Photoperiodic Regulation of Affective Responses and Hippocampal Cell Morphology in Siberian Hamsters

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Abstract

Seasonal affective disorder (SAD) is characterized by depressive episodes during winter that are alleviated during summer and by morning bright light treatment. Currently, there is no animal model of SAD. However, it may be possible to use rodents that respond to day length to understand how day length can shape brain and behavior in humans. For instance, Siberian hamsters use day length to time seasonal cycles of reproduction and also exhibit changes in nonreproductive behaviors dependent on day length. Specifically, short-day Siberian hamsters increase floating in the forced swim test (a behavioral test used to screen antidepressant compounds). Current research in depression and animal models of depression suggests that hippocampal atrophy may underlie the symptoms of depression and depressive-like behaviors, respectively. The goal of this study was to determine whether altered depressive-like responses after exposure to short days are associated with photoperiod-mediated plasticity within the hippocampus of Siberian hamsters. Hamsters were housed in either short (8:16 LD) or long days (16:8 LD) for 10 weeks. At the end of 10 weeks hamsters were tested in the forced swim test and 48 h later, brains were removed and stained using the Golgi impregnation method. Brains were processed for hippocampal dendritic length, branching, and spines, as well as cell body size. Short days significantly reduced cell body size and dendritic complexity in the CA1 region of the hippocampus. This suggests that altered depressive-like behavior induced by exposure to

short days may be a consequence of reduced complexity (and perhaps connectivity) in the hippocampus.

Introduction

Current research in depression and animal models of depression suggests that hippocampal atrophy may underlie much of the neuroendocrine phenomena (such as blunted circadian rhythm of cortisol and impaired negative feedback) and psychological symptoms of depression. Recent research with antidepressants suggests that selective serotonin reuptake inhibitors (while exerting their effect on serotonin in the short-term), induce their therapeutic effects by stimulating hippocampal regeneration through neurogenesis and synaptic growth (Bessa et al., 2009; Pittenger & Duman, 2008; J. W. Wang, David, Monckton, Battaglia, & Hen, 2008). The latency in recovery of depressed individuals after beginning an SSRI may result from the time course during which SSRIs alter creation, proliferation, survival, and connectivity of neurons within the hippocampus.

Seasonal changes in brain morphology are well documented in birds. Avian song control nuclei undergo dramatic volume reductions in the nonbreeding season which corresponds with an absence in singing behavior (Meitzen, Moore, Lent, Brenowitz, & Perkel, 2007; Tramontin & Brenowitz, 2000). Seasonally breeding rodents also undergo changes in brain morphology across a year. Wild-caught rodents have reduced hippocampal volume and exposure to short-days in the laboratory reduces whole brain and hippocampal volume (Perrot-Sinal, Kavaliers, & Ossenkopp, 1998; Pyter, Reader, & Nelson, 2005).

The goal of this study was to determine if altered depressive-like responses after exposure to short days is a functional consequence of photoperiod-mediated plasticity within the hippocampus in Siberian hamsters. Little is known about the mechanisms governing photoperiod-induced changes in affective responses. Currently, we know that short days alter dendritic spine density in white-footed mice (*Peromyscus leucopus*), another seasonally breeding rodent (Pyter, Reader, & Nelson, 2005; Workman, Bowers, & Nelson, 2009). Although these studies investigated hippocampal plasticity in conjunction with spatial learning, it provides evidence for functional consequences of brain plasticity in the context of psychological disorders. Indeed, hippocampal atrophy in depressed individuals is associated with poor performance in cognitive tasks.

Methods

Animals

Siberian hamsters were weaned from our colony at approximately 21 d (± 2) of age and immediately placed into either short photoperiod (8:16 LD) or maintained in their natal, long photoperiod (16:8 LD). Hamsters were also assigned to either a behavioral testing or no behavioral testing condition. Hamsters were housed in their respective photoperiods for 10 weeks prior to behavioral testing. All hamsters had *ad libitum* access to food (Harlan Teklad 8640) and water. All procedures were conducted in accordance with the Institutional Animal Care and Use Committee at Ohio State and complied with Guidelines for the Care and Use of Animals.

Behavioral testing

At lights-off (1300 h EST), hamsters were moved to a testing room and allowed to habituate for 30 m. To assess depressive-like responses (Porsolt, Le Pichon, & Jalfre, 1977), hamsters were placed individually in room-temperature water ~17 cm deep within an opaque, cylindrical tank (24 cm diameter, 53 cm height). Swimming behavior was recorded on video for 5 m under dim red light and scored by an observer unaware of experimental treatment assignments with The Observer software (Version 8, Exeter Software, Setauket, NY) to quantify total number of floating bouts, and total time spent floating. More floating is interpreted as an increased depressive-like response (Porsolt, Le Pichon, & Jalfre, 1977).

Tissue collection and processing

Forty-eight h after behavioral testing, hamsters were anesthetized and body mass and pelage score were assessed. Then, hamsters were rapidly decapitated, trunk blood was collected and brains were removed and processed for golgi impregnation using the FD Rapid GolgiStain™ Kit (FD NeuroTechnologies Inc., Ellicott City, MD) according to the manufacturer's instructions. Hamsters were killed between 0800 and 1000 h Eastern Standard Time (EST). Testes, epididymides, fat pads, and seminal vesicles were also removed at this time and weighed to assess reproductive responsiveness to photoperiod.

Cortisol radioimmunoassay

Blood samples were kept on ice after collection and subsequently centrifuged for 30 min at 6000 RPM at 4 °C. Plasma was drawn from the top and stored in 1.5 ml centrifuge tubes at -80 °C. All plasma samples were measured in the same assay using an ^{125}I kit from Diagnostic

Systems Laboratories (Diagnostic Systems Laboratories, Webster TX). The assay was performed according to the manufacturer's instructions and the intra-assay coefficient of variation was 11%.

Histology and microscopy

Brains were sliced at 80µm, counterstained with cresyl violet (Sigma) and otherwise processed according to the manufacturer's instructions. Brains were assessed for hippocampal cell morphology in three subfields in the dorsal hippocampus: dentate gyrus (DG), CA1, and CA3. Sections were visualized using a Nikon E800 brightfield microscope and neurons were traced using Neurolucida software (MicroBrightField, Burlington, VT, USA) at a magnification of 20×. Six representative neurons were selected per area, per animal for tracing. Selected neurons had to meet 3 criteria prior to tracing: neurons had to be fully impregnated, dendrites could not be truncated, and, for the DG, neurons had to be granule cells with somas lying within the granule cell layer and for the CA1 and CA3 regions, neurons had to be pyramidal cells with somas lying within the pyramidal cell layer. Whole cell traces were analyzed using the accompanying NeuroExplorer software (MicroBrightField, Burlington, VT). Cell body size and perimeter and dendritic length were calculated. Sholl analyses were also conducted. Because the Sholl analyses revealed that short days reduced dendritic complexity of CA1 pyramidal cells, I then counted branch points of apical and basal arbors of each trace to determine whether this effect was limited to dendrites in either orientation.

For spine density analysis, six neurons (in granule cell layer or pyramidal cell layer, depending on area) were again selected per area, per animal. Dendritic segments were traced at 100× in Neurolucida. For DG granule cells, four 20 micron dendritic segments were selected for

counting if they were beyond at least one branch point. For pyramidal cells in the CA1 and CA3 regions, cells were selected if they had both apical and basal arbors; both of which were counted for each cell. For basal dendrites in both regions, four 20-micron dendritic segments beyond at least one branch point were traced in the *stratum oriens*. For apical dendrites in both regions, four 20-micron dendritic segments beyond at least one branch point were traced in the *stratum radiatum*. Spines were traced regardless of attributes (i.e., I counted filopodia as well as mature spines) as long as they made a continuous connection with the dendritic shaft. Spine density (spines per 1 μm) was calculated for each trace in NeuroExplorer software and then averaged per cell, per area, and per animal.

Statistical analyses

Measures of floating were log transformed and analyzed by one-tailed Student's *t*-tests with photoperiod as the independent variable. I predicted that short days would provoke hamsters to increase floating based on previous studies (Prendergast & Nelson, 2005; Pyter & Nelson, 2006), which permits analysis with a one-tailed t-test. Reproductive and somatic (except pelage score) measures and cortisol concentrations were also analyzed by two-tailed Student's *t*-tests with photoperiod as the independent variable. Pelage scores were analyzed with a Mann-Whitney U test. Data from Sholl analyses were analyzed using repeated measures ANOVAs. Behavioral testing did not significantly alter any dependent measure, so groups were collapsed and analyzed by photoperiod only. Analyses were conducted using StatView software (v. 5.0.1, Cary, NC, USA). All mean differences and correlation coefficients were considered statistically significant if $p \leq 0.05$.

Results

Behavioral measures

Short days significantly increased float bouts ($t_{18} = 2.017$; $p = 0.059$) and time spent floating ($t_{18} = 2.358$; $p < 0.05$) in the forced swim test. Short days also significantly extended the latency to float ($t_{18} = 3.457$; $p = 0.079$).

Reproductive and somatic measures

Short days significantly reduced body mass ($t_{28} = 3.838$; $p < 0.01$), absolute paired testes mass ($t_{29} = 23.395$; $p < 0.01$), paired fat pad mass ($t_{29} = 7.193$; $p < 0.01$), paired epididymides mass ($t_{29} = 7.778$; $p < 0.01$) compared with long days. Short days also yielded a significantly lighter pelage color ($p < 0.01$).

Cortisol

Photoperiod did not alter cortisol concentrations ($t_{22} = 0.788$; $p > 0.05$).

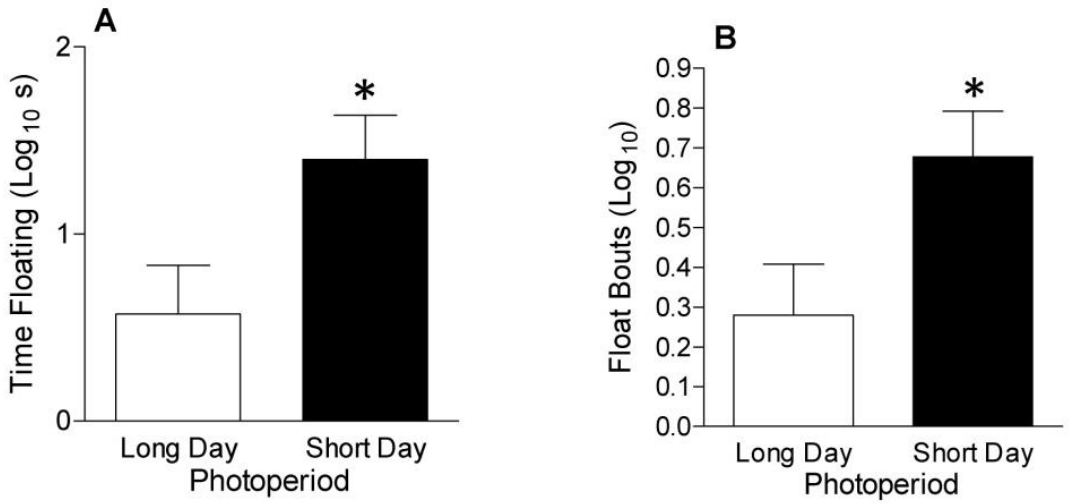

Figure 7.1: Floating in the forced swim test.

A) Mean ± SEM of time (Log_{10} s) spent floating in the forced swim test. Short days significantly increased time spent floating in the 5 min test. B) Mean ± SEM number (Log_{10}) of float bouts. Short days significantly increased float bouts.

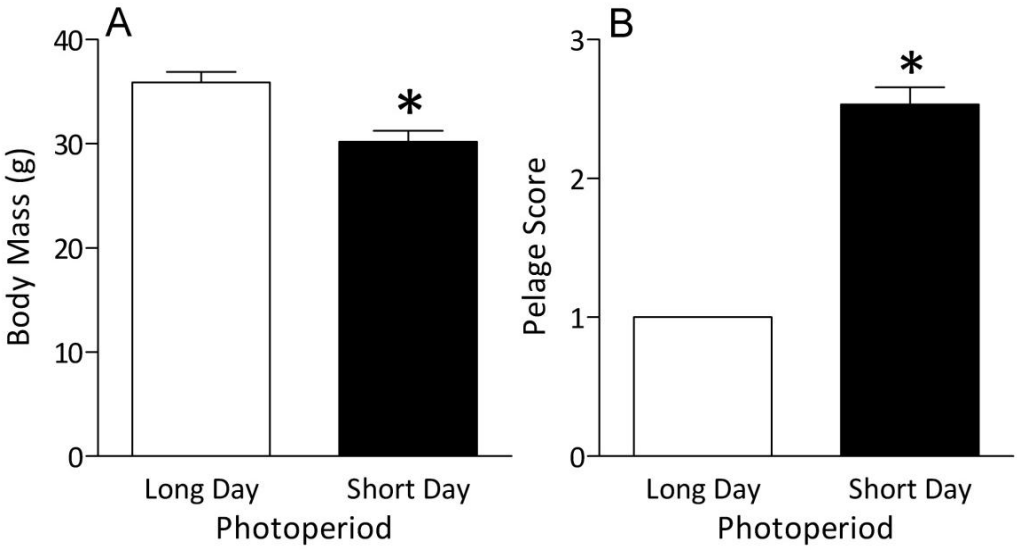

Figure 7.2: Somatic responses to photoperiod.

A) Mean ± SEM body mass in grams. Short days significantly reduced body mass. B) Mean ± SEM pelage score. Higher numbers indicate a lighter colored pelage on a 1 – 4 point scale (Duncan & Goldman, 1984a, , 1984b). Short days yielded significantly lighter pelage ($p < 0.05$). Note: all long-day hamsters had a pelage score of 1.

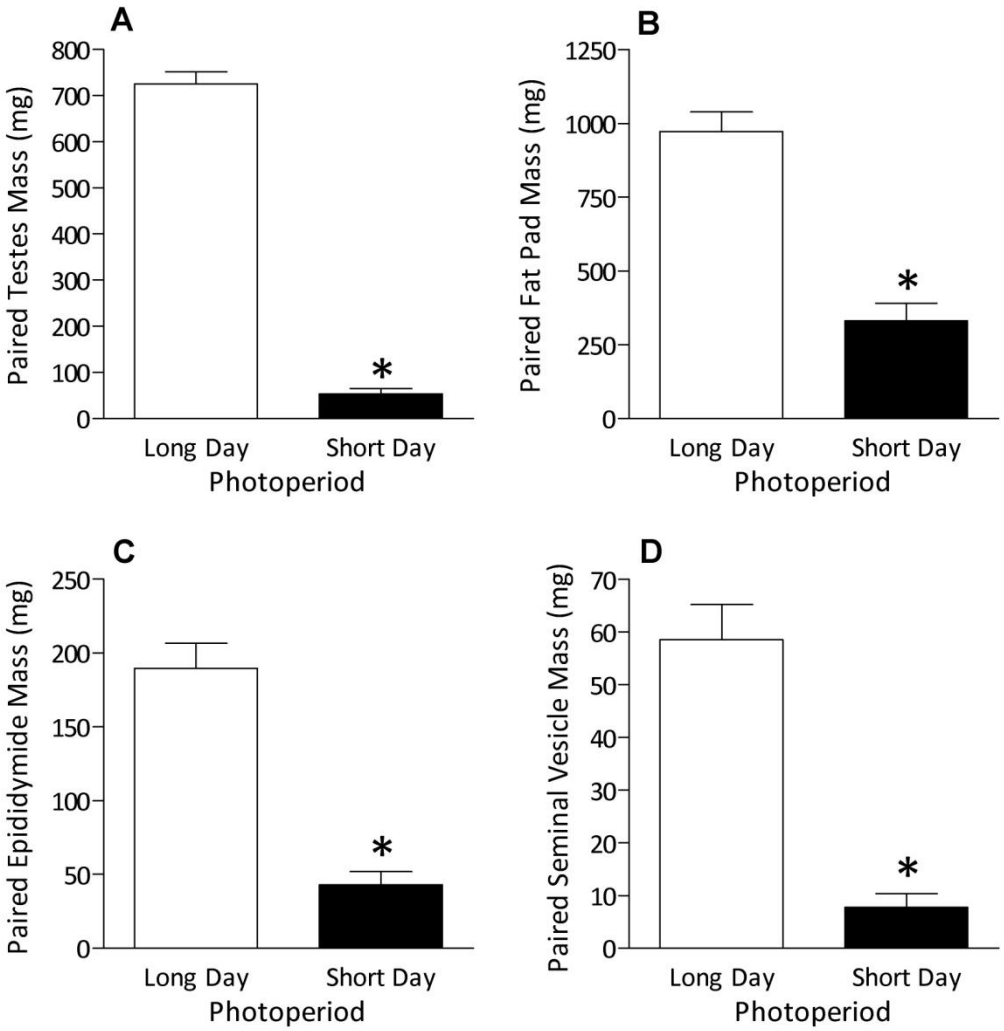

Figure 7.3: Reproductive responses to photoperiod.

Mean ± SEM paired organ masses in mg. Short days significantly reduced A) testes mass, B) fat pad mass, C) epididymides mass, and D) seminal vesicle mass.

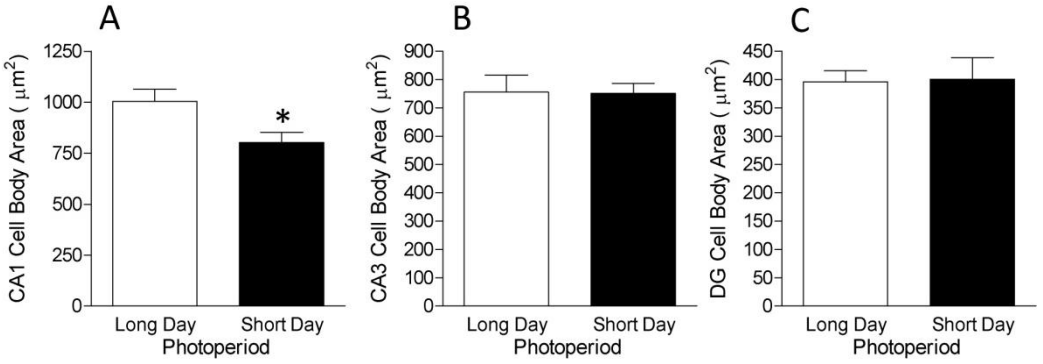

Figure 7.4: Cell body area in three hippocampal regions.

Mean ± SEM area in microns^2 of somas in the A) CA1, B) CA3, and C) dentate gyrus subfields of the hippocampus. Short days significantly reduced cell body size of pyramidal cells in the CA1, but not pyramidal cells in the CA3 or granule cells in the dentate gyrus.

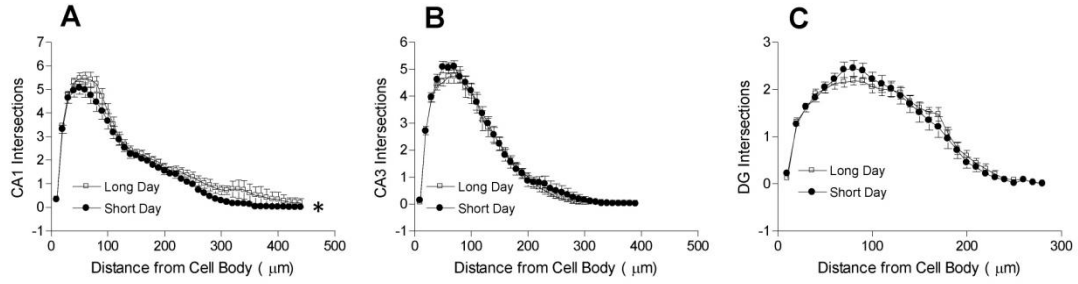

Figure 7.5: Sholl analysis data from the hippocampal regions.

Mean ± SEM number of intersections of dendrites in the A) CA1, B) CA3, and C) dentate gyrus of the hippocampus. Short days significantly reduced the number of intersections of dendrites in the CA1 region, but not the CA3 or dentate gyrus.

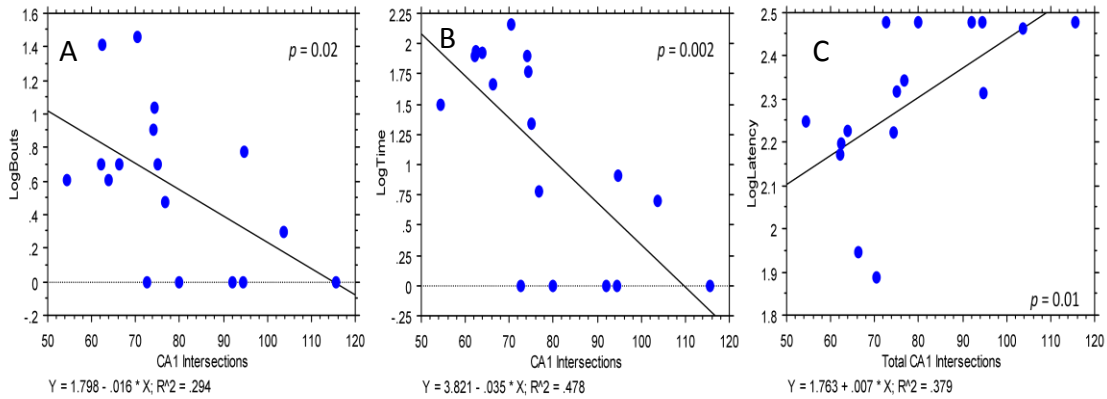

Figure 7.6: Correlations between behavior and number of intersecting dendrites in the CA1 region.

Scatter plots with simple regression lines depicting the relationship between CA1 dendritic complexity and behavioral measures in the forced swim test. CA1 intersections significantly negatively correlated with A) floating bouts and B) time spent floating and C) significantly positively correlated with the latency to float.

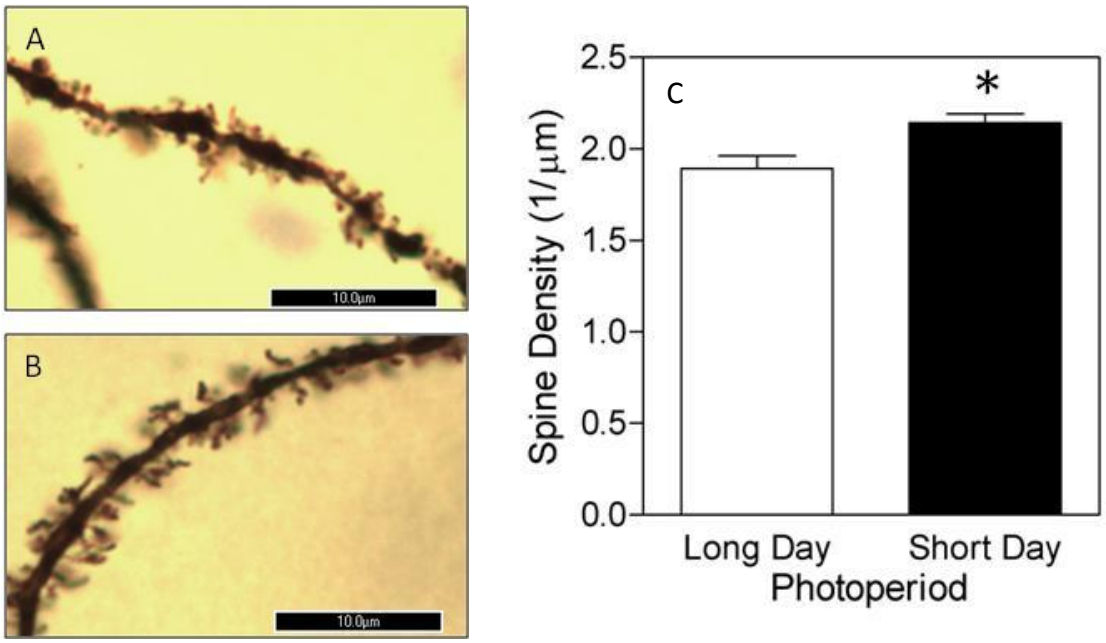

Figure 7.7: Spine density of granule cells within the dentate gyrus.

Representative photographs of A) spine density of a long-day hamster and B) of a short-day hamster. Scale bar represents 10 µm. C) Short days significantly reduced spine density in the dentate gyrus; $*p < 0.05$.

Hippocampal measures

Short days significantly reduced soma area of pyramidal cells in the CA1 region ($F_{1,21}$ = 4.392; $p < 0.05$). Photoperiod did not alter soma area of granule cells in the dentate gyrus (t_{24} = 0.792; $p > 0.05$) or pyramidal cells in the CA3 region ($t_{25} = 0.782$; $p > 0.05$). Photoperiod did not alter soma perimeter or dendritic length in the CA1, CA3, or dentate gyrus ($p > 0.05$ in all cases). Short days significantly reduced the number of intersections of dendrites in the CA1 region ($F_{1,946} = 4.86$; $p < 0.05$). Short days did not alter number of intersections in the DG or CA3 regions ($p > 0.05$ in both ANOVAs). Short days significantly increased spine density within the dentate gyrus ($t_{25} = 2.357$; $p < 0.05$).

Correlations

Total CA1 intersections (derived from the Sholl analysis) significantly negatively correlated with both float bouts ($r = -0.542$; $p < 0.05$) and time spent floating ($r = -0.691$; $p < 0.01$) and positively correlated with latency to float ($r = 0.616$; $p < 0.01$). Soma area in the CA1 was significantly positively correlated with CA1 intersections ($r = 0.552$; $p < 0.05$) but not with behavioral measures in the forced swim test ($p > 0.05$ in all cases). CA1 soma area was also significantly negatively correlated with spines in the dentate gyrus ($r = -0.529$; $p < 0.05$).

Discussion

The hippocampus is important in regulating both cognitive and emotional processes (Fanselow & Dong, 2010). Here, I demonstrate that an environmental cue that precipitates adaptations in preparation for winter, i.e., short days, increases depressive-like responses and

reduces soma size and dendritic complexity in the CA1 region and increases spine density in the dentate gyrus. Moreover, CA1 dendritic complexity was significantly correlated with behavioral measures in the forced swim test, which suggests that short-day-induced changes in the hippocampus are behaviorally relevant. This is the first study to associate hippocampal plasticity with photoperiod-induced changes in affective processes and may be important for understanding how day length influences neural processes and symptoms in people with SAD. Several other studies have investigated the effect of short days on other species, including diurnal and nonseasonally-breeding rodents with similar results: many species increase depressive-like responses when exposed to short days (Ashkenazy-Frolinger, Kronfeld-Schor, Juetten, & Einat, 2010; Ashkenazy, Einat, & Kronfeld-Schor, 2009a, , 2009b; Prendergast & Kay, 2008). Previously-employed animal models of depression have focused on the role of stress or high circulating glucocorticoids in precipitating a depressive-like behavioral phenotype and evoking structural changes in the hippocampus (Bessa et al., 2009; Watanabe, Gould, & McEwen, 1992). Chronic mild stressors or social stressors cause apical dendrites in the CA3 region to retract (Magarinos, McEwen, Flugge, & Fuchs, 1996; Watanabe, Gould, & McEwen, 1992) and alter spine density on CA3 dendrites (Bessa et al., 2009); deficits that are reversed by antidepressants.

Hippocampal plasticity has been associated with many biological rhythms that are characterized by changes in behaviors such as activity, learning and memory, and now, depressive-like behaviors (Magarinos, McEwen, Saboureau, & Pevet, 2006; Popov, Bocharova, & Bragin, 1992; Popov et al., 2007; Pyter, Adelson, & Nelson, 2007; Pyter, Reader, & Nelson, 2005). For example, estrogens induce changes in hippocampal spines over the estrous cycle such that CA1 pyramidal cells display a significant reduction in spine density from proestrus to late

estrus (Woolley, Gould, Frankfurt, & McEwen, 1990). Hibernation is also associated with changes in dendritic complexity and spines: In European hamsters (*Cricetus cricetus*), CA3 pyramidal neurons undergo retraction of dendrites and reduction in spines over the course of hibernation (Magarinos, McEwen, Saboureau, & Pevet, 2006). Seasonally hibernating ground squirrels also (*Citellus undulates)* undergo rapid and reversible retraction of dendrites in the CA1 region of the hippocampus (Popov, Bocharova, & Bragin, 1992), as well as a reduction in spine density (Popov et al., 2007). The individual roles of the CA1 and CA3 regions in hibernation and depressive-like responses have not been dissociated so the differences in changes across hippocampal regions associated with hibernation is not clear at present. Future research should focus on investigating individual roles. Nevertheless, the hippocampus can be viewed as a functional circuit that involves connections from the dentate gyrus to the CA3 and in turn to the CA1. Disruption at any particular point will disturb hippocampal output.

The mechanisms that underlie changes hippocampal structure are numerous. As mentioned, excessive glucocorticoids significantly disrupt both structural and functional processes within the hippocampus in both humans and animals through facilitating glutamate release. CA3 dendritic retraction may be an adaptive response to stress that protects neurons from stress-induced glutamate excitotoxicity (Conrad, 2008). As previously mentioned, short-day-induced hippocampal changes may also represent an adaptive process to conserve energy during a time typically associated with intense energetic demands. However, in the present study, photoperiod did not induce changes in cortisol concentrations. And as evidenced in Chapter 5, short days are not associated with gross alterations in stress responses. Additionally, cortisol dysregulation would likely affect the CA3 region first, as it is more sensitive to the effects of glucocorticoids. More likely, there are other factors influencing these changes.

There are numerous other hormones that could alter hippocampal plasticity and could play a role in photoperiod-mediated plasticity. First, extended melatonin duration could directly mediate hippocampal structure and behavioral output. However, the role of melatonin is not fully elucidated. Previous research has indicated that melatonin can alter neurogenesis and depressive-like responses (Ramirez-Rodriguez, Klempin, Babu, Benitez-King, & Kempermann, 2009). However, this previous study administered melatonin at the onset of the dark phase which induced a peak in melatonin concentration, but did not alter duration. This study also found that melatonin increases cell survival and reduces depressive-like responses. In another study, chronic melatonin induced depressive-like responses, similarly to exposure to short days (Ashkenazy, Einat, & Kronfeld-Schor, 2009b). Additionally (and as outlined in Chapter 6), melatonin suppresses long-term potentiation (LTP) in both CA1 (L. M. Wang, Suthana, Chaudhury, Weaver, & Colwell, 2005) and CA3 neurons (Zeise & Semm, 1985) *in vitro*. However, melatonin seems to also have a protective effect on the hippocampus and behaviors associated with hippocampal function. For instance, acute melatonin administration prevents spatial learning deficits induced by alcohol (Gönenç et al., 2005) and cerebral ischemia (Gonzalez-Burgos, Letechipia-Vallejo, Lopez-Loeza, Morali, & Cervantes, 2007). Chronic melatonin may more closely mimic the effect of short day lengths on the brain. Chronic melatonin treatment prevents spatial learning deficits associated with streptozotocin administration (Sharma & Gupta, 2001). Certainly, more research is necessary to understand how physiological doses of melatonin that extend duration rather than increase amplitude alter hippocampal structure and function.

Thyroid hormones may play a role in photoresponsiveness and photorefractoriness to day length (Prendergast, Nelson, & Zucker, 2009) and can induce structural changes in the

hippocampus (Gould, Allan, & McEwen, 1990; Gould, Woolley, & McEwen, 1991). In humans with hypothyroidism, rates of depression are higher than in the general population (Joffe & Sokolov, 1994). However, thyroid-related hormones may be less important in photoperiodic adjustments in Siberian hamsters than Syrian hamsters or avian species (Prendergast, Nelson, & Zucker, 2009). Another hormone that plays a role in some photoperiod-regulated traits is prolactin. Specifically, reduced prolactin in short days allows hamsters to molt to their white, winter pelage (Duncan & Goldman, 1984a). Additionally, prolactin may be important for photperiod adjustments in immune function (Nelson & Demas, 1996) and torpor (Ruby, Nelson, Licht, & Zucker, 1993). Prolactin also seems to play a protective role in neurogenesis in both the olfactory bulb in dams (Bridges & Grattan, 2003) and the hippocampus (Torner et al., 2009). It is possible that short-day reductions in prolactin permit changes in the structure of hippocampal neurons.

In sum, short days increased floating in the forced swim test and altered dendritic complexity in the CA1 region and spine density in the dentate gyrus. CA1 dendritic intersections were correlated with floating in the forced swim test. This research adds to our understanding regarding environmental factors that influence hippocampal plasticity and depressive-like responses. This research could aid in our understanding of the processes that occur in SAD as well as lead to new therapeutic insights.

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