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Review article

Theoretical frameworks for human behavioral endocrinology

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ABSTRACT

How can we best discover the ultimate, evolved functions of endocrine signals within the field of human behavioral endocrinology? Two related premises will guide my proposed answer. First, hormones typically have multiple, simultaneous effects distributed throughout the brain and body, such that in an abstract sense their prototypical function is the coordination of diverse outcomes. Second, coordinated output effects are often evolved, functional responses to specific eliciting conditions that cause increases or decreases in the relevant hormones. If we accept these premises, then a natural way to study hormones is to hypothesize and test how multiple eliciting conditions are mapped into coordinated output effects via hormonal signals. I will call these input–output mappings "theoretical frameworks." As examples, partial theoretical frameworks for gonadal hormones will be proposed, focusing on the signaling roles of testosterone in men and on estradiol and progesterone in women. Recent research on oxytocin in humans will also be considered as an example in which application of the theoretical framework approach could be especially helpful in making functional sense of the diverse array of findings associated with this hormone. The theoretical framework approach is not especially common in the current literature, with many theories having eschewed explicit consideration of input–output mappings in favor of parsimony-based arguments that attempt to find the one main thing that a hormone does with respect to psychology or behavior. I will argue that these parsimony-based models have many shortcomings, and conclude that the construction and testing of theoretical frameworks provides a better means of discovering the evolved functions of human endocrine signals.

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1. Introduction

I once asked a 'why' question of a speaker who had just given a fascinating talk on human testosterone responses to competitive interactions. The speaker had reviewed evidence that testosterone may increase after status-promoting victories, which might then promote further status competition. The crux of my question was this: given that testosterone is known to have many effects throughout the brain and body—some of which, like immunosuppression, may be harmful—why use testosterone in particular as a signal that encourages further competition after competitive victories? Why not avoid the costs of testosterone by instead producing the same responses to social events via neurotransmitters within the relevant neural networks? The speaker paused, and then replied: "That, as they say, is a good question."

In sketching possible answers to such why questions, it is likely important that hormones, unlike most neurotransmitters, are often released into the general circulation where they usually have effects on multiple downstream targets. Given this, hormones may be used as signals primarily when multiple outcomes are being produced in a coordinated way. Indeed, as described in the section below, coordination may be the prototypical function[1] of endocrine signals. If we accept this premise, then understanding the functions of hormones becomes an exercise in mapping, for each hormone, the coordinated outputs that it produces in response to the eliciting circumstances associated with release of the hormone.

Let us call the mapping between eliciting conditions and coordinated outputs a "theoretical framework" for a given hormone. Theoretical frameworks will essentially be lists of input conditions associated with increases or decreases in a hormone, combined with lists of output effects associated with such increases or decreases. Insofar as output effects appear to be functional responses to specific elements of the input conditions, a core functional logic for a given hormonal signal may emerge from the theoretical framework. That core logic may then facilitate interpretation of new findings, and may also generate novel hypotheses regarding linkages between variables that should co-occur given the functional logic of the theoretical framework. In what follows, I will first elaborate briefly on the idea of hormones as coordinators, before then proceeding to apply the theoretical framework approach to example endocrine signals that are being actively studied in human field and behavioral endocrinology.

2. Hormones as coordinators

The idea that the prototypical function of hormones is coordination is not an original one, and many scholars have previously emphasized this position. Beach (1974), for instance, described the endocrine system as "an integrated, finely tuned coordinating mechanism sensitive to changes in both the internal and external environment and adapted to promotion of the physiological and behavioral effectiveness of the total organism" (p. 15). Many textbooks on endocrinology open with descriptions of coordinating functions. Adkins-Regan (2005) wrote: "In general, hormones are coordinators: of reproduction, of suites of physiological and behavioral components, of different parts of the brain with body… They help adjust behavior to circumstances and contexts: physical, social, and developmental" (p. 3). Likewise, Ellison (2001) characterized endocrine systems as follows:

> …endocrine glands release specific molecules—hormones—into our general circulation. They are carried throughout the body by the circulatory system, potentially reaching a large majority of our cells. …This system is especially effective in communicating a given signal to lots of target cells, which may be located in many different places. The responses of those targets can be quite different as well, but they will be *coordinated* by their relationship to the common signal. … The endocrine system is the system that the body uses to achieve *integrated* responses among various cells, tissues, and systems, integration that is necessary to many critical biological processes, such as growth, metabolism, and reproduction (p. 13, emphasis added).

Central to the notion of coordination in the above quotes is that the multiple, diverse effects of hormones are *functional* responses to the "circumstances and contexts" associated with changes in hormone production. As a concrete example of functional coordination, consider the multiple effects of elevated circulating androgens in males of many seasonally breeding species during the breeding season (for reviews, see Andersson, 1994; Daly and Wilson, 1983; Folstad and Karter, 1992; Ketterson and Nolan, 1992). Androgens promote the growth of morphological ornaments and armaments involved in inter- or intrasexual competition, respectively, but often obtain energy for such growth in part via inhibitory effects of androgens on fat storage and immune function. These diverse effects in the soma occur simultaneous to androgen effects on brain structures that promote increased behavioral aggressiveness and sexual motivation, often concomitant with reduced time spent foraging or resting. More subtle physiological effects accompany these, such as changes in metabolic rate, sperm production, and levels of hemoglobin (e.g., Evans, 2010; Ketterson and Nolan, 1992). Here, a core functional logic to this coordination emerges, as all of the diverse effects of androgens align to promote effective mate competition precisely when the presence of fecund females means that such competition can promote reproductive success; the fall in androgens during the nonbreeding season then contributes to an alternative alignment of effects that address biological problems other than immediate mate competition. These diverse effects of androgens exemplify nicely Beach's point in the above quote regarding "promotion of the physiological and behavioral effectiveness of the total organism"—the suite of effects considered together promotes mate competition and reproductive success, even if individual effects (e.g., inhibition of some immune responses) may appear harmful.

The above example demonstrates the partial construction of a theoretical framework linking coordinated output responses to specific eliciting conditions in such a way that a basic functional logic of particular endocrine signals begins to emerge. The goal of the rest of the article is to apply this theoretical framework approach to example lines of research in human behavioral endocrinology.

3. Theoretical frameworks in human behavioral endocrinology

As defined earlier, theoretical frameworks map the eliciting conditions that affect hormone release to the output effects caused by changes in hormones. The phrase "eliciting conditions" is meant to be construed very broadly. Thus, it includes both immediate external triggers of hormone release, such as exposure to potential mates, but also internal signals representing dynamic variables such as energy balance. A variable like energy balance may ultimately be linked to ecological variables related to food availability, but may be indexed by internal endocrine messengers (e.g., insulin or leptin) that in turn act as inputs

[1] Throughout the article, function is used as in evolutionary biology: a phenotypic trait is functional if its effects promoted biological fitness on average during the evolution of the trait, and if those effects help explain the trait's origin and maintenance (see Tooby and Cosmides, 1992; Wakefield, 2016; Williams, 1966). On this definition, a trait may be functional even if it produces harmful effects in modern environments, as long as it promoted reproductive success in the environments in which it evolved. A hormone that reduced thresholds for physical aggression may have promoted reproductive success when released in specific circumstances in ancestral environments, for instance, even if those same effects would produce maladaptive outcomes in modern societies in which violence is legally proscribed. An overarching (but reasonable) assumption is that at least some of the signaling properties of human hormones evolved by natural selection because the specific effects of those signals promoted greater lifetime reproductive success relative to alternative phenotypes. Thus, although some properties of hormones may have resulted from selectively neutral evolutionary processes (such as genetic drift), or be by-products of other components of the phenotype, other properties should be functional, and articulating those functions is necessary to achieve a basic science of human behavioral endocrinology.

to yet other hormonal signals (e.g., gonadal hormones; see Ellison, 2001, 2009). Behavior itself may in effect act as an eliciting condition, as when hormones respond to sexual or fighting behaviors; in such cases, there may be complex interactions in which hormones affect behaviors that in turn feed back on hormone production. Other relevant input variables may be more abstract, such as internal registers of an individual's age. Essentially, eliciting conditions can include any internally represented circumstance that may affect the production of endocrine signals and thereby produce endocrine-mediated responses to that circumstance.

Theoretical frameworks can be constructed for either organizational or activational effects of hormones. In fact, the case for coordinating functions of hormones is perhaps clearest when considering organizational (i.e. relatively irreversible, developmental) effects, as with the roles of gonadal hormones in sexual differentiation. There, genetic sex can be considered the eliciting condition that leads to early sex differences in gonadal hormone production, which in turn produce a wide array of sex-typical developmental outcomes distributed throughout the brain and body. Gonadal hormones are known to promote genital, reproductive tract, and other sex-typical morphological development (for a review, see Breedlove, 1992), but simultaneously exert organizational effects in the brain, as exemplified by classic research in rodents showing that early hormone manipulations alter sexual behavior patterns in response to activational administration of hormones in adulthood (e.g., Phoenix et al., 1959). Controlled manipulations of early hormone exposure have demonstrated many other organizational effects in the brain, affecting outcomes such as aggressive behaviors (e.g., Meaney and McEwen, 1986), courtship behaviors like birdsong (e.g., Konishi, 1989), and sex-typical navigation strategies (Williams et al., 1990). Coordinating functions of multiple organizational effects are often obvious: a female reproductive tract needs to be combined with female sexual behaviors and sexually selected reproductive strategies in order to best promote reproductive success, with corresponding arguments applicable to males. Organizational effects of hormones are less comprehensively studied in humans since ethical considerations prevent early hormone interventions, although a number of clinical conditions provide evidence for coordinated morphological and psychological/behavioral effects of early androgen exposure (for reviews, see Collaer and Hines, 1995; Kimura, 2000). Given that activational effects of hormones appear to be the more active area of investigation currently, most of this review will apply the theoretical framework approach to activational effects of particular hormones in humans.

Three example cases will be considered: testosterone in men, estradiol and progesterone in women, and oxytocin in both men and women. The theoretical framework approach has not been consistently applied in any of the three examples, which has often left 'why' questions separated from 'how' questions. At least partial theoretical frameworks for the gonadal hormones have been previously proposed, and these will be described, elaborated upon, and used to organize research findings on these signals in humans. For oxytocin, however, very little of the extant literature has attempted to link natural eliciting conditions to coordinated output effects in the service of discerning functions of this signal in humans. Research on human oxytocin is thus covered as an example of a case for which the construction of a novel theoretical framework may be especially important to bring explanatory coherence to a disjointed research literature.

3.1. Example 1: life history approaches to the signaling roles of testosterone in human males

3.1.1. Overview

Many reviews of the behavioral effects of testosterone in humans do not mention coordinating functions and instead attempt to abstract from research findings the most parsimonious possible description of the role of testosterone in social interactions. For instance, a number of reviews argue against the idea that testosterone's primary role is the regulation of physical aggression, and argue instead that testosterone primarily promotes the pursuit of social status and dominance (e.g., Booth et al., 2006; Eisenegger et al., 2011; Mazur and Booth, 1998). Such arguments do not account for the diverse, multiple effects of androgens throughout the brain and body that are made possible by the widespread expression of androgen receptors in many different organs and cell types (e.g., Takeda et al., 1990). Likewise, they provide no explanatory account of why testosterone in particular has this role, leaving unanswered the types of why questions that opened this article.

A partial theoretical framework that provides functional accounts of the multiple effects of testosterone has been developed by biological anthropologists. This framework uses life history theory to explain the coordinating effects of androgens. The framework in question has focused on somatic effects to the relative exclusion of behavioral variables, but behavioral and psychological outcomes may be assimilated to this approach in order to construct a more complete understanding of the role of testosterone in humans.

Life history theory addresses how organisms are designed to manage tradeoffs in the investment of finite resources across the lifecourse in order to promote lifetime reproductive success (Ellison, 2001; Stearns, 1992). This approach is broader than endocrinology, and encompasses any mechanisms whereby organisms determine the allocation of resources to broad tasks such as growth, survival maintenance (e.g., energy storage, pathogen defense), and reproduction (encompassing mate competition, sexuality, and parenting effort). Because such allocations are often somewhat separated in time in association with either age-related life-stages or changing social and ecological circumstances, individuals face the problem of playing different coordinated strategies at different times, thus necessitating internal signals that can coordinate multiple outcomes appropriate for the current strategy. Hormones are ideally suited to act as such signals, for the reasons specified above, and have been an empirical focus of research motivated by life history theory.

Bribiescas (2001), for instance, proposed an energy allocation model in which androgens like testosterone modulate somatic investment between broadly defined survival effort (e.g., fat storage and immune function) and mating effort (e.g., increased muscle anabolism), with androgens generally shunting energy to mating effort. The functional logic of such modulation is similar to that proposed in the earlier example of coordinating effects of androgens in seasonally breeding species: during life-history stages in which men have competed for mating opportunities, the costs of diverting energy away from survival-related functions may have been outweighed by the enhanced prospects for successful mate acquisition associated with outcomes such as increased skeletal muscle mass.

The theory that circulating testosterone causes outcomes that promote mate competition—but at a cost to investment in alternative priorities—generates specific predictions regarding the pattern of input–output mappings that should be associated with androgen production in men. Fig. 1 presents a partial and simplified representation of such input–output mappings. An interesting implication of this theoretical framework is the hypothesis that brain mechanisms regulating behavior are coordinated with patterns of energy investment in the rest of the body. Although evidence for the framework depicted in Fig. 1 is incomplete, as reviewed below, versions of this theoretical framework have been highly useful for hypothesis generation and the organization of research findings, and it thus serves as an example of the type of theoretical structure that may best advance understanding of human behavioral endocrinology.

3.1.2. Eliciting conditions

Two factors underlie the functional logic of the input cues specified on the left side of Fig. 1. First, if testosterone is in fact modulating tradeoffs in the investment of energy to different biological systems, then testosterone production itself should be calibrated by fluctuations in the energetic needs of those systems. Thus, when facing an acute

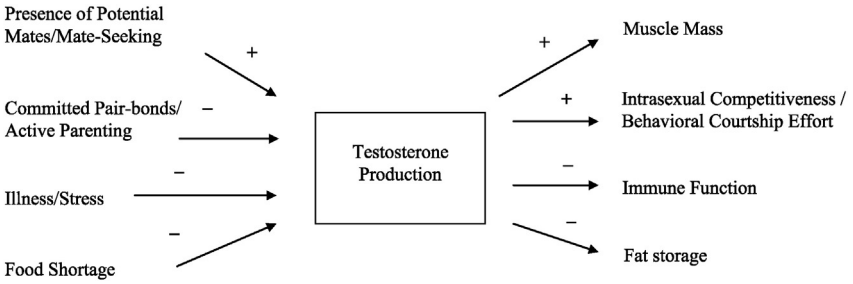

Fig. 1. A schematic depiction of some of the major input–output relationships associated with testosterone production in human males.

pathogen infection, for instance, testosterone may be temporarily reduced to avoid energy distribution away from the immune system. Second, if the broad function of elevated testosterone is the facilitation of mating effort, then testosterone production should be modulated by the degree to which men are currently engaged in mate seeking.

Field studies have provided evidence for these particular eliciting conditions. Chronic illness, traumatic injury, and severe food deprivation are all associated with declines in testosterone in men (for reviews, see Bribiescas, 2001; Muehlenbein and Bribiescas, 2005). Other evidence supports more finely grained androgen responses to these types of energetic stressors. Muehlenbein et al. (2005), for instance, demonstrated that Honduran men upon diagnosis with malaria had lower testosterone than an uninfected comparison group, but that patients' testosterone rose steadily until equal to the comparison group over eight days of treatment with anti-malarial drugs. Likewise, other studies have reported declines in men's testosterone after influenza vaccination (Simmons and Roney, 2009) and the day after missing only a single evening meal (Trumble et al., 2010).

In terms of social predictors of testosterone, a growing number of studies have supported declines in men's testosterone after entry into committed, romantic relationships, with further declines associated with fatherhood (for reviews, see Gettler, 2014; Gray and Campbell, 2009; Roney and Gettler, 2015). Although many such studies have been cross-sectional, Gettler et al. (2011) demonstrated in a cohort of men in their early twenties that the largest within-subject drops in testosterone over a four year period were found in men who transitioned from being single to being married fathers (for other longitudinal evidence, see Mazur and Michalek, 1998). Although a formal meta-analysis on this topic may be warranted before drawing firm conclusions, a large number of studies from different investigators and across multiple cultures have now shown partnering and parenting effects on men's testosterone, strongly supporting the idea that these social variables complement energetic variables in the regulation of men's androgen production.

Degree of paternal involvement, furthermore, may modulate the relationship between fatherhood and testosterone production. Muller et al. (2009), for instance, showed that testosterone did not differ between fathers and non-fathers among the pastoralist Datoga in which men had little direct involvement with child-care, but that fathers had lower testosterone than non-fathers among the Hadza, for whom frequent contact with children (including co-sleeping) was the norm. Other studies have likewise shown that variables like co-sleeping with children (Gettler et al., 2012) and ratings of overall paternal investment (Alvergne et al., 2009) negatively predict testosterone concentrations among fathers.

Tradeoffs between time and effort invested in mate-seeking vs. parenting may help explain the effects of variables like degree of paternal investment on men's testosterone. Roney and Gettler (2015) summarize evidence for possible bi-directional relationships between mate-seeking motivation and men's testosterone. For instance, among American college students, higher interest in extra-pair mating generally appears to predict higher testosterone among men in relationships (e.g., McIntyre et al., 2006), and polygynous mating relationships (in which individuals may still be seeking additional partners) have been associated with elevated testosterone relative to monogamous ones in various cultures (e.g., Gray, 2003; van Anders et al., 2007; cf. Gray et al., 2007). Taken together, then, the overall evidence suggests that testosterone tends to be elevated during life stages in which greater time and effort are invested in mate competition (i.e. when unpaired or paired but interested in additional partners) but reduced when resources are instead being invested directly in paternal effort within the context of monogamous relationships.

The studies demonstrating relationship status effects on men's testosterone are all correlational, thus leaving the precise nature of causal relationships somewhat ambiguous. A causal relationship between mate-seeking and increased testosterone has been supported at shorter time-scales. Brief social interactions with young women have been shown to trigger rapid (i.e. within 15–45 min. from the onset of the interactions) increases in men's testosterone in controlled laboratory experiments (e.g., Roney et al., 2003, 2007, 2010; van der Meij et al., 2008), with such effects also corroborated under more naturalistic field conditions (Flinn et al., 2012). These reactive hormone increases may act as signals of the current importance of mate pursuit, and promote output responses that promote mate competition over short-term time-scales (for reviews of this argument, see Roney, 2009, 2016). Muller et al. (2009) similarly postulated an interesting hypothesis that links such short-term testosterone increases to relative investment in mate seeking vs. paternal care. Citing evidence that Hadza men spend less time with their children when staying in camps with larger numbers of fecund women (Marlowe, 1999), they postulated that reactive testosterone increases in response to interactions with such women may calibrate relative investment in extra-pair mating to the potential payoffs from such investment. The flip side of this argument is that relative investment in paternal care should be higher when its functional consequences are greater—as when children are younger—and indeed in their sample of Hadza men diurnal decline in testosterone from morning to evening was greatest in men with the youngest children (Muller et al., 2009). In sum, consistent with the postulated eliciting conditions in Fig. 1, men's testosterone appears to respond positively to mating-related stimuli and psychological orientations directed toward mate pursuit, but negatively to investments in monogamous relationships and paternal care.

3.1.3. Outputs

The theory that testosterone modulates investment in mating vs. survival effort makes the broad prediction that heightened testosterone should promote mating success, other things equal. Consistent with this, Gettler et al. (2011) showed that testosterone concentrations among single men at about age 21 positively predicted the probability of becoming married fathers four years later, suggesting that testosterone concentrations prospectively predicted mating success. Studies in other cultures have likewise shown positive associations between testosterone and lifetime number of sex partners (e.g., Peters et al., 2008; Pollet et al., 2011), although direction of causality is more ambiguous in these cross-sectional samples.

Whether testosterone promotes mating success via the hypothesized downstream effects depicted on the right side of Fig. 1 is not certain. That androgens like testosterone do in fact coordinate the phenotypic outcomes listed is almost certainly true when considering developmental life stages, given evidence for large effects of pubertal androgens on muscle development, fat catabolism, and the onset of sexual interest and behavioral courtship effort (e.g., Arslanian and Suprasongsin, 1997; Halpern et al., 1998; McClintock and Herdt, 1996; Rogol et al., 2002; Round et al., 1999). Likewise, treatment of delayed puberty with luteinizing hormone (LH)—which triggered testosterone increases—led to very large drops in various immune cell counts in boys (Yesilova et al., 2000), and sex hormones have been implicated in the typical sex differences whereby women appear to have greater investment in immune responses than do men (Bouman et al., 2005; Muehlenbein and Bribiescas, 2005; Trigunaite et al., 2015). In response to life-stage related input cues associated with age and pubertal maturation, then, human males appear to coordinate energetic and behavioral investments in ways consistent with those postulated in Fig. 1.

Evidence has been more mixed when considering effects of testosterone fluctuations in the adult male range. With respect to effects on muscle mass, Lassek and Gaulin (2009) reported a positive correlation between testosterone and limb muscle volume in a large sample in the United States; furthermore, muscle mass positively predicted number of sex partners but negatively predicted measures of innate immunity, consistent with testosterone modulation of tradeoffs between mating and survival effort. Field studies in other cultures, however, have sometimes reported null associations between testosterone and measures of men's muscularity (e.g., Campbell et al., 2003; Gettler et al., 2010). Finally, controlled laboratory experiments have provided evidence for positive and negative effects of testosterone on muscle mass and fat storage, respectively. The best controlled such studies pharmacologically blocked natural production before adding back testosterone at various doses (Bhasin et al., 2001; Finkelstein et al., 2013). Although the largest effects in these studies were found when comparing supra- to sub-physiological testosterone replacement doses, a close reading of the articles reveals that testosterone also had significant positive effects on muscle mass and negative effects on fat mass when comparing testosterone doses in the physiological range. These experiments appear to confirm the hypothesized effects of testosterone on muscle mass and fat storage, at least under highly controlled conditions.

Alvarado et al. (2015) in a field study, however, recently demonstrated conditions under which muscle mass was relatively elevated despite reduced testosterone concentrations. In a sample of Polish men, they replicated the finding of lower testosterone in fathers vs. non-fathers, but also reported that, controlling for age, fathers had larger arm muscle circumference and chest and grip strength, secondary to higher manual workloads associated with family provisioning. Furthermore, testosterone was not a significant predictor of strength measures in multiple regression models that included age, work hours, and paternal status. In essence, Alvarado et al. (2015) argue that the importance of muscle mass for parenting effort as well as for mate competition has caused the evolution of mechanisms in humans in which muscle mass responds largely to workload as a means of maintaining strength for paternal provisioning despite reduced testosterone associated with parental status.

The findings of Alvarado et al. (2015) highlight the fact that the variables on the right side of Fig. 1 are also affected by inputs other than testosterone. Muscle mass may more strongly respond to heavy workloads than to adult hormone fluctuations as a means of allowing flexibility in energy allocation when greater strength is necessary for survival or parenting effort. Nonetheless, the evidence reviewed above supports positive effects of testosterone on muscle accretion both developmentally at puberty and under more precisely controlled laboratory conditions in which energy intake and muscle usage are more similar across subjects (e.g., Bhasin et al., 2001). Even in the Alvarado et al. sample, it may be relevant that age of adult men exhibited very strong negative correlations with measures of strength, suggesting that some single, young men were stronger than older men who were fathers, despite the lighter workloads of the younger men. Although that pattern could be a function of senescence, it may also reflect in part testosterone-mediated, life-stage related investments in mate competition.

Testosterone may drop even among fathers who maintain high muscle mass in order to avoid the behavioral and psychological outputs associated with elevated androgens. In some nonhuman species, experimental manipulations of testosterone have been shown to shift behavioral investments away from paternal provisioning and toward mate-seeking and territory defense (e.g., Hegner and Wingfield, 1987; for a review, see Gettler, 2014). The links between testosterone and men's interest in extra-pair mating reviewed above likewise suggest possible diversion of effort away from paternal care given heightened testosterone in men.

Other studies have tested relationships between testosterone and behavioral proclivities related to mate competition that may be coordinated with the somatic effects of androgens. Status-seeking and dominance contests may largely function as mating effort given evidence of women's mate preferences for markers of higher status (e.g., Buss, 1989; Li et al., 2002), positive correlations between measures of status and reproductive success in hunter-horticultural groups (e.g., von Rueden et al., 2011), and positive correlations between ratings of fighting ability and number of sex partners in male college students (Hill et al., 2013). Studies that have tested for correlations between circulating testosterone and various trait measures of dominance have generally produced fairly mixed results, however, although a meta-analysis reported evidence for a modest, positive relationship (Archer, 2006).

Clearer evidence for psychological and behavioral effects of testosterone may come from studies that have looked at downstream effects of reactive hormone increases. Carre and Olmstead (2015) recently reviewed the growing number of studies that have reported positive correlations between the size of transient testosterone increases and the magnitudes of subsequent behaviors ranging from reactive aggression (e.g., Carre et al., 2013), decisions to compete with another participant (e.g., Mehta and Josephs, 2006), weight-lifting performance (Cook and Crewther, 2012), and courtship-like behaviors directed toward women confederates (van der Meij et al., 2012). Transient increases were reactions to stimuli in these studies, but other research has shown that exogenous testosterone administration can produce effects such as reduced fear responses (e.g., Hermans et al., 2006) and increased amygdala and hypothalamic reactivity to angry faces (Goetz et al., 2014). The functionality of this overall suite of effects after testosterone increases have been triggered by input cues such as exposure to potential mates should be intuitively clear, as these physical and psychological outcomes should all increase the willingness and/or ability to compete for mating opportunities. Most of the studies on behavioral correlates of reactive testosterone increases have been laboratory experiments, however, and a challenge for future research is to investigate such effects under more naturalistic field conditions.

3.1.4. Summary and implications

Fig. 1 provides a simplified example of the type of theoretical framework that may best promote an integrated understanding of human behavioral endocrinology. The framework offers ultimate, functional explanations for why particular hormones may be associated with particular eliciting conditions and output phenotypes, as well as straightforward linkages to phylogenetic origins via its connections to similar models in nonhuman species (e.g., Ketterson and Nolan, 1992). Insofar as hormones typically do have coordinating functions, furthermore, the framework importantly accounts for these by hypothesizing how multiple biological systems both regulate and respond to androgen production.

Theoretical frameworks have heuristic value via their ability to assimilate additional findings and suggest new hypotheses. Due to

space limitations, many relevant lines of research were not included in Fig. 1, but could be assimilated within the functional logic of the theoretical framework. A growing literature that examines testosterone responses to competitive interactions is one example (for reviews, see Archer, 2006; Carre and Olmstead, 2015; Mazur and Booth, 1998). Outcomes of competitive interactions are relevant to social status and thus mate competition, and may sometimes trigger testosterone increases to facilitate further status pursuit. If this assimilation of competition effects to the theoretical framework in Fig. 1 is correct, then other variables that appear in the figure should moderate the magnitude of testosterone responses to competition. Energy limitations, for example, might inhibit reactive testosterone increases in order to prioritize survival-related functions under conditions of shortage, and to temporarily reduce motivation for additional status competitions until conditions have improved. Consistent with this, Booth et al. (1993) reported that wrestlers who fasted in order to achieve weight-class target weights did not exhibit testosterone increases after matches, whereas wrestlers who had not fasted did show reactive elevations. Likewise, if testosterone facilitation of status competition is at least partly a form of intrasexual mate competition (paternal provisioning in humans complicates this story, since status-mediated access to material resources may improve such provisioning), then current orientation toward mate seeking may moderate the size of testosterone responses to competitive interactions. Whether men in committed long-term relationships or fathers of young children show smaller testosterone responses to competitive interactions has not been directly tested, to my knowledge, but is the type of novel hypothesis that follows from the functional logic of this theoretical framework.

Finally, this theoretical framework suggests possible answers to the why question posed at the beginning of the article. A hormonal signal is superior to local neurotransmission alone if multiple output effects are being functionally coordinated. Even a short-term testosterone response could have somatic effects such as rapidly increasing glucose uptake in muscle cells (Tsai and Sapolsky, 1996), which could then be coordinated with brain-mediated psychological effects such as reduced fear or risk-aversion (e.g., Hermans et al., 2006). A concomitant short-term inhibition of immune activation may function to divert energy to competitive behaviors. In addition, calibrating competitive behaviors in part to testosterone responses may make such behaviors more sensitive to costs as well as benefits, insofar as testosterone responses are inhibited by eliciting conditions such as illness and energy shortage. In sum, theoretical frameworks have additional heuristic value from their ability to generate functional hypotheses, with empirical tests of those hypotheses holding the potential to provide explanatory accounts of why particular hormones are used as signals in particular circumstances.

3.2. Example 2: ovarian hormones as regulators of women's reproductive effort

3.2.1. Overview

In sexually reproducing nonhuman species, a primary function of ovarian hormones is often argued to be temporal coordination of sexual behavior with somatic events in the reproductive tract that make females fertilizable. Adkins-Regan (2005) encapsulated this argument: "Gamete maturation is hormonally regulated, and so one reason that mating behavior is hormonally regulated is to ensure that the behavior is coordinated with the presence of fertilizable gametes" (p. 3). This section of the article will use this simple idea to guide the construction of a theoretical framework for understanding the signaling roles of estradiol and progesterone in women.

Although the theoretical framework developed below is a straightforward application of similar ideas from the nonhuman literature, it is nonetheless not the case that this approach is commonly applied to understanding women's reproductive effort. With respect to women's sexual motivation, for instance, there have been common arguments in the medical and basic science literatures to the effect that androgens like testosterone are the main regulators of women's libido (for critical reviews, see Cappelletti and Wallen, 2016; Wallen, 2001, 2013). Setting aside the empirical evidence for this claim, what is relevant here is the absence of any clear functional reason for testosterone to play this role. What eliciting conditions are signaled by elevated testosterone such that it would be a functional regulator of sexual desire? Fecundity (i.e. the likelihood of successful conception and gestation given unprotected intercourse) is not very strongly coupled to testosterone concentrations due to the substantial adrenal contributions to androgen production (for a review, see Roney, 2015). Testosterone could be signaling something other than fecundity, but if so, what this might be is not clearly specified in the extant literature. As such, conclusions in this case were drawn based on inductive generalizations from particular empirical findings in the absence of any clear functional theory. The theoretical framework proposed next attempts to provide a functional context for understanding hormonal regulation of variables like sexual motivation.

Fig. 2 presents a schematic representation of the proposed theoretical framework. Cues of sufficient resources for successful gestation and lactation are the primary eliciting conditions determining likelihood of follicle development, ovulation, and associated hormone release. Specific ovarian hormones in turn have downstream effects that in broad terms coordinate endometrial development in the soma with the priming of specific neural structures regulating motivational priorities in the brain. Essentially, ovarian hormones are proposed to link physiological preparation for implantation, mate seeking, and sexual behavior with those energetic and social conditions most conducive for successful reproduction.

A few clarifications regarding Fig. 2 are in order before proceeding to a more detailed consideration of proposed inputs and outputs. First, the input cues on the left point to follicle maturation as an intervening step to indicate that it is the specific, cyclic pattern of hormone production associated with dominant follicle and subsequent corpus luteum development that carries information regarding fecundity to brain structures. Fig. 3 depicts the prototypical pattern of estradiol and progesterone production in an ovulatory menstrual cycle. Importantly, this pattern depends on sufficient gonadotropin (follicle stimulating hormone (FSH) and LH) stimulation from the pituitary to trigger dominant follicle maturation (see Zeleznik, 2004), and absent this stimulation ovulation

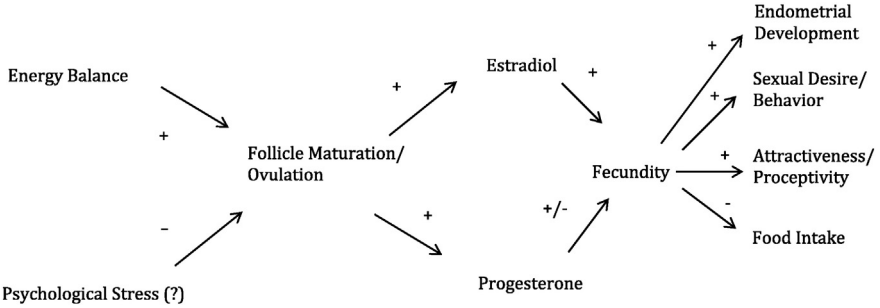

Fig. 2. A schematic depiction of some of the major input–output relationships associated with production of the ovarian hormones estradiol and progesterone in human females.

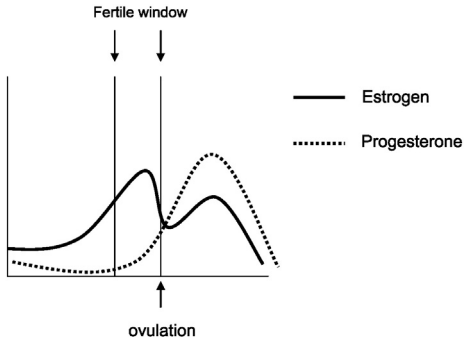

Fig. 3. Prototypical patterns of estradiol and progesterone production in an ovulatory human menstrual cycle. The x-axis from left to right runs from menses to the end of a given cycle. The fertile window represents days when conception is possible.

does not occur and both estradiol and progesterone remain low across time. Insufficient gonadotropin stimulation occurs during conditions of energetic stress during adulthood, as reviewed below, but also before puberty; after menopause, depletion of follicles prevents ovulation. Thus, the cyclic pattern of estradiol and progesterone production depicted in Fig. 3 occurs only during reproductive life-stages and in cycles with sufficient energetic resources for reproduction. As such, specific combinations of estradiol and progesterone can in effect act as signals of fecundity, allowing reproductive effort to be linked to fecundity via its regulation by these hormones.

Within the time-scale of an individual ovulatory cycle, fecundity should be efficiently signaled by the combination of high estradiol and low progesterone, which characterizes the fertile window, as depicted in Fig. 3. At this within-cycle time-scale, furthermore, high progesterone effectively signals low fecundity, since progesterone peaks in the luteal phase on days when conception is impossible (see Wilcox et al., 1998). A variable like sexual motivation could thus be linked to fecundity at the within-cycle time-scale via excitatory effects of estradiol combined with inhibitory effects of progesterone. At a longer, life-stage or between-cycle time-scale, however, both estradiol and progesterone should be positively correlated with fecundity. When comparing an ovulatory cycle to a post-menopausal time period, for instance, both estradiol and progesterone will be higher in the ovulatory cycle such that both hormones could positively signal the presence of a reproductive life-stage. The arrow from progesterone to fecundity in Fig. 3 is labeled with a plus and minus to indicate these opposing relationships with fecundity at the within-cycle and life-stage time-scales. Most research in both nonhuman species and in humans has focused on correlates of fecundity at the within-cycle time-scale—which will therefore be the focus of the present review—but it is possible that a hormone like progesterone has different effects when comparing across life stages than when comparing across phases within an individual ovulatory cycle.

3.2.2. Eliciting conditions

Research on human reproductive ecology has provided strong evidence that energy availability regulates women's ovarian function (for reviews, see Ellison, 1994, 2001). Energy balance—that is, energy intake minus expenditure—appears to be a key variable. Complete cessation of ovulation and menstruation is common during intensive lactation, for instance, when energy expenditure often exceeds intake. Various lines of research have supported negative energy balance as the main regulator of this lactational amenorrhea, such as food supplementation in nursing mothers leading to faster resumption of ovarian hormone production and shorter inter-birth intervals relative to no supplementation in a natural fertility population (Lunn et al., 1981; see also Ellison and Valeggia, 2003; Valeggia and Ellison, 2004). Absence of follicle development is the extreme end of a continuum from ovarian quiescence to fully functional cycles (see Ellison, 1994), however, and energetic variables have been shown to have effects across this entire continuum. Even moderate increases in exercise or small weight loss secondary to dieting have been associated with drops in estradiol or progesterone in samples from industrialized countries (e.g., Bullen et al., 1985; Ellison and Lager, 1985; Lager and Ellison, 1990; Schweiger et al., 1988). Field studies in natural fertility populations have likewise demonstrated similar effects of reduced energy intake (e.g., Bentley et al., 1998; Ellison et al., 1989; Vitzthum et al., 2002) and increased energy expenditure (e.g., Jasienska and Ellison, 1998; Panter-Brick and Ellison, 1994).

Inhibition of hormone production and associated fecundity in response to negative energy balance probably functions to delay conception under conditions in which resources may be insufficient for successful reproduction. A broadly similar logic has motivated speculation that psychosocial stress may also inhibit ovarian function (e.g., Wasser and Isenberg, 1986). Such stress may have been predictive of low future social support in ancestral environments, for instance, which may have predicted lower rates of reproductive success.

Despite interest in possible effects of psychological stress on ovarian hormones, little evidence has clearly supported this relationship. As such, a question mark appears next to stress as a possible input variable in Fig. 2. Schweiger et al. (1988) reported that a retrospective rating of stress in the previous month negatively predicted luteal estradiol and progesterone concentrations in that month within a small sample of athletes. In a larger sample, Ellison et al. (2007) did not find differences in salivary estradiol and progesterone when comparing the month before and after an important exam, despite higher subjective stress ratings preceding the exam. Finally, at a more fine-grained time-scale, Roney and Simmons (2015) reported in a daily diary study that salivary estradiol concentrations were lower on days with higher self-reported stress relative to others days within the same cycles. Although that effect was independent of energetic variables—such as self-reported food intake—the study did not assess cortisol concentrations and thus it was possible that effects of stress were secondary to the catabolic and thus energetic effects of transient cortisol increases. In summary, unlike energetic regulators of ovarian function that are now well established, there are mixed findings regarding the relationship between psychological stress and ovarian hormone production, and further research on this topic appears necessary.

3.2.3. Outputs

A primary function of estradiol and progesterone is preparation of the uterine lining for possible implantation should conception occur (for reviews, see Hall, 2004; Lessey and Young, 2014). Estradiol has proliferative effects on the endometrium during the follicular phase, whereas progesterone stimulates secretory effects in the luteal phase that are necessary for survival of the conceptus. Effects of these hormones appear to be somewhat continuous as evidence suggests that higher hormone concentrations promote greater fecundity in part due to their effects on the endometrium (for a review, see Lipson and Ellison, 1996). Because hormones produced by the ovaries also enter the general circulation, neural structures can essentially monitor events in the ovaries and endometrium in order to coordinate behavioral regulation with hormonal indices of fecundity.

In most mammals, female sexual receptivity and proceptivity is largely limited to days when conception is possible. A number of early reviews of nonhuman sexual motivation argued that hormonal signals associated with within-cycle fecundity predict sexual motivation across mammalian females (e.g., Beach, 1949, 1976; Young, 1961). Estradiol positively signals fecundity via its association with dominant follicle development and ovulation, and has been positively associated with sexual behavior in all species investigated. Progesterone has more complex relationships with both fecundity and sexual motivation. In some species without spontaneous luteal phases, such as rats and mice, an acute progesterone peak precedes ovulation during the time that conception is possible, and in these species experiments

demonstrate that precisely timed progesterone administrations acutely facilitate female sexual behaviors after prior estrogen priming (for a review, see Blaustein, 2008). In species with spontaneous luteal phases, progesterone reaches post-ovulatory concentrations that are generally much higher than the smaller elevations that precede ovulation, and these luteal concentrations of progesterone typically have strong inhibitory effects on sexual motivation, even if pre-ovulatory progesterone elevations remain excitatory (for partial reviews, see Roney, 2015; Young, 1961). Although many details regarding dose and timing effects are glossed over here, the unifying principle appears to be that hormone patterns associated with the peri-ovulatory region in natural cycles facilitate sexual behaviors, whereas hormone patterns characteristic of the non-fecund phases inhibit them. These patterns support the general conclusion that brain structures have evolved to read species-specific hormonal signals of fecundity in order to coordinate sexual behavior with time intervals when conception is possible.

Do humans conform to this same pattern whereby hormonal signals associated with within-cycle fecundity predict increased sexual motivation? Numerous studies have demonstrated mid-cycle elevations of desire or woman-initiated sex (for a review, see Wallen, 2001), which indirectly implicates roles for ovarian hormones given the hormone secretion patterns (see Fig. 3). However, early studies that tested for within-cycle correlations between hormones and measures of women's sexual motivation reported null results (Dennerstein et al., 1994; Morris et al., 1987; Persky et al., 1978a, 1978b; Van Goozen et al., 1997), although these studies generally had low power and did not employ newer statistical techniques for the analysis of non-independent data. More recently, with a much larger sample size and use of multi-level regression models for data analysis, Roney and Simmons (2013, 2016) reported positive, within-cycle correlations between fluctuations in women's estradiol and daily self-report ratings of their sexual desire, and even larger negative correlations between progesterone and desire. Testosterone was not associated with desire in this study. Furthermore, desire peaked on average during the fertile window, and exhibited a pronounced drop in the mid-luteal phase when progesterone was at its peak (for a similar cycle phase pattern for sexual behavior in partnered women, see Wilcox et al., 2004). These patterns are highly similar to correlations demonstrated in group-living nonhuman primates (e.g., Wallen et al., 1984), with experimental investigations in primate species having corroborated casual roles for both estradiol (e.g., Zehr et al., 1998; Zumpe et al., 1983) and progesterone (e.g., Kendrick and Dixson, 1985). As such, as in many nonhuman species, evidence supports fluctuations in women's sexual motivation being coupled to those hormonal signals that best index within-cycle changes in fecundity.

Sexual motivation appears to track fecundity at a life-stage timescale, as well. Many studies converge in showing declines in sexual motivation, on average, after natural or surgical menopause (for a review, see Alexander et al., 2004). Longitudinal studies have provided evidence that it is the decline in estradiol, and not testosterone, that best predicts decreases in sexual motivation across the menopausal transition (e.g., Dennerstein et al., 2005), although non-hormonal relationship variables such as the formation of a new partnership are also significant independent predictors. Finally, hormone replacement with estradiol at concentrations typical of the fertile window in ovulatory cycles can increase sexual motivation in menopausal women, whereas testosterone administration appears to have efficacy only at supra-physiological doses (Cappelletti and Wallen, 2016). Taken together, the within-cycle and life-stage findings converge in suggesting that sexual motivation in women is calibrated to hormone patterns that are predictive of current fecundity.

In many rodent species, ovarian hormone concentrations characteristic of fecund cycle phases are required for mating to take place, whereas in most primates sexual behavior can occur at any time of the cycle but ovarian hormones still modulate motivation for sex (Wallen, 1990, 1995). In most rodents, males provide only sperm to females, and thus sexual behavior entirely restricted to fecund time periods avoids the costs of sex (including opportunity costs in terms of alternative behaviors, or negative outcomes such as increased risk of predation or sexually transmitted infection) when conception is absent as the only countervailing fitness benefit. Species in which at least some nonconceptive sex takes place are said to exhibit "extended sexuality," which has been argued to promote male delivery of nongenetic ("direct") benefits of some form (for an extensive discussion, see Thornhill and Gangestad, 2008). For instance, in some nonhuman primates, paternity confusion resulting from female nonconceptive sex with multiple males may discourage male mistreatment of female offspring (reviewed in Thornhill and Gangestad, 2008).

Humans exhibit extensive extended sexuality, with sexual behavior occurring during both non-fecund cycle days and life-stages. How is this reconciled with the evidence reviewed above for greater sexual motivation associated with hormonal indices of fecundity? The hormone effects may have the evolved function of avoiding the fitness costs of sex, other things equal, when conception is not possible, as in nonhuman species. Extended sexuality, on the other hand, may primarily be regulated by non-hormonal variables, and function to promote male partners' long-term investment in a pair-bond partner and her offspring. Theorists have argued that a minimum baseline level of sexual receptivity even during non-fecund time periods evolved in women in order to help conceal cues of ovulatory timing and thereby promote more continuous male partner investment in pair-bonds (see Strassmann, 1981; Symons, 1979). In addition, sexual desire appears to respond to variables such as new relationship initiation independently of ovarian hormone production (e.g., Dennerstein et al., 2005), with heightened desire early in relationships potentially acting as a courtship tactic that signals commitment to a new partner. These and other social variables are proposed to modulate sexual desire independently from the phylogenetically conserved hormonal influences that increase sexual motivation when fecundity is elevated (for more extensive discussion, see Roney, 2015; Roney and Simmons, 2016).

Hormones often modulate tradeoffs in attention and behavioral investment across competing motivational priorities. In a wide range of nonhuman mammalian species, females' sexual motivation trades off against feeding and foraging behaviors, with ovarian hormones often having opposite effects on the two priorities (for a review, see Schneider et al., 2013). In nonhuman primates, in particular, estradiol has been shown to decrease females' food intake, progesterone reverses the inhibitory effect of estradiol, and the combined effects of the two hormones leads to a pronounced nadir in eating just before ovulation when females are fecund (e.g., Bielert and Busse, 1983; Czaja and Goy, 1975; Kemnitz et al., 1989). This pattern is nearly a perfect mirror image of the above-described pattern of findings for sexual motivation.

A number of studies have likewise provided evidence for drops in women's food intake just before ovulation within the fertile window, with subsequent increases in eating during the luteal phase (for reviews, see Buffenstein et al., 1995; Fessler, 2003). Most of these studies have used error-prone counting methods to assess cycle phase, however, and did not have hormonal measures. In the Roney and Simmons (2013) study reviewed above that examined hormonal predictors of sexual motivation, women also self-reported daily estimates of total food intake. Although data for this variable are not yet published, the patterns were remarkably similar to those seen in nonhuman primates: negative and positive effects of estradiol and progesterone, respectively, on food intake, with the two hormones having statistically mediated a significant drop in food intake within the fertile window. These patterns suggest that, as in nonhuman species, ovarian hormones modulate tradeoffs in women's attentional and motivational priorities, with a shift toward focus on non-sexual adaptive problems during non-fecund portions of the cycle when, historically, the benefit-cost ratio of sexual behavior should have been lower, on average.

Opposite effects of ovarian hormones on feeding and sexual motivation provide a clear example of the coordinating functions of

hormones across different neural structures. In nonhuman species, satiety promoting signals from the digestive tract (e.g., cholecystokinin (CCK)) are potentiated by hormones like estradiol in their effects on specific, appetite-regulating brain structures, such as the nucleus tractus solitarius (for reviews, see Asarian and Geary, 2006; Schneider et al., 2013). Simultaneously, estradiol has effects on different brain structures, such as the ventromedial hypothalamus, in the facilitation of sexual behaviors (e.g., Pfaff and Schwartz-Giblin, 1998). These simultaneous effects then lead to a coordinated increase in sexual but decrease in feeding motivation when females are fecund.

Finally, in many nonhuman species, females' attractiveness to males increases when females are in a fecund portion of the cycle, with such effects often at least partly attributable to morphological changes (e.g., odor cues, genital swellings) under the positive influence of estradiol (for reviews, see Beach, 1976; Emery Thompson, 2009). Some evidence supports cycle phase shifts in humans, with enhanced attractiveness of faces, voices, and scent when women are within the fertile window (for a review, see Haselton and Gildersleeve, 2011). Very little research has directly assessed the hormonal predictors of such shifts. An exception is a study by Puts et al. (2013) that collected both salivary measures of estradiol and progesterone as well as ratings of women's voice and face attractiveness on two occasions, with one testing day in the estimated late follicular phase and the other in the luteal phase. Within-women changes in progesterone across the two sessions negatively predicted within-women changes in both voice and face attractiveness, whereas the two hormones negatively interacted in the prediction of voice attractiveness (suggesting more positive effects of estradiol when progesterone was lower). These findings suggest small decreases in face and voice attractiveness in the non-fecund luteal phase (relative to the follicular phase), although in all likelihood such effects are small compared to more stable between-women differences in attractiveness, and Puts et al. (2013) interpreted their findings as reflecting leakage of subtle hormone cues rather than as direct signals of ovulatory timing as in some nonhuman species.

Other studies have assessed proceptive, behavioral enhancement of attractiveness with respect to cycle phase. Some research has supported women's choice of more attractive clothing when near ovulation (Durante et al., 2008; Haselton et al., 2007), as well as a greater likelihood of wearing red clothing (Beall and Tracy, 2013; cf. Prokop and Hromada, 2013), with previous research having supported positive effects of red coloration on ratings of women's attractiveness (e.g., Elliot and Niesta, 2008). Direct hormone measures were absent from these studies. With respect to the red clothing finding, Eisenbruch et al. (2015) assessed the color of clothing women wore naturally across 4–8 days, with salivary hormones also measured on those same days. In within-subjects analyses, they found that the frequency of red clothing choices was higher within the estimated fertile window, and that the estradiol to progesterone ratio both positively predicted the odds of wearing red clothing and statistically mediated the effect of fertile window timing on this variable. Such effects support behavioral enhancement of attractiveness as another downstream effect of hormone patterns that are predictive of within-cycle fecundity.

3.2.4. Summary

In females of many sexually reproducing nonhuman species, hormones associated with fecund time periods have a suite of coordinated effects that include increased sexual receptivity, enhanced morphological and behavioral attractiveness to males, and reduced motivation for behavioral priorities that may compete with mating, such as feeding and foraging. Past research on correlates of menstrual cycle phase had supported similar effects in women during the fertile window relative to other cycle days, but only recently have human studies with detailed hormone measurements begun to test the endocrine predictors of these effects. As reviewed above, these studies provide evidence that estradiol fluctuations are positively associated with measures of sexual motivation, subtle changes in physical attractiveness, and behavioral enhancements of attractiveness, whereas progesterone fluctuations are negatively correlated with these same outcomes. Preliminary evidence supports the opposite effects of these hormones on eating behavior, with total food intake negatively associated with estradiol fluctuations but positively associated with changes in progesterone. From these findings, a core functional logic emerges in which ovarian hormones indicative of heightened fecundity promote somatic and behavioral investment in mating effort during those time periods when conception is most likely. Although many other variables that are tested for associations with ovarian hormone fluctuations have been excluded due to space limitations (e.g., cognitive variables such as memory performance; for a review, see Sherwin, 2003), the theoretical framework presented in Fig. 2 may provide a functional context in which such variables could be assimilated as outputs that are coordinated with those depicted in the figure.

3.3. Example 3: recent research on effects of oxytocin in humans

The rapidly expanding body of research investigating effects of oxytocin in humans has generally proceeded without clear theorizing regarding how this signal may coordinate multiple outputs in response to specific eliciting conditions. This has been especially true of research that employs exogenous oxytocin administration via nasal sprays. These studies examine effects of oxytocin administration relative to placebo on outcomes such as trust behavior in economic games (e.g., Kosfeld et al., 2005; cf. Nave et al., 2015), the ability to read emotional expressions from faces (Domes et al., 2007), and ratings of trustworthiness in others' faces (Theodoridou et al., 2009; for a review of administration studies, see Meyer-Lindenberg et al., 2011). Such studies provide no clear information about eliciting conditions since the oxytocin increases are under experimenter control and may be occurring in contexts in which they do not occur naturally. Artificial administration contexts may also change the output effects of oxytocin, since under natural eliciting conditions neural networks are likely activated simultaneous to oxytocin release (as well as other hormonal signals that may be co-released), and alteration of these contextual factors could alter effects of the hormone. Despite these limitations, theorizing about the role of oxytocin in human psychology and behavior has leaned heavily on the results of administration studies under the implicit assumption that findings reflect effects that occur in natural circumstances.

A number of prominent review articles, for example, have used results of administration studies in attempts to provide the most general and parsimonious possible description of oxytocin's behavioral and psychological effects. In other words, these papers seek to define the one general thing that oxytocin does that in turn explains its effects on measured variables. For example, Bartz et al. (2011) argued that oxytocin might primarily increase the perceptual salience and processing of social cues, with the other documented effects of the hormone following from this increased social salience. They argued that greater attention to social cues may explain some of the ostensibly conflicting effects of oxytocin administration, such as promoting increased prosocial behavior when interacting with trusted others but decreasing prosociality when interacting with out-group members (e.g., De Dreu et al., 2010). Churchland and Winkielman (2012) suggested that oxytocin might primarily have anxiety-reducing effects that in turn explain other correlated outcomes of exogenous administration. They also argued explicitly for the value of parsimonious and general levels of description when seeking the best characterization of oxytocin's effects.

These parsimony-based theories are quite different from the theoretical framework approach advocated here. First, they do not clearly specify the eliciting conditions under which oxytocin produces outcomes such as anxiolysis or enhanced social salience. Second, they do not explain why oxytocin is a good (i.e. functional) signal for promotion of such effects, as opposed to transmitter-based signaling or any number of other hormonal signals. Third, they do not posit coordinating functions of this hormone. If coordination is a prototypical function of

hormones, as argued earlier, then the very point of endocrine signals will often be the production of multiple, simultaneous effects. As such, theories that posit the one general thing that hormones do are likely to be incomplete, if not misguided.

Oxytocin, like other hormones, is likely to coordinate many outcomes. Its receptors are very widespread, having been found expressed in the uterus, follicular cells, corpus luteum, testes and prostate, mammary glands, kidneys, pancreas, heart, thymus, fat cells, adrenal gland, osteoblasts, and in a wide range of areas within the central nervous system (for reviews, see Cunningham and Sawchenko, 1991; Gimpl and Fahrenholz, 2001; Uvnas-Moberg, 1997). Although much has been made of the potential for oxytocin to be released independently within the brain and the periphery (e.g., Churchland and Winkielman, 2012), the evidence that some oxytocin-producing hypothalamic neurons have projections to both brain regions and the posterior pituitary (from which peripheral release occurs) supports an anatomical arrangement that specifically facilitates coordinated signaling (for reviews, see Neumann and Landgraf, 2012; Ross and Young, 2009). Indeed, research in nonhuman species that measures oxytocin via microdialysis in the brain and concomitantly via assays in the periphery demonstrates that central and peripheral release occurs in a coordinated way specifically within ethologically relevant contexts, as summarized by Neumann and Landgraf (2012):

> … numerous physiological stimuli trigger both central and peripheral oxytocin release, including birth, suckling, sexual activity, and various forms of stress, with essentially synergistic behavioral and physiological actions of centrally (maternal behaviors, sexual behavior, anxiolysis, social preference and recognition) and peripherally (labor, milk ejection, orgasm) released oxytocin, respectively (pp. 649–650).

Thus, although there are cases in which oxytocin increases have been detected in the hypothalamus but not in the periphery (Engelmann et al., 2004), there are many other eliciting conditions in which simultaneous release appears to coordinate central and peripheral output responses.

Notice, furthermore, that many of the behavioral output effects of oxytocin in ethologically relevant contexts appear more specific than the very general effects proposed within the parsimony-based theories mentioned earlier. Consider the role of oxytocin in pair-bonding within species such as prairie voles. In females, oxytocin increases in response to vaginal stimulation associated with copulation appear to produce both improved social recognition and preferences for the specific male mating partner, with these output effects reproducible via oxytocin administration in the absence of copulation with a co-habiting male partner (e.g., Williams et al., 1994). Other research suggests that oxytocin may promote specific processing connections between the olfactory bulb and medial amygdala in promoting the recognition of (and perhaps assigning positive valence to) the odors of mating partners (for a review, see Ross and Young, 2009). Although more evidence is needed, similar roles for oxytocin in pair-bond formation may be found in humans: oxytocin increases have been documented after orgasm in both men and women (e.g., Carmichael et al., 1987), and circulating oxytocin measures in new romantic partners have positively predicted both measures of engagement in the relationships and the probability of the couples staying together over time (Schneiderman et al., 2012).[2] Such findings suggest that oxytocin responses to specific eliciting conditions may promote specific, functional output effects. Rather than attempting to discover the one general thing that oxytocin does, then, a productive strategy for understanding the psychological effects of this hormone in humans may entail the careful mapping of output effects that are observed across a range of naturally occurring eliciting conditions.

Although in some cases coordinating effects of oxytocin are obvious (e.g., effects on both milk let-down and the onset of maternal behaviors in some nonhuman species; see Ross and Young, 2009), most theories regarding its functions do not attempt to explain its very wide range of both peripheral and behavioral influences. In an exception, Uvnas-Moberg (1997) described a suite of behavioral and physiological effects that tend to occur both after exposures to non-noxious stimuli (such as massage-like touch, warm temperatures, or gentle vibration) that can trigger oxytocin responses, and after exogenous oxytocin administration. These effects include reduced blood pressure, inhibition of adrenocorticotropic hormone (ACTH) and cortisol release, stimulation of gastrointestinal tract hormones such insulin and CCK (leading to enhanced satiety and digestive and anabolic processes), changes in glucose metabolism, sedation or anxiety reduction, enhanced pain tolerance, and increased sociability. (Enhanced immune responses and faster wound healing have also been supported; see Ross and Young, 2009.) Uvnas-Moberg (1997) characterized this as an "anti-stress" pattern in which the individual is currently investing resources in digestion, energy storage, growth, and social affiliation. This coordinated pattern may be especially functional during events such as lactation when reduced reactivity to many stimuli facilitates the relative immobility required for sustained infant care (see Carter and Altemus, 1997), and when enhanced digestive activity helps to sequester energetic resources for milk production. Oxytocin increases in response to expressions of social support, trust, food sharing, or the formation of pair-bonds (for a review of such inputs, see Crockford et al., 2014; Uvnas-Moberg et al., 2015) could likewise have a functional role in priming the coordinated anti-stress pattern when the presence of social support provides a safe environment for lowering vigilance to threats and instead investing finite resources into digestion, anabolic processes, immune response, and social interaction. The anti-stress position suggests a core functional logic for oxytocin as a signal, offers explanations for the simultaneous peripheral and central effects of the hormone, and posits explicit linkages between the eliciting conditions that trigger changes in oxytocin and the output effects associated with those changes. As such, this position seems especially promising as a starting point for the construction of a useful theoretical framework for understanding the roles of this hormone in humans.

Complicating interpretation of the pattern of effects described by Uvnas-Moberg (1997) are cases of elevated oxytocin among individuals (and especially women) experiencing depression or relationship distress (for a review, see Crespi, 2016). Taylor et al. (2010), in an article demonstrating such correlations, suggest that oxytocin may act as a biological signal that a relationship is threatened, presumably to motivate attempts to rescue it. They acknowledge that this seems inconsistent with the calming effects of oxytocin, but suggest that "when social relationships are not comforting, it is possible that OT passes into the bloodstream without involving the downstream opioid and dopamine pathways that are believed to account at least partially for the calming, relaxing effects sometimes attributed to OT alone" (p. 6). This idea is consistent with what Ketterson and Nolan (1992) referred to as "compartmentalization" of hormone effects, in which mechanisms restrict downstream outputs to a subset of the total hormone effects under specific circumstances. For oxytocin, possible mechanisms for compartmentalization could include activation of different subsets of oxytocin producing neurons (with distinct downstream projections) under different eliciting conditions, the co-release of other hormonal signals under specific circumstances that alters the effects of oxytocin on specific output targets, and the differential expression of oxytocin receptors in diverse target tissues under different circumstances (Gimpl and Fahrenholz, 2001).

An alternative possibility, however, is that oxytocin is released in distressing circumstances *because* of its anti-stress properties as a

[2] Human studies that measure circulating oxytocin have been criticized for use of assay techniques that may produce inaccurate estimates of hormone concentrations (McCullough et al., 2013). Clearly, the development of validated assay techniques that are widely accepted as accurate is crucially important to advance understanding of the signaling roles of oxytocin in humans.

means of regulating and containing other elements of stress responses (Carter, 2014; Neumann and Slattery, 2016). This in fact appears to be a standard interpretation of findings from rodent experiments. For instance, rodents release oxytocin in the central amygdala during forced swim stressors, but its effects there promote calmer responses to the stressor, such as greater time spent floating (Ebner et al., 2005). Ebner et al. wrote: "… summarizing these behavioral and physiological effects within the central amygdala, our data suggest that oxytocin may contribute to general sedation to prevent excessive stress responses" (p. 228). Optogenetic activation of oxytocin neuron axons within the central amygdala likewise reduced fear-conditioned freezing responses (Knobloch et al., 2012; cf. Grillon et al., 2013), and the positive effect of oxytocin on maternal aggression in rodent females has been interpreted as being secondary to anxiolytic effects of the hormone (for a review, see Bosch, 2013). If oxytocin is playing similar regulatory roles in humans, then it is possible that individuals with distressed relationships would experience even greater anxiety and less effective coping in the absence of elevated oxytocin. In that case, even cases of elevated oxytocin during distress might be understood based on the hormone's coordinated anti-stress effects. Essentially, the meaning of a hormonal signal depends on the linkages between inputs and outputs that the signal mediates, and cannot be fully understood via reference to the inputs or outputs alone.

In summary, theorizing about the effects of oxytocin in humans has generally neglected the construction of theoretical frameworks that specify functional input–output relationships. Prior theories have instead focused on summarizing the common denominator for effects of exogenous oxytocin administration, which is useful for applied purposes, but may be sub-optimal for discovering the basic, evolved functions of this signal. Research in nonhuman species has identified specific output effects—such as onset of maternal behaviors and social preferences for specific partners—that occur under specific eliciting conditions, but that are also often accompanied by a broader pattern of effects related to digestion, immune function, blood pressure, sedation, anxiolysis, adrenal hormone production, etc. An "anti-stress" pattern that promotes finite resource investment in growth, energy storage, immunity, nurturance, and social affiliation under propitious circumstances—but that may also be partially activated to prevent excessive responses to stressors—may provide an abstract, functional characterization of the hormone's multiple effects. The findings from nonhuman species provide a rich set of hypotheses that can guide the construction of useful theoretical frameworks for understanding the signaling functions of oxytocin in humans. A logical strategy for human research thus entails detailed investigation of oxytocin responses to the types of eliciting conditions known to trigger increases in nonhuman species, combined with systematic assessment of diverse output responses to these increases. Research that tests peripheral responses to oxytocin in conjunction with measurement of psychological and behavioral variables may be especially valuable for testing coordinating functions of this signal in humans.

4. Limitations and future directions

An obvious limitation of the arguments made here is that space limitations precluded comprehensive reviews of the evidence for the proposed theoretical frameworks. Many other potential eliciting conditions and output effects could be discussed for each of the example hormones, and even those covered could easily have entire articles written about each of them. The variables discussed are examples intended to demonstrate the heuristic value of the theoretical framework approach.

The theoretical framework approach can be expanded to consider interactive effects of multiple endocrine signals that may be co-released in response to particular eliciting conditions. Target cells often express receptors for multiple hormones, and thus the effect of a given hormone may change depending on other concomitant signals. As just one example, in male zebra finches, testosterone implants reduced cell-mediated immune responses relative to control males, but co-administration of leptin with testosterone reversed this effect (Alonso-Alvarez et al., 2007). The authors predicted these results based on the idea that a core function of testosterone is to drive finite energetic resources toward mating effort at the cost of investment in forms of survival effort; if energy reserves are high (as indexed by leptin), however, then the individual may be able to afford high levels of investment in both immune responses and sexual signaling. This example illustrates how theoretical frameworks can help predict and interpret effects of multiple endocrine signals. The example also illustrates "compartmentalization" of hormone effects in the sense described by Ketterson and Nolan (1992): with sufficient energy reserves, the effects of testosterone on immune responses may be absent but its other effects preserved.

The use of multiple endocrine signals to compartmentalize effects of specific hormones in specific circumstances greatly increases the possible specificity and nuance of functional mappings between eliciting conditions and patterns of output responses. A functional response to exposure to a potential mate or a competitive defeat may depend on a host of relevant variables, such as whether one is sick or healthy, single or paired, socially supported or alienated, young or old, nourished or hungry, dominant or subordinate, observed by others or alone, etc. Different combinations of both basal and reactive endocrine signals may be mapped into different patterns of output responses depending on the values of these variables. In principle, if theoretical frameworks for many endocrine signals were worked out in sufficient detail, then specific patterns of multiple hormone responses to specific combinations of eliciting conditions could be predicted as mathematical input functions, with corresponding output functions predicted from the concurrent values of the multiple endocrine signals. Viewed in this way, combinations of hormones are essentially codes for particular combinations of eliciting conditions (that in turn prime coordinated output responses to those conditions) and behavioral endocrinology is essentially an exercise in code breaking.

The "dual hormone hypothesis" (Mehta and Josephs, 2010) provides an example from human behavioral endocrinology that posits interactive effects of multiple hormones. The hypothesis holds that testosterone is positively associated with outcomes such as dominance or leadership only when cortisol is low; in fact, some findings suggest that testosterone may negatively predict measures of dominance when cortisol is high (Mehta and Josephs, 2010).[3] The consideration of multiple endocrine signals is important, but a functional account of this pattern seems underdeveloped. Left unexplained, for instance, is why cases of high testosterone and high cortisol occur at all; if high cortisol indexes conditions that contraindicate dominance competition, then why in such cases is testosterone sometimes also elevated? Theoretical frameworks can help answer such questions. By considering the eliciting conditions for testosterone and cortisol simultaneously, the relative production of the two hormones under specific circumstances can be predicted and tested, with downstream output effects then mapped to patterns of joint hormone production. Of course, two is arbitrary for the number of hormones tested (there is no reason to think that "dual" effects are most important), and this approach can be expanded to any number of signals to investigate physiological codes that link eliciting conditions to coordinated output responses. Although the investigation of such multiple signal codes is empirically challenging, it is also an exciting direction for future research in human behavioral endocrinology.

[3] It may be worth pointing out that the theoretical framework postulated for ovarian hormones also demonstrates combined effects of multiple hormones, since estradiol has larger influences on many outcomes when progesterone is low. In this case, there is a clear functional logic to such combined effects given that within-cycle fecundity is associated with high estradiol and relatively low progesterone.

5. Conclusion

A main premise of this article is that understanding the evolved functions of hormones requires mapping how endocrine signals mediate relationships between environmental and other eliciting conditions and output effects that are adaptive responses to those conditions. Frank Beach made a similar point over 40 years ago: "Explication of the interactions and interdependencies between hormones, the environment, and the individual's behavior is essential to a full understanding of the adaptive and evolutionary significance of hormonal function, and this in turn is a primary goal of behavioral endocrinology" (1974; pp. 15–16). Theoretical frameworks are simply ways of organizing hypotheses and research findings about hormones that make explicit input–output mappings and thus facilitate the evaluation of evolved functions. A second premise of the article is that hormones typically have multiple targets that they affect in coordinated ways. By listing how eliciting conditions are mapped into multiple output effects, theoretical frameworks organize and clarify hypotheses regarding coordinating functions.

Although the theoretical framework approach seems like an obvious way to think about hormones, its application is not especially common in research on human hormones. When the claim is made or tested that oxytocin is a "trust" hormone, what input–output relationship has been postulated? What coordinating functions have been stipulated? Breaking potentially complex, multi-signal endocrine codes is a challenging empirical task, but it will never happen if researchers do not think about input–output mappings in the first place.

Research on evolved functions in some cases appears to be neglected as a matter of principle. Claims have been made that specific hormones "may not have a 'function'" (Churchland and Winkielman 2012, p. 398), and it is not uncommon to encounter the position that evolutionary explanations should be avoided entirely in favor of focus on more concrete empirical claims (e.g., Mazur in press). We cannot accept as a given that hormones have coordinating functions, but then simultaneously argue that hormones may not have functions or that we should not study function. To be consistent, researchers need to decide whether functional considerations will guide investigation of human endocrine signals. Clearly, I side with Beach's position that understanding adaptive and evolutionary functions of hormones should be a "primary goal" of behavioral endocrinology. The main contention of this article is that the theoretical framework approach is the best way to achieve this goal.

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