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Review

Social functions of individual vasopressin–oxytocin cell groups in vertebrates: What do we really know?

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ABSTRACT

Vasopressin–oxytocin (VP–OT) nonapeptides modulate numerous social and stress-related behaviors, yet these peptides are made in multiple nuclei and brain regions (e.g., >20 in some mammals), and VP–OT cells in these areas often exhibit overlapping axonal projections. Furthermore, the magnocellular cell groups release peptide volumetrically from dendrites and soma, which gives rise to paracrine modulation in distal brain areas. Nonapeptide receptors also tend to be promiscuous. Hence, behavioral effects that are mediated by any given receptor type (e.g., the OT receptor) in a target brain region cannot be conclusively attributed to either VP or OT, nor to a specific cell group. We here review what is actually known about the social behavior functions of nonapeptide cell groups, with a focus on aggression, affiliation, bonding, social stress, and parental behavior, and discuss recent studies that demonstrate a diversity of sex-specific contributions of VP–OT cell groups to gregariousness and pair bonding.

1. Interpretational dilemmas and cautionary notes

1.1. A case study

The behavioral functions of the vasopressin–oxytocin (VP–OT) nonapeptides have now been explored in thousands of studies, primarily through pharmacological manipulations of receptors – for instance, using agonists, antagonists, antisense oligonucleotides or viral vectors (reviews: Carter et al., 2008; Goodson, 2013; Stoop, 2012; Neumann, 2009; Neumann and Landgraf, 2012; Goodson and Thompson, 2010; Young et al., 2011; Veenema and Neumann, 2008). Yet despite this vast literature, an extraordinarily large gap exists in our information about the specific contributions of the various peptide-producing cell groups to social and stress-related processes. To characterize this gap, we begin with a short case study that readily stands as a microcosm of the literature as a whole.

In the early 1980s, Geert De Vries and colleagues described an extremely large sexual dimorphism – specifically, that whereas male rats exhibit large numbers of VP cells in the medial bed nucleus of the stria terminalis (BSTm) and a dense VP innervation of the lateral septum (LS), these VP elements are largely absent in females (van Leeuwen et al., 1985). Subsequent findings show that this is one of the most dramatic and phylogenetically widespread dimorphisms ever reported, being found in a variety of mammals, reptiles, amphibians and birds [(Fig. 1) De Vries and Panzica (2006) and Goodson and Bass (2001)]. De Vries et al. also demonstrated that castration results in a virtual disappearance of both VP-immunoreactive (-ir) neurons in the BSTm and VP-ir fibers in the LS (De Vries et al., 1985), and that the VP-ir innervation of the LS was virtually eliminated by lesions of the BSTm (De Vries and Buijs, 1983). This led to the natural assumption that VP neurons in the BSTm provide the majority of VP supply to the LS. Shortly after these discoveries, it was demonstrated that V_{1a} receptor (V1aR) activation in the LS potently facilitated agonistic flank marking in male Syrian hamsters (*Mesocricetus auratus*) (Irvin et al., 1990), and thus the interpretation of the combined data seemed logical: Males exhibit more BSTm cells and LS fibers than do females, and this circuit promotes male aggression.

There are multiple problems with this interpretation. First, it is now known that Syrian hamsters do not exhibit detectable VP-ir neurons or VP mRNA in the BSTm at all, and exhibit virtually no VP-ir innervation of the LS (Bolborea et al., 2010; Ferris et al., 1995; Albers et al., 1991). Hence, VP modulation of agonistic flank marking in the LS must rely upon paracrine modulation by neurons that lie outside of the BSTm (likely in the POA or various nuclei of the hypothalamus). Second, although septal vasotocin (Ile^3-VP)

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† We are saddened to learn that James L. Goodson passed away on August 14, 2014. An online obituary has been published at http://obits.dignitymemorial.com/dignity-memorial/obituary.aspx?n=James-Goodson&lc=7162&pid=172109205&mid=6085179

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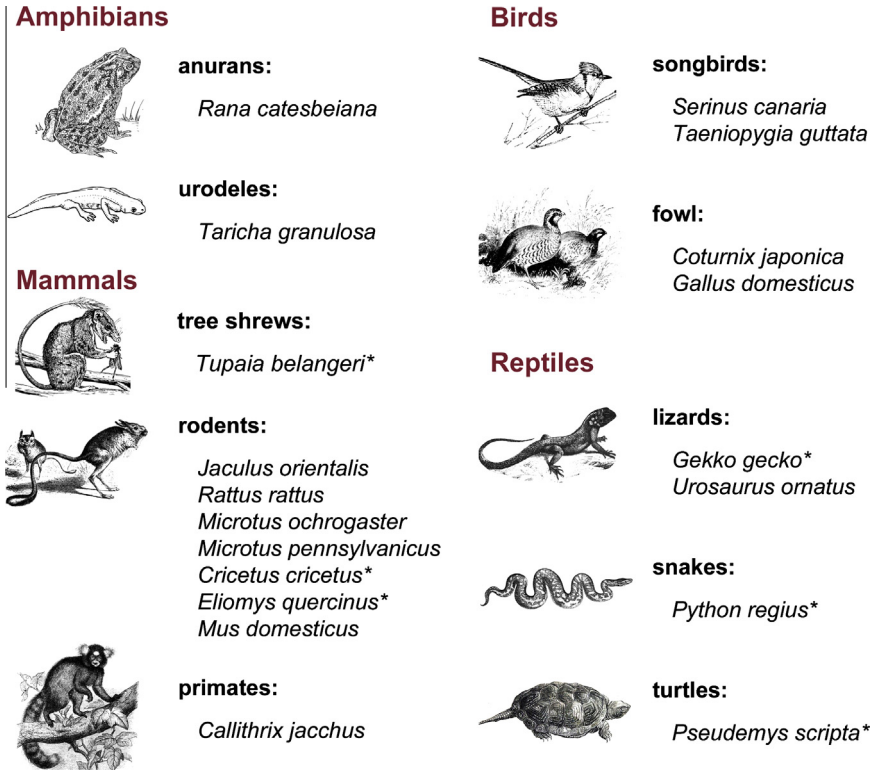

Fig. 1. Tetrapod species for which male-biased sexual dimorphism has been described in the VP cell group of the BSTm and/or in the VP fiber innervation of major BSTm targets, such as the LS and lateral habenula. Asterisks indicate that data are available only for fiber innervation. References: anurans (Boyd et al., 1992); urodeles (Moore et al., 2000); rodents (van Leeuwen et al., 1985; De Vries and Buijs, 1983; Rood et al., 2013, 2008; Lakhdar-Ghazal et al., 1995; Bamshad et al., 1993; Buijs et al., 1986; de Vries et al., 1981; De Vries et al., 1983; Hermes et al., 1990; Miller et al., 1989; Wang, 1995; Ni et al., 2014); primates (Wang et al., 1997); songbirds (Kabelik et al., 2010; Voorhuis et al., 1988, 1991; Kimura et al., 1999); fowl (Jurkevich et al., 1997, 1999; Panzica et al., 1996; Panzica et al., 1998); lizards (Kabelik et al., 2008; Stoll and Voorn, 1985); snakes (Smeets et al., 1990); turtles (Smeets et al., 1990). Images courtesy of Wikimedia Commons.

facilitates agonistic communication in field sparrows (*Spizella pusilla*), as shown for hamsters, it also *inhibits* offensive, resident-intruder aggression in both sparrows (Goodson, 1998a) and violet-eared waxbills (*Uraeginthus granatina*, an estrildid finch) (Goodson, 1998b). Thus, it is possible that septal VP may not actually facilitate overt aggression in rodents, but rather inhibit it, as shown in birds. Furthermore, a variety of recent data show that VP neurons in the BSTm of birds and mammals are not excited by aggressive stimuli at all (Ho et al., 2010; Xie et al., 2011), and in fact, antisense knockdown of BSTm VP production dramatically *facilitates* aggression in zebra finches (*Taeniopygia guttata*) (Kelly and Goodson, 2013a). Multiple other findings in birds and mammals likewise support the view that BSTm VP neurons do not promote aggression, but suppress it (Compaan et al., 1993; Goodson and Wang, 2006; Goodson et al., 2012).

Based on the information above, it is apparent that multiple VP cell groups modulate agonistic behavior and that some of this modulation occurs in the absence of direct innervation. Indeed, as addressed in the next section, VP and OT are released in a variety of ways, including large-volume ("volumetric") release from dendrites and soma that is distal from possible sites of action (Ludwig and Leng, 2006; Landgraf and Neumann, 2004). Thus, as shown in the example above, conclusions based on basic anatomy and conventional pharmacological approaches can lead to interpretations about the functions of specific cell groups that are fundamentally flawed. Thus, if we are to determine which cell groups contribute to the behavioral effects of VP or OT, direct interrogation of the cell groups is necessary. The purpose of the present review is therefore to critically evaluate what we actually know about the behavioral functions of the various nonapeptide cell groups in the brain, and to highlight areas that need further investigation.

1.2. Signaling diversity = interpretational difficulty

Although it is common and convenient to discuss "the" VP system or "the" OT system, VP-OT peptides are made in many cell groups in the brain (see Section 2) and those cell groups signal in a diversity of ways, including peptide release from axon terminals, dendrites and soma (Ludwig and Leng, 2006; Landgraf and Neumann, 2004). Volumetric release from dendrites and soma has been extensively studied in relation to the magnocellular neurons, which are capable of releasing vast quantities of peptide into the periphery via axon terminals in the posterior pituitary, *and independently*, large quantities of peptide into the brain from dendrites and soma, which are packed with large dense-core vesicles containing peptide (Ludwig, 1998; Moos et al., 1989; Ludwig et al., 1994). This volumetric release has the potential to modulate very distal sites. For instance, activation of VP–OT neurons in the supraoptic nucleus (SON) of rats is associated with significant increases in the peptide content of both the septum and cerebrospinal fluid (Engelmann et al., 1994, 2000; Coombes et al., 1991). Hence, even if an area is shown to receive direct innervation from VP-ir or OT-ir neurons, we cannot conclude that the cell group(s) giving rise to that innervation are the source of all local peptide effects.

1.3. Peptide variants, receptor paralogues, and binding promiscuity

One of the greatest challenges in the study of VP–OT functions is that there are many VP and OT forms, and extensive species-specificity in the structure and binding properties of their receptors. Thus, before we further consider specific cell groups, we will make a digression to describe the various nonapeptides and

receptors, such that signaling can be more readily discussed. The most extensive data on peptide-receptor affinities has been generated for rats (Manning et al., 2008), and even here it is clear that the "OT receptor" (OTR) also binds VP, and conversely, that the various "VP receptors" bind OT as well. Indeed, VP 1a receptors (V1aRs) and OTRs are promiscuous in both mammalian and non-mammalian species, and in some cases the receptors do not appear to bind VP–OT forms differentially (Leung et al., 2009; Searcy et al., 2011). This receptor "promiscuity" has clear functional consequences; for instance, septal VP promotes partner preference behavior in male prairie voles via OTRs in addition to V1aRs (Liu et al., 2001); OT induces analgesia in mice via the V1aR (Schorscher-Petcu et al., 2010); and Ile^3-VP (vasotocin, the non-mammalian form of VP) promotes oviposition in birds via the OTR (Takahashi and Kawashima, 2008). Thus, based on this receptor promiscuity alone, it is clear that we cannot infer that OTR-mediated effects reflect endogenous functions of OT, or that effects mediated via V1aRs are related to endogenous release of VP. Further complicating the picture is that there is substantial diversity in the structure of the VP–OT peptides and their receptors, such that we cannot assume that receptor affinities are comparable across species, even across species in the same vertebrate class.

The structure of Arg^8-VP and the canonical form of mammalian OT, Leu^8-OT, were first described in 1953 by Du Vigneaud et al. (1953a, 1953b), followed closely by the team of Acher (Acher and Fromageot (1955)), who has made the greatest contributions to our understanding of the vertebrate nonapeptide forms and their evolution (for relevant reviews, see (Acher, 1972; Acher and Chauvet, 1995; Acher et al., 1995). In brief, early vertebrates expressed only a single nonapeptide, arginine vasotocin (Ile^3-VP). This condition is retained in jawless vertebrates, which are the hagfish and lampreys (cyclostomes). Because the appearance of jawed vertebrates is associated with the appearance of two nonapeptide forms, which are primarily produced in the same regions of the POA and hypothalamus, it is thought that the vasotocin gene duplicated, giving rise to peptide lineages that include the canonical forms of OT and VP.

We now know that the family of vertebrate nonapeptides includes many form variants, although these are all recognized as being VP- or OT-like, and all jawed vertebrates exhibit one form of each. The most common forms in the OT lineage include (1) isotocin (Ser^4, Ile^8-OT), which is found in bony fish; (2) Ile^8-OT, or mesotocin, which is found in lobe-finned fish (e.g., lungfish), most amphibians, reptiles, birds and some marsupials; and (3) Leu^8-OT, which is found in most eutherian mammals. Numerous other forms of OT have also been identified, including Pro^8-OT in New World monkeys; seritocin (Ser^5, Ile^8-OT) in at least one toad species; and at least six forms in cartilaginous fish (e.g., sharks and rays), including the canonical ("mammalian") Leu^8 form (Acher and Chauvet, 1995; Hoyle, 1998; Lee et al., 2011). Somewhat less variation is present on the VP side of the family. Most mammals express Arg^8-VP and most nonmammalian species express Ile^3-VP. Other variants include Lys^8-VP, which is found in a variety of marsupials and suiform mammals (e.g., pigs and hippopatamuses); and Phe^2-VP, which is found in some marsupials (Acher and Chauvet, 1995; Hoyle, 1998).

Despite the fact that all jawed vertebrates express a single form of VP and a single form of OT, *no less than 14 names are currently assigned to the various forms, and additional forms are still being discovered* (Acher and Chauvet, 1995; Hoyle, 1998; Lee et al., 2011). No other family of neurochemicals is burdened with such a cumbersome nomenclature. Thus, because the canonical mammalian forms of VP and OT were described and named first (Du Vigneaud et al., 1953a, 1953b), and because they are the most common forms discussed in the literature, "vasopressin" and "oxytocin" are the logical names to apply to all vertebrate forms, making clarifications of the amino acid substitutions as necessary and relevant to the topic at hand. This does not mean that all forms will have identical affinities for the various receptors. However, because receptor structures also differ across species, we cannot infer that a given peptide form (e.g., Leu^8-OT) will have the same binding properties from one mammal to the next, one bird to the next, etc. Hence, for ease of communication, we will here refer only to VP and OT, without further distinctions unless necessary.

The nomenclature for the vertebrate nonapeptide receptors is likewise scattered and overly taxon-specific, and different nomenclatures have been adopted in the various vertebrate classes, even when homologies to the mammalian receptor subtypes are clear (Lagman et al., 2013; Ocampo Daza et al., 2012; Yamaguchi et al., 2012). For instance, the four receptors in birds have simply been named in the order of their discovery, from VT1 to VT4 (Baeyens and Cornett, 2006; Leung et al., 2011). Despite this nomenclature, phylogenetic analysis reveals that birds express a V1aR, V1bR, V2R and OTR, as in mammals (Ocampo Daza et al., 2012; Yamaguchi et al., 2012; Leung et al., 2011). But there is a twist. Unlike the mammalian V2R, which is the primary renal receptor, the avian V2R (VT1) is found in the brain (Leung et al., 2011).

The resolution to this V2R paradox comes from two very illuminating studies. In the first, receptor sequences were identified from a genome screen in 12 species of jawed vertebrates, including all major groups (cartilaginous fish, bony fish, amphibians, reptiles, birds and mammals), and a phylogenetic analysis was then performed (Ocampo Daza et al., 2012). The result? *The ancestral state for jawed vertebrates is not the expression of four nonapeptide receptor subtypes, but five, including two V2Rs – the V2aR and V2bR*. Of the species examined, only cartilaginous fish and amphibians express all five. Mammals have apparently lost the V2bR; birds have apparently lost the V2aR (the canonical mammalian V2R); and teleost fish have apparently lost the V1bR. However, various fish species exhibit multiple copies of the V1aR, OTR and V2Rs (Ocampo Daza et al., 2012).

A virtually identical view of nonapeptide receptor phylogeny has been provided by Yamaguchi et al. (2012), who also provide novel functional data for the V2bR from the cartilaginous elephant fish (*Callorhinchus milii*). Their analysis shows that V2bR activation induces Ca^{2+} signaling, not cAMP signaling as with the mammalian V2aR. Interestingly, the Ca^{2+} signaling mode is characteristic of the V1 receptor subtypes, and furthermore, based on key amino acid residues, the avian V2bR may exhibit binding properties that are very similar to the V1aR (Acharjee et al., 2004). Hence, based on data regarding binding properties (from birds) and intracellular signaling mechanisms (from elephant fish), we hypothesize that the V2bR may serve many of the brain functions in nonmammalian taxa that the V1aR does in mammals.

In summary, a wealth of data now available firmly support the view that there are two nonapeptide forms in all jawed vertebrates that can be most clearly named OT and VP, and five nonapeptide receptor types that can be most clearly named the V1aR, V1bR, V2aR, V2bR, and OTR (Lagman et al., 2013; Ocampo Daza et al., 2012; Yamaguchi et al., 2012). Nonetheless, there is substantial diversity in the structures of those peptides and receptors - a fact that further limits our ability to attribute pharmacological effects (e.g., antagonist effects) to the functions of a particular peptide, much less to the functions of a specific peptide cell group.

1.4. Neuromodulatory patterning

Behavior is not the product of a single peptide acting via a single receptor type in a single brain area. Nonetheless, we often study behavioral modulation as if that was the case; for instance, by examining the effects of V1aR antagonism in a specific neural

locus. Such approaches do have great utility, but we must also consider that neuromodulators such as VP and OT likely exert effects via coordinated release in multiple brain regions, effectively modifying functional connectivity across the numerous nodes of behavioral regulatory networks (Goodson and Kabelik, 2009). In fact, variation in social behavioral state is not driven by context-specific activation of circuits that are dedicated to a specific kind of behavior (sexual behavior, aggressive behavior, etc.), but is rather associated with variation in the relative activity of nodes in the brain's core "social behavior network" (a network common to all vertebrates) (Goodson, 2005; Goodson and Kingsbury, 2013; Newman, 1999). The VP–OT peptides are important modulators of this network and also modulate associated components of the mesolimbic dopamine system (Goodson and Kingsbury, 2013; O'Connell and Hofmann, 2011). Thus, we can expect that peptide effects are based on both (1) the *pattern* of modulation across brain networks ("neuromodulatory patterning"), and (2) the pre-existing state of those networks ("neural context") Goodson and Kabelik, 2009. Only by directly manipulating the various VP–OT cell groups (e.g., through RNA interference) can we alter the overall neuromodulatory pattern of a given cell group and gain insights into its behavioral functions. This is not an alternative to site-specific manipulations in sites of action (e.g., through receptor antagonism), but represents an essential complement to those approaches if we are to gain an understanding of how VP–OT circuits operate. Unfortunately, very few studies have directly manipulated specific VP–OT cell groups, leaving much of our circuit "knowledge" in a state of semi-educated speculation.

2. The vertebrate VP–OT cell groups

In amniote vertebrates (i.e., reptiles, mammals, birds), the largest populations of VP and OT neurons are located in the SON and paraventricular nucleus of the hypothalamus (PVN). The SON contains only magnocellular neurons, whereas the PVN contains both magnocellular and parvocellular subdivisions. VP is also produced in the suprachiasmatic nucleus of the hypothalamus (SCN), the BSTm (a component of the medial extended amygdala), and the medial amygdala proper in some mammals. Although these represent the major cell groups, both VP and OT are produced in numerous small cell groups that are distributed throughout the basal telencephalon, hypothalamus, thalamus and brainstem. Although sites of VP and OT production extensively overlap, the peptides are produced in separate subpopulations of neurons, as shown in Fig. 2 (reviews: Moore and Lowry, 1998).

Detailed comparisons of these small cell groups across vertebrate taxa are extremely few, although Moore and Lowry (1998) have provided a comparative framework for the VP populations across fish, amphibians, reptiles, mammals and birds, which include up to 19 VP cell groups in any given species (Lowry et al., 1997). As discussed in Section 7, there are good reasons to think that some of these small VP populations actually have large effects on behavior. Also noteworthy are the recent, exhaustive works of Rood and De Vries (2011) and Rood et al. (2013) in mice, which detail all sites of VP production, fiber distributions, sensitivity to gonadectomy, sex differences, and likely sites of origin for various projections. Briefly, mice produce VP in the medial amygdala, BSTm, PVN, SON, SCN, periventricular POA-hypothalamus, ventrolateral POA, and numerous other hypothalamic areas (anterior hypothalmus, AH; perifornical region; peduncular lateral hypothalamus; striohypothalamic region; nucleus circularis; and retrochiasmatic SON).

In general, the sites of OT production are more limited than for VP, but there is substantial species variation. For instance, naked mole rats (*Heterocephalus glaber*) exhibit OT-ir cell groups in the PVN, SON, and basal POA, in addition to scattered neurons in the hypothalamus, POA, posterior BSTm and medial amygdala (Rosen et al., 2008), whereas mustached bats (*Pteronotus parnellii*) exhibit 23 sites of OT production in the forebrain alone. These include OT-ir neurons in the frontal and auditory cortices, amygdala, septal complex and numerous other areas (Prasada Rao and Kanwal, 2004).

Anamniotes (amphibians and fish) do not exhibit an SON or PVN, but rather express VP and OT in homologous magnocellular and parvocellular cell groups that are located in the POA (Moore and Lowry, 1998). Amphibians otherwise exhibit basic distribution features that are consistent with other tetrapods (but there are also many species-specific characteristics within any given vertebrate class) (Lowry et al., 1997; Gonzalez and Smeets, 1992; Hilscher-Conklin et al., 1998). In contrast, most fish exhibit VP and OT neurons only in the POA, although in addition to the common parvocellular and magnocellular cell groups, fish also exhibit gigantocellular VP neurons, which are of uncertain homology (Holmqvist and Ekstrom, 1995; Goodson and Bass, 2000; Goodson et al., 2003; Batten et al., 1990). Finally, some fish also exhibit a small population of VP neurons in the lateral aspect of the anterior tuberal nucleus (Goodson et al., 2003; Greenwood et al., 2008), which is homologous in part to the ventromedial nucleus of the hypothalamus of amniotes (Goodson, 2005). This latter cell group may be homologous to one of the accessory cell groups found in the hypothalamus of amniotes, but this is not clear.

3. Functional properties of BSTm VP neurons

3.1. Sex differences and steroid regulation

A wide range of experiments has shown that various aspects of VP and OT anatomy are steroid-sensitive and/or sexually dimorphic. This literature has been extensively reviewed in other publications (De Vries and Panzica, 2006; Goodson and Bass, 2001; De Vries, 2008; Gabor et al., 2012) and a full treatment of the topic is beyond the scope of the present paper. However, the functional consequences of sexual dimorphism and steroid sensitivity (or lack thereof) in the BSTm VP cell group is now becoming clear (Kelly and Goodson, 2013a, 2013b; Kelly et al., 2011), and thus we will briefly describe these characteristics. As described in Section 1.1, the VP cell group of the BSTm and its projections to the LS and habenula are sexually dimorphic, with males exhibiting more neurons and higher fiber densities than females (see Fig. 1; note that many other areas of the basal forebrain and midbrain also appear to be innervated) (reviews: De Vries and Panzica, 2006; Goodson and Bass, 2001). In many species, such as rats and Japanese quail (*Coturnix japonica*), these dimorphisms are extreme. The VP population of the medial amygdala, which is found in some mammals, shares these characteristics in species where it is present. Numerous hormones appear to regulate the BSTm cells (progesterone, testosterone, estradiol), although the effects of estradiol are particularly strong. Remarkably, although the activational effects of sex steroids on VP anatomy are similar in rats and quail, organizational effects are reversed (De Vries and Panzica, 2006). Thus, whereas estradiol developmentally masculinizes VP cell numbers and fiber densities in rats, it feminizes these anatomical features in quail, although the resulting sexual dimorphism is still the same (male > female) De Vries and Panzica, 2006; Goodson and Bass, 2001.

Consistent with this steroid sensitivity, VP production in the BSTm and relevant VP-ir projections are highly seasonal in many species (De Vries and Panzica, 2006; Goodson and Bass, 2001). However, at least in some species that are opportunistic or otherwise aseasonal breeders, activational sensitivity to sex steroids

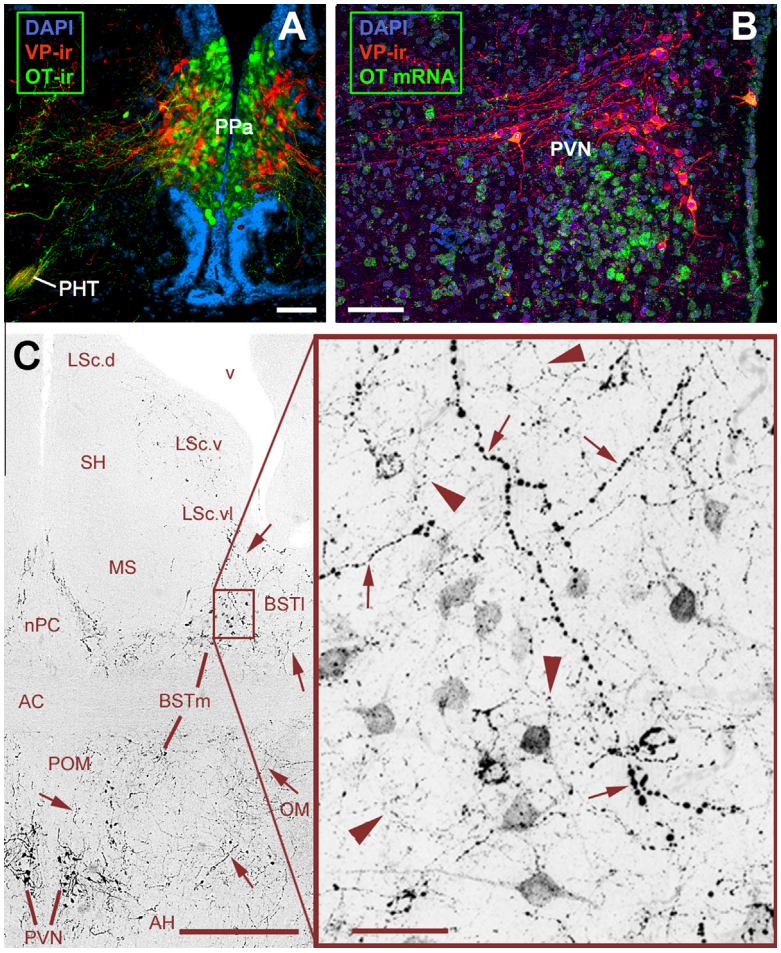

Fig. 2. Major parvocellular cell groups in a representative anamniote (fish) and amniote (bird). (A) VP- and OT-ir neurons in the parvocellular POA (PPa) of a type II male midshipman fish. Note the lack of colocalization. These neurons are homologous to those of the PVN in amniotes. Scale bar = 200 μm. Abbreviation: PHT, preoptico-hypophyseal tract. Modified from Goodson et al. (2003). (B) The PVN of a male zebra finch, showing the separate populations of VP and OT neurons. Note that low levels of OT mRNA extend in the surrounding hypothalamus and are not restricted to the PVN. Scale bar = 50 μm. Modified from Goodson et al. (2012). (C) VP-ir cells and fibers at the level of the anterior commissure (AC) in a male zebra finch, showing cell groups of the PVN and BSTm, and apparent overlapping projections from these cell groups in the BSTm and ventral LS. Large-caliber, heavily beaded axons (small arrows) are observed coursing from the PVN through the BSTm and directly into the ventrolateral zone of the caudal LS (LSc.vl). Relatively heavier projections are observed to the lateral BST (BSTl), but terminate immediately adjacent to the BSTm and LSc.vl. Within the BSTm (box), fine-caliber, beaded axons of local origin (large arrowheads) mix with the heavier axons of apparent PVN origin. Scale bars = 200 μm (left) and 20 μm (right). Other abbreviations: AC, anterior commissure; AH, anterior hypothalamus; LSc.d, dorsal zone of the LSc; LSc.v, ventral zone of the LSc; MS, medial septum; nPC, nucleus of the pallial commissure; OM, occipital-mesencephalic tract; POM, medial preoptic nucleus; SH, septohippocampal septum. Modified from Goodson and Kabelik (2009).

appears to have been lost, presumably in order to maintain breeding readiness. For instance, numerous estrildid finch species that breed opportunistically or semi-opportunistically do not exhibit seasonal variation in VP-ir cell numbers in the BSTm (Kabelik et al., 2010). Furthermore, adult zebra finches treated with flutamide (an androgen receptor antagonist) and letrozole (an aromatase inhibitor) exhibit no alterations in VP-ir cell numbers, although basal levels of Fos expression in VP-ir cells (as measured in the dark phase) are nonetheless reduced (Kabelik et al., 2010). A limited amount of data suggest that this condition is similar in humans; e.g., VP-ir neurons were detected in the BSTm of a post-menopausal woman who had received anti-estrogen treatment (Fliers et al., 1986). These observations suggest that VP circuits arising in the BSTm of finches and humans are available to modulate non-reproductive behaviors that are expressed outside of the context of breeding, and as described below in Section 3.4, these circuits appear to have been evolutionarily co-opted for such functions in at least two estrildid finch species – the zebra finch and Angolan blue waxbill (*Uraeginthus angolensis*) (Kelly and Goodson, 2013a, 2013b; Kelly et al., 2011).

3.2. Valence sensitivity and species-specific response

Neuroimaging studies in humans have shown that amygdala activity is associated with the successful encoding of positive and negative stimuli (Anders et al., 2004; Kensinger and Schacter, 2006), and cellular recordings in monkeys demonstrate that amygdalar neurons track the valence of visual stimuli (Paton et al., 2006). However, the neurochemical phenotypes and connections of neurons underlying valence sensitivity are not known.

A variety of Fos studies in birds and rodents now demonstrate that BSTm VP neurons are sensitive to valence, and to our knowledge, these neurons are the first valence-sensitive neurons of the extended amygdala to be neurochemically identified. VP-Fos colocalization in the BSTm increases in response to positive social stimuli (e.g., courtship; see Fig. 3A), but typically decreases or shows no change in response to aversive stimuli (Goodson and Wang, 2006; Goodson et al., 2009). This sensitivity to valence is reflected in species-specific neuronal responses to social stimuli across five species of estrildid finches that differ in their grouping and territorial behavior. For example, in the highly gregarious

zebra finch, which often flocks in groups of hundreds (Zann, 1996), exposure to a same-sex conspecific through a wire barrier significantly increases the percent of BSTm VP neurons that co-express Fos. This is observed in both males and females (Fig. 3B). Conversely, in the territorial violet eared waxbill, a species in which same-sex conspecifics are typically avoided or attacked (Goodwin, 1982; Goodson and Kingsbury, 2011), exposure to a same-sex individual produces a *reduction* in VT-Fos colocalization (Fig. 3C). Note that subjects were killed 90 min after exposure (i.e., approximately two half-lives of the Fos protein (Herdegen and Leah, 1998)), allowing such a decrease to be observed. However, when violet-eared waxbills are exposed to their pair bond partner, a presumably positive social stimulus, BSTm VP neurons exhibit a very large Fos response (Fig. 3C). Conversely, courtship-induced increases in VP-Fos colocalization are blocked by intense subjugation in a mate competition paradigm in male zebra finches (Goodson and Wang, 2006).

Consistent with these findings in finches, BSTm VP cells exhibit a robust Fos response to copulation in male mice (Fig. 3D) and a very modest Fos response to nonaggressive, same-sex chemoinvestigation. However, if same-sex interactions culminate in a fight, no additional colocalization is observed above the level produced by chemoinvestigation alone, regardless of whether the subject is dominant or subordinate (Fig. 3E; Ho et al., 2010). Similarly, BSTm VP cells express Fos in response to copulation, but not agonistic interactions in chickens (Xie et al., 2011). Copulation also strongly induces VP-Fos colocalization in male brown anoles (*Anolis sagrei*), although in this species, a weak and highly variable response to aggressive interactions is also observed. Notably, however, VP-Fos colocalization correlates positively with the number of sexual behaviors exhibited, but not with the number of aggressive behaviors exhibited (Kabelik et al., 2013).

Interestingly, the BSTm VP cell group appears to provide the vast majority of direct VP innervation to the LS and lateral habenula, which are areas that are involved in the prediction of reward and aversive outcomes (Lammel et al., 2012). For instance, experiments in rhesus monkeys (*Macaca mullata*) demonstrate that neurons in the lateral habenula are excited in response to the absence of reward or the presence of punishment, and are also excited by the actual punishment itself and inhibited by the reward (Matsumoto and Hikosaka, 2009). In addition, selective and graded information about reward uncertainty is encoded by neurons in the monkey dorsal LS (Monosov and Hikosaka, 2013), and findings in mice show that the dorsal LS is essential for context-specific disinhibition of the mesolimbic dopamine system associated with reward (Luo et al., 2011).

Peptide modulation of dorsal LS neurons may therefore reflect the modulation of reward-related processes, and interestingly, nonapeptide receptors in the dorsal LS differentiate animals that are more or less social. For instance, gregarious finch species exhibit higher OTR densities in the dorsal LS than do territorial species (Goodson et al., 2009), and maternal behavior correlates positively with both dorsal LS OTR and V1aR densities in mice (Curley et al., 2012). Finally, male prairie voles that investigate females at a high level exhibit relatively more V1aRs in the LS than do males that investigate at low levels (Ophir et al., 2009).

3.3. Sexually differentiated reproductive functions

As described in previous sections, male-biased production of VP in the BSTm represents one of the largest and most phylogenetically widespread sexual dimorphisms ever identified in the vertebrate brain. However, despite the fact that this sex difference

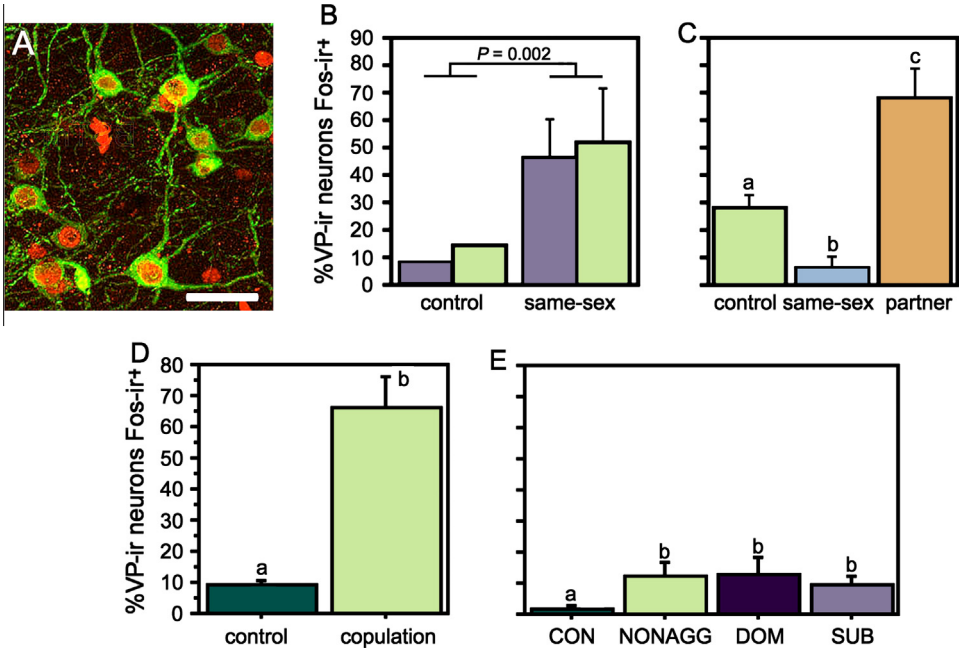

Fig. 3. Valence sensitivity of VP neurons in the BSTm of birds and mice, as measured by socially-induced changes in VT/VP immunocolocalization with the immediate early gene Fos. (A) Representative colocalization of VP (green) and Fos (red) in the BSTm of a male zebra finch following a courtship interaction. Scale bar = 20 μm. Modified from Goodson et al. (2009). (B) In the highly gregarious zebra finch, isolation followed by exposure to a same-sex conspecific through a wire barrier produces a robust increase in VP neuronal activity, with a clear lack of sex differences. Male and female data are shown in the purple and green bars, respectively. Modified from Goodson and Wang (2006). (C) In contrast, this same manipulation (exposure to a same-sex conspecific) produces a significant *decrease* in VP-Fos colocalization in a related territorial finch, the violet-eared waxbill, a species that does not naturally exhibit same-sex affiliation. However, exposure to a presumably positive stimulus, the subject's pairbond partner, produces a robust increase in neuronal activity. Sexes are shown pooled. Modified from Goodson and Wang (2006). (D and E) VP-Fos colocalization increases robustly following copulation in male C57BL/6 J mice (D) and following nonaggressive same-sex chemoinvestigation (E). Fighting does not induce greater colocalization than chemoinvestigation alone in either the dominant or subordinate males. Modified from Ho et al. (2010). In all panels, different letters denote significant group differences ($P < 0.05$) following significant ANOVA or Kruskal–Wallis.

was discovered more than 30 years ago, the functional significance of the dimorphism has remained unknown until recently.

Because BSTm VP production is activationally regulated by sex steroids and typically collapses outside of the breeding season (reviews: De Vries and Panzica, 2006; Goodson and Bass, 2001), we hypothesized that the dimorphism serves to modulate reproductive functions that are male-specific and/or male-biased in their expression. A variety of findings suggest what those reproductive functions might be. For instance, as discussed in the previous section, BSTm VP neurons increase their transcriptional activity in response to sexual interactions in lizards, rodents, and birds (Ho et al., 2010; Xie et al., 2011; Kabelik et al., 2013). Similarly, in male prairie voles, overnight cohabitation with a female increases VP mRNA in the BSTm (Wang et al., 1994). Male zebra finches that reliably fail to court females exhibit only about a third as many VP-ir neurons in the BSTm as do males that reliably court (Goodson et al., 2009). Thus, these neurons relate positively to sexual behavior, and interestingly, they also appear to relate negatively to aggression. For instance, male mice selected for lower aggression (long attack latency) exhibit more VP-ir neurons in the BSTm and a denser VP-ir innervation of the LS than do more aggressive males that exhibit short attack latencies (Compaan et al., 1993). VP release within the BSTm of male rats correlates negatively with intermale aggression, and retrodialysis of synthetic VP into the BSTm significantly reduces aggression in high-aggressive subjects (Veenema et al., 2010). Consistent with these findings, VP immunolabeling in the BSTm correlates negatively with male aggression in free-living sparrows and differentiates the less aggressive field sparrow from the more aggressive song sparrow (*Melospiza melodia*) (Goodson et al., 2012). Furthermore, intraseptal infusions of VP reduce territorial aggression in territorial sparrows and waxbills (Goodson, 1998a, 1998b).

Thus, based on these observations, we hypothesized that the sexual differentiation of the BSTm VP cell group serves to promote male-specific affiliation in the context of reproduction while concomitantly suppressing aggression. In order to test this hypothesis, we infused VP antisense oligonucleotides or scrambled oligonucleotides into the dorsolateral aspect of the BSTm in male and female zebra finches and measured numerous social, aggressive, and maintenance behaviors in a colony setting (Kelly and Goodson, 2013a). Consistent with our predictions, antisense knockdown of VP production in the BSTm significantly increased aggressive behavior in males, but not females (Fig. 4A). This effect is particularly strong in the first session of colony observations when the competition for mates is most intense. Also consistent with our predictions, knockdown of BSTm VP synthesis produced a substantial reduction in courtship singing (Fig. 4B). Interestingly, no negative effects on pair bonding were observed, although it is important to note that a surplus of potential partners is provided in these tests (five potential partners for each four birds of the focal sex) (Kelly and Goodson, 2013a). This design allows us to disambiguate effects on the ability or motivation to pair bond from other relevant behavioral processes, such as courtship and competitive aggression.

All together, the indirect evidence from numerous vertebrate taxa (e.g., from Fos studies), plus the direct evidence from antisense manipulations, strongly support the hypothesis that the male-biased dimorphism of the BSTm VP cell group and its projections serve to focus males on affiliation in reproductive contexts while concomitantly offsetting the tendency for males to be more aggressive than females. This last observation is consistent with an idea advanced by De Vries – that not all sex differences in the brain actually serve to *promote* sex differences in behavior or physiology, but may also serve to *compensate* (or offset) other sex differences in phenotype (De Vries, 2004).

3.4. Evolutionary co-option for nonreproductive functions in opportunistic breeders (and humans, too?)

In contrast to seasonally breeding species, in which VP production in the BSTm collapses outside of the breeding season, several opportunistically or semi-opportunistically breeding finch species in the family Estrildidae are known to maintain stable production of VP in the BSTm year-round (Kabelik et al., 2010) (see Section 3.1). Given this derived condition, BSTm VP neurons and their projections should be available to modulate nonreproductive behavior (in addition to reproductive behavior) in flexible breeders such as the zebra finch and Angolan blue waxbill. Because (1) VP-Fos colocalization increases in the BSTm following exposure to same-sex stimuli in gregarious finch species, but decreases in territorial species (Goodson and Wang, 2006), (2) receptor densities across the LS sub-nuclei are substantially different in territorial and flocking species (Goodson et al., 2009), and (3) gregariousness in zebra finches is reduced by peripheral, intraventricular and intraseptal infusions of an OTR antagonist (Goodson et al., 2009), we hypothesized that the BSTm neurons may influence affiliation not only in reproductive contexts, as discussed in the previous section, but in nonreproductive contexts, as well.

In order to test this hypothesis, male and female zebra finches and Angolan blue waxbills were bilaterally cannulated and infused with either VP antisense oligonucleotides or scrambled oligonucleotides into the dorsolateral aspect of the BSTm, as described above (Kelly and Goodson, 2013a, 2013b; Kelly et al., 2011). Subjects were tested in the choice apparatus shown in Fig. 5A, in which subjects could spend time adjacent to a group of two same-sex conspecifics on one side of the testing cage, ten same-sex conspecifics on the other side, or neither (i.e., in the large central portion of the cage). This test yields two measures – "social contact," which is operationally defined as the percent of test time that the subject spends in close proximity to the small group and large group combined, and "gregariousness," operationally defined as the percent of that social contact time that is spent with the larger group. In addition to this assay, we also employed two measures of anxiety: (1) novelty suppression of feeding and (2) exploration of a novel environment.

Given that the BSTm cell group exerts male-specific effects in a reproductive environment, we predicted that VP knockdown would produce effects on nonreproductive behaviors that are likewise male-specific or male-biased. In addition, because anatomical features of the BSTm-LS circuit (VP cell numbers and OTR distributions) differ between zebra finches and Angolan blue waxbills, we predicted that any observed effects may also vary across species. Both of these predictions were correct. Antisense knockdown of BSTm VP production significantly decreases gregariousness in male zebra finches (Fig. 5B; Kelly et al., 2011), but has no effect on gregariousness in females (Fig. 5D; Kelly and Goodson, 2013a). In contrast, VP knockdown dramatically increased anxiety-like behavior in both males and female zebra finches, as measured in the novelty suppression of feeding test (Fig. 5C and E), although only males showed increased anxiety in the exploration assay (Kelly and Goodson, 2013a; Kelly et al., 2011). Knockdown of BSTm VP synthesis yields a different pattern of results in Angolan blue waxbills: Social contact is reduced, and significantly more so in males (Fig. 6), but no effects are observed on gregariousness or anxiety (Kelly and Goodson, 2013b).

These findings suggest that, in species that do not seasonally collapse VP production in the BSTm (presumably in order to maintain breeding readiness), VP neurons have been evolutionarily co-opted to promote nonreproductive affiliation behaviors in addition to reproduction-specific affiliation behaviors, as addressed in the previous section. Hence, although we would not predict *a priori* that flocking behavior is modulated in a sexually differentiated

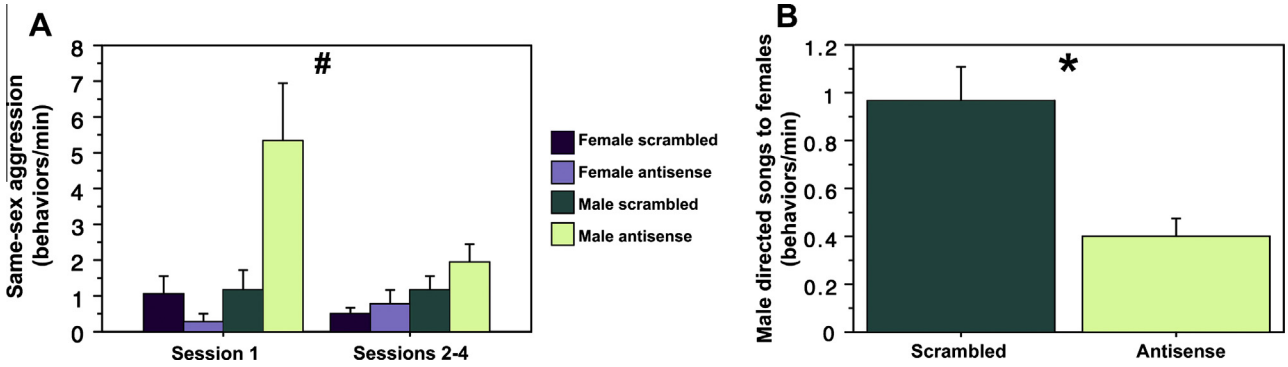

Fig. 4. Knockdown of VP production in the BSTm promotes same-sex aggression in male zebra finches, but not females. Focal observations were conducted twice daily following the establishment of mixed-sex colonies. (A) Antisense-treated males exhibited significantly more same-sex aggression, particularly in Session 1 when subjects are competing for mates ($^{\#}$Session × Sex × Treatment $P = 0.006$). (B) Males infused with VP antisense oligonucleotides into the BSTm exhibited significantly fewer directed songs to females than control males ($^{*}P = 0.001$). Data are shown as the number of songs per minute off of the nest (means ± SEM). Modified from Kelly and Goodson (2013a).

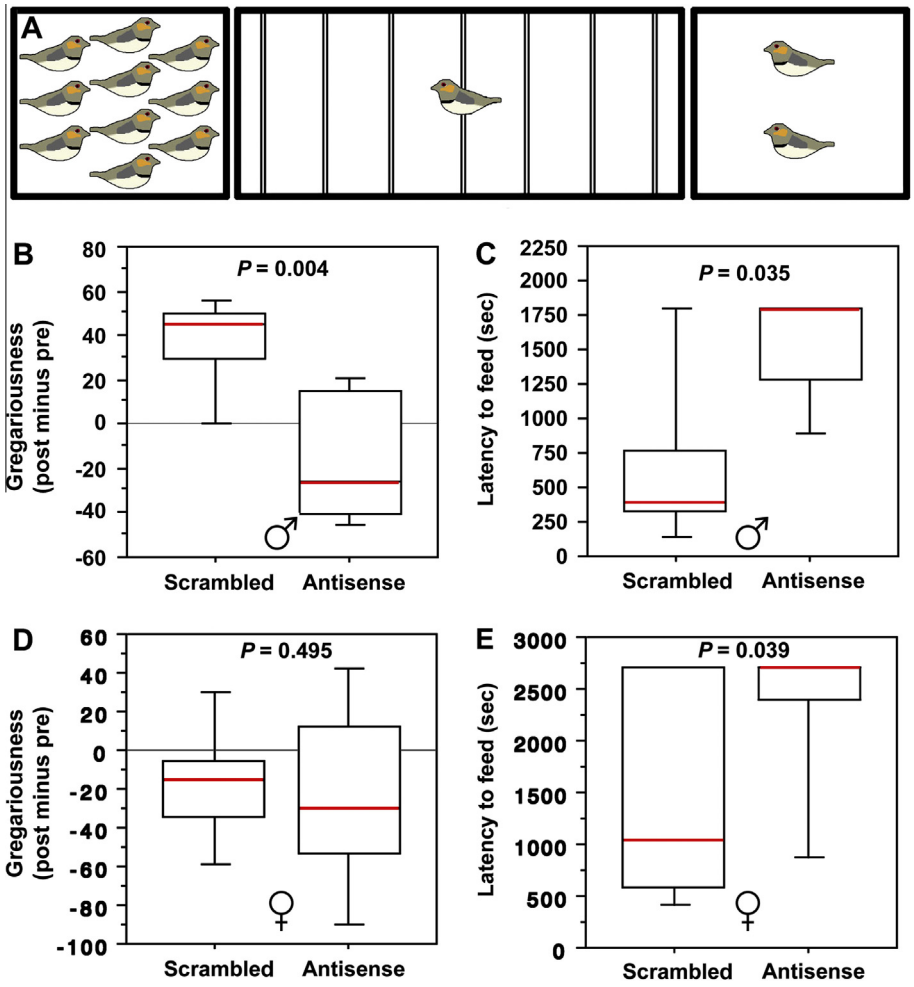

Fig. 5. Antisense knockdown of VP production in the BSTm of zebra finches reduces gregariousness in male-specific manner, but increases anxiety in both sexes. (A) Choice apparatus design. A 1 m wide testing cage was subdivided into zones by seven perches (indicated by thin lines). Subjects were considered to be within close proximity when they were within 4 cm of a stimulus cage (corresponding to the perches closest to the sides). Stimulus cages contained either 2 or 10 same-sex conspecifics. "Social contact" is operationally defined as the percent of test time spent in close proximity to the stimulus cages, and "gregariousness" is operationally defined as the percent of social contact time spent with the larger group. Modified from Kelly et al. (2011). (B and C) Antisense knockdown of BSTm VP production reduces gregariousness in males (B) and increases anxiety in the novelty suppression of feeding test. (D and E) Antisense knockdown of BSTm VP production has no effect on gregariousness in females (D) but increases anxiety in the novelty suppression of feeding test (E) in a manner consistent with males. Modified from Kelly and Goodson (2013a). Data for gregariousness are shown as the post-treatment change from pre-surgical baseline. Anxiety testing was conducted only post-treatment. Box plots show the median (red line), 75th and 25th percentile (box), and 95% confidence interval (whiskers).

manner (given that the behavior is not sexually differentiated), the evolutionary history of male-specific VP functions appears to have produced just that result. As will be addressed below, these male-biased effects are paralleled in females by comparable sex-specific functions of OT neurons in the PVN.

The profile of BSTm VP neurons in finches may provide very useful insights into VP functions of another species that does not breed seasonally – humans. Relatively little anatomical work has been conducted on the BSTm VP cell group in humans, but interestingly, VP neurons have been found in the BSTm of a post-menopausal woman receiving anti-estrogen treatments (Fliers et al., 1986). This suggests that VP neurons in the human BSTm may not be activationally sensitive to sex steroids and that they continue to produce peptide in post-reproductive years. In addition, intranasal VP increases cooperation (in response to perceived partner cooperation) in men playing The Prisoner's Dilemma game, and this behavioral effect is statistically associated with a locus of activation centered on the dorsal LS (Rilling et al., 2012). These findings suggest that endogenous VP released from BSTm neurons in humans may have the potential to modulate nonreproductive affiliation, as found for birds. Furthermore, because gregariousness in zebra finches is reduced by intraseptal infusions of OTR and V1aR antagonists (Kelly et al., 2011; Goodson et al., 2009), the locus of those affiliation effects may also be the same in humans and birds.

4. VP–OT neurons of the SON: Not just for peripheral modulation

SON neurons project primarily to the posterior pituitary (neurohypophysis) and release VP and OT directly into the periphery, where they regulate cardiovascular tone, hydromineral balance, and smooth muscle functions, including the reflexes of parturition and milk letdown in mammals (Carter et al., 2008; Neumann, 2009). Homologous peptides and peptide neurons likewise influence hydromineral balance and egg-laying in other vertebrate taxa (Moore and Lowry, 1998; Moore, 1992). These peptide functions (Fujino et al., 1999; Oumi et al., 1996; Ukena et al., 1995) and the magnocellular neuronal phenotype (Tessmar-Raible et al., 2007) actually pre-date the evolution of vertebrates (and hence, the vertebrate brain), and thus many of the centrally mediated social functions of the nonapeptides are likely built upon their basic egg-laying functions. However, we are unaware of any data directly demonstrating that SON neurons centrally modulate social behaviors, even maternal behaviors that occur in the context of milk letdown (note that central and peripheral release is regulated independently; see Section 1.2).

Nonetheless, some educated hypotheses can be advanced based upon less than direct evidence. For instance, OT axon collaterals lightly innervate the nucleus accumbens in prairie voles, where OT promotes female pair bonding (Ross et al., 2009), and also innervate the central amygdala, where OT reduces fear (Knobloch et al., 2012). However, these sites receive OT innervation from the PVN, as well (Ross et al., 2009; Knobloch et al., 2012), and it remains to be clarified whether these converging inputs yield redundant (potentially additive) influences, or whether there is context-specific release from each cell group. For instance, mating-induced OT release into the nucleus accumbens might arise strictly from the PVN or SON, but not from both. A similar interpretational difficulty arises with regard to volumetric release. It is known that (1) peptide concentrations in the septum are significantly elevated by stimuli that activate hypothalamic

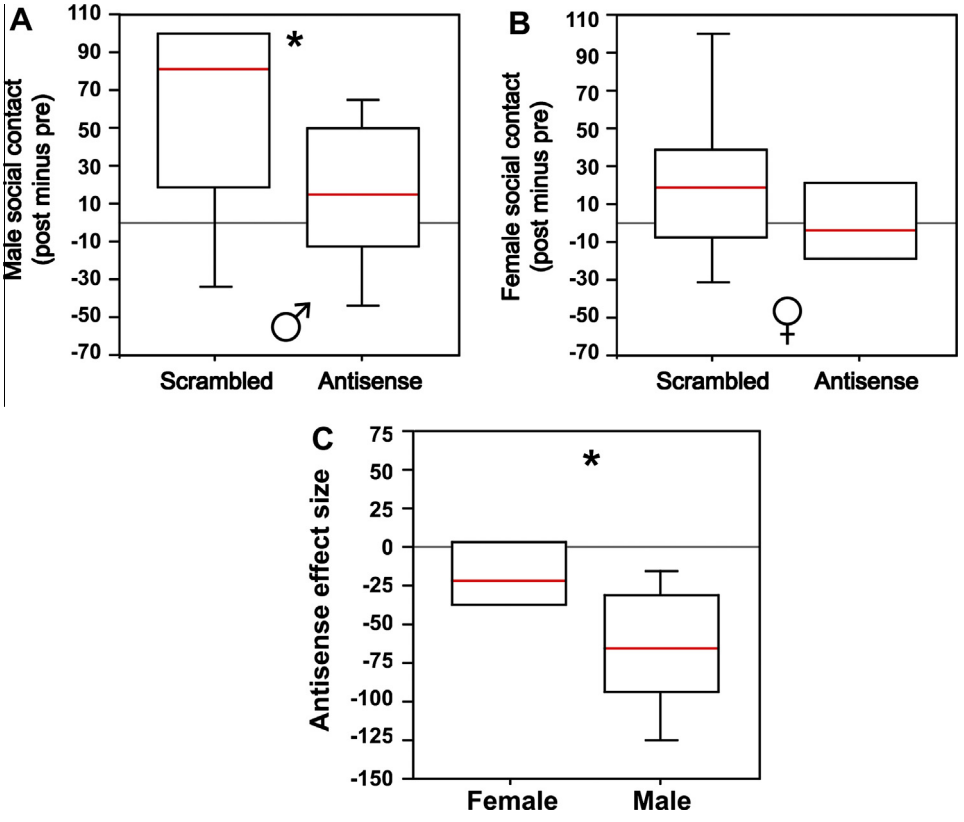

Fig. 6. Antisense knockdown of VP production in the BSTm reduces social contact in a male-biased manner in the modestly gregarious Angolan blue waxbill. See Fig. 5A for test design. (A–C) Social contact is reduced following VP knockdown in males (A), but not females (B), and the pre-post knockdown difference is significantly stronger in males (C). $^{*}P < 0.05$. Note that testing was conducted in two 2-min phases, with sides of the large and small stimulus groups switched at 2 min, and data shown here are for the full 4 min of testing. Females exhibit a significant reduction in contact during the first 2 min only. Modified from Kelly and Goodson (2013b).

magnocellular neurons (Engelmann et al., 1994, 2000), and (2) VP and OT act within the septum to modulate a variety of behaviors, such as parental care (Wang et al., 1994; also see (Curley et al., 2012; Olazábal and Young, 2006), agonistic behavior (Irvin et al., 1990; Goodson, 1998a, 1998b) and social recognition (Bielsky et al., 2005; Everts and Koolhaas, 1999; Popik et al., 1992; Van Wimersma Greidanus and Maigret, 1996; Dantzer et al., 1988). Again, however, it is not possible to differentiate between the contributions of PVN and SON magnocellular neurons.

Perhaps the most suggestive evidence relates to aggression: Maternally separated male rats exhibit significantly greater aggression as adults than do controls, and also exhibit significantly higher levels of VP mRNA in the SON following resident-intruder interactions (Veenema et al., 2006). Similarly, VP-Fos colocalization increases in the medial subdivision of the SON following aggressive interactions and play fighting in hamsters (Cheng et al., 2008; Delville et al., 2000).

5. Functional properties of VP–OT neurons in the PVN

5.1. Effects of social stress

Parvocellular OT and VP neurons of the PVN are major modulators of the hypothalamic–pituitary–adrenal (HPA) axis (Landgraf and Neumann, 2004; Antoni, 1986). Across the vertebrate taxa, VP derived from the PVN acts synergistically with corticotropin releasing hormone to stimulate secretion of adrenocorticotropic hormone, which in turn stimulates production of glucocorticoids in the adrenal cortex, or interrenal gland in anamniotes (Landgraf and Neumann, 2004; Baker et al., 1996; Gillies et al., 1982; Kuenzel et al., 2013). Conversely, OT exerts inhibitory effects on the basal and stimulated activity of the HPA axis (Neumann et al., 2000). However, the majority of available data relate to nonsocial sources of stress. For example, restraint stress increases PVN VP mRNA in rats (Bartanusz et al., 1994) and VP-Fos colocalization in the PVN of rats and mice (Pirnik et al., 2009; Miyata et al., 1995). Similarly, forced swimming and chronic restraint stress enhance OT mRNA expression in the PVN in rats and mice, respectively (Babygirija et al., 2010; Wotjak et al., 1996). Despite these apparent similarities in VP and OT neuronal response, the consequences for HPA activity are opposed. As described above, PVN VP neurons are important drivers of the HPA axis, whereas OT reduces HPA responses to a wide variety of social and physical stressors in rodents (Neumann et al., 2000; Windle et al., 1997). Similar findings are obtained in primates, including humans (Quirin et al., 2011; Hall et al., 2012; Heinrichs et al., 2003; Parker et al., 2005). In general, OT also appears to dampen autonomic responses to stress in rodents, (Grippo et al., 2009, 2012), although the relevant literature in humans is more limited and extensively focused on effects of exogenous OT, which are sometimes sex-specific (Ditzen et al., 2012; Norman et al., 2011; Gamer and Buchel, 2012). Because OT projections to autonomic regions of the brainstem appear to arise exclusively from the PVN (De Vries and Buijs, 1983), it seems likely that these autonomic effects are derived from PVN OT neurons, although paracrine modulation from other sources (particularly the SON) cannot be ruled out.

In addition to these nonsocial stress responses, PVN OT and VP neurons also respond to a diversity of social stressors. For example, social defeat induces intra-PVN VP release in rats (Wotjak et al., 1996), elevates VP-Fos colocalization in the PVN of mice (Litvin et al., 2011), and upregulates VP mRNA in the PVN of mice (Keeney et al., 2006). In addition, V1bR antagonism attenuates the effects of social defeat on anxiety-like behavior and VP-Fos colocalization in the PVN, suggesting that PVN VP is anxiogenic (Litvin et al., 2011). Conversely, OT, along with its influences on social behavior, have been shown to have anxiolytic effects. For example, immobilization stress increases anxiety-like behavior in female prairie voles that recovered alone, but not in females that recovered in the presence of their pair bond partner (Smith and Wang, 2013). This social buffering by the male partner was accompanied by an increase in OT release in the PVN. Interestingly, in females that recovered alone, injection of OT into the PVN attenuated anxiety-like behavior and corticosterone responses to immobilization, whereas injection of an OTR antagonist blocked the effects of social buffering in females that recovered with their male partner (Smith and Wang, 2013). Although the source(s) of intra-PVN release are not clear, it seems likely that it is of local origin. PVN-derived OT may also offset social stress associated with low rank, given that in naked mole rats, subordinate males exhibit relatively more OT-ir cells in the PVN than do dominant breeders (Mooney and Holmes, 2013). Because PVN OT-ir cell numbers decrease in subordinate males when they are removed from the colony and housed in either same-sex or opposite-sex pairs, the elevated level of PVN OT-ir neurons in colony-housed subordinate males is likely due to lower social status, which is associated with antagonistic reproductive suppression by the queen (Mooney and Holmes, 2013).

In addition to these data related to the PVN per se, a variety of other findings have demonstrated that OT is more strongly associated with anxiolysis whereas VP tends to be anxiogenic, at least in some studies (Windle et al., 1997; Blume et al., 2008; Landgraf et al., 1995; Liebsch et al., 1996). It is worth noting, however, that endogenous OT effects on anxiety are not seen uniformly across contexts, but are most pronounced in contexts in which OT release is elevated, such as copulation, parturition, and lactation (Figueira et al., 2008; Jonas et al., 2008; Neumann et al., 2001, 2000).

5.2. Maternal care and maternal aggression

Over 30 years ago, Pedersen and colleagues demonstrated that ICV infusions of OT induce spontaneous maternal care in virgin rats (Pedersen and Prange, 1979); VP promotes maternal care with a delayed onset (Pedersen et al., 1982); and subsequently, that infusions of an OT antiserum impair onset of maternal care (Pedersen et al., 1985). It is now known that both OTRs and V1aRs are critically important not only for pup care (Bosch and Neumann, 2008), but for maternal aggression, as well (Bosch, 2013). Nonapeptides produced in the PVN are thought to be of particular importance in the regulation of maternal behavior, given that electrolytic lesions of the PVN delay onset of maternal behavior (Insel and Harbaugh, 1989) and reduce maternal aggression (Consiglio and Lucion, 1996). Furthermore, microdialysis studies show that OT release within the PVN increases during parturition (Da Costa et al., 1996), suckling, and lactation (Neumann et al., 1993), and also during maternal defense in lactating female rats (Bosch et al., 2004). Interestingly, whereas no change in PVN VP release is observed during maternal aggression in Wistar rat lines bred for high and low anxiety, lactating Sprague–Dawley rats exhibit an increase in VP release within the PVN during maternal aggression (Bosch, 2013).

Gene expression studies also suggest that PVN VP and OT neurons are involved in parental care. For example, PVN VP mRNA expression increases in both male and female prairie voles postpartum (Fig. 7A), and PVN OT mRNA expression increases in females postpartum (Fig. 7B) (Wang et al., 2000). Pup exposure also increases VP-Fos and OT-Fos colocalization in male prairie voles relative to a control stimulus (Fig. 7C; Kenkel et al., 2012), further suggesting the importance of these neurons for parental care in males. A caveat here is that we would expect this result if parents were simply more stressed or experienced higher demands on

autonomic functions (see Section 5.1), and thus it is not clear that the changes in neuronal activity reflect more direct contributions to parental behavior per se.

Unfortunately, only one experiment to date has directly manipulated PVN nonapeptide neurons to determine their contributions to parental behavior. This study demonstrates that knockdown of PVN OT synthesis via antisense oligonucleotides increases maternal aggression in postpartum rats (Giovenardi et al., 1998), suggesting that PVN OT neurons suppress maternal aggression. However, other studies demonstrate that OT effects on maternal aggression vary according to anxiety state (Bosch, 2013; Bosch et al., 2005), and thus further studies are needed before generalizations can be made.

5.3. Other affiliation behaviors and bonding

Effects of VP and OT on pair bonding have been examined almost exclusively in the socially monogamous prairie vole, primarily using approaches such as site-specific antagonist infusions or infusions of viral vectors to overexpress receptors. These studies have demonstrated that OTRs in the nucleus accumbens are critical for the formation of partner preferences in females, whereas V1aRs in the ventral pallidum (a major target of accumbal projections) are essential for preference formation in males (reviews: Young et al., 2011; Young and Wang, 2004). Based on experiments conducted only in males, it is also known that VP promotes pair bonding via its actions at both OTRs and V1aRs in the LS (Liu et al., 2001). Finally, OTR and V1aR densities vary in relation to alternative mating tactics (Ophir et al., 2012; Zheng et al., 2013). However, the specific cell groups that promote pair bonding in prairie voles remain to be identified. Striatopallidal areas receive direct peptidergic projections from the medial extended amygdala (Rood et al., 2013), PVN and SON (Ross et al., 2009), but it should be considered that VP and OT may modulate a diversity of striatopallidal functions unrelated to bonding, and the potential for paracrine modulation must also be taken into account.

Although peptide effects on vole pair bonding were established more than 20 years ago, it remains unknown whether OT and VP exert similar effects in other mammalian species. Social monogamy is rare in mammals, and because it has evolved independently numerous times, we cannot assume that the relevant neural mechanisms will always be the same (Goodson, 2013). In fact, although V1aR receptor densities are an important determinant of pairing behavior in male voles (Lim et al., 2004; Pitkow et al., 2001), receptor densities do not mirror mating systems across eight *Peromyscus* mouse species (Turner et al., 2010), and OTR antagonism does not impair the formation of pair bonds in common marmosets, although it does alter intrapair affiliation (Smith et al., 2010).

Very recent experiments now show that OTR activation is necessary for the establishment of pair bonds in zebra finches, with effects being much stronger in females, consistent with the findings in voles (Klatt and Goodson, 2013; Pedersen and Tomaszycki, 2012). These effects are attributable to the actions of PVN OT neurons, at least in large part. As shown in Fig. 8A, antisense knockdown of PVN OT synthesis profoundly impairs pair bonding in a female-specific manner, increasing the latency to pair bond and decreasing the number of observation sessions in which the female had a partner (Kelly and Goodson, 2014b). Although no effects were observed for pair bonding in males, side-by-side perching (“clumping”) was reduced by knockdown of PVN OT production in both sexes (Fig. 8B; Kelly and Goodson, 2014b). Clumping is a behavior most commonly observed between pair bonded individuals, suggesting that while pair bond status was not affected in males, affiliation behavior within pair bonds was nonetheless impaired. In contrast to OT knockdown, VP knockdown in the PVN produced no detectable impairments in pair bonding or side-by-side perching (Kelly and Goodson, 2014b).

Although these findings suggest some similarities in the mechanisms of pair bonding in prairie voles and zebra finches, it is important to note that zebra finches do not exhibit OTR mRNA or binding in the striatopallidum, but do exhibit high levels of OTRs in the LS (Leung et al., 2009, 2011). Hence, the relevant neural circuits may be only partially similar.

Using the assay of social contact and gregariousness shown in Fig. 5A, we have additionally shown that antisense knockdown of PVN VP synthesis significantly impairs gregariousness in both males and females (Fig. 9A), whereas knockdown of PVN OT production reduces gregariousness in females only (Fig. 9B) (Kelly and Goodson, 2014b). Similarly, high social-interaction male mice exhibit greater expression of PVN OT mRNA (Fig. 10A) and PVN VP mRNA (Fig. 10B) compared to low social-interaction mice, and time spent in social interaction also correlates positively with PVN OT and VP mRNA expression (Flanagan et al., 1993). Again, however - a caveat: Such correlations may reflect variation in the autonomic and HPA axes that are downstream of behavior and not behaviorally causative.

Finally, OT-Fos colocalization in the PVN increases following sexual behavior in both male and female rats (Flanagan et al., 1993; Nishitani et al., 2004; Witt and Insel, 1994), and a variety of data further suggest that PVN OT neurons are important regulators of erectile function. For instance, infusions of OT directly into the PVN potently facilitate erections, as do infusions into the

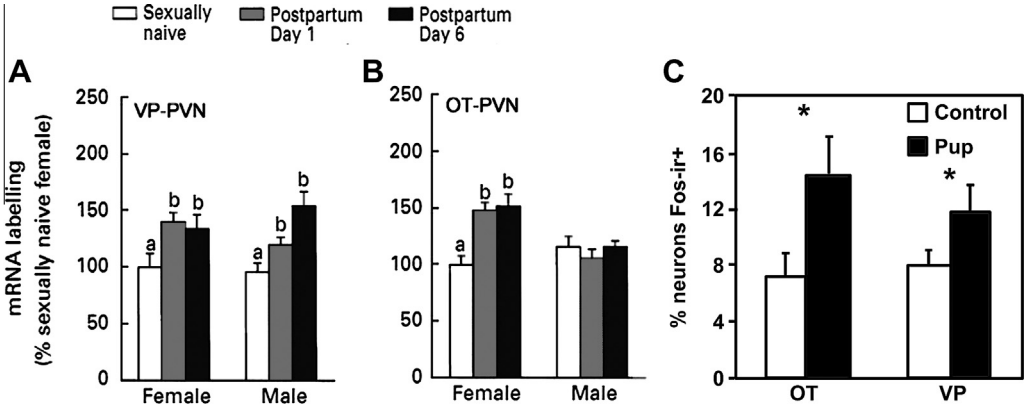

Fig. 7. VP and OT mRNA in the PVN and neuronal Fos response reflects parental state in the biparental prairie vole. (A and B) PVN mRNA expression for VP and OT increases postpartum in both male and female prairie voles. Data are shown as a percentage of expression in sexually naive females. Different letters above the error bars denote significant group differences ($^{*}P < 0.05$). Modified from Wang et al. (2000). (C) Pup exposure increases VP-Fos and OT-Fos colocalization in male prairie voles relative to a control stimulus (a wooden dowel). $^{*}P < 0.05$. Modified from Kenkel et al. (2012). Data in all panels are shown as means ± SEM.

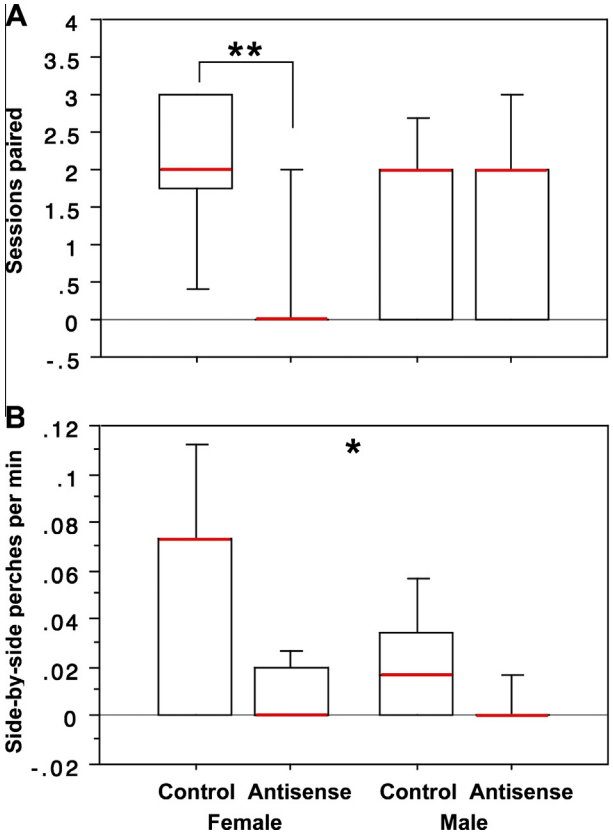

Fig. 8. Knockdown of OT synthesis in the PVN produces female-specific deficits in pair bonding and virtually abolishes side-by-side perching in both male and female zebra finches. Focal observations were conducted twice daily following the establishment of mixed-sex colonies (4 sessions total). (A) Antisense-treated females were paired for significantly fewer sessions than control females (**$P < 0.01$), whereas no effect is observed in males. (B) Antisense-treated males and females exhibit a profound reduction in side-by-side perching (shown as behaviors per minute not on the nest; *$P = 0.03$). Box plots show the median (red line), 75th and 25th percentiles (box), and 95% confidence interval (whiskers). Modified from Kelly and Goodson (2014b).

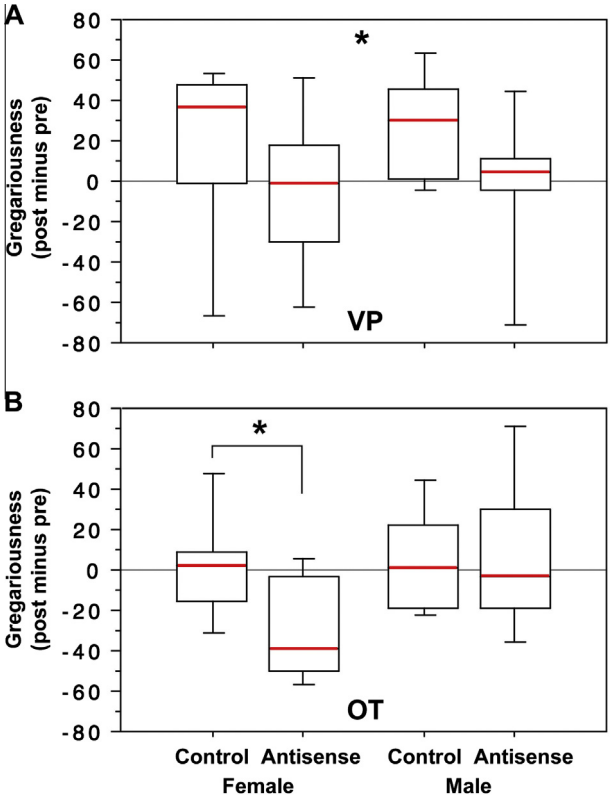

Fig. 9. Antisense knockdown of VP and OT production in the PVN reduces gregariousness, but in a sexually differentiated manner. Testing was conducted as shown in Fig. 5A. (A) Relative to controls, VP knockdown in the PVN reduces gregariousness in both males and females (i.e., with sexes pooled; *$P < 0.05$). (B) In contrast, OT knockdown reduces gregariousness in females only (*$P < 0.05$). Box plots show the median (red line), 75th and 25th percentiles (box), and 95% confidence interval (whiskers). Modified from Kelly and Goodson (2014b).

spinal cord and a variety of other extrahypothalamic regions that PVN OT neurons are known to project to (Melis and Argiolas, 2011). Consistent with these findings, sexually impotent male rats exhibit reduced OT production in the PVN (Arletti et al., 1997).

5.4. Aggression outside of the maternal context

Little is known about the roles of PVN VP and OT neurons in aggression outside of the maternal context. Although exogenous OT exerts anti-aggressive effects in rats (Calcagnoli et al., 2013), PVN OT-ir neuron numbers actually correlate *positively* with aggression in field sparrows, and a similar trend is observed in song sparrows (Goodson et al., 2012; see Table S7). However, the functional significance of these relationships remains to be determined.

As addressed in Section 7.1, the bulk of data linking hypothalamic VP neurons to aggression relates to small accessory cell groups and VP neurons of the nucleus circularis. Nonetheless, a variety of immediate early gene studies do demonstrate that PVN VP neurons exhibit responses to aggressive interactions. For instance, VP-Fos colocalization increases in the PVN in response to a resident-intruder encounter in subordinate, but not dominant, male mice (Ho et al., 2010). In contrast, VP-Fos colocalization in the PVN increases following a male-male aggressive encounter in lizards, but only in the most aggressive subset of animals (Kabelik et al., 2013). Immediate early gene activation of PVN VP neurons also increases following a simulated territorial intrusion in male song sparrows (Goodson and Evans, 2004), but in contrast to the lizard findings, VP-Fos colocalization in the PVN correlates negatively with aggression (Goodson et al., 2005). These studies suggest that PVN VP neurons may influence same-sex aggression, perhaps inhibiting it, but antisense knockdown of PVN VP synthesis in zebra finches actually has no effect on male-male or female-female aggression (Kelly and Goodson, 2014b). Hence, because PVN VP neurons are important regulators of the HPA (see Section 5.1), the Fos results just described may reflect aggression-associated stress response, rather than the aggressive behavior per se. Regardless, VP knockdown in the PVN of zebra finches does alter aggression directed towards opposite-sex birds, albeit in a sex-specific manner – decreasing aggression in females and facilitating it in males (Kelly and Goodson, 2014b). Finally, male rats that experienced maternal separation as pups exhibit greater expression of VP mRNA in the PVN after an aggressive encounter than do control animals, although expression does not differ under basal conditions (Veenema et al., 2006). Hence, developmental experiences are likely important mediators of the relationship between PVN VP neurons and either aggression or aggression-related stress response.

6. VP neurons of the SCN

VP neurons are one of two principal cell types in the brain's master circadian clock, the SCN. As such these cells are important

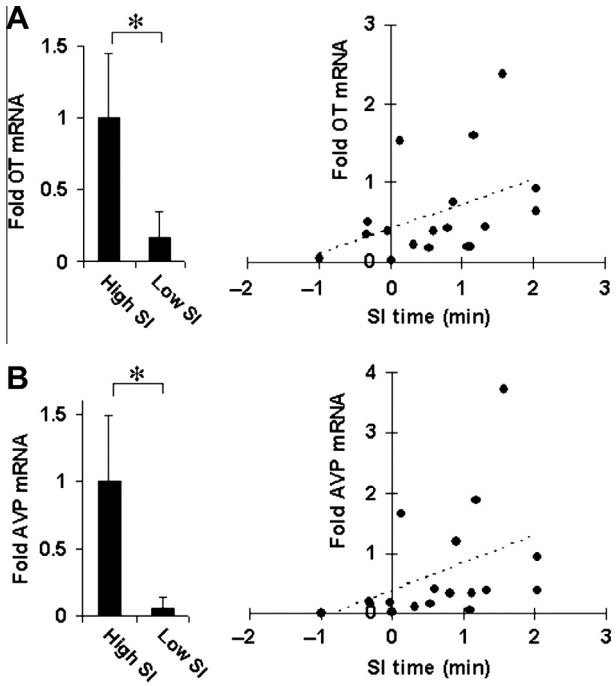

Fig. 10. OT and VP expression in the PVN is positively related to social interaction (SI) in mice. OT (A) and VP (B) mRNA in the PVN, shown as the ratio relative to the average in high-SI mice. OT and VP mRNA in low-SI mice was substantially lower, being only 13% of high-SI levels for OT and 5% for VP (left). Positive correlations with social interaction time are observed for both OT ($r^2 = 0.41$) and VP ($r^2 = 0.40$). *$P < 0.05$. Modified from Murakami et al. (2011).

for the temporal organization of myriad processes, including daily rhythms in physiology and behavior. Recent data by Rood et al. (2013) show that lesions of the SCN produce significant reductions in the VP-ir innervation of forebrain regions that are important for such processes, including the BSTm, POA, dorsomedial hypothalamus, and numerous areas of the medial hypothalamus (Rood et al., 2013). Nonetheless, to our knowledge contributions of SCN VP neurons to social behavior have been experimentally addressed in only one study, which demonstrated that lesions of the SCN in male Syrian hamsters fail to influence flank-marking, a VP-dependent behavior (Delville et al., 1998).

7. Functions of the "accessory" and smaller VP cell groups

7.1. Modulation of aggression and pair bonding by accessory neurons of the AH

A wide variety of pharmacological studies have been conducted on the aggression-related functions of VP and V1aRs within the AH of rodents, most extensively in male Syrian hamsters. A full consideration of this literature is beyond the scope of the present paper, but has been extensively reviewed elsewhere (Albers, 2012; David et al., 2004; Melloni and Ricci, 2009). It is important to note that much of this work has been conducted with an explicit intent to model pathological aggression, using hamsters that have been treated with anabolic steroids, trained as fighters, or isolated for long periods of time. Interestingly, V1aR activation in the AH promotes offensive aggression in these models (Albers, 2012; David et al., 2004; Melloni and Ricci, 2009), but does not do so in socially housed males (Albers, 2012), suggesting strong plasticity in V1aR-mediated behavioral effects. We must therefore be cautious in extrapolating to other contexts. AH VP circuits may also modulate behavior in a sex-specific manner, given that activation of V1aRs in the AH actually *inhibits* aggression in female hamsters (Gutzler et al., 2010).

In the models of pathological aggression described above, the display of offensive aggression is associated with Fos activation of VP neurons in the medial division of the SON and in the nucleus circularis, a small cell group of the AH (Albers, 2012; David et al., 2004; Melloni and Ricci, 2009). This same pattern is observed in association with juvenile play fighting (Cheng et al., 2008). However, it remains to be determined whether VP neurons of the medial SON or nucleus circularis directly influence aggression, or whether these neurons influence aggression-related aspects of physiology. The connections of these cells certainly suggest that they are the source of AH VP release (Albers, 2012; David et al., 2004; Melloni and Ricci, 2009), but for the reasons addressed elsewhere in this review, the complexity of nonapeptide signaling dictates caution in our interpretations.

An interesting parallel with these experiments comes from male prairie voles, which are relatively docile prior to mating, but afterwards become extremely aggressive towards intruders (Carter et al., 1995). This mating-induced aggression is also associated with increased VP-Fos colocalization in the nucleus circularis (Gobrogge et al., 2007). Interestingly, pair bonded males exhibit higher V1aR binding in the AH than do sexually naive males, and viral vector-mediated upregulation of V1aRs in the AH enhances offensive aggression (Gobrogge et al., 2009). Hence, pairing-associated plasticity in the AH appears to support the lasting effects of pair bonding on aggression. This same pattern of V1aR plasticity and enhanced aggression is observed following repeated exposure to amphetamines in male prairie voles (Gobrogge et al., 2009), and following social isolation in hamsters (Albers et al., 2006), whereas the plasticity associated with anabolic steroid administrations is presynaptic (Melloni and Ricci, 2009).

7.2. A "new" VP population in the olfactory bulb is required for social recognition

In 2010, Tobin et al. (2010) presented novel evidence for the presence of VP neurons in the olfactory bulb of rats. These cells are localized primarily to the external plexiform layer close to the glomeruli. One dendrite of each VP neuron arborizes within a single glomerulus and other dendrites penetrate the external zones of neighboring glomeruli. Hence, these cells are well positioned to receive olfactory nerve afferents, but because they do not project out of the olfactory bulb, they likely modulate processing within the olfactory bulb itself. This may occur via dendritic release into the glomeruli, given that the dendrites are packed with VP-containing vesicles. Indeed, a variety of experiments demonstrate that local VP modulation is required for normal social discrimination. Social discrimination is impaired by simultaneous V1aR/V1bR blockade, infusions of V1aR siRNA, and selective destruction of VP neurons in the olfactory bulb. Remarkably, these manipulations have no effect on olfactory object recognition, indicating that intrinsic VP circuits of the olfactory bulb specifically modulate social discrimination, and in a manner that is similar to VP–OT effects on social recognition within other parts of the forebrain (e.g., LS Gabor et al., 2012; Ferguson et al., 2002).

8. Personality and complex patterns of neuromodulation

In the preceding sections we have reviewed what is known about the behavioral functions of individual nonapeptide cell groups. However, as discussed in Section 1, complex behavioral output is likely not the result of a single peptide acting via a single receptor type in a single brain area. Rather, given that (1) each cell group likely influences multiple brain targets, (2) patterns of

modulation arising from individual cell groups are likely overlapping (Ludwig and Leng, 2006; Landgraf and Neumann, 2004), and (3) VP–OT receptors are promiscuous (Manning et al., 2008; Leung et al., 2009; Searcy et al., 2011), behavior is likely the product of coordinated neuromodulation across several brain regions and multiple receptor types (Goodson and Kabelik, 2009).

This idea receives strong support from a recent experiment that was focused on the relationships between BSTm and PVN cell groups, personality, sex, and social context in zebra finches. Based upon principal components (PC) analysis of extensive behavioral measures in social and nonsocial contexts, we first described three complex dimensions of phenotype (''personality'') for male and female zebra finches. These three PCs of behavior can be generally characterized as: Social competence/dominance (PC1; a component that may reflect individual differences in the mechanisms of social cognition), which strongly loads variables such as dominance behaviors, latency to pair bond, and preferences for familiar social partners; Gregariousness (PC2), which strongly loads only measures of group-size preference; and Anxiety (PC3), which primarily loads measures of novelty-suppressed feeding and exploration. We further demonstrate that the phasic Fos response of VP and OT neurons in the PVN and VP neurons in the BSTm are significantly predicted by these three personality dimensions, sex, and social context (i.e., interactions with novel versus familiar individuals), as well the interactions of these variables (Kelly and Goodson, 2014a).

We then conducted a PC analysis that includes both VT-MT cell numbers and the numbers of those neurons that were double-labeled for Fos. This yields three ''neural PCs.'' Neural PC1 loads all variables in a positive manner. In contrast, neural PC2 loads BSTm VT variables positively; loads PVN MT variables negatively; and shows very weak loadings for PVN VT variables. Only PVN VT variables load strongly on neural PC3. Subsequent analyses show that the neural PCs are strongly predicted by sex, social context and all three behavioral PCs. Importantly, each behavioral PC (i.e., personality dimension) relates to a distinct subset of neural PCs, suggesting that personality is indeed reflected in complex patterns of neuromodulation that arise from multiple VP–OT cell groups (Kelly and Goodson, 2014a).

9. Conclusions

Although hundreds of studies demonstrate that VP and OT systems are involved in a very wide range of behavioral functions, only a handful of studies have directly manipulated specific cell populations to determine their contributions to social behavior. However, direct experimental manipulations are necessary in order to determine function, given (1) the extent of overlapping projections from different cell groups, (2) receptor promiscuity, and (3) the large number of neural loci where VP and OT are produced. To date, social behavior functions have not been directly demonstrated for most VP–OT cell groups, and remarkably, these include major populations such as the VP–OT neurons of the SON and VP neurons of the SCN. Similarly, although socially relevant features of the BSTm VP cell group have been studied for decades (e.g., focused on hormonal regulation, sexual differentiation, and correlations with behavior), experimental evidence for the behavioral functions of these neurons has only recently been generated. These data show that BSTm VP neurons promote male affiliation and concomitantly suppress aggression in finches. The majority of direct experimental data derive from studies of VP–OT neurons in the PVN, but even here, our ability to draw conclusions about social behavior functions is limited. It is clear that PVN OT neurons promote maternal behavior in mammals and that PVN VP–OT neurons influence a diversity of social behaviors in birds, such as pair bonding, grouping, and intrapair affiliation. However, as with other cell groups, the majority of findings for the PVN are correlational and must be interpreted with extreme caution. As an example, male-male aggression in songbirds correlates negatively with VP-Fos colocalization in the PVN (Goodson and Kabelik, 2009), but antisense knockdown of PVN VP production does not alter male-male aggression (Kelly and Goodson, 2014b). Hence, the negative correlation between VP neurons and behavior likely reflects a negative relationship between HPA activation and behavior, not a direct contribution of PVN VP neurons to aggressive behavior. When we consider the large number of hormonal and autonomic variables that are modulated by VP and OT, it becomes clear that many correlations between VP–OT neurons and behavior may not have anything to do with the direct modulation of social behavior, but rather with the modulation of physiological parameters that are themselves associated with social behavior. In summary, direct experimental data are absolutely essential if we are to understand the functional properties of nonapeptide circuits and their relevance to translation.

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