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Review article

Songbirds: A novel perspective on estrogens and the aging brain

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Abstract

Songbirds perform some remarkable feats of memory, including forming memories for songs and for complex spatial features of their environments. Research into the neural and hormonal control of these behaviors reveals discrete circuits that can retain considerable plasticity in adulthood. The songbird brain is also a prominent site of estrogen synthesis and a target of estrogen action. Estrogens contribute to the plasticity of the adult songbird brain and contribute to the bird's capacity to form and retrieve some memories. We describe the brain, behavior and endocrinology of songbirds and discuss these findings within the context of the neurology of the aging brain.

Introduction

It is difficult now to consider the aging brain without wondering if estrogens from natural or pharmacological sources might offer it some degree of protection. These thoughts arise because recent discoveries from animal models have changed our perspective on hormones and the brain. First, plasticity is viewed as a property of a healthy brain and there is considerable recent research on several vertebrate species showing a role for estrogens in neural plasticity (Gould et al. 1990; Tramontin et al. 2003; Hung et al. 2003; Gahr 2004; Kretz et al. 2004). Second, there are a variety of studies on animal models implicating estrogens in learning and memory (e.g., Oberlander et al. 2004; Erickson et al. 2005), behaviors thought to be at particular risk during aging. Third, animal studies show that estrogens have a clear role in protecting the brain from the damage resulting from mechanical or physical trauma, including damage from ischemia that more commonly afflicts the elderly (Wise and Dubal 2000; Wise 2002; Garcia-Segura et al. 2003; Wynne and Saldanha 2004). Finally, while there is disagreement about a role for estrogens in preserving the aging human brain, there is some evidence suggesting appropriate estrogen exposure protects against memory loss and some of the devastation associated with some dementias (Iivonen et al. 2004; Erickson et al. 2005).

Estrogen effects on the brain have been detected in a wide diversity of species and seem to occur from early development to late in adulthood. Why estrogen should have such phylogenetically and ontogenetically enduring trophic effects on the brain is unclear. This class of steroid hormone was first identified as a reproductive hormone, particularly in females, and the view of the most potent natural estrogen, estradiol (E_2), as a female reproductive hormone continues to dominate our thinking. It is curious that a sex specific reproductive hormone should play such a prominent role in memory and in the plasticity of both male and female neural circuits, especially those neural processes unrelated to reproduction. Studies

on non-human models, particularly songbirds, offer some hints as to why estrogens are so important to the brain.

The research from our laboratories investigates estrogen synthesis and action in the avian brain with a particular focus on various species of songbirds. Studies of these birds have created a fascinating perspective on hormonal effects on the brain, including roles in neural plasticity. In this review we describe some of the unique behavioral and neurobiological features of this group of birds. We then describe our studies on the role of the enzyme aromatase and of estrogens in natural and injury-induced neural plasticity in these animals. Throughout, we relate these findings to concepts of the aging brain.

Oscine songbirds and memory-related behavior

Songbirds (Order Passeriformes; Oscine Suborder) have attracted the attention of behavioral ecologists, endocrinologists and neurobiologists for two main reasons. These birds sing complex songs that have for years stimulated the curiosity of ornithologists and non-ornithologists alike (Nottebohm 1996). Early investigators were well aware that in many species the males and not the females, sing the most and do so predominantly when breeding. Over many years, researchers found that the basis of the male-specific and seasonal performance of song was the seasonal gonadal secretion of testosterone (T) (for review see Schlinger and Brenowitz 2002). Investigators also discovered that male birds learn their songs by listening to their fathers when they are young and retain this song in memory for many months or even years. When it is time for them to sing they undergo a period of vocal practicing until they perfectly recreate the memorized song of their fathers (or tutors) (Marler 1997).

In light of these compelling discoveries about the behavioral and endocrine control of song, investigators then turned an eye to the brain. They discovered a remarkable neural circuitry underlying the motor control of the syrinx, the bird's vocal organ, and the learning and memorization of song (for a current map of the neural song system see Prather and Mooney 2004). Two largely telencephalic overlapping circuits separately control the motor output of song and the learning of song. Research has identified how auditory and hormonal inputs act on these circuits to impact the neural encoding and motor output of song (Brainard and Doupe 2002).

In addition to their capacity to learn song, these birds also demonstrate other amazing forms of learning that have attracted the attention of biologists and psychologists (e.g., Clayton 2002). Birds of many species acquire significant and detailed knowledge of their environment, store the information for extended periods of time and then retrieve and use that information. Many of these examples involve forms of spatial learning. Notable examples include the storage and subsequent retrieval of food over large areas of the environment (e.g., Shettleworth et al. 1995; Healy and Suhonen 1996; Bednekoff et al. 1997; Moller et al. 2001, Gibson and Kamil 2005) and accurate migration over vast distances across the planet (Berthold et al. 2003). For example, some birds that endure long periods over winter with no obvious food sources will store many thousands of seeds during the autumn. These seeds sustain them through the winter, so if the sites of these food caches were forgotten the birds would likely perish. Consequently, there has been strong selection pressure for these birds to develop accurate and seasonally enduring memories for these cache sites. Many billions of birds migrate from arctic or temperate breeding sites to wintering grounds in tropical or warm temperate environments. In many cases the birds return to the exact wintering and breeding quarters used the year before, flawlessly making this site-faithful round-trip year after year.

In the case of the memorized map that guides orientation during migration, the spatial memories involved seem to be held intact for the life of the bird. Unfortunately, we know very little about the neural circuitry that might underlie this spectacular form of learning or how the memories are held intact for the duration of the bird's life (Bingman and Able 2002). In the case of food caches, however, spatial memories are held for just days or months and then discarded, making way for the encoding of locations of new cache sites. There is considerable evidence that the hippocampus is the brain area most involved in memorizing food caches (Hampton and Shettleworth 1996; Sherry and Duff 1996). In the case of song, some birds retain their memory for song for life, while in other cases new song features are added across time.

Why is it important to consider these natural forms of learning and memory in songbirds when consid-

ering questions about the aging human brain? The principal reason is that we can use songbirds to investigate the unique adaptations of those neural circuits that form lifelong memories or those that store memories for specified short-term periods of their lives. It appears that the seasonal reconstruction of neural circuits underlies the short-term learning and memory of both song and environmental spatial information (Nottebohm 1981; Tramontin and Brenowitz 2000). These neural reconstructions represent substantive and biologically relevant forms of neural plasticity. Were these kinds of plasticity to fail, the birds would surely die, or at the very least reproduce poorly. Amazingly, some songbirds are long-lived, especially for their size and high metabolic rate, yet we have no evidence that they suffer decrements in these mental functions. Quite the contrary, older animals are often more successful, as if they retain the fruits of their many experiences and discard memories that are no longer of use. Further, some of the morphological plasticity seen in the adult songbird brain resembles properties of juvenile brains. This finding makes the impression that songbirds have devised strategies to retain a more youthful brain. It is no wonder many of us investigate those age-defying mechanisms.

Aromatase in the songbird brain

In the case of song learning, androgens seem to promote the long-term retention of song, but estrogens promote the plasticity needed for learning (Bottjer and Johnson 1997; Schlinger 1997; White et al. 1999). Thus, one strategy that might be used by songbirds to retain adult neural plasticity is the evolution of a significant capacity to make estrogen in the adult brain. Estrogens are derived from the enzyme aromatase (Cytochrome P450 arom or CYP19) which converts some C19 androgens into C18 estrogens. Although identified originally as a gonadal, primarily ovarian, enzyme, we have known for 30 years that this enzyme is expressed in the brains of both males and females of virtually every vertebrate species studied (Naftolin et al. 1971, Callard 1984). As a result, the aromatization reaction can be viewed as a fundamental biochemical feature of the vertebrate brain. The role for aromatase in making estrogen for the organization and activation of masculine copulatory behaviors and aggression has been reviewed many times previously (Lephart 1996; Balthazart and Ball 1998; Roselli and Resko 2001). In general, these studies lead to the view that aromatase in the brain is naturally expressed in neurons (but with a relatively restricted distribution), predominantly in the hypothalamus and preoptic area and less so in the amygdala, hippocampus and cortex. The general belief is that in males testosterone (T) from the testes circulates to the brain, where it can be converted to E_2 for actions on estrogen receptors. In developing rodents this process leads to the growth of neural circuits controlling masculine reproductive behaviors. In adult rodents, this neurally formed estrogen activates masculine reproductive motivation. In contrast to this general pattern seen in higher vertebrates, aromatase is extremely active in the brains of most fish, often exceeding that seen in ovaries (Pasmanik and Callard 1985). Although some fish species may express aromatase in neurons (Callard et al. 1993), there is clear evidence that, in others, aromatase is expressed in glia (Forlano et al. 2001).

Whereas many bird species demonstrate a pattern of neural aromatization that resembles that of mammals (Balthazart et al. 1996), the oscine songbirds (the most recently evolved of all birds) have a different pattern of neural aromatase expression. We study a diversity of songbird species, and find that aromatase in songbirds is especially abundant in neurons of the telencephalon, including the hippocampus and caudal forebrain (Shen et al. 1995; Saldanha et al. 1998, 1999, 2000; Soma et al. 1999, 2003). Some of the areas are known to be near or in regions associated with song learning and expression (the neural song system and auditory processing areas), spatial memory formation (the hippocampus) and adult neural plasticity (some ventricular borders). Surprisingly, the hippocampus and most song nuclei have few if any aromatase-expressing cells, but aromatase-positive neurons project into these brain regions (Saldanha et al. 2000) with axons and synaptic terminals that contain aromatase (Peterson et al. 2005). Consequently, these regions can have a significant capacity to make estrogens (Vockel et al. 1990) but do so mostly at the synapse (Peterson et al. 2005). The synapse may be an especially important site of estrogen synthesis and perhaps estrogen action (see below).

Aromatase has traditionally been seen as a metabolic enzyme in brain using as its substrate T synthesized and secreted into the general circulation by the gonads or the adrenals; however, there is mount-

ing evidence that this view is too narrow. We have evidence that the brain itself might synthesize androgens that could serve as substrates for neural aromatization (London et al. 2003). In addition, when aromatase in brain functions coordinately with another steroidogenic enzyme, 3β-HSD, then dehydroepiandrosterone (DHEA) can be an important substrate for the formation of active estrogens in the songbird brain (Vanson et al. 1996; Soma et al. 2004). In humans, DHEA is secreted in substantial amounts by the adrenals and it declines with age (e.g., Perrini et al. 2005). There is much recent evidence for a role for DHEA in neuroplasticity and in neuroprotection in mammals (e.g., Allolio and Arlt 2002; Lu et al. 2003; Hajszan et al. 2004). Songbirds show some of the most conspicuous evidence for functional actions of DHEA on brain and behavior, especially in adult non-breeding birds (Soma and Wingfield 2001; Soma et al. 2002). For this reason, songbirds warrant our attention towards understanding the natural neurobiological actions of DHEA.

Estrogens and adult neurogenesis

Songbirds have played an especially important role in the identification of adult neurogenesis, a particularly significant form of neuroplasticity. Recent interest in this topic has been fuelled by compelling evidence that the adult mammalian brain is capable of generating new neurons (Eriksson et al. 1998). This interest stems from a revolutionary reversal of dogma. Although the adult mammalian brain had not been considered capable of generating mitotic neurons (see Gould and Gross 2002), adult neurogenesis has been documented in other vertebrate classes (Nottebohm 2004), and indeed had been suggested in the mammalian brain some 40 years ago (Altman 1962). The observation that the number of mitotic neurons in the adult mammalian brain decreases during aging underscores the relevance of this particular form of neural plasticity to the structural and functional capabilities of the maturing CNS.

It may come as no surprise that the circuitry that underlies the learning and expression of song has proven an important model for understanding adult neuroplasticity. Early studies that documented the incidence, migration, and function of newly born neurons in the adult vertebrate brain exploited two characteristics of songbirds and their brains. First, the species used were open-ended learners; animals who restructure their songs year after year during adult life. Second, the well-conserved neural circuitry that supported the memorization and faithful replay of song during development was likely the very circuit used for song restructuring during adulthood. Landmark studies in the canary (*Serinus canaria*) first showed that newly mitotic cells were observable not only in the subventricular zones of the adult brain but were also located some distance away in song nucleus HVC (Goldman and Nottebohm 1983). The neuronal nature of the observed cells was strongly suggested by the presence of synaptic profiles on thymidine-labeled perikarya, a compelling, albeit not unequivocal neuronal characteristic. Definitive evidence of adult neurogenesis in the canary brain was presented by Paton and Nottebohm (1984) who showed that mitotic neurons within HVC not only responded to auditory stimuli with temporally locked synaptic currents, but also were capable of firing action potentials either spontaneously or upon induced depolarization. Taken together this wealth of data began a revolution: *the adult brain is capable of generating new neurons*. Questions remained, nevertheless, including how new neurons are born and why.

The first of these questions has been intensely examined in the songbird. Much like the mechanisms responsible for brain development, the adult songbird brain contains precursor cells within the subventricular zone, the division of which results in radial glia and neurons. Both cell types are detectable in the subventricular zone of adult canaries (Alvarez-Buylla and Nottebohm 1988). The migration of neurons from the subventricular zone out to distal loci occurs along the processes of these radial glia, sometimes over distances of several millimeters (Alvarez-Buylla et al. 1990a). It should be noted that the level of adult neurogenesis and recruitment in the songbird brain is robust enough for all the aforementioned processes to be faithfully mimicked in slice-culture preparations from adult canary brain (Goldman 1990; Goldman and Nedergaard 1992; Goldman et al. 1992). Thus, the inherent plasticity of the songbird brain has provided critical data on the incidence and mechanisms of adult neuroplasticity.

New neurons have been directly observed in the subventricular zone in adults of all investigated species of songbird including canaries, zebra finches

(*Taeniopygia guttata*), mountain chickadees (*Peocile gambelii*), and starlings (*Sturnus vulgaris*). It is likely, therefore, that adult neurogenesis is widespread among oscine songbirds, since many species have the capacity to remodel the overall volumes and the numbers of neurons within specific brain areas (see Goodson et al. 2005). In the canary HVC neurogenesis peaks in October and March (Kirn et al. 1994). Although the function of neuronal replacement remains unclear, newly born neurons in the adult canary brain project from HVC to RA (Kirn and Nottebohm 1993) and may underlie changes in song learning and production (Alvarez-Buylla et al. 1990b; Kirn et al. 1994).

The song circuit is not privileged in terms of recruiting neurons during adulthood. As mentioned previously, some songbirds store food reserves during the autumn and winter. In one such species, the black-capped chickadee, mitotic neurons migrate into the adult hippocampus (Barnea and Nottebohm 1996), thereby increasing hippocampal volume via changes in neuron number (Smulders et al. 1995, 2000; but see Hoshooley and Sherry 2004). Importantly, peaks in hippocampal recruitment occur in good temporal agreement with increases in food-storing and retrieval. This suggests the possibility that different parts of the adult songbird brain recruit new neurons in a season- and behavior-specific manner. In chickadees cell number in the hippocampus (which is necessary for food retrieval) is maximal in October, whereas cell numbers in HVC and Area X (necessary for singing) are maximal in June (Saldanha et al. 2004a). These data on the song system and hippocampus point to the exaggerated capability of the adult passerine brain to reorganize behaviorally relevant circuitry during adulthood.

The dynamics of neuron addition, survival, and death are affected by a variety of factors including experience, hormones and age. In the non-photoperiodic zebra finch, deafening decreases the number of mitotic neurons incorporated into HVC. Interestingly, the turnover of newly recruited neurons is also decreased (Wang et al. 1999). These data suggest that auditory experience has potent effects on adult neurogenesis in the songbird. Additionally, the incorporation of new neurons into HVC decreases quite dramatically with age. Since the total number of neurons in older zebra finches rivals that of their younger conspecifics, the data suggest that cell death in HVC is also decreased (Wang et al. 2002). It will be crucial to understand which component of cell turnover changes during aging in the songbird.

There is much evidence to support the belief that estrogens participate in the overall process whereby neurons newly born in the adult songbird brain differentiate, migrate and incorporate into functional neural circuits. First, there is a substantial literature showing that sex steroids (T or its androgenic or estrogenic metabolites) impact song development and song learning when these events occur early in development or yearly in adult seasonal breeding birds (Schlinger and Brenowitz 2002). In addition, although estrogens may not regulate neurogenesis itself (Brown et al. 1993), more newly born neurons reach the song nucleus HVC intact when adult female canaries are exposed to estrogen (Hidalgo et al. 1995a). We have also examined estrogen effects on cell proliferation by labeling mitotically active cells with BrdU. We find that 24 hrs after injection of adult female zebra finches with BrdU, there are many fewer labeled cells in birds treated with the aromatase inhibitor fadrozole than in fadrozole-treated birds given estrogen replacement (Lee et al. submitted). It is quite likely that cells newly born along the ventricular proliferative zone migrate though a layer of ER-expressing cells that somehow assist in the proper survival or differentiation (Hidalgo et al. 1995b). Estrogens stimulate neurotrophins (Sohrabji et al. 1994; Dittrich et al. 1999) which may be the ultimate molecular signals leading to successful neuronal recruitment.

Estrogens, the hippocampus and learning

Song learning and cache-retrieval are two memory-reliant behaviors that involve an often dramatic restructuring of the adult CNS (Goodson et al. 2005). Notably, expression of these behaviors is strongly seasonal in photoperiodic songbirds suggesting the involvement of hormones. An exciting new avenue towards understanding the mechanisms that regulate songbird neuroplasticity presented itself when it was found that the songbird hippocampus itself was a significant site of estrogen synthesis (Shen et al. 1995; Saldanha et al. 1998). Though estrogen effects on song circuits are well documented (Schlinger and Brenowitz 2002), little was known about the involvement of aromatase or estrogen on the songbird hippocampus.

The songbird hippocampus presents a unique research opportunity towards unraveling the interactions among neuroplasticity, estrogen, and spatial memory performance. Every species of songbird investigated expresses high levels of aromatase in the hippocampus. In stark contrast aromatase is low or even undetectable in the hippocampus of some non-songbirds and mammals (Saldanha et al. 1998). Thus the involvement of local estrogen synthesis in hippocampal physiology is perhaps best tested in songbirds. Indeed, our recent data show that estrogen provision has dramatic effects on the structure and function of the zebra finch hippocampus. In adult castrated males, those implanted with either T or E_2 demonstrate quicker acquisition of a spatial memory task than dihydrotestosterone (DHT)- or blank-implanted birds. This finding strongly implicates aromatization as a modulator of hippocampal function since the non-aromatizable androgen, DHT, failed to increase spatial memory acquisition (Oberlander et al. 2004). A corresponding increase in soma size was detected in the anterior hippocampus of subjects implanted with T or E_2 relative to those implanted with DHT or empty capsules. Thus, estrogen provision via neural aromatization appears to modulate structural and functional plasticity in the songbird hippocampus.

We have reason to believe that local estrogen synthesis may also be critical in the maintenance of hippocampal (HP) structure in the songbird. Adult zebra finches were either treated with fadrozole (20 mg in 20 μl saline per day orally) or 20 μl saline l saline (per day orally) for 40 days. Following this treatment coronal sections through the brain were collected, stained with Thionin and examined under the light microscope. On each section an individual blind to the experimental condition of the animals measured the area of the HP as well as the telencephalon. These measures were integrated into volumetric measures across the number of sections. Resultant data revealed that the HP volume and HP volume relative to telencephalic volume of fadrozole-treated birds was significantly lower that that of control birds. Telencephalic volume did not differ across groups. Interestingly, an analysis of differences in sectional area across the antero-posterior extent of the HP revealed that this effect obtained from differences in the anterior and not the posterior HP (see Figure 1). Taken together, these data suggest that local estrogen synthesis may maintain HP volume in the adult songbird via an effect on the anterior HP. Future research will determine the basis of this sensitivity.

Early evidence suggests that this sensitivity of HP volume to estrogen may be mediated via the NMDA receptor (NMDAR). In the zebra finch hippocampus all cells that express aromatase also express NR1, the requisite subunit of functional NMDAR. Additionally, estrogen treatment increases the density of NR1-expression, the number of synapses onto NR1-expressing neurons, and overall synaptic densi-

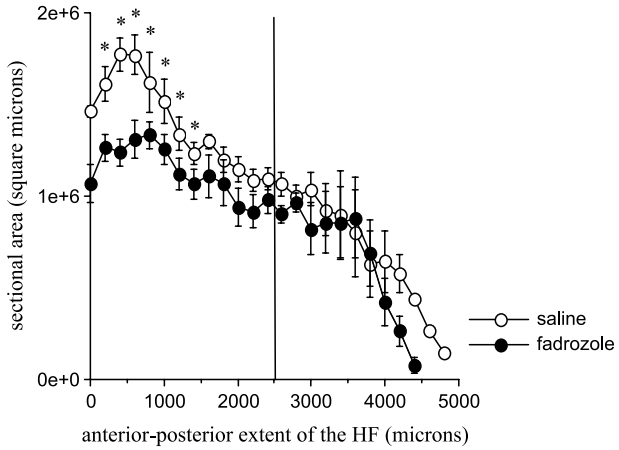

Figure 1. Differences in the hippocampal formation (HF) volume between zebra finches treated with saline and fadrozole. The rostro-caudal extent of the HF was standardized across birds by centering the reconstruction around the section containing the anterior commissure (vertical line at 2,500 on the *X*-axis). Thus, each point reflects the mean and standard error of the area of the HF of fadrozole-treated ($N = 6$) and control ($N = 7$) zebra finches. As shown, the anterior HF of fadrozole-treated birds is significantly smaller than controls (LSM comparisons; $F_{(1,12)} : p < 0.05$).

ty in the hippocampus (Saldanha et al. 2004b). This exciting interaction between cells that synthesize estrogen and those that mediate excitatory-neurotransmission promises to be a fruitful area of future research.

Songbirds, estrogens and neural injury

In birds and mammals, aromatase is expressed exclusively, or most abundantly, in neurons (Canick et al. 1986). Consequently, the identification of aromatase in astrocytes in primary cell cultures of the zebra finch brain (Schlinger et al. 1994), and then later in the mammalian brain (Zwain et al. 1997), proved perplexing. We now understand that, after injury to brains of adult birds and mammals, aromatase expression is upregulated in glia (Garcia-Segura et al. 1999). In the zebra finch, a penetrating (mechanical) injury to the brain induces aromatase mRNA and protein expression within 24 h and this expression persists for at least seven days (Peterson et al. 2001). Interestingly, an injury of the zebra finch hippocampus that is relatively close to the lateral ventricle induces aromatase in radial glia lining the ventricle (Peterson et al. 2004).

We have good evidence that glial aromatization can lessen the impact of a neural injury. In adult male zebra finches, we induced mechanical injuries in both telencephalic lobes. One lobe received an injection of saline (control) while the contralateral hemisphere received an injection of fadrozole. After 72 h, we measured the size of induced lesion in both hemispheres. Neural damage in the lobe that received fadrozole was significantly greater than the hemisphere that received saline. These data suggest that the upregulation of aromatase around neural injury may function to limit the extent of damage (Wynne et al. 2004). Indeed, one pathway whereby glial aromatization limits neural damage is through the arrest of apoptotic pathways. Hemispheres injected with fadrozole contained almost twice as many apoptotic nuclei compared to the contralateral hemisphere (Wynne and Saldanha 2004). This effect is mediated by estrogen delivery, presumably of glial origin. In a similar experiment, we injected one hemisphere with fadrozole and the other with fadrozole and estradiol. Delivery of estradiol dramatically lessened apoptosis and the size of neural damage (Saldanha et al. 2005). Thus, injury-induced glial aromatase functions to limit secondary damage in the songbird brain. It will be particularly interesting to ask if the dynamics of the upregulation of glial aromatase and/or the impact of glial estrogen delivery changes as a function of age.

Summary

Studies of the neurobiology of songbirds have helped forge a new view of the adult vertebrate brain as one that can retain considerable plasticity in adulthood (Nottebohm 2002, 2004). Studies on the hormonal control of song and song learning show that the sex steroids, and in particular estrogens, impact the songbird brain in diverse and often powerful ways, including significant actions on neural plasticity (Schlinger and Brenowitz 2002). The songbird brain not only responds to sex steroids, but has also evolved the capacity to make estrogens in large amounts (Schlinger 1995), perhaps even making active sex steroids fully from cholesterol (Holloway and Clayton 2001; London et al. 2003; Soma et al. 2004). The complex steroidogenic and steroid metabolic capability of the songbird brain suggests that we may identify new neurotrophic steroids or new mechanisms of neurosteroid action. Collectively, these new perspectives on the brain stand to teach us even more about ways in which hormones may contribute to the preservation of a healthy brain and avert some of the neurological problems that occur as we age.

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