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Age-related dendritic hypertrophy and sexual dimorphism in rat basolateral amygdala

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Abstract

Little research has examined the influence of aging or sex on anatomical measures in the basolateral amygdala. We quantified spine density and dendritic material in Golgi-Cox stained tissue of the basolateral nucleus in young adult (3–5 months) and aged (20–24 months) male and female Long-Evans rats. Dendritic branching and spine density were measured in principal neurons. Age, but not sex, influenced the dendritic tree, with aged animals displaying significantly more dendritic material. Previous findings from our laboratory in the same set of subjects indicate an opposite effect of aging on dendritic material in the medial prefrontal cortex and hippocampus. We also report here a sex difference across ages in dendritic spine density, favoring males.

Keywords

aging; basolateral nucleus; dendrites; dendritic spines; Golgi-Cox; sex difference

1. Introduction

Emotion is increasingly recognized to play an essential role in modulating what is attended to, learned, and remembered [4,76], and the basolateral amygdala (BLA) appears to be the major structure critically involved in mediating the effects of emotional arousal on cognition and behavior [66,75]. The BLA is also essential for at least some kinds of emotional learning and memory, both aversive [54,58] and appetitive [27,86]. However, the effects of aging on BLA structure and function are not well characterized. In rats, performance of the BLA-dependent cued fear conditioning task is preserved with age [24,73,91], although an age-related impairment in this task has been reported in mice [39]. In humans, the literature on emotional memory and amygdala function in old age is mixed, with evidence for preservation [23,53,

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Disclosure statement

The authors have no conflicts of interest to disclose.

Treatment of animal subjects in this study and all experimental procedures were in accordance with National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee at the University of Illinois.

55,62] and, particularly when negative or fearful stimuli are used, impairment [11,29,49,92, 101].

Most anatomic studies of the aging human amygdala are volumetric, and have provided evidence both for relative amygdala preservation [38,40,50] and for volumetric decreases [70,72,99]. Unfortunately, *in vivo* imaging studies of the human amygdala lack the resolution to reliably distinguish among individual amygdalar nuclear groups [108]. However, a handful of aging-related changes in the BLA of rats and mice have been reported [3,95,96,106], with significant implications for its functional connectivity. For example, the ability to prolong hippocampal long-term potentiation by stimulation of the BLA is lost in aged rats [3]. Aging in mice is accompanied by marked decreases in the density of tyrosine hydroxylase-positive fibers in the BLA [95]. Because the modulatory effects of emotional arousal on learning and memory are mediated by catecholaminergic innervation of the BLA [80] these losses may also be expected to significantly impact BLA interactions with other cognitive areas of the brain. These and other [96,106] findings of BLA changes in rodent aging and the mixed literature regarding BLA function in old age suggest the need for further study characterizing aging effects in the cognitively important nuclei of the BLA. One question addressed by the present study relates to the morphology of its principal neurons. Are there age-related losses in the dendritic tree and/or spine density, such as have been described in the aged rat neocortex and hippocampus [41,60,61,90]?

Like aging, sex effects on anatomical measures of the BLA have not been well explored. This is despite some intriguing evidence of functional sex differences in humans [10,12,52] and rats [5,35,104]. In rats, for example, the effects of stress on hippocampal-dependent learning and memory, which are mediated by the BLA [80,81], are sexually dimorphic, impairing performance by rats of one sex – which sex suffers impairment depends on the stress and task paradigms – and enhancing performance by the other [5,15,104]. Similar studies using female rats with and without high ovarian hormone levels show parallel interactions between gonadal steroids and stress effects on learning and memory [6,84,104]. More direct evidence that the BLA may be influenced by sex hormones includes the finding that estradiol dramatically decreases EPSP amplitude in BLA neurons *in vitro* [103], and that high doses of estradiol to ovariectomized rats impair performance on the BLA-dependent conditioned place preference task [35]. However, the vast majority of studies of anatomical sex differences in the amygdala have been limited to examination of the reproductively important amygdalar nuclei associated with the vomeronasal system, particularly portions of the medial nucleus and extended amygdala and the posteromedial cortical nucleus [e.g., 1,17,18,19,42,43,47,79,94,102].

The present study was therefore designed to investigate the influence of aging, sex, and (in females) ovarian hormones on neuronal morphology in the basolateral nucleus of intact male and female rats. Dendritic material and spine density of principal neurons were quantified in Golgi-Cox stained tissue (figure 2). Ovarian hormone effects were investigated in young adults by comparing brains of females sacrificed in the proestrus phase, when estrogen and progesterone are at their highest levels of the estrous cycle, versus those in the estrus phase, when these hormone levels are at their lowest [87]. Aged females were sacrificed in one of two phases of reproductive senescence: persistent estrus, characterized by moderate levels of circulating estrogens and progesterone, or persistent diestrus, characterized by similar levels of estrogen but elevated progesterone [60].

2. Methods

2.1. Subjects

Subjects used for the examination of dendritic material were young adult (3–5 months) and aged (20–24 months) male and female Long-Evans hooded rats, first generation descendents

from stock obtained from Simonsen Laboratory (Gilroy, CA), bred in the Psychology department at the University of Illinois. The age ranges chosen represent those typically employed in studies of aging in Long-Evans rats [7,83,90]. There were 6 groups: young adult males (n = 7), young adult females in proestrus (n = 4), or estrus (n = 5), aged males (n = 5), and aged females in persistent estrus (n = 5) or persistent diestrus (n = 4). Spine density was evaluated in a largely overlapping group of subjects, in the same groups of the following numbers: young males (n = 6), proestrous females (n = 3), estrous females (n = 3), aged males (n = 4), aged females in persistent estrus (n = 6), and persistent diestrus (n = 5). The aged rats were retired breeders. Hippocampal and prefrontal cortex tissue from subjects in all groups were examined and reported in two previous studies [60,61]. Four additional males were included in the dendritic branching analysis: two young males (sham gonadectomy at least three months prior to sacrifice), and two aged males (one had a sham gonadectomy 9 months prior to sacrifice).

Rats were housed in the vivarium of the Psychology department, in same-sex pairs in clear plexiglass cages, in a temperature-controlled environment, on a 12-hr light-dark cycle (lights off at 1900h). The aged rats were pair-housed following retirement from breeding, at approximately 12 months of age. Rat chow and water were available *ad libitum*. Animal care and experimental procedures were in accordance with National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee.

2.2. Handling and estrous cycle determination

To minimize the effects of handling stress at sacrifice, all the rats were handled weekly following weaning at postnatal day 25 (young adult rats), or following retirement from breeding (aged rats), until two weeks prior to sacrifice, at which time all the rats were handled daily.

Estrous and estropausal phase were determined from vaginal cells obtained by the lavage method. Young adult females were used only after showing three consecutive, normal 4–5 day estrous cycles. Aged females were used only after they were reliably determined to be in either persistent estrus or persistent diestrus for a minimum of 10 consecutive days.

2.3. Histology

The rats were sacrificed with a lethal dose of sodium pentobarbital between 1600h and 1900h, brains were removed, and the cerebellum was cut away. The brains were immersed in 100 ml of Golgi-Cox solution according to Van der Loos [93] for approximately 18 days [60,61]. Golgi-Cox solution was prepared from 5% solutions of potassium dichromate, mercuric chloride and potassium chromate, in a 5:5:4 volume parts ratio [37]. Tissue was blocked coronally at the optic chiasm, dehydrated, embedded in a celloidin solution, hardened and stored in butanol until sectioning. Before sectioning, the celloidin-embedded tissue was coded so that all quantification was made blind to group. Several blocks of the coded tissue were randomly selected on each day of sectioning and processing, which was completed over a period of months. Brains were sectioned in the coronal plane on a sliding microtome at a thickness of 150 μm. Processing of the sections involved development in ammonium hydroxide, fixation in photographic fixative, dehydration, and clearing in xylene. Sections were mounted on slides with permount and coverslipped.

2.4. Identification of principal neurons of the basolateral nucleus

The basolateral nucleus (BL) was identified by location, after an examination of Nissl stained tissue through the BL of several rat brains, and by the orientation and morphological characteristics of its neurons, which differ markedly from those of most surrounding nuclei [64]. Figure 1 shows the area of the BL in Nissl (1a) and Golgi-Cox (1b) stains and figure 2 shows representative principal neurons (2a) and dendritic spines (2b). Neurons of the dorsally

adjacent lateral nucleus, which are morphologically similar to those of the BL, were distinguishable by location and by their smaller somata [20,64]. Neurons outside of the BL were further avoided with the precaution of restricting analysis to neurons sufficiently far from its borders.

Principal, also known as class I or pyramidal, neurons were sampled (figure 2a). These represent about 85% of neurons in the BLA [71], are the most frequently impregnated BL neurons in Golgi-Cox stained tissue, and are easily distinguished from spine-sparse interneurons which are also impregnated by the Golgi-Cox stain [64]. Principal neurons of the BL are frequently noted for their similarity to pyramidal neurons of the cerebral cortex [13, 63,65]. Though their orientation is irregular, principal neurons of the BL are large, spiny, and frequently exhibit a pyramidal or semi-pyramidal cell body, from which approximately five to seven primary dendrites arise [64]. Some of these neurons display one or two thicker, apical-like dendrites, which arborize more extensively than their thinner, “basal” dendrite-like counterparts. Other class I neurons of the BL are more stellate in shape, with primary dendrites of approximately equal calibers [64].

2.5. Analysis of dendritic material

Dendritic arbors of principal BL neurons were drawn at 500X with the use of a camera lucida. Neurons were selected only if they were unquestionably within the BL, fully impregnated, and dendritic material could be distinguished from that of other neurons. While the great majority of neurons were fully contained within the sections examined, the irregular orientation of dendritic material made it impractical to exclude every neuron containing a truncated branch. Branches that were either cut off or which ran into glia and could not be reliably followed were noted on the drawings. Up to 14 neurons per subject fitting these criteria were drawn, with a minimum of 7 (one case) and an average of 12 neurons per subject. Average number of neurons examined did not differ by group. Total dendritic length was estimated by Sholl ring analysis [88], in which a series of concentric rings were calibrated (20 μm apart in this study), copied onto a transparency, and laid over the drawings, centered on the somata. Figure 3 illustrates Sholl rings laid over camera lucida drawings. The number of intersections made by dendritic material was counted to index the amount of dendritic arborization overall (figure 4) and at each successive ring (figure 5). In addition to Sholl analysis, the number and order of dendritic branches on each neuron were counted.

2.6. Spine density analysis

Spine density was quantified at 1250X under oil on dendritic branches of principal neurons. Eleven to 15 camera lucida drawings per subject were made of short (range 12–30 μm) lengths of dendritic segments, on which the dendritic diameter was measured and the number of spines was counted. Typically no more than one or two dendritic segments were used from the same neuron, though occasionally three segments, originating from different primary branches, were used. Dendritic segments were 0.8–1.6 μm in diameter, with average diameter 1.08 μm. Because principal neurons of the BL do not exhibit regular branching as in neocortex, quantification was not limited to a particular branch order. Instead, dendritic segments were selected from a set range (40–100 μm) of distance from somata. To further control variability only segments at least 50 μm from their terminal ends were used. Only dendritic segments oriented parallel to the plane of the section were selected. Parallel orientation was necessary to maximize spine visibility and avoid foreshortened estimates of segment lengths. Spine density was calculated as average number of spines per 10 μm of dendritic length per subject.

3. Results

3.1. Dendritic material

Total dendritic length was estimated by the number of Sholl ring intersections. Initial, two-tailed *t*-tests were made comparing the average total number of intersections in the proestrous vs. estrous females and the persistent estrous vs. persistent diestrous aged females, to determine whether either of the two female age groups should be combined for ANOVA analysis. These comparisons revealed no effect of estrous phase ($t(7) = 0.34$, ns) or estropausal phase ($t(7) = 0.78$, ns) on Sholl ring intersections; accordingly, the young adult females were combined into a single group (n = 9), as were the aged females (n = 9).

A two-way ANOVA with one repeated measure (sex, age, and Sholl ring as the repeated measure) revealed a significant effect of age on number of intersections ($F(1,26) = 9.34$; $P = 0.005$), due to an age-related increase in dendritic material of 14% (figure 4). Sex did not significantly influence dendritic material ($F(1,26) = 2.26$; $P = 0.144$), nor did sex interact with age ($F(1,26) = 0.002$, ns; figure 4), indicating the age-related increase in dendritic material occurred in both sexes.

The within-subject repeated measure revealed a significant effect of Sholl ring (i.e., distance from soma) on dendritic material ($F(13,338) = 645.87$; $P < 0.001$), as well as a significant age x ring interaction ($F(13,338) = 2.85$; $P = 0.001$), indicating that distance from soma affected dendritic material differently in the young vs. the aged rats. Sex did not interact with Sholl ring ($F(13,338) = 0.78$; $P = 0.682$). The age x Sholl ring interaction was explored with *post hoc* comparisons of the number of intersections in aged vs. young adult rats at each ring. Aged rats had significantly greater numbers of Sholl ring intersections at each point quantified between 80 (Sholl ring 4) and 200 μm (ring 10) from the soma (Sholl ring 4 ($P = 0.038$), 5 ($P = 0.015$), 6 ($P = 0.016$), 7 ($P = 0.015$), 8 ($P = 0.005$), 9 ($P = 0.013$), 10 ($P = 0.028$); figure 5). There were no age effects at either the most proximal points measured (20 through 60 μm from the soma; rings 1, 2 and 3) or the most distal (220 through 280 μm; rings 11 through 14), suggesting age did not influence the number of primary dendrites emerging from the soma (see next paragraph) or the overall reach of the distal dendritic field. Figure 3 shows camera lucida drawings of principal neurons from female adult (3a) and aged (3b) subjects, with the area of Sholl rings 4 and 10 marked.

Quantification of the total number of dendritic branches at each order revealed an average of 5.5 primary branches per neuron, and an average total of 59.4 branches. There was no effect of age ($F(1,26) = 0.96$; $P = 0.337$) or sex ($F(1,26) = 0.38$; $P = 0.545$) on the total number of branches or in the number of branches at any order.

Analysis of the number of branches either cut off by the section or unresolvable (average = 0.36 per neuron) revealed no effect of age ($F(1,26) = 0.34$; $P = 0.855$) or sex ($F(1,26) = 1.21$; $P = 0.281$) on this measure, or in the ratio of cut-off/irresolvable terminals to all terminals (for age: $F(1,26) = 0.10$; $P = 0.756$); for sex: $F(1,26) = 1.33$; $P = 0.259$), indicating no group bias in the analysis due to these factors.

3.2. Spine Density

Spine density was measured as average number of spines per 10 μm per group. Initial, two-tailed *t*-tests comparing the young adult females in proestrus vs. estrus revealed that spine density did not significantly change with estrous phase ($t(4) = 2.04$; $P = 0.112$), although the near-trend (favoring estrous over proestrous females) suggests that an effect of cycle, which could not be detected with the small number of subjects examined (n = 3 per group), may exist. A *t*-test comparing spine density in the two aged female groups showed no effect of estropausal

phase ($t(9) = 0.86$; $P > 0.41$). Accordingly, aged females were grouped for overall analysis (n = 11), as were the young adult females (n = 6).

A two-way ANOVA (sex, age) revealed a significant effect of sex on spine density ($F(1,23) = 8.60$; $P = 0.007$), with males having 12% greater spine density than females (figure 6). Age did not influence spine density (F (1,23) =1.25; $P = 0.274$), nor did sex interact with age in influencing this variable (F (1,23) = 0.053, ns), indicating the sex difference occurred across ages.

Branch order on which spines were counted (average = 3rd-order) did not differ between groups (F (1,23) < 1.0, ns for sex, age, and sex × age interaction). Analysis of the diameter of dendritic segments on which spines were counted revealed no significant sex difference in this measure ($F(1,23) = 1.38$; $P = 0.252$). However, dendritic segments on which spines were counted were slightly thicker in the aged than in the young subjects ($F(1,23) = 5.09$; $P = 0.034$), with average dendrite thickness of 1.1 μm for aged, vs. 1.05 μm for young adult subjects. However, there were no differences in spine head diameters or spine lengths between groups and the dendritic segment thickness difference represented less than 5% of average spine length. This minimal difference is well within the normal variability of dendrites from the same population [48], such that correction for hidden spines [28] would not meaningfully affect the relative number of spines between groups and is therefore considered unnecessary [48].

4. Discussion

These results demonstrate that aging and sex have significant, and distinct, effects on the morphology of principal neurons of the basolateral nucleus (BL) of the rat: dendritic arborization increases with age and is not significantly affected by sex, while spine density is sexually dimorphic, and unaffected by age.

We found an age-related increase in dendritic material of principal neurons, of approximately 14%. This is the first study, to our knowledge, to examine changes in dendritic morphology of neurons of the BLA in aged rats. Whether there is continual growth of the BL dendritic field or a non-linear pattern is not yet clear. Previous studies in human hippocampus [31] and rat hypothalamus [32] have described dendritic growth followed by regression in older age. If this is also the case in the BL, future studies including both intermediate and very old ages [14] can help to pinpoint whether dendritic losses occur after the age (20–24 months) examined here, or perhaps peak before this age and begin to regress thereafter.

Though aging effects have not previously been examined in the dendritic tree of the rat BLA, age-related changes on this measure have been described in neocortical and hippocampal pyramidal neurons, which bear a close resemblance to principal neurons of the BL [13,63, 65], and that literature is decidedly mixed. For example, in rat neocortex, age-related dendritic regression [41,60,90] and growth [67,105] have both been described. There are likewise reports of dendritic regression [61] and growth [78] in area CA1 of the rat hippocampus. In humans, normal aging is accompanied by dendritic increases in pyramidal cells of the parahippocampal gyrus [8], and no changes in pyramidal cell dendrites of the subiculum [30] or the CA fields [33,44]. Some age-related dendritic regression has been described in pyramidal neurons of superior temporal cortex in macaques [26]. Thus, the finding here of increased dendritic material in aged subjects is not unique. It was nevertheless somewhat unexpected, in that age-related losses of dendritic material were found in the same tissue examined here, in both the medial prefrontal cortex (mPFC) [60] and, among the males, in area CA1 of the hippocampus [61].

This internal control eliminates variability from subject variables (age, strain) and housing and animal handling protocols that may differ across laboratories. The circumstance of examining

the BL in tissue where two other brain areas have already been studied also creates an advantage in interpreting the data despite some caveats regarding quantitative analysis of Golgi-stained tissue. For example, any age-related differences in impregnation (though we have no evidence of this) would bias aging data; but since these data reflect an opposite aging effect in the BL vs. both the mPFC and hippocampus, any potential aging effect decreasing or increasing impregnation in the tissue would have been overcome by the relative difference. Two-dimensional analysis of dendritic material does underestimate the length of dendrites. However, there is no reason to assume this bias would differ in young adult vs. aged rats, and the lack of any group differences in the number of branches cut off by the section supports this. A more definitive estimate of true length can be obtained with three-dimensional analysis of neurons with intracellular fills that can be followed through sections. However, in contrast to intracellular fills, Golgi stains provide the advantage that many neurons from a given animal can be quantified.

The present finding of dendritic hypertrophy in aged rats demonstrates differential effects of aging on hippocampal [61] and mPFC [60] pyramidal neurons vs. principal neurons of the basolateral nucleus of the amygdala. This result fits a pattern of contrasting roles of the amygdala with each of these brain areas. In the case of the hippocampus, the same variable (here, aging) often affects that structure differently than it affects the BLA [2,97,98]. For example, estradiol has excitatory effects on hippocampal electrophysiology [100], but inhibitory effects on BLA electrophysiology [103]. And, in parallel to our findings in this tissue, chronic stress induces dendritic atrophy in hippocampal CA3 pyramidal neurons, and dendritic hypertrophy in principal neurons of the BLA [98]. The mPFC likewise undergoes dendritic atrophy following chronic stress [16], and the amygdala also can have opposite effects from both the hippocampus and mPFC in regulating the hypothalamic-pituitary-adrenal axis, as both mPFC and hippocampal efferents lead to net inhibition, and amygdala efferents to net excitation, of neurosecretory cells of the paraventricular nucleus [45,46]. The mPFC and BLA have a number of other opposing roles, and in some cases mutually inhibitory interactions [36,56,82,89]. For example, stimulation of the mPFC has been shown to suppress responses to conditioned stimuli in the lateral nucleus of the BLA [82], and a recent tract-tracing and electron microscopy study confirmed that basolateral nucleus efferents monosynaptically innervate inhibitory local circuit neurons of the mPFC [34]. Indeed, a disrupted ability of the mPFC to regulate affective responses via its interactions with the amygdala is widely thought to contribute to the pathophysiology of depression and post-traumatic stress disorder [25,56].

We also found a sexual dimorphism on the measure of spine density, with male rats exhibiting 12% greater spine density than females on principal cell dendrites (figure 6). The greater spine density observed in males reflects the possibility for more excitatory inputs from any number of afferent populations. Excitatory projection neurons providing inputs to principal BL neurons include those originating from the hippocampus (both the ventral subiculum and area CA1), thalamus, and cerebral cortex [63,71]. Other excitatory inputs come from the lateral nucleus of the BLA and other amygdala divisions, and from collaterals of axons of BL principal neurons themselves [71]. While the cause of this sex difference is not known, the current literature suggests a possible role for estrogen. Estrogen applied to BLA neurons *in vitro* decreases EPSP amplitude by a rather astonishing 77% [103], and high doses of estradiol also impair performance of the BLA-dependent conditioned place preference task [35].

The functional implications of this sex difference are nevertheless not obvious. For example, data on sex differences in performance of the BLA-dependent fear conditioning task are mixed [59,77]. Sex differences in the stress response are well documented [51], and both chronic and acute stress have been shown to increase spine density in the BL, at least among male rats [69]. However, if the observed sex difference in spine density were due to basal sex differences in response to normal stressors, one would expect an alteration with age, because of changes

in both the stress response and sex differences therein with age [51]; instead, we observed no main effect of age and no change in the sex difference in spine density with age. However, both sex [5,15,57,104] and ovarian hormones [6,84,104] have been repeatedly shown to affect the BLA-dependent modulatory effects of stress on hippocampal-dependent learning and memory. It is possible that the sex difference seen here is related to that phenomenon, perhaps for instance reflecting more efficient BLA-hippocampal interactions in males.

The functional implication of age-related dendritic growth is not known. The observed increases of dendritic material in the 80–200 μm range coupled with the lack of differences in the number of dendritic branches suggest an age-related growth of branch length in this middle range. It has been posited that dendritic hypertrophy in aging may occur as a compensatory response to neuronal losses or to decreased afferentation [8,31,105] and some evidence exists for dendritic increases accompanied by neuronal loss [74]. Another possibility is that dendritic growth in the BL, which occurs in response to chronic stress [98] as well as aging, is related to age-associated changes in the stress response [21,68,107], including decreases in corticotrophin-releasing factor (CRF)-binding protein in the BLA of aged rats [106]. For instance, a decreased capacity to regulate CRF levels might render the aged BLA more vulnerable to stress-induced dendritic hypertrophy. On the other hand, given the very different findings of hippocampal and mPFC vs. BLA dendritic changes with aging seen here within the same group of rats, it is perhaps noteworthy that another contrast between the BLA and both the hippocampus and mPFC is that cognitive processes supported by the latter areas are widely known to suffer age-related declines [reviewed in 9,22], whereas there is at least some evidence to support preserved amygdala function with age in rats [24,73,85,91] and in humans [23,53,55,62]. We are currently quantifying neuron and glial cell number in BLA nuclei of male and female young and aged rats, which will provide a better context for interpreting the present findings, particularly in the case of the aged rats.

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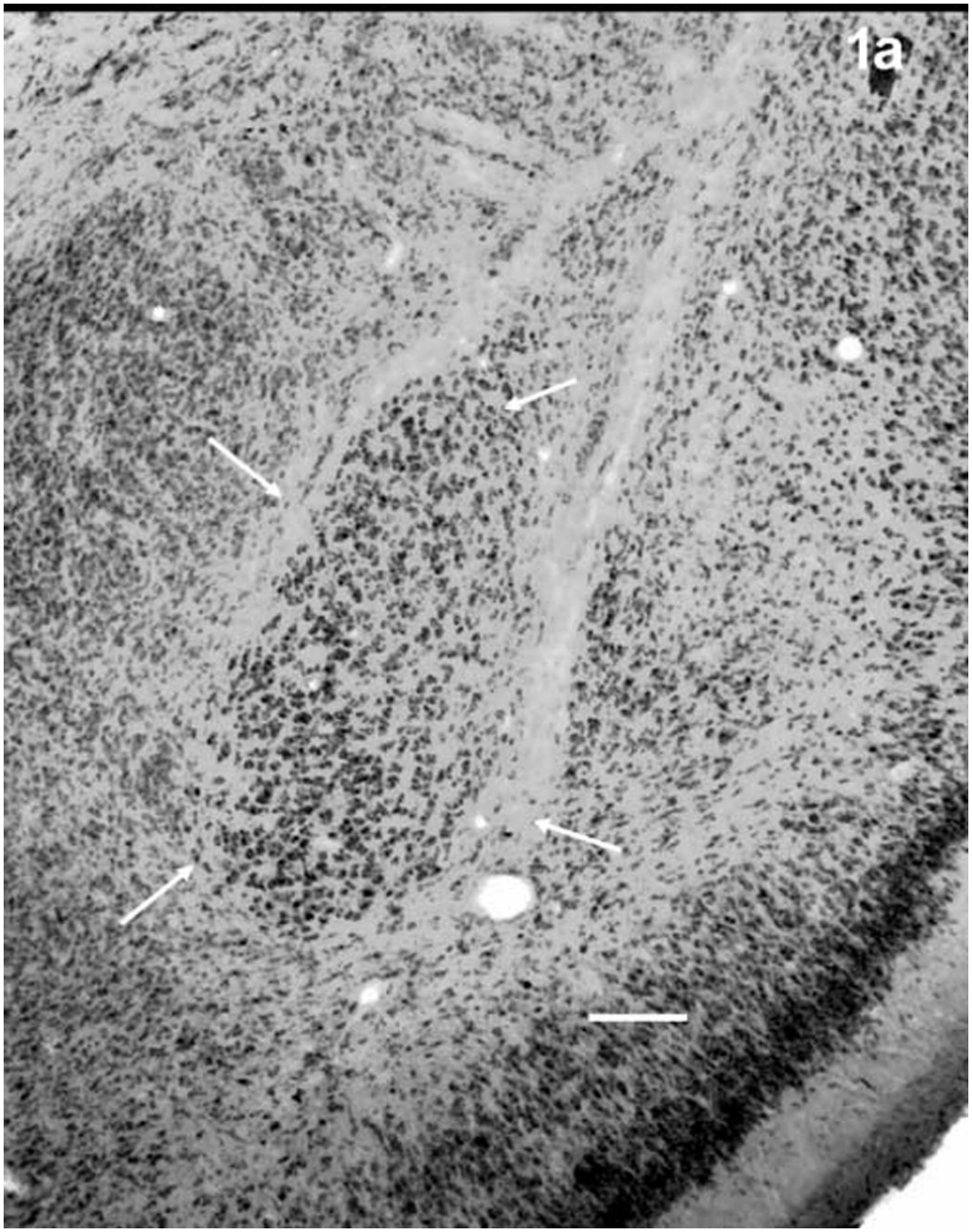


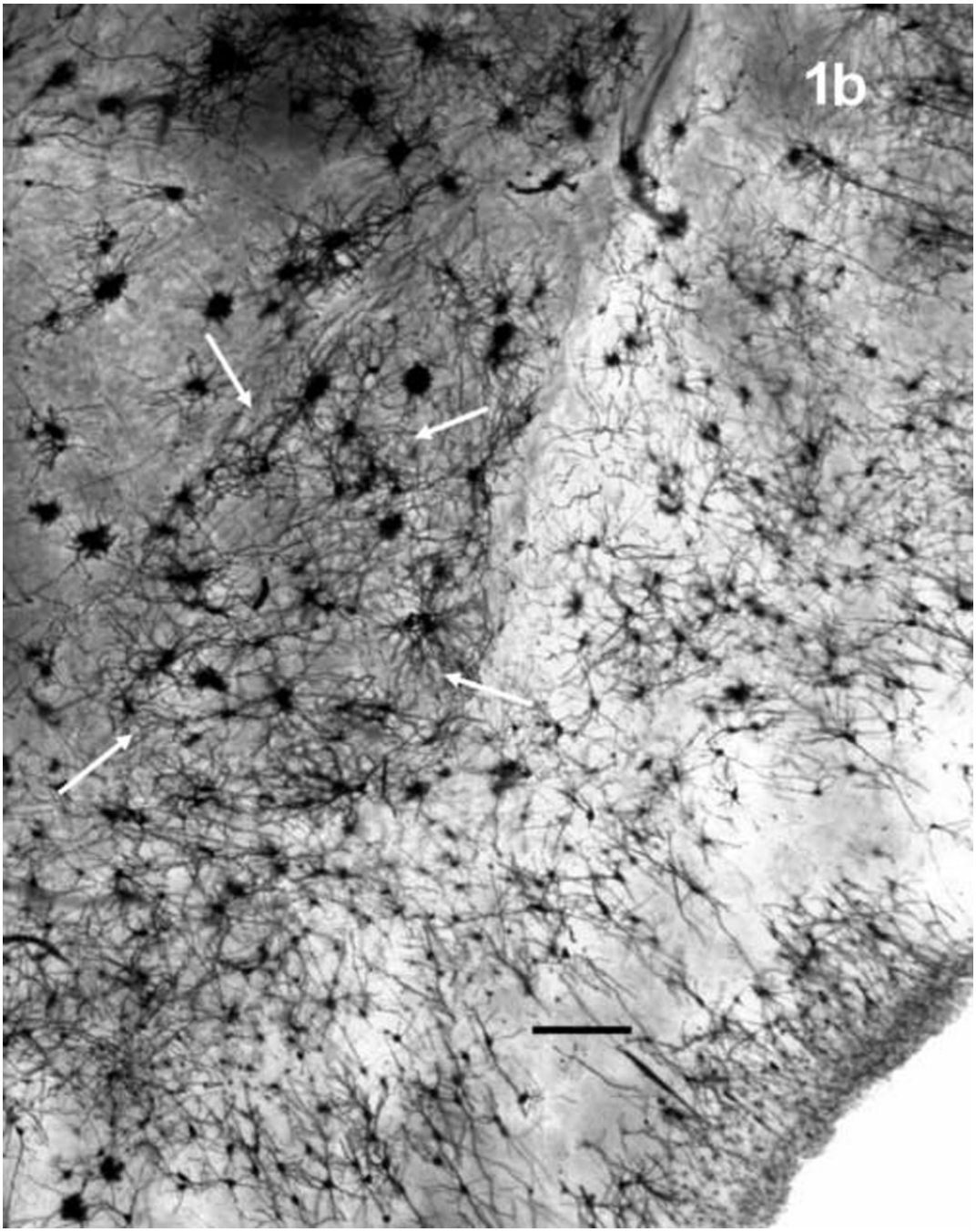
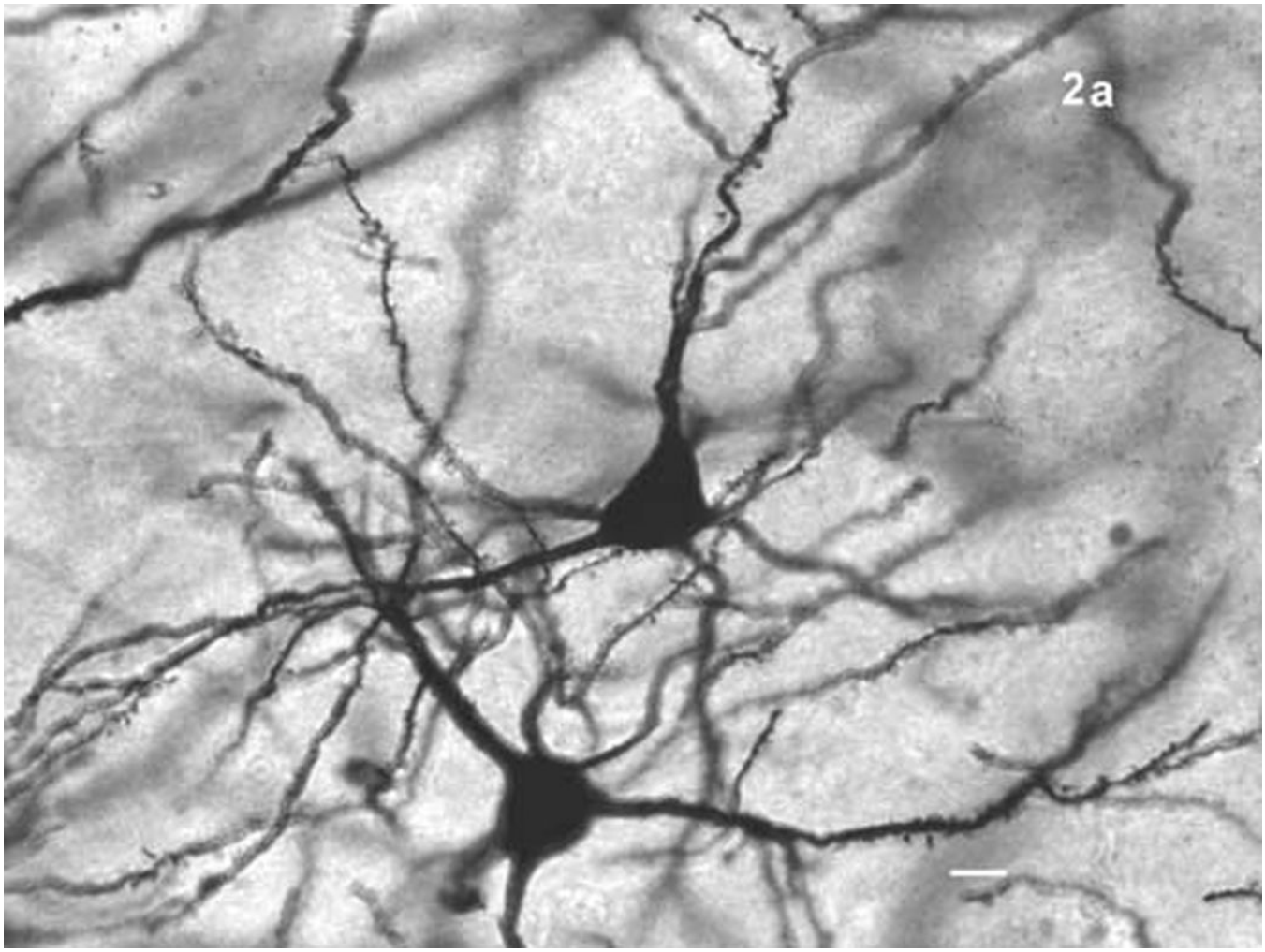


Figure 1.
The basolateral nucleus of the amygdala (arrows) in Nissl-stained tissue (a) and Golgi-Cox stained tissue (b). Scale bars = 200 μm.



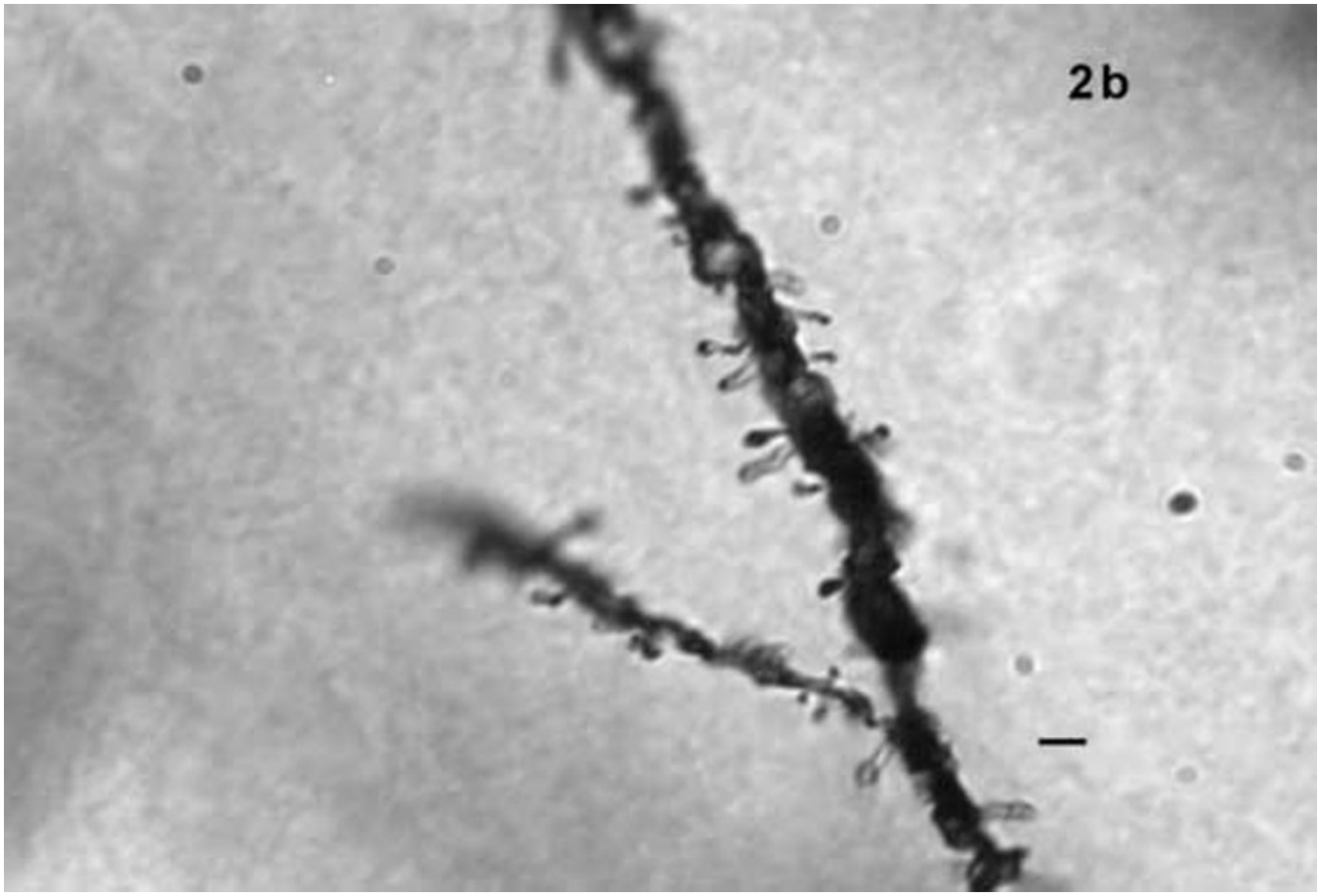
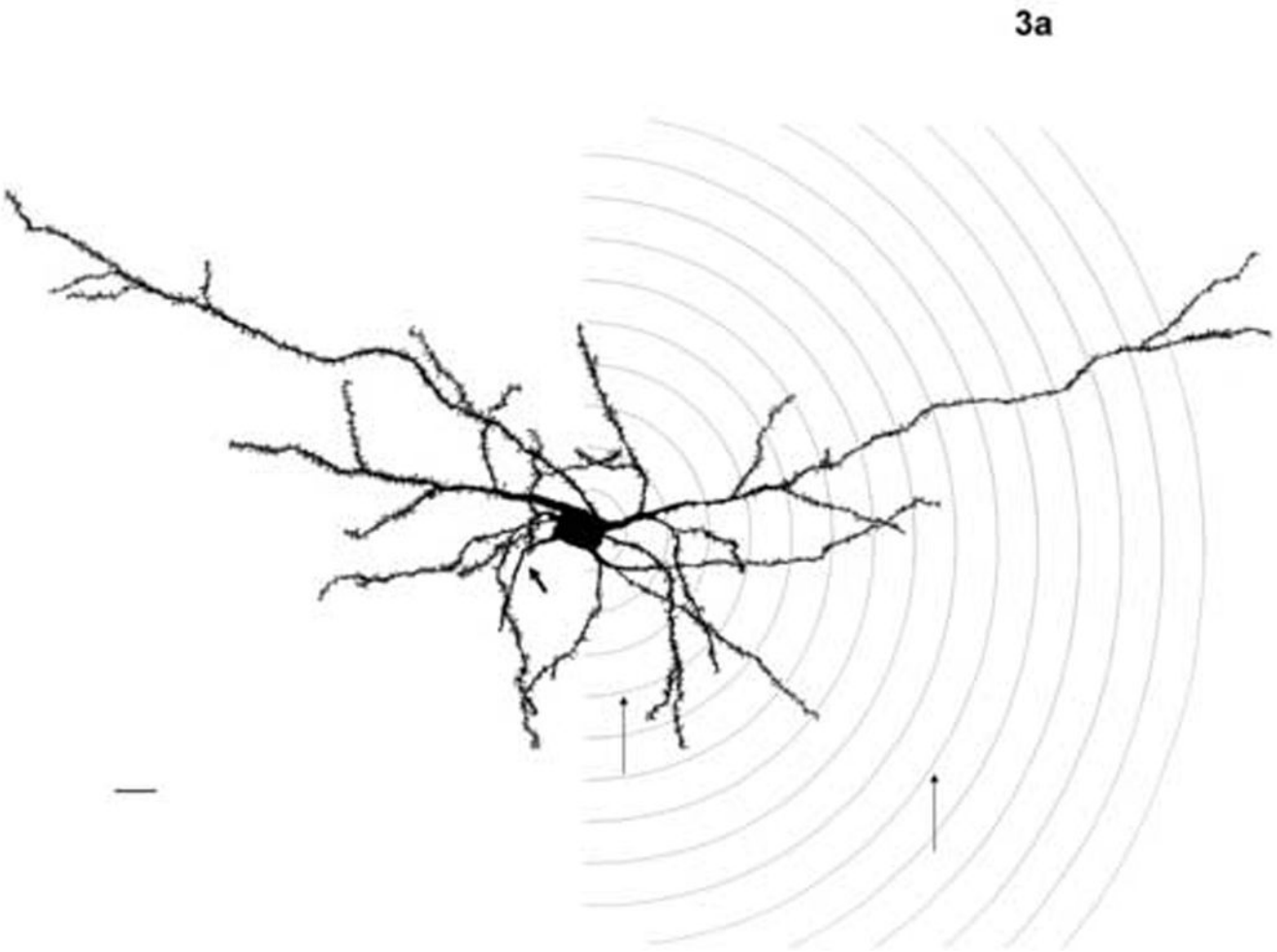


Figure 2.
(a) Two principal neurons of the basolateral nucleus visualized with Golgi-Cox. Scale bar = 10 μm. (b) Dendritic spines on a basolateral nucleus principal neuron. Scale bar = 2 μm.



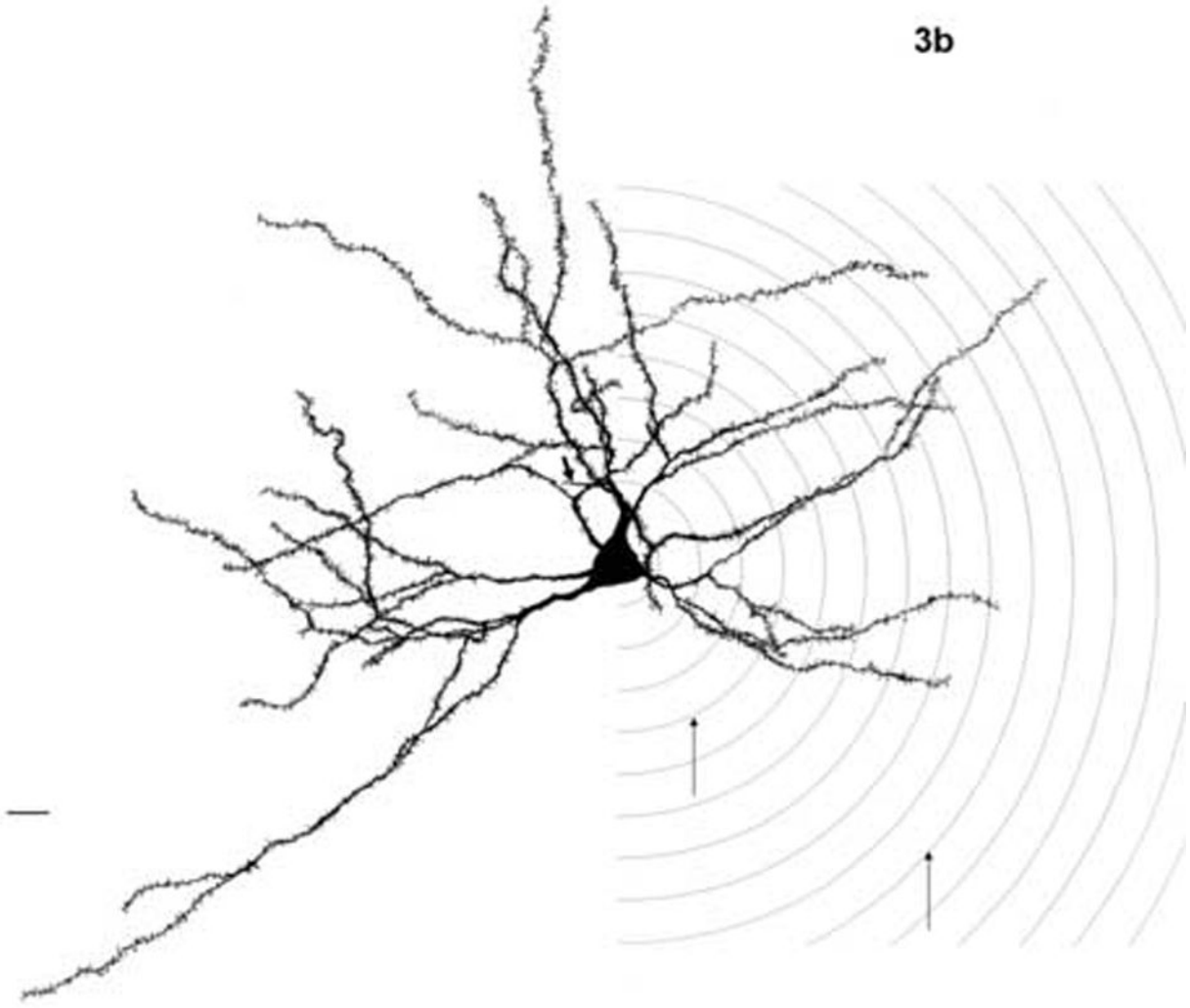


Figure 3.
Camera lucida drawings of basolateral nucleus principal neurons from young adult (a) and aged (b) subjects, both female. Thick arrow indicates axon in both figures. Sholl rings are illustrated on the right half of the illustrations. Thin arrows indicate rings 4 and 10, boundaries of the 80–200 μm range from the soma center where age differences were found. Scale bars = 20 μm.

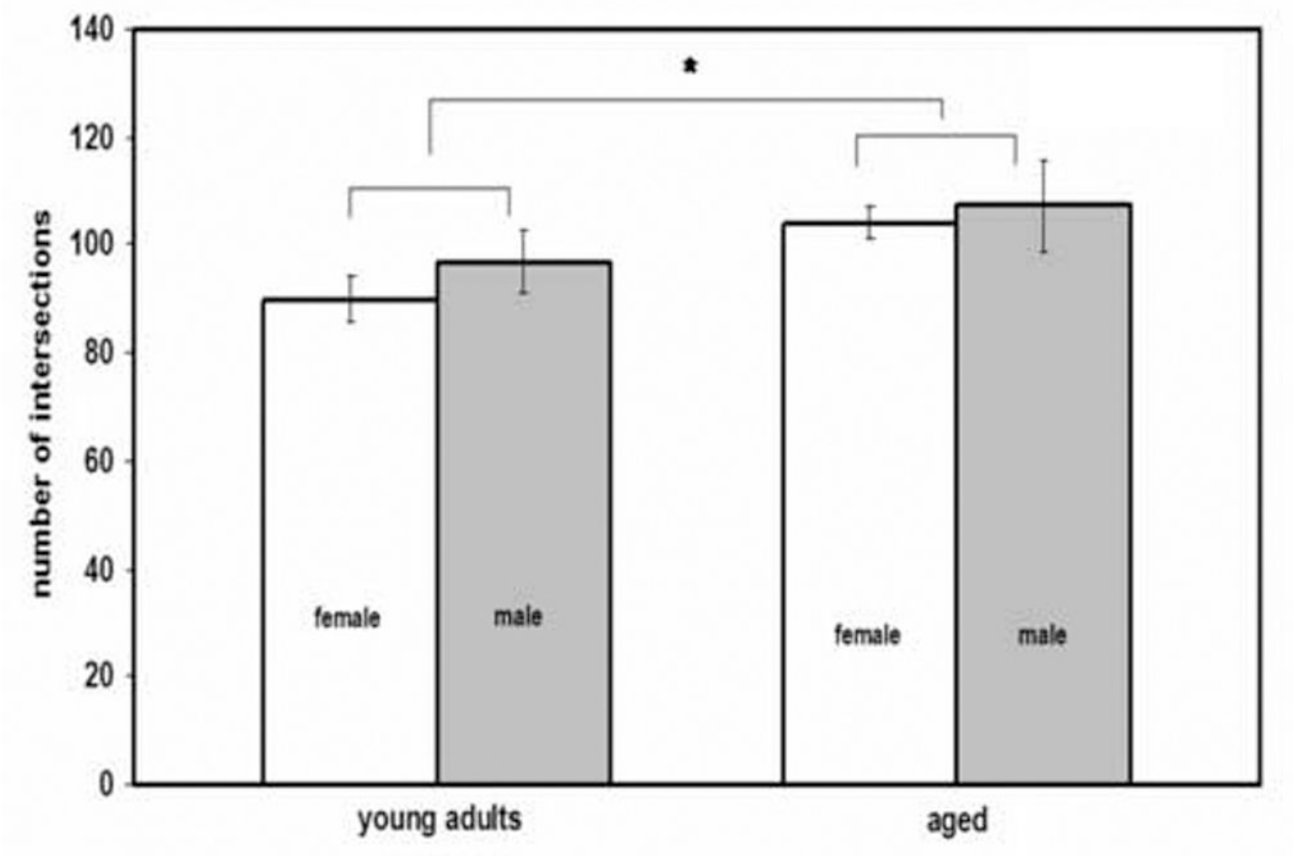


Figure 4.
Age-related increase in dendritic material of principal neurons of the basolateral nucleus as measured by intersections with Sholl rings. Error bars, +/− SEM. **P* = 0.005 for age.

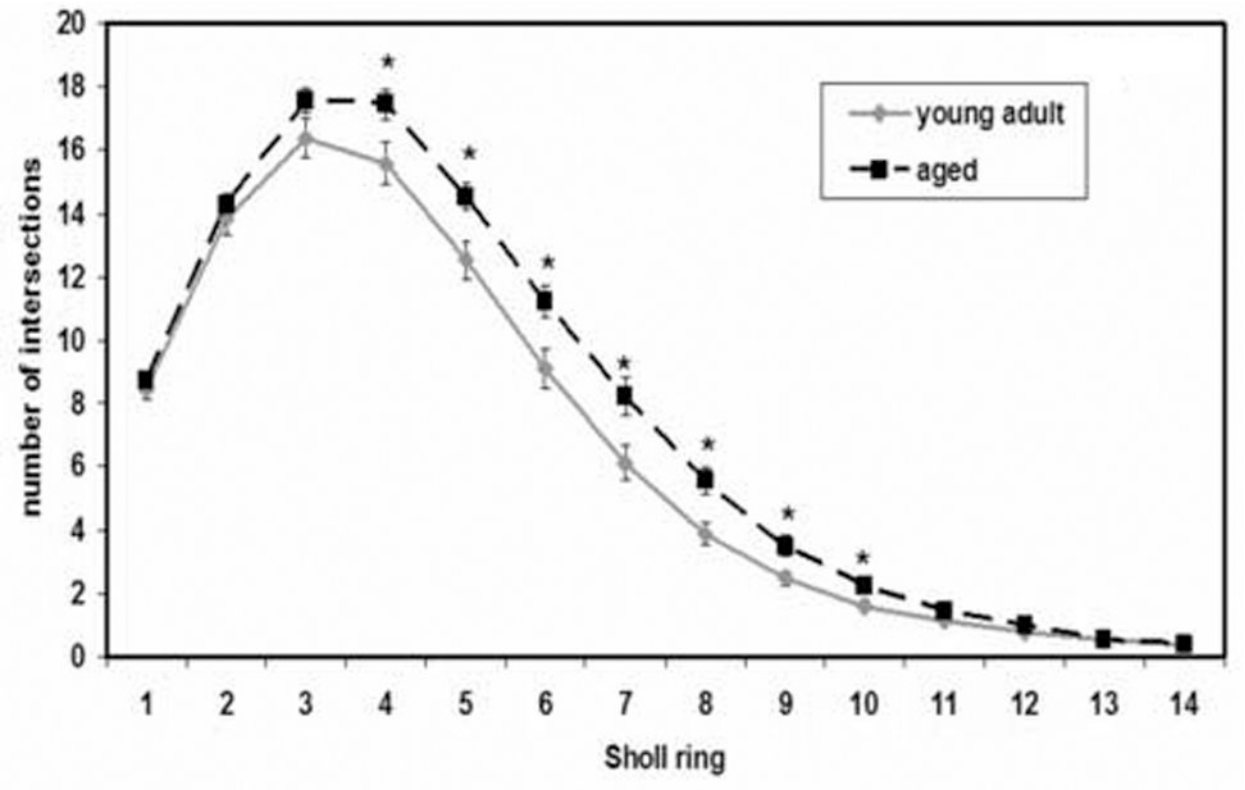


Figure 5.
Average number of intersections for young adult and aged rats, collapsed across sex, at successive Sholl rings. Error bars, +/− SEM. *$P < 0.04$.

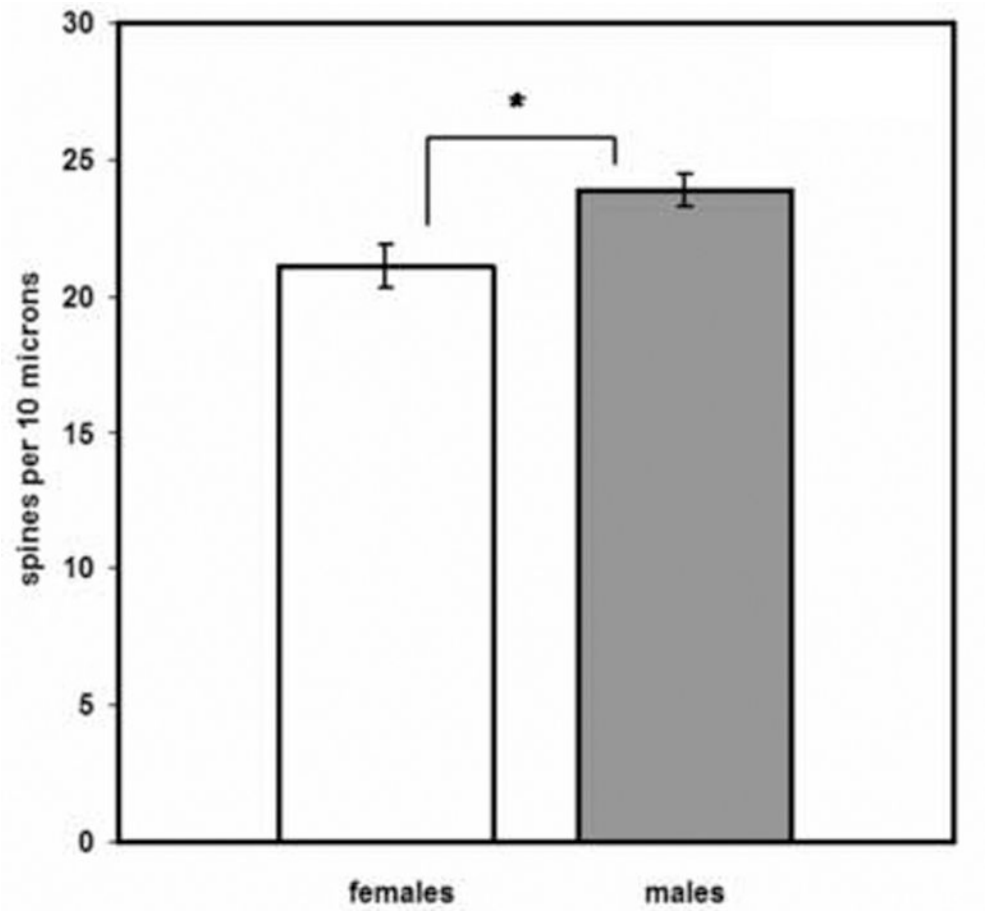


Figure 6.
Sexually dimorphic spine density in principal neurons of the rat basolateral nucleus. Data are shown collapsed across age. *P = 0.007. Error bars, +/− SEM.