Relationship of estrogen synthesis capacity in the brain with obesity and self-control in men and women

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Gonadal hormones are linked to mechanisms that govern appetitive behavior and its suppression. Estrogens are synthesized from androgens by the enzyme aromatase, highly expressed in the ovaries of reproductive-aged women and in the brains of men and women of all ages. We measured aromatase availability in the amygdala using positron emission tomography (PET) with the aromatase inhibitor [^{11}C]vorozole in a sample of 43 adult, normal-weight, overweight, or obese men and women. A subsample of 27 also completed personality measures to examine the relationship between aromatase and personality traits related to self-regulation and inhibitory control. Results indicated that aromatase availability in the amygdala was negatively associated with body mass index (BMI) (in kilograms per square meter) and positively correlated with scores of the personality trait constraint independent of sex or age. Individual variations in the brain's capacity to synthesize estrogen may influence the risk of obesity and self-control in men and women.

aromatase | obesity | estrogen | amygdala | PET imaging

Obesity, defined as having a body mass index (BMI) of 30 or more, is a major public health problem affecting the quality of life and life expectancy of millions of individuals (1–4). The causes of obesity are complex (5, 6), and despite significant investment in behavioral and public health measures focused on intervention and prevention (7–9), the prevalence of obesity continues to rise (10) and most treatment approaches have only a modest short-term benefit (e.g., ref. 6). Sex hormones are known to influence adiposity in both men and women through brain as well as peripheral (11) mechanisms. Estradiol is a well-characterized anorexic agent, while androgens appear to have the opposite effect (reviewed in ref. 12). Estrogenic stimulation has been shown to inhibit feeding behavior in rodents, primarily through estrogen receptor α (ERα), in several brain regions including the extended amygdala (12–16). In addition to direct effects on ingestive behavior, central estrogenic effects also mediate a range of neurocognitive traits (17, 18), in particular inhibitory behavior in the context of uncertainty or stress (19, 20), which may contribute to individual differences in feeding behavior and self-control (21–23). The latter hypothesis is supported by recent reports linking personality traits related to self-control to amygdala levels of aromatase, the last and obligatory enzyme in the biosynthesis of estrogens from androgenic precursors (24, 25).

Aromatase activity in the human fetal brain was described in the early 1970s (26). However, it took several decades for the presence and activity of aromatase in the adult human and animal brain and other organs to be described (27, 28) and for its contributions to human physiology (29) and specific estrogen effects on the brain, including hippocampal integrity (30), memory (31), and aggression (32, 33) to be appreciated.

The possible contribution of regional aromatase in the brain and its resultant brain region-specific estrogen production in the context of human obesity has not been investigated to date. The amygdala is a brain region that has been shown to contain very high levels of aromatase in rodents, monkeys, and humans (27, 28, 34, 35). It is central to the control of emotional arousal and has been implicated in control of feeding behavior in animals (36–41). In humans, the amygdala has been shown to be involved in hunger-enhanced memory for food stimuli, cued appetitive response to food (42), and cognitive inhibition of brain activation elicited by food stimulation (43). Functional imaging studies support activation of these amygdala networks when viewing food/eating images, especially when hungry (44–47), and their dysregulation among obese men and women. Consequently, the amygdala offers a viable target for local brain estrogen to influence the effective neuronal circuitry that underlies cue responsivity and decision making in response to food environments.

Here, we compared aromatase availability in the amygdala, measured with positron emission tomography (PET) and the aromatase-specific radiotracer [^{11}C]vorozole (34, 35), in otherwise-healthy obese, overweight, and healthy-weight men and women. We hypothesized a negative relationship between brain aromatase availability, as measured by [^{11}C]vorozole in the amygdala, and BMI, because of the amygdala's specific role in feeding-related memory (46), food preference (48), ability to override hypothalamic signaled satiety (38–40), and estrogen sensitive function (47). Consistent with

Significance

Obesity is a major public health problem in a growing proportion of children and adults in the developed world. Estrogen influences body weight and behavioral responses to appetitive stimuli. Estrogen biosynthesis is catalyzed by the enzyme aromatase in all organs measured, including the brain. Using the aromatase radiotracer [^{11}C]vorozole, we measured aromatase availability in the amygdala in healthy-weight to obese adults. Obesity was associated with lower aromatase availability and less constraint independent of sex and age. Variability in brain estrogen synthesis may contribute to obesity by directly regulating feeding and broadly by affecting self-control. These findings suggest that brain aromatase imaging offers a method for characterizing the role of brain estrogen in obesity and other impairments in self-regulation.

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Table 1. Comparison between men and women on aromatase availability, age, and personality trait constraint

	Men (n = 12)	Women (n = 15)
Age	41.2 ± 16.4	37.5 ± 16.8
Aromatase in amygdala (V_T)	2.8 ± 0.60	3.0 ± 0.82
Constraint	54.3 ± 8.0	56.5 ± 7.7

Note. There were no significant differences between groups (>0.05).

this hypothesis, we further examined the relationship between aromatase availability and trait level constraint in a subset of the sample. We predicted a positive relationship between amygdala aromatase and constraint, consistent with findings that obese individuals generally show higher trait levels of disinhibition and food cue impulsivity (47). These deficits in self-control are implicated in the individual risk found in a growing worldwide obesogenic environment (49).

Results

The participants (n = 43) were on average 40.4 ± 14.2 y old with a BMI of 28.1 ± 6.8 kg/m^2. Table 1 summarizes differences in study variables by sex. A sex-by-weight category two-way ANOVA indicated healthy-weight women (n = 9, 42 ± 18 y old) and men (n = 7, 38.8 ± 17.9 y old,) overweight women (n = 8, 37.2 ± 11.5) and men (n = 7, 43.3 ± 11.7 y old), and obese women (n = 7, 43.4 ± 15.8) and men (n = 5, 36 ± 8.0 y old) did not significantly differ on age by sex (F = 0.13, P = 0.72) or weight category (F = 0.015, P = 0.98).

Regression models indicated moderate negative relationships between amygdala aromatase availability and BMI (β = −8.40, SE = 2.18, $P < 0.001$) when controlling for age and sex [$F_{(4,38)}$ = 7.06, $P < 0.0001$, adjusted R^2 = 0.37]. As summarized in Fig. 1, slopes did not significantly differ between men and women (β = −0.19, SE = 6.84, P = 0.98). Circulating testosterone and estrogen were not predictive of BMI and did not significantly improve the fit to the model.

Amygdala aromatase availability in men and women (n = 27) positively correlated with individual differences in the trait constraint (β = 4.94, SE = 2.24, $P < 0.05$), and this relationship did not differ by sex (β = −3.43, SE = 12.10, P = 0.78). Fig. 2 summarizes the regression model. Aromatase availability explained 15.5% of the variance (Fig. 2) in constraint, controlling for age and sex. Table 2 summarizes correlations by gender for constraint and its component traits: Harm-Avoidance, Control, and Traditionalism.

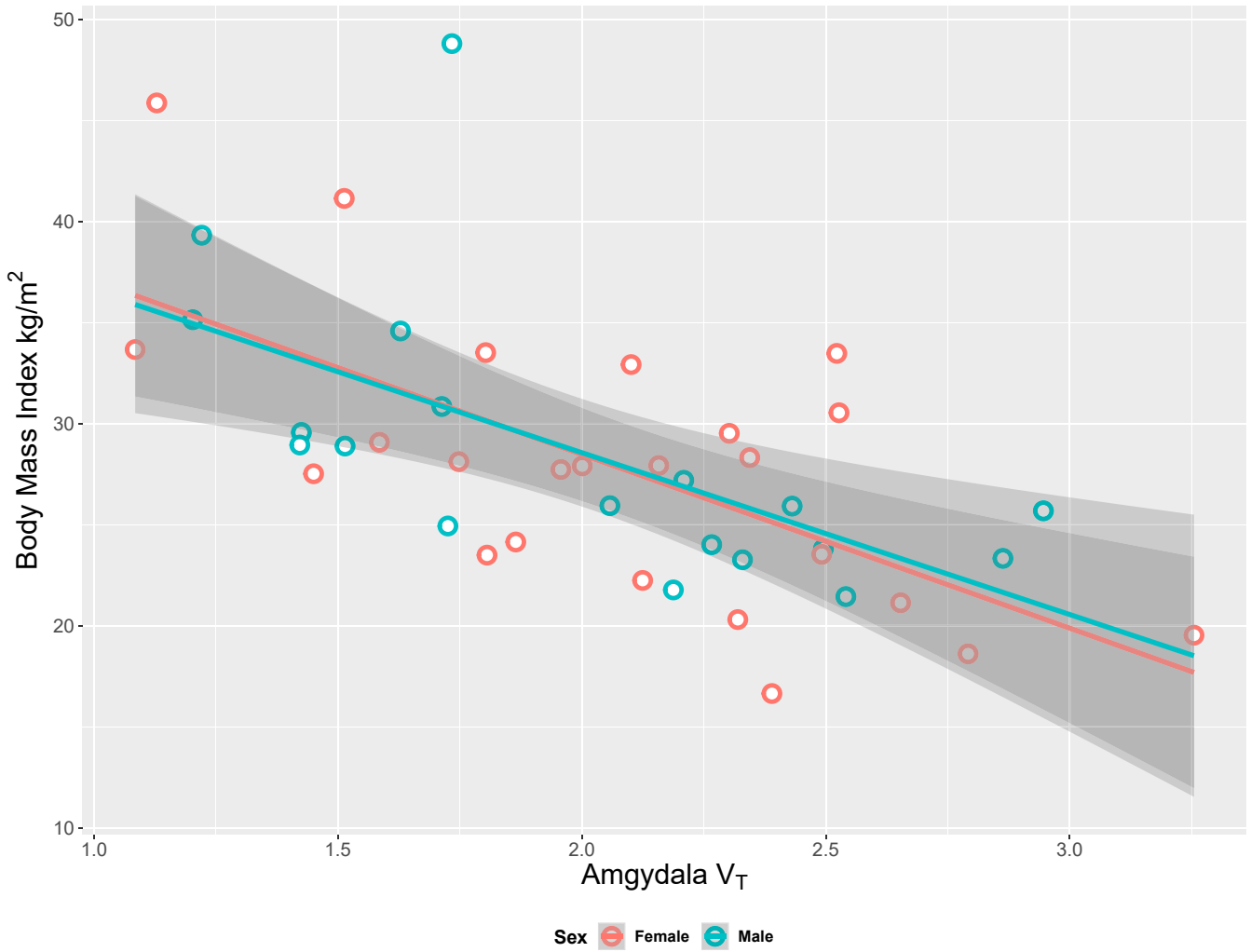

Fig. 1. [^{11}C]Vorozole in amygdala and body mass index (BMI) in men and women. The negative relationship between BMI (in kilograms per square meter) and aromatase availability (V_T) in amygdala showed no significant difference between men and women. The gray bands represent 95% confidence intervals. V_T, total volume of distribution.

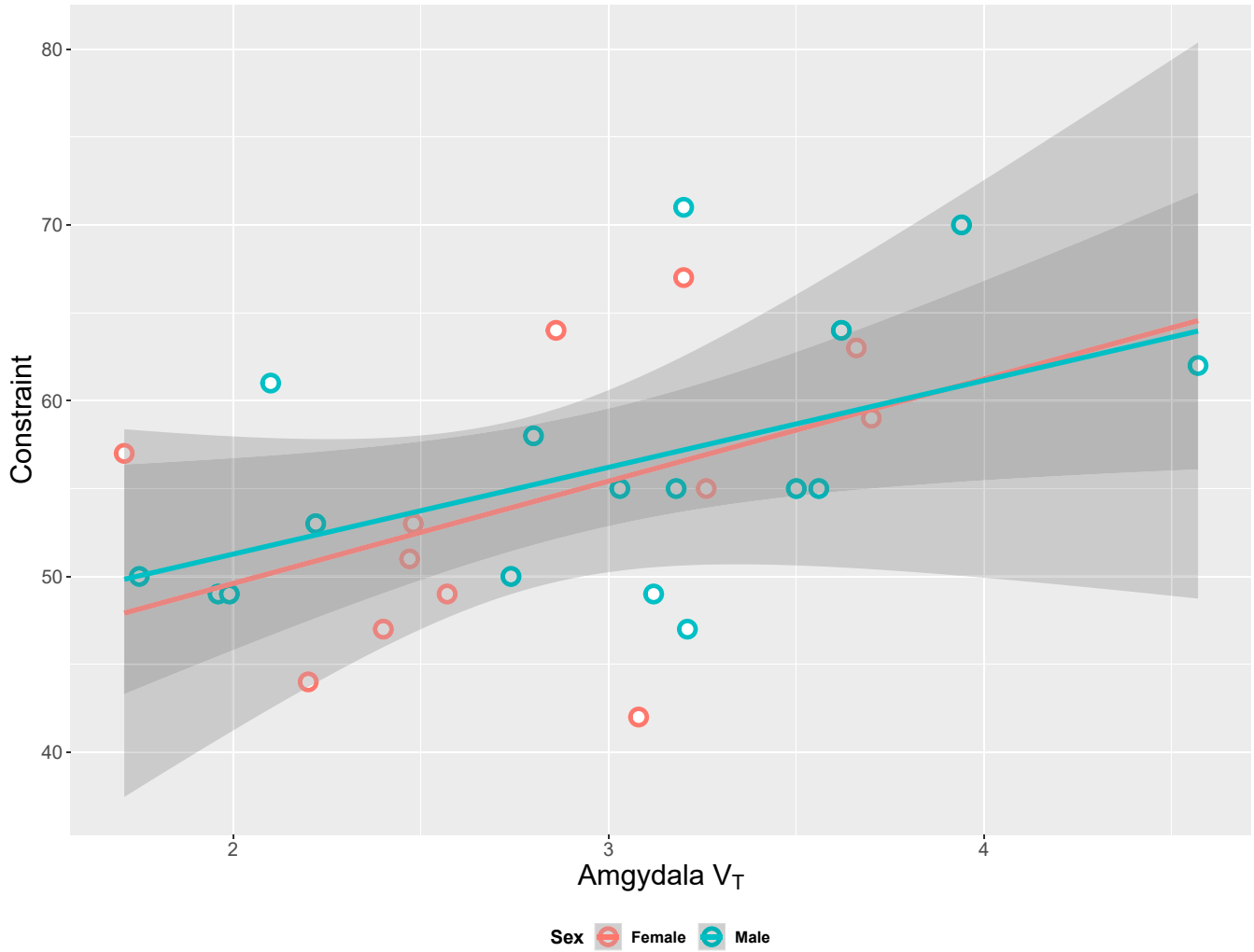

Fig. 2. [^{11}C]Vorozole in amygdala and trait constraint in men and women. The positive relationship between trait level constraint and aromatase availability (V_T) in amygdala did not significantly differ between men and women. The gray bands represent 95% confidence intervals. V_T, distribution volume.

Discussion

Using a combination of in vivo imaging and neuropsychology, we show that aromatase availability in the amygdala, representing estrogen synthesis capacity in this region, is significantly and negatively correlated with BMI in healthy men and women. Aromatase availability in the amygdala also positively correlated with scores on the personality trait constraint as measured by the Multidimensional Personality Questionnaire (MPQ) (50). Many personality theories consider the personality construct of constraint (related to behavioral disinhibition) as a key component of human behavior. Indeed, some suggest that constraint represents a biologically based system of effortful control that is associated with conscientiousness and moderates impulsive behavior—particularly as it relates to health behaviors (50–53). These results are consistent with recent work completed by Takahashi et al. (24) demonstrating similar relationship with trait harm avoidance. Taken together, these results support the hypothesis that estrogen produced locally in the amygdala contributes to the regulation of BMI via an intracrine mechanism (54) affecting the ability to inhibit feeding behavior in response to stress (55).

This interpretation does not exclude additional mechanisms, the relative contribution of which may vary with sex and hormonal status (e.g., menstrual cycle, menopause). To elaborate, ovarian aromatase activity in premenopausal women, which fluctuates across the menstrual cycle, is responsible for high (relative to males and postmenopausal females) although fluctuating levels of estrogens in the circulation. Estrogens freely cross the blood–brain barrier and interact with brain ER. This interaction appears to be synergistic with that of brain-derived estrogen in suppressing eating behavior, as evidenced by the inverse correlation between eating behavior and plasma estrogen across the menstrual cycle (12, 13, 56, 57). It is also possible that, in men, the primary mechanism responsible for the negative correlation between brain/amygdala

Table 2. Pearson correlations between aromatase amygdala availability and personality measures

	Aromatase availability: amygdala		
MPQ personality traits	Total sample (n = 27)	Men (n = 12)	Women (n = 15)
Constraint	0.49**	0.43	0.52*
Control	0.27	−0.02	0.41
Harm Avoidance	0.38	0.17	0.50
Traditionalism	0.24	0.65*	0.05

Note. *Correlation is significant at the $P < 0.05$ level; **correlation is significant at the $P < 0.01$ level.

aromatase availability and obesity is not only the increase in estrogens but also the concomitant decrease in testosterone and resultant decreased stimulation of brain androgen receptors (ARs). High levels of ARs appear to present in all of the brain regions expressing aromatase (58), including amygdala, and AR density is higher in the male brain relative to the female brain in all regions tested, while the opposite is true for ER (59–61). Since androgens increase meal size (62, 63) and estrogen decreases meal size (12, 16), the effect of aromatase on eating behavior is likely to result from its effect on both hormones, but increased levels of estrogens exert a stronger effect in females and the concomitant decrease in testosterone is more important in men.

We did not observe significant sex differences in our study. Despite greater prevalence of obesity among women (64), weight loss efficacy appear to be similar (65–67) or favor better longer-term weight outcomes for women (68), with some evidence of modest short-term benefits for men (69). This finding also raises the potential for amygdala aromatase to be a sex-neutral contributor to BMI, although longitudinal analyses are necessary to determine whether amygdala aromatase levels moderate weight loss outcomes for obese men and women.

In summary, this study shows a direct correlation between aromatase availability in the human amygdala and BMI. A potential extension of this work is to examine other brain regions where estrogen was shown to regulate appetite and energy utilization (although some of these are too small to be visualized with the spatial resolution of available PET scanners) and determine the value of aromatase measures to discriminate between binge eating and healthy populations (16) or predict weight changes in adult populations. Until direct measures of brain ER and AR density or occupancy are available for human in vivo studies, aromatase offers an important measure of the brain estrogen system in men and women.

Methods and Materials

Participants. Forty-three healthy men (n = 19) and women (n = 24), with a mean age of 40.4 y (range, 21 to 67) and mean BMI of 28 (range, 17 to 49) responded to advertisements placed in local newspapers or flyers posted and had brain scans performed in Brookhaven National Laboratory. A subgroup of 29 participants (17 women, 12 men; mean age, 41.2 ± 16.4 y) also underwent neuropsychological evaluation. All reproductively competent women were scanned in the follicular phase of the menstrual cycle (5–10 d from the beginning of menstrual flow). Participants were included if they were healthy adults and ≤50 BMI. Exclusions included 1) obesity of known genetic or endocrine origin; 2) current or history of hypertension, major depression, Parkinson's disease, stroke, or diabetes; 3) physical (e.g., brain trauma) or behavioral conditions (e.g., substance abuse) that can alter brain structure and function; 4) current or past use of hormone replacement therapy or aromatase inhibitors; 5) positive toxicology screen for psychoactive substance or medication. All participants had a full physical, psychiatric, and neurological examination. The study received human subjects approval from Stony Brook University, and all participants provided written informed consent prior to participation.

Personality Measures. Participants completed the MPQ (50, 56), a three-factor, self-report structural model of personality. The MPQ models three high-order dimensions of personality: Negative Emotionality (constructed from the subscales: Stress Reaction, Alienation, and Aggression) reflects the tendency toward emotional distress. Positive Emotionality (constructed from Well-Being, Social Potency, Achievement, and Social Closeness) reflects an individual's positive affect through interpersonal engagement. Constraint (from Control, Harm Avoidance, and Traditionalism) measures tendency of self-regulation. For some, Constraint is motivated by avoiding potentially harmful events or people as in Harm Avoidance and by the need for self-control, while for others Constraint is motivated by traditional views on sex roles and justice (65). Studies show that individuals who score low on Constraint will score high on measures of impulsivity (65, 66).

PET Scans. PET scans were run on a whole-body positron emission tomograph (Siemen's HR+, 4.5 × 4.5 × 4.8 mm at center of field of view) in three-dimensional dynamic acquisition mode as previously described (34, 35). Briefly, participants received an injection of [^{11}C]vorozole (3 to 8 mCi; specific activity >0.1 Ci/μmol at time of injection) and were scanned for a total of 90 min. Arterial blood samples were obtained and centrifuged to obtain plasma, which was counted, and selected samples assayed for the presence of unchanged [^{11}C]vorozole as described previously (34). Circular regions of interest were placed over the amygdala bilaterally guided by each individual's MRI and the resultant time–activity curves and metabolite corrected plasma input function were used for kinetic analysis and calculation of the total volume of distribution (V_T) using Logan graphic analysis and the two-tissue compartment model, as previously described in baboons and humans (70, 71). We chose this method, which requires placement of arterial lines, over the simpler alternatives such as calculating standardized uptake values, as we have recently done when performing breast imaging with [^{11}C]vorozole in a homogeneous population of elderly women (72) without arterial input. In this study, we included men and women with a wide age and BMI range. Biological sex, age, hormonal environment, and obesity are all likely to affect tracer kinetics and clearance from plasma so it was considered imperative to obtain individual arterial input functions and conduct full kinetic analysis to control for these effects.

Statistical Analyses. We used ANOVA and linear regression to model relationship between amygdala V_T and BMI, controlling for age. We also performed two-tailed Pearson correlations between amygdala V_T and MPQ dimensions both across the whole sample and as a function of sex. We further tested the difference in regression slopes between the separate personality-by-sex correlations. We set the a priori α level at $P < 0.05$.

Data Availability. All study data are included in the article and *SI Appendix*.

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