

Sex hormones, sex chromosomes, and sexual differentiation of the brain

Published: 11-10-2010

Last updated: 04-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON36349

Source

ToetsingOnline

Brief title

Sex hormones, sex chromosomes, and the brain

Condition

- Other condition
- Reproductive tract and breast disorders congenital
- Sexual dysfunctions, disturbances and gender identity disorders

Synonym

disorder of sex development, testicular feminization

Health condition

Sexual differentiation of the brain

Research involving

Human

Sponsors and support

Primary sponsor: Netherlands Institute for Neuroscience

Source(s) of monetary or material Support: NWO Vici

Intervention

Keyword: brain development, complete androgen insensitivity, sex differences, sexual differentiation

Outcome measures

Primary outcome

The parameters of interest include brain morphology, the ability to detect AND, CEOAE scores, 2D:4D ratios, brain activity in the resting state as well as in response to AND presentation and two cognitive tasks during the fMRI experiment, and estrogen (estradiol and ethinylestradiol), LH, FSH, progesterone and testosterone levels on the test day.

Secondary outcome

N/A

Study description

Background summary

The sexual differentiation of the brain, to be male- or female-typical, is an active area of research in both humans and in non-human animal models. The precise factors that produce such sexual differentiation have yet to be fully elucidated, but many aspects of this process have been described. The determination of sex begins with the sex chromosomes. Females typically have two X-chromosomes and males typically have one X- and one Y-chromosome. The presence of the Y-chromosome begins a cascade toward the development of the male gonads (testes), and in the absence of this chromosome, female gonads (ovaries) develop. Sexual differentiation of the body and brain to produce a male or female-typical phenotype is then patterned by the presence of testosterone from testes in males, and the absence of testosterone in females. Testosterone, acting at androgen receptors or estrogen receptors (testosterone

can be converted to estrogen by the enzyme aromatase in local tissues) produces changes throughout the body and brain to produce a typical male, while the absence of testosterone results in a typically female body and brain.

Recent work has shed light on previously unknown details in this process. In particular, the contribution of the Y-chromosome, independent of its role in directing the formation of the gonads, appears to be important in producing sex-typical brain structure and function. The presence or absence of the Y-chromosome, independent of testicular formation and testosterone production, can alter sexual behavior in mice, indicating its importance in the development of male-typical brain and behavior.

There are individuals for whom sexual development does not follow the usual path. These individuals provide a unique opportunity to study how sex hormones and sex chromosomes act to produce sexual differentiation of the brain. Women with complete androgen insensitivity syndrome (CAIS) have XY chromosomes (like males), but cannot respond to testosterone due to genetic mutations resulting in a non-functional androgen receptor. Therefore, while they carry the Y-chromosome, develop testes, and produce testosterone, the absence of the androgen receptor results in a female phenotype. However, other genes on the Y-chromosome may be producing developmental effects that are male-typical, as in mice. CAIS women then enable us to study how the absence of the ability to respond to androgens, and the presence of the Y-chromosome, independent of its role in the development of the testes, produce sexual differentiation of the brain.

Study objective

Our objective is to determine the role of androgens and the Y-chromosome in sexual differentiation of the brain. Women with CAIS, who only differ from typical women in that they have a Y-chromosome, and from men in that they cannot respond to androgens, will be compared to typical males and females in measures of brain structure and function. If androgens are necessary for the sexual differentiation of the male-typical brain, then CAIS woman will have at least some female-typical brain structure/function when compared to control males. If the Y-chromosome is sufficient for the sexual differentiation of the male-typical brain, independent of sex hormones, then CAIS women will have at least some male-typical brain structure/function when compared to control females.

Study design

Our subjects, CAIS women and age/education-matched heterosexual males, heterosexual females, heterosexual transsexuals and homosexual transsexuals (controls), will fill out questionnaires pertaining to their demographics, health, sexuality, and gender identity. The subjects will then engage in a

number of tasks that produce sex differences in brain activity. Olfactory performance and the ability to detect the chemosignal androstadienone (AND) will be determined for each individual. We will record click-evoked otoacoustic emissions (CEOAEs) at subjects' ears and take a photocopy of both hands in order to measure the length of the second and fourth digit to determine the 2D:4D ratio. We will measure functional brain activity with functional magnetic resonance imaging (fMRI) in response to AND, two cognitive tasks and during the resting state, and we will also obtain structural MRI scans. We will also take blood samples from our subjects to measure their estrogen (estradiol and ethinylestradiol), LH, FSH, progesterone and testosterone levels on the testing day. We will then use between- and within-group comparisons on these measures to examine the role of sex androgens and the Y-chromosomes in the sexual differentiation of brain structure and function.

Study burden and risks

Subjects will be asked to come to the lab once. In this session, lasting approximately 2.5 hours, subjects will fill out our neuropsychological questionnaires, smell different odors and be asked questions about them, have click-evoked otoacoustic emissions recorded and digit length measured (by photocopy), participate in fMRI scans, and provide a blood sample.

The risks associated with participation are considered negligible. Distress due to neuropsychological testing is expected to be minimal and olfactory chemosignal presentation is not expected to adversely affect subjects. The fMRI scan procedure is not expected to produce any adverse effects.

This study can only be completed with the CAIS subject group because of their unique sex chromosomal makeup.

Subjects will be compensated with a gift voucher worth € 40,- and for their travel expenses.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

All subjects: Right-handed, Normative olfactory performance, Written informed consent obtained; Healthy Volunteers: Heterosexual orientation, Sex-typical gender identity; Transsexual controls: Genetically male, sex-atypical gender identity; Patients: Diagnosis of complete androgen insensitivity syndrome (CAIS)

Exclusion criteria

All subjects: Smoking, Excessive drug/alcohol use, Psychiatric and Neurological illness, Significant physical illness (excluding diagnosis of CAIS), Anosmia or hyposmia, MRI contraindications ; Healthy Volunteers (20 men and 20 of 40 women): Hormone therapy or birth control pills

Study design

Design

Study type: Observational non invasive

Intervention model: Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	05-07-2011
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO	
Date:	11-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	05-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	14-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	08-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32740.029.10