The role of central reward and satiety centers in the etiology of obesity: genetic and environmental influences

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The overarching goal of this proposal is to investigate the environmental and genetic influences on the activity of CNS reward and satiety circuits, and to investigate whether these differences are causal to the development of obesity in humans.In...

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

Summary

ID

NL-OMON40336

Source
ToetsingOnline

Brief title
Obesity and Brain: Genes and Environment

Condition

- Other condition

Synonym
Obesity, overweight

Health condition

obestas

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw Vernieuwingsimpuls Veni

Intervention

Keyword: Brain, Environment, Genes, Obesity

Outcome measures

Primary outcome

Study 1:

The difference in neuronal activity in CNS reward and satiety circuits (including striatum, amygdala, orbitofrontal cortex, insula, hypothalamus) as represented by BOLD fMRI signal change from baseline (%) in response to food-related stimuli within 15 obesity discordant MZ twin pairs.

Study 2:

a. The difference in neuronal activity in CNS reward and satiety circuits (including striatum, amygdala, orbitofrontal cortex, insula, hypothalamus) as represented by BOLD fMRI signal change from baseline (%) in response to food-related stimuli between individuals at high verses those at low genetic obesity risk based on measured risk alleles from genome wide association studies.

b. The difference in neuronal activity in CNS reward and satiety circuits (including striatum, amygdala, orbitofrontal cortex, insula, hypothalamus) as represented by BOLD fMRI signal change from baseline (%) in response to food-related stimuli between lean and obese subjects with either high or low

genetic obesity risk.

Secondary outcome

Secondary study parameters (study 1 and study 2):

We will investigate the influence of environment and genetics on the following potential underlying mechanisms by performing additional tests in study 1 and study 2 respectively:

1. eating behavior measured as quantitative (kcal) and qualitative (energy density, macronutrient composition) dietary intake using a choice lunch buffet on the visit day and assessing dietary habits at home using the 24 hours recall method on two week days and one weekend day at home;
2. physical activity measured as metabolic equivalent of task (METs)-hours per week using seven-day ActiGraph triaxial accelerometry at home and using available longitudinal data from NTR surveys;
3. basal metabolic rate measured in kcal/day using oxygen consumption and carbon dioxide production measured with indirect calorimetry;
4. fasting plasma biomarkers (glucose, insulin, glucagon) measured in a fasting blood sample;
5. autonomic nervous system balance assessment based on measurements of heart rate variability (HRV), respiratory rate (RR) and respiratory sinus arrhythmia (RSA) using a portable electro- and impedance cardiogram (VU University Ambulatory Monitoring System, VU-AMS).

Exploratory study parameters (study 1 and study 2):

Conditional to available budget we will investigate the influence of environment and genetics on the following potential underlying mechanisms by performing additional tests in study 1 and study 2 respectively:

1. gut microbiota composition assessed by identifying microbial phylotypes using 16S rRNA molecule-based approaches of diagnostic analysis on collected fecal samples;

2. epigenetic changes by measuring DNA methylation in a blood sample;

3. exploratory fasting plasma biomarkers (leptin, GLP-1, PYY and ghrelin) will be determined in a fasting blood sample;

4. white matter tract integrity, functional connectivity of the brain and metabolic changes in the hypothalamus will be investigated using Diffusion Tensor Imaging MRI (DTI-MRI), Resting State fMRI (RS-fMRI) and Magnetic Resonance Spectroscopy (MRS), respectively.

Study description

Background summary

It has been suggested that obese individuals are characterized by excessive eating due to altered central nervous system (CNS) reward and satiety responses to the consummation of food. This is comparable to the role for CNS reward and satiety responses in drug addiction. Differences between individuals in CNS reward and satiety circuits are likely to be influenced by a multitude of genetic and environmental factors, but whether environmental and genetic risk factors affect the brain in the same pathways in the brain is unknown. An additional unresolved question is to what extent the alterations in CNS reward and satiety circuits are a cause of the development of obesity and to what extent they are a consequence of obesity.

Study objective

The overarching goal of this proposal is to investigate the environmental and

genetic influences on the activity of CNS reward and satiety circuits, and to investigate whether these differences are causal to the development of obesity in humans.

In order to achieve this aim we will address the following main study objectives:
1. Do food-stimuli related responses in CNS reward and satiety circuits differ within obesity-discordant monozygotic twin pairs?
2.a. Do food-stimuli related responses in CNS reward and satiety circuits differ between individuals at high versus those at low genetic obesity risk?
2 b. Are the genetic effects on CNS reward and satiety circuits independent of current obesity status?

Study design

The above defined objectives will be investigated in 2 cross-sectional studies.

Study 1:
In study 1, we will address the first objective by assessing neuronal activity in CNS and reward and satiety circuits in response to visual and taste related food-stimuli, measured as blood oxygen level-dependent (BOLD) response by functional magnetic resonance imaging (fMRI), according to a special design of *clonal controls,* i.e. rare monozygotic twins discordant for obesity. Fifteen monozygotic twin pairs with an intrapair BMI difference of > 3 kg/m2 will be selected from the Netherlands Twin Registry for analysis. Neuronal activity will be expressed as signal change from baseline (%) in response to the food-related stimuli.

Study 2:
In study 2 we will address the second objective (2a and 2b). Neuronal activity in CNS reward and satiety circuits will be assessed in 60 subjects who are classified to be at low or high genetic risk based on measured obesity risk alleles from genome-wide association studies (objective 2a). Neuronal activity will be measured with BOLD fMRI using the same protocol as in study 1. Changes in CNS satiety and reward circuit responses may not only be a cause, but also a consequence of obesity. To investigate the extent to which the impact of genetic predisposition is independent of current obesity status both obese and lean individuals with low and high count of obesity risk alleles will be included (objective 2b).

To study other underlying mechanisms involved in the etiology of obesity, we will include the role of eating behavior, by assessing dietary habits using the 24 hours recall method during three days and measuring qualitative and quantitive food intake during a choice-buffet; the role of biomarkers and hormones in the fasting state, the role of physical activity level, as assessed by triaxial accelerometry; and basal metabolic rate, measured by indirect calorimetry. Furthermore, we will assess the role of altered autonomic nervous

system balance by measuring heart rate variability using a small non-invasive electro- and impedance cardiogram; and the potential role of gut microbiota species by collecting and analyzing feces samples using phylogenetic microarrays. Finally, epigenetic changes will be studied by measuring DNA methylation in a blood sample.

Study burden and risks

We are aware of the possible demand that may be imposed on the participants in this observational study. Screening will be performed in part by phone to keep the number of visits to the research unit by one. After the telephone call participants will travel one time to the study location. The duration of this visit is aproximately 4 hours. A maximum amount of 70 mL blood will be drawn during a single venipuncture. The risks associated with participation in this study are the risks of venous blood drawing: hematoma and/or flebitis. During the week after the visit dietary assessment will be done using the 24 hours recall method during a telephone call on three separate days (2 weekdays and 1 weekendday). The duration of each phone call is about 30 minutes. Also, participants will be wearing a small accelerometry device placed on their hip with a belt for 7 days (only during the day and removing it for water-based activities as swimming and showering). We decided to use these methods so that participants won't have to keep track of what they eat and how much they particpate in physical activity themselves (for instance by keeping a diary). For the collection of the feces sample we will provide participants with a specially designed feces-collection-container to make this collection as feasible as possible. Also, we decided to get the feces samples picked up at home by a research physician/assistant so participants won't need to make a second visit to the research clinic. The research physician will be daily available for questions. We will try to make this study as bearable as possible for our participants. All tests will be done by one researcher.

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

For all participants (study 1 and study 2):
- Age 18-65 years
- Male or female
- Stable bodyweight (< 5% reported weight change during the previous 3 months)
- Females: pre- or postmenopausal. In premenopausal females menstruation must be regular (to schedule females for fMRI in the follicular phase of the menstrual cycle to rull-out possible menstruation cycle effects).;For participants in study 1 (30 subjects):
15 Monozygotic twin pairs discordant for obesity (BMI difference > 3kg/m2 between cotwins);For participants in study 2 (60 subjects):
- Available information on genetic material as well as body weight
- 15 Subjects with calculated low genetic predisposition risk for obesity and low BMI
- 15 Subjects with calculated low genetic predisposition risk for obesity and high BMI
- 15 Subjects with calculated high genetic predisposition risk for obesity and low BMI
- 15 Subjects with calculated high genetic predisposition risk for obesity and high BMI

Exclusion criteria

- Self reported type 2 diabetes mellitus
- Irregularity of menstruation in premenopausal females defined as: cycle lengths shorter than 21 or longer than 35 days and/or menses periods shorter than 2 or longer than 8 days
- Neurological illness
- Psychiatric illness including eating disorders and depression
- Malignancy
- Pregnancy or breast feeding
- Alcohol abuse defined as: for men > 21 units/week, for women > 14 units/week

- History of claustrophobia or presence of metal objects/implants (because of MRI protocol)
- Current or chronic use of the following medication: weight lowering agents (within 3 months before screening); antihyperglycemic agents (within 3 months before screening); glucocorticoids, centrally acting drugs, cytostatic drugs or immunomodulatory agents (alle of these within 2 weeks immediately prior to screening, because of the possible effects on cerebral functioning); opiates, narcotics, tranquilizers, and other potentially addictive medications
- Visual disability, not correctable with glasses or contact lenses
- Inability to understand the study protocol and/or inability to give informed consent

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-01-2014
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	28-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2014
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	NL44735.029.13