Cognitive effects of testosterone and finasteride administration in older hypogonadal men

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Abstract: Serum concentrations of neuroactive androgens decline in older men and, in some studies, low testosterone is associated with decreased cognitive function and incidence of depression. Existing studies evaluating the effect of testosterone administration on cognition in older men have been largely inconclusive, with some studies reporting minor to moderate cognitive benefit, while others indicate no cognitive effect. Our objective was to assess the cognitive effects of treating older hypogonadal men for 1 year with a supraphysiological dose of testosterone, either alone or in combination with finasteride (a type II 5α-reductase inhibitor), in order to determine whether testosterone produces cognitive benefit and whether suppressed dihydrotestosterone influences cognition. Sixty men aged ≥60 years with a serum testosterone concentration of ≤300 ng/dL or bioavailable testosterone ≤70 ng/dL and no evidence of cognitive impairment received testosteroneenanthate (125 mg/week) versus vehicle, paired with finasteride (5 mg/day) versus placebo using a 2×2 factorial design. Testosterone caused a small decrease in depressive symptoms as assessed by the Geriatric Depression Scale and a moderate increase in visuospatial memory as assessed by performance on a recall trial of the Rey-Osterrieth Complex Figure Test. Finasteride caused a small increase in performance on the Benton Judgment of Line Orientation test. In total, major improvements in cognition were not observed either with testosterone or finasteride. Further studies are warranted to determine if testosterone replacement may improve cognition in other domains. **Keywords:** cognition, depression, 5 alpha reductase, testosterone enanthate

Introduction

Loss of testosterone in older men is associated with a substantial long-term impairment in visual and verbal memory, visuospatial functioning, visuomotor scanning, and visual memory, and with increased incidence and earlier onset of depression. These findings are supported by rodent studies in which orchiectomy has been shown to impair spatial memory in Y-maze testing³ and Morris water maze testing,⁴ with testosterone administration preserving memory. Despite this evidence, a recent clinical study indicates that short-term (6 weeks) androgen deprivation does not significantly impair cognition (assessed in a variety of domains) in men.5

Existing studies of testosterone administration in older men are typically 1 year or less in duration and have demonstrated only moderate improvements in visuospatial cognition, but not in other domains such as verbal cognition or mood. For example, Janowsky et al treated older eugonadal men for 3 months with testosterone by transdermal patch (15 mg/day). Testosterone improved performance on the block design subtest of the Wechsler Adult Intelligence Scale (WAIS) – Revised, but did not improve performance on other cognitive tests. The latter included vocabulary subtest of the WAIS, California Verbal Learning Test, Profile of Mood States, Trail Making Tests A and B, and Grooved Pegboard Test.⁶ Gray et al⁷ administered graded doses of testosterone (25 to 600 mg/ week) to older men and observed that testosterone did not alter mood (measured by

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the Hamilton Depression Inventory and Young Mania Rating Scale) and produced a marginal improvement in visuospatial cognition (computer-based checkerboard test). Cherrier et al⁸ treated older men with testosterone (100 mg/week, intramuscularly [IM]) for 6 weeks and observed improved spatial memory (route test) and constructional abilities (WAIS block design subtest) and increased route test and word list recall. In contrast, Vaughan et al administered testosterone (200 mg biweekly, IM) and failed to demonstrate improvement in visuospatial function or visual memory using the Benton Judgment of Line Orientation test and Benton Visual Retention test, respectively. As such, some inconsistency exists in the literature regarding the effects of testosterone administration on cognitive function in older men.

Our objective was to determine whether treatment of older hypogonadal men with a supraphysiological dose of testosterone for 1 year reduces depressive symptoms, improves wellbeing, and improves visuospatial cognition, and whether co-treatment with finasteride influences these results. We have recently shown that treatment with testosterone plus finasteride provides musculoskeletal and lipolytic benefits without prostate enlargement, ¹¹ providing sound rationale for this combination pharmacologic therapy. A second objective was to determine whether finasteride has any effects on cognition.

Methods

Study design and subject selection

Qualifying participants were men aged 60 years or more who had a total serum testosterone level of ≤300 ng/dL or a bioavailable testosterone (BioT) level of ≤70 ng/dL. Participants were randomized to one of four treatment groups – vehicle– placebo, testosterone-enanthate (TE)-placebo, vehiclefinasteride, or TE-finasteride – using a 2×2 factorial design. A total of 60 subjects were randomized, 16 to vehicle plus placebo, 13 to vehicle plus finasteride, 14 to TE plus placebo, and 17 to TE plus finasteride. Treatment lasted 12 months and consisted of Proscar® (Merck & Co., Inc., Whitehouse Station, NJ, USA) (5 mg/day finasteride, per oral) versus placebo, and Delatestryl® (Novartis International AG, Basel, Switzerland) (125 mg/week TE, IM) versus vehicle. Proscar® and matching placebo were donated by Merck & Co., Inc. Delatestryl® was donated by Novartis International AG and matching vehicle was prepared by WestLab Pharmacy, Gainesville, FL, USA. Participants were not paid for participation other than receiving reimbursement for travel mileage.

This study was approved by the Institutional Review Board of the University of Florida. All participants gave written informed consent. Potential participants underwent screening to determine eligibility, including structured medical history, blood acquisition (performed twice between 8 am and 10 am, separated by at least 30 minutes), and a physical exam, as previously reported. Two blood samples were obtained during screening because the Endocrine Society recommends repeated measurements to confirm low testosterone prior to initiating testosterone treatment.

We excluded individuals who failed the Mini-Cog test¹³ to ensure that participants did not present with dementia and that they could fully understood the study protocol. We also excluded: those with a history of prostate or breast cancer, severe benign prostatic hypertrophy, American Urological Society/International Prostate Symptom Score (AUA/IPSS) score \geq 25, class 3 or 4 congestive heart failure, sleep apnea, hematocrit >49%, prostate specific antigen \geq 2.6 ng/mL, body mass index >35, or orthopedic limitations (precluding strength testing); or those who had received testosterone within 4 weeks, finasteride/dutasteride within 6 months, or who were taking Coumadin® (a contraindication for IM injections).

Protection from risks

Participants underwent thorough health screenings every 3 months throughout the study, as previously reported. Participants were removed from the study if the following occurred: hematocrit \geq 54%; serum prostate specific antigen \geq 4.0; increase in AUA/IPSS \geq 4 points; or if gynecomastia or peripheral edema were noted at physical exam.

Hormone assays

Serum samples were obtained 1 week after TE/vehicle injection. Total testosterone was assessed in the Clinical Laboratory, Malcom Randall VA Medical Center by Cobas® (Hoffman-La Roche Ltd., Basel, Switzerland) electrochemiluminescence immunoassay (intra-assay coefficient of variance [CV] =2.9%, inter-assay CV =3.4%). Serum samples were stored at -80°C and analyzed for estradiol (E2) by ELISA (enzyme-linked immunosorbent assay; American Laboratory Products, Salem, NH, USA) (intra-assay CV =7.6%, inter-assay CV =8.8%). BioT and bioavailable estradiol (BioE2) were assessed by ammonium sulfate precipitation of samples spiked with 3H-testosterone or ³H-E2. ¹⁴ Dihydrotestosterone (DHT) was assessed by liquid chromatography – mass spectroscopy – mass spectroscopy at Laboratory Corp of America (Calabasas Hills, CA, USA) (intra-assay CV =8.6%, inter-assay CV =9.9%).

Cognitive testing

Cognitive testing was performed at baseline and after 3, 6, 9, and 12 months of treatment. Life Satisfaction Index

A and B were used to measure multiple components of psychological wellbeing, with a higher score indicating greater wellbeing. The Geriatric Depression Scale (GDS) short form was used to assess depressive symptoms, with a higher score indicating more depressive symptoms. The GDS short form consists of the 15 items from the GDS long form that have the highest correlation with depressive symptoms.

Trail Making Test A (subject draws a line connecting a sequence of numbers in ascending order with a pencil) was

Trail Making Test A (subject draws a line connecting a sequence of numbers in ascending order with a pencil) was used to assess attention. Trail Making Test B (subject draws a line connecting an alternating sequence of numbers and letters in ascending order with a pencil) was used to assess executive functioning.¹⁸ Trail Making Tests are scored as time (seconds) taken to successfully complete the task. Benton Judgment of Line Orientation test Form H was used to assess visuospatial skills, with a higher score indicating better performance.¹⁹ This is a 30-item task in which the subject must match a pair of angled lines appearing on the stimulus drawing to two identically oriented lines (out of eleven choices) drawn below the stimulus. The Rey-Osterrieth Complex Figure Test was used to assess visuospatial constructional functions, visuographic memory, and some aspects of planning.²⁰ The subject was asked to make a copy of a stimulus drawing comprised of a complex design, which was then scored on 18 identifiable details with a maximum score of 36 points possible and a higher score indicating better performance. The subject then drew the figure from memory 5 minutes later, and again 30 minutes later. Drawings were scored by a licensed neuropsychologist (CF).

Musculoskeletal assessment

Muscle strength was assessed as one-repetition maximal strength on a selectorized resistance exercise machine for six upper- and lower-body exercises. Body composition was assessed by dual x-ray absorptiometry using a General Electric Lunar Prodigy fan-beam densitometer (Fairfield, CT, USA). Prostate volume was assessed by transrectal ultrasound sizing using a General Electric LOGICQ P5 scanning system (General Electric, Fairfield, CT, USA).

Statistical model and analysis

The following mixed effects models were used to fit the data with three covariance structures considered – compound symmetry, autoregressive (Equation 1), and unstructured – as shown in the following:

$$\begin{split} y_{ijk} &= \alpha_0 + \alpha_{trt} \ I(I=1) + \alpha_1 \ I(k=3) + \alpha_2 \ I(k=6) + \\ &\alpha_3 \ I(k=9) + \alpha_4 \ I(I=1) \ I(k=3) + \\ &\alpha_5 \ I(I=1) \ I(k=6) + \alpha_6 \ I(I=1) \ I(k=9) + u_{ij} + \epsilon_{ijk} \end{split} \tag{1}$$

$$y_{ijk} = \alpha_0 + \alpha_{trt} I(i=1) + \alpha_1 I(k=3) + \alpha_2 I(k=6) + \alpha_3 I(k=9) + u_{ij} + \epsilon_{ijk}$$
(2)

where y_{iik} is the response (ie, change-depression, etc) of subject j, measured at time point k with respect to the change from the baseline, under treatment I; I(x=value) is the indicator function (ie, 1 if x= value and 0 otherwise); α_{tr} represents the treatment effect; $\alpha_1 - \alpha_2$ represent the time effect; $\alpha_4 - \alpha_6$ represent the interactions between time and treatment effects; u_{ii} is the cluster effect due to subject j under treatment i and is assumed to follow $N(0,\Sigma)$ with Σ being the covariance matrix of 4×4 dimension; and u_{ii} characterizes the correlation for the responses from subject j. Three model selection criteria were used to select the best-fit model among the six candidate models for the data, namely Akaike information criterion, corrected Akaike information criterion, and Bayesian information criterion. ε_{ijk} is the random measurement error following normal distribution. P-values ≤ 0.05 were considered statistically significant. Analyses of results reported are based on the selected best-fit model.

Nontechnical description of statistics

We chose the linear mixed model above for two reasons: first, it has the advantage over the alternative of pre-/post-differences in that it utilizes all the time point data; and second, it is more robust against missing data. As a secondary analysis, for the variable that we found to be significant on the main testosterone effect, we applied the same analysis separately to the two subgroups (one with and one without finasteride) to see if testosterone differences were dependent on finasteride. The study was powered on the primary outcomes of Borst et al¹¹ and not for cognitive end points.

Results

The musculoskeletal findings and hormone concentrations from this study have been published.¹¹ Briefly, testosterone administration increased maximal muscle strength by 8%–14% (on all six exercises), increased bone mineral density by 1.96% in the hip and by 4.19% in the lumbar spine, reduced fat mass by 3.87 kg, and increasing prostate volume by 11.4 cm³. Coadministration of finasteride prevented testosterone-induced prostate enlargement, but did not affect other responses to testosterone. TE elevated nadir testosterone and BioT, representing 1.8-fold and 2.2-fold increases over baseline, respectively. Coadministration of finasteride did not affect those increases. TE elevated E2 and BioE2, representing 1.7-fold and 2.2-fold increases over baseline, respectively. Coadministration of finasteride did not affect those increases. TE elevated serum DHT by 2.4-fold and finasteride lowered DHT by 65%.

Table I Baseline characteristics for participants receiving vehicle-placebo, vehicle-finasteride, TE-placebo, and TE-finasteride

Variable	Vehicle-placebo	Vehicle-finasteride	TE-placebo	TE-finasteride
Age, years	70.8±9.7	69.5±9.2	69.2 <u>+</u> 8.0	64.2±4.8
BMI, kg/m ²	30.4±3.4	28.8±3.9	29.4±4.6	31.1±2.5
Testosterone, ng/dL	264±92	240±110	245±73	242±147
BioT, ng/dL	46±22	41±17	46±17	44±20
E2, pg/mL	12.7±9.5	13.6±7.4	25.8±34.4	26.0±30.2
BioE2, pg/mL	4.7±3.1	4.7±2.1	11.0±17.2	9.8±9.2
DHT, ng/dL	25.2±15.1	18.9±12.7	21.4±6.3	21.9±22.4

Note: Values are means \pm standard deviation.

Abbreviations: BioE2, bioavailable estradiol; BioT, bioavailable testosterone; BMI, body mass index; DHT, dihydrotestosterone; E2, estradiol; TE, testosterone enanthate.

Subject baseline characteristics are shown in Table 1. Treatment effects of testosterone and finasteride are shown in Table 2. TE administration resulted in statistically significant reduction in depressive symptoms on the GDS by 0.74 points on a 15 point scale, with most of the change occurring within the first 3 months of treatment. TE also significantly improved performance on the 30-minute recall trial of the Rey-Osterrieth Complex Figure Test (Rey30) by 2.87 points on a 36 point scale. In order to test the hypothesis that the true population effect size on GDS or Rey30 for testosterone versus placebo is the same whether finasteride is given or not, we applied the same analyses to the two subgroups (ie, with finasteride versus without). P-values of 0.48 and 0.72 were obtained for GDS and Rey30, respectively, indicating that no testosterone and finasteride interaction exists for either end point. Finasteride significantly improved performance in the Benton Judgment of Line Orientation test by 1.89 points on a 30 point scale.

Correlations between serum hormones and cognitive performance at baseline are shown in Table 3. Higher baseline E2 (P=0.039) and BioE2 (P=0.050) were positively associated with wellbeing on the Life Satisfaction Index A test, but not on the Life Satisfaction Index B. Increased age was associated with fewer depressive symptoms on the GDS (P=0.014), and with increased wellbeing as assessed by Life Satisfaction Index A (P=0.006) and B (P=0.047), but with poorer performance on the Trail Making Test A (P<0.001) and Trail Making Test B (P=0.006) tests. The positive effect of TE on depressive symptoms was unchanged when the data were reanalyzed and controlled for age as a covariate.

Discussion

The main findings of this study are that testosterone treatment reduced depressive symptoms and improved visuospatial memory on the Rey30. The presence of finasteride did not inhibit these effects. In addition, finasteride administration produced an unexpected minor increase in visuospatial skill

on the Benton Judgment of Line Orientation test. Higher serum E2 and BioE2 values at baseline were correlated with a greater sense of wellbeing on Life Satisfaction Index A and B. Increased age was associated with improved scores on the GDS and Life Satisfaction Index A and B.

A review by Holland et al shows that existing studies on the effects of testosterone administration on depression in older men have produced mixed results.²¹ Haren et al treated older men for 1 year with an oral dose of testosterone undecanoate that produced only a small increase in serum testosterone and found that treatment did not affect scores on the GDS.²² Vaughan et al treated older men with a supraphysiologic dose of testosterone for 36 months and found that scores on the Beck Depression Scale were unchanged. 10 However, other studies have reported positive effects of testosterone on mood. Pope et al treated older hypogonadal men with refractory depression for 8 weeks with a moderate dose of testosterone and found improvement on the Hamilton Depression Rating Scale.²³ Wang et al treated older hypogonadal men with testosterone gel for 3 months and found that testosterone increased self-assessed positive moods and decreased negative moods.24 Perry et al treated older men with major depression for 6 weeks with a supraphysiological dose of testosterone and found an improvement in Hamilton Depression Rating Scale scores only in men with onset of depression at age ≥45 years.²⁵ Shores et al reported that testosterone gel improved Hamilton Depression Rating Scale scores in hypogonadal men with minor depression.²⁶ We observed that 12 months of testosterone administration produced an improvement in scores on the GDS.

Existing studies on the effects of testosterone on visuospatial cognition have also produced mixed results. Janowsky et al treated older men for 12 weeks with a transdermal dose of testosterone sufficient to raise serum testosterone by 50% and found a significant improvement on the block design subtest of the WAIS. Cherrier et al treated older men with mild cognitive impairment with supraphysiological testosterone

 Table 2 Effects of testosterone and finasteride on cognition

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genority 312-91.3 312-81.4 36-9187 36-9187 orig Test B ^{III} Baseline 310-12.6 30-64.9 437-44.9 1 months 310-12.6 39-64.6 437-44.9 (seconds) 3 months 111.84.3.7 106-75.6 131-24.9 (seconds) 4 months 110.34.18.8 90-64.45 37-64.47 131-24.73 1 months 10 months 30-64.45 37-64.67 131-24.78 132-24.3 20 4 months 11.62.20 12.24.51 13-44.78 13-24.47 20 4 months 13-24.24 97-24.9 13-24.33 11-24.6 13-24.47 20 4 months 13-24.24 11-24.33 11-24.53 13-24.35 14-13.34 3 4 months 19-22.9 15-24.9 15-24.35 13-24.45 13-24.55 4 5 4 months 19-22.9 15-24.5 15-24.5 13-24.5 13-24.5 4 4 4 months 19-22.9 15-24.5 15-24.5	Time (seconds)	3 months	38.5±16.5	33.5±7.08	44.3±27.5	42.1±17.6	to 3.81)	to 2.00)
9 months 10 th 12.6 39 Chi 6.4 9 437449 10 months 29 1±15.8 39 Chi 6.4 9 437449 20 months 11 18.4±18 10 0.6±37.0 3 months 11 33.4±18 10 0.6±37.3 12.2±37.3 4 months 11 33.4±18 10 0.6±37.3 12.2±37.3 5 months 13.8±3.1 10.6±2.3 12.2±37.3 5 months 20 0.6±3.2 22.2±3.3 12.2±37.3 6 months 13.8±3.3 12.2±6.1 12.2±5.1 1 months 13.7±3.33 11.2±6.16 12.2±5.1 1 months 13.7±3.33 11.2±6.16 12.2±5.1 1 months 13.7±3.33 11.2±6.16 13.2±5.1 1 months 19.2±2.49 15.2±3.3 13.2±4.5 1 months 19.2±2.49 15.2±5.0 13.2±5.1 1 months 19.2±2.49 15.2±6.1 15.2±6.1 2 months 19.2±2.49 15.2±6.3 13.2±6.5 3 months 19.2±2.40 15.2±6.3 13.2±6.5 4 months 25.2±4.1 25.2±4.3 26.2±5.5 5 months 25.2±4.1 25.2±5.4 26.2±5.5 6 months 25.2±4.1 25.2±4.3 26.2±5.5 7 months 25.2±4.1 25.2±4.3 26.2±5.5 8 months 25.2±4.1 25.2±4.3 26.2±5.5 9 months 25.2±4.1 25.2±4.3 26.2±5.5 1 months 25.2±4.1 25.2±4.3 26.2±5.5 1 months 26.2±5.0 27.2±5.4 28.2±5.1 1 months 26.2±6.7 27.2±5.4 27.2±5.4 2 months 26.2±6.7 27.2±5.4 27.2±5.4 3 months 26.2±6.7 27.2±5.4 27.2±5.4 4 months 26.2±6.7 27.2±5.4 27.2±5.4 5 months 26.2±6.7 27.2±5.4 27.2±5.4 5 months 27.2±5.4 27.2±5.4 27.2±5.4 6 months 27.2±5.4 27.2±5.4 27.2±5.4 9 months 27.2±5.4 27.2±5.4 27.2±5.4 9 months 26.2±6.7 27.2±5.4 27.2±5.4 9 months 27.2±5.4 27.2±5.4 27.2±5.4 9 months 27.2±5.4 27.2±5.4 27.2±5.6 9 months 27.2±5.4 27.2±5.4 27.2±5.4 9 months 27.2±5.4 27.2±5.4 27.		6 months	32.9±12.3	31.2±8.14	36.9±18.7	39.0±16.6	P=0.78	P=0.29
gazeline 1118453 95±10.3 437459 geconds) Baseline 11184637 1067±61.8 1373±33 geconds) 3 months 1134463 1067±61.8 1373±33 feeconds) 6 months 1134463 1067±61.8 1373±33 1134402 feeconds) 6 months 1134460 86.5455.3 1134418 1134418 20 3 months 126±2.29 12.2±51.5 14.1±3.4 16.6±12.7 20 3 months 12,4±2.7 12,2±5.1 14.1±3.4 14.1±3.4 24 6 months 15,1±2.7 12,2±5.1 14.1±3.4 14.1±3.4 24 8 months 19,6±0.65 15,7±4.3 18,8±4.6 18,8±4.6 3 months 19,6±0.65 17,2±4.3 18,8±4.0 18,8±4.6 18,8±4.6 4 months 19,6±0.65 17,2±4.3 18,8±4.6 18,8±4.6 18,8±4.6 4 months 25,9±1.18 26,9±3.7 26,0±4.5 26,0±4.5 26,0±4.5 50 6 months 27,9±5		9 months	31.0±12.6	29.0±6.49	43.7±44.9	38.5±13.1		
(seconds) Baseline 1113.24183 106.74618 1123.24739 (seconds) 6 months 110.62436 97.64447 137.241478 1 months 110.62436 86.24535 113.4478 2 months 110.62429 13.24273 13.24473 20 Baseline 13.24333 11.24616 13.24432 20 months 13.24333 11.24616 13.24432 20 months 12.4229 12.24516 14.143.54 20 months 19.24249 11.24616 13.244.32 24 months 19.24249 12.24513 19.244.0 24 months 19.24249 15.4440 18.244.0 24 months 19.244 18.244.0 18.244.0 25 months 19.244.9 18.244.0 18.244.0 26 months 25.241.8 26.444.0 18.244.0 25 months 25.241.8 26.444.0 18.244.0 26 months 25.241.8		12 months	29.1±15.8	39.5±10.3	43.7±45.9	40.0±15.4		
(seconds) amonths 1133±18 8 1008±37 0 1318±102.2 (seconds) 6 months 110.6±6.3 97.6±6.4 137±14.78 137±14.78 9 months 10.6±6.43 85.5±35.3 13.3±12.0 16.6±12.7 13.3±12.0 20 83.8±10.0 86.5±35.3 11.3±6.0 12.6±12.9 13.3±13.1 13.4±6.0 12.6±12.7 13.3±16.0 16.6±14.3 13.3±12.0 12.6±12.9 11.3±4.60 12.6±12.7 13.3±12.0 12.6±12.9 12.2±1.1 12.2±1.1 13.3±12.0 12.6±12.7 13.3±12.0 14.1±13.4<	Trail Making Test B ¹⁸	Baseline	111.8±63.7	106.7±61.8	122.3±73.9	122.3±54.5	-25.15 (-52.72	-4.04 (-32.36
femonths 1104±36.3 97 66±46.7 1373±147.8 femonths 9 months 906±45.3 86,±35.3 126±15.7 20 1 months 138±41.0 13±45.6 13±17.0 20 3 months 12,±51.15 11,±54.60 12,±43.2 20 4 months 137±3.3 11,±54.16 13±4.56 20 9 months 15,1±2.71 12,±51.15 13±4.76 24 3 months 19,6±0.65 17,2±4.33 18,±45.6 24 3 months 19,6±0.65 17,2±4.33 19,±3.02 24 3 months 19,6±0.65 17,2±4.33 19,±3.04 30 6 months 19,0±2.91 16,1±5.97 18,±4.40 18,±4.40 30 6 months 25,±1.18 26,±4.64 18,±3.30 19,±3.37 30 6 months 25,±1.18 26,±4.64 26,±4.40 18,±4.40 18,±4.40 30 6 months 25,±1.18 26,±2.66 20,±4.40 26,±4.40 18,±3.30 14,±4.40	Time (seconds)	3 months	113.3±18.8	100.8±37.0	131.8±102.2	120.3±74.9	to 2.42)	to 24.29)
faction Index AI ⁵ Bode433 82,527.3 1264:152.7 faction Index AI ⁵ Baseline 83,834.10 86,535.5 113,347.0 20 3 months 12,642.29 12,245.15 14,143.4 20 3 months 12,422.2 12,245.15 14,143.54 20 6 months 13,122.7 12,245.16 13,445.6 24 6 months 15,122.7 12,245.33 11,245.03 13,145.11 24 3 months 19,022.91 15,745.03 18,447.6 13,445.1 24 3 months 19,022.91 16,444.90 18,447.6 18,447.6 24 3 months 19,022.91 16,444.90 18,244.91 19,444.91 3 months 10,022.91 16,444.90 18,244.91 18,444.91 18,444.91 3 months 25,04.18 26,043.05 20,445.9 20,445.9 18,444.91 3 months 26,043.00 20,444.9 20,444.9 20,444.9 20,444.9 3 months 26,847.71 20,444.9		6 months	110.6±26.3	97.6±46.7	137.2±147.8	106.2±47.8	P=0.08	P=0.78
faction Index A ¹⁵ Baseline 1348451 134460 13441270 20 3 months 1348331 11,2446 12,64432 20 3 months 12,44229 12,24515 14,14354 6 months 14,74292 11,24616 13,54450 13,54450 1 Lannths 15,74292 11,24612 13,4447 13,4447 24 Baseline 19,4249 15,74533 19,14302 24 6 months 19,64291 16,4459 18,3474 12 months 19,242,49 17,24433 19,14302 24 6 months 19,242,49 16,4459 18,3474 12 months 18,342,40 15,544,99 18,343,40 18,4440 12 months 25,040,23 25,044,22 25,644,51 25,443 25,444,40 18,344,66 12 months 25,344,1 25,44,39 25,444,40 18,344,66 24,644,51 25,444,40 18,344,76 25,444,40 18,344,76 25,444,40 18,344,76 25,444,40 18,344,76 25		9 months	90.6±43.5	82.5±27.3	126.6±152.7	107.8±16.4		
faction Index A15 Baseline 138±3.51 11.3±4.60 12.6±4.32 20 6 months 12.6±2.29 12.2±5.15 14.1±3.54 20 6 months 13.7±3.33 11.2±6.16 13.5±4.56 9 months 14.7±2.92 11.5±5.03 13.8±4.56 1 months 15.1±2.71 12.7±6.53 13.8±4.76 24 3 months 19.6±0.29 15.7±5.03 18.8±4.76 24 6 months 19.5±1.41 16.4±4.40 18.3±3.61 1 months 19.5±1.41 16.4±4.40 18.3±3.61 1 months 19.5±1.41 16.4±4.40 18.3±3.71 1 degment Baseline 25.6±1.73 25.6±4.53 25.6±4.51 3 months 25.9±1.18 26.0±3.05 25.6±4.53 26.4±4.64 25.6±4.53 3 months 25.9±1.18 26.0±3.05 25.0±6.73 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 26.4±4.64 </td <td></td> <td>12 months</td> <td>83.8±41.0</td> <td>86.5±35.5</td> <td>113.3±127.0</td> <td>131.0±95.7</td> <td></td> <td></td>		12 months	83.8±41.0	86.5±35.5	113.3±127.0	131.0±95.7		
20 3 months 1.24±1.29 1.24±1.6 1.41±3.54 9 months 1.37±3.33 11.24±1.6 13.54±5.6 9 months 1.47±2.7 11.24±1.6 13.54±5.6 1 months 15.14±2.7 12.74±5.33 13.84±4.7 24 3 months 19.24±4.9 15.74±5.03 13.84±4.7 24 3 months 19.24±4.9 15.74±5.03 19.14±3.02 24 3 months 19.24±4.4 16.44±4.0 18.24±3.0 1 months 19.24±4.4 16.44±4.0 18.24±3.0 1 months 24.24±4.4 16.24±3.0 18.24±3.0 1 months 25.24±0.7 25.24±3.0 25.44±3.0 3 months 25.24±4.4 26.44±4.9 18.24±4.9 3 months 25.24±3.0 25.44±3.0 25.44±5.0 3 months 25.24±4.9 26.44±5.9 26.44±5.9 3 months 25.24±4.9 26.44±5.9 26.44±5.9 1 months 25.24±6.9 26.44±5.9 26.44±5.9 3 months 26.44±5.9 <t< td=""><td>Life Satisfaction Index A¹⁵</td><td>Baseline</td><td>13.8±3.51</td><td>11.3±4.60</td><td>12.6±4.32</td><td>12.0±5.71</td><td>-0.87 (-2.18</td><td>0.18 (-1.15</td></t<>	Life Satisfaction Index A ¹⁵	Baseline	13.8±3.51	11.3±4.60	12.6±4.32	12.0±5.71	-0.87 (-2.18	0.18 (-1.15
femonths 1374333 11.24616 13.54456 pomonths 1474292 11.545.03 13.145.11 fercion Index B1s Baseline 19.242.44 15.445.53 18.447.6 24 months 19.242.94 15.745.03 18.042.90 24 months 19.042.91 16.145.97 18.344.76 24 months 19.042.91 16.145.97 18.343.61 12 months 19.24.44 18.444.0 18.243.30 24 months 18.24.44 18.244.0 18.243.31 30 months 25.941.18 26.043.05 26.044.51 26.044.53 30 months 25.441.97 26.043.05 26.044.54 26.044.53 30 months 25.641.97 26.043.05 26.044.54 26.044.54 30 months 25.641.97 26.043.05 29.245.47 26.044.53 26.044.53 46 months 25.642.91 26.043.05 29.245.47 26.044.53 26.044.53	Max = 20	3 months	12.6±2.29	12.2±5.15	14.1±3.54	12.1±6.01	to 0.44)	to 1.51)
faction Index B15 Pmonths 14.72.92 11.55.03 13.145.11 faction Index B15 Baseline 19.22.49 15.745.03 13.844.76 24 3 months 19.62.24 15.745.03 18.042.90 24 6 months 19.62.24 17.244.33 19.143.02 24 9 months 19.54.141 16.145.97 18.343.61 1 months 19.54.141 16.444.40 18.844.36 1 months 25.04.54 25.843.79 26.44.91 3 months 25.04.18 26.043.05 26.44.91 3 months 25.941.18 26.043.05 26.44.91 4 months 25.941.18 26.043.05 25.044.54 3 months 25.941.18 26.043.05 26.44.54 26.44.51 4 months 25.841.97 26.44.56 26.44.56 26.44.51 3 months 25.841.97 26.44.33 26.44.56 26.44.56 26.44.56 4 months 27.422.11 26.44.33 27.44.49 27.44.49 <td></td> <td>6 months</td> <td>13.7±3.33</td> <td>11.2±6.16</td> <td>13.5±4.56</td> <td>14.4±4.95</td> <td>P=0.20</td> <td>P=0.79</td>		6 months	13.7±3.33	11.2±6.16	13.5±4.56	14.4±4.95	P=0.20	P=0.79
faction Index B1s 12 months 15.1±271 12.7±6.25 13.8±4.76 24 Baseline 19.2±2.49 15.7±5.03 18.0±2.90 24 Baseline 19.2±2.49 16.1±5.97 18.0±2.90 24 months 19.0±2.91 16.1±5.97 18.0±2.02 9 months 19.5±1.44 16.1±5.97 18.2±3.01 12 months 18.3±2.40 15.9±4.98 18.8±3.74 3 months 25.0±0.73 25.0±4.22 25.6±4.91 3 months 25.9±1.18 26.0±3.05 25.0±4.55 3 months 25.9±1.18 26.0±3.05 25.0±4.55 3 months 25.6±1.97 26.1±2.66 24.0±6.52 3 months 25.8±1.91 26.1±2.66 24.0±6.52 3 months 27.9±5.50 29.2±5.47 28.8±5.16 3 months 27.0±8.2 29.0±4.3 29.0±5.4 3 months 15.6±7.34 12.0±3.95 12.3±6.6 4 from memory 3 months 15.8±6.7 12.0±3.95 4 from memory 12.4±5.05		9 months	14.7±2.92	11.5±5.03	13.1±5.11	13.4±4.16		
faction Index B15 Baseline 19,2±2,49 15,7±5,03 18,0±2,90 2.4 6 months 19,6±0,65 17,2±4,33 19,1±3,02 2.4 6 months 19,6±0,65 17,2±4,33 19,1±3,02 9 months 19,5±1,41 16,4±4,40 18,3±2,61 18,3±2,61 12 months 2,45±4,54 2,5,8±3,79 2,6±4,91 2,6±4,91 3 months 2,50±0,73 2,5,8±3,79 2,6±4,91 2,6±4,91 3 months 2,5±1,18 2,6,0±3,05 2,5±4,91 2,6±4,91 3 months 2,5±1,18 2,6,0±3,05 2,6±4,54 2,6±4,91 3 months 2,5±1,18 2,6,0±3,05 2,0±4,54 2,6±4,51 3 months 2,6±1,57 2,0±4,54 2,6±4,57 2,6±4,57 3 months 2,6±1,57 2,0±4,54 2,2±4,18 2,5±4,50 2,0±4,54 4 months 2,0±8,27 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54 2,0±4,54		12 months	15.1±2.71	12.7±6.25	13.8±4.76	12.5±5.40		
24 3 months 19,6±0.65 17,2±4.33 19,1±3.02 9 months 19,0±2.91 16,1±5.97 18,3±3.61 9 months 19,5±1.41 16,4±4.40 18,3±3.61 1 months 18,3±2.40 15,9±4.98 18,8±3.74 1 months 25,0±0.73 25,0±3.79 26,6±4.51 3 months 25,9±1.18 26,0±3.05 25,0±4.54 3 months 25,3±4.1 25,7±3.02 25,0±4.54 3 months 25,3±4.1 25,7±3.02 24,9±6.07 3 months 25,3±4.1 25,7±3.02 24,0±6.52 3 months 25,8±7.91 29,2±5.47 28,0±5.53 3 months 27,0±8.52 29,2±5.47 28,0±6.53 4 months 27,0±8.52 29,0±3.63 29,2±5.16 5 months 27,0±8.52 29,0±3.63 29,2±5.16 1 months 15,6±7.34 15,0±4.34 12,0±5.37 3 months 15,6±7.34 15,0±4.36 12,0±3.86 1 months 16,2±8.17 16,4±4.76 12,0±5.29	Life Satisfaction Index B ¹⁵	Baseline	19.2±2.49	15.7±5.03	18.0±2.90	17.3±5.79	0.33 (-0.85	0.38 (-0.81
6 months 19,0±2.91 16,1±5.97 18,3±3.61 9 months 19,5±1.41 16,4±4.40 18,5±4.30 1 c months 18,3±2.40 15,9±4.98 18,8±3.74 1 c months 25,0±0.73 25,0±4.22 25,6±4.91 3 months 25,5±1.18 26,0±3.05 25,6±4.91 3 months 25,3±4.1 25,0±4.22 25,6±4.91 1 months 25,3±4.1 25,1±3.02 24,6±4.91 3 months 25,2±4.1 25,1±3.02 24,0±6.52 3 months 25,2±1.18 26,1±2.66 24,0±6.52 3 months 27,9±5.50 29,2±5.47 28,0±5.37 3 months 27,9±5.50 29,2±5.47 28,0±5.37 3 months 27,0±8.22 27,5±4.98 27,4±4.99 4 months 15,6±7.34 12,0±4.36 12,4±2.6 4 months 15,6±7.34 15,8±5.6 11,3±6.2 3 months 16,4±4.76 12,4±3.7 12,4±2.9 4 months 16,4±4.76 12,4±3.7 12,4±3.7 4 months	Max = 24	3 months	19.6±0.65	17.2±4.33	19.1±3.02	16.9±4.86	to 1.51)	to 1.56)
9 months 19.5±1,41 16.4±4,40 18.5±3.30 12 months 18.3±2,40 15.9±4,98 18.8±3.74 12 months 24.5±4,54 25.8±3.79 24.6±4,91 Drientation ¹⁰ 3 months 25.0±0,73 25.0±4,22 25.0±4,55 30 6 months 25.5±1,18 26.0±3.05 25.0±4,54 30 9 months 25.5±1,37 26.1±2,66 24.0±6,57 Baseline 27.9±5,50 29.2±4,77 26.1±2,66 24.0±6,57 30 9 months 26.8±7,91 26.1±2,66 24.0±6,57 36 6 months 27.4±2,11 26.0±3,37 29.0±5,37 36 9 months 28.0±6,33 29.0±3,47 29.0±5,37 36 9 months 15.6±7,34 15.8±6,52 12.3±6,53 4from memory 3 months 16.9±8,17 16.4±7,6 12.2±6,53 36 12 months 16.9±8,7 16.4±7,6 16.2±6,7 36 12 months 16.9±8,7 16.2±6,7 16.2±6,7 36		6 months	19.0±2.91	16.1±5.97	18.3±3.61	16.7±6.04	P=0.58	P=0.54
L2 months 18.3±2.40 15.9±4.98 18.8±3.74 udgment Baseline 24.5±4.54 25.8±3.79 24.6±4.91 Prientation** 3 months 25.0±0.73 25.0±4.22 25.6±4.55 30 6 months 25.9±1.18 25.0±4.22 25.6±4.54 30 6 months 25.3±4.1 25.0±3.05 25.0±4.54 Baseline 27.9±5.50 29.2±5.47 24.9±6.07 30 25.6±1.97 26.1±2.66 24.0±6.52 Baseline 27.9±5.79 29.2±5.47 28.8±5.55 36 9 months 27.0±5.79 29.0±5.37 29.0±5.37 36 9 months 27.0±6.33 29.0±3.63 29.2±5.16 10 months 27.0±6.52 27.5±4.98 27.4±4.99 Baseline 13.3±1.24 12.0±3.63 29.0±3.63 36 9 months 15.6±7.34 15.8±5.62 36 12 months 16.2±7.64 12.4±7.6 40 12.4±7.68 16.2±5.73 16.2±5.7 40 12.		9 months	19.5±1.41	16.4±4.40	18.5±4.30	17.3±5.27		
udgment Baseline 24,54,54 25,843.79 24,644.91 Prientation III 3 months 25,040.73 25,044.22 25,644.55 30 6 months 25,344.1 26,043.05 25,644.55 30 9 months 25,344.1 26,743.02 24,946.07 12 months 25,641.97 26,112.66 24,046.52 36 6 months 26,847.91 29,245.47 28,845.55 36 6 months 27,945.20 29,245.47 28,845.55 36 9 months 28,046.33 29,045.37 29,045.37 12 months 27,048.52 27,244.98 27,444.99 Baseline 13,341.24 12,064.395 12,346.26 13 months 16,547.48 12,444.76 12,444.76 12,444.76 36 9 months 16,244.76 12,444.76 12,444.76 12,444.76 12 months 16,444.76 12,444.76 12,444.76 12,444.76 12,444.76 12 months 16,444.76 12,444.76 12,444.76		I2 months	18.3±2.40	15.9±4.98	18.8±3.74	15.6±6.02		
Prientation of the months of the months of months of months of the months of	Benton Judgment	Baseline	24.5±4.54	25.8±3.79	24.6±4.91	24.3±2.90	0.59 (-0.87	1.89 (0.05
30 6 months 25.9±1.18 26.0±3.05 25.0±4.54 9 months 25.3±4.1 25.7±3.02 24.9±6.07 12 months 25.6±1.97 26.1±2.66 24.0±6.52 Baseline 27.9±5.50 29.2±5.47 28.8±5.55 figure 3 months 26.8±7.91 29.0±5.37 28.8±5.55 36 6 months 27.4±2.11 28.0±4.33 28.8±5.16 9 months 28.0±6.93 29.0±3.33 28.5±5.16 12 months 27.0±8.52 27.5±4.98 27.4±4.99 Baseline 13.3±12.4 12.0±3.95 12.3±6.26 from memory 3 months 15.6±7.34 15.8±5.62 11.8±8.07 sinutes 6 months 16.5±7.68 18.4±7.76 12.6±7.29 sionths 16.5±7.68 18.6±6.18 15.6±8.97 Baseline 12.4±5.05 12.8±6.17 16.2±5.75 from memory 3 months 16.2±6.75 14.0±8.95 sise 12.2±6.77 16.2±5.77 16.4±8.77 12 months	of Line Orientation ¹⁹	3 months	25.0±0.73	25.0±4.22	25.6±4.55	25.4±4.35	to 2.04)	to 3.74)
9 months 25.3±4.1 25.7±3.02 24.9±6.07 12 months 25.6±1.97 26.1±2.66 24.0±6.52 Baseline 27.9±5.50 29.2±5.47 28.8±5.55 figure 3 months 26.8±7.91 29.2±5.47 28.8±5.55 3.6 6 months 27.4±2.11 28.0±4.33 28.5±5.16 9 months 28.0±6.93 29.0±3.63 29.0±3.73 12 months 27.0±8.52 27.5±4.98 27.4±4.99 Baseline 13.3±12.4 12.06±3.95 12.3±6.26 from memory 3 months 15.6±7.34 15.8±5.62 11.8±8.07 sinutes 6 months 15.6±7.34 16.4±4.76 12.6±7.29 sinutes 6 months 16.5±7.68 18.6±6.19 15.6±8.97 from memory 3 months 16.5±7.68 16.2±5.75 12.5±5.40 minutes 6 months 15.7±8.01 16.2±5.75 14.0±8.95 36 9 months 15.2±8.07 16.4±8.75 16.4±8.77 12 months 16.2±6.77 16.2±	Max = 30	6 months	25.9±1.18	26.0±3.05	25.0±4.54	25.1±3.98	P=0.43	P=0.05*
12 months 25.6±1,97 26.1±2.66 24.0±6.52 Baseline 27.9±5.50 29.2±5.47 28.8±5.55 figure 3 months 26.8±7.91 29.2±5.47 28.8±5.55 3.6 6 months 27.4±2.11 28.0±4.33 28.5±5.16 9 months 28.0±6.93 29.0±3.63 29.2±3.58 12 months 28.0±6.93 29.0±3.63 29.2±3.58 12 months 12.0±8.72 12.8±6.26 12.3±6.26 from memory 3 months 15.6±7.34 15.8±5.62 11.8±8.07 sinutes 6 months 15.8±8.77 16.4±4.76 12.6±7.29 sinutes 12 months 16.5±7.68 18.6±6.18 15.6±8.97 from memory 3 months 16.4±4.76 12.8±6.12 from memory 3 months 16.4±7.65 16.2±5.75 12.5±5.40 minutes 6 months 15.2±8.07 14.0±8.95 14.0±8.95 36 9 months 15.2±8.07 16.4±8.77 16.4±8.77 16.4±8.77 12 months 1		9 months	25.3±4.1	25.7±3.02	24.9±6.07	23.8±3.69		
figure Baseline 27.9±5.50 29.2±5.47 28.8±5.55 figure 3 months 26.8±7.91 29.3±3.77 29.0±5.37 3.6 6 months 27.4±2.11 28.0±4.33 28.5±5.16 9 months 28.0±6.93 29.0±3.63 29.2±3.58 12 months 28.0±6.93 29.0±3.63 29.2±3.58 12 months 12.0±8.2 27.4±4.99 27.4±4.99 Baseline 15.6±7.34 15.8±5.62 11.8±8.07 sinutes 6 months 15.8±8.77 16.4±4.76 12.6±7.29 sinutes 12 months 16.5±7.68 18.6±6.18 15.6±8.97 from memory 3 months 16.4±4.76 12.8±6.12 12.8±6.12 from memory 3 months 16.2±7.68 16.2±5.75 14.0±8.95 side 9 months 15.2±8.07 14.0±8.95 14.0±8.95 side 9 months 15.2±8.07 16.4±8.77 16.4±8.77 16.4±8.77 side 9 months 15.2±8.77 16.2±5.77 16.4±8.77 16.4±8		I2 months	25.6±1.97	26.1±2.66	24.0±6.52	25.5±3.16		
figure 3 months 2.68±7.91 29.3±3.77 29.0±5.37 3.45 6 months 27.4±2.11 28.0±4.33 29.0±5.37 28.5±5.16 9 months 27.0±8.22 27.5±4.98 27.5±4.99 27.5±4.	Rey0 ²⁰	Baseline	27.9±5.50	29.2±5.47	28.8±5.55	29.3±3.13	-1.11 (-3.53	-0.04 (-2.46
36 6 months 27.4±2.11 28.0±4.33 28.5±5.16 3 9 months 28.0±6.93 29.0±3.63 29.2±3.58 29.2±3.59 29.	Copy figure	3 months	26.8±7.91	29.3±3.77	29.0±5.37	29.6±2.63	to 1.30)	to 2.39)
9 months 28.0±6.93 29.0±3.63 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±3.58 29.2±4.59 29.2±4.59 29.2±4.59 29.2±4.59 29.2±4.59 29.2±4.59 29.2±4.29 <th< td=""><td>Max = 36</td><td>6 months</td><td>27.4±2.11</td><td>28.0±4.33</td><td>28.5±5.16</td><td>30.1±2.20</td><td>P=0.37</td><td>P=0.98</td></th<>	Max = 36	6 months	27.4±2.11	28.0±4.33	28.5±5.16	30.1±2.20	P=0.37	P=0.98
12 months 27.0±8,52 27,5±4,98 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±4,99 27,4±6,26 27,2±6,29 27,2		9 months	28.0±6.93	29.0±3.63	29.2±3.58	23.8±3.69		
Baseline 13.3±12.4 12.06±3.95 12.3±6.26 from memory 3 months 15.6±7.34 15.8±5.62 11.8±8.07 sinutes 6 months 16.9±8.17 16.4±4.76 12.6±7.29 3.6 9 months 15.8±8.67 17.3±3.63 15.8±8.33 12 months 16.5±7.68 18.6±6.18 15.6±8.97 from memory 3 months 16.2±5.75 12.8±6.12 minutes 6 months 15.7±8.21 17.3±5.59 14.0±8.95 36 9 months 15.2±8.67 18.0±5.00 15.5±7.73 12 months 16.8±7.71 19.2±6.57 16.4±8.75		12 months	27.0±8.52	27.5±4.98	27.4±4.99	28.5±3.57		
from memory 3 months 15.647.34 15.845.62 11.848.07 11.848.07 11.848.07 15.647.34 15.845.62 11.848.07 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.647.29 12.648.07 12.645.08 12.645.08 12.645.08 12.645.08 12.645.09 12.64	Rey5 ²⁰	Baseline	13.3±12.4	12.06±3.95	12.3±6.26	12.5±6.74	1.38 (-1.20	1.98 (-0.57
induces 6 months 16.9±8.17 16.4±4.76 12.6±7.29 1.05±7.29 1.05±8.67 15.8±8.67 17.3±3.63 15.8±8.33 15.8±8.67 12.05±7.29 1.05±7.2	Draw from memory	3 months	I 5.6±7.34	15.8±5.62	11.8±8.07	13.2±3.15	to 3.97)	to 4.52)
36 9 months 15.8±8.67 17.3±3.63 15.8±8.33 15.8±8.33 15.8±8.33 15.8±8.33 15.8±8.33 12.8±6.18 12.6±6.97 12.8±6.12 12.8±6	at 5 minutes	6 months	16.9±8.17	16.4±4.76	12.6±7.29	15.1±5.10	P=0.30	P=0.13
12 months 16.5±7.68 18.6±6.18 15.6±8.97 Baseline 12.4±5.05 12.8±3.78 12.8±6.12 from memory 3 months 16.6±7.45 16.2±5.75 12.5±5.40 minutes 6 months 15.7±8.21 17.3±5.59 14.0±8.95 36 9 months 15.2±8.67 18.0±5.00 15.5±7.73 12 months 16.8±7.71 19.2±6.57 16.4±8.75	Max =36	9 months	I 5.8±8.67	17.3±3.63	15.8±8.33	15.0±7.61		
Baseline 12.4±5.05 12.8±3.78 12.8±6.12 from memory 3 months 16.6±7.45 16.2±5.75 12.5±5.40 minutes 6 months 15.7±8.21 17.3±5.59 14.0±8.95 36 9 months 15.2±8.67 18.0±5.00 15.5±7.73 12 months 16.8±7.71 19.2±6.57 16.4±8.75		12 months	16.5±7.68	18.6±6.18	15.6±8.97	I 4.8±5.53		
3 months 16.6±7.45 16.2±5.75 12.5±5.40 (6 months 15.2±8.21 17.3±5.59 14.0±8.95 14.0±8.95 15.2±8.67 18.0±5.00 15.5±7.73 12 months 16.8±7.71 19.2±6.57 16.4±8.75	$Rey30^{20}$	Baseline	12.4±5.05	12.8±3.78	12.8±6.12	13.5±4.91	2.87 (0.70	1.37 (-0.89
6 months 15,7±8,21 17,3±5,59 14,0±8,95 1 9 months 15,2±8,67 18,0±5,00 15,5±7,73 1 12 months 16,8±7,71 19,2±6,57 16,4±8,75	Draw from memory	3 months	16.6±7.45	16.2±5.75	12.5±5.40	12.8±4.96	to 5.04)	to 3.63)
9 months 15.2±8.67 18.0±5.00 15.5±7.73 12 months 16.8±7.71 19.2±6.57 16.4±8.75	at 30 minutes	6 months	15.7±8.21	17.3±5.59	14.0±8.95	16.1±6.12	P=0.01*	P=0.24
16.8+7.71 19.2+6.57 16.4+8.75	Max =36	9 months	15.2±8.67	18.0±5.00	15.5±7.73	15.1±6.81		
		12 months	16.8±7.71	19.2±6.57	16.4±8.75	15.0±7.23		

Notes: Test results are means ± standard deviation. Treatment effects are shown with 95% confidence intervals in parentheses. ∜Statistically significant results, P<0.05.

Abbreviations: Max, maximum score; Rey, baseline Rey-Osterrieth Complex Figure Test; Rey5, 5-minute recall trial of the Rey-Osterrieth Complex Figure Test. Rey5, 5-minute recall trial of the Rey-Osterrieth Complex Figure Test.

Table 3 Baseline correlation analysis

Cognitive or psychological test	Age	Testosterone	BioT	DHT	E2	BioE2
Depression ^{16,17}	-0.31 (P=0.014)*	-0.22 (P=0.090)	-0.23 (P=0.07)	-0.17 (<i>P</i> =0.18)	-0.044 (P=0.74)	-0.068 (P=0.60)
Trail Making Test A ¹⁸	0.45 (P<0.001)*	0.22 (P=0.082)	0.034 (P=0.79)	0.25 (P=0.054)	-0.15 (P=0.25)	-0.17 (P=0.19)
Trail Making Test B ¹⁸	0.35 (P=0.006)*	0.074 (P=0.575)	-0.10 (P=0.41)	0.15 (P=0.24)	-0.09 (P=0.45)	-0.17 (P=0.19)
Life Satisfaction Index A ¹⁵	0.35 (<i>P</i> =0.006)*	0.10 (<i>P</i> =0.432)	0.046 (P=0.73)	0.15 (<i>P</i> =0.24)	0.27 (<i>P</i> =0.039)*	0.26 (<i>P</i> =0.050)*
Life Satisfaction Index B ¹⁵	0.26 (<i>P</i> =0.047)*	0.17 (<i>P</i> =0.186)	0.17 (<i>P</i> =0.18)	0.19 (<i>P</i> =0.13)	0.043 (<i>P</i> =0.75)	0.053 (<i>P</i> =0.69)
Benton Judgment of Line Orientation ¹⁹	-0.17 (<i>P</i> =0.17)	-0.010 (<i>P</i> =0.937)	-0.20 (P=0.12)	-0.03 (<i>P</i> =0.79)	0.16 (<i>P</i> =0.20)	0.16 (<i>P</i> =0.21)
Rey0 ²⁰	-0.011 (<i>P</i> =0.93)	0.11 (P=0.421)	-0.10 (P=0.45)	0.12 (P=0.35)	0.02 (P=0.84)	0.066 (P=0.62)
Rey5 ²⁰	-0.029 (P=0.83)	-0.092 (P=0.501)	-0.17 (P=0.20)	-0.034 (P=0.80)	0.072 (P=0.59)	0.10 (P=0.44)
Rey30 ²⁰	-0.023 (<i>P</i> =0.86)	-0.059 (<i>P</i> =0.668)	-0.25 (P=0.06)	0.010 (<i>P</i> =0.943)	0.001 (P=0.99)	-0.011 (<i>P</i> =0.93)

Notes: Values are Pearson correlation coefficients. *P*-values are for two-sided correlation test. *Statistically significant result, *P*<0.05. **Abbreviations:** BioE2, bioavailable estradiol; BioT, bioavailable testosterone; DHT, dihydrotestosterone; E2, estradiol; Rey0, baseline Rey-Osterrieth Complex Figure Test; Rey5, 5-minute recall trial of the Rey-Osterrieth Complex Figure Test; Rey30, 30-minute recall trial of the Rey-Osterrieth Complex Figure Test.

for 6 weeks and also found improved performance on the block design subtest of the WAIS.⁸ However, Vaughan et al,¹⁰ Haren et al,²² Gray et al,⁷ and Young et al⁵ have all treated older men with testosterone and found no changes in visuospatial cognition. However, we found that testosterone improved visuospatial cognition as assessed by the Rey-Osterrieth Complex Figure Test. We also found that finasteride improved visuospatial performance on the Benton Judgment of Line Orientation test. Finasteride blocks tissue-specific conversion of testosterone to DHT, resulting in somewhat higher serum concentrations of testosterone and E2. However, the mechanism by which finasteride might improve visuospatial cognition is unclear.

We found that increased age was associated with poorer performance on the Trail Making Tests A and B, with fewer depressive symptoms on the GDS, and with increased wellbeing as assessed by Life Satisfaction Index A and B. Normative studies show that performance on Trail Making Tests declines with age.²⁷ However, in similar studies, age is not associated with lower depression scores²⁸ or improved Life Satisfaction Index scores.²⁹ The association of increased age with improved depression and Life Satisfaction Index scores may result from the fact that the oldest subjects in our study would have had to be exceptionally healthy in order to participate in a study demanding intensive subject participation.

Beneficial cognitive effects of testosterone may result directly from binding of testosterone to androgen receptors or indirectly following conversion of testosterone to DHT 5-alpha reductase. There is evidence that DHT specifically reduces neuroinflammation.³⁰ In humans, it has been shown that the cerebral cortex³¹ and hippocampus³² express 5-alpha reductase isoform I, but not isoform II. Therefore, it is unlikely that finasteride significantly lowers DHT concentrations in

these regions. Our data are consistent with the hypothesis that, whether or not cognitive benefits of testosterone require conversion of testosterone to DHT, finasteride would not be expected to reduce those benefits.

Consistent strong cognitive benefits resulting from testosterone administration have not been identified to date. However, a limited number of cognitive domains have been the subject of past studies, leaving the question of whether benefits may occur in domains that have not yet been tested. A large amount of literature supports the role of testosterone in social dominance and approach motivation.^{33,34} Anecdotally, some subjects report that testosterone treatment increases feelings of energy and motivation. However, the effects of testosterone treatment on motivation in hypogonadal men has not been tested. Aarts and van Honk have reported that acute administration of testosterone to young women increased motivation, as assessed by a computerized test of responses to neutral nonsexual cues.³⁵ Future studies are warranted to investigate the potential benefits of testosterone on the areas of drive, motivation, and other as yet untested cognitive domains.

In conclusion, we report that testosterone produced small improvements in depressive symptoms and visuospatial cognition. Our results are generally consistent with the literature, which shows that testosterone treatment produces somewhat inconsistent improvements in cognition.

Disclosure

The authors report no conflicts of interest in this work.

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