Could androgens maintain specific domains of mental health in aging men by preserving hippocampal neurogenesis?

Mark I Ransome

Florey Neurosciences Institute, Melbourne Brain Centre, the University of Melbourne, Parkville, Victoria 3010, Australia

Abstract
Interest surrounds the role of sex-hormones in regulating brain function outside of reproductive behaviour. Declining androgen production in aging males has been associated with cognitive impairment, depression and increased risk of developing Alzheimer’s disease. Indication for testosterone replacement therapy is based on biochemically determined low circulating testosterone combined with manifest symptoms. However, which aspects of age-related cognitive decline are attributable to low circulating testosterone remain ambiguous. Studies examining cognition in aging men receiving testosterone replacement therapy have yielded equivocal results. The exact role of testosterone in maintaining cognitive function and the underlying neural mechanisms are largely unknown, though it would appear to be domain specific. Clarity in this area will provide clinical direction toward addressing an increasing healthcare burden of mental health decline coincident with increasing longevity. The premise that androgens contribute to maintaining aspects of mental health in aging men by preserving hippocampal neurogenesis will be used as a forum in this review to discuss current knowledge and the need for further studies to better define testosterone replacement strategies for aging male health.

Key Words
androgen; hippocampus; neurogenesis; aging; cognition; male; testosterone

Research Highlights
(1) The population of aged men is growing, together with their health care burden.
(2) Testosterone production progressively falls in aging men and some studies associate low testosterone with the development of depression and impaired spatial ability.
(3) Animal models link depression and spatial ability with hippocampal function and neurogenesis.
(4) The degree to which low testosterone participates in the functional decline of these specific cognitive domains remains uncertain.
(5) The merit of testosterone therapy for aged men is a contentious issue.
(6) Further research is required to evaluate a causative relationship between age-related declines in hippocampal function, testosterone production and hippocampal neurogenesis.
(7) New research may determine whether testosterone therapy could maintain hippocampal neurogenesis levels and thereby preserve hippocampal function in aging men.

Abbreviations
LH, luteinising hormone; FSH, follicle stimulating hormone; SHBG, sex-hormone binding globulin; BrdU, 5-bromo-2’deoxyuridine; FGF, fibroblast growth factor; BDNF, brain derived neurotrophic factor
INTRODUCTION

Considerable improvements in health care during the course of the last century have led to unprecedented increases in current life expectancies. However, longevity continues to favor women and as a consequence Chinese and Australian national health policies recognize the need to address male health in aging[1-3]. While increased life expectancy is a broad consequence of quality health care, it also produces an aging population whose health care burden suggests wellbeing has not equally paralleled longevity. Several areas of male health decline with age with increasing incidence of impaired spatial ability and depression being significant barriers to mental health.

A sex difference in longevity intuitively points to a role of sex-hormones in maintaining health during aging. The sex-hormone testosterone is the primary androgen produced in men and circulating levels progressively decrease from 30 years onward so that by 60 years of age, up to 1 in 4 men have developed androgen deficiency[4-5]. With increasing longevity the proportion of androgen deficient or hypogonadal men is likely to grow, along with predicted adverse consequences for male health[6]. Although clinically diagnosed hypogonadism is remediable with testosterone replacement therapy, understanding a causative relationship between age-related physiological decline and reduced androgen levels will enable better defined interventional strategies.

The hippocampus is a key component of the temporal lobe and is notable for retaining ongoing adult neurogenesis within the dentate gyrus subregion[7]. The dentate gyrus is implicated in declining hippocampal function in aging humans[8-9]. Impaired hippocampal function resulting from neurogenesis deficits is hypothesised to contribute to the etiology of both depression and spatial memory impairment[7, 10-12]. In considering the collective clinical and rodent model data, a coincident age-related decline in circulating testosterone, hippocampal neurogenesis and hippocampal function becomes evident. However, a causal relationship between the age-related decline of these factors has yet to be established. This review raises a hypothesis that testosterone contributes to preserving hippocampal function in aging men by maintaining neurogenesis levels. Herein, the intention is to briefly discuss the available evidence and highlight the necessity of further studies to establish, or refute, clinically relevant causal relationships. The key elements of this review are schematically represented in Figure 1.

ANDROGEN PRODUCTION DURING MALE AGING

Testosterone is the primary male androgen and is produced through the co-ordinated actions of the hypothalamic-pituitary-testes (HPT) axis[13]. While there is normal variation among men, serum total testosterone in men aged under 35 years generally exceeds 20 nM[14, 15]. According to several endocrinology health
bodies serum concentrations of total testosterone below 12 nM constitute a clinical diagnosis of hypogonadism, which can be further classified according to a taxonomy that directs remedial strategies\[16\]. For example, testicular dysfunction, or primary hypogonadism, manifests in the presence of high luteinizing hormone/follicle stimulating hormone (LH/FSH) and is potentially indicated for testosterone replacement therapy. Secondary hypogonadism occurs when hypothalamic/pituitary pathology fails to produce LH/FSH in sufficient levels to stimulate testicular androgen production. In this case, exogenous LH and/or FSH might be indicated to restore testicular function including testosterone production. Age-related low circulating testosterone can be the result of either primary or secondary hypogonadism\[4-5\]. Otherwise normal aging is associated with reduced total circulating testosterone levels (below 20 nM) concomitant with increased sex-hormone binding globulin (SHBG)\[17-18\]. Testosterone bound to SHBG is not bioactive and can affect the clearance rate of testosterone by the liver\[17\]. However, the age-related increase in SHBG levels has been shown to be independent of the age-related decline in bioactive testosterone levels\[18\].

Testosterone replacement therapy is advised based on symptomatic low circulating testosterone levels\[16, 19\]. However, applying this criterion to aging men presents potential limitations. Firstly the age at which testosterone levels become low is an important determinant of resulting symptoms\[16\]. Age-related, or late-onset hypogonadism, may therefore elicit a unique spectrum of symptoms that are yet to be fully established. Secondly, controversy surrounds the reliability of widely used measures of total and free serum testosterone to detect low circulating levels\[20\]. As symptoms other than sexual dysfunction and frailty are not readily attributed to low circulating testosterone, symptomatic testosterone deficiency could be more common than generally recognised\[21\]. Testosterone therapy in aging men has hitherto been directed toward treating sexual and cardiovascular dysfunction, muscle mass loss and immobility\[16\]. Emerging evidence now points to an added role for androgens in maintaining cognitive health\[22\]. Hence, the symptom profile of late-onset hypogonadism may well include declining mental health.

**COGNITIVE IMPAIRMENT WITH ADVANCING AGE**

Although there are cross-sectional variations in measures of cognitive ability, a more robust decline is observed in longitudinal analyses\[23-24\]. Notwithstanding the view held by some that age-related cognitive decline is normal, maintaining cognition in longevity at young levels would have an undeniable impact on wellbeing. Memory is a chief cognitive function that declines with age\[25\]. Importantly, not all types of memory decline with normal age. Procedural memory remains largely unaffected, whereas declarative memory, particularly episodic memory shows demonstrable decline with increasing age\[26-27\]. Declarative memory as a whole is closely associated with temporal lobe function and abilities related to spatial memory are intimately coupled with the hippocampus\[28-29\]. The decline in spatial ability of aging men is a domain of cognition particularly studied in relation to testosterone levels\[30\]. This interest may be attributed to the fact that aspects of spatial ability are superior in men compared to women\[31-34\]. A sex bias in spatial ability is also reflected in rodent studies that have been largely demonstrated using maze navigation tasks\[35\]. Men and women employ the same brain regions, including the hippocampus, when undertaking spatial navigation tasks\[36-37\]. These observations suggest that testosterone may target the hippocampus in a manner that enhances spatial ability in men.

Notions of sex differences in brain anatomy and function have centred largely on the effects of sex hormones in development\[38\]. Evidence supports a possible organisational role of androgen signalling during brain development that imparts superior spatial cognitive ability in adulthood\[39-41\]. Importantly, not all types of memory decline with normal age. Procedural memory remains largely unaffected, whereas declarative memory, particularly episodic memory shows demonstrable decline with increasing age\[26-27\]. Declarative memory as a whole is closely associated with temporal lobe function and abilities related to spatial memory are intimately coupled with the hippocampus\[28-29\]. The decline in spatial ability of aging men is a domain of cognition particularly studied in relation to testosterone levels\[30\]. This interest may be attributed to the fact that aspects of spatial ability are superior in men compared to women\[31-34\]. A sex bias in spatial ability is also reflected in rodent studies that have been largely demonstrated using maze navigation tasks\[35\]. Men and women employ the same brain regions, including the hippocampus, when undertaking spatial navigation tasks\[36-37\]. These observations suggest that testosterone may target the hippocampus in a manner that enhances spatial ability in men.

**ANDROGENS AND HIPPOCAMPAL PLASTICITY AND FUNCTION**

Androgens protect the adult brain from degenerative insults such as stroke and traumatic brain injury\[49-56\].
Adult hippocampal neurogenesis is tightly regulated by physiological, environmental and pharmacological factors. Adult hippocampal neurogenesis proceeds through a series of sequential steps: asymmetric division of neural stem cells, proliferative expansion of neural progenitors, neuronal differentiation and finally survival of mature neurons including both efferent and afferent synaptogenesis. Intrinsic proliferation and differentiation markers together with exogenous markers such as 5-bromo-2’-deoxyuridine (BrdU; which is incorporated into dividing cells and can assess proliferation and survival at short and longer time-points, respectively) are widely used to measure adult hippocampal neurogenesis. Mechanisms of age-induced reductions in adult hippocampal neurogenesis include decreased progenitor proliferation and neuronal survival, but factors mediating these mechanisms remain unknown. Notions of sex-specific regulation of adult hippocampal neurogenesis were a significant impetus for exploring the effects of sex hormones on proliferation, differentiation and survival of adult-generated hippocampal neurons (reviewed in [88]). There is more hippocampal neurogenesis in neonatal male rats than females and several studies have demonstrated sex-specific rates of hippocampal neurogenesis in adult rodents. Whether there is a sex-specific decline in adult hippocampal neurogenesis with advancing age remains hitherto unestablished.

Early studies withdrawing androgen through gonadectomy in young male rats showed no effect on proliferation but reduced neuronal survival as demonstrated by a reduction in the number of 30-day-old BrdU-labelled cells in the dentate gyrus. Repletion of testosterone at high but not low levels in these animals restored adult hippocampal neurogenesis in an androgen receptor-dependent manner. In contrast, another study showed that exogenous injections of nandrolone, a synthetic derivative of testosterone and androgen receptor agonist, reduced adult hippocampal...
neurogenesis by decreasing neuronal precursor proliferation in young adult male rats\(^9\). Our own recent work demonstrated that chronic testosterone therapy in young male adult mice had no effect on precursor proliferation as measured by the intrinsic marker Ki67, but did promote adult hippocampal neurogenesis through increased neuronal survival and differentiation 28-days after BrdU administration\(^5\). We measured hippocampal neurogenesis during the last 4 weeks of 3 months of supraphysiological doses of testosterone through sustained-release pellets\(^5\), whereas a similar dosage limited to 3 days via repeated injections had no effect on neurogenesis\(^9\). Another study of young male mice demonstrated that precursor proliferation also measured by Ki67 expression was unchanged, while the generation of maturing neurons measured by another intrinsic marker doublecortin, was decreased in the absence of androgen through gonadectomy\(^9\). Single administration of BrdU to measure precursor proliferation in gonadectomised young adult male rats untreated or made replete with physiological levels of testosterone showed no effect of androgen withdrawal\(^9\). However, the same study showed that testosterone exacerbated the up-regulated proliferation in response to the anti-depressant imipramine. In a contrasting finding, Ki67 was used to demonstrate a decrease in precursor proliferation in gonadectomised young male rats compared to sham-surgery controls\(^9\). This study also employed BrdU to further examine survival and neuronal differentiation, showing that androgen withdrawal through gonadectomy decreased surviving 24-day-old BrdU-labelled cells in the dentate gyrus without change in neuronal differentiation\(^9\). Furthermore, polysialic acid-neural cell adhesion molecule (PSA-NCAM) was used to demonstrate androgen withdrawal decreases maturing/migrating neurons\(^9\). Using a different approach, intact male rats given placebo or testosterone and BrdU to measure proliferation, survival and differentiation showed no effect of exogenous androgen on any of these hippocampal neurogenesis parameters\(^9\).

Manipulating testosterone levels in young male rats by gonadectomy or exogenous administration to intact rats showed that testosterone therapy had a capacity to decrease hippocampal neurogenesis\(^9\). The authors of this study make a pertinent argument that testosterone's effects on hippocampal neurogenesis may be dose and duration-dependent and specific to the developmental stage of newly-generated neurons. In addition, the mode of hormone delivery, repeated injections versus constant release implants likely impacts on serum testosterone levels\(^9\). Hence differences in delivery mode could confound direct comparisons between studies in which serum testosterone levels are reported\(^5\). This notion is reflected clinically, where testosterone therapy through long-term skin patches could provide better efficacy compared to repeated surges that accompany periodic injections\(^1\). Further potential confounds reside in the methodology used to measure hippocampal neurogenesis, for example intrinsic markers such as Ki67, PSA-NCAM and doublecortin versus the timing and dose of exogenous markers like BrdU. More importantly, the manipulations of testosterone levels in young male rodents in these studies do not recapitulate the late-adult onset and gradual decrease in circulating androgen manifest in normal aging. Hence, extrapolating these data to explain a possible causal relationship between low testosterone and declining adult hippocampal neurogenesis in age is limited and specific longitudinal studies examining models of normal aging are required\(^9\).

### ANDROGEN RECEPTOR-MEDIATED EFFECTS ON ADULT HIPPOCAMPAL NEUROGENESIS

Androgen receptor signal transduction incorporates both genomic mechanisms and non-genomic pathways including; cAMP response element-binding protein (CREB), extracellular signal-regulated kinase (ERK) and Akt signalling\(^1\). These non-genomic signalling pathways in particular could represent intrinsic cellular mechanisms by which testosterone directly effects hippocampal neurogenesis\(^1\). However, despite androgen receptor expression in the dentate gyrus region\(^5\), whether neural stem cells, transient precursor intermediates or maturing neurons exhibit differential expression is unclear. Cultured neural stem cells have been found to express androgen receptor, though these in vitro studies used cells derived from the sub-ventricular zone of adult female rats\(^9\). Hence it remains to be determined if hippocampal neurogenesis can be directly affected by testosterone or whether effects are transmitted by cellular and/or molecular intermediates.

The local microenvironment, or neurogenic niche, is considered to play a significant role in regulating neurogenesis levels in the adult hippocampus\(^1\). Astrocytes are an integral cellular component of the neurogenic niche that support hippocampal neurogenesis through mechanisms not fully understood but includes promoting neuronal differentiation and maturation\(^1\). One mechanism by which astrocytes
stimulate hippocampal neurogenesis is through the secretion of soluble neurotrophic factors such as fibroblast growth factor (FGF)-2. Expression of FGF-2 by astrocytes residing in the hippocampal neurogenic microenvironment decreases during aging and may contribute to the age-related decline in hippocampal neurogenesis\[104-105\]. Hippocampal astrocytes in male rats express androgen receptor\[62\] and hence testosterone could influence hippocampal neurogenesis indirectly. Testosterone triggers FGF-2 production in germ-line stem cells of the adult male testis that may play a role in spermatogenesis\[106\]. Whether such signalling also occurs in neural stem cells to promote hippocampal neurogenesis and whether reductions in this signalling precipitate age-related decline in hippocampal neurogenesis remains untested. Brain derived neurotrophic factor (BDNF) is another compound that both maintains and mediates up-regulation of hippocampal neurogenesis in rodents and is decreased in the aged hippocampus\[107-108\]. The ability of testosterone to promote survival of adult-generated neurons in adult canaries is mediated by BDNF\[109-110\]. Testosterone plays a role in regulating BDNF levels in the neuromuscular system of rodents\[111\]. However, fluctuations in circulating testosterone during the early development of male mice are independent of hippocampal BDNF levels\[112\]. Studies using aging rats have shown no sex-specific changes in declining hippocampal BDNF levels, nor any correlations between levels of serum oestrogen or testosterone with hippocampal BDNF in aging male rats\[113-114\]. The collective evidence would suggest that age-related declining serum testosterone and hippocampal BDNF levels are independent and do not interact to cause falling hippocampal neurogenesis. However, BDNF could still mediate stimulatory effects of testosterone therapy on hippocampal neurogenesis. Evidence supports a direct association between circulating and hippocampal BDNF levels in rats\[115\]. This association could be important in aging men given the recent findings that circulating BDNF levels are; higher in aging women compared to men, negatively correlated with age in men and positively correlated with bioavailable circulating testosterone levels in men\[116\]. These observations raise a possibility that BDNF could be a systemic factor mediating the cognitive efficacy of testosterone therapy. Moreover, age-related decline in cellular and molecular elements including signal transduction pathways necessary to mediate testosterone's effects could significantly impact on the effectiveness of androgen therapy and underscores the importance of their elucidation. The physiological metabolism of testosterone is another important consideration in elucidating the mechanisms of cognitive efficacy. Testosterone is metabolised by 5α-reductase into the high-affinity androgen receptor ligand dihydrotestosterone and by aromatase into the oestrogen receptors and ligand 17β-estradiol. Thus, whether it be intrinsic production or the result of exogenous therapy, effects of circulating testosterone can be mediated through either androgen or oestrogen receptors. However, while both androgen and oestrogen mediated signalling contribute to preserving CA1 synaptic density in females, the same effect in males is androgen receptor dependent\[62, 117\]. Although one study using rats showed that testosterone therapy tended to increase circulating levels of 17β-estradiol (albeit a non-statistically significant increase), oestrogen activity was not responsible for the increased adult hippocampal neurogenesis\[91\].

**EFFECTS OF TESTOSTERONE THERAPY ON COGNITION IN ELDERLY MEN**

The ability of testosterone therapy to restore declining spatial ability in aging rats was tested in advance of the general acceptance of adult hippocampal neurogenesis\[118\]. Intriguingly, this study showed no efficacy of testosterone therapy in preserving spatial ability. More recent studies administering testosterone to aged rats however, have shown restorative effects on declining spatial ability\[113\]. Moreover, studies examining the effects of androgens on spatial abilities in rodents across life-span have yielded complex results\[119-120\] that more generally reflect the collective clinical data examining aging men. The relationship between testosterone levels and different parameters of cognition in aging men has been recently reviewed in detail\[121\]. Decreased circulating testosterone in aging men is linked to poorer performances on tasks requiring spatial ability\[122\]. Several clinical studies show that spatial ability is improved in aging men receiving testosterone therapy\[123-124\]. This effect of testosterone is also seen in men suffering mild cognitive impairment and even Alzheimer's disease\[125\]. However, others have shown no effect of testosterone therapy on cognitive parameters in healthy and mildly cognitive impaired aged men\[126-127\]. The magnitude of demonstrated spatial ability improvements have varied and may dependent on the dose of testosterone and the length of therapy\[128-130\]. Spatial ability varies with endogenous circulating testosterone levels in aging men and appears to respond better to intermediate doses of exogenous testosterone.
comparing low and supraphysiological doses that show no efficacy\cite{122, 129}. Circulating 17β-estradiol levels could change in elderly men receiving testosterone therapy as a consequence of peripheral aromatisation. However, the efficacy of testosterone therapy on spatial ability in aging men appears to be independent of oestrogen activity, though 17β-estradiol may mediate concomitant improvements in verbal memory\cite{128, 131}. Prospective clinical studies of prostate health support the idea that both testosterone and 17β-estradiol levels impact on male aging\cite{132}. Both rodent and clinical studies suggest spatial ability in aged males is enhanced when high testosterone is coincident with low 17β-estradiol levels\cite{44, 113, 122, 133}. Thus, in parallel with the notion of optimal testosterone levels, is the view that the balance of testosterone and 17β-estradiol plays a significant role in spatial ability\cite{134}. Debate over the function of adult hippocampal neurogenesis has evolved to include a specific role in pattern separation, which is to encode and retrieve similar events and is linked to dentate gyrus function\cite{135-136}. The strongest evidence from rodent studies also suggest an association between age-related decline in adult hippocampal neurogenesis and impaired pattern separation ability\cite{137-138}. Emerging evidence now supports a reduction in pattern separation ability in aging humans\cite{139-140}. Given the relative infancy of interest in age-related pattern separation impairment, there is hitherto no definitive evidence for sex differences in the decline of this domain of spatial cognition. It therefore remains possible that testosterone therapy in aging men may preserve pattern separation ability, which could be mediated through maintaining neurogenesis levels in the aging dentate gyrus.

The notion that androgens subserve specific domains of mental health includes effects on emotion-based behaviours. Furthermore, along with spatial ability, adult hippocampal neurogenesis has also been linked with emotion-based behaviour. A hypothesis based on several associative links posits that impaired adult hippocampal neurogenesis elicits depression and that efficacy of antidepressant interventions is mediated through adult hippocampal neurogenesis\cite{12, 73-74, 141}. How does a link between depression and adult hippocampal neurogenesis relate to testosterone levels and advancing age? As with memory loss, age is a risk factor for depression\cite{142}. Gender difference in the incidence of depression disappears with advancing age\cite{143} and the occurrence of depression in elderly men is associated with low testosterone\cite{144-146}. To explore these observations in the context of declining adult hippocampal neurogenesis requires a consideration of a functional distinction in hippocampal structure. The discussion has hitherto observed the classic tri-synaptic circuitry intrinsic to the hippocampus mediated through the interconnectiveness of the dentate gyrus, CA1 and CA3 subregions. However, on a more global level the rodent hippocampus has been regionalised into dorsal (septal pole or posterior in humans) and ventral (temporal pole or anterior in humans) functional subregions\cite{147}. This regionalisation has partly been based on functional assessments, differential gene expression and connectivity, with spatial ability and emotion-based behaviour preferential to the dorsal and ventral hippocampal regions, respectively\cite{148}. Neurogenesis rates may be higher in the dorsal compared to the ventral region of young adult hippocampus\cite{77, 149}, but this regional difference attenuates with advancing age, indicating a relatively higher impact of age on dorsal hippocampal neurogenesis. Clinical efficacy of antidepressant treatment is associated with specific increases in adult neurogenesis in the anterior hippocampus in depressed patients\cite{150}. Whether androgen deficiency with advancing age differentially affects neurogenesis rates along the septal-temporal axis in the adult hippocampus in parallel with functional deficits such as depression and impaired spatial ability is not known.

The question of whether antidepressant and spatial ability efficacy of testosterone therapy for aging men is mediated by region-specific hippocampal neurogenesis remains intriguing. Intriguing in part, because addressing this cause-effect relationship will help refine the neurogenesis-depression and neurogenesis-cognition hypotheses\cite{151} and also elucidate links between impaired neural substrates, hypogonadism and symptoms of cognitive dysfunction. This latter point will in turn help define position statements that advocate testosterone therapy based on low testosterone in conjunction with manifest symptoms\cite{19, 152}. Clinical studies using testosterone therapy in elderly men showing either benefit or no effect rather than deterioration in cognition have employed inconsistent and even inadequate measures of mental health\cite{128, 153-154}. A significant point to consider in evaluating this literature is the notion that androgens likely affect mental health in a domain-specific manner\cite{155}. Moreover, conclusions drawn from clinical studies will depend significantly on the cognitive measures used.

**CONCLUDING REMARKS**

Uncertainty as to what biochemically measured level of circulating free testosterone constitutes late-onset
Studies examining these questions will address the aromatisation\[^{168-169}\]. What role in maintaining levels of 17β-male androgen production, aging men retain higher precipitous event compared to the gradual decline in testosterone and neurogenesis levels\[^{161-163}\], is aerobic -estradiol play?\[^{8}\]

β does testosterone aromatisation into 17β-hippocampal neurogenesis and function in aging men gonadotropin-releasing hormone (GnRH) and their role, The hippocampus expresses receptors for LH and steroidogenesis, in age-related decline is directly or indirectly through promoting local males\[^{168}\]. Because menopause is a far more symptoms in women that manifest early than in menopause-mediated oestrogen withdrawal is posited than negative evidence\[^{16, 152}\]. Ethical and technical limitations in clinical studies, including varied cognitive assessment methodologies, study inclusion criteria and population size and age range of participants have played a large part in generating this equivocal evidence\[^{121}\]. This review premises that reduced testosterone is a mediating factor of impaired spatial ability and depression incidence in aging males because of reduced dorsal and ventral hippocampal neurogenesis, respectively. In discussing the known effects of both androgen withdrawal and therapy on hippocampal function and plasticity, it is clear new understanding will be needed to establish a causal relationship between these factors in the context of normal male aging. There remain several key questions concerning the role androgens play in regulating adult hippocampal neurogenesis, including age-related decline and mediation of stimulatory factors such as exercise\[^{158}\]. An active lifestyle predicts higher circulating testosterone levels in aging men; could testosterone mediate the ability of physical activity to promote neurogenesis and function in the aged hippocampus\[^{78, 159-160}\]? If so, given that intensity could determine the effects of exercise on testosterone and neurogenesis levels\[^{161-163}\], is aerobic or anaerobic exercise best? Emerging studies showing the cognitive benefit of resistance training in the elderly could provide a paradigm shift in the way physical activity is prescribed to preserve mental health\[^{164-166}\]. Testosterone promotes synaptogenesis in the CA1 subregion; does testosterone support synaptogenesis in neurons generated in the aging dentate gyrus?\[^{81, 167}\]. Menopause-mediated oestrogen withdrawal is posited to play a role in cognitive decline and depressive symptoms in women that manifest early than in males\[^{168}\]. Because menopause is a far more precipitous event compared to the gradual decline in male androgen production, aging men retain higher levels of 17β-estradiol through peripheral aromatisation\[^{168-169}\]. What role in maintaining hippocampal neurogenesis and function in aging men does testosterone aromatisation into 17β-estradiol play? The hippocampus expresses receptors for LH and gonadotropin-releasing hormone (GnRH) and their role, directly or indirectly through promoting local steriodogenesis, in age-related decline is uncertain\[^{5, 124, 170-171}\].

Studies examining these questions will address the paucity in knowledge regarding the areas of impaired mental health to which low testosterone predisposes and also elucidate ongoing debate surrounding the clinical relevance of adult hippocampal neurogenesis\[^{172}\]. New clinical and basic research endeavours that encompass measures of hippocampal-dependent spatial memory, pattern separation and depression in conjunction with serum measures of HPT axis hormones will shed further light on physiological roles of testosterone in maintaining mental health in aging men.

Acknowledgments: The author would like to gratefully acknowledge the assistance of Professor Malcolm Horne and Dr Wah Chin Boon, both of the Florey Neurosciences Institutes and Emeritus Professor John P Coghlan of the University of Melbourne for their advice on preparing this manuscript.

Funding: This study was supported by a National Health and Medical Research Council (Australia) postdoctoral fellowship. 

Author contributions: Mark I Ransome conceived, drafted and wrote the final version including figure preparation entirely.

Conflicts of interest: None declared.

REFERENCES


[40] Igles C, Sengelaub DR. Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. Horm Behav. 1998;34:183-198.


[45] Frick KM. Estrogens and age-related memory decline in rodents: what have we learned and where do we go from here? Horm Behav. 2009;55:2-23.


