Characteristics of Men Who Report Persistent Sexual Symptoms After Finasteride Use for Hair Loss

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Context: Some men who use finasteride for hair loss report persistent sexual and other symptoms after discontinuing finasteride therapy.

Objective: To determine whether these persistent symptoms after discontinuation of finasteride use are due to androgen deficiency, decreased peripheral androgen action, or persistent inhibition of steroid 5α-reductase (SRD5A) enzymes.

Participants: Finasteride users, who reported persistent sexual symptoms after discontinuing finasteride (group 1); age-matched finasteride users who did not report sexual symptoms (group 2); and healthy men who had never used finasteride (group 3).

Outcomes: Sexual function, mood, affect, cognition, hormone levels, body composition, functional magnetic resonance imaging (fMRI) response to sexually and affectively valenced stimuli, nucleotide sequences of androgen receptor (AR), *SRD5A1*, and *SRD5A2*; expression levels of androgen-dependent genes in skin.

Setting: Academic medical center.

Results: Symptomatic finasteride users were similar in body composition, strength, and nucleotide sequences of *AR*, *SRD5A1*, and *SRD5A2* genes to asymptomatic finasteride users and nonusers. Symptomatic finasteride users had impaired sexual function, higher depression scores, a more negative affectivity balance, and more cognitive complaints than men in groups 2 and 3 but had normal objectively assessed cognitive function. Testosterone, dihydrotestosterone, 5α-androstane-3α,17β-diol-glucuronide, testosterone to dihydrotestosterone and androsterone glucuronide to etiocholanolone glucuronide ratios, and markers of peripheral androgen action and expression levels of AR-dependent genes in skin did not differ among groups. fMRI blood oxygen level-dependent responses to erotic and nonerotic stimuli revealed abnormal function in brain circuitry linked to sexual arousal and major depression.

Conclusions: We found no evidence of androgen deficiency, decreased peripheral androgen action, or persistent peripheral inhibition of SRD5A in men with persistent sexual symptoms after finasteride use. Symptomatic finasteride users revealed depressed mood and fMRI findings consistent with those observed in depression. **(*J Clin Endocrinol Metab* 101: 4669–4680, 2016)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received July 18, 2016. Accepted September 19, 2016.
First Published Online September 23, 2016

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Abbreviations: ADT-G, androsterone glucuronide; AR, androgen receptor; BDI, Beck Depression Inventory; BOLD, blood oxygen level dependent; DHT, dihydrotestosterone; ETIO-G, etiocholanolone glucuronide; fMRI, functional magnetic resonance imaging; IIEF, International Index of Erectile Function; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MAC-Q, Memory Complaint Questionnaire; PF10, Physical Function Domain; PHQ-9, Patient Health Questionnaire-9; PSA, prostate-specific antigen; *SRD5A2*, 5α-reductase type 2.

Finasteride, an inhibitor of steroid 5α-reductase type 2 (*SRD5A2*), is approved for the treatment of benign prostatic hyperplasia (1) and androgenic alopecia (2, 3). Although a higher frequency of sexual side effects has been noted in finasteride-treated men (4, 5), the effects of finasteride on hormone levels and prostate volume in patients with benign prostatic hyperplasia and androgenic alopecia been reported to be reversible (6, 7). Recent reports of persistent sexual symptoms, low mood, anxiety, and cognitive complaints in some men, who had used finasteride for hair loss (8–17), even after discontinuation of finasteride therapy, led the Food and Drug Administration to require that the Propecia labels include a warning about persistent libido, ejaculation, and orgasmic problems after drug discontinuation. However, despite a large number of patients seeking medical care, ongoing litigation, and a vast amount of anecdotal information available on the internet, even the basic pathophysiologic attributes of this condition, such as the hormone levels, body composition changes, cognitive function, mood, and other characteristics of patients, who report persistent sexual symptoms after discontinuation of finasteride therapy for hair loss, have not been rigorously investigated. Therefore, the underlying pathophysiologic mechanisms remain unknown.

Here, we characterized men who reported persistent sexual symptoms after discontinuation of finasteride therapy for hair loss and compared them with men who were finasteride users but did not experience symptoms, as well as to men who had never used finasteride. We elucidated the pathophysiologic mechanisms that might contribute to these persistent symptoms. Because the symptoms reported by these patients resemble those of androgen deficiency, we determined whether persistent symptoms are due to sustained suppression of the hypothalamic-pituitary-testicular axis by finasteride, irreversible suppression of SRD5A, off-target suppression of androgen receptor (AR) action, or effects on brain regions that regulate sexual function and mood. To avoid confounding due to age-related changes in hormone levels and sexual function, we recruited adult men below 50 years. We excluded men who reported depression or sexual dysfunction before finasteride use. We performed a comprehensive assessment of hormone levels using highly specific liquid chromatography tandem mass spectrometry assays, body composition, mood, affect, and cognitive function. We also characterized the nucleotide sequences of the *AR*, *SRD5A1*, and *SRD5A2* genes, as well as the expression levels of AR-dependent genes in skin biopsies. Additionally, to evaluate activity of brain regions that regulate sexual function and mood, the functional magnetic resonance imaging (fMRI) response to sexually and affectively valenced stimuli was assessed.

Materials and Methods

Study design

The study protocol was approved by the institutional review board of Brigham and Women's Hospital. All participants provided written informed consent. The first participant enrolled on June 13, 2013, and the last participant completed the study on October 30, 2014.

Participants

We studied 3 groups of men. Group 1 (symptomatic finasteride users) included community-dwelling men, 18–50 years, who had used finasteride for hair loss for more than or equal to 7 days but had not used finasteride in the preceding 4 months, who reported erectile dysfunction defined as a score of less than or equal to 25 on the erectile function domain of the International Index of Erectile Function (IIEF) (18), but who had normal blood counts, chemistries, and physical examination. The eligibility criterion to include men who had used finasteride for hair loss for more than or equal to 7 days was informed by our clinical experience, in which we observed enormous variation in the duration of finasteride exposure before the onset of symptoms. Some patients reported the development of symptoms after ingesting just a few doses of finasteride, whereas others developed symptoms after months or years of finasteride use. Group 2 (nonsymptomatic finasteride users) included men, 18–50 years, who had used finasteride for hair loss, but who did not have sexual symptoms after discontinuation of finasteride. Group 3 consisted of healthy men, 18–50 years, who had never used finasteride and who had no sexual symptoms.

We excluded men who were using currently or had used in the preceding 4 months any androgen, antiandrogen, aromatase inhibitor, or human Chorionic Gonadotropin; had recent illness; cancer; diabetes; body mass index more than 40 kg/m^2; or had depression before starting finasteride.

Participant recruitment

The men who reported persistent symptoms after discontinuation of finasteride use were recruited by solicitation from physicians. Healthy men who had never used finasteride were recruited by advertising in newspapers and direct mailing. The men who had used finasteride but did not report symptoms were recruited by solicitation from physicians and by advertising in newspapers. Those who responded to advertisement underwent telephone screening using a structured questionnaire to ascertain sexual symptoms. Those who met the eligibility criteria during the telephone screening were invited for an in-person visit, during which an informed consent was obtained, and physical examination and blood tests were performed.

Assessments

History of finasteride use and pubertal development was obtained, and a structured physical examination was performed. Hair growth was ascertained by Ferriman Galloway scale, acne by Palatzi scale, and testicular volume by Prader orchidometer.

Sebum production was assessed using Sebu-Tapes. Sexual function was assessed using the IIEF (18). This information was supplemented by Male Sexual Health Questionnaire (19) for more precise assessment of sexual desire and ejaculatory function than is provided by IIEF. Sexual activity was ascertained using sexual encounter profile diaries for a period of 7 days. Mood/depression was assessed using Patient Health Questionnaire-9 (PHQ-9) depression scale (20), Beck Depression Inventory (BDI) (21), and Hamilton Depression Scale 17 (22), and affect using the Positive and Negative Affect Scale (23).

Table 1. Characteristics of Symptomatic Finasteride Users, Nonsymptomatic Finasteride Users, and Healthy Nonusers

Variable	Finasteride Users, Symptomatic (Group 1) n = 25	Finasteride Users, Nonsymptomatic (Group 2) n = 13	Healthy Nonusers, Control (Group 3) n = 18	*P* Value
Race, n (%)				<.001
Black/African American	1 (4.0)	2 (15.4)	9 (50.0)	
White	22 (88.0)	8 (61.5)	9 (50.0)	
Asian	1 (4.0)	3 (23.1)	0 (0)	
Other	1 (4.0)	0 (0)	0 (0)	
Age (y)	35.7 (7.2)	37.0 (8.3)	36.8 (8.8)	.65
BMI (kg/m^2)	27.6 (4.3)	27.6 (3.9)	27.3 (3.2)	.79
Weight (kg)	88.6 (15.9)	89.7 (14.6)	87.5 (14.3)	.83
Glucose (mg/dL)	92.4 (8.5)	90.0 (6.2)	95.1 (9.2)	.37
Creatinine (mg/dL)	1.00 (0.09)	1.03 (0.16)	0.97 (0.16)	.58
Hemoglobin (g/dL)	15.4 (0.88)	14.9 (1.37)	14.6 (0.95)	.02
Hematocrit (L/L)	46.3 (2.7)	44.9 (3.9)	44.8 (2.8)	.10
PSA (ng/mL)	0.7 (0.5, 1.0)	0.7 (0.6, 0.9)	0.95 (0.6,1.4)	.24
Testes Sizes (cc)				
Left	25.9 (3.2)	26.5 (2.4)	25.2 (3.2)	.50
Right	25.9 (3.7)	27.1 (2.7)	25.8 (2.9)	.94
Gynecomastia	8.3% (2/24)	15.3% (2/13)	11.1% (2/18)	.86
Finasteride use				
Mean dose (mg)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	N/A	.31
Duration of treatment (y)	1.7 (0.5, 6.0)	1.0 (0.7, 2.0)	N/A	.55
Time since last dose (y)	3.5 (2.0, 5.0)	3.0 (2.0, 3.0)	N/A	.19
Sebum production scores				
Forehead	5 (4, 5)	5 (4, 5)	4 (4, 5)	.83
Nose	3 (3, 4)	4 (3, 4)	4 (3, 4)	.19
Back	2 (2, 2)	2 (2, 2)	2 (2, 2)	.34
Hair				
Facial				
None	1 (4.2)	0 (0)	0 (0)	.47
Sparse	4 (16.7)	3 (23.1)	1 (5.6)	
Dense, dark	19 (79.2)	10 (76.9)	17 (94.4)	
Chest				
None	0 (0)	1 (7.7)	0 (0)	.65
Sparse	5 (20.8)	3 (23.1)	3 (16.7)	
Dense, dark	19 (79.2)	9 (69.2)	15 (83.3)	
Pubic				
Sparse	1 (4.2)	1 (7.7)	0 (0)	.71
Dense, dark	23 (95.2)	12 (92.3)	18 (100.0)	
Acne				
Face				
None	22 (91.7)	12 (92.3)	18 (100.0)	.46
Few	2 (8.3)	1 (7.7)	0 (0.0)	
Chest				
None	24 (100.0)	13 (100.0)	17 (94.4)	.56
Few	0 (0.0)	0 (0.0)	1 (5.6)	
Back				
None	11 (45.8)	9 (69.2)	16 (88.9)	.02
Few	12 (50.0)	3 (23.1)	2 (11.1)	
Many	1 (4.2)	1 (7.7)	0 (0.0)	

The data are mean (SD), median (Q1, Q3) for continuous data and n (%) for categorical data. The data were analyzed using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed and ordinal data; χ^2 and Fisher exact tests for categorical data. Sebum production was assessed using Sebu-Tape and the scores range from 1 to 5 (highest). Hair growth was assessed using Ferriman Galloway scale; score range, 0 (none) to 2 (dense, dark). Acne were assessed using the Palatzi scale; score range, 0 (none) to 3 (pustular, dense [>15]). BMI, body mass index; PSA, prostate specific antigen.

Detailed methods for assessment of cognitive function, fMRI, hormone levels, and gene expression are described in the Supplemental Methods. Briefly, memory complaints were ascertained using the Memory Complaint Questionnaire (MAC-Q); spatial cognition by the full Card Rotation test; verbal memory using the Wechsler Memory Scale-Revised Logical Memory II; visual memory using the Benton Visual Retention test; working memory and executive function using the Trail Making tests A and B; and global cognitive function was ascertained using the Modified Mini Mental State Examination (24). Personality was evaluated using the Eyesenck Personality test, which scores individuals in 4 personality domains (25).

Whole-body and regional lean and fat mass were measured using dual energy x-ray absorptiometer, calibrated using a soft tissue phantom. Leg press strength was assessed using the Keiser leg press machine. Self-reported physical function was assessed using the Physical Function Domain (PF10) of the Medical Outcomes Study Short Form 36 (26).

Hormone levels were measured in a morning fasting sample in the Brigham Research Assay Core Laboratory. Total testosterone concentrations were measured using a previously published liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay, which has been certified by the Centers for Disease Control's HoST Program (27). The lower limit of quantitation was 1 ng/dL, and interassay coefficient of variation 7.9% at 48.6 ng/dL, 7.7% at 241 ng/dL, 4.4% at 532 ng/dL, and 3.3% at 1016 ng/dL, respectively. Dihydrotestosterone (DHT) concentrations were measured using an LC-MS/MS assay (27), whose lower limit of quantitation was 1 ng/dL, and interassay coefficients of variation at serum concentrations of 5.2, 22.0, and 44.1 ng/dL were 6.1%, 6.5%, and 8.6%, respectively.

Estradiol levels were measured using LC-MS/MS after derivatization with dansyl chloride (27). The lower limit of quantitation for both hormones is 2 pg/mL. Interassay coefficients of variation for estrone are 4.5%, 7.7%, and 6.9% at concentrations of 8, 77, and 209 pg/mL, respectively, and for estradiol 6.9%, 7.0%, and 4.8% at concentrations of 8, 77, and 206 pg/ml, respectively (27). Free testosterone was measured using tracer equilibrium dialysis (27).

Serum levels of androsterone glucuronide (ADT-G), etiocholanolone glucuronide (ETIO-G), androstane-3α,17β-diol 3-glucuronide (3α-diol-3G) and androstane-3α,17β-diol 17-glucuronide (3α-diol-17G) were measured by LC-MS/MS, using a Poroshell 120 EC-C18 75 × 3 mm, 2.7-μm unit column. Ammonium formate (4mM) in tetrahydrofuran/2 propanol/water (4/5/91) was used as mobile phase A, whereas methanol was used as mobile phase B. The transition monitored for 3α-diol-3G was 467.3–85.1 with collision energy set at −47 V. Serum 5α-androstane-3α,17β-diol-glucuronide and 5α-androstane-3α, 3β-diol-glucuronide were measured using LC-MS/MS as markers of peripheral SRD5A activity (28). We also measured ADT-G to ETIO-G ratio as a marker of relative steroid 5α- and 5β-reductase activities (28). Serum LH, FSH, prostate-specific antigen (PSA), sex hormone-binding globulin, and dehydroepiandrosterone sulfate were measured using immunochemilumiscense assays (27).

Analyses of AR, *SRD5A1*, and *SRD5A2* genes

To identify sequencing variants in the coding and splice-sites (+/− 1–2) of the AR, *SRD5A1*, *SRD5A2*, an amplicon based enrichment approach followed by next-generation sequencing was carried out at the Translational Genomics Core (29, 30).

Statistical methods

Probability distributions were explored using histograms and Q-Q plots. Baseline characteristics are presented as mean and SDs of the mean and interquartile ranges for normally distributed and skewed data, respectively, and proportions for categorical data. Group differences were tested using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed and ordinal data, and χ^2 or Fisher exact tests for categorical data. Cognitive function scores were tested using generalized linear model with adjustment for years of education. Log transformation of cognitive outcomes was performed to comply with normality assumption. All tests were 2-sided; type I error was set at $\alpha = 0.05$. Post hoc between-group comparisons (eg, group 1 vs 2) were corrected by Bonferroni's adjustment. Statistical analyses were performed using SAS 9.3 software and R software (version 2.15.1). fMRI analyses are described in Supplemental Methods.

Results

Among 282 men who underwent telephone screening, 132 were screened in person, and 25 were included in group 1, 13 in group 2, and 18 in group 3 (Supplemental Figure 1).

The mean age and body size were similar in the 3 groups (Table 1). The men in groups 1 and 2 had used finasteride at a median daily dose of 1.0 and 1.0 mg, respectively, for an median duration of 1.7 and 1.0 years, respectively. The median time elapsed since the last finasteride dose in groups 1 and 2 was 3.5 and 3.0 years, respectively. Testicular volumes and the proportion of men with gynecomastia were similar across groups.

Hormone levels

Serum total and free testosterone, DHT, LH, FSH, estradiol, and sex hormone-binding globulin levels did not differ significantly among groups ($P > .1$) and were within the normal range for healthy young men (Figure 1). Serum testosterone to DHT ratio, 5α-androstane-3α,17 β-diol-glucuronide and 5α-androstane-3α,3 β-diol-glucuronide concentrations, and the ratio of ADT-G to ETIO-G did not differ among groups (Figure 1).

Markers of peripheral androgen action

Hair growth, acne, sebum production, and testosterone-responsive markers, hematocrit and PSA, did not differ significantly among groups (Table 1). The expression levels of nuclear AR and β-catenin protein in the sebaceous glands and epidermis (Supplemental Figure 2), and other androgen-regulated mRNA transcripts in skin biopsies (Supplemental Figure 3) did not differ among groups.

AR and steroid SRD5A genes

Next-generation sequencing of the coding regions and splice sites of *AR*, *SRD5A1*, and *SRD5A2* failed to reveal

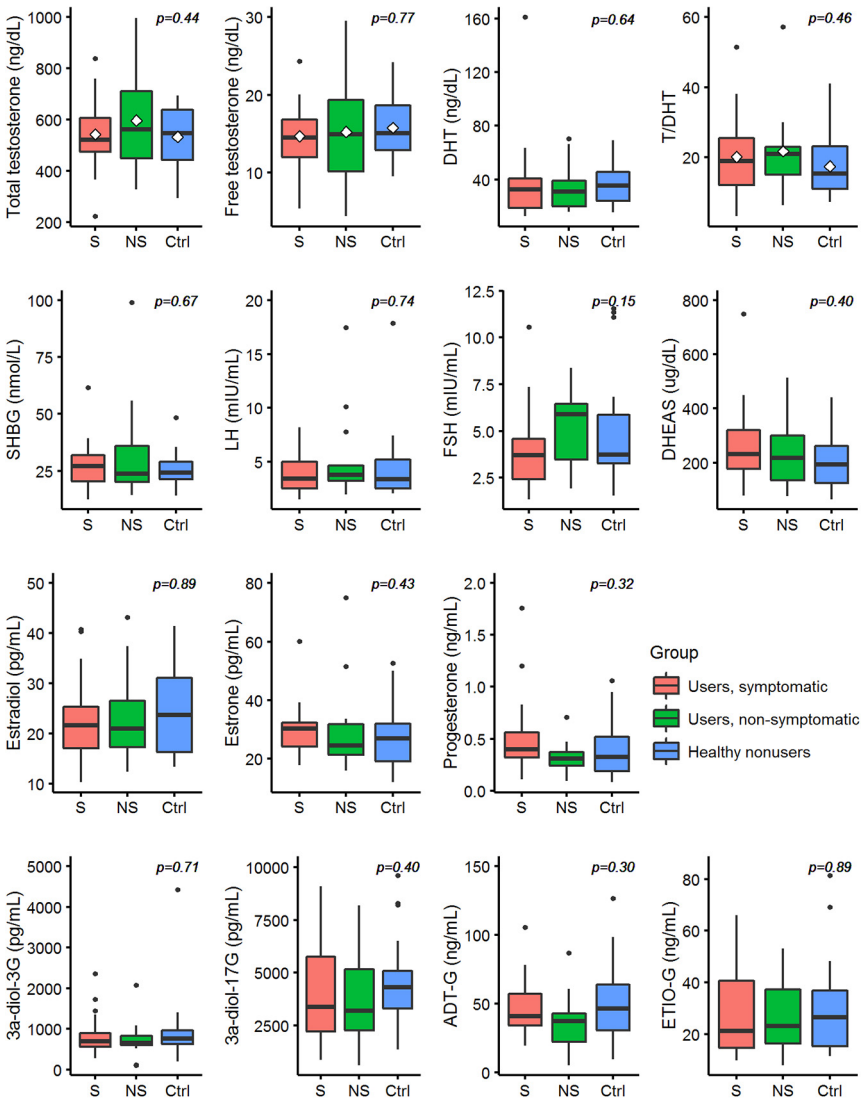

Figure 1. Hormone levels. The box and whisker plots of hormone levels show the mean (diamond marker shown only for the normally distributed data), median (horizontal line in the middle of the box), quartile range (the upper and lower bounds of the box), and the range of hormone values. The data were analyzed using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed data. SHBG, sex hormone-binding globulin; T to DHT ratio, testosterone to DHT ratio; DHEA-S, dehydroepiandrosterone sulfate; 3α-diol-3G: 5α-androstane-3α, 3β-diol-glucuronide; 3α-diol-17G: 5α-androstane-3α,17β-diol-glucuronide.

Sexual function and activity

The men in group 1 had significantly lower IIEF composite score (median [quartile range]: 30.0 [23.0–35.0], 67.0 [65.0–68.0], and 68.5 [67.0–71.0] for groups 1, 2, and 3, respectively; $P < .001$ overall and for each between-group comparison) and significantly lower scores for each of its domains of erectile function, sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction than men in groups 2 and 3. Men in group 1 had significantly fewer vaginal penetrations ($P = .01$) and satisfactory sexual encounters ($P < .001$) than in men in groups 2 or 3 (Figure 2A). The Male Sexual Health Questionnaire confirmed significantly lower sexual desire ($P < .001$ overall and for each between-group comparison; median [quartile range]: 17.0 [16.0–21.0], 28.0 [26.0–30.0], and 29.5 [26.0–31.0] for groups 1, 2, and 3, respectively) and worse ejaculatory function ($P < .001$; median [quartile range]: 14.0 [13.0–15.0], 17.0 [16.0–17.0], and 17.0 [15.0–17.0] for groups 1, 2, and 3, respectively) in group 1 than in groups 2 ($P < .001$) and 3 ($P = .006$) (Figure 2A). The IIEF composite score was not significantly related to either the duration of finasteride treatment ($r = 0.059$, $P = .725$) or the time elapsed since the discontinuation of finasteride treatment ($r = -0.215$, $P = .194$).

any significant variants with potentially deleterious changes (nonsense or frameshift variants) in any sample. Although a few missense variants of unknown impact on the protein were identified in some individuals, none were enriched in any cohort, and these were reported at similar frequencies as in general population databases such as 1000 Genomes (http://www.1000genomes.org/) and Exome Aggregation Consortium (http://exac.broadinstitute.org/). The lengths of the CAG repeats in exon 1 did not differ significantly among groups (mean [95% confidence limits]: group 1, 22.2 ± 2.2; group 2, 21.8 ± 2.5; and group 3, 21.0 ± 2.3; $P = .236$).

Mood, affect, and personality type

The PHQ-9 depression scores were significantly higher in group 1 than in the other 2 groups ($P < .001$ overall and for each between-group comparison; median [quartile range]: 11.0 [7.0–17.0], 1.0 [1.0–2.0], and 1.0 [0–2.0] for groups 1, 2, and 3, respectively); the median scores of group 1 patients were in the moderate depression range (Figure 2B). The PHQ-9 score was not significantly related to either the duration of finasteride treatment ($r = 0.139$, $P = .406$) or the time elapsed since the discontinuation of finasteride treatment ($r = -0.222$, $P = .180$). BDI ($P < .001$) and Hamilton Depression Inventory (overall and

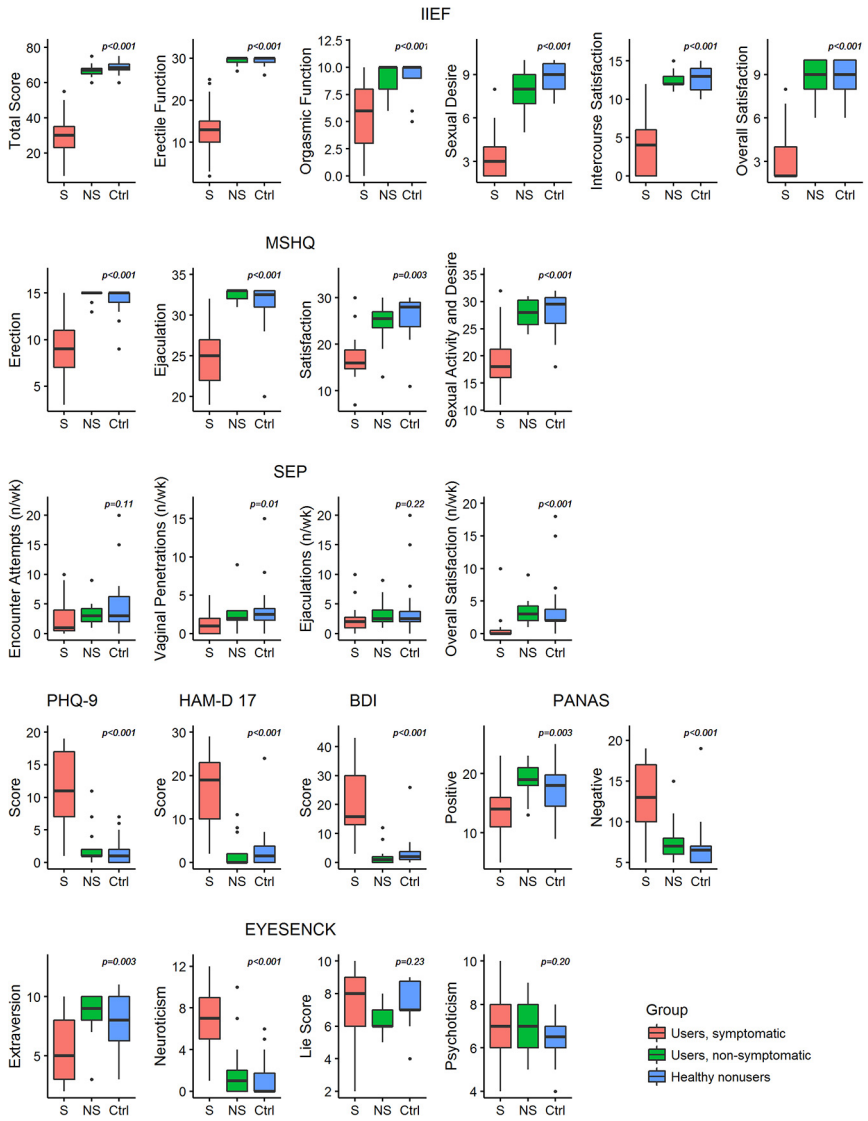

Figure 2. Measures of various domains of sexual function and sexual activity, and of mood, affect, and personality. The box and whisker plots show the median (horizontal line in the middle of the box), quartile range (the upper and lower bounds of the box), and the range of values. The data were analyzed using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed data. MSHQ, Male Sexual Health Questionnaire; SEP, sexual encounter profile diaries. PHQ-9 is 9-item questionnaire, score range: 0 (no depression) to 27 (severe depression). Hamilton Depression Scale 17 (HAM-D 17) is 17-item questionnaire, score range: 0 (no depression) to 52 (severe depression). BDI is 21-item questionnaire, score range: 0 (no depression) to 63 (extreme depression). Positive and Negative Affect Scale (PANAS) is 10-item questionnaire (5-positive, 5-negative), score range: 5 (lowest) to 25 (highest). Eyesenck Personality is 48-item questionnaire, 12 questions for each of 4 domains, score range for each domain is 0 (lowest) to 12 (highest).

between-group comparisons $P < .001$) also revealed significantly higher depression scores in men in group 1 than in men in groups 2 or 3. The men in group 1 reported substantially higher scores for negative affect (overall and between-group comparisons, $P < .001$) and significantly lower scores (overall, $P = .003$; group 1 vs 2, $P = .006$; group 1 vs 3, $P = .02$) for positive affect compared with those in groups 2 and 3 (Figure 2B). The men in group 1 scored significantly lower on the extroversion scale ($P = .003$) and higher on the neuroticism scale ($P < .001$) than men in groups 2 and 3 (Figure 2B).

Body composition, strength, and physical function

Whole-body lean and fat mass, truncal and appendicular lean and fat mass, trunk to limb fat ratio, and visceral adipose tissue mass did not differ significantly (all $P > .1$) among groups (Figure 3).

Leg press strength did not differ significantly among groups, but PF10 score was significantly lower in men in group 1 than in men in groups 2 and 3, although the absolute difference was small ($P = .002$; median [quartile range]: 28.0 [25.0–30.0], 30.0 [30.0–30.0], and 30.0 [29.0–30.0] for groups 1, 2, and 3, respectively) (Figure 3).

Cognitive function

The men in group 1 reported higher subjective memory complaints than healthy nonusers, after adjusting for years of education (overall, $P = .02$; mean ± SD MAC-Q scores: 20.8 ± 4.9, 18.4 ± 3.8, and 16.9 ± 3.3 for groups 1, 2, and 3, respectively); however, between-group differences were not significant. The 3 groups did not differ significantly on paragraph recall test, Trail Making tests A and B, Card Rotation test, and the Paragraph Recall test (Table 2). Scores on Benton Visual Retention test showed borderline differences among groups (overall, $P = .05$; group 1 vs 2, $P = .32$; group 1 vs 3, $P = .04$).

Functional MRI

Two separate fMRI activation tasks, one targeting affective dysfunction and one focused on sexual arousal, were conducted. We hypothesized that with increasing sexual dysfunction, there would be abnormal function in the brain network associated with sexual arousal, which would correlate with IIEF scores. In addition, there would be abnormalities in neural circuitry similar to those seen in patients with major depression, which would correlate with measures of negative mood (2–4).

Word valence ratings were significantly different among negative, neutral, and positive words. The 3 groups

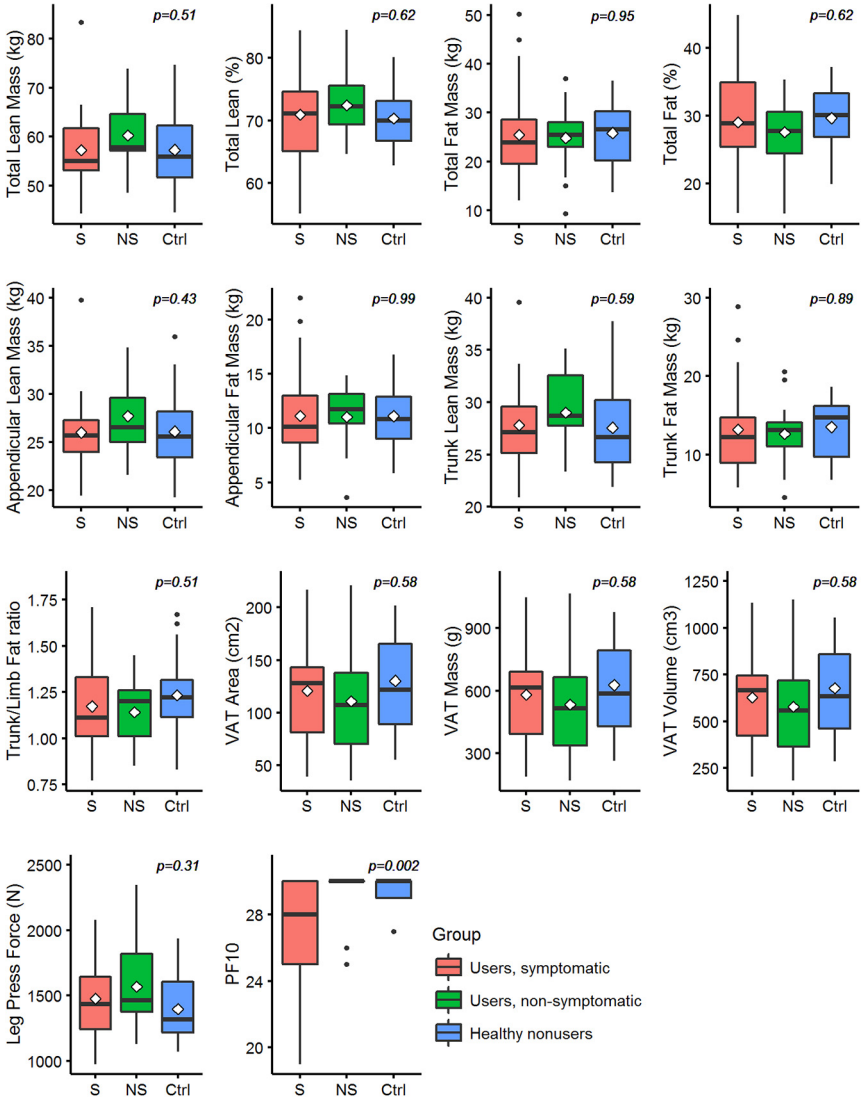

Figure 3. Body composition, maximal voluntary muscle strength, and self-reported physical function. The box and whisker plots show the mean (diamond marker shown only for the normally distributed data), median (horizontal line in the middle of the box), quartile range (the upper and lower bounds of the box), and the range of values. The data were analyzed using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed data. Body composition was assessed using DXA, calibrated using a soft tissue phantom. Muscle strength was assessed using 1-repetition maximum in the leg press exercise using the Keiser Leg Press machine. VAT, visceral adipose tissue. PF10 is 10-item questionnaire derived from Medical Outcomes Study Short Form 36, score range: 10 (inactive) to 30 (active).

did not differ significantly in their rating of all 3 word types or in their recognition rates corrected for the distracter words in the form of discrimination index *d'* in all 3 word types (Supplemental Table 1).

There was a significant main effect of image type on emotional intensity ($P < .001$), positivity ($P < .001$), and sexual intensity ($P < .001$) ratings, indicating the intended stimulus perception (Supplemental Table 1). There were significant differences in emotional intensity ratings between neutral and positive erotic images ($P < .001$) and between neutral and positive nonerotic images ($P = .048$) but not between positive erotic images. However, there was no significant main effect of group on any image rating scale. Sexual intensity ratings showed significant differences between neutral and positive erotic images ($P < .001$) and between positive nonerotic and erotic images ($P < .001$).

A correlation analysis was performed across all finasteride users to assess the hypothesized association between blood oxygen level-dependent (BOLD) activation levels during exposure to erotic images (compared with nonerotic images matched for valence and level of arousal), and IIEF scores. A negative correlation was observed between IIEF score and BOLD activity in the hypothalamus, bilateral thalamus, right posterior cingulate cortex ($P < .01$). Positive correlations were observed between IIEF score and BOLD activity in the right mid cingulate, right posterior cingulate, left insula, right precentral gyrus, left inferior parietal cortex, left caudate ($P < .01$), and left putamen ($P < .05$) (Figure 4 and Supplemental Table 2).

A significant positive correlation between negative attitude scores on the BDI and BOLD activity levels was identified in regions associated with major depression, including the right nucleus accumbens, left pregenual anterior cingulate cortex, right insula, right lateral orbito-frontal cortex, and left posterior cingulate ($P < .01$). There was negative correlation between the BDI subscores and BOLD activity in regions, including the right parahippocampal/fusiform gyrus (Figure 4 and Supplemental Table 2).

Discussion

This systematic evaluation of men, who reported persistent sexual symptoms after discontinuation of finasteride therapy for hair loss, found no evidence of androgen deficiency. Serum DHT levels, testosterone to DHT ratios, and circulating markers of tissue testosterone metabolism through the SRD5A pathway, 5α-androstane-3α, 17β-diol-glucuronide, and 5α-androstane-3α, 3β-diol-gluc-

Table 2. Measures of Cognitive Function for Symptomatic Finasteride Users, Nonsymptomatic Finasteride Users, and Healthy Nonusers

Variable	Finasteride Users, Symptomatic (Group 1) n = 25	Finasteride Users, Nonsymptomatic (Group 2) n = 13	Healthy Nonusers, Control (Group 3) n = 18	*P* Value	*P* Value*
Education (y)	19.3 (3.6)	19.3 (3.2)	16.2 (3.2)	.03	
3MSE	96.0 (92.0, 99.0)	98.0 (95.0, 99.0)	97.0 (94.0, 98.0)	.68	.39
Cognitive Function test					
MAC-Q	20.8 (4.9)	18.4 (3.8)	16.9 (3.3)	.003	.02
WMS-R LM II					
Immediate recall	10.0 (7.5, 10.5)	10.5 (9.5, 12.0)	8.8 (6.5, 9.5)	.07	.08
Delayed recall	7.5 (6.5, 10.0)	9.0 (8.0, 11.5)	7.3 (5.0, 9.5)	.18	.10
Trail Making test (s)					
Part A	26.0 (20.0, 30.0)	25.0 (19.0, 27.0)	29.5 (21.0, 35.0)	.18	.20
Part B	64.0 (45.0, 87.0)	56.0 (47.0, 88.0)	70.5 (48.0, 108.5)	.53	.43
Number of discontinued	0/25	1/13	2/18	.23	
Benton Visual Retention test	8.0 (7.0, 9.0)	7.0 (6.0, 7.0)	6.5 (5.0, 8.0)	.10	.051
Card Rotation test	47.0 (33.0, 58.0)	44.0 (32.0, 72.0)	42.5 (33.0, 51.0)	.75	.98

The data are mean (SD) or median (Q1, Q3). For *P* value, the data were analyzed using one-way ANOVA *F* test for normally distributed data, Kruskal-Wallis test for nonnormally distributed data. *P* values* for group effect adjusted for years of education (general linear model performed on log-transformed outcomes for nonnormal distributed data, education data available for 41 participants). 3MSE, the Modified Mini Mental Status Examination; score range, 0–100 (best). MAC-Q, score range: 5–30 (most memory complains). WMS-R LM II, Wechsler Memory Scale-Revised Logical Memory II, higher score represents better function. Trail Making test, higher score represents worse function. Benton Visual Retention test; score range, 0–10 (best). Card Rotation test; score range, 0–80 (best). MAC-Q, Memory Complaint Questionnaire.

uronide levels, and the ratio of ADT-G to ETIO-G, were similar among groups, providing no evidence of persistent inhibition of peripheral *SRD5A* activity by prior finasteride use. The nucleotide sequences of the AR, *SRD5A1*, and *SRD5A2* genes did not reveal any explanatory variation in the coding regions or splice sites or in CAG repeat length in men with persistent symptoms. Furthermore, the peripheral markers of androgen action (hair growth, acne, and sebum production, hematocrit, PSA levels, lean body mass, and the expression levels of nuclear AR and β-catenin proteins, and other androgen-regulated mRNA transcripts in the skin) did not differ among groups. Although we did not have a control group of profoundly hypogonadal men such as those receiving androgen deprivation therapy, the analyses of differential gene expression did not reveal patterns of alterations in gene expression that have been reported previously after androgen deprivation or androgen supplementation in preclinical and clinical models (31, 32). Thus, persistent sexual symptoms in men who had previously used finasteride, are unlikely to be due to androgen deficiency, variations in the coding regions of the *AR*, *SRD5A1*, or *SRD5A2* genes, persistent peripheral inhibition of *SRD5A1* and *SRD5A2* genes, or to persistent off-target inhibitory effects of finasteride on peripheral androgen action.

Because these men were recruited based on persistent sexual symptoms after discontinuation of finasteride therapy, the findings of erectile dysfunction and low sexual desire are not surprising. These men also exhibited depressed mood; the average scores of symptomatic finasteride users on the 3 depression scales were in the range exhibited by men with moderately severe depression. Symptomatic finasteride users also had higher levels of negative affect and lower levels of positive affect compared with healthy controls. Although we excluded men who were depressed before initiating finasteride, we do not know whether the depressed mood in men in group 1 was causally related to finasteride use, alopecia itself (33), or nocebo effect (34).

This study used 2 separate fMRI activation probes to target-specific symptoms reported by these patients: sexual dysfunction and depression (specifically negative attitude). Studies (35, 36) of the neurobiology of sexual arousal have converged on a multidimensional network comprising cognitive (parietal, anterior cingulate, thalamus, insula), emotional (amygdala, insula), motivational (precentral gyrus, parietal cortex), and physiological (hypothalamus, thalamus, insula) components. As sexual function worsened (ie, as IIEF scores went down), there was increasing activity in the neural circuits corresponding to sexual arousal and decreasing activity in brain regions associated with higher level cognitive and motivational networks in symptomatic finasteride users in response to erotic stimuli. This dissociation in activity may be a marker of neural changes postfinasteride use. Similar abnormalities in these brain regions have been identified in psychogenic erectile dysfunction (38, 39). We also found a significant positive correlation between a subset of BDI

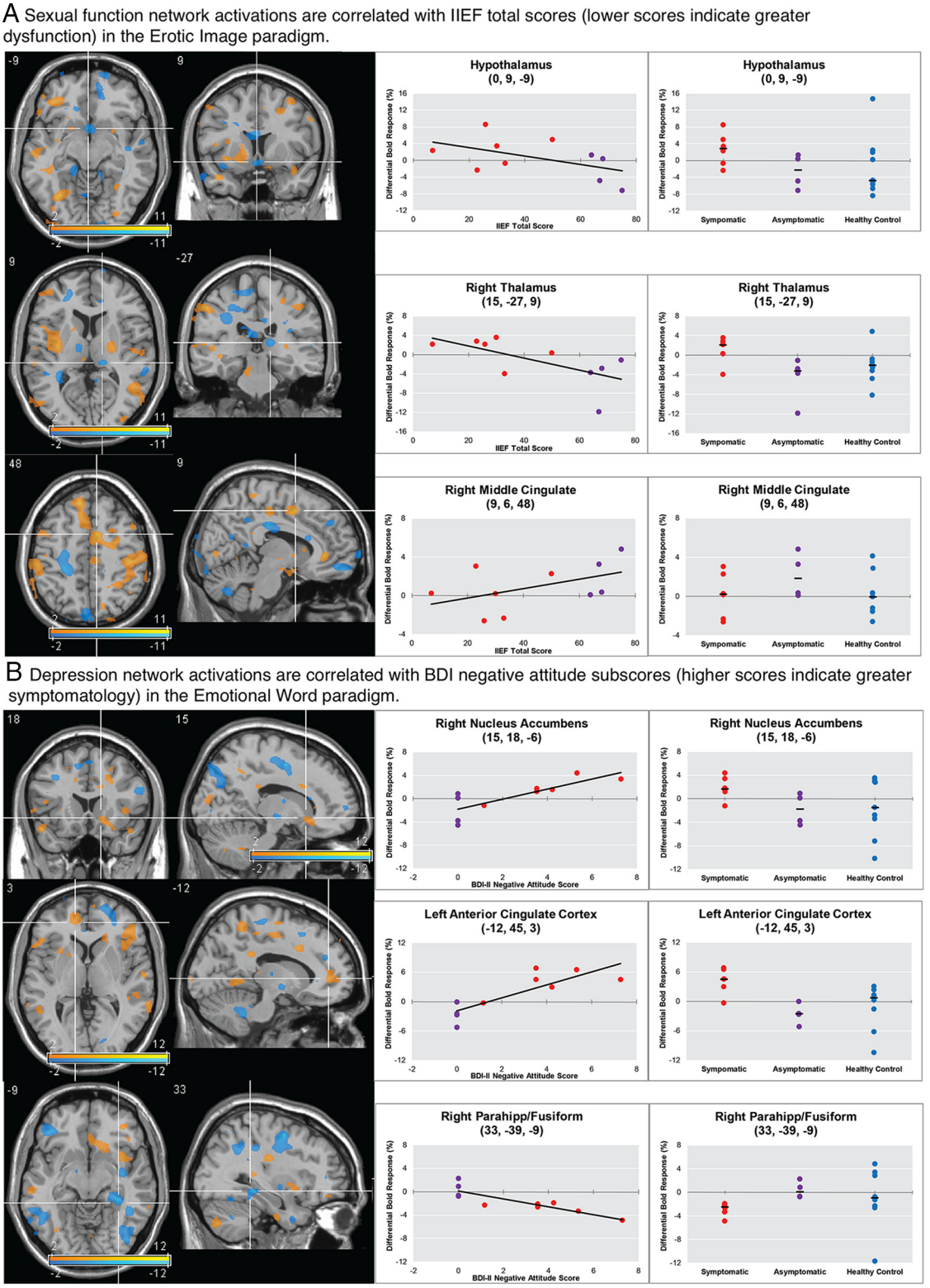

Figure 4. A, Sexual function network activations correlated with IIEF total scores (lower scores indicated greater dysfunction) in the Erotic Image paradigm. The fMRI studies were performed in right-handed males (10 postfinasteride patients: 6 symptomatic and 4 nonsymptomatic; mean age, 33.4 y; range, 26–49) and 10 healthy controls (mean age, 35.1 y; range, 26–47). In the upper panel, the statistical parametric maps show the correlation in *t* statistic between the differential BOLD neural activation changes in the erotic vs nonerotic image contrast and the IIEF total scores, thresholded at a voxelwise $P = .05$ for visualization purposes. In the erotic vs nonerotic image contrast, negative correlations were identified in the hypothalamus ([0, 9, −9]; peak z-score = −3.09; corrected $P = .014$, and right thalamus ([15, −27, 9]; peak z-score = −3.3; corrected $P = .008$). Positive correlation was identified in the right mid cingulate cortex ([9, 6, 48]; peak z-score = 3.55; corrected $P = .005$). In the corresponding plots with regression lines (center), individual patient's differential BOLD neural activation changes in the erotic vs nonerotic image contrast are plotted against their corresponding IIEF total scores: red indicates symptomatic postfinasteride patients, and purple indicates asymptomatic postfinasteride

scores related to negative attitude and BOLD activity in the right nucleus accumbens, left pregenual anterior cingulate cortex, right insula, right lateral orbito-frontal cortex, and left posterior cingulate as well as a negative correlation between BDI subscores and BOLD activity in the right parahippocampal/fusiform gyrus. This neural circuitry overlaps with functional abnormalities that have been identified in major depression (40, 41). These 2 fMRI experiments suggest that there are underlying neurobiological abnormalities in symptomatic finasteride users, which can be linked to circuitry that has been implicated in both depression and in sexual arousal.

Symptomatic finasteride users also reported a slightly greater number of subjective cognitive complaints. However, we found no objective evidence of cognitive deficits using comprehensive tests of multiple domains of cognition. It is possible that mood and cognitive complaints may be related to reduced neurosteroid production due to persistent local inhibition of SRD5A activity in specific brain regions (42), which was not reflected in changes in peripheral DHT levels.

These findings need confirmation in larger prospective studies. Because of the cross-sectional nature of the study, a causal relation between prior finasteride use and persistent sexual symptoms, mood changes, cognitive complaints, or fMRI findings cannot be inferred. It is possible that the depressive symptoms and prior finasteride use are coincidental or that the depressed mood may contribute to sexual dysfunction. It is unclear why only a subset of finasteride users experience persistent sexual symptoms and low mood. Although we did not find evidence of sequence variation in *AR*, *SRD5A1*, or SRD5A2 genes, or of significant alterations in expression of AR-dependent genes in the skin, we cannot exclude the possibility of variations in other genes or in the gene expression levels in other tissues or specific brain regions involved in regulation of mood and sexual function. It is also possible that finasteride may exert epigenetic effects which may account for persistent symptoms.

The clinical implications of these findings are that symptomatic finasteride users are unlikely to benefit from treatment with testosterone, DHT, or any other androgen, because these patients do not have evidence of androgen deficiency, persistent *SRD5A* inhibition, or androgen insensitivity. Attention may be focused instead on the treatment of depression and sexual symptoms. Furthermore, because men seeking treatment for alopecia have higher prevalence of depression and sexual dysfunction than the general population (33), it would be appropriate to ascertain history of depression or sexual dysfunction before starting treatment.

In conclusion, in a subset of men who reported persistent sexual symptoms after prior finasteride use, we found no evidence of androgen deficiency, persistent inhibition of peripheral *SRD5A* activity, or diminished peripheral androgen action. The men reporting persistent sexual symptoms had depressed mood, negative affectivity balance, and patterns of brain activity that correlated specifically with sexual and negative affective symptoms and included regions known to be involved in sexual function and depression, respectively.

Figure 4. (Continued). patients. In the corresponding plots on the right, individual subject's differential BOLD neural activation changes in the erotic vs nonerotic image contrast are plotted by group with group median indicated with a horizontal bar in black: symptomatic postfinasteride patients (red), asymptomatic postfinasteride patients (purple) and healthy control subjects (blue) at the same coordinates, for reference. B, Depression network activations correlated with BDI negative attitude subscores (higher scores indicate greater symptomatology) in the Emotional Word paradigm. Statistical parametric maps show the correlation in *t* statistic between the differential BOLD neural activation changes in the negative vs neutral word contrast and the BDI negative attitude subscores, thresholded at a voxelwise $P = .05$ for visualization purposes. In the negative vs neutral word contrast, positive correlations were identified in the right nucleus accumbens ([15, 18, −6]; peak z-score = 2.55; corrected $P = .049$), and left anterior cingulate cortex ([−12, 45, 3]; peak z-score = 2.45; corrected $P = .040$). Negative correlation was identified in the right parahippocampal/fusiform gyrus ([33, −39, −9]; peak z-score = −3.53; corrected $P = .005$). In the corresponding plots with regression lines (center), individual patient's differential BOLD neural activation changes in the negative vs neutral word contrast are plotted against their corresponding BDI negative attitude subscores: red indicates symptomatic postfinasteride patients, and purple indicates asymptomatic postfinasteride patients. In the corresponding plots on the right, individual subject's differential BOLD neural activation changes in the negative vs neutral word contrast are plotted by group with group median indicated with a horizontal bar in black: symptomatic postfinasteride patients (red), asymptomatic postfinasteride patients (purple), and healthy control subjects (blue) at the same coordinates, for reference; n = 7 in each of the 3 groups.

Acknowledgments

We thank the assistance of Jane Epstein in the implementation of the fMRI protocol for this study.

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This work was supported in part by the Post-Finasteride Syndrome Foundation (a nonprofit organization whose goal is to support research on the characterization, underlying biologic mechanisms and treatments of postfinasteride syndrome, and to increase global public awareness of postfinasteride syndrome) and by the Harvard Clinical Translational Research Institute (Catalyst) and the Center for Clinical Investigation at the Brigham and Women's Hospital.

Disclosure Summary: S.Ba. has received grant support from Abbott Pharmaceuticals for investigator-initiated studies unrelated to this study and has previously consulted for Eli Lilly, Inc. S.Bh. has received research grant support from Abbvie Pharmaceuticals, Transition Therapeutics, Takeda Pharmaceuticals, and Eli Lilly, Inc for investigator-initiated research unrelated to this study; has served as a consultant to AbbVie, Regeneron, Novartis, and Eli Lilly & Co; has a financial interest in Function Promoting Therapies, LLC, a company aiming to develop innovative solutions that enhance precision and accuracy in clinical decision making and facilitate personalized therapeutic choices in reproductive health; and his interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. All other authors have nothing to disclose.

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