Published in final edited form as:

Drug Alcohol Depend. 2013 March 1; 128(3): 250–254. doi:10.1016/j.drugalcdep.2012.08.024.

Relationship between sex hormones and cognitive performance in men with substance use*

Mihail F. Zilbermint⁽¹⁾, Amy B. Wisniewski⁽²⁾, Xiaoqiang Xu⁽³⁾, Ola A. Selnes⁽⁴⁾, and Adrian S. Dobs^{(5)**}

⁽¹⁾Program on Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health Building 10/CRC 1-3140, 10 Center Drive, Bethesda, Maryland 20892-1109 USA mihail.zilbermint@nih.gov

⁽²⁾Department of Urology, University of Oklahoma Health Sciences Center, 920 Stanton L. Young Boulevard WP 3150 Oklahoma City, Oklahoma 73104 USA

⁽³⁾Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21287 USA

⁽⁴⁾Department of Neurology, Cognitive Neuroscience Division, Johns Hopkins University School of Medicine Reed Hall East, Suite 2206, 1620 McElderry Street, Baltimore, Maryland 21287 USA

Abstract

BACKGROUND—Hypogonadism is common with opiate-like drug use and may contribute to cognitive abnormalities. With the increasing epidemic of HIV and substance use (SU) worldwide, it is important to understand the impact of these conditions on cognition, which may affect quality of life and possibly decrease adherence to treatment. We hypothesized that men with SU, by virtue of hypogonadism secondary to HIV and/or SU, may demonstrate impaired cognition.

METHODS—We recruited men aged 18-50 from a population of low income, innercity individuals. Details of HIV and SU status, serum blood levels of total testosterone (TT), free testosterone (FT) and estradiol (E2) were assessed. All subjects were administered ten neuropsychological tests.

RESULTS—Our sample consisted of 68 men (mean age: 43.2 years (SD 5.8), African Americans: 86.6%). The recruited population was primarily from low socioeconomic status and unemployed. The mean level of TT was 553.9 ng/dL (SD 262.0), the mean level of FT was 69.5 pg/mL (SD 34.8), mean E2 was 3.2 pg/mL (SD 4.4). We found that 30.9% were hypogonadal and it was associated with higher SU.

*Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

(5) **Corresponding author Johns Hopkins Clinical Research Network, The Johns Hopkins University School of Medicine Division of Endocrinology and Metabolism 1830 Monument Street, Suite 328, Baltimore, Maryland 21287 USA Tel: +1 410 955 2130 Fax: +1 410 955 8172 adobs@jhmi.edu.

Conflict of interest The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Contributors Author Mihail F. Zilbermint wrote the manuscript. Authors Amy B. Wisniewski and Ola A. Selnes contributed to the design the study. Author Xiaoqiang Xu undertook the statistical analysis. Author Adrian S. Dobs designed the study, received the grant, and assisted in writing and proofreading the final manuscript. All authors contributed to and approved the final manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

RESULTS—We observed some relationships between sex hormones and cognitive domains, however, after adjustment for age, drug use category, education, depression, HIV, there was no statistically significant correlation between cognitive performance and sex hormone levels.

CONCLUSIONS—In this cross-sectional study of men with a high prevalence of SU and hypogonadism, endogenous levels of TT, FT or E2 were not related to cognitive performance. Other factors need to be identified which may contribute to poor cognitive function in the setting of SU.

Keywords

Testosterone; estradiol; sex hormones; cognitive function; illicit drug users; substance use

1. INTRODUCTION

The effects of sex hormones on brain function are unclear. It is known that sex hormones, mainly testosterone, may influence cognition; substance use (SU) and HIV infection may alter the function of hypothalamic-pituitary-gonadal (HPG) axis. With the increasing epidemic of HIV and SU worldwide, it is important to understand the possible impact of these conditions on cognitive function, which may affect quality of life, and possibly decrease adherence to treatment.

Substantial impairment of executive control has been recognized in a variety of dependent drug using groups (Hoff et al., 1996; Bolla et al., 1999; Simon et al., 2000; Rosselli et al., 2001; Fillmore and Rush, 2002; Goldstein et al., 2004; Lundqvist, 2005; McHale and Hunt, 2008). An association between executive control deficits and dysfunction in prefrontal, orbitofrontal and anterior cingulate regions has been identified using neuroimaging studies (Bolla et al., 2000, 2003). A number of neuropsychological studies suggested the working memory is impaired in chronic cannabis users (Lundqvist, 2005). Chronic cocaine and heroin users may exhibit neuropsychological deficits (Grant et al., 1977; Hill et al., 1979; O'Malley et al., 1992; Holman et al., 1993).

A low serum testosterone level may contribute to cognitive decline in men as they age (Moffat, 2005). Even though the relationship between various sex hormone levels and several cognitive domains has been studied, the results are inconsistent (Nelson et al., 2008; Ulubaev et al., 2009). Most of the studies measured total testosterone (TT), free testosterone (FT), estradiol (E2), and administered batteries of cognitive tests in aging populations. Some authors reported a curvilinear correlation (U-shaped) between testosterone and cognition (Moffat and Hampson, 1996; Barrett-Connor et al., 1999); others acknowledged a positive linear relationship (Silverman et al., 1999; Janowsky, 2006; Thilers et al., 2006; Fukai et al., 2009), yet others report an inverse relationship (Gouchie and Kimura, 1991; Yeap et al., 2008). Interestingly, some researchers found no statistically significant correlation between various sex hormone levels and cognitive domains (Fonda et al., 2005; Martin et al., 2008; Young et al., 2010; Anonymous, 2010; Advani, 2011). In fact, Martin et al. (2007b) reported that higher TT and FT are associated with poorer executive function and verbal memory.

One can speculate that the reports were inconsistent due to small sample sizes (Sherwin, 2003), different ages of subjects, dissimilar research methodologies (Martin et al., 2007a), timing of sex steroid measurements (LeBlanc et al., 2010), and “practice” effects (Salminen et al., 2004).

Hormonal changes in patients with SU are well recognized (Lafisca et al., 1985; Rasheed and Tareen, 1995; Rajagopal et al., 2004; Kalyani et al., 2007), including decreased FT and

TT. This may be due to direct and indirect effects of illicit drugs on the HPG axis (de la Rosa and Hennessey, 1996).

HIV infection, often a comorbidity of SU, is shown to result in central nervous system impairment and altered cognitive performance: decreased attention, poor memory and psychomotor slowing (Egan et al., 1992; McArthur et al., 1993; Silberstein et al., 1993). In contrast, Selnes et al. (1997) observed no association between HIV infection and the progression of cognitive symptoms in SU. Equally important, endocrine abnormalities, especially hypogonadism, were reported in HIV-infected men and women (Grinspoon et al., 1997; Rabkin et al., 1997, 2000; Dobs, 1998). It is unclear if endocrine abnormalities relate to HIV-infected individuals independently of SU.

We hypothesized that males with SU, by virtue of hypogonadism secondary to HIV and/or SU, may exhibit impaired cognition. This report presents a cross-sectional investigation of the effects of endocrine health on mental performance of men using drugs, in a study entitled CHIEF (Cognitive Health in Endocrine Function; Dobs and Wisniewski, 2004).

2. METHODS

2.1. Participants

161 men, 18-50 years old, from Baltimore, Maryland were enrolled in the study between 2004 and 2008. For the cross-sectional analysis, subjects were classified into four categories: non-users (no drug use in the past three years), occasional users (cocaine and/or heroin use less than three times per week), heavy users/methadone maintenance (methadone, cocaine and/or heroin use more than three times per week or methadone maintenance). Complete hormonal and cognitive performance data was available in 68 individuals. We excluded subjects with a known gonadal impairment, chronic neurological and psychiatric disorders (see full exclusion criteria in Supplementary Material Item 1¹).

After signing the informed consent, participants were interviewed. Information about substance use, sociodemographic status, medical history, use of medications and highly active antiretroviral therapy was obtained. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977; Golub et al., 2004). The Johns Hopkins University Medicine Institutional Review Boards approved the study.

2.2. Hormone measurements

Blood samples were collected before 10:00h for measurement of TT, FT, sex hormone binding globulin (SHBG), and E2 concentrations. TT was measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) (Singh, 2008). SHBG was measured by radioimmunoassay (RIA). FT was measured via tracer equilibrium dialysis calculation. E2 was measured by LC-MS/MS. Normal testosterone range is still not clearly defined (Wheeler and Barnes, 2008). We used commonly accepted levels to define male hypogonadism in adults (serum TT <300 ng/dL or FT < 50 pg/mL).

2.3. Cognitive tests

Participants were administered ten standardized neuropsychological tests with established reliability and validity (Lezak et al., 2004) to evaluate working memory, verbal learning and memory, verbal fluency, and visuospatial, graphomotor and psychomotor abilities (Table 1).

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

2.4. Statistical analysis

Analysis of covariance (ANCOVA) models were constructed to compare sex hormone levels, including TT, FT, and E2, among the three drug use groups. Age was included in the model as a covariate, since it is a strong factor affecting the hormone levels. If a cross-group significance is observed, then pair-wise comparisons were performed.

The primary objective was to test the correlation between TT, FT, and E2 with cognitive tests. First, we treated the hormones as continuous variables. Multi-linear regression models were constructed with cognitive test scores as dependent variables and hormones as the independent variables. Other covariates were drug use category, education, depression, HIV status, since they show effect on cognitive test results. An adaptive step-up Bonferroni method was used for multiple comparison correction across the cognitive tests (Hochberg and Benjamini, 1990). Then the cognitive test results were compared using ANCOVA models between hypogonadal and normogonadal men, with age, depression, HIV status, education and drug use category as covariates. Two-sided P values < 0.05 were considered statistically significant.

3. RESULTS

3.1. Demographics

Our sample consisted of 68 men (mean age: 43.2 years (SD 5.8), African Americans: 86.6%). The population was primarily unemployed, not married, and heavy substance users. The mean level of TT was 553.9 ng/dL (SD 262.0), median 507 ng/dL, the mean level of FT was 69.5 pg/mL (SD 34.8), median 70.5 pg/mL, mean E2 was 3.2 pg/mL (SD 4.4), median 2.1 pg/mL. We found that 30.9% were hypogonadal. Socio-demographic characteristics of subjects are listed in Table 2.

3.2. Relationship between substance use and sex hormone levels

Sex hormone levels across the substance use groups were evaluated (Supplementary Material Item 2²). Heavy users/methadone maintenance group had a statistically significant lower FT ($p=0.014$). After using the pair-wise comparison, this group had a lower FT, as compared to occasional substance users ($p=0.004$).

3.3. Relationship between cognitive performance and sex hormone levels

After adjustment for age, education, drug use category, depression, and HIV, we observed that higher TT level predicted better performance in the copying of Rey-Osterrieth Complex Figure (coeff.=0.0081, $p=0.022$), as well as higher levels of E2 (coeff.=0.4383, $p=0.033$). Higher E2 predicted better performance in the scoring of identical pictures (coeff.=0.4234, $p=0.013$). TT and E2 predicted a better performance for non-dominant hand use in the Grooved Pegboard test (TT coeff. = -0.0206, $p = 0.019$; E2 coeff. = -1.0788, $p = 0.035$). Only higher E2 predicted a better performance for the dominant hand in the Grooved Pegboard test (coeff.= -1.1165, $p=0.008$). Higher E2 levels predicted better performance in the forward span length with sequence errors in Wechsler Digit Span Test (coeff.=0.0851, $p=0.042$) and in the backward span length with sequence errors (coeff.=0.1080, $p=0.015$). Higher TT and FT were positively correlated with the total recall scoring in the Hopkins Verbal Learning test (TT coeff.=0.0051, $p=0.054$; FT coeff.=0.4, $p=0.054$). Similarly, higher TT and FT predicted better performance in the learning index of the Hopkins Verbal Learning test (TT coeff.= 0.003, $p=0.036$; FT coeff.=0.0231, $p=0.038$).

²Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

Nevertheless, with the use of Bonferroni correction, results were lost. Overall, we did not observe statistically significant correlation between cognitive performance and sex hormone levels (see Supplementary Material Item 3³).

3.4. Comparison of cognitive performance of normogonadal and hypogonadal men

Hypogonadal participants scored better on the Adapted Mini-Mental Status Exam ($p=0.042$), had a superior total recall score in the Hopkins Verbal Learning task ($p=0.045$). These results were lost after Bonferroni correction. Cognitive performance showed a noteworthy overlap in scores, irrespective of hypogonadal state (see Supplementary Material Item 4⁴).

4. DISCUSSION

In this cross-sectional study of men with SU versus group controls, we investigated whether TT, FT and E2 levels were associated with cognitive performance, based on standardized cognitive testing. We found a high prevalence of male hypogonadism (30.9%), consistent with other studies (Brambilla et al., 1977; Celani et al., 1984; Brown et al., 2006), and this was associated with higher SU. The mechanism is likely multifactorial: due to an opiate-related suppression gonadotropin releasing hormone, and possibly a cytokine-mediated inhibition of steroidogenesis in the testis. We suggest screening for hypogonadism in this high-risk population for the possibility that treatment with sex steroids might be beneficial for androgen deficiency syndromes.

Our data suggested that low levels of serum FT and TT did not predict lower cognitive performance in men with SU, independently of age, education, depression, HIV status, and drug use category. Hence, we rejected our hypothesis that low FT and TT were related to cognitive impairment in our cohort.

4.1. Testosterone effects on the brain

Even though clinical and animal data suggested that sex steroids influence cognition (Leranth et al., 2003; Almeida et al., 2004; Schoning et al., 2007), clinical studies are conflicting. A curvilinear relationship between endogenous testosterone and visuospatial abilities has been reported where subjects with intermediate levels performed better than those who had higher and lower testosterone levels (Shute et al., 1983; Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Thilers et al., 2006). Memory and processing capacity and speed performance had a similar relationship (Muller et al., 2005). Silverman et al. (1999) observed a positive correlation between testosterone and visuospatial abilities and Thilers et al. (2006) found a similar association between FT and better visuospatial abilities. Moreover, subjects with higher FT had better semantic memory and episodic memory (Thilers et al., 2006). Yeap et al. (2008) observed higher FT was associated with better performance on the Standardized Mini-Mental State Examination (SMMSE) in a large cohort of older men. A similar positive association was seen in general cognitive performance in other groups (Barrett-Connor et al., 1999; Yaffe et al., 2002). Contrarily, others report no such relationships (Fonda et al., 2005; Martin et al., 2008). Overall, low endogenous testosterone may be associated with some cognitive impairment in older adults; however, we did not find this relationship in our cohort of men with SU. Size of the study, ability to control for multiple confounders may account for some of the differences from previous reports.

³Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁴Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

4.2. The limitations and strengths

We studied men with SU, from a lower socioeconomic background, and with high prevalence of hypogonadism. Thus results should be extrapolated to other settings with prudence. The information of age at exposure to HIV is not available. However, the strengths of this study are well-validated assays and extensive cognitive testing.

5. CONCLUSION

We found a high prevalence of hypogonadism (30.9%) in our study population of men from low socioeconomic status and high prevalence of SU, which has been previously reported. However, endogenous levels of total testosterone, free testosterone or estradiol were not associated with cognitive performance.

We suggest future studies should look into the value of screening for hypogonadism in this high-risk population to examine whether adjunctive therapy with sex steroids might be beneficial for androgen deficiency syndromes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the assistance of Ann V. Munson with data collection. We thank Maya Nadison and Jeffrey Nadison who assisted with proof-reading the manuscript. We especially thank all participants of the Effects of Endocrine Health on Mental Performance of Men and Women Using Drugs study.

Role of Funding Source This research was supported in part by the Johns Hopkins University and by the National Institute on Drug Abuse, National Institutes of Health (grants: 1R01DA014098-01A2, 5R01DA014098-02, 3R01DA014098-03S1, 5R01DA014098-03, 5R01DA014098-04, 5R01DA014098-05). These organizations had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00245531) identifier: NCT00245531.

REFERENCES

- Advani A. Introduction: defining the role of testosterone in the male. *J. Pharm. Pract.* 2011; 24:365. [PubMed: 21984772]
- Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology.* 2004; 29:1071–1081. [PubMed: 15219659]
- Anonymous. Testosterone for ‘late-onset hypogonadism’ in men. *Drug Ther. Bull.* 2010; 48:69–72. [PubMed: 20530029]
- Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. *J. Clin. Endocrinol. Metab.* 1999; 84:3681–3685. [PubMed: 10523014]
- Benton, AL.; Hamsher, KD. Multilingual Aphasia Examination: Manual of Instruction. University of Iowa; Iowa City: 1976.
- Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage.* 2003; 19:1085–1094. [PubMed: 12880834]
- Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology.* 2000; 54:2285–2292. [PubMed: 10881254]
- Bolla KI, Rothman R, Cadet JL. Dose-related neurobehavioral effects of chronic cocaine use. *J. Neuropsychiatry Clin. Neurosci.* 1999; 11:361–369. [PubMed: 10440013]

- Brambilla F, Sacchetti E, Brunetta M. Pituitary-gonadal function in heroin addicts. *Neuropsychobiology*. 1977; 3:160–166. [PubMed: 331136]
- Brandt, J.; Benedict, RHB. Professional Manual. Psychological Assessment Resources, Inc.; Lutz, FL: 2001. Hopkins Verbal Learning Test—Revised.
- Brown TT, Wisniewski AB, Dobs AS. Gonadal and adrenal abnormalities in drug users: cause or consequence of drug use behavior and poor health outcomes. *Am. J. Infect. Dis.* 2006; 2:130–135. [PubMed: 17364020]
- Celani MF, Carani C, Montanini V, Baraghini GF, Zini D, Simoni M, Ferretti C, Marrama P. Further studies on the effects of heroin addiction on the hypothalamic-pituitary-gonadal function in man. *Pharmacol. Res. Commun.* 1984; 16:1193–1203. [PubMed: 6522443]
- de la Rosa RE, Hennessey JV. Hypogonadism and methadone: hypothalamic hypogonadism after long-term use of high-dose methadone. *Endocr. Pract.* 1996; 2:4–7. [PubMed: 15251556]
- Dobs AS. Androgen therapy in AIDS wasting. *Baillieres Clin. Endocrinol. Metab.* 1998; 12:379–390. [PubMed: 10332560]
- Dobs, AS.; Wisniewski, AB. Effects of Endocrine Health on Mental Performance of Men and Women using Drugs. *Clin. Trial.* 2004. NCT00245531
- Educational Testing Service. Hidden Figures Test. Educational Testing Service; Princeton: 1962.
- Egan V, Brett RP, Goodwin GM. The Edinburgh cohort of HIV-positive drug users: pattern of cognitive impairment in relation to progression of disease. *Br. J. Psychiatry.* 1992; 161:522–531. [PubMed: 1393340]
- Ekstrom, RB.; French, JW.; Harman, H.; Derman, D. Kit of Factor-Referenced Cognitive Tests. Educational Testing Service; Princeton, N.J: 1976.
- Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend.* 2002; 66:265–273. [PubMed: 12062461]
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 1975; 12:189–198. [PubMed: 1202204]
- Fonda SJ, Bertrand R, O'Donnell A, Longcope C, McKinlay JB. Age, hormones, and cognitive functioning among middle-aged and elderly men: cross-sectional evidence from the Massachusetts Male Aging Study. *J. Gerontol. A Biol. Sci. Med. Sci.* 2005; 60:385–390. [PubMed: 15860479]
- Fukai S, Akishita M, Yamada S, Hama T, Ogawa S, Iijima K, Eto M, Kozaki K, Toba K, Ouchi Y. Association of plasma sex hormone levels with functional decline in elderly men and women. *Geriatr. Gerontol. Int.* 2009; 9:282–289. [PubMed: 19702939]
- Goldstein RZ, Leskovjan AC, Hoff AL, Hitzemann R, Bashan F, Khalsa SS, Wang GJ, Fowler JS, Volkow ND. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia.* 2004; 42:1447–1458. [PubMed: 15246283]
- Golub ET, Latka M, Hagan H, Havens JR, Hudson SM, Kapadia F, Campbell JV, Garfein RS, Thomas DL, Strathdee SA, STRIVE Project. Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the Beck Depression Inventory. *J. Urban Health.* 2004; 81:278–290. [PubMed: 15136661]
- Gouchie C, Kimura D. The relationship between testosterone levels and cognitive ability patterns. *Psychoneuroendocrinology.* 1991; 16:323–334. [PubMed: 1745699]
- Grant I, Adams KM, Carlin AS, Rennick PM. Neuropsychological deficit in polydrug users. A preliminary report of the findings of the collaborative neuropsychological study of polydrug users. *Drug Alcohol Depend.* 1977; 2:91–108. [PubMed: 15818]
- Grinspoon S, Corcoran C, Miller K, Biller BM, Askari H, Wang E, Hubbard J, Anderson EJ, Basgoz N, Heller HM, Klibanski A. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *J. Clin. Endocrinol. Metab.* 1997; 82:1332–1337. [PubMed: 9141512]
- Hill SY, Reyes RB, Mikhael M, Ayre F. A comparison of alcoholics and heroin abusers: computerized transaxial tomography and neuropsychological functioning. *Curr. Alcohol.* 1979; 5:187–205. [PubMed: 755621]

- Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat. Med.* 1990; 9:811–818. [PubMed: 2218183]
- Hoff AL, Riordan H, Morris L, Cestaro V, Wieneke M, Alpert R, Wang GJ, Volkow N. Effects of crack cocaine on neurocognitive function. *Psychiatry Res.* 1996; 60:167–176. [PubMed: 8723307]
- Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M. The Hopkins Verbal Learning Test and screening for dementia. *Dement. Geriatr. Cogn. Disord.* 2002; 13:13–20. [PubMed: 11731710]
- Holman BL, Mendelson J, Garada B, Teoh SK, Hallgring E, Johnson KA, Mello NK. Regional cerebral blood flow improves with treatment in chronic cocaine polydrug users. *J. Nucl. Med.* 1993; 34:723–727. [PubMed: 8478703]
- Janowsky JS. The role of androgens in cognition and brain aging in men. *Neuroscience.* 2006; 138:1015–1020. [PubMed: 16310318]
- Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. *Endocrinol. Metab. Clin. North Am.* 2007; 36:333–348. [PubMed: 17543722]
- Klove H. Clinical neuropsychology. *Med. Clin. North Am.* 1963; 47:1647–1658. [PubMed: 14078168]
- Lafisca S, Bolelli G, Franceschetti F, Danieli A, Tagliaro F, Marigo M, Flamigni C. Free and bound testosterone in male heroin addicts. *Arch. Toxicol. Suppl.* 1985; 8:394–397. [PubMed: 3938270]
- LeBlanc ES, Wang PY, Janowsky JS, Neiss MB, Fink HA, Yaffe K, Marshall LM, Lapidus JA, Stefanick ML, Orwoll ES. Association between sex steroids and cognition in elderly men. *Clin. Endocrinol. (Oxf.)*. 2010; 72:393–403. [PubMed: 19744108]
- Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. *J. Neurosci.* 2003; 23:1588–1592. [PubMed: 12629162]
- Lezak, MD.; Howieson, DB.; Loring, DW.; Hannay, HJ.; Fischer, JS. *Neuropsychological Assessment.* Oxford University Press; USA: 2004.
- Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol. Biochem. Behav.* 2005; 81:319–330. [PubMed: 15925403]
- Martin DM, Wittert G, Burns NR. Gonadal steroids and visuo-spatial abilities in adult males: implications for generalized age-related cognitive decline. *Aging Male.* 2007a; 10:17–29. [PubMed: 17454979]
- Martin DM, Wittert G, Burns NR, Haren MT, Sugarman R. Testosterone and cognitive function in ageing men: data from the Florey Adelaide Male Ageing Study (FAMAS). *Maturitas.* 2007b; 57:182–194. [PubMed: 17287097]
- Martin DM, Wittert G, Burns NR, McPherson J. Endogenous testosterone levels, mental rotation performance, and constituent abilities in middle-to-older aged men. *Horm. Behav.* 2008; 53:431–441. [PubMed: 18190916]
- McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, Graham NM, McArthur JH, Selnes OA, Jacobson LP. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology.* 1993; 43:2245–2252. [PubMed: 8232937]
- McHale S, Hunt N. Executive function deficits in short-term abstinent cannabis users. *Hum. Psychopharmacol.* 2008; 23:409–415. [PubMed: 18421794]
- Moffat SD. Effects of testosterone on cognitive and brain aging in elderly men. *Ann. N. Y. Acad. Sci.* 2005; 1055:80–92. [PubMed: 16387720]
- Moffat SD, Hampson E. A curvilinear relationship between testosterone and spatial cognition in humans: possible influence of hand preference. *Psychoneuroendocrinology.* 1996; 21:323–337. [PubMed: 8817730]
- Muller M, Aleman A, Grobbee DE, de Haan EHF, van der Schouw YT. Endogenous sex hormone levels and cognitive function in aging men: is there an optimal level? *Neurology.* 2005; 64:866–871. [PubMed: 15753424]
- Nelson CJ, Lee JS, Gamboa MC, Roth AJ. Cognitive effects of hormone therapy in men with prostate cancer: a review. *Cancer.* 2008; 113:1097–1106. [PubMed: 18666210]
- O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. *Am. J. Drug Alcohol Abuse.* 1992; 18:131–144. [PubMed: 1562011]

- Rabkin JG, Rabkin R, Wagner GJ. Testosterone treatment of clinical hypogonadism in patients with HIV/AIDS. *Int. J. STD AIDS*. 1997; 8:537–545. [PubMed: 9292341]
- Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch. Gen. Psychiatry*. 2000; 57:141–7. discussion 155–6. [PubMed: 10665616]
- Radloff LS. The CES-D Scale. *Appl. Psychol. Measure*. 1977; 1:385–401.
- Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer*. 2004; 100:851–858. [PubMed: 14770444]
- Rasheed A, Tareen IA. Effects of heroin on thyroid function, cortisol and testosterone level in addicts. *Pol. J. Pharmacol*. 1995; 47:441–444. [PubMed: 8868137]
- Reitan R. The validity of the Trail Making Test as an indicator of organic brain damage. *Percept. Mot. Skills*. 1958; 271:276.
- Reitan RM. The relation of the Trail Making Test to organic brain damage. *J. Consult. Psychol*. 1955; 19:393–394. [PubMed: 13263471]
- Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie*. 1964; 122:340–382.
- Rosselli M, Ardila A, Lubomski M, Murray S, King K. Personality profile and neuropsychological test performance in chronic cocaine-abusers. *Int. J. Neurosci*. 2001; 110:55–72. [PubMed: 11697211]
- Salminen EK, Portin RI, Koskinen A, Helenius H, Nurmi M. Associations between serum testosterone fall and cognitive function in prostate cancer patients. *Clin. Cancer Res*. 2004; 10:7575–7582. [PubMed: 15569988]
- Schoning S, Engelien A, Kugel H, Schafer S, Schiffbauer H, Zwislerlood P, Pletziger E, Beizai P, Kersting A, Ohrmann P, Greb RR, Lehmann W, Heindel W, Arolt V, Konrad C. Functional anatomy of visuo-spatial working memory during mental rotation is influenced by sex, menstrual cycle, and sex steroid hormones. *Neuropsychologia*. 2007; 45:3203–3214. [PubMed: 17689571]
- Selnes OA, Galai N, McArthur JC, Cohn S, Royal W 3rd, Esposito D, Vlahov D. HIV infection and cognition in intravenous drug users: long-term follow-up. *Neurology*. 1997; 48:223–230. [PubMed: 9008522]
- Sherwin BB. Steroid hormones and cognitive functioning in aging men: a mini-review. *J. Mol. Neurosci*. 2003; 20:385–393. [PubMed: 14501023]
- Shute VJ, Pellegrino JW, Hubert L, Reynolds RW. The relationship between androgen levels and human spatial abilities. *Bull. Psychonom. Soc*. 1983; 21:456–468.
- Silberstein CH, O'Dowd MA, Chartock P, Schoenbaum EE, Friedland G, Hartel D, McKegney FP. A prospective four-year follow-up of neuropsychological function in HIV seropositive and seronegative methadone-maintained patients. *Gen. Hosp. Psychiatry*. 1993; 15:351–359. [PubMed: 8112557]
- Silverman I, Kastuk D, Choi J, Phillips K. Testosterone levels and spatial ability in men. *Psychoneuroendocrinology*. 1999; 24:813–822. [PubMed: 10581652]
- Simon SL, Domier C, Carnell J, Brethen P, Rawson R, Ling W. Cognitive impairment in individuals currently using methamphetamine. *Am. J. Addict*. 2000; 9:222–231. [PubMed: 11000918]
- Singh RJ. Validation of a high throughput method for serum/plasma testosterone using liquid chromatography tandem mass spectrometry (LC-MS/MS). *Steroids*. 2008; 73:1339–1344. [PubMed: 18703076]
- Thilers PP, Macdonald SW, Herlitz A. The association between endogenous free testosterone and cognitive performance: a population-based study in 35 to 90 year-old men and women. *Psychoneuroendocrinology*. 2006; 31:565–576. [PubMed: 16487665]
- Ulubaev A, Lee DM, Purandare N, Pendleton N, Wu FCW. Activational effects of sex hormones on cognition in men. *Clin. Endocrinol. (Oxf.)*. 2009; 71:607–623. [PubMed: 19250266]
- Wechsler, D. Wechsler Adult Intelligence Scale-Revised Manual. The Psychological Corporation; New York: 1981.
- Wechsler, D. Wechsler Memory Scale-III. The Psychological Corporation; New York: 1997.

- Weckowicz TE. Perception of hidden pictures by schizophrenic patients. *AMA Arch. Gen. Psych.* 1960; 2:521–527.
- Wheeler MJ, Barnes SC. Measurement of testosterone in the diagnosis of hypogonadism in the ageing male. *Clin. Endocrinol. (Oxf.)*. 2008; 69:515–525. [PubMed: 18616710]
- Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. *J. Am. Geriatr. Soc.* 2002; 50:707–712. [PubMed: 11982672]
- Yeap BB, Almeida OP, Hyde Z, Chubb SAP, Hankey GJ, Jamrozik K, Flicker L. Higher serum free testosterone is associated with better cognitive function in older men, while total testosterone is not. The Health In Men Study. *Clin. Endocrinol. (Oxf.)*. 2008; 68:404–412. [PubMed: 17888021]
- Young LA, Neiss MB, Samuels MH, Roselli CE, Janowsky JS. Cognition is not modified by large but temporary changes in sex hormones in men. *J. Clin. Endocrinol. Metab.* 2010; 95:280–288. [PubMed: 19880786]

Table 1

Cognitive tests.

Cognitive domain	Test	Description
Baseline cognition	Adapted Mini-Mental Examination (Folstein et al., 1975)	Participants are required to provide a vocal response that covers orientation, memory, and attention. They are then being tested for the ability to name, follow written and verbal commands, and copy a complex picture.
Working memory	Wechsler Digit Span Test (Wechsler, 1981)	The examiner verbally presents digits at a rate of one per second. The “forward test” required the subject to repeat the digits verbatim. The “backward test” obliged the subject to say again the digits in reverse order. The number of digits increases by one until the subject consecutively fails to repeat the numbers twice, in the same digit span length.
	Letter Number Sequencing Test (WAIS-III) (Wechsler, 1997)	Participants are asked to recall combinations of numbers and letters, numbers in ascending order, and then letters in alphabetical order.
Verbal learning and memory	The Hopkins Verbal Learning Test (Brandt and Benedict, 2001; Hogervorst et al., 2002)	Participants are required to recall a list of words immediately after presentation and following a 20 minutes delay. In addition, participants are asked to recognize which words were originally presented to them from a list of target and distracter words.
Verbal fluency	FAS Verbal Fluency Test (Benton and Hamsher, 1976)	Participants are required to generate lexical words that begin with given letters (F, A, and S).
Visuomotor and visuoconstruction abilities	Rey-Osterrieth Complex Figure (copy, immediate and delayed recall) (Rey, 1964)	Participants are asked to copy a complex two-dimensional drawing, and then the original figure was removed from view, and the subject was asked to reproduce the figure from memory 20 minutes later (delayed recall).
Visuospatial abilities	Card Rotation Test (Ekstrom et al., 1976)	Participants are required to mentally rotate a 2-dimensional object in their mind and match the rotated figure to one of a series of possible answers.
	Hidden Figures Test (Weckowicz, 1960; Educational Testing Service, 1962)	Participants are required to decide which piece of a figure is embedded in a more complex figure from five response options.
Graphomotor and psychomotor speed, executive function, and divided attention	Trail Making Tests (Parts A and B) (Reitan, 1955; Reitan R., 1958)	Participants are required to connect consecutively numbered circles with a line (Part A). Additionally to connect consecutively numbered and lettered circles in sequence, alternating between numbers and letters (Part B).
Psychomotor and fine motor performance	Identical Pictures Test (Ekstrom et al., 1976)	Participants are required to match a test item to an identical picture. Participants are required to identify a picture amongst a group of similar-appearing distracting images.
	Grooved Pegboard Test (Klove, 1963)	Participants are required to place 25-keyed pegs into an array of 25 slotted holes as quickly as possible. The dominant and nondominant hands are tested separately.

Table 2

Socio-demographic characteristics of patients

	n = 68	n (%)
Age	<40	16 (23.5%)
	40-50	52 (76.5%)
Race	African Americans	58 (86.6%)
	Other	9 (13.4%)
Income per year	<\$5,000	15 (29.4%)
	\$5,001-10,000	36 (70.6%)
Education	<12 years	29 (42.6%)
	12 years	39 (57.4%)
HIV Status	Not infected	32 (47.1%)
	Infected	36 (52.9%)
Drug use status	Non-users	20 (29.4%)
	Occasional users	14 (20.6%)
	Heavy users / methadone maintenance	34 (50%)
Gonadal status	Hypogonadal	21 (30.9%)
	Normogonadal	47 (69.1%)
Marital status	Not married	60 (89.6%)
	Married	7 (10.4%)
Public Assistance?	No	38 (56.7%)
	Yes	29 (43.3%)
In the past year received public assistance	No	39 (59.1%)
	Yes	27 (40.9%)
In the past year been homeless	No	48 (72.7%)
	Yes	18 (27.3%)
Currently employed	No	59 (86.8%)
	Yes	9 (13.2%)
In the past year been unemployed	No	18 (26.5%)
	Yes	50 (73.5%)