which I mean in natural and evolutionary contexts, with the same precision currently possible in “model organisms.” This mini-review, like those of Beach, Adkins-Regan, and Phelps et al., will largely focus on work related to social regulation, though comparative approaches have clearly also made significant contributions to our understanding of hormone mechanisms involved in stress, appetite, and even cognition. Unfortunately, I will also fall short of Beach's admonition that we should be reporting more work in insects.

2. Comparative contributions to understanding sexual differentiation

If one takes a broad perspective on comparative approaches, whereby the choice to study a species because of a compelling aspect of its life history qualifies it for inclusion, then one can argue that the most influential framework for understanding sexual differentiation, and how sex steroids generally affect behavior, originated from a comparative approach. The Organization/Activation Model, which attributes the development of sex differences to a serial set of actions from genetic sex to, ultimately, brain/behavioral sex, with testosterone being the hormonal driver, came from work in guinea pigs that took advantage of the long gestation in that species to manipulate the hormonal environment of the offspring *in utero* (Phoenix et al., 1959).

Since the model's inception, comparative approaches have also been critical for establishing what can be generalized and extended from that model, as well as providing early indications of its limits. Early work in birds extended the model by showing that the key steroid hormones are those associated with gonadal development in the heterogametic sex (Adkins, 1975, 1976), and work in lizards and turtles demonstrated that environmental factors, particularly incubation temperature, can replace the genetic switch and drive active, steroidogenic-dependent mechanisms of sexual differentiation in both sexes (Crews et al., 1994; Gutzke and Crews, 1988). Further, that behavioral effects of sex steroids, in development or adulthood, are associated with the establishment of morphological sex differences in the brain was first reported in birds (Nottebohm and Arnold, 1976). However, comparative work also offered early challenges to the central tenant of the Organization Model that early elevations of sex hormones, once the gonads develop, are the sole drivers of all subsequent differentiation processes. Work in marsupials (wallabies) demonstrated somatic differentiation that precedes gonadal maturation (O et al., 1988), and subsequent studies in birds showed that masculinization of the brain and some behaviors, notably song in zebra finches (Wade and Arnold, 1996; Wade et al., 1996) and sexual behavior in Japanese quail (Gahr, 2003), can likewise be dissassociated from gonadal sex. Ultimately, transgenic mice in which the genetic locus that determines gonadal differentiation could be dissociated from other genes on the Y-chromosome were developed, which conclusively demonstrated that not all masculine/feminine phenotypes are uniformly coordinated by gonadal hormones, but rather that some depend on direct gene actions independent of gonadal differentiation, even in mammals (De Vries et al., 2002; Gatewood et al., 2006). It can thus be argued that comparative challenges to the established Organization model drove the development of approaches in a “model organism” that allowed us to begin unraveling, with more and more precision, the complexity of sexual differentiation processes. That work recently culminated in a comprehensive theory of sexual differentiation that acknowledges the importance of heterogametic sex chromosome genes important for gonadal differentiation and the subsequent, downstream consequences of sex hormones, but also emphasizes the contributions of heterogametic sex chromosome genes not involved in gonad development, the dosing of homogametic sex chromosome genes, experience, and complex interactions among all those factors (Arnold, 2017).

Additionally, comparative approaches gave early indications that sexual differentiation does not always lead to a brain with circuits that support only male- or female-typical behaviors. Again, it was work in lizards, this time an all-female parthenogenic species of whiptail lizards, which demonstrated that females could display female- or male-typical courtship, depending on their reproductive state (Crews and Fitzgerald, 1980; Moore et al., 1985). Although clearly a derived trait in Cnemidophorus lizards, results from sex-changing fish were also consistent with the idea that brains could be bi-potential, as transitions from the expression of female-typical to male-typical behaviors were shown to occur almost immediately after the environmental conditions that trigger sex-change, independent of the gonads and rather in association with changes in brain vasotocin (Godwin et al., 1996; Godwin et al., 2000; Semsar and Godwin, 2003). Initially, these kinds of findings were seen as incredible examples of the diversity that exists in nature for sexual differentiation of the brain, but perhaps as little else by researchers entrenched in the dichotomous male/female brain framework that continued to dominate from work with conventional laboratory species. However, these findings again foreshadowed work in mice indicating that both male and female circuits are present and capable of producing behavioral output, even in mammals, once the presence of olfactory inhibition that typically occurs in mating contexts is removed (Kimchi et al., 2007). While it must be noted that some follow up tests have produced results inconsistent with those findings (Baum, 2009), and that even proponents of strict organization models would agree there is some masculinization of female brains from *in utero* testosterone exposure in some species, the work nonetheless highlights that mammals, like other vertebrates, show something other than “either-or” sexual brain circuit organization. Together with the aforementioned work demonstrating the diversity of mechanisms that influence sexual differentiation of the brain and behavior, originally described in fish, lizards, and birds, but eventually in model, transgenic organisms as well, it should not be surprising that recent research has demonstrated a compelling case for sexually mosaic brains and behavior in humans, likely the result of unique contributions from multiple developmental mechanisms interacting with individual experiences (Joel et al., 2015).

Finally, although the original work in ring doves showing that social experience can induce the immigration of mast cells into the brain was not in the context of sexual differentiation, the work did suggest the phenomenon is associated with reproductive function because those cells were immunoreactive for gonadotropin-releasing hormone (Zhuang et al., 1993). Thus, they foreshadowed recent work elegantly demonstrating that mast cell mechanisms underlie how testosterone induces masculinization in laboratory rodents (Lenz et al., 2018). This example, as well as those outlined above, suggest that data from comparative studies, while sometimes appreciated for demonstrating interesting, but idiosyncratic things that “other” organisms do, may actually hold early clues about deeper, fundamental mechanisms associated with neuroendocrine signaling across vertebrates.

3. Comparative contributions to the social behavior network

Perhaps nowhere have comparative approaches played a larger role in establishing the generalities of a theoretical framework than they have in broadening our understanding of the neural Social Behavior Network (SBN). The conceptual framework of the SBN was originally proposed by Sarah Newman to describe how a core network of interconnected, steroid-sensitive subcortical nodes within rodent brains produce different social outputs through unique patterns of activity across the network, in which each node contributes to the expression of multiple social outputs (Newman, 1999). Subsequent work in reptiles, birds, and fish clearly established that the core nodes are all steroid sensitive, highly interconnected, and each involved in the regulation of multiple social outputs {see comprehensive reviews in (Goodson, 2005; Goodson and Kabelik, 2009; Goodson and Kingsbury, 2013; O'Connell and Hofmann, 2011)}. Further, comparative work has demonstrated that hormones can change patterns of activity across the network in relation to their promotion of context-dependent behavioral output. For example, in white-throated sparrows the same social stimulus (male song) can induce distinct patterns of activity across the network in females in different reproductive contexts as a function of levels of circulating estradiol (Maney et al., 2008). Additionally, oxytocin antagonist treatments that disrupt pair bonding in prairie voles also decrease the correlated activation across core nodes of the SBN, as well as several in an extended pair bond network (see further discussion below), that otherwise occurs when the animals mate (Johnson et al., 2016). Work in lizards and fish has also indicted that distinct patterns of activation within the SBN are associated with responses to different types of social stimuli. In brown anoles, sexual responses are associated with increases in functional connectivity within the core nodes of the network, but agonistic responses with decreases (Kabelik et al., 2018), and in Mozambique tilapia unique patterns of activation within the SBN are associated with perceptions of, and aggressive responses toward, different social stimuli in the absence of correlations between activation in any given node and those responses (Almeida et al., 2019). An earlier study in Tungara frogs likewise tested if distinct patterns of activity across brain networks are associated with different social outputs, though it did not specifically focus on patterns within the core SBN (Hoke et al., 2007). What was striking about that work, however, was that the distinct patterns of activity associated with responses to different social stimuli were primarily between forebrain networks that include, but are not limited to, traditional SBN nodes and midbrain sensorimotor integration areas, most notably the torus semicircularis (inferior colliculus homologue), not the core premotor area associated with SBN motor output, the periaqueductal gray. The work therefore suggests that a key role of hormones and neuroendocrine modulators could be to link the core SBN nodes to sensorimotor integration mechanisms directly involved processing social stimuli and/or transforming associated neural responses into behavioral output, not simply changing patterns of activity within the core network. Consistent with that possibility, the work discussed above showing that an oxytocin antagonist can influence patterns of activation across several traditional SBN nodes also found that it changed the coupling of activity between those nodes and a more extended pair bond network that included a presumed sensory input nucleus, the accessory olfactory nucleus (Johnson et al., 2016). Work in roughskin newts has also demonstrated the importance of neuroendocrine modulation within sensorimotor brain regions outside of, but linked to, core nodes of the SBN (Rose and Moore, 2002). For example, the processing of somatosensory cues associated with the pressure of a female on a male's cloaca in hindbrain neurons that integrate that sensory input into the maintenance of a courtship clasp is enhanced by the pheromonal activation of vasotonergic input, likely originating from one of the core SBN nodes in which it is produced (Thompson et al., 2008). Comparative work also suggests that activity within the SBN could be gated by hormone effects on early stages of sensory processing; in stingrays and plainfin midshipman, chronic sex steroid manipulations alter sensitivity of the auditory nerve to the electrical and auditory signals used for reproductive communication in those species, respectively (Sisneros et al., 2004; Sisneros and Tricas, 2000), thus filtering the information that can reach the SBN across different seasons/reproductive contexts. Additionally, in goldfish testosterone can, through its aromatization to estradiol, rapidly amplify retina responses to the visual stimuli of potential mates, allowing immediate social/environmental contexts to gate what likely gets to the SBN to activate behavioral responses (Yue et al., 2018).

A limitation of the SBN model that has thus become evident from comparative work is that our conceptualization of the network is too narrow, from the recognition that conserved meso-limbic reward circuits need to be linked to the SBN across vertebrates into a Social Decision-Making Network (SDN), as argued by O'Connell and Hofmann from a comprehensive review of gene expression, anatomical, and behavioral studies across vertebrates (O'Connell and Hofmann, 2011), to the need to include sensorimotor coupling mechanisms into the SBN, as discussed above. Further, comparative studies highlight the need to include additional forebrain nodes. For example, knockdowns of nonapeptides in the vasopressin/oxytocin family in the paraventricular nucleus reduce gregariousness in finches (Kelly and Goodson, 2014), indicating this nucleus, typically conceived as part of a stress network, also plays a role in social regulation. Additionally, studies in prairie voles have shown the importance of nonapeptide links between traditional SBN nodes where the peptides are produced and hippocampal and cortical regions where their release likely modulates key social functions (Phelps et al., 2010). What is now needed are more tests using statistical network analyses like those discussed above of whether distinct patterns of activity within the core SBN nodes are associated with different social outputs across a wider range of species, as well as tests of whether hormones change the functional coupling between the network, as a whole, with sensory, sensorimotor, and/or cortical processing regions potentially involved in complex social decisions. Work in prairie voles has demonstrated that oxytocin signaling in the nucleus accumbens is critical for the coupling of activity in that reward-related extension of the SDN with the traditional core of the SBN (Johnson et al., 2017), but it is possible that neuroendocrine signals may affect the coupling of core nodes to even more extended sensorimotor or cortical processing regions. Ultimately, comparative work will be critical for determining if and how we need to expand the SBN model further because of the range of sensory inputs and motor outputs that occur across species. This is especially important because, as was argued by Hoke and Pitts (2012), what may be true of the neuroendocrine mechanisms that mediate social responses to pheromones typically used by the rodents in which the concept of an SBN was originally developed may not easily generalize to species in which a variety of different social signals are used, and in which motor output related to expressions of social behavior can be quite diverse. However, as we interpret the data from those studies it will be important to distinguish the truly fundamental network properties that are critical for social regulation across vertebrates from those that are specialized to support species-specific behavioral repertoires, which will likely be vast, lest we become bogged down by a plethora of networks that obscure the generalities that should be represented by a truly robust model of behavioral organization.

It will also be critical that we ultimately adopt the tools developed in model organisms to achieve the resolution made possible by that work for the study of SBN networks in non-traditional organisms. For example, recent work in mice using single cell, multiplexed, error-resistant fluorescent *in situ* hybridization (MERFISH) has made it possible to subdivide nodes within the SBN, thus far the preoptic area (Moffitt et al., 2018) and ventromedial hypothalamus (Kim et al., 2019), into unique clusters based on transcriptome profiles. Those studies have shown that, at least within those nuclei, some clusters uniquely active immediate early gene responses to particular social stimuli, consistent with a columnar, "labelled lines" pattern of organization, and some to multiple types of social input, consistent with the SBN patterned activity model in which the same cell groups should contribute to multiple social outputs. Similarly, integrated electrophysiological and genetic approaches have shown that some, but not all, estrogen-sensitive cells in the ventromedial hypothalamus selectively respond to aggressive/dominance or mating related stimuli, respectively (Hashikawa et al., 2017; Lin et al., 2011). Furthermore, some of those cells exclusively modulate output related to aggression or mating, while others can influence both types of social outputs, depending on their level of activation (Lee et al., 2014). These elegant studies have thus confirmed, as was originally proposed by Goodson and Kabelik (2009) based upon a survey of work done in a variety of species, from songbirds to laboratory rodents, that columnar patterns of circuit organization *and* patterned activity across social brain networks play roles in social organization. Undoubtedly, work in laboratory mice and other "model organisms" will help us probe, with increasing resolution, how individual cells, including those that are sensitive to hormones, act within columnar circuits and across distributed neural networks to regulate social behavior. However, to fully establish the generalities of any such findings, as well as to generate new insights into how such mechanisms work in natural contexts, it will also be critical to develop and employ similar techniques in ecologically-relevant behavioral tests across a range of species whose social interactions are associated with diverse sensory inputs and motor outputs. Ultimately, such comparative approaches will be necessary to fully evaluate the utility of the SBN model for understanding how hormones act within the brain to modulate social behaviors in the real world of nature.

4. Comparative frameworks and context dependent hormone mechanisms

Finally, I would like to highlight comparative approaches that have shaped the way we think about how hormones allow animals to match behavioral output to social and environmental contexts, above and beyond how changes in patterned activity within the SBN may relate to context-dependent behavioral output, as discussed above. Most notably in that regard is the development of the Challenge Hypothesis by John Wingfield after he demonstrated that a simulated territorial intrusion in song sparrows can induce a rapid surge in circulating testosterone (Wingfield, 1985). Although it was already known that sexual stimuli can induce surges of gonadotropins, the speed with which testosterone was elevated by a social challenge was unprecedented, and likely the result of direct neural stimulation rather than a secondary consequence of gonadotropin elevations. This led Wingfield and colleagues to propose that the surges facilitate behavioral responses that promote reproductive success in the face of such a challenge (Wingfield et al., 1990). That work, and a tremendous amount of research that followed, much of it comparative, is reviewed by several of the scientists who developed the original framework, as well as by numerous researchers who have contributed to its growth since then, in a recent special issue of Hormones and Behavior (Wingfield et al., 2019). Therefore, I will not track the impact it has had in this article, other than to say that it was a key to understanding how steroid hormones help shape behavioral responses to immediate social contexts. However, I will suggest here, as one for whom this was certainly true, that the theoretical framework of the Challenge Hypothesis, developed from a comparative approach, played a significant role in stimulating the burgeoning body of work on non-genomic mechanisms of steroid action as we tried to find a mechanism through which steroid surges *could* rapidly impact ongoing behavior, something that seemed impossible through classic genomic mechanisms. Conversely, if the Challenge Hypothesis is viewed in a larger context and extended to encompass rapid steroid fluctuations in response to a variety of stimuli that help animals adapt behavioral responses to changing social environments, then it has provided the natural context in which rapid neurophysiological and behavioral effects of steroids operate. For example, the rapid elevations of 11-keto-testosterone that occur in male gulf toadfish in response to the vocalizations of other males can rapidly alter their own vocalization rates through rapid androgenic influences on neurons within the hindbrain motor circuit that produces those vocalizations (Remage-Healey and Bass, 2006). Comparative work, particularly that done in birds, also extended the original Challenge framework to encompass not only the actions of peripheral surges in steroids, but also socially-induced surges in neurosteroids in the brain. Following up on work in zebra finches demonstrating that the brain is capable of synthesizing its own steroids (London et al., 2006; Schlinger and Arnold, 1992), Remage-Healey and colleagues demonstrated that social stimuli (song) can rapidly increase local estradiol synthesis within brain regions that process song, and that those local surges can rapidly shape the perception of song (Remage-Healey et al., 2010; Remage-Healey et al., 2008). Additionally, elevating estradiol in song sparrows rapidly increases aggression, though only outside of the breeding season when peripheral levels of steroids are low but when social stimuli alter local steroid synthesis in the brain (Charlier et al., 2011; Heimovics et al., 2015). Likewise, estradiol only produces rapid, non-genomic effects on aggression in short-day photoperiods characteristic of the non-breeding season in Siberian hamsters (Laredo et al., 2013). Estradiol also rapidly increases aggression in white-throated sparrows, likely also reflecting the actions of endogenous elevations in local brain regions during social interactions, but only in a particular morphologic phenotype (white-stripe animals) in which a gene inversion has changed functions of the ERα receptor (Merritt et al., 2018). Together, these comparative studies not only demonstrate rapid neurosteroid effects on behavior, but that those mechanisms must be considered in light of how they operate in natural and evolutionary contexts because they only influence behavior at certain times of year and/or in partiuclar phenotypes, depending on the species. Studies in songbirds are also beginning to extend the social contexts, and hormonal players, to which principles of the Challenge Hypothesis apply; food deprivation rapidly increases aggression, circulating dehydroepiandrosterone, and local estradiol in brain regions that control aggression, suggesting that aggression in response to food competition may be causally linked to the rapid conversion of elevated dehydroepiandrosterone into estradiol in the brain (Fokidis et al., 2013). Work in birds has even demonstrated *how* social stimuli can produce rapid, local changes in steroid synthesis; in Japanese quail, social stimuli rapidly alter the phosphorylation of aromatase through changes in glutamate release, thereby altering the enzyme's kinetics and thus local estradiol production (Balthazart et al., 2001, 2006; de Bournonville et al., 2017). That such locally produced estradiol likely modulates synaptic functions had already been suggested by observations, also in quail, of aromatase localized in axon terminals (Balthazart and Foidart, 1993). In true comparative spirit, those findings were subsequently extended to rodents and primates, including humans, to establish the generality of the enzyme's role in modulating synaptic chemistry (Naftolin et al., 1996). Importantly, this comparative work, much of it stimulated, directly or indirectly, by Wingfield's initial formulations of the Challenge Hypothesis, laid the groundwork for elegant studies recently done in humans on rapid, presumably non-genomic effects of testosterone on human aggression that appear related to rapid elevations of T in aggressive contexts, though those effects appear to depend on direct androgen receptor activation, not aromatization and subsequent ER activation (Carre et al., 2017; Geniole et al., 2019; Welker et al., 2017).

While comparative work has thus greatly contributed to our understanding of how rapid steroid fluctuations, in circulation or locally within the brain, can alter ongoing behavior, comparative work in mammals was also the first to demonstrate long-term consequences of those fluctuations. The fluctuations in testosterone that occur in California mice, but not in the closely-related white-footed mice, work together with the experience of winning the fight to increase aggression and the likelihood of winning in future encounters (Fuxjager et al., 2011). This work is not only elegant for confriming a long-standing hypothesis that surges in steroid hormones might alter future behaviors through the classic genomic mechanism, but also for pointing out, once again, that such mechanisms only operate in particular evolutionary contexts.

Finally, with regard to understanding how neuroendocrine mechanism work in relation to social context, I would be remiss if I did not include work on vasopressin/oxytocin, including, in case you are purist, their non-mammalian homologues, vasotocin/mesotocin/isotocin. Since the early work in roughskin newts showing a central effect of vasotocin on courtship behavior (Moore and Miller, 1983), a wide-body of comparative work has demonstrated a great deal of species diversity and sex differences in how nonapeptides in this family affect behavior as a function of the differential development of circuits that support distinct behaviors across species or between the sexes and/or differences in patterns of receptor expression within those circuits (see comprehensive reviews in Albers, 2015; Godwin and Thompson, 2012; Goodson and Bass, 2001; Goodson and Thompson, 2010). Comparative approaches also made it clear, while documenting species differences in the effects of the nonapeptides, that they also produce context-dependent effects. For example, in the gregarious zebra finch, vasotocin promotes aggression in mate-competition contexts, but inhibits it in colonial, group-living contexts (Goodson and Kabelik, 2009; Kabelik et al., 2009). In a similar, context-dependent manner, vasopressin facilitates aggression in male prairie voles in association with mating (Winslow et al., 1993), as does vasotocin in medaka (Yokoi et al., 2015). The specific cell groups involved in promoting different, context-dependent effects of these peptides have even been identified in several of these species. In prairie voles and several finches, vasopressin cells in the anterior hypothalamus are responsible for the peptide's stimulation of aggression in pair-bonding/courtship contexts (Gobrogge et al., 2017; Gobrogge et al., 2009; Goodson et al., 2012), whereas vasotocin/vasopressin neurons in the bed nucleus of the stria terminalis respond to positively valanced social stimuli, as first demonstrated in several gregarious finch species and subsequently in laboratory mice, and promote gregariousness while concurrently inhibiting aggression, at least in the group living finches (Goodson et al., 2009; Ho et al., 2010; Kelly and Goodson, 2013).

Further, comparative work has been instrumental for demonstrating that the nonapeptides produce effects that depend not only on context, but also on individual characteristics. In perhaps the most extreme example, the peptides produce different effects on the neural circuity that produces social vocalizations in male plainfin midshipman that adopt territorial or sneaker phenotypes, respectively, with vasotocin and isotocin producing effects in the latter like those observed in females, not their male brethren (Goodson and Bass, 2000). Effects that depend on phenotypic variations that are more commonly observed across vertebrates, particularly those associated with dominance and subordinance, have also been observed; vasotocin stimulates responses related to aggression in dominant animals, while inhibiting aggression and/or promoting subordinance in subordinate individuals in at least one species of weakly electric fish, the banded knifefish (Perrone and Silva, 2018), as well as in violet-eared waxbills (Goodson and Kabelik, 2009). However, even such individual phenotypes can be context-dependent; the same individual may be dominant in one context, or when interacting with a particular individual, and subordinate in another, and comparative work suggests that peptide effects likely depend on such complex interactions. In A. burtoni, a cichlid fish, vasotocin selectively increases aggression in subordinate fish, but only if they are given the opportunity to rise in social status (Huffman et al., 2015). Together, these comparative studies indicate that vasotocin/vasopressin can promote behavioral responses appropriate for the unique social context of an individual. However, in blue-headed wrasse, vasotocin can promote aggressive/territorial responses in subordinates even in conditions in which ascent is otherwise unlikely (Semsar et al., 2001), highlighting the comparative golden rule that generalizations cannot always be universally made across all species, at least not without first understanding how those mechanisms may work in natural contexts. For example, it is possible that in A. burtoni, but not blue-headed wrasse, the receptors that mediate the peptide's stimulation of aggression are modulated by context, so exogenous vasotocin cannot promote aggression until the context changes, whereas in wrasse perhaps only the release of the peptide changes across contexts. Thus, in this case the discrepancy of results across species leads to predictions about mechanism that could differ between species, but ultimately underlie how the same peptide might similarly promote behavioral responses that match social contexts.

In fact, the diversity of effects described across and within species in comparative studies should have been a safeguard against the overgeneralization of oxytocin and vasopressin as “prosocial” molecules that occurred in the initial avalanche of human research that stemmed, in part, from the initial, groundbreaking work demonstrating their roles in pair bonding in prairie voles (*e.g.*, see Debiec, 2007; Ishak et al., 2011; Meyer-Lindenberg, 2008). However, the complexity predicted by the comparative work is now beginning to be reflected within the human literature on these peptides, which has now shown that they produce effects that depend on personality variables/anxiety (Alvares et al., 2012; Bartz et al., 2015; Feng et al., 2015; Ma et al., 2015; Schumacher et al., 2018; Strang et al., 2017), and that they can promote negative/antisocial responses toward others, as well as positive ones, in some contexts (Alcorn et al., 2015; De Dreu et al., 2011; Declerck et al., 2014; Lambert et al., 2017; Shamay-Tsoory et al., 2009). The Social Saliency model that has emerged from these studies (Shamay-Tsoory and Abu-Akel, 2016), whereby oxytocin, at least, amplifies the processing of social cues and promotes context-appropriate responses, is consistent with the diverse effects originally observed in other vertebrate classes. Indeed, the diversity of nonapeptide signaling mechanisms that evolved in different organisms predicts that a range of mechanisms involving distinct circuits may ultimately be discovered in humans, in which complex social pressures likely led to the evolution of multiple regulatory mechanisms similar to those observed across the animal kingdom. Again, it would therefore behoove researchers studying how these molecules work in humans to pay close attention to the diverse mechanisms being documented across a wide-range of species in order to more accurately predict the effects these molecules are likely to have in different individuals and contexts, as well as where within the brain they likely exert those effects.

5. The future of comparative research

As I have alluded to throughout this paper, it is critical that we, as a community of comparative scientists, embrace the advances that have come from those who have engaged in hunts of the Boojum. Rather than disappearing, those scientists developed the tools that will ultimately make it possible for us to better understand the fundamental principles of neuroendocrine regulation, provided the same tools can ultimately be applied in non-traditional organisms. Indeed, there are several examples that already illustrate how powerful that approach can be. Pioneering work in voles applied transgenic and epigenetic approaches to selectively manipulate vasopressin signaling mechanisms and thus determine, with great precision, how they participate in pair-bonding in that species (Wang et al., 2013; Young et al., 1999). More recently, genetic ablation and optogenetic methods have been developed in zebra finches to identify the circuits critical for song learning in that species (Hisey et al., 2018), and CRRISP/Cas9 technologies have been utilized to determine how prostaglandins influence female reproductive behavior in cichlids (Juntti et al., 2016), as well as to study the roles of estrogen receptors in tilapia reproductive functions (Yan et al., 2019). The more that we adapt the tools developed in model organisms to address, with the precision made possible by those technologies, how neuroendocrine signaling mechanisms influence behavior in natural and evolutionary contexts, the greater the impact comparative work will have. And increasing the impact of our work is critical to ensure that scientists now being trained in such approaches will get the jobs and grants necessary for them to carry on with the mission of understanding animal behavior, including its neuroendocrine mechanisms, in natural and evolutionary contexts. It is therefore important to not only train students how to frame questions in such contexts and to utilize the diversity present in nature to answer those questions, but also how to adapt the technologies developed in model organisms into their work with non-traditional species. In sum, we have to be ready to hunt Snark in all its varieties, including the Boojum.

Acknowledgements

I wish to thank Elizabeth Adkins-Regan for feedback on an earlier draft. Additionally, I would like to acknowledge the inspiration that I know the late Jim Goodson provided for so many cited in this paper, myself included. I will always be thankful for his friendship, which challenged and sustained me, professionally and personally, as I developed into a scientist. This work was supported by the National Science Foundation grant # 1656596.

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