

THE SIZE OF NON-HIPPOCAMPAL BRAIN REGIONS VARIES BY SEASON AND SEX IN RICHARDSON'S GROUND SQUIRREL

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Abstract—Sex- and season-specific modulation of hippocampal size and function is observed across multiple species, including rodents. Other non-hippocampal-dependent behaviors exhibit season and sex differences, and whether the associated brain regions exhibit similar variation with sex and season remains to be fully characterized. As such, we examined the brains of wild-caught Richardson's ground squirrels (RGS; *Urocitellus richardsonii*) for seasonal (breeding, non-breeding) and sex differences in the volumes of specific brain areas, including: total brain volume, corpus callosum (CC), anterior commissure (AC), medial prefrontal cortex (mPFC), total neocortex (NC), entorhinal cortex (EC), and superior colliculus (SC). Analyses of variance and covariance revealed significant interactions between season and sex for almost all areas studied, primarily resulting from females captured during the breeding season exhibiting larger volumes than females captured during the non-breeding season. This was observed for volumes of the AC, mPFC, NC, EC, and SC. Where simple main effects of season were observed for males (the NC and the SC), the volume advantage favoured males captured during the NBr season. Only two simple main effects of sex were observed: males captured in the non-breeding season had significantly larger total brain volume than females captured in the non-breeding season, and females captured during the breeding season had larger volumes of the mPFC and EC than males captured in the breeding season. These results indicate that females have more pronounced seasonal differences in brain and brain region sizes. The extent to which seasonal differences in brain region volumes vary with behaviour is unclear, but our data do suggest that seasonal plasticity is not limited to the hippocampus and that RGS is a useful mammalian species for understanding seasonal plasticity in an ecologically relevant context. © 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: seasonal differences, sex differences, Richardson's ground squirrels, brain volumes, non-biased stereology.

INTRODUCTION

Sexual dimorphisms in brain size and its constituent regions are widely recognized across vertebrate species. Examples of this include the song system of songbirds (MacDougall-Shackleton and Ball, 1999; Tramontin and Brenowitz, 2000; Ball et al., 2008) and, in mammals, the hippocampus (Yaskin, 1994; Galea et al., 1999; Iaskin, 2011), prefrontal cortex (Kingsbury et al., 2012), medial amygdala (Hines et al., 1992), white matter tracts (Noonan et al., 1998; Franklin et al., 2000) and various other limbic and hypothalamic structures (Spring et al., 2007; Campi et al., 2013; Sawada et al., 2013). Functionally, sexually dimorphic volumes of brain regions are associated with sex differences in behaviour. Typically, the sex that exhibits the larger volume exhibits improved ability in a task (Sherry et al., 1992; Reboreda et al., 1996; Ball et al., 2008; de Vries and Sodersten, 2009; Costa et al., 2011; Krohmer et al., 2011; Campi et al., 2013; Keeley et al., 2013). Many studies have demonstrated that some of these sex differences arise from the effects of endogenous variation in steroid hormone concentrations on brain anatomy (Williams et al., 1990; Vanhaaren et al., 1990; Roof and Havens, 1992; McEwen, 2002; Isgor and Sengelaub, 2003; Korol, 2004; Schoening et al., 2007; Ball et al., 2008; Brenowitz, 2008; Mitsushima et al., 2009; Mizuno and Giese, 2010). For example, hippocampal volume varies throughout the estrous cycle in mice (*Mus musculus*; Qiu et al., 2013), and hippocampal grey matter varies throughout the menstrual cycle in humans (Protopopescu et al., 2008).

The effect of reproductive status is perhaps most prominent in seasonally reproducing vertebrates where the size of the brain and/or individual brain regions may fluctuate dramatically throughout the year (Yaskin, 1994; Jacobs, 1996; Tramontin and Brenowitz, 2000; Kabelik et al., 2006; Bartkowska et al., 2008; Burger et al., 2013). Indeed, seasonal changes in overall brain volumes occur in mammals (Dark et al., 1990; Weiler, 1992; Yaskin, 1994; Prendergast et al., 2002) and other vertebrates (Nottebohm, 1981; Kirn et al., 1989). In the avian song system, seasonal changes in the size of the song nuclei can be more than 200% in the breeding compared to non-breeding periods, and this seasonal change is generally larger in males than in females (Tramontin

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Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; AC, anterior commissure; Br, breeding; CC, corpus callosum; EC, entorhinal cortex; mPFC, medial prefrontal cortex; NC, neocortex; NBr, non-breeding; RGS, Richardson's ground squirrels; SC, superior colliculus.

and Brenowitz, 2000). In seasonally reproducing rodents, the hippocampus also exhibits significant seasonal changes in overall size, dendritic branching, mossy fiber projections and cell proliferation (Huang et al., 1998; Galea and McEwen, 1999; Galea et al., 1999; Lavenex et al., 2000; Pyter et al., 2005; Workman et al., 2009, 2011; Burger et al., 2013; Yaskin, 2013). Given the wide array of reproductive and non-reproductive behavioral variation known to correspond with the seasons (e.g. Michener, 1998), there is the potential for seasonal changes to occur across many brain regions and for these differences to be expressed differently in males and females.

Despite the potential for seasonal effects to interact with sex differences, direct comparisons within a population have primarily been limited to the song system (Kirn et al., 1989; MacDougall-Shackleton et al., 2003; Jawor and Macdougall-Shackleton, 2008), hippocampus (Clayton et al., 1997; Galea and McEwen, 1999; Lavenex et al., 2000; Burger et al., 2013, 2014) or hypothalamus (Takami and Urano, 1984; Crews et al., 1993; Kabelik et al., 2006; Beck et al., 2008). This is somewhat surprising given that variations in steroid hormones can cause anatomical changes in brain areas outside of the above-mentioned regions (Johansen et al., 2004; Kabelik et al., 2006; Bailey et al., 2011; Haraguchi et al., 2012). Thus, here, we specifically looked for seasonal and sex differences in the size of multiple, non-hippocampal and non-hypothalamic brain regions in a wild rodent, Richardson's ground squirrel (RGS; *Urocitellus richardsonii*).

The RGS is a suitable species to test for neuroanatomical differences between sexes and seasons because they exhibit significant sex and seasonal differences in behaviour (Michener, 1998). Males and females differ from one another in relative brain size, body mass, growth pattern, hibernation period, home range size, immigration/dispersal patterns and food caching (Michener, 1983, 1992, 1993, 1998; Michener and Locklear, 1990a; Michener and McLean, 1996; Charge, 2001; Iwaniuk, 2001). As obligate hibernators with a restricted breeding season (Michener, 1998), they also exhibit marked seasonal differences in behaviour. Males emerge from the hibernation period earlier than females, but almost immediately following their emergence, both males and females are reproductively primed. Competition for mates is particularly intense in this species (Michener and McLean, 1996), resulting in high mortality rates in males during the breeding season. In fact, very few males survive more than one breeding season (Michener, 1989; Michener and Locklear, 1990a,b). Once females have weaned their litter, both the adult females and their weaned offspring begin preparing for hibernation. The young males disperse, create new burrows and cache food in a larder within their hibernaculum (Michener, 1993, 1998; Charge, 2001). The young females remain at their natal site, living in close proximity to their female relatives and prepare a hibernaculum but without any stored food (Michener, 1998).

In two recent studies, we showed that the size of the hippocampus and dentate gyrus, as well as number of

doublecortin immuno-positive cells, varied with both season and sex (Burger et al., 2013, 2014). Here, we build upon these initial studies by focusing on the measurement of non-hippocampal and non-hypothalamic brain regions that exhibit sex differences in volume in other mammalian species, including: the corpus callosum (CC; Berrebi et al., 1988; Franklin et al., 2000; Spring et al., 2007), the anterior commissure (AC; Allen and Gorski, 1992; Noonan et al., 1998), the medial prefrontal cortex (mPFC; Kingsbury et al., 2012), the entorhinal cortex (EC; Roof et al., 1993) and the neocortex (NC; Goldstein et al., 2001; Sawada et al., 2013). As others have found that the total brain volume, CC, AC and total NC volume are typically larger in other male mammals, we predicted that male RGS would have larger volumes than females, regardless of season (Dark et al., 1990; Franklin et al., 2000; Spring et al., 2007; Sawada et al., 2013). Because the mPFC plays key roles in modulating social behaviour (Kolb, 1984; Uylings et al., 2003; Bell et al., 2009), we predicted that the mPFC would be larger in females than males, regardless of season, as female RGS maintain kinship-based social groupings in which they remain amicable toward their mother and siblings (Michener, 1981). Conversely, as males maintain larger home ranges, particularly during the breeding season but also across seasons as compared to females, we predicted that the EC would be larger in males (Michener and McLean, 1996). However, given the unique spatial demands of the breeding season, we predicted that the EC would be larger in breeding males than non-breeding males (Michener and McLean, 1996). Lastly, we included the superior colliculus (SC) as a 'control' region because it is unlikely that aspects of visual attention mediated by the midbrain (Krauzlis et al., 2013) would be sexually dimorphic or seasonally variable in RGS.

EXPERIMENTAL PROCEDURES

Animals

All of the procedures were done in accordance with the Canadian Council for Animal Care guidelines and were approved by the University of Lethbridge Animal Welfare committee (protocol #0904). The Alberta Department of Environment and Sustainable Resource Development issued collection (47081, 35358) and research (47095, 49890) permits.

RGS were captured on campus at the University of Lethbridge and several private properties near Lethbridge, Alberta, Canada. We selected 32 individuals to measure based primarily upon the quality and clarity of the staining in order to have a sample size of eight for each sex and season (see below) for all of the regions of interest. Of these, 15 animals were trapped in 2010 and were used in a previous study on the hippocampus (Burger et al., 2013). The remaining 17 were captured during the fall of 2011 and spring of 2012 and were also included in a recent study on neurogenesis (Burger et al., 2014). Trapping activities in all years were divided into two seasons: the breeding (Br; Feb–Apr) and non-breeding season (NBr; Jul–Sep), as described

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