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SEXUAL DIFFERENTIATION OF CENTRAL VASOPRESSIN AND VASOTOCIN SYSTEMS IN VERTEBRATES: DIFFERENT MECHANISMS, SIMILAR ENDPOINTS

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Abstract

Vasopressin neurons in the bed nucleus of the stria terminalis and amygdala and vasotocin neurons in homologous areas in non-mammalian vertebrates show some of the most consistently found neural sex differences, with males having more cells and denser projections than females. These projections have been implicated in social and reproductive behaviors but also in autonomic functions. The sex differences in these projections may cause as well as prevent sex differences in these functions. This paper discusses the anatomy, steroid dependency, and sexual differentiation of these neurons. Although the final steps in sexual differentiation of vasopressin/vasotocin expression may be similar across vertebrate species, what triggers differentiation may vary dramatically. For example, during development, estrogen masculinizes vasopressin expression in rats but feminizes its counterpart in Japanese quail. Apparently, nature consistently finds a way of maintaining sex differences in vasopressin and vasotocin pathways, suggesting that the function of these differences is important enough that it was conserved during evolution.

Keywords

sex differences; testosterone; estrogen; bed nucleus of the stria terminalis; amygdala; lateral septum

Sex differences in vasopressin (AVP) projections of the bed nucleus of the stria terminalis (BST) and medial amygdaloid nucleus (MeA) were first described in rats and were discovered by chance while we were studying what we thought were developing AVP projections of the suprachiasmatic nucleus (SCN) (De Vries et al., 1981). AVP cell bodies in the BST and MeA had yet to be discovered (Van Leeuwen and Caffé, 1983). A study of the development of vasopressin-immunoreactive (AVP-ir) fibers in the lateral septum and habenular nucleus revealed a disturbingly large variability, prompting us to run a second series, separating animals by sex. This revealed a large sex difference with males having a much denser AVP-ir fiber network in the lateral septum and lateral habenular nucleus than females (Fig. 1A). Later we showed that AVP expression in these areas critically depended on circulating gonadal steroids (De Vries et al., 1984), and that AVP-ir cells in the BST and MA showed corresponding sex differences and steroid responsiveness (DeVries et al., 1985; Van Leeuwen et al., 1985). Since these first findings, homologous sex differences have been found in many different species, in mammals as well as other vertebrates (Table 1).

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Sources of sexually dimorphic AVP and vasotocin innervation

In rats, the BST and MeA provide a major part of AVP innervation in the forebrain. These two areas belong to the extended amygdala, a cohort of nuclei in the BST and centromedial amygdala with striking similarities in cytoarchitecture and neurochemistry (de Olmos and Heimer, 1999). The sexual dimorphism and steroid responsiveness of AVP neurons in BST as well as MeA underscore these similarities. In vertebrates with less extensive encephalization than mammals, the areas homologous to the BST and amygdala are not physically separated by the internal capsule (Johnston, 1923). In such animals, the sexually dimorphic vasotocin-immunoreactive (AVT-ir) cells typically form a single, undivided cluster (e.g. Boyd et al., 1992; Marler et al., 1999).

Given the wide acceptance of our proposal that the BST and MeA are the sources of sexually dimorphic AVP-ir and, by extension, AVT-ir innervation of the brain, it is important to point out that this idea is based on a rather limited set of experiments (De Vries and Buijs, 1983). To locate the source of the sexually dimorphic AVP-ir innervation of the lateral septum, we used knife cuts ventral to the septum, which showed that AVP-ir fibers enter the septum ventrorostrally. We retrogradely traced connections to the lateral septum (regardless of neuropeptide expression), which favored the BST as a source over other likely candidates, i.e. the SCN and paraventricular nucleus (PVN). Finally, because lesions of the SCN had already disqualified the SCN as a likely source of septal AVP-ir innervation (Hoorneman and Buijs, 1982), we lesioned the PVN bilaterally, which spared septal AVP-ir innervation, and the BST unilaterally, which decimated septal AVP-ir innervation ipsilaterally (bilateral lesions caused high mortality). The conclusion that the BST is an important source of septal AVP-ir fibers therefore rests on solid evidence (De Vries and Buijs, 1983). Evidence for other projections from the BST and MeA is less firm. When we found that castration deleted AVP-ir cell bodies in the BST and MeA but not in other areas, and AVP-ir fibers in all areas where unilateral lesions of the BST had eliminated AVP-ir fibers, we proposed that the BST and MeA project to all areas where castration eliminated AVP immunoreactivity and not to areas where AVP immunoreactivity remained (Fig. 1B; DeVries et al., 1985). Later Caffé et al. (1987) combined retrograde tracing with AVP immunocytochemistry to confirm that the BST projects to the lateral septum and show that the MeA projects to the ventral hippocampus as well as lateral septum. Differences in the effects of BST and MeA lesions on septal AVP innervation, however, suggest that the BST provides the lion's share of the septal AVP-ir innervation (Al Shamma and De Vries, unpublished observations). None of the other BST and MeA projections have been independently confirmed. Even less certainty exists about homologous projections in other vertebrates. The only other tracing study was done in Japanese quail, which demonstrated that AVT-ir neurons in the BST project to the medial preoptic nucleus (POM; Absil et al., 2002). However, given the often striking similarity in distribution, sexual dimorphism, and steroid sensitivity of AVP and AVT systems across vertebrates, it is unlikely that the anatomy of these systems differs fundamentally among species.

There are some intriguing species differences, however. For example, Moore et al. (2000) find similar sex differences in roughskin newts as are found in rats. However, they also find more AVT-expressing cell groups than have been found in any other species. Some of these cell groups exhibit differences favoring males, others females. Any number of these cell groups could contribute to sexually dimorphic AVT-ir innervation. One could even imagine that some of these cell groups cancel out differences in fiber density if cell groups with opposite differences project to overlapping areas. Like roughskin newts, Japanese quail show similar differences in the BST as do rats, but male quail also have more AVT-ir cell bodies in the POM than do females (Panzica et al., 2001). As the POM projects to the lateral septum (Balthazart et al., 1994), these cell bodies may contribute to differences in septal AVT-ir innervation as well. Sex differences have also been found in AVP/AVT neurons in the PVN in mammals,

including humans (Ishunina and Swaab, 1999), and the preoptic area in non-mammalian vertebrates, especially in fish (e.g. Grober and Sunobe, 1996; Semsar and Godwin, 2003). Many of these neurons appear neurosecretory, however, and may therefore not contribute to central AVP/AVT-ir innervation.

AVP-ir fibers in the lateral septum are sometimes used as a yardstick for the AVP projections from the BST and MeA. For example, macaques, marmosets, and humans show virtually no AVP-ir fibers in the lateral septum and therefore no clear sex difference in this area either. These primates, however, have AVP-ir cells in the BST, and male marmosets have more of these cells than do females (Caffé et al., 1989; Fliers et al., 1986; Wang et al., 1997). In fact, primate and rodent AVP innervation may be quite similar, because many areas that receive steroid-sensitive AVP innervation in rats, such as the ventral pallidum, dorsal raphe nucleus, and midbrain central gray, also contain dense AVP-ir innervation in macaques (Caffé et al., 1989). As human brains have not been studied as comprehensively, sex differences in AVP projections in the human brain cannot be discounted.

There are major outliers, however. For example, Syrian hamsters lack homologous steroid-sensitive AVP cells in the BST and MeA and AVP innervation in areas such as the lateral septum that would have received innervation from those cells (Albers et al., 1991; Ferris et al., 1995; Miller et al., 1999). Within mammals, Syrian hamsters are exceptional, however. Given that homologous AVT cells have never been reported for fish either (Goodson and Bass, 2001), fish may be the only vertebrate class that does not have the steroid-sensitive systems reviewed in this paper. However, these systems may have escaped detection; AVP cells were discovered in BST and MeA only after colchicine treatment (Van Leeuwen and Caffé, 1983), and visualizing them without colchicine required increasing the sensitivity of immunocytochemistry and *in situ* hybridization (De Vries et al., 1985; Miller et al., 1988).

Hormonal and genetic factors in sexual differentiation of AVP/AVT pathways

The development of sex differences in the steroid-sensitive AVP/AVT projections have been studied in a limited number of species only (Table 1). Here, we will review rats, the animals most extensively studied, contrasting them with other species in case fundamental differences have been found.

In mammals, the main factors in sexual differentiation of the brain are gonadal hormone levels during development and in adulthood (Becker et al., 2005). Gonadal hormones influence sexual differentiation in at least two ways. Early in life, they permanently direct the development of neural circuitry that will generate male- or female-typical functions and behaviors in adulthood. These developmental effects are called *organizational*. For example, testosterone exposure during development increases the likelihood that animals will show male sexual behavior as adults. However, to show male sexual behavior, animals have to be exposed to testosterone in adulthood as well. This adult effect is transient and therefore called *activational*. Sex differences in AVP/AVT innervation of the brain depend on organizational and activational effects of gonadal hormones and possibly also directly on sex chromosomal complement.

In adulthood, AVP projections from the BST and MeA are exquisitely sensitive to circulating gonadal hormones. Gonadectomy eliminates AVP expression and replacement of hormones reinstates it (e.g. De Vries et al., 1984; Miller et al., 1992). Sex differences in circulating gonadal hormones, however, cannot explain all differences in AVP expression because males and females exposed to similar steroid levels still differ (De Vries and al Shamma, 1990; De Vries et al., 1994). Circulating hormones may, however, be the main factor in species such as prairie voles, where differences in AVP-ir fiber density (Bamshad et al., 1993) or AVP mRNA expression (Wang et al., 1994) are extreme. These differences are still impressive, but smaller if adult male and female voles are treated with similar levels of testosterone (Lonstein et al.,

2005). Like prairie voles, Japanese quail and chickens show extreme sex differences with females showing virtually no AVT-immunoreactivity in the BST and its projections, and barely any AVT mRNA signal (Viglietti-Panzica et al., 1994; Jurkevich et al., 1997; Aste et al., 1998). These differences remain extreme in quail treated similarly with testosterone (Fig. 1C; Panzica et al., 1998). In rats as well as quail, such residual differences are due to organizational effects of hormones (Wang et al., 1993; Panzica et al., 1998; Han and De Vries, 2003).

In mice, sex chromosomal complement (XX versus XY in mammals and ZW versus ZZ in birds) may bias form and function of neural systems independently of its effects on gonadal differentiation (Arnold, 2004). We showed that this is true for AVP innervation by using a cross in which sex chromosomal complement was varied independently of gonadal sex. This cross generated XX and XY mice lacking the *Sry* gene on the Y chromosome, which normally directs testis growth; these mice developed a female phenotype. This cross also generated XX and XY animals with an *Sry* transgene on an autosomal chromosome; these mice developed a male phenotype. Whether male or female, XY mice had a slightly denser AVP innervation than did XX mice even though gonadal hormone levels were kept constant (De Vries et al., 2002).

Mechanisms that trigger sexual differentiation of AVP/AVT systems may differ markedly among vertebrates. For example, in voles, testes are essential for masculinization of AVP innervation. However, administering testosterone to females or to neonatally castrated males does not masculinize this system, raising doubt that the testis uses testosterone to masculinize AVP expression (Lonstein et al., 2005). Even more striking differences are found between rats and Japanese quail. In both species, testosterone activates AVP/AVT expression mainly by acting via estrogenic metabolites (De Vries et al., 1986, 1994; Viglietti-Panzica et al., 2001). Notwithstanding this and other striking similarities in steroid responsiveness in adulthood (Panzica et al., 2001), hormones act in opposite directions during sexual differentiation. In rats, estrogen *masculinizes* AVP innervation (Han and De Vries, 2003); in quail, estrogen *feminizes* its AVT counterpart (Fig. 1C; Panzica et al., 1998). Even though the triggers of sexual differentiation may differ, the consistency of sex differences in AVP and AVT systems suggests that cellular processes that shape these differences may be similar among vertebrates.

Cellular processes behind sexual differentiation of AVP /AVT pathways

Differences in number of AVP and AVT cells may account for differences in fiber density. In theory, two fundamentally different sets of processes could determine AVP/AVT cell number: processes that determine absolute cell number, such as cell birth, cell death, or cell migration, or processes that influence the phenotype of existing cells. Differential cell birth and migration are unlikely players because AVP cells are born on embryonic days 12 and 13 (al Shamma and De Vries, 1996), at least a week before hormones trigger their sexual differentiation (Wang et al., 1993). Differential cell death is also unlikely. Recently, we compared wild-type mice and mice with a null mutation in the gene coding for the cell death factor, *Bax*. This mutation thwarts most neuronal cell death and eliminates sex differences in cell number of several brain areas (Forger et al., 2004) but not sex differences in AVP cell number (De Vries, Reza, and Forger, unpublished observations). It did increase AVP cell number in both sexes, though, suggesting that developmentally programmed cell death determines the final number of potential AVP cells in males and females but not the differences between them.

All evidence points at testosterone stimulating already existing cells to express AVP. After discovering that practically all AVP cells in the BST co-express galanin, but not all galanin cells AVP, and that males have more AVP cells than do females but similar numbers of galanin cells, Planas et al. (1995) proposed that differences in AVP expression depend on the

percentage of galanin cells that co-express AVP. During development, testosterone may simply stimulate more galanin neurons to co-express AVP in males. In support, AVP and galanin neurons in the BST and MeA show an equally unusual birth profile: both are born days earlier than most surrounding cells (Han and De Vries, 1999). A similar situation may apply in Japanese quail, where AVT-ir and galanin-ir cells overlap in the BST (Aste et al., 1996; Azumaya and Tsutsui, 1996), and in songbirds, where AVT-ir and galanin-ir fibers overlap in the lateral septum (Goodson et al., 2004).

It is unknown whether gonadal steroids target AVP and AVT cells directly or act via other cells. In adult rats, steroid actions may be direct because AVP-ir cells in the BST and MeA express estrogen receptor alpha, androgen, and progesterone receptors (Axelson et al., 1992; Zhou et al., 1994; Auger and De Vries, 2002). It is unknown whether these cells also express gonadal steroid receptors during sexual differentiation. Finally, no study has addressed co-localization of AVP and AVT steroid receptors and these cells in other vertebrates.

A unique opportunity

There are at least two reasons to be enthusiastic about the sex difference in AVP and AVT systems, or for that matter about any sex difference in the brain. First, the possibility of hormonal manipulation provides a unique perspective for studying how specific neural systems develop. Second, sex differences allow one to study how differences in brain structure translate into differences in function. Solving these questions may also explain why so many behavioral and neurological disorders show marked sex differences (Swaab et al., 2003). This applies to AVP as well because it has been implicated in mood, anxiety, and other behavioral disorders that show marked sex differences (Ring, 2005). However, nature has been reluctant to give up its secrets. Although we know which hormones control sexual differentiation and when they do that, we do not know how. Only a smattering of molecular and cellular processes that mediate hormonal effects on sexual differentiation has been identified (e.g. Amateau and McCarthy, 2004; Auger et al., 2000; Forger et al., 2004), and none of these explain sexual differentiation of AVP and AVT expression. In addition, except for a handful of sexually dimorphic cell groups that control specific sexually dimorphic muscle systems (e.g. the spinal nucleus of the bulbocavernosus, which innervates muscles at the base of the penis; Morris et al., 2004), the functional significance of most sex differences in the CNS is unknown (De Vries and Boyle, 1998). Several features of the AVP/AVT innervation of the brain make it an ideal system to tackle some of these issues.

With AVP being one of the first two peptides to be named a neuropeptide (de Wied, 2000), hundreds of studies have addressed the functions of central AVP and AVT pathways. These functions include, for example, learning and memory (de Wied et al., 1993), reproductive and other social behaviors (Goodson and Bass, 2001; Panzica et al., 2002; Rose and Moore, 2002; Young and Wang, 2004). More recently, studies have exploited the sexually dimorphic and steroid-sensitive character of this system (e.g. Dantzer, 1998; Pittman et al., 1998). Interestingly, this system may cause as well as prevent sex differences in centrally regulated functions and behavior (De Vries and Boyle, 1998), the latter presumably to compensate for sex differences in physiology that, if left unchecked, could cause undesirable differences (De Vries, 2004). Also, with AVP-secreting neurons being relatively easily accessible for electrophysiological, biochemical, and molecular analysis, much is known about cellular and molecular aspects of AVP/AVT expression, release, and neurotransmission (Watters et al., 1998; Young and Gainer, 2003). Given that sexual differentiation of this system depends on phenotypic differentiation, this knowledge should help in identifying where phenotypic decisions may be made. Finally, with many laboratories studying comparative aspects of this system (Goodson and Bass, 2001; Moore and Lowry, 1998; Panzica et al., 2001; Rose and Moore, 2002), the general applicability of knowledge on development and function of its

dimorphism may become clearer than it is for most other sex differences in the brain. Comparative studies may also reveal more differences as extreme as those found in Japanese quail and chicken, which should make identifying factors underlying differentiation of these systems easier. This confluence of behavioral, physiological, cellular and molecular, and comparative studies, therefore, creates a unique opportunity to deepen our understanding of the development and functional significance of sex differences in the brain.

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Abbreviations

AVP, vasopressin; AVP-ir, vasopressin-immunoreactive; AVT, vasotocin; AVT-ir, vasotocin-immunoreactive; BST, bed nucleus of the stria terminalis; MeA, medial nucleus of the amygdala; POM, medial preoptic nucleus; PVN, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus.

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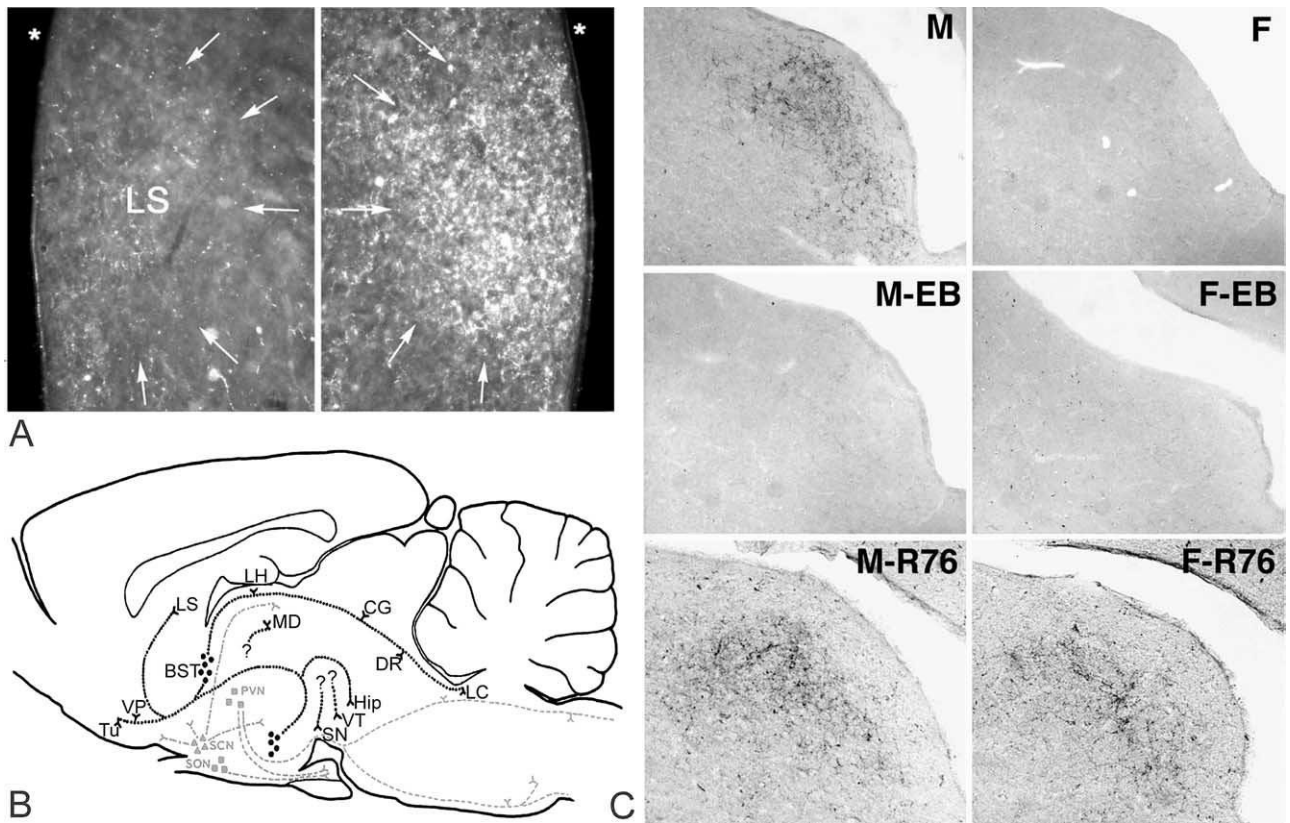
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**Fig 1.**

Sexually dimorphic AVP and vasotocin (AVT) projections in rat and quail brains. (A) Dark-field microphotographs of AVP-ir fiber networks (arrows) in the lateral septum (LS) of a female (left) and male rat (right); * lateral ventricle. (B) Diagram of most prominent AVP-ir projections in rats, modified from De Vries et al. (1985). Steroid-sensitive projections (black lines) run from BST (circles) and MeA (MA, circles) to LS, ventral pallidum (VP), olfactory tubercle (Tu), lateral habenular nucleus (LH), midbrain central gray (CG), dorsal raphe nucleus (DR), locus coeruleus (LC), and ventral hippocampus (Hip). Question marks indicate projections to Hip, mediodorsal nucleus of the thalamus (MD), ventral tegmental area (VT), substantia nigra (SN), which disappeared after castration but not after lesioning the BST. Steroid-insensitive projections (gray lines) originate in SCN (triangles), PVN (squares), and supraoptic nucleus (SON, squares). (C) Bright-field photomicrographs of AVT-ir fiber networks in the lateral septum of male (M) and female Japanese quail (F), treated during development with oil (top panels), estradiol benzoate (EB; middle panels), or the aromatase inhibitor R76 (R76; bottom panels), gonadectomized three weeks post-hatching, and treated with testosterone for another two weeks. Note that AVT fibers are absent in the oil-treated female and EB-treated male and female quail.

Table 1
Studies on sex differences and steroid effects in AVP and AVT expression in BST / MeA and homologous systems

	Projections	Cell bodies	Dimorphism	Seasonal	Activational	A vs. E	Organizational	Tracing
Mammals								
Rat, <i>R. rattus</i>	1, 8	3, 8, 6, 21	2, 10, 25	2, 5, 43	7, 8, 26, 37	12, 42, 48, 56	27, 45, 48	4, 14
Mouse, <i>M. musculus</i>	19	19	20	—	20	20, 80, 86	—	—
Siberian hamster, <i>P. sungorus</i>	49	58, 49	49*	58	49	—	58	—
Prairie vole, <i>M. ochrogaster</i>	41, 51	41, 51	41, 51	—	44	72	88	—
Mongolian gerbil, <i>M. unguliculus</i>	34	34	34	—	34	—	34	—
Gerboa, <i>J. orientalis</i>	55	55	55	55	—	—	—	—
Meadow vole, <i>M. pennsylvanicus</i>	41, 51	41, 51	41, 51	—	—	—	—	—
Dormouse, <i>E. quercinus</i>	28	—	28	28	—	—	—	—
European hamster, <i>C. cricetus</i>	11	—	11	11	—	—	—	—
Guinea pig, <i>C. porcellus</i>	24	24	24*	—	—	—	—	—
Human, <i>H. sapiens</i>	13	13	13*	—	—	—	—	—
Macaque, <i>M. fascicularis</i>	23	23	23*	—	—	—	—	—
Marmoset, <i>C. jacchus</i>	65*	65	65	—	—	—	—	—
Montane vole, <i>M. montanus</i>	61	61	61	—	—	—	—	—
Pine vole, <i>M. pinetorum</i>	61	61	61	—	—	—	—	—
Brazilian opossum, <i>M. domestica</i>	54	—	54	—	—	—	—	—
Cat, <i>F. catus</i>	—	15	—	—	—	—	—	—
California mice, <i>P. californicus</i>	69	69	—	—	—	—	—	—
Mustached bat, <i>P. parnellii</i>	85	85	—	—	—	—	—	—
Syrian hamster, <i>M. auratus</i>	30*	30*	—	—	—	—	—	—
White-footed mice, <i>P. leucopus</i>	69	69	—	—	—	—	—	—
Birds								
Japanese quail, <i>C. japonica</i>	39, 50, 77	66, 66, 77	39, 66, 66, 77	—	50, 74, 60	78	68, 90	79
Canary, <i>S. canaria</i>	17	17	22	31	—	—	22*	—
Zebra finch, <i>T. guttata</i>	40	40	71, 40*	40*	40*	—	—	—
Chicken, <i>G. domesticus</i>	64	57/64	64	70	—	—	—	—
Junco, <i>J. hyemalis</i>	75	75	—	—	84	—	—	—
White-throated sparrow, <i>Z. albicollis</i>	89	89	89	—	—	—	—	—
Budgerigar, <i>M. undulatus</i>	82*	82*	—	—	—	—	—	—
Angolan blue waxbill, <i>U. angolensis</i>	83	—	—	—	—	—	—	—

	Projections	Cell bodies	Dimorphism	Seasonal	Activational	A vs. E	Organizational	Tracing
Song sparrow, <i>M. melodia</i>	83	—	—	—	—	—	—	—
Spice finch, <i>L. punctulata</i>	83	—	—	—	—	—	—	—
Violet-eared waxbill, <i>U. granatina</i>	83	—	—	—	—	—	—	—
Reptiles								
Ball python, <i>P. regius</i>	29	29	29	—	—	—	—	—
Gecko, <i>G. gecko</i>	9, 18	9, 18	9, 18	—	—	—	—	—
Green anole, <i>A. carolinensis</i>	38	38	38	—	—	—	—	—
Red-eared slider, <i>P. scripta</i>	29	29	29	—	—	—	—	—
Jararaca pitviper, <i>B. jararaca</i>	81	81	—	—	—	—	—	—
Chameleon, <i>C. chamaeleon</i>	52*	52*	—	—	—	—	—	—
Amphibia								
Bullfrog, <i>R. catesbaiana</i>	33	33	32, 33	46	47	47	47	—
Roughskin newt, <i>T. granulosa</i>	63	63, 87	32, 76	76*	—	—	—	—
Cricket frog, <i>A. crepitans</i>		73	73	—	—	—	—	—
South African clawed frog, <i>X. laevis</i>	35	35	—	53	—	—	—	—
Wood frog, <i>R. sylvatica</i>	59	59	—	59	—	—	—	—
Marsh frog, <i>R. ridibunda</i>	36	36	—	—	—	—	—	—
Rubber eel, <i>T. compressicauda</i>	62	62	—	—	—	—	—	—
Rubber eel, <i>T. natans</i>	67	67	—	—	—	—	—	—
Spanish ribbed newt, <i>P. waltlii</i>	36	36	—	—	—	—	—	—
Japanese toad, <i>B. japonicus</i>	16	—	—	—	—	—	—	—
Red-legged salamander, <i>P. shermani</i>	—	87	—	—	—	—	—	—

* feature not found.