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SYMPOSIUM

# Putting it in Context: Linking Auditory Processing with Social Behavior Circuits in the Vertebrate Brain

Christopher L. Petersen and Laura M. Hurley[1]

Department of Biology, Indiana University, Bloomington, 47405 IN, USA

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[1]E-mail: lhurley@indiana.edu

**Synopsis** Context is critical to the adaptive value of communication. Sensory systems such as the auditory system represent an important juncture at which information on physiological state or social valence can be added to communicative information. However, the neural pathways that convey context to the auditory system are not well understood. The serotonergic system offers an excellent model to address these types of questions. Serotonin fluctuates in the mouse inferior colliculus (IC), an auditory midbrain region important for species-specific vocalizations, during specific social and non-social contexts. Furthermore, serotonin is an indicator of the valence of event-based changes within individual social interactions. We propose a model in which the brain's social behavior network serves as an afferent effector of the serotonergic dorsal raphe nucleus in order to gate contextual release of serotonin in the IC. Specifically, discrete vasopressinergic nuclei within the hypothalamus and extended amygdala that project to the dorsal raphe are functionally engaged during contexts in which serotonin fluctuates in the IC. Since serotonin strongly influences the responses of IC neurons to social vocalizations, this pathway could serve as a feedback loop whereby integrative social centers modulate their own sources of input. The end result of this feedback would be to produce a process that is geared, from sensory input to motor output, toward responding appropriately to a dynamic external world.

## Introduction

The ability for an animal to contextualize communication signals has strong fitness consequences. For instance, an animal in a reproductive stage of its cycle may be responsive to courtship signals produced by potential mates (Chakraborty and Burmeister 2009; Forlano and Bass 2011; Maney and Pinaud 2011). However, identical cues received in a non-reproductive phase (Maney et al. 2006; Lynch and Wilczynski 2008; Maney et al. 2008) or in the presence of a predator (Bernal et al. 2007; Grimsley et al. 2013) might be perceived as less salient, and fail to elicit a behavioral response. Therefore, an animal's contextual state, which comprises the interaction between external events or context and an animal's physiological state and past experience, contributes to the adaptive value of communication (Maney 2013) (Fig. 1). Sensory systems play an important role in this process by transforming the physical components of external cues (i.e., sound waves, odorants, etc.) into meaningful neural representations that are critical to the assessment of social signals. Sensory systems are also the first stage at which cues from the external environment can be coordinated with internal representations of state or salience. There is ample evidence that sensory systems are responsive to contextual state on time scales related to both predictable seasonal changes that induce concomitant changes in internal physiology (Caras 2013; Forlano et al. 2015), and to the more unpredictable dynamics of social interactions (Remage-Healey et al. 2008; Hall et al. 2011; Keesom and Hurley 2016). Furthermore, context- and state-dependent sensory processing contributes to the behavioral outcomes of social interactions (Lynch and Wilczynski 2008; Grimsley et al. 2013; Marlin et al. 2015). Despite many examples of these phenomena, the neural pathways that

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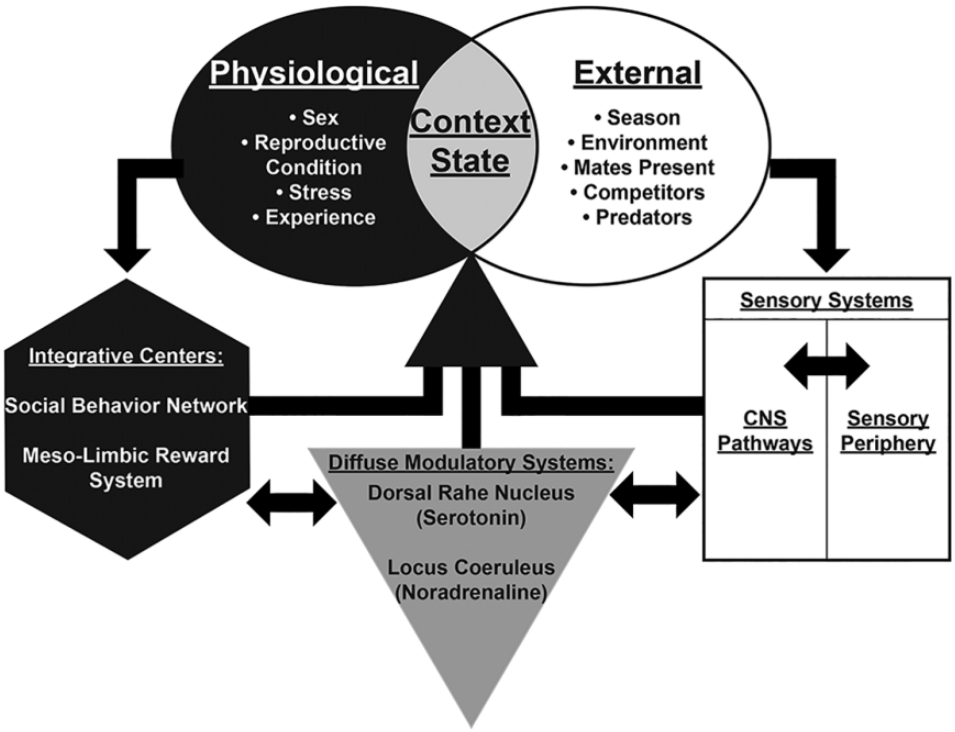


**Fig. 1** The emergence of contextual state. An animal's contextual state is established by a complex interaction between internal physiology, environmental conditions, and the neural circuitry sensitive to both.

connect brain regions that evaluate external context and physiological state with sensory systems are not clear.

Here, we discuss studies demonstrating that sensory systems are sensitive to changes in internal state and external circumstances, which facilitate the ability for an animal to respond appropriately to socially relevant sensory cues. Next, we review work from our lab demonstrating that the neuromodulator serotonin is one mechanism through which contextual state may be conveyed to the auditory system. Finally, we present evidence in support of an emerging model of centralized neuromodulatory systems such as the serotonergic system as a link between neurochemical systems nested within social behavior circuits (e.g., the nonapeptides oxytocin and vasopressin) and primary sensory systems.

## Salient states and events influence sensory systems

Long-term shifts in the response characteristics of sensory systems are one way that animals can adapt to predictable changes in internal state, such as during the reproductive phases of seasonal or cyclical breeders. For example, steroid hormones organize peripheral sensory systems to preferentially encode social signals that are salient only with respect to an animal's reproductive condition. Female midshipman fish (*Porichthys notatus)* depend on their auditory systems to locate the nests of vocally courting males during annual spawning seasons (Brantley and Bass 1994). The inner ears of reproductive females are more sensitive to the higher frequencies of male vocalizations than those of non-reproductive females, a mechanism that is thought to aid in sound source localization (Sisneros and Bass 2003). Treating non-reproductive females with testosterone or estradiol induces a reproductive auditory phenotype, suggesting that seasonal fluctuations of steroid hormones induce auditory plasticity that is both adaptive and a signal of reproductive state (Sisneros et al. 2004; Coffin et al. 2012). In an analogous circumstance, female mice (*Mus musculus*) which rely heavily on olfactory signaling for reproduction and survival, become "smell blind" to male urine during diestrus, a non-reproductive phase of the estrous cycle (Dey et al. 2015). During diestrus, progesterone silences a subset of vomeronasal sensory neurons (VSNs) that bind behaviorally salient male urinary proteins, which in turn reduces female preference for male urine. Importantly however, VSNs that bind ligands within cat urine remain stable throughout the estrous cycle (Dey et al. 2015). Changes in the sensitivity of peripheral sensory systems are therefore not only confined to reproductive phases, but are also selective for reproductively relevant stimuli.

On event-related time scales, neuromodulators such as the nonapeptides oxytocin and vasopressin, which are nested within functionally heterogeneous social behavior circuits, are engaged to influence sensory systems (Caldwell and Young 2006; Albers 2015; Bester-Meredith et al. 2015). Sensory modulation also occurs via centralized integrative centers like the serotonergic dorsal raphe nucleus (DRN) or the noradrenergic locus coeruleus (Hurley et al. 2004). Despite differences in neural architecture, developmental trajectories, and evolutionary histories (Jacobs and Azmitia 1992; Stoop et al. 2015), these systems show strong functional parallels in their regulation of sensory information. Modulatory neurons strongly respond to external events, and further may respond best to specific qualities of these events indicating behavioral relevance (Bharati and Goodson 2006; Ho et al. 2010; Petersen et al. 2013; Dass and Vyas 2014; Kelly and Goodson 2015). As a result, these modulatory pathways can alter the responses of sensory neurons to stimuli. For example, chemically ablating noradrenergic neurons abolishes the selectivity of transcriptional activation by conspecific versus heterospecific songs in auditory forebrain regions of female canaries *(Serinus canaria)* (Lynch and Ball 2008). Similarly, ablating noradrenergic neurons in female canaries reduces copulatory responses to otherwise salient male courtship songs (Appeltants et al. 2002). Although neuromodulatory pathways broadly coordinate responses to salient events across neural systems (Lee et al. 2008; Mitre et al. 2016; Smith et al. 2017), only a few studies have directly addressed the influence of modulation within sensory regions on behavior. For example, locally increasing oxytocin within the auditory cortex of virgin female mice causes pup retrieval behavior to develop more rapidly than for control treatments (Marlin et al. 2015). Although these studies demonstrate a key role for sensory modulation in altering the behavior of receivers, the pathways that lead to release of neuromodulators within sensory systems are not well understood.

Sensory regions receive direct projections from modulatory systems. In rodents, the inferior colliculus (IC), an auditory midbrain structure important for processing species-specific vocalizations, receives the vast majority of its serotonergic innervation from the DRN (Klepper and Herbert 1991). Serotonin increases within the IC of mice during social or stressful encounters and its release is thought to be indicative of the salience of external conditions (see below). However, the DRN is not embedded within the brain's social behavior network (SBN) (Jacobs and Azmitia 1992). Rather, "top-down" mechanisms are required to recruit DRN neurons in a context-dependent manner (Challis and Berton 2015). The DRN receives projections from over 100 functionally distinct nuclei including each node of the SBN (Pollak Dorocic et al. 2014; Weissbourd et al. 2014). The DRN's afferent profile may provide it with the flexibility to convey features of social and non-social context to sensory systems, including the IC. Likewise, the DRN's extensive projections make it highly suitable to distribute these features to wide array of brain regions (Jacobs and Azmitia 1992).

## Serotonin release in IC is context dependent and valence sensitive

The IC is an obligate gate through which most ascending auditory information from the brainstem must pass (Winer and Schreiner 2005). Due to the combination of inhibitory and excitatory inputs from lower auditory areas, acoustic responses are more selective to species-specific calls within the IC than in its brainstem afferents (Bauer et al. 2002; Klug et al. 2002; Xie et al. 2005). In addition to receiving projections from the auditory thalamus (Senatorov and Hu 2002) and cortex (Xiong et al. 2015), IC receives neuromodulatory afferents from serotonergic, noradrenergic, and dopaminergic neural populations (Klepper and Herbert 1991; Hurley and Thompson 2001; Nevue et al. 2015), which can potentially convey information on contextual state to auditory regions. To demonstrate that neuromodulation within the IC is indicative of contextual state, it is necessary to use a measurement technique that captures dynamic fluctuations in modulator levels on timescales relevant to salient events like social interactions. Our lab uses carbon-fiber voltammetry to monitor *in vivo* changes of the neuromodulator serotonin in freely behaving laboratory mice (CBA/J; Jackson Labs). This technique provides us with an *in vivo* assay to measure how levels of serotonin fluctuate within IC while mice navigate various social and non-social contexts

Serotonin release in the IC is dependent on external events. Within 5 min after the onset of restriction stress, serotonin not only increases in the IC of male and female mice, but is also maintained at an elevated level throughout the duration of restriction (Fig. 2) (Hall et al. 2010; Hall et al. 2012; Hanson and Hurley 2014). Similarly, exposure to broadband noise elicits a rapid increase of serotonin in the IC of male mice that is sustained over the course of the stimulus (Fig. 2) (Hall et al. 2010). However, no such increase is observed when mice are presented with food or light stimuli (Fig. 2) (Hall et al. 2010), each of which has been demonstrated to affect levels

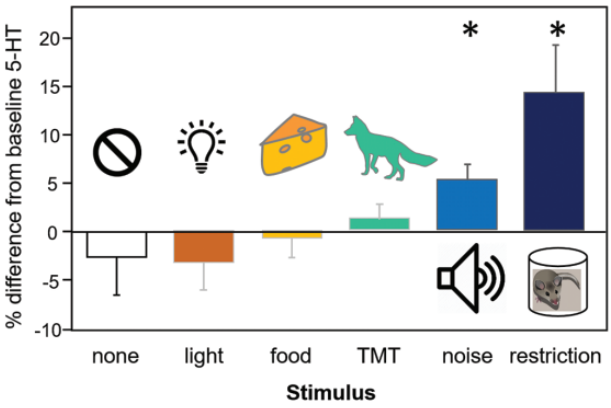


**Fig. 2** Serotonergic increases within the IC are dependent on specific external events. Of the five non-social conditions tested, only the presentation of noise and the restriction of movement within a cylindrical arena significantly increased serotonin relative to no stimulus. Figure adapted from Hall et al. 2010, J Exp Bio 213:1009–1017.

of Fos, an immediate early gene product and putative marker for neural activation, (Clayton 2000) within serotonergic neurons in DRN (Hale et al. 2008; Takase and Nogueira 2008). Interestingly, exposure to TMT (2,5-dihydro-2,4,5-trimethylthiazoline; a component of fox urine) increases levels of serotonin in dialysate obtained from the prefrontal cortex and central amygdala (Smith et al. 2006), but not during voltammetric recordings within IC (Hall et al. 2010). A direct comparison between these studies is difficult as different methods (i.e., voltammetry vs. microdialysis) capture distinct aspects of serotonergic signaling. In particular, voltammetry with large carbon fibers likely captures a "volume transmission" mode of serotonin release, rather than more localized synaptic events (Bunin and Wightman 1998). Regardless, it is intriguing that a salient cue such as predator odor does not affect voltammetrically-measured serotonin in the IC given that similar cues (i.e., cat fur) reduce behavioral preference for female vocalizations in male mice (Grimsley et al. 2013). Together these studies show that not every change in a mouse's external context is sufficient to increase levels of serotonin in IC, nor does serotonin release in IC appear to be an indicator of generally aversive contexts. Rather, serotonin increases in IC may accompany non-social contexts in which auditory processing is important, such as noisy conditions or restricted environments in which acoustically locating conspecifics may lead to escape.

Mice use vocal communication during social encounters, making conspecific interactions a prime candidate for modulation of auditory information by contextual state. Male mice modulate the production of ultrasonic courtship vocalizations depending on the estrous state of their female social partner (Hanson and Hurley 2012). Female mice emit audible broadband vocalizations that may have positive or negative valence for males depending on when over the time course of a social interaction they are emitted (Finton et al. 2017). While the exact information that these social vocalizations carry remains unknown, we would predict that serotonin increases in the IC during social encounters in order to processes salient vocal acoustic cues. This is indeed the case. During social interactions with novel, opposite sex conspecifics, male (Fig. 3b) and female mice have increased IC serotonin relative to isolated controls (Hanson and Hurley 2014; Keesom and Hurley 2016). In contrast to non-social contexts in which serotonin increases relatively quickly (<5 min), quantitative differences in IC serotonin are not observed in opposite sex interactions until at least 12 min after the introduction of a social partner. Serotonin also increases over a similar time scale within the IC of males in direct social contact with a novel male (Hall et al. 2011). The presence of a social partner, however, is insufficient to gate serotonin release into IC, as focal males show no such increase when same sex interactions occur through a perforated barrier (Hall et al. 2011). This suggests that serotonin release in the IC is achieved through a particular combination of multi-modal cues. Finally, serotonin levels fluctuate relative to both self-generated and received behaviors. Across male-male interactions, IC serotonin a) decreases with the total time focal animals are immobile, and b) positively correlates with the frequency of anogenital investigation (Hall et al. 2011). In contrast, during opposite sex interactions, the level of IC serotonin in focal males decreases with the amount of rejection-like behaviors a male receives from female partners (Fig. 3c) (Keesom and Hurley 2016). These behavioral results are particularly intriguing as they demonstrate that the fluctuation of serotonin within the IC is not only sensitive to external context, but is also an indicator of the valence of event-based changes within individual social interactions.

In summary, the predominant characteristic of serotonin release in the IC is its dependence on contextual state. The external contexts that evoke serotonin release are not only varied, but also specific to a small fraction of the circumstances during which serotonergic neurons within DRN are engaged. Specificity in serotonergic signaling emerges in part through inputs from functionally distinct afferent nuclei (Hale and Lowry 2011; Challis and Berton 2015). Of particular interest to

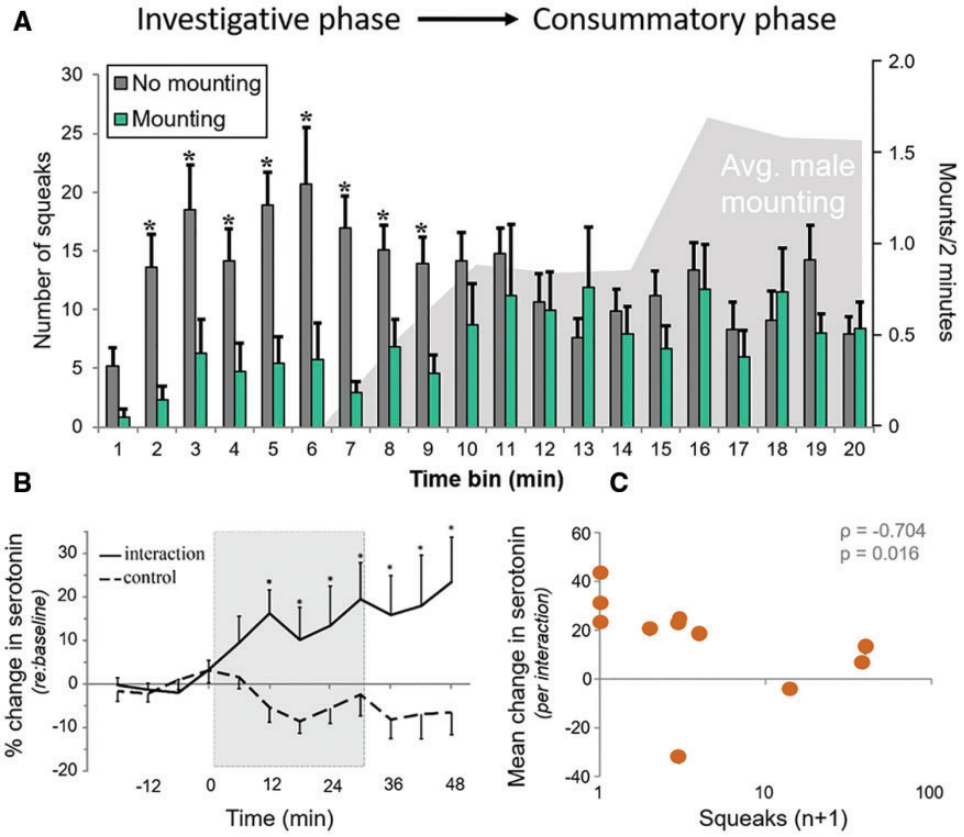


**Fig. 3** Serotonin in the IC parallels the valence of social interactions for males interacting with females. (**A**) Females squeak at low levels in the initial phase of interactions that proceed to mounting (light bars), but at high levels in the initial phase of interactions that do not proceed to mounting (gray bars). (**B**) Serotonin increases in the IC of males following the presentation of novel female partners ("interaction") as opposed to no partner ("control"). (**C**) The amplitude of increases in serotonin correlate inversely with the number of female squeaks. Figures adapted from Finton et al. 2017, Anim Behav 126:163–175 (A) and Keesom and Hurley 2016, J Neurophysiol 115:1786–1796 (B, C).

context-specific serotonin release in IC are DRN afferents within the social behavior network (SBN).

## The social behavior network: an afferent effector of the dorsal raphe?

The SBN, which was first described in mammals (Newman 1999) and later extended to teleost fishes, birds (Goodson 2005), and reptiles (Crews 2003), comprises eight discrete nuclei: the medial extended amygdala (medial amygdala, MeA, and bed nucleus of the stria terminalis, BNST), preoptic area (POA), lateral septum (LS), ventromedial hypothalamus (VMH), anterior hypothalamus (AH), paraventricular hypothalamus (PVN) (Goodson and Kingsbury 2013), the periaqueductal gray (PAG) and ventral tegmental area (VTA). Together, these regions form the core neural architecture for vertebrate social behavior. In mammals, the SBN works in tandem with the mesolimbic reward system in a combined social decision making network (SDMN) which has been proposed to produce and reinforce appropriate social decisions (O'Connell and Hofmann 2011) (but see (Goodson and Kingsbury 2013) for limitations of the SDMN as a pan-vertebrate model). The topographic distribution of individual nuclei or "nodes" across the basal forebrain (LS, MeA, BNST), hypothalamus (VMH, AH, PVN), and midbrain (PAG, VTA) allows the SBN to receive information from functionally and anatomically segregated regions such as memory (Risold and Swanson 1997), endocrine (Tsigos and Chrousos 2002), and sensory systems (Thompson 2005). Reciprocal connections within the SBN allow information from disparate systems to be integrated and processed by each distinct node and the network as a whole. Unsurprisingly, as the SBN is characterized by functional and anatomical heterogeneity, it is the coordinated pattern of activity or "functional connectivity" (Hoke et al. 2005) across the network that establishes the neural contexts (McIntosh 2004) indicative of a particular salient state or behavioral response rather than the activity of a single node (Goodson and Kabelik 2009).

It should not be implied, however, that functional specialization does not exist within SBN. Individual nodes are differentially engaged in a task-dependent manner. For example, the PVN is weighted to modulate neuroendocrine axes (Tsigos and Chrousos 2002), while the BNST is weighted toward valence assessment (Goodson and Wang 2006; Lebow and Chen 2016). Additionally, within discrete nodes, functional specialization is observed at the level of individual cell types: subpopulations of oxytocin and vasopressin-producing neurons in the PVN are generally considered to underlie anxiolytic and anxiogenic processes, respectively, (Kelly and Goodson 2014b). Importantly, functional specialization within different nodes of the SBN mirror functional specialization within the DRN. For example, serotonin increases in IC during restriction stress and direct social contact; these relatively disparate contexts also engage populations of AVP-producing neurons within the PVN and BNST respectively (Ho et al. 2010; Zavala et al. 2011). The functional parallels and anatomical connectivity between subpopulations of AVP neurons and the DRN suggest that the former could gate information on valence/social context to the latter.

While species differences and individual differences exist, AVP-producing neurons are found primarily within five mammalian brain regions: the medial amygdala and BNST in the extended amygdala, and the suprachiasmatic, supraoptic, and paraventricular nucleus (PVN) in the hypothalamus (De Vries and Buijs 1983; Goodson and Bass 2002; De Vries and Panzica 2006; Rood and De Vries 2011; Kelly and Goodson 2014a). AVP exerts modulatory influence via direct synaptic contact or volumetric release from these regions (Albers 2015), and underlies a variety of social behaviors including olfactory processing and species recognition, aggression, affiliation/sociality, pair bonding, and vocal-acoustic production. The diverse functions that AVP influences suggest that it could be a key facilitator of intra-SBN neural context. Likewise, AVP output may signal salient events to extra-SBN nuclei such as DRN. In particular, AVP populations in the PVN and BNST meet several assumptions for a candidate neuromodulator to gate serotonin release into IC. First, AVP immunoreactive (-ir) projections from PVN and BNST are found within DRN (Rood and De Vries 2011; Rood et al. 2013; Pollak Dorocic et al. 2014). Second, these two AVP populations each respond to contexts that trigger serotonin release within the IC.

Within the PVN of rats, restriction paradigms similar to those during which serotonin increases in the IC trigger an up-regulation of AVP mRNA (Bartanusz et al. 1994), and an increased Fos response in AVP-ir neurons (Zavala et al. 2011). Forced swim tests also increase levels of Fos within the PVN (Cullinan et al. 1996) and DRN (Roche et al. 2003), although it is unknown whether serotonin increases in the IC during this paradigm. Functional overlap between the AVP and serotonergic systems is also observed during social defeat: serotonergic neurons in the mouse DRN have an increased Fos response following social defeat (Challis et al. 2013), whereas subordinate male mice have a higher percentage of AVP-ir neurons co-labeled with Fos-ir in the PVN than do their dominant partners after a social interaction (Ho et al. 2010). In addition to these functional similarities, there are direct projections from AVP-ir neurons within PVN to serotonergic neurons in DRN (Pollak Dorocic et al. 2014).

Similar to DRN, BNST serves a role within the circuitry that encodes positive and negative valence (Lebow and Chen 2016; Namburi et al. 2016). The hypothesis that BNST encodes valence sensitivity through functional specialization of cell types was derived from an elegant suite of comparative studies in estrildid finches (family: Estrildidae). Goodson et al. (2005) demonstrated that violet-eared waxbills (*Uraeginthus granatina*), a territorial estrildid, have a greater Fos response in the BNST than did highly social zebra finches when each was individually engaged with a same-sex conspecific. However, within a subset of AVP-ir neurons in BNST, the opposite is true: gregarious zebra finches have a higher percentage of AVP-Fos-ir co-labeled neurons in response to a same-sex conspecific than do violet-eared waxbills. Importantly, violet-eared waxbills have an increased Fos response in BNST AVP neurons in response to their pair bond partner, suggesting that these neurons code positive social valence (Goodson and Wang 2006). Homologous neurons in mice show a similar response profile: AVP-ir neurons show a large Fos response to copulation, and a smaller yet significant Fos response to male-male chemoinvestigation. AVP producing neurons in the BNST project to intra-SBN targets including the LS and PAG (De Vries and Buijs 1983); BNST AVP neurons are steroid-sensitive, and represent a prominent and evolutionarily conserved sexual dimorphism in the vertebrate brain (De Vries and Panzica 2006; Rood et al. 2013). As in most vertebrates, male mice have more AVP-ir neurons in the BNST than females. Castration not only eliminates AVP-ir neurons in BNST, but also reduces AVP-ir fibers within DRN of male mice, suggesting that BNST is a major source of AVP to DRN (Rood et al. 2013) [but see (Pollak Dorocic et al. 2014)].

DRN afferents affect the production of sensory-driven behavior (Challis et al. 2013; Challis et al. 2014). This can be achieved by modulating the activity of serotonergic neurons either through direct synaptic contact or through non-serotonergic DRN interneurons (Pollak Dorocic et al. 2014; Rood and Beck 2014). Bathing the DRN with AVP indirectly increases the firing rate of serotonergic neurons by activating the vasopressin 1a receptor (V1aR) on excitatory interneurons *in vitro* (Rood and Beck 2014). Single-cell transcriptomics have revealed that serotonergic neurons within the lateral wings, a sub-region of DRN that projects to the IC (Muzerelle et al. 2016), express the *avpr1a* gene (Spaethling et al. 2014). In a more systematic approach, two independent studies have employed viral tract tracing techniques to provide an exhaustive list of monosynaptic inputs into the DRN (Pollak Dorocic et al. 2014; Weissbourd et al. 2014). These studies show that AVP neurons target both serotonergic and $\gamma$-aminobutyric acid (i.e., GABAergic) neurons within the DRN. Variations in the neurochemical targets of monosynaptic inputs into the DRN are based on the nucleus of origin. For example, AVP-ir neurons within the PVN provide monosynaptic input to serotonergic neurons (Pollak Dorocic et al. 2014), whereas the BNST tends to project more heavily onto DRN GABAergic neurons (though the chemical identity of these projections is unknown) (Weissbourd et al. 2014). Taken together, there is evidence for three potential routes through which AVP neurons could influence the firing of serotonergic DRN neurons: directly, or through glutamatergic or GABAergic intermediaries. These pathways provide an anatomical substrate where functionally distinct types of information, communicated via populations of AVP neurons in the PVN and BNST, could recruit serotonergic neurons in a context-dependent manner.

## Functional effects of DRN-IC pathway

The release of serotonin within the IC shapes ascending auditory information. The IC has a rich infrastructure for mediating signals from the DRN. It receives dense serotonergic projections arising mostly from the DRN, and to a lesser extent from the median raphe nucleus and other raphe nuclei (Klepper and Herbert 1991). However, the functional topography of these projections remains unknown [but see: (Muzerelle et al. 2016)]. Serotonergic fibers are seen not only in the mammalian IC, but also in homologous auditory midbrain regions including the anamniote torus semicircularis and avian dorsal lateral mesencephalic nucleus (Cuadrado et al. 1992; Endepols et al. 2000; Matragrano et al. 2012; Matragrano et al. 2013). Once released, serotonin binds to a wide array of different types of serotonin receptors that are expressed by IC neurons themselves; members of five of the seven major families of serotonin receptor have been reported in the IC (reviewed in Hurley and Sullivan 2012). These different receptor types act through divergent intracellular pathways, so that the effect of serotonin release on a given neuron depends on the types of receptors that it expresses, as well as the effects of serotonin on the microcircuitry in which it is embedded (Hurley and Sullivan 2012).

In general, serotonin and its receptors have strong effects on the responses of single IC neurons and neuron populations to acoustic stimuli. Serotonin and its receptors often increase or decrease the amplitudes of responses to simple stimuli like tones, and change the timing of spike trains (Hurley 2006, 2007; Hurley et al. 2008). The integrated effects of multiple receptor types together may shape these aspects of neural responses (Baldan Ramsey et al. 2010). The prevalence of serotonergic effects on responses to simple acoustic stimuli is paralleled by its effects on the responses of single neurons and neuron populations to playback of species-specific vocalizations. In Mexican free-tailed bats *(Tadarida brasiliensis)*, serotonin predominantly increases the selectivity of single IC neurons for an array of social vocalizations, by causing neurons to respond to fewer vocalization types (Hurley and Pollak 2005). This causes the representation of a given call to be more disparate among pairs of neurons on average. In female lab mice, the systemic manipulation of serotonin has effects on immediate early gene activation that depend on both the external context and on estrous phase (Hanson and Hurley 2016). Pharmacologically increasing serotonin release suppresses Fos activity in a non-socially relevant context but not in a socially relevant one. At the same time, elevated serotonin increases Fos activation during proestrus or estrus, but decreases Fos activation during diestrus, while pharmacologically depleting serotonin has the opposite effects. Together, these findings strongly suggest that not only does serotonin shape the responsiveness and selectivity of IC neurons for social vocalizations, but also that its effects are sensitive to contextual state.

## Model of contextual feedback to the auditory midbrain

The sections above broadly outline a pathway that could potentially feed back information on the salience of auditory stimuli into the auditory system via the dorsal raphe nucleus. Such a pathway would be capable of importing integrated information from

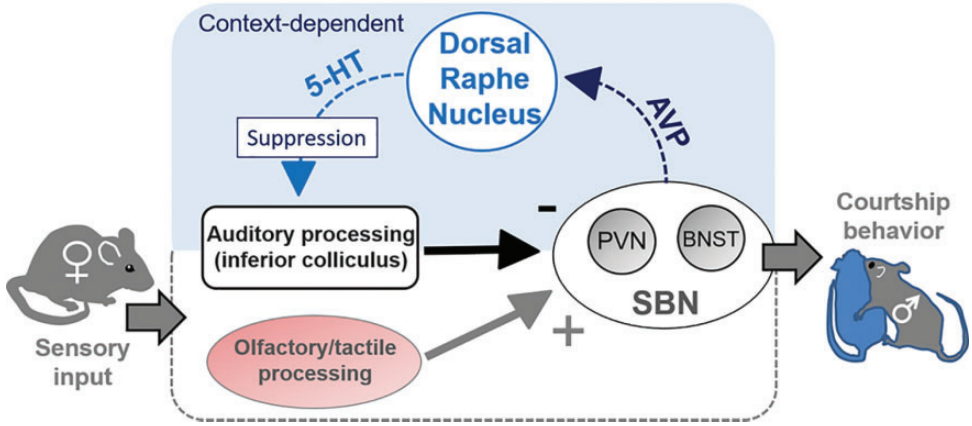


**Fig. 4** Model of context-dependent feedback from the SBN to the inferior colliculus, through the dorsal raphe nucleus. AVP-positive neurons in the PVN and BNST respond to threatening or social events, and subsequently influence firing rates of neurons in the dorsal raphe nucleus, which release serotonin in sensory regions like the IC. Modulation of firing patterns of IC neurons by serotonin could in turn alter ascending sensory information.

non-auditory sensory channels, as well as "interpreted" representations of external events, such as valence. Although there is strong evidence for each of the individual segments of this pathway, it is not clear which types of behavioral functions it could serve.

In general, such a feedback pathway could modify responses to auditory stimuli based on internal state and salient external circumstances (i.e., contextual state). To illustrate this idea, we will consider a behavioral perception task in lab mice that requires responding to acoustic information in a sex-specific and valence-dependent way: interpreting vocal signals during opposite-sex interaction. Similar to heterosexual interactions in other rodent species, these interactions in lab mice have distinct phases (Pierce et al. 1989). The phases include an initial investigative phase, and a later consummatory phase during which males mount females (Fig. 3a). Whether an interaction proceeds to mounting or not corresponds to female behavior. High amounts of rejection behavior during the initial investigative phase, including the production of human-audible calls ("squeaks"), corresponds to males subsequently reducing courtship behavior (Fig. 3a) (Finton et al. 2017). In contrast, when females show low levels of squeaking and other rejection behavior during the investigative phase, interactions are more likely to proceed to subsequent mounting. When this happens, female squeaks are produced in bursts around mounting events, and overlap in time with a type of male ultrasonic signal with a ~50 kHz harmonic that is also associated with mounting (Hanson and Hurley 2012). From a male's perspective, female-produced squeaks may therefore have very different significance in the investigative and consummatory phases of an interaction.

Within the auditory midbrain, serotonin parallels these events, in terms of both its timecourse and valence-dependence (Keesom and Hurley 2016). Voltammetrically measured serotonin increases in the IC of males interacting with females, but not until later time points corresponding to the consummatory phase. Increases in serotonin are also conditionally dependent on female behavior, so that they inversely correlate with the numbers of female squeaks and other rejection behaviors. Thus, serotonin levels would be high in the male IC only under the condition of low levels of initial female rejection, and only at a time when female squeaks are paired with mounting.

Moreover, activating serotonergic pathways in the IC strongly influences responses of IC neurons to playbacks of squeaks. Activating the 5-HT1A receptor, a type which is strongly expressed within the IC (Thompson et al. 1994; Peruzzi and Dut 2004; Smith et al. 2014), greatly decreases the responses of IC neurons to squeaks (Hurley and Nigam 2014). 5-HT1A activation also consolidates squeak-evoked action potentials in time, so that information on the temporally varying acoustic structure of squeaks is also reduced. Combined with the conditional elevation of serotonin in the IC, this means that the representation of female squeaks in the ascending auditory system of males is thus likely to vary with levels of female rejection.

The model of functional circuitry in Fig. 4 represents how all of these events could be tied together. In this model, sensory information regarding female behavior is integrated by at least the level of the social behavior network, and conveyed to the dorsal raphe nucleus by specific neuron populations, such as AVP-expressing neurons in the BNST or PVN.

The resulting patterns of serotonergic elevation in sensory regions like the IC therefore depend on a range of contextual factors encoded by these higher regions. As serotonin influences the representation of acoustic stimuli, ascending information on social signals like squeaks is altered. In the model presented in Fig. 4, auditory and nonauditory sensory information plays a crucial role. Cues associated with female presence and acceptance such as tactile or olfactory information play a facilitatory role that ultimately engages serotonin release and corresponds to escalating male courtship and copulatory behaviors. On the other hand, squeaks and other sensory information conveying female rejection play an inhibitory role, decreasing activation of the serotonergic pathway as well as male behaviors.

A range of studies supports a generalized model of contextual feedback to sensory systems via the dorsal raphe nucleus. Perhaps the most suggestive piece of evidence in this regard is the observation that neuromodulatory signals within sensory regions reflect not simply the presence of a social partner, but the valence of a specific interaction as it develops (Keesom and Hurley 2016). However, many of the details of the model must still be directly tested to establish how these pathways are engaged during specific behavioral contexts, and whether they are capable of influencing social behavior. It is also important to note that the model is a greatly simplified representation of the intersection among widely projecting systems, which could provide the opportunity for additional layers of feedback. For example, similar to the IC, serotonin release in the medial preoptic area of males occurs during consummatory phases of sexual interaction, and depends on the sexual availability of females (Fumero et al. 1994; Mas et al. 1995; Rubio-Casillas et al. 2015). Broadly projecting neuromodulators such as serotonin from the DRN could thus increase functional connectivity between multiple anatomically and functionally distinct regions within the pathway. Second, there are many projections from nuclei within the SBN to the DRN (Pollak Dorocic et al. 2014; Weissbourd et al. 2014). Multiple projections could therefore act synergistically with populations of AVP neurons to gate information on stressors and social valence. Finally, neurochemical systems other that the ones depicted in Fig. 4, such as noradrenergic or cholinergic pathways, are also engaged by salient behavioral events (Stark and Scheich 1997; Phillips-Farfán and Fernández-Guasti 2009; Metherate 2011; Devilbiss et al. 2012). These additional modulatory systems could also potentially interact with the neural pathways of Fig. 4 at many different levels.

This model can be useful in several different ways. Experimentally, it can support predictions on the coordination of ascending sensory and descending modulatory signals, as well as on the modulation of diverse types of signals that are associated with valence in different ways. This may be relevant for the many signaling systems for which particular signal structures correspond to different circumstances. For example, different vocal signals may be used to court members of the opposite sex versus to signal alarm or distress (Lupanova and Egorova 2015; Egnor and Seagraves 2016). In a system like this, our model might predict the differential regulation of auditory responses to structurally distinct courtship and alarm calls by modulators like serotonin. Thematically, our model suggests that the process of representing external events such as "valence" recruits many neural systems in addition to those that have typically been implicated. In this view, representations like valence may be more akin to transient brain-wide states (i.e., neural contexts (McIntosh 2004)) requiring coordination among many systems. The end result would be to produce a process that is geared, from sensory input to motor output, toward responding appropriately to a dynamic external world.

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