

**GONADAL STEROIDS AND COGNITIVE
FUNCTIONING IN MIDDLE-TO-OLDER AGED
MALES**

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TABLE OF CONTENTS

Acknowledgements	iii
Statement of Originality and Authenticity	iv
List of Tables	v
List of Figures	vii
Key to Abbreviations	viii
Papers arising from this Thesis	xi
Summary	xii
Preamble	xiv
1. Gonadal Steroids and Visuo-Spatial Ability in Males	1
1.1. Summary	1
1.2. Sex differences in cognition	1
1.3. Gonadal steroids and visuo-spatial cognition	5
1.3.1. Organisational effects	5
1.3.2. Activational effects	10
1.4. Testosterone and mental rotation ability in ageing males	20
1.4.1. Research aim	21
1.4.2. Specific hypotheses	21
2. Gonadal Steroids and Cognitive Functioning in Ageing Males	23
2.1. Summary	23
2.2. Endogenous testosterone levels and cognitive functioning in ageing males	23
2.3. Ageing and cognition	24
2.4. Processing speed and endogenous testosterone levels in men	25
2.5. Pre-frontal decline and endogenous testosterone levels in men	29
2.6. Are the processing speed and pre-frontal decline theories complementary accounts of cognitive ageing?	32
2.7. Study rationale	33
2.8. Research aim	34
2.9. General hypothesis	34
2.10. Specific hypotheses	35
2.11. Significance of project	35
2.12. Studies detailed in this thesis	36
2. Testosterone and Cognitive Function in Middle-to-Older Aged Men: Data from the Florey Adelaide Male Ageing Study (FAMAS)	37
3.1. Summary	37
3.2. Introduction	38

3.3. Method	39
3.4. Results	47
3.5. Discussion	55
4. Common Methodologies	60
4.1. Summary	60
4.2. Introduction	60
4.3. Participants and selection criteria	60
4.4. Materials and apparatus	61
4.5. Study procedure	69
5. Endogenous Testosterone Levels, Mental Rotation Performance, and Constituent Abilities in Middle-to-Older Aged Men	71
5.1. Summary	71
5.2. Introduction	72
5.3. Method	76
5.4. Results	78
5.5. Discussion	86
6. Free Testosterone, Attentional Control, and Processing Speed Performance in Middle-to-Older Aged Men	92
6.1. Summary	92
6.2. Introduction	93
6.3. Method	96
6.4. Results	98
6.5. Discussion	106
7. General Discussion	112
7.1. Gonadal steroid level and cognitive functioning in middle-to-older aged men	112
7.2. Free testosterone levels and generalised age-related cognitive decline in men	113
7.3. Potential mechanism by which free testosterone levels may moderate cognitive function in men	115
7.4. Study limitations	119
7.5. Conclusions	122
References	123

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STATEMENT OF ORIGINALITY AND AUTHENTICITY

I declare that this thesis contains no material that has been accepted for the award of any other degree or diploma in any university or tertiary institution and to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made.

I give consent to this copy of my thesis, when deposited in the University of Adelaide, being available for loan and photocopying if accepted for the award of the degree.

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LIST OF TABLES

Table 1.	Summary of the effects of T supplementation of tests of visuo-spatial ability in older adult males	22
Table 2.	Summary of the effects of endogenous T levels on processing speed in older adult males	29
Table 3.	Descriptive data of study variables ($N = 1046$)	49
Table 4.	The effects of age on hormone levels ($N = 1046$)	50
Table 5.	Unstandardised regression coefficients (b) and p values for the effects of both hormones and age on cognitive functioning ($N = 1046$)	51
Table 6.	Partial correlation coefficients and significance levels from the regression analyses for the effects of T and age on FOME performance ($N = 1046$)	53
Table 7.	Age group differences in descriptive data	79
Table 8.	Age group differences in cognitive measures controlling for Information Scores	80
Table 9.	Partial Pearson correlation coefficients between Vandenberg and Kuse mental rotation performance, age, cEFT, TT, and composite cognitive performance measures controlling for Information scores for men aged over 50 years ($N = 65$)	83
Table 10.	Predictors of Vandenberg and Kuse mental rotation test performance ($N = 94$)	85
Table 11.	Age group effects on demographic, hormone, and cognitive measures ..	99
Table 12.	Age group effects on Ex-Guassian parameters	100
Table 13.	The effect of cEFT tertiles on Ex-Guassian parameters	102
Table 14.	Ex-Guassian parameters as predictors of cognitive functioning	103

Table 15. Correlations between age, cEFT levels, Ex-Gaussian parameters, and cognitive function measures	105
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LIST OF FIGURES

Figure 1. Represents the effects of log transformed quintiles of T levels on Trails A from the Trail Making Test	52
Figure 2. Represents the quadratic moderation effect of log transformed quintiles of cEFT levels and age on Total Recall from the Fuld Object Memory Examination (FOME)	54
Figure 3. The relationship between tertiles of cEFT levels and (A) Processing Speed, (B) Executive Function, and (C) Perceptual Discrimination in men aged 50-70 years ($N = 65$)	82
Figure 4. Path diagrams. (A) Hypothesised Model 1. (B) The final reduced Model 2.	86
Figure 5. Mean Ex-Gaussian parameter estimates derived from the different reaction time tasks	101
Figure 6. Model of the associations between age, cEFT levels, tau, and processing speed performance ($N = 95$)	106

KEY TO ABBREVIATIONS

AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
BDI	Beck Depression Index
BIMC	Blessed Information Memory Concentration test
BT	Bioavailable testosterone
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
cEFT	Calculated free testosterone levels
COMT	Catechol <i>O</i> -methyltransferase
CRT	Choice reaction time
DHEA-S	Dehydroepiandrosterone sulphate
DHT	Dihydrotestosterone
DLPFC	Dorsolateral pre-frontal cortex
DT	Decision time
E2	Estradiol
FAMAS	Florey Adelaide Male Ageing Study
FOME	Fuld Object Memory Evaluation
FSH	Follicle stimulating hormone
FT	Free testosterone
FTI	Free testosterone index
fMRI	Functional magnetic resonance imaging

Gc	Crystallised intelligence
GFI	Goodness of fit index
Gs	General processing speed
HPG	Hypothalamic-pituitary-gonadal axis
IHH	Idiopathic hypogonadotrophic hypogonadism
ISD	Intra-individual reaction time standard deviation
IT	Inspection time
LH	Luteinising hormone
MRT	Mental rotation test
MWT	Morris Water Task
MT	Movement time
PD	Parkinson's disease
PET	Positron emission tomography
OMO	Odd-Man-Out test
PFC	Prefrontal cortex
PMA	Primary Mental Abilities
rCBF	Regional cerebral blood flow
RT	Reaction time
SALT	Spatial Array Learning Tests
SART	Sustained Attention to Response Test
SD	Standard deviation
SEM	Structural equation modelling
SHBG	Sex hormone binding globulin
SOA	Stimulus onset asynchrony
SOPT	Self ordered pointing task

SRT	Simple reaction time
T	Testosterone
TT	Total testosterone
VE	Virtual environment
VMWT	Virtual Morris Water Task
Vsp	Visualisation speed
WM	Working memory
WMH	White matter hyperintensities
WPR	Worse performance rule

PAPERS ARISING FROM THIS THESIS

Martin, D. M., Wittert, G., & Burns, N. R. (2007). Gonadal steroids and visuo-spatial abilities in adult males: implications for generalized age-related cognitive decline. *Aging Male, 10*, 17-29.

Martin, D. M., Wittert, G., Burns, N. R., Haren, M. T., & Sugarman, R. (2007). Testosterone and cognitive function in ageing men: data from the Florey Adelaide Male Ageing Study (FAMAS). *Maturitas, 57*, 182-194.

Martin, D. M., Wittert, G., Burns, N. R., & McPherson, J. (2008). Endogenous testosterone levels, mental rotation performance, and constituent abilities in middle-to-older aged men. *Hormones and Behavior, 53*, 431-441.

Martin, D. M., Burns, N. R., & Wittert, G. (submitted). Free testosterone, attentional control, and processing speed performance in ageing men.

GONADAL STEROIDS AND COGNITIVE FUNCTIONING IN MIDDLE-TO- OLDER AGED MALES

Summary

The basis for sex differences in cognitive ability remains poorly defined and controversial both scientifically and politically. One of the biological hypotheses on sex differences, of particular relevance to this thesis, concerns the role of gonadal steroids, specifically testosterone (T) and oestrogen, and their relationship to individual differences in the performance of specific cognitive tasks. In addition, the role that age-related changes in these hormones play in relation to generalised and pathological cognitive ageing in males is studied. It is important to determine whether decreases in T levels that occur with ageing in males are associated with age-related decreases in cognitive performance because T levels can potentially be modified.

Males have consistently been found to outperform females on measures of visuo-spatial function; performance on the Vandenberg and Kuse Mental Rotation Test (MRT) shows the largest and most robust of sex differences. Gonadal steroids have both organisational and activational effects which contribute to both within-sex variability and between-sex differences in visuo-spatial cognition. As males age, endogenous plasma T levels decline gradually yet variably between individuals. Studies in older males show improvement in visuo-spatial cognition following T supplementation; however, it remains to be resolved whether decreases in endogenous T levels with ageing are associated with poorer MRT performance.

Some recent studies in older males have reported positive correlations between measures of plasma T levels and cognitive functioning, including processing speed and executive function measures. These data are inconsistent,

however, and important questions remain concerning, for example: the age at which the effect is strongest; whether there are different effects at different ages; whether there is an optimal level at which T levels affect particular abilities; and which abilities show the strongest association with endogenous plasma T levels.

Increased intra-individual variability in performance on Choice Reaction Time (RT) tasks has recently been shown to be a strong predictor of cognitive functioning in university students. Methodological advances in the analyses of RT distributions has allowed for the calculation of robust estimates of intra-individual RT variability. The association between these estimates and cognitive performance in middle and older aged males, however, remains to be determined. Further, the association between endogenous plasma T levels and intra-individual RT variability in aged males is unknown.

The thesis addresses these issues; firstly, through cross-sectional analyses of the associations between different measures of plasma T levels, learning and memory, processing speed, and executive function performance in a large population based sample of 1046 men aged between 35 and 81 years. Secondly, further cross-sectional analyses are reported from a subsequent study in a healthy sub-sample of 96 of these men on the associations between endogenous plasma T levels, MRT performance, constituent abilities related to MRT performance, and performance on composite measures of both processing speed and executive function. In a third study, these data are re-analysed in relation to intra-individual variability in RT performance.

In light of the results of these studies, the role that age-related declines in plasma T levels play in relation to generalised age-related cognitive decline in males is discussed.

PREAMBLE

The purpose of the research detailed in this thesis was to address two primary aims; firstly, to investigate the association between gonadal steroid levels and visuo-spatial ability in adult males; and secondly, to determine whether the changes in gonadal steroid levels that occur with ageing in males were associated with declines in visuo-spatial ability or in ability measures indicative of generalised age-related cognitive decline, or both of them. In order to introduce the research on these two aims, I have provided two introductory chapters reviewing background literature on each aim. In Chapter One, a detailed literature review is provided on the role of gonadal steroids in the male advantage on visuo-spatial ability. Evidence is reviewed for both the organisational and activational effects of gonadal steroids and their contribution to both within-sex variability and between-sex differences in visuo-spatial cognition. Methodological problems associated with this research are outlined and tentative conclusions are drawn. In Chapter Two, I have provided both the background to and a review of recent studies which have supported the suggestion that changes in gonadal steroid levels that occur with ageing in males may be associated with generalised age-related cognitive decline. In this chapter, I have outlined both the changes that occur in gonadal steroid levels as males age and the normal age-related changes in cognitive function. In addition, two dominant theories of cognitive ageing are introduced, namely, processing speed theory, and the theory of prefrontal decline. Recent research in support of the hypothesis that declines in T levels with ageing in males may be associated with generalised age-related cognitive decline is reviewed. Both general and specific hypotheses pertaining to the two primary aims of this thesis are then presented, followed by a brief outline of the research studies constituting this thesis.