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Commentary

Towards meeting Tinbergen's challenge

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A half-century ago, the great pioneers of ethology (e.g., Tinbergen, 1951) and neuroscience (e.g., Hebb, D. O., 1949. The organisation of behaviour. Wiley-Interscience, New York.) recognized that the need to bridge the gap between the "ethologist" and the "physiologist" was crucial if we are to achieve a clear understanding of the behavior of the "intact animal." Arguably among Tinbergen's greatest gifts to those of us interested in the study of behavior were his *Four Questions* (Tinbergen, 1963). Tinbergen outlined that behavior had many different sides, each of which could teach us something more about the subject of study. One could observe the same individual and ask several questions, with each providing independent answers from the others. These included: 1) "describing the course of evolution," 2) the course of development, 3) "the genetics proper of behavior," and 4) "the directional changes under the influence of natural selection" (Tinbergen, 1951). Tinbergen was clear that each question allowed a scientist to investigate a given behavior from a very different perspective; by looking at the same object from different angles, something unique and new about that object is revealed. As students, we have been taught to approach these different levels of analysis independently—this is particularly true for proximate and ultimate questions (Kennedy, J. S., 1992. The new antrhopomorphism. Cambridge University Press, Cambridge.; Krebs, J. R., Davies, N. B., 1997. Behavioural Ecology. Blackwell, Oxford.; Mayr, E., 1961. Cause and effect in biology. Science. 134, 1501–1506.; Williams, G. C., 1966. Adaptation and natural selection. Princeton University Press, Princeton.). However, understanding one level can tell us a great deal about the others (Thierry, B., 2005. Integrating proximate and ultimate causation: Just one more go! Current Science. 89, 1180–1183.), and Tinbergen himself noted that these modes of analyses were isolated only for convenience of description and analysis (Tinbergen, N., 1963. On aims and methods in ethology. Zeitschrift für Tierpsychologie. 20, 410–433). Since Tinbergen's time, integrative approaches in biology have steadily gained in popularity, which may reflect scientists' growing appreciation for behavior as a primary driving force in evolution. Perhaps ironically, the emphasis on integrative approaches, paired with increasing technological advances, has caused the distinctions Tinbergen outlined to coalesce. Multi-level approaches are increasingly more feasible; genetic and phenotypic engineering, for example, offer the opportunity to gain a better account of genetic, physiological, and neurological factors governing behavior. Such approaches offer great insight into the causes of both the evolution and behavior of Tinbergen's "intact animal." Here I highlight some of

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the work by Goodson and colleagues, with special focus on Kelly et al. (2011) published in this issue of *Hormones and Behavior*, which embodies this scientific framework. This set of studies has pioneered the hypothesis that septal peptides facilitate social grouping preferences. I offer my own speculation that attempts to find common denominators in neuropeptide control of social behavior by integrating this apparent "sociality continuum" with that of another related spectrum of social behavior, mating system.

Integrating levels of analysis: estrildids

In this issue, Kelly et al. (2011) build on work coming from their lab group that represents efforts toward achieving a deeper understanding of animal behavior by bringing together several approaches. This earlier work combines cross-species comparisons, genetic manipulation, an attempt to understand the physiological mechanisms that mold behavior, and efforts to consider these mechanisms as consequences of directional changes under the influence of natural selection.

In an attempt to identify the mechanisms that promote flocking behavior in the zebra finch, a highly gregarious estrildid species, Kelly et al. (2011) elegantly demonstrate that social grouping preferences are under the direct control of vasotocin (VT) in the medial portion of the bed nucleus of the stria terminalis (BSTm) and its receptors (V1a-like) in the lateral septum (LS). By use of antisense knockdown of the hormone at the source, and infusion of receptor antagonist at the target, Kelly et al. (2011) demonstrate that this circuit is integral for shaping social grouping preferences, but not affiliative preferences. An important inference from this study is that several related but independent mechanisms of "sociality" operate to promote social behavior (see below).

Beyond modulating aggregation in zebra finches, this research group has shown that these populations of cells modulate valence for rewarding social stimuli (such as affiliation-related cues) but not punishing stimuli (such as social subjugation) with their work using the immediate early gene *c-Fos* (Goodson et al., 2009a; Goodson and Wang, 2006). Estrildid finches range in their affinity for grouping; some join flocks of hundreds, whereas others form selective territorial pairs. Goodson and his colleagues investigated five species of monogamous and bi-parental estrildid finches and demonstrated that gregarious birds appear to be more sensitive to VT in the BSTm-LS circuit compared to asocial finches. For instance, gregarious birds show high *c-Fos* activity in VT cells after exposure to conspecifics (Goodson and Wang, 2006). In contrast, territorial birds show decreased *c-Fos* activity to conspecifics unless the territorial bird is exposed to its partner, in which case VT neurons show increases in *c-Fos*. Furthermore, flocking species have more VT neurons in the BSTm, they have more active VT neurons in the BSTm, and they have more V1aR-like binding sites in the LS (Goodson et al., 2006; Goodson and Wang, 2006). However, pharmacological comparisons are needed to conclusively determine species differences in VT sensitivity.

These species differences in mechanisms of social grouping extend beyond vasotocin to include at least one other nonapeptide, mesotocin (a common non-mammalian homologue for oxytocin). Distribution of oxytocin-like receptors predicts social grouping preferences across estrildid finches. For instance, the dorsal LS has higher OTR and the ventral LS has lower OTR density in gregarious finches (Goodson et al., 2009b), however the significance of dorso-ventral relationship has not yet been elucidated in finches or identified in other species. Moreover, infusions of an oxytocin antagonist reduce gregariousness in zebra finches (Goodson et al., 2009b), suggesting that septal mesotocin is necessary for social grouping in finches. Taken together, this research group has begun to characterize an emerging continuum between social and asocial species mediated by BSTm-LS nonapeptide interactions. This provides an important piece to the larger story that this and other labs have begun to construct: that nonapeptide expression patterns are crucial to social structure and social behavior within and between species.

Other models of social behavior: voles

Estrildid finches are a promising emerging Avian model system for understanding mechanisms of social behavior. Although, the call for understanding human (or non-human) social behavior need not come from a mammalian model *per se*, the roles of these mechanisms in social interactions may be domain specific for certain species, and having taxonomically broad comparisons strengthens our understanding of the generalities of these mechanisms.

Another promising model comes from a group of rodents from the genus *Microtus*. Indeed, voles have become one of the major models for understanding the prosocial influences of nonapeptides on social behavior. Much of this work has focused on individual and species differences in nonapeptide patterns in social organization and mating system. This body of work has been reviewed elsewhere (Carter et al., 1995; Insel and Young, 2001; Young and Wang, 2004; Young et al., 2005), and I will only briefly point out a few interesting points given the current backdrop. Monogamous prairie voles form intense attachment with partners and offspring, defend territories, and they are bi-parental (Getz and Hofmann, 1986; Getz et al., 1981, 1993; Insel et al., 1995; Thomas and Birney, 1979; Winslow et al., 1993). In contrast, non-monogamous voles do not form selective attachment, attempt to mate multiply, show seasonal variation in social grouping, and—like most mammals—are uni-parental (Beery et al., 2009; DeCoursey, 1957; Findley, 1951; Gruder-Adams and Getz, 1985; Madison, 1980; Madison et al., 1984; Wang et al., 1994; Webster and Brooks, 1981). With regard to nonapeptides, receptor density for both V1aR and oxytocin receptor (OTR) predicts social organization in monogamous prairie and pine voles and non-monogamous meadow and montane voles (Cho et al., 1999; Insel and Shapiro, 1992; Insel et al., 1994; Wang et al., 1998; Young et al., 1997). Manipulation of either hormone or their receptors influences the propensity to form bonds; infusion of nonapeptide agonists facilitates bonding, whereas receptor antagonists eliminate affiliative bonds (Cho et al., 1999; Lim and Young, 2004; Liu et al., 2001; Williams et al., 1994; Winslow et al., 1993).

The primary focus of this work has been on the influence of peptides on the "pairbonding neural circuit" which includes the LS, the extended amygdalar complex (e.g., medial amygdala and BST), and other structures involved in reward such as the nucleus accumbens (NAcc) and ventral pallidum (VPall) (Young and Wang, 2004; Young et al., 2005). Although the septum has received comparatively less attention for its role in bonding, V1aR antagonists delivered to the LS eliminate bonding in prairie voles (Liu et al., 2001). Considering this result in the context of the work presented by Kelly et al. (2011) might lead to the pre-mature conclusion that septal vasopressin (the mammalian homologue of VT) mediates social bonding in prairie voles in the same manner as it mediates social grouping in estrildid finches; blockade of V1aR eliminates social affinity.

Forms of sociality: distinction between affiliation and grouping

There are, however, at least two important problems with equating (socially) affiliative prairie voles with (socially) gregarious finches. First, although convention has co-opted both terms under the larger term "sociality," there is a fundamental difference between social affiliation and social grouping. For instance, an animal may form a bond with a single individual but be socially averse to groups. On the contrary, socially repose animals may demonstrate an inability to form meaningful bonds with a single individual. The fact that nonapeptides mediate two distinct aspects of social behavior may not be sheer coincidence (Goodson, 2008; Goodson and Bass, 2001),