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Social information changes the brain

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Social animals live in complex physical and social environments requiring them to attend and rapidly respond to social and environmental information by changing their behavior. A key social influence is rank or status, a ubiquitous element in animal societies. Rank typically regulates access to reproduction and other resources, among other consequences for individuals. Because reproduction is arguably the most important event in any animals' life, understanding how reproduction is regulated by social status and related physiological factors can instruct our understanding of evolutionary change. This article reviews evidence from a model social system in which reproduction is tightly controlled by social status. Surprisingly, changes in social status have rapid and profound effects over very short time scales and radically alter overt behavior, as well as physiological, cellular, and molecular factors that regulate reproductive capacity.

brain plasticity | cichlid fish | immediate early gene | social rank

Social rank is a ubiquitous element in social systems and an essential organizing principle for understanding social behavior (1). Typically, dominance in animals is established by repeated agonistic interactions with a consistent outcome in favor of one individual (2). Dominance hierarchies can take many forms, and in humans socioeconomic status (SES) is the nearest approximation to hierarchical social rank. Status has been shown to dramatically influence the quality of an individual's life, as seen in the strong, inverse relationship between employment level and mortality rate identified in the British civil servant system (3). In animals, there are plentiful examples of the importance of rank on biological systems. In rhesus macaques (*Macaca mulatta*), for example, social rank regulates the immune system, with low-status individuals increasing gene expression in their immune response to inflammation (4), and social status predicts wound healing rate in wild baboons (*Papiocynocephalus anubis*) (5). Although rank must alter health through specific mechanisms, little is known about the biological representations and consequences of social stratification.

Awareness of status is a salient component of social interactions in humans and other animals. Social rank is conceptually represented by 15-mo-old human infants (6), used by 2-y-olds (7), and activates discrete brain regions in human adults (8, 9). The importance of rank is underscored by the fact that many nonprimate species can predict social rank through observation of others using transitive inference, including birds (10) and the cichlid fish that is our model system (11).

In this review we will describe a cichlid fish model system in which we can mimic the natural social and physical environment to analyze how social interactions control reproduction. Because social status is central to the social regulation of reproduction in this species, we then review research describing the rapid response of the animals we study to an opportunity to ascend in rank, how these fish collect and use social information, and where this information is represented in the brain. Taken together, these studies reveal a core set of mechanisms that have evolved to regulate reproduction and are likely conserved across phylogeny.

Model System

Reproduction in all vertebrates is controlled by the evolutionarily conserved hypothalamic–pituitary–gonadal (HPG) axis. At its apex are the gonadotropin-releasing-containing (GnRH1) neurons in the hypothalamic–preoptic area of the brain that ultimately control reproduction. GnRH1 neurons integrate information from social and environmental signals with internal state, including nutritional and hormonal condition. The synthesis of these signals controls GnRH1 production in the brain and its release to the pituitary gland. However, how are these neurons regulated by social interactions?

In our model system, an African cichlid fish species, *Astatotilapia burtoni*, the GnRH1 neurons are directly controlled by social status, a highly dynamic aspect of the social life of this species. *A. burtoni* is a maternal mouth-brooding cichlid species endemic to shallow shore pools of Lake Tanganyika, Africa (Fig. 1). Males exist as one of two phenotypes: (*i*) dominant territorial males constituting ∼10–30% of population, which are brightly colored, aggressively defend a spawning territory, and actively court and spawn with females using 19 distinct behavioral patterns; and (*ii*) subordinate nondominant males that resemble and school with females, express only a few submissive behaviors, and do not court females (12).

Males Have a Rapid Response to Social Opportunity

Males can rapidly and reversibly switch between dominant and subordinate states, depending on the composition of the social environment, and such transformations produce a suite of remarkable behavioral and physiological changes (e.g., refs. 12 and 13). When subordinate males ascend in social status, they dramatically change their body coloration and increase dominance behaviors in minutes (14, 15). Further, within 20 min, the immediate early gene (IEG) *egr-1* is up-regulated in the GnRH1 neurons located in the preoptic area of the brain (Fig. 2) (16). *Egr-1* is both an immediate early gene and a transcription factor for GnRH1 expression, meaning the neurons controlling the reproductive axis are genomically activated within minutes of the recognition of social opportunity. Moreover, levels of GnRH are increased in the brain 30 min after social ascent. After these extremely rapid behavioral and brain genomic responses, other physiological changes may take up to 1 wk to achieve levels comparable to what is found in dominant males (e.g., ref. 17) (Fig. 3).

After social ascent, a dramatic change occurs in the size of GnRH1 neurons: They become approximately eightfold larger in volume in dominant compared with nondominant males and subsequently can enlarge and shrink repeatedly as an animal transitions between dominant and nondominant status, potentially many times in its lifetime (18). GnRH1 cell size increase

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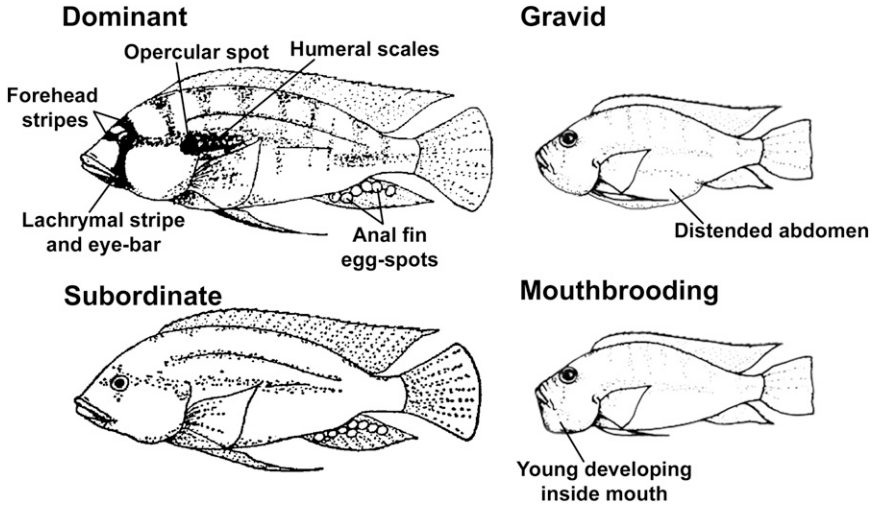

Fig. 1. Body patterns for typical dominant (territorial; *Upper Left*) and nondominant (nonterritorial; *Lower Left*) *A. burtoni* males, and sexually receptive, gravid (*Upper Right*) and mouthbrooding (*Lower Right*) females. Dominant males have a bright basic color (yellow or blue), with distinct yellow-orange egg-spots on their anal fins, dark forehead stripes, a dark opercular spot on the caudal edge of the gill cover, a dark lachrymal stripe or eye-bar extending from the eye to the lower jaw, and a bright orange-red patch on the humeral scales. Subordinate males are pale and similar in color to females. Females cycle between a gravid and receptive phase, in which they develop distended abdomens from growing oocytes, and a mouthbrooding phase, in which their mouths distend to accommodate the developing young inside the mouth. Modified from ref. 15.

can be detected within 1 d after ascent and reaches full size within ~4 d (17, 18). The larger GnRH1 neurons in dominant males also have increased dendritic complexity compared with subordinate males (19, 20). Clearly nondominant males are poised to become dominant males, and their response to the opportunity is rapid, extending from behavior to genomic expression in the brain.

The primary targets of the GnRH1 peptide released from the brain are the gonadotropin-producing cells in the anterior pituitary gland via direct neuronal projections in teleost fish. There it binds to GnRH receptors on the gonadotrope cells to induce synthesis and cause the release of the two gonadotropin hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which then target the gonads (testes or ovaries) to stimulate steroid production and gamete development. In *A. burtoni*, there are two types of GnRH receptors (21, 22), and the pituitary mRNA levels of *GnRH-R1*, but not *GnRH-R2*, are socially regulated so that dominant males have higher levels than nondominant males. This increase after social ascent occurs more slowly (days) than changes in mRNA levels of other genes that occur within minutes to hours (14, 22). However, pituitary mRNA levels of the IEG *egr-1* and of the β-subunits of LH and FSH are increased 30 min after social ascent, suggesting that GnRH1 release quickly activates the pituitary gland (14, 23). Moreover, circulating levels of LH and FSH are also higher by 30 min after ascent, suggesting that GnRH1 in the pituitary stimulates both the release and synthesis of gonadotropins (23). Thus, just minutes after an animal perceives and responds behaviorally to a social opportunity, the brain–pituitary portion of the HPG axis has begun to prepare the animal for reproduction.

In addition to small GnRH1 neurons and low HPG axis activity, nondominant males also have small testes. However, if the nondominant male was recently dominant, despite their reduced size, the testes continue to produce sperm more slowly during the suppression period and retain viable sperm, consistent with slower cell addition generally in nondominant males (24, 25). Residual sperm retention by nondominant males may allow a reproductively suppressed male to spawn with females upon social ascent without having to wait the 5–7 d for the testes to grow and the 10–11 d required for new sperm production (24). Perception of social opportunity also triggers changes in mRNA levels in the testes, on both rapid (minutes to hours; folicle-stimulating hormone receptor, androgen receptors, corticosteroid receptors) and slow (days; leuteinizing hormone receptor, aromatase, estrogen receptors) time scales (14). During the subordinate to dominant male social

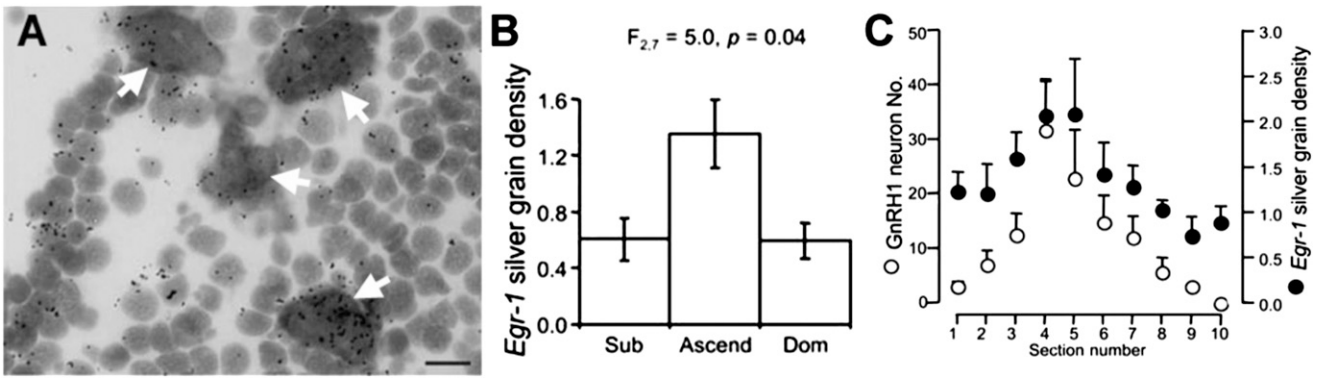

Fig. 2. Rapid increase in mRNA expression of the immediate early gene *egr-1* in GnRH1 neurons and throughout the nuclei of the SBN in males transitioning from subordinate to dominant status. (*A*) Photomicrograph of *egr-1* silver grains (small black dots; in situ hybridization) on GnRH1 neurons (arrows) in the anterior parvocellular preoptic nucleus (aPPn) of a male *A. burtoni*. (Scale bar, 10 μm.) (*B*) *Egr-1* silver grain density (mean ± SE) of the entire aPPn in subordinate (Sub), ascending (Ascend), and dominant (Dom) males shows greater *egr-1* staining at 20 min after social opportunity in ascending males compared with the stable social states. (*C*) GnRH1 neuron number (open circles) and *egr-1* silver grain density (filled circles) (mean ± SE) within adjacent sections of the aPPn to show the greater *egr-1* staining in sections that have more GnRH1 neurons. Modified from ref. 16.

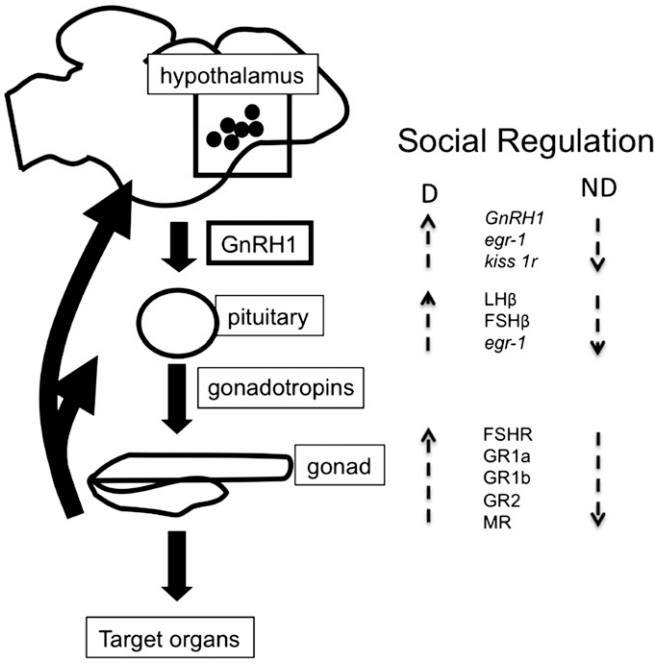

Fig. 3. Schematic illustration of the HPG axis showing genes and peptides regulated in males by the occasion of social opportunity. Information about social status is processed by the brain, which, in turn communicates with the gonads via the HPG axis. Physiological signals regulated by the ascent in status are indicated in the table on the right. All these are up-regulated as a male becomes dominant (D) and down-regulated when a male becomes nondominant. For more detail, see ref. 14.

transition, the morphological and structural changes in testicular cell composition and relative testes size change takes several days, whereas many molecular changes in the testes occur more quickly (26). This rapid transcriptional response in the most distal physiological target of the HPG axis highlights how sensitively the system responds to social information and the plasticity of the entire reproductive system. We now know that significant changes in transcriptional activity in tissues from the brain to the testes all occur within minutes of a social opportunity, which is much more rapid than suspected. These rapid molecular changes in the testes raise the possibility that there may be signaling pathways parallel to the inferred linear cascade from brain GnRH1 signals causing pituitary LH/FSH release to testicular gonadotropin receptor activation.

Collecting Social Information

The remarkably rapid genomic responses to social change suggest that *A. burtoni* use social information to guide their behavioral choices. However, how do they collect useful information, and when do they do it? One of the most obvious problems facing both dominant and nondominant males is the relative fighting strength of conspecifics and more specifically close neighbors because dominance depends on winning fights. However, for a male to test his relative dominance empirically would require pairwise fights with other males to establish a dominance hierarchy. Such fights would be quite numerous, energetically costly, and would require time better spent courting females. The natural habitat of *A. burtoni* is a rather unstable physical and social environment where foraging and reproductive opportunities change frequently (12). Because reproduction is linked directly to an individual's dominance position, it is particularly important for males to ascend in rank to reproduce. This suggests that acquiring information by watching others and learning from social encounters might be a way around this problem. In a series of experiments, we have measured how animals acquire information and how it changes their brains and behavior.

To understand how information is collected, we first tested which sensory systems play a role when one male influences another to understand how dominant males suppress the behavior and physiology of other males. Chen and Fernald (27) tested the role that visual cues alone from a larger dominant male had on the behavior, reproductive physiology, and stress response of a smaller male. By allowing two dominant males, differing in size by a factor of 4, to establish adjacent territories out of view of one another and to be able to court females, these two males behaved as prototypical dominant males. When the opaque barrier between them was removed, leaving only the transparent barrier, the small male suppressed all dominance behaviors and coloration patterns. However, it did not suppress the internal expression of genes associated with his prior dominant state. For example, mRNA expression of reproductive and stress-related genes in the brain (GnRH1, corticotrophin-releasing factor system, arginine vasotocin), as well as circulating androgens and testes size, did not differ from controls and were more similar to dominant male levels. This experiment suggests that visual cues are extremely important for regulation of behavior but that additional sensory cues are needed for complete suppression of physiology and reproduction. In the visual presence of larger animals, small males seem to use an opportunistic strategy and behave like subordinate males to minimize aggressive attacks and potential injury from other males, while maintaining the physiology of a dominant male, perhaps in anticipation of an opportunity to regain a territory and reproductive competence in the future. Acoustic and chemosensory signals seem to be additional potentially important sources of sensory information (28, 29).

In another set of studies, we recently discovered that males can actually infer the relative dominance among five animals simply by watching those individuals in pairwise fights. To do this, they use transitive inference, the ability to infer relationships among items or individuals that have not been seen together, to rank those items (11). Observer males saw staged pairwise fights between size-matched males with an implicit hierarchy (a > b > c > d > e) and were then tested for their ability to predict the outcome of contests they had not seen, such as whether "b" beat "d" in a fight. The animals' success in inferring the outcome of these fights revealed that they had established a reliable ranking of the individuals they had observed fighting in pairs. This knowledge would allow animals to judge which neighbors they might choose to challenge. Gleaning information as a bystander allows males to decide whether to engage in costly fights with novel competitors. We had previously observed that *A. burtoni* spend a great deal of time observing one another, possibly collecting social information useful for guiding their behavior.

Because dominant males frequently engage in fights and border disputes with neighboring males, how do these agonistic confrontations influence their subsequent behavior? We first watched dominant and nondominant animals in a seminatural situation and observed that nondominant animals transiently acted aggressively when the dominant male could not see them (30). The animals behaved as if they had an "attention" hierarchy, similar to that reported for primate societies in which dominant individuals are the focus of attention of those holding subordinate status in the group (31). That is, in *A. burtoni*, the nondominant males attended to the behavior of dominant males more or less continuously, and nondominant male behavior was contingent on dominant male behaviors.

We then tested the response of males when they were being watched to ask whether the watched animals were also attending to their local social context. We found that male behavior changes depending on who is watching. Males fought more

intensely when being watched by a gravid female and less intensely when being watched by a larger, more-dominant male (30). These data suggest a rich interwoven nexus of behaviors depending on the status of the individual and the social context. It also implies a sophisticated behavioral system tuned to subtle social cues used to guide behavioral decisions. However, where and how is this information being processed in the brain?

Brain Responses to Social Information and Behavior

Social behaviors in vertebrates are coordinated by conserved networks of neural circuits that are believed to evaluate the salience of inputs and their context, resulting in changes in behavior. Specifically, a "social behavior network" (SBN) has been implicated in the regulation of many social behaviors, including aggression, parental care, mating, sexual behaviors, and communication (32). The SBN comprises six brain nuclei, or nodes (lateral septum, medial extended amygdala/bed nucleus of the stria terminalis, preoptic area, anterior hypothalamus, ventromedial hypothalamus, and midbrain periaqueductal gray/tegmentum) that are reciprocally connected and express high levels of steroid receptors. Originally identified in mammals (32), homologous regions have been found in reptiles (33), fish (34, 35), and birds (33), providing a useful framework for analyzing the neural bases of social behaviors (36, 37). The expression of steroid receptors in the SBN nuclei suggests that these nodes are also important neural substrates for integration of social behavior with an animal's hormonal state. The SBN is an example of an identified brain network involved in social behavior, but other core neural networks, such as the "mesolimbic reward system," also conserved among vertebrates, may interact with the SBN and others to form a larger "social decision-making network" that regulates adaptive behavior (37), although there are not comparable experimental data to fully indentify the interactions of this larger network.

The recognition of key social behaviors and, more exactly, social opportunities is likely to activate many neural and genomic circuits. For example, as a male ascends to dominance he quickly expands his behavioral repertoire from 3 to 19 distinct behaviors accompanied by his transformation in appearance and changes in physiology. To assess the activity of vertebrate brains in relation to these networks, IEGs such as *egr-1*, *cfos*, *jun*, *arc*, and others have proven useful as they reflect underlying neural responses, known as "genomic action potentials" (38–40). The cellular IEG response occurs within minutes and indicates *changes* in relative neuronal activity leading to downstream transcriptional changes in the cell (39–41), providing important information about brain regions involved in the activation of neural circuits.

We measured IEG expression in several contexts, including social ascent, to identify brain regions activated during important behavioral events. Specifically, we measured mRNA levels of IEGs (*egr-1, cfos*) from microdissected brain regions as a proxy for transcriptional–neuronal activation in behavioral paradigms ranging from social ascent to more subtle behavioral tests of observed social interactions. These data illuminate how the SBN is implicated not only in social behavior but also in processing social information.

Nondominant males given an opportunity to rise in social rank compared with stable subordinate and dominant individuals revealed a dramatic increased response throughout the SBN (Fig. 4). Other studies that use IEGs to examine brain activation in response to social information typically reveal differential patterns of expression depending on the social context, such that, for example, male aggression and male sexual behavior can have distinctly different expression patterns across the SBN nodes (32, 34). Social ascent in *A. burtoni*, however, is associated with simultaneous reproductive and aggressive/territorial contexts, producing a combined activation pattern of all of the SBN nuclei. It is also possible that social opportunity produces a widespread response, initiating changes in neural and cognitive processing required for the new social rank. We also found rapid (30 min) region-specific changes in sex steroid receptor mRNA levels induced by social opportunity, most notably in estrogen receptor subtypes in brain areas that regulate social aggression and reproduction. These data suggest that estrogenic signaling pathways may be more important during male social transitions than previously known. Sex steroid receptor changes also occurred in regions homologous to the mammalian lateral septum and bed nucleus of the stria terminalis, two nuclei shared by SBN and reward circuits, suggesting an important functional role in the integration of social salience, hormonal state, and adaptive behaviors. The rapid transcriptional response suggests that the SBN is involved in the integration of social inputs with internal hormonal state to facilitate the transition to full dominance.

Because females should be choosier than males about prospective mates because of the high costs of inappropriate mating decisions, we suspected they might also be collecting information about males before mate choice. We tested this experimentally by having a gravid female indicate a preference between two socially equivalent males, using only visual cues. Females then saw fights between the same two males in which her preferred male either won or lost, and as before females only saw the fight and its outcome (36). We then measured IEG expression levels

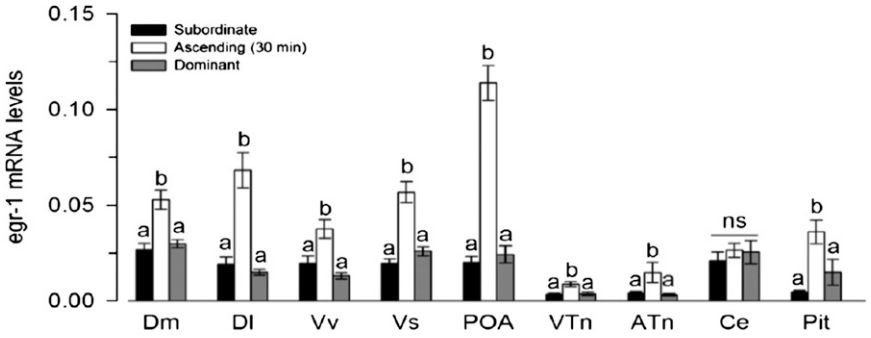

Fig. 4. Social opportunity rapidly increases *egr-1* mRNA levels (measured by quantitative PCR in nuclei of the SBN. Relative mRNA levels (normalized to the geometric mean of the reference genes *18s* and *g3pdh*) were higher in ascending males compared with the stable subordinate and dominant male states. Different letters indicate significant differences among social groups at $P < 0.05$. ns, not significant. ATn, anterior tuberal nucleus; Ce, cerebellum; Dm, medial part of the dorsal telencephalon; Dl, lateral part of the dorsal telencephalon; Pit, pituitary; POA, preoptic area; Vs, supracommissural nucleus of the ventral telencephalon; VTn, ventral tuberal nucleus; Vv, ventral nucleus of the ventral telencephalon. Reproduced from ref. 34.

in brain nuclei including those in the vertebrate SBN. When the female saw her preferred male win a fight, SBN nuclei associated with reproduction were differentially activated, but when she saw her preferred male lose a fight, the lateral septum, a nucleus associated with anxiety, was highly activated instead (Fig. 5). Thus, social information alone, independent of physical social interactions, activates specific brain regions that differ significantly depending on what the female sees. In female brains, reproductive centers are activated when she chooses a winner, and anxiety-like response centers are activated when she chooses a loser.

In contrast to our knowledge about the physiological consequences of social ascent, relatively little is known about changes in gene expression that occur during social descent when a dominant male loses his territory and is forced to become subordinate (17, 42). During social descent, within minutes of losing a territory, previously dominant males lose body coloration, turn off their eye-bar, and perform only submissive behaviors such as fleeing (18, 42). In contrast, physiological changes in GnRH1 soma size, GnRH1 mRNA levels, and testes size takes several weeks to decline to stable subordinate male levels (17). In another study, GnRH1 mRNA levels in the brain were increased at 24 h after social descent, possibly functioning as a short-term defense mechanism against status loss to help maintain the HPG axis in anticipation of a quick return to dominance (42). In a recent study, we showed that the mean latencies between ascent and descent were not different [~12 min (43)], suggesting that males can evaluate their immediate fate quickly and respond appropriately despite the different valence. However, the neural signatures of ascent and descent are distinctly different. Social ascent is associated with rapid changes from the organismal to the molecular level, and the molecular mechanisms responsible for social descent seem to occur on a slower time scale, possibly as an adaptation temporarily preserving reproductive opportunities. There may be additional subtle differences between these processes in animals after their first and subsequent social ascents or descents.

Gathering spatial information from the environment is also important for group-living species such as *A. burtoni*, where substrate for territories is often a limiting resource and critical for reproductive success. Quickly identifying suitable or vacant territories and hiding places to avoid predators is important for survival. However, we know little about spatial learning capacities in *A. burtoni*, despite its importance in the natural habitat. To test how *A. burtoni* might learn, males were trained in a biologically relevant spatial task that was to gain access to shelter and proximity to females. After training, mRNA levels of IEGs (*egr-1*, *cfos*, *bdnf*) were measured in socially relevant brain regions, including the SBN, after their tenth learning trial using the techniques described above (44). Fish trained in the task fell naturally into three distinct categories: fish that could be trained (learners), fish that could not be trained (nonlearners), and fish that never attempted the task (nonattempters). Learners had higher IEG mRNA levels (*egr-1*, *bdnf*) in brain regions typically associated with spatial learning and memory, specifically, the lateral part of the dorsal telencephalon, Dl, which is the homolog of the mammalian hippocampus. These animals also had lower plasma cortisol levels and were more motivated to complete the task. In contrast, nonattempters had the lowest IEG levels in Dl and highest plasma cortisol levels. These results suggest that there is a continuum in learning types reflected in differential IEG expression patterns in the brain. It is clear that stress, as reflected in cortisol levels, plays an important role on learning and performance in a spatial task (44).

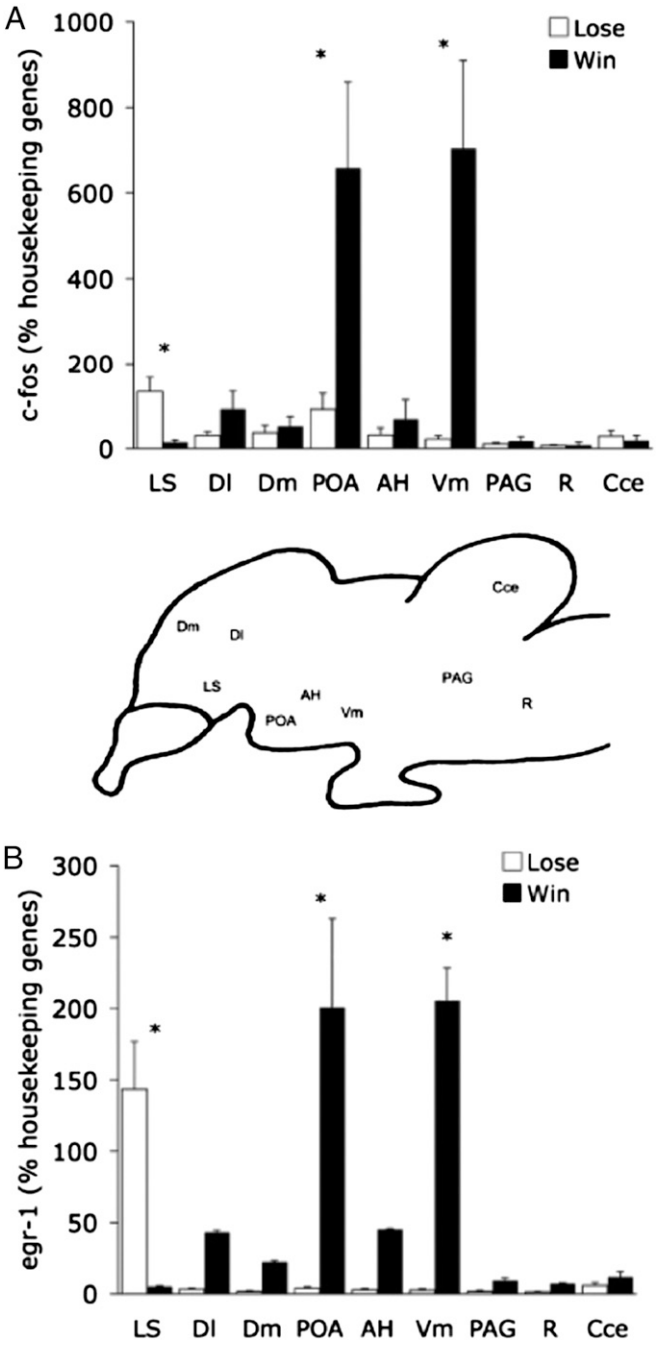

Fig. 5. Relative levels of mRNA expression of *cfos* (*A*) and *egr-1* (*B*) for each of the six nodes of the SBN, plotted as a function of whether females saw their preferred males win (filled bars) or lose (open bars) a fight. Asterisks above pairs of values (mean + SE) indicate significant differences (*t* tests, corrected for multiple comparisons). Between *A* and *B* is a schematic sagittal section of the *A. burtoni* brain showing the approximate locations of the microdissected brain regions sampled. AH, anterior hypothalamus; Cce, cerebellum; Dm, medial part of the dorsal telencephalon; Dl, lateral part of the dorsal telencephalon; LS, lateral septum; PAG, periaqueductal gray; R, raphe nucleus; Vm, ventromedial hypothalamus. Modified from ref. 38.

Conclusions

Social status has left an unmistakable mark on behavior, physiology, and gene expression in this model system. Essentially, every aspect of the reproductive axis where we investigated, the effects of social behavior could be identified at all levels of investigation. Social information and consequent behavior profoundly influence the brain in general but specifically the highly conserved reproductive axis. Our results suggest that detailed examinations of other species will reveal similar adaptations in the service of reproduction.

However, far less is known about how this social information influences the key neural circuits and patterns of gene expression. There are critical unanswered questions about the links between social behavior, reproductive function, and the genome. For example, what signal pathways link reception/perception of a constellation of social cues that lead to changes in gene expression along the HPG axis? It seems clear that the next step is to use the many advances in proteomics, transcriptomics, microtranscriptomics, and epigenomics, combined with comparative systems approaches including single-cell analyses, optogenetics, and transgenic methods. The regulatory roles of epigenetic and small RNAs (e.g., microRNAs) in mediating socially induced changes along the reproductive axis is also an exciting area of future work (45, 46) that should provide insights into our understanding of the mechanisms governing social and seasonal reproductive plasticity across taxa. The cichlid fish *A. burtoni*, with its complex and experimentally manipulable social system, wealth of background knowledge about the social control of HPG axis function, and the newly available genomic resources will become a valuable vertebrate model system for studying how the social environment influences genomic plasticity and function of the reproductive axis.

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