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Neuropsychologia 39 (2001) 1385–1394

NEUROPSYCHOLOGIA

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Activational effects of testosterone on cognitive function in men☆

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Received 24 August 2000; received in revised form 6 April 2001; accepted 11 April 2001

Abstract

Objectives: The effect of testosterone (T) on sexual function in men is well established. However, less is known about its effects on cognitive function. The aim of this study is to investigate the relationship between T levels and sex-typed cognitive abilities in both eugonadal and hypogonadal men. *Design:* A single-blind placebo-controlled design was employed in this study. *Methods:* Thirty healthy eugonadal men and seven hypogonadal men participated in the study. Eugonadal men were randomised into one of two treatment regimens: (1) active group – receiving 200 mg of T enanthate i.m. weekly for 8 weeks (raising T levels into the supraphysiological range) or (2) placebo group – receiving 200 mg of sodium chloride i.m. weekly for 8 weeks. The hypogonadal group received the physiological replacement dose of 200 mg T enanthate i.m. bi-weekly for 8 weeks. All groups underwent a battery of neuropsychological tests and had circulating T measured at baseline, and at weeks 4 and 8 during treatment. *Results:* A significant time by group interaction effect was found in the measure of spatial ability (i.e., block design test) indicating that the active group's performance declined significantly at week 4, compared to placebo group ($F(4,64) = 3.78$, $P < 0.01$). Conversely, the active group performed significantly better than the placebo group in the measure of verbal fluency (i.e., the Controlled Oral Word Association Test) at week 4 ($F(4,64) = 2.54$, $P < 0.05$). No significant changes were found on any of the other tests. Generally, the hypogonadal group performed less well than the eugonadal groups on all tests. *Conclusions:* These results offer support to the notion that increased T has a differential effect on cognitive function, inhibiting spatial abilities while improving verbal fluency in eugonadal men.

Keywords: Activational; Spatial ability; Verbal fluency; Estradiol; Hypogonadal; Eugonadal

1. Introduction

In humans, established gender differences exist in cognitive functioning with men generally outperforming women on visuospatial tasks and women outperforming men on verbal fluency and perceptual speed tasks [14,17,22]. Several biologically plausible mechanisms have been proposed. It has been suggested that endogenous sex hormones affect cognitive functioning through their pre- and perinatal organisational effects on sexually dimorphic brain structures [9,10,29]. However, the activational effects of sex hormones on cognitive function in men have also received considerable attention [1,4,12,18,19,21,36,38]. These studies have yielded inconsistent results. Some findings suggest a linear relationship between testosterone (T) and aspects of cognitive function, in particular visuospatial ability [6,7] whereas others suggest a non-linear, inverted U relationship [12,18,27,35]. Others have not found any association between sex hormones and cognitive function [19,25]. Given these inconsistent data, it is important for researchers to establish whether T has an activational influence on spatial behaviour and if so, what is the exact form of this relationship, in this way further providing evidence that variation in cognitive performance is underpinned by inter-individual differences in reproductive hormones.

Most previous studies have been correlational in nature, with the following exceptions [1,18,36,38,41]. VanGoozen et al. [38] found a significant increase in

☆ This work was supported by the World Health Organisation (program no. 96374 to Wu and Archer).

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0028-3932/01/$ - see front matter
PII: S0028-3932(01)00067-7

visuospatial ability after androgen treatment in female-to-male trans-sexuals accompanied by a deteriorating effect on verbal fluency. Slabbekoorn et al. [36] replicated this finding in another sample of female-to-male trans-sexuals, although improved spatial ability was not accompanied by reduced verbal fluency. These findings are also consistent with data investigating the effects of exogenous T in older men [18], in which improved performance in spatial ability was found following T replacement. More recently, a study found that a single injection of T blocks the practice effect in verbal fluency in elderly men after 5 days, but has no effect on spatial or verbal memory [41]. In contrast, Alexander et al. [1] found that T levels were unrelated to visuospatial ability in eugonadal men receiving exogenous T as part of a contraceptive trial. Overall, the data from these experimental studies suggest that T administration increases visuospatial abilities and decreases verbal abilities in subjects with low androgen levels. To our knowledge, no previous investigation has used a placebo-controlled design to examine the effects of supraphysiological levels of T on cognitive abilities in young men. There is also a dearth of controlled-data in hypogonadal men [1,16,31]. This group is distinct from older men as their androgen-deficiency is generally a consequence of hypogonadotropic hypogonadism (hypogonadal as a result of Kallmann's or pituitary disease) or hypergonadotropic hypogonadism (hypogonadal as a result of Klinefelter's syndrome or orchidectomy). The effect of T replacement on spatial ability requires further investigation in this clinical sample.

The aim of this study is to investigate the dose-response relationship (i.e., positive, linear, curvilinear?) between T levels and sex-typed cognitive abilities in men. An active group receiving supraphysiological levels of T and a hypogonadal group receiving physiological replacement levels of T are compared with a placebo control group. Having reviewed the literature (including both the correlational and experimental studies), the relationship between T and particular cognitive functions is inconsistent and not altogether clear. Therefore, we hypothesise that (1) improved performance on the visuospatial task in the active and hypogonadal groups after T administration would support the existence of a positive linear dose-response relationship with T levels. Enhanced performance in only the hypogonadal group would support a curvilinear relationship, (2) reduced performance on the verbal fluency task in the active and hypogonadal groups would provide evidence of a negative linear dose-response relationship with T levels. Reduced performance in only the hypogonadal group would suggest a curvilinear relationship.

2. Methods

2.1. Subjects

Thirty healthy male volunteers (mean age = 28.2 years; range 19–45 years) and seven hypogonadal male patients (mean age = 31.4 years; range 23–40 years) participated in the study. The eugonadal men were recruited from local radio and newspaper advertisements. All volunteers were interviewed (by the first author) and underwent a screening medical examination. Volunteers were excluded if they were diabetic, hypertensive, hypogonadal, abused alcohol or drugs in the previous 12 months, had a psychiatric history, were depressed, taking medication (including steroids), or failed any of the routine screening blood tests. The hypogonadal patients were recruited from the Department of Endocrinology, Manchester Royal Infirmary and Hope Hospital, Manchester, UK. The hypogonadal group consisted of three men with Kallmann's syndrome, two with Klinefelter's syndrome and two who had a bilateral orchidectomy receiving maintenance T replacement for a mean of 5 years (range 0–14 years). Several studies have identified Klinefelter's syndrome patients as having a generalised learning disability, relating specifically to language and verbal ability: although they display average to above average global IQs, there is a substantial discrepancy with verbal IQ [11,26,34]. Less is known about the psychoeducational profile of Kallmann's syndrome patients. One study found a sample of hypogonadal men including Kallmann's syndrome patients scored significantly higher on a verbal ability task when compared to a subsample of Klinefelter's syndrome patients [1].

2.2. Design

Volunteers who met the admission criteria after medical screening were randomised into two treatment groups ($n = 15$) to receive: (1) 200 mg T enanthate (Cambridge Laboratories, UK), intramuscularly, once weekly for 8 weeks; the active group or (2) 200 mg 0.9% sodium chloride solution, intramuscularly, weekly for 8 weeks; the placebo group. One participant from the active group had to withdraw from the study before week 4 for personal reasons unrelated to the study. A wash-out period of 6–8 weeks was required for the hypogonadal group (to allow endogenous T levels to fall to the low hypogonadal range < 6 nmol/l, the normal range being 10–35 nmol/l) before they were admitted to the study. The hypogonadal group received 200 mg T enanthate, intramuscularly, bi-weekly for 8 weeks. No significant age differences were found between the groups ($F(2,35) = 0.97$, NS). Educational level (i.e., years of education) was recorded for all groups. The active group had a mean of 14.57 years (range 11–19 years) of education, the placebo group had a mean of 14.80 years (range 12–23 years) and the hypogonadal group had 13.43 years (range 11–17 years). No statistically significant difference was found between the groups ($F(2,35) = 0.72$, NS) for educational level. All participants provided written consent. The study was approved by the Central Manchester Research Ethics Committee for Medical Research.

Cognitive testing and blood sampling were performed at baseline (week 0), weeks 4 and 8. All plasma samples were stored at −20°C until assay. T was measured using a time-resolved fluoroimmunoassay (AutoDELFIA™ Testosterone Kit) with an assay sensitivity of 0.4 nmol/l.

2.3. Neurospsychological tests

The Vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was employed to provide a proxy estimate of verbal intellectual functioning [40]. This is a measure of crystallised intelligence, and therefore is not expected to change as a result of T administration. It was administered to ascertain whether the treatment groups differed on a general measure of intelligence.

The block design subtest of the WAIS-R was used as a measure of visuospatial abilities, in particular visual perception and spatial construction. Standardised scoring procedures were used with the raw scores as the dependent variable. A measure of spatial cognition was included as well-established gender differences have been reported demonstrating a relationship between sex hormones and spatial performance (Section 1). In particular, the block design test has previously been found to be sufficiently sensitive to detect effects after administration of exogenous T in a sample of older men [18].

The Grooved Pegboard Test was used to assess fine visuomotor dexterity and speed [37]. This measure was employed because it has been found to demonstrate a reliable female-biased gender difference and therefore might be influenced by T administration [13]. Dominant and non-dominant hands were tested using the standardised procedure. The time required to insert the pegs into the pegboard for each hand (starting with the dominant hand) is the dependent variable. Dominant hand results are only reported here.

The Trail-Making Test parts A and B was administered to measure cognitive flexibility and perceptual motor speed [3]. On this test, the participant is urged to connect numbered dots on a page (part A) and then connect the same number of consecutively numbered and lettered circles alternatively between the two sequences. The time to connect all the dots serves as the measure of performance. This measure was employed as gender differences have been found for measures of perceptual speed, albeit inconsistent differences [9]. Therefore, performance might be influenced by T administration.

Verbal fluency was assessed using the Controlled Oral Word Association Test (COWAT) [5]. There are two parts to this test, word and category fluency. The word fluency test consists of three 60 s word-naming trials using words beginning with the following letters F, A, and S. Volunteers are instructed to exclude proper nouns, numbers and the same word with a different suffix. The category fluency test consists of a 60 s category-naming trial (e.g., animals, fruit and vegetables, parts of a car). The score is the sum of all the correctly produced words in the three 60 s trials and the single 60 s trial. A measure of verbal fluency was administered as this function has previously demonstrated significant female-biased gender differences (Section 1) and therefore might be influenced by T administration.

The Rey Auditory Verbal Learning Test (RAVLT) was administered to measure short- and long-term retention of verbal information [32]. This test consists of five verbal presentations of a 15-word list with immediate recall after each presentation, one presentation of a second 15-word list with immediate recall, and a sixth recall trial. Delayed recall was examined after 30 min. The score used was the sum of the number of words correctly recalled for the five presentations. A measure of memory was included as previous studies have suggested that sex hormone administration may influence aspects of memory in men and women [19,20].

Three forms of the neuropsychological test battery were constructed to facilitate repeated assessments and to reduce learning effects. Three forms of the RAVLT and the COWAT were utilised in a counterbalanced fashion. Specifically, three different word lists are available for the RAVLT to facilitate repeated measures testing (i.e., List A, List B and List C). These were randomly presented to volunteers across testing sessions (baseline, weeks 4 and 8) and by group (active, placebo and hypogonadal) to control for practice and learning effects. Similarly, alternative versions of the COWAT have been developed in order to assist repeated measures testing (i.e., FAS, CFL and PRW). The presentation of these stimuli were also randomised across testing sessions and by group.

2.4. Data analysis

Descriptive statistics were calculated for each of the variables and Pearson's product moment correlation co-efficients were used to investigate the relationship between plasma T levels and cognitive abilities. Two-factor analysis of variance for a mixed design was used to assess performance differences across testing sessions (time factor: baseline, weeks 4 and 8) and between groups (group factor: active, placebo and hypogonadal groups). Multiple comparisons were also made using Bonferroni post hoc tests. All data were analysed using SPSS for Windows Version 9.0.

3. Results

3.1. Testosterone levels

Two-factor ANOVA revealed significant main effects for time ($F(2,66) = 47.58$, $P < 0.01$) and group ($F(2,33) = 35.77$, $P < 0.01$). A significant time by group interaction ($F(4,66) = 15.36$, $P < 0.01$) was also found. Post hoc analyses indicated that exogenous T administration significantly increased T levels from a baseline of 21.7 ± 1.6 to 34.4 ± 1.7 nmol/l at week 4 to 38.4 ± 2.1 nmol/l at week 8 in the active group (Fig. 1). In contrast, T levels of the placebo group did not change from a baseline level of 20.1 ± 1.4 nmol/l (weeks 4 and $8 = 18.9 \pm 1.3$ and 20.0 ± 1.8 nmol/l, respectively). The hypogonadal group responded to T treatment with a significant increase into the normal range from a baseline of 4.1 ± 1.2 to 18.2 ± 1.7 nmol/l at week 4 to 22.6 ± 2.6 nmol/l at week 8.

Results of cognitive function testing for each of the groups are summarised in Table 1.

3.2. Block design test

A significant main effect was found for time ($F(2,64) = 5.95$, $P < 0.01$) consistent with improved performance over testing sessions (i.e., practice effects). No significant main effect was found for group. However, there was a significant time by group interaction ($F(4,64) = 3.78$, $P < 0.01$) due to significantly lower performance in the active group compared to the placebo group at week 4 ($t = 2.23$, $P < 0.05$). This suggests that T treatment may have reduced performance in the block design test (Fig. 2). Performance returned to baseline levels at week 8, indicating an absence of practice effects, clearly evident in the other groups.

3.3. COWAT – word fluency

A statistically significant main effect was found for both time ($F(2,66) = 8.16$, $P < 0.01$) and for group ($F(2,33) = 4.10$, $P < 0.05$). The time by group interaction was on the borderline of significance ($F(4,66) = 2.45$, $P = 0.054$). However, when a participant (from the placebo group) who reported having been tested on verbal fluency several times in the previous 6–10 months was removed (to eliminate exaggerated learning effects) the group by time interaction became statistically significant ($F(4,64) = 2.54$, $P < 0.05$). The main effects for group and time period remained unchanged. Post hoc analyses revealed that by week 4, there was a statistically significant improvement in word fluency performance in the active group compared to that of the placebo group and the hypogonadal group ($F(2,34) = 10.37$, $P < 0.01$). The interaction effect suggests that the improvement in performance by week 4 in the active group was a T treatment effect rather than the result of practice effects (Fig. 3). Performance on this task remained significantly enhanced compared to baseline at week 8 ($t = 3.84$, $P < 0.01$), although not significantly different from the placebo group.

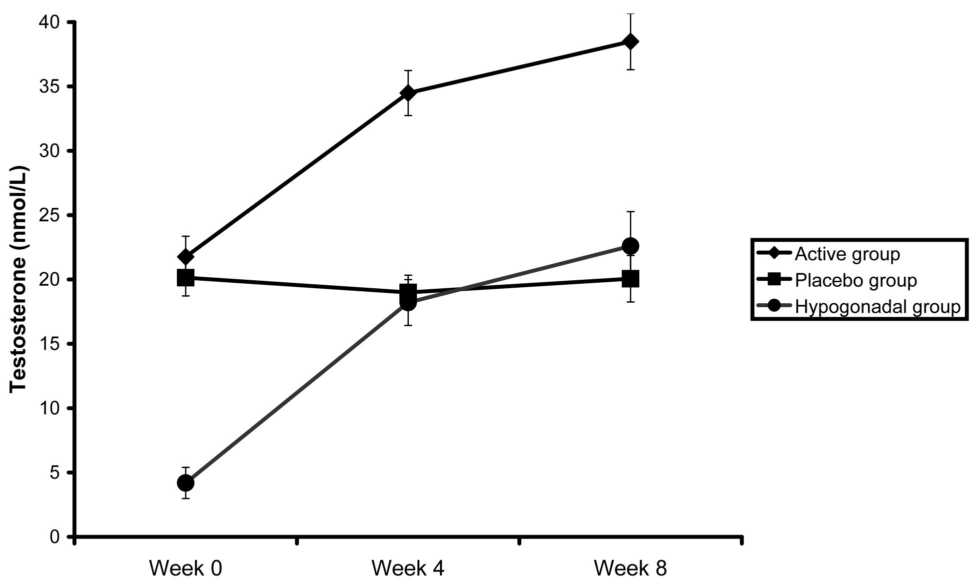


Fig. 1. Testosterone levels in the active, placebo and hypogonadal groups at baseline (week 0), week 4 and week 8.

Table 1
Descriptive statistics for performance on each cognitive function test at weeks 0, 4 and 8[a]

	Week 0	Week 4	Week 8
Block design test			
Active group	39.62 (2.07)	36.00 (2.22)	39.71 (2.70)
Placebo group	40.40 (1.74)	42.13 (1.67)	44.07 (1.41)
Hypogonadal group	33.86 (3.09)	36.71 (2.45)	38.86 (3.42)
COWAT – word fluency			
Active group	39.50 (2.32)	49.5 (2.10)	47.57 (3.35)
Placebo group	36.40 (2.82)	37.67 (2.67)	41.67 (2.38)
Hypogonadal group	32.29 (5.02)	32.29 (4.92)	37.71 (4.10)
COWAT – category fluency			
Active group	20.29 (0.99)	22.36 (1.91)	20.79 (1.46)
Placebo group	21.87 (1.63)	23.33 (1.62)	22.00 (1.60)
Hypogonadal group	19.57 (1.96)	18.00 (0.98)	21.14 (2.64)
Trail-making test – part A[b]			
Active group	27.43 (2.54)	21.29 (1.56)	22.42 (1.89)
Placebo group	26.33 (1.45)	23.66 (1.24)	22.41 (1.37)
Hypogonadal group	36.29 (3.11)	29.00 (3.51)	28.29 (3.56)
Trail-making test – part B[b]			
Active group	57.79 (4.06)	47.93 (3.28)	45.71 (3.98)
Placebo group	58.33 (5.13)	49.87 (3.67)	49.93 (3.70)
Hypogonadal group	69.57 (5.16)	62.57 (4.75)	57.28 (4.89)
Grooved pegboard-dominant[b]			
Active group	45.64 (8.20)	56.71 (5.30)	59.00 (2.00)
Placebo group	58.60 (2.95)	60.13 (1.88)	58.13 (1.57)
Hypogonadal group	63.57 (2.30)	62.71 (2.16)	62.86 (3.21)
Rey auditory verbal learning test			
Active group	52.64 (2.32)	55.29 (2.25)	56.43 (2.53)
Placebo group	56.33 (1.86)	55.73 (1.85)	59.47 (1.43)
Hypogonadal group	47.86 (2.47)	48.57 (3.30)	50.43 (4.37)

[a] Standard error of means are given in parentheses.
[b] Given in s.

3.4. COWAT – category fluency

No significant main effects were found for group or time and there was no significant interaction effect. The lack of a significant main effect for the time period factor suggests that this test is not susceptible to practice effects.

3.5. Trail-making test – part A

A significant main effect was found for time ($F(2,66) = 15.77$, $P < 0.01$) and group ($F(2,33) = 4.19$, $P < 0.05$). Post hoc analyses indicate that the hypogonadal group significantly under performed compared to both the active and placebo groups at all time points ($P < 0.05$).

3.6. Trail-making test – part B

A significant main effect was found for time ($F(2,66) = 13.77$, $P < 0.01$), consistent with practice effects. No other significant effects were found.

3.7. Grooved pegboard – dominant hand

No statistically significant main effects were found for the group or time factors. However, again the hypogonadal group performed least well at all time points ($P < 0.10$).

3.8. Rey auditory verbal learning test

A significant main effect was found for time ($F(2,66) = 3.25$, $P < 0.05$) and group ($F(2,33) = 3.38$, $P < 0.05$). Post hoc analyses revealed that the hypogonadal group performed significantly less well at all time points compared to only the placebo group. Although, the active group also outperformed the hypogonadal group at all time points, this difference failed to reach significance. The absence of an interaction effect suggests that T did not influence performance in the active group.

3.9. WAIS vocabulary subtest

No statistically significant group differences were found on the WAIS vocabulary subtest ($F(2,33) = 2.28$, $P = 0.12$). Although there was a trend for lower scores in the hypogonadal group (mean score (SEM) = 41.00 (4.39)) compared to the active (mean score (SEM) = 48.57 (2.06)) and placebo (mean score (SEM) = 49.85 (2.33)) groups.

3.10. Relationship between testosterone and cognitive abilities

Pearson's product moment correlation coefficients were calculated for measures of T levels and men's scores on the cognitive tasks. Firstly, all groups were entered into the analysis thus providing greater variability in T levels. Secondly, the analysis was re-run excluding the hypogonadal group (Table 2). Three statistically significant correlations emerged from this analysis. T levels were found to be significantly positively correlated with block design scores, the measure of visuospatial ability, ($r = 0.42$, $P < 0.05$) and negatively with both part A and B of the trail-making test ($r = -0.43$, $P < 0.01$, $r = -0.39$, $P < 0.05$, respectively), indicating that higher levels of endogenous T are associated with better performance on both tests. However, when the hypogonadal group was excluded from the analysis T levels were only significantly correlated with block design scores ($r = 0.34$, $P < 0.05$).

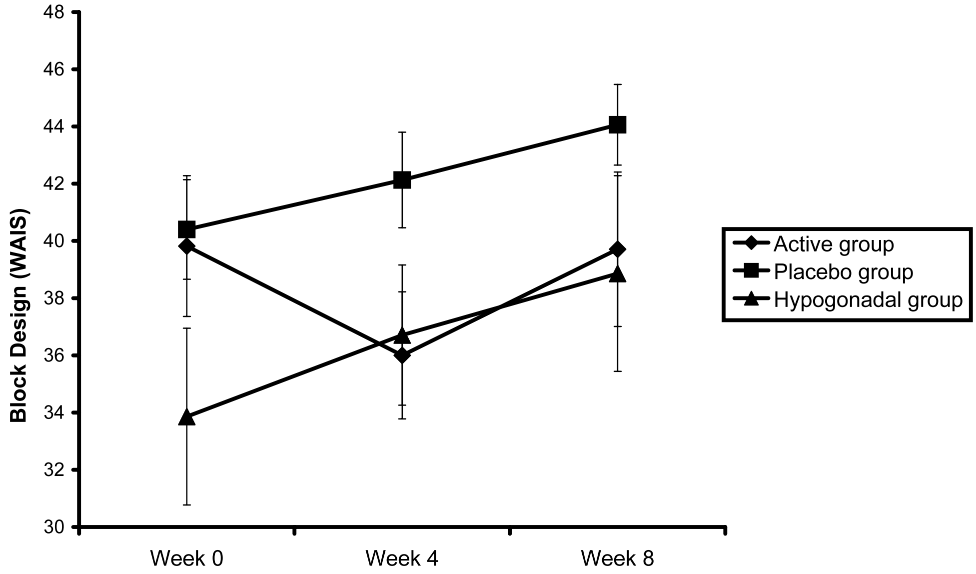


Fig. 2. Wechsler Adult Intelligence Scale–Block Design subtest performance in all groups at baseline (week 0), week 4 and week 8.

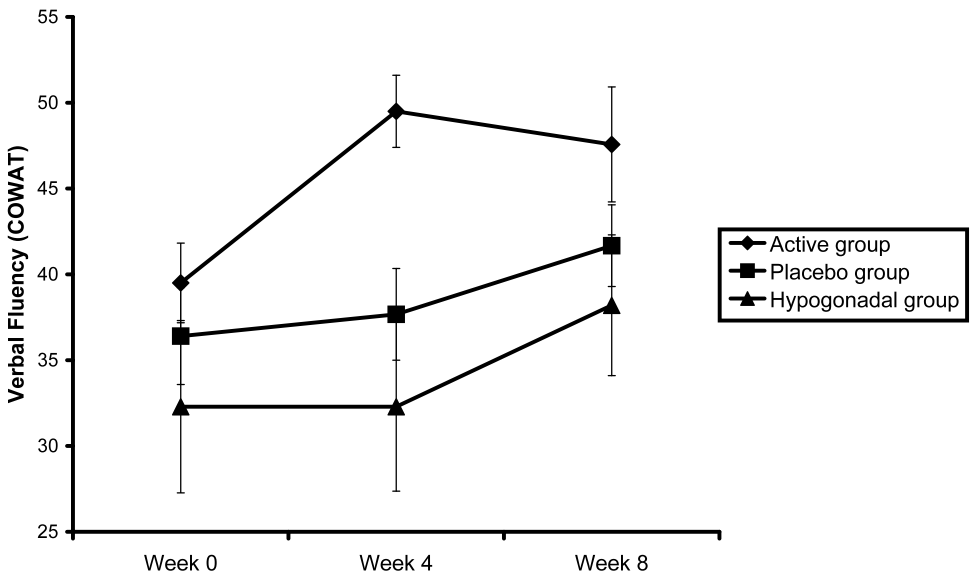


Fig. 3. Controlled Oral Word Association Test–word fluency performance in all groups at baseline (week 0), week 4 and week 8.

Table 2
Correlations between T and cognitive test performance for all groups (All), all groups minus the hypogonadal group (−hypo) and the hypogonadal group (hypo)

Cognitive test	Week 0			Week 4			Week 8		
	All	−Hypo	Hypo	All	−Hypo	Hypo	All	−Hypo	Hypo
Trail-making A	−0.43*	−0.10	−0.43	−0.39*	−0.33	−0.65	0.13	0.23	−0.33
Trail-making B	−0.39*	−0.09	−0.11	−0.23	−0.06	−0.76*	−0.04	0.00	−0.35
Pegboard–dominant hand	−0.34	−0.21	0.03	0.05	0.14	0.05	−0.04	0.08	−0.51
Verbal fluency	0.33	0.09	0.08	0.48*	0.49**	0.13	0.24	0.30	0.16
Category fluency	0.02	−0.16	0.34	−0.17	0.02	0.35	0.12	−0.13	0.13
Block design test	0.42*	0.34*	−0.17	−0.27	−0.45*	0.59	−0.16	−0.28	0.45

* $P<0.05$.

** $P<0.01$; underlined coefficients – trend towards significance.

At week 4, two significant correlations were found when the groups were taken as a whole. T levels were found to be negatively associated with part A of the trail-making test ($r = -0.39$, $P < 0.05$) and positively associated with verbal fluency performance ($r = 0.48$, $P < 0.05$). Also, there was a trend towards significance for the block design test ($r = -0.27$, $P = 0.11$). Again, two significant correlations emerged when the hypogonadal group was excluded. Verbal fluency scores remained significantly correlated with T levels ($r = 0.49$, $P < 0.01$), and scores on the block design test became statistically significant (-0.45, $P < 0.05$). These findings support our multivariate analyses and suggest that as T levels increase, performance on the block design test decreases and performance on the verbal fluency task increases. At week 8, no significant associations were found when the groups were considered together (All) or when the hypogonadal group was excluded (−hypo). Although, in the latter group both the coefficients for verbal fluency and the block design test approached significance in the predicted direction (Table 2).

In the hypogonadal group, no significant correlations were found at week 0 between T levels and any of the cognitive tests. At week 4, performance on part B of the trail-making test was found to be negatively correlated with T levels ($r = -0.76$, $P < 0.05$) and there was a trend towards a positive correlation with block design scores ($r = 0.59$, $P = 0.16$). Both results suggest that higher levels of T are associated with better performance on fine visuomotor dexterity and cognitive flexibility. Again, at week 8 no statistically significant correlations emerged from the analysis.

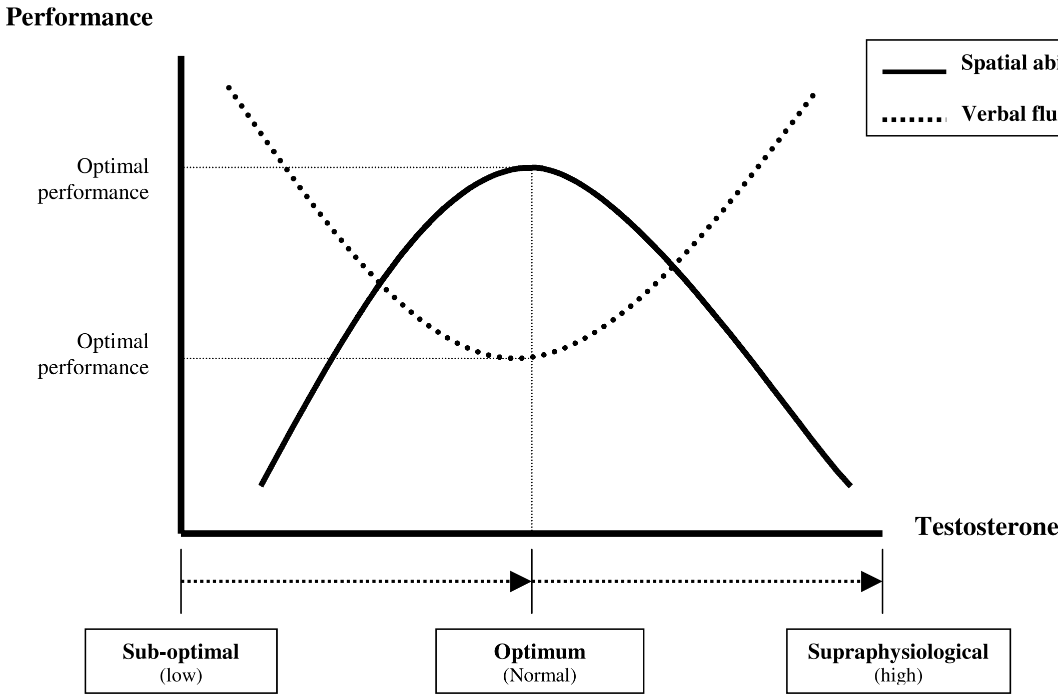
4. Discussion

We found that exogenous T administration lowered spatial ability as assessed by the block design subtest of the WAIS-R whilst it enhanced verbal fluency as assessed by the COWAT in normal men after 4 weeks of treatment. However, this treatment effect was not sustained by week 8 for spatial ability, although scores remained below the expected level. It appears that the supraphysiological levels of T in the active group may have an inhibitory effect on both the performance on the spatial task and prevented practice effects. Reduced spatial performance accompanied by supraphysiological T levels suggests the existence of an optimum level of T and supports the notion of a non-linear, inverted U relationship. This paradoxical result indicates that increasing T levels do not necessarily lead to an amplification of male typed characteristics. These data are consistent with other studies, which propose that high levels of T may be associated with poorer spatial performance [12,23,27]. Gouchie and Kimura [12] found that men with comparatively low levels of T tended to perform better on spatial and mathematical tasks than men with higher levels of T. In fact, in a later study by Moffat and Hampson [27] a significant negative correlation was found ($r = -0.44$) between T levels and visuospatial ability (and evidence for an inverted quadratic relationship) in a sample of normal men. Moreover, Janowsky et al.'s [18] study of elderly men offers support for the lower end of the curvilinear spectrum (i.e., where T levels are considerably below the normal range) in that improvements in visuospatial ability were demonstrated after T levels were restored to the normal range. These findings are also consistent with data reported by Roof and Havens [33] in the rat. They found that after increasing T levels neonatally into the supraphysiological range, the spatial performance of the rat did not increase in a linear fashion. Instead, it may have been impaired.

Our findings are also congruent with those of Van-Goozen et al. [38] who found that T administration exerted a differential effect at the other end of the T spectrum (i.e., low-to-normal physiological range) on sex-typed cognitive abilities in female-to-male trans-sexuals; as one function improved the other deteriorated. In our study (i.e., normal-to-high supraphysiological range), we found an increase in verbal fluency was accompanied by a decrease in visuospatial ability in response to supraphysiological levels of T. VanGoozen et al. found that spatial performance improved and verbal fluency deteriorated after T levels were increased into the physiological range for men. Therefore, the evidence suggests the existence of an optimal hormone level that activates in a curvilinear fashion for different cognitive functions (Fig. 4). Although it was marginally significant, the correlation between the increase in verbal fluency and decrease in visuospatial ability was large in terms of its associated effect size ($r = -0.52$, $P = 0.07$) [8]. This suggests that the cognitive effects of T treatment may be mediated by a common mechanism.

Inspection of the positive correlation between T levels and the block design scores at baseline (Table 2) initially seems not to be consistent with the finding that T treatment interfered with performance on the same test. This can be reconciled in two ways. Firstly, this positive correlation may only reflect one part of the curve [12]. Secondly, by week 4 there is a statistical trend towards a negative relationship ($r = -0.27$), which reaches significance when the hypogonadal men are removed from the analysis ($r = -0.45$, $P < 0.05$). This suggests that supraphysiological levels of T are associated with lower performance on the block design test.

It has been suggested that oestradiol may be the critical hormone, which affects cognitive function, as androgenic steroids are aromatised to oestrogens locally in the brain [18,21,24,30]. Previous studies have shown that circulating oestradiol is significantly increased in proportion to T in normal men receiving T enanthate,



Low-to-normal T levels = improved performance on spatial tasks, reduced on verbal fluency tasks
Normal T levels = optimum performance on both tasks
Normal-to-high T levels = reduced performance on spatial tasks, improved performance on verbal fluency tasks

Fig. 4. Proposed relationship between testosterone levels, spatial ability and verbal fluency.

200 mg IM weekly [2,39]. Fluctuations in cognitive function across the menstrual cycle have also been described [15,21]. Women have been found to score significantly higher on female-favoured tasks (e.g., verbal fluency tasks) whilst lower on male-favoured tasks (e.g., visuospatial tasks) when oestrogen levels are relatively high during the menstrual cycle. Furthermore, Slabbekoorn et al. found that the learning effect on a visuospatial task was overridden by the effects of oestrogen and anti-androgen therapy in a sample of male-to-female trans-sexuals after three months treatment [36]. A recent study presented evidence that T and estradiol are able to modulate spatial cognition during the menstrual cycle [15]. As the focal point of this present study was the effects of T and given our data, we are unable to discount the role of other metabolites of T such as estradiol or dihydrotestosterone in activating the observed changes in performance.

Both the main T treatment effects were not clearly sustained at week 8. Performance on the block design test returned to baseline in the active group while performance on the verbal fluency measure remained significantly greater than baseline, although not significantly different from the placebo group. Two explanations may account for these findings. First, the increasing practice effects associated with repeat testing over a relatively short period of time (i.e., three testing sessions over 8 weeks) may have obscured the actual treatment effects by week 8. Secondly, these differential effects on cognitive function may only be detected following acute rises of T (e.g., week 4), which then fade with time even when the higher levels are maintained. This apparent tolerance to the psychological effects of T is commonly observed in clinical practice when hypogonadal patients are initiated on androgen replacement.

It is of interest that the hypogonadal group performed less well at all time points compared to the eugonadal groups. Over and above practice effects, there was no evidence to indicate improved performance after T replacement. This is contrary to findings reported recently by Alexander et al. who found a significant improvement in a measure of verbal fluency in a group of hypogonadal men (excluding men with Klinefelter's syndrome) after T replacement [1]. It is possible that we did not find any significant treatment effects in our hypogonadal patients because of a relatively short pre-study washout phase and/or a small heterogeneous sample. Slabbekoorn et al. have recently demonstrated that cross-sex hormone treatment effects did not disappear after a 5 weeks wash-out period in a sample of trans-sexuals [36]. However, other data would suggest that the deficit is fixed, and the lack of improvement is the result of the permanent organising effects on the brain of androgens before or at puberty [16]. This study demonstrated that 19 men with idiopathic hypogonadotrophic hypogonadism exhibited impaired spatial ability compared to controls and a small sample of acquired hypogonadotrophic hypogonadal men. Androgen-replacement in six of these men failed to exert any significant improvement in their spatial ability.

Nonetheless, our finding that hypogonadal patients may have persistent cognitive deficits beyond impaired visuospatial ability is an important observation, which should be further investigated. Klinefelter's syndrome patients have previously been found to have impaired verbal ability and other learning disabilities [11,26,28,34], however, little is known about cognitive effects of other forms hypogonadism.

Several shortcomings of this present study require further comment. The number of volunteers recruited to the study was relatively small (particularly, in the hypogonadal group). This may have implications for the representativeness and generalisability of the results to both clinical and normal samples and should be borne in mind when extrapolating these data. Further to this, some of the cognitive measures may have been poorly chosen and insufficiently sensitive to detect other real effects. This study only employed one measure of spatial ability, the block design test. This may be problematic as it makes comparisons with other studies very difficult and may actually tap a different type of spatial ability to that investigated in some other studies. Therefore, future research should endeavour to employ larger samples, utilise a range of cognitive function measures (to assess different aspects of spatial ability) in a double-blind placebo-controlled, crossover fashion.

In conclusion, we have shown for the first time that supraphysiological levels of T can have differential effects on cognitive function causing a reduction in visuospatial ability and an improvement in verbal fluency performance in eugonadal men. T treatment therefore does not improve cognitive functions universally and indeed may lead to deterioration in some aspects. Our data also suggest that T influences cognitive functions in men in a curvilinear fashion. Hypogonadal men on maintenance therapies appear to have significant cognitive deficits.

Acknowledgements

We are grateful to the World Health Organisation (program no. 96374) for funding this study; to Dr Helen Buckler and Sister Marie Vickers (Hope Hospital, Manchester, UK) for assisting recruitment of hypogonadal patients; and to the Radioimmunoassay Laboratory personnel (Central Manchester Healthcare NHS Trust, UK) for T measurement. We would like to thank the anonymous reviewers for their helpful comments on an earlier draft of this paper.

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