

# A neuroscience perspective on anxiety proneness - sex differences, monoaminergic pathways and treatment response

<b>Submission date</b> 08/07/2011	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 02/08/2011	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 27/06/2016	<b>Condition category</b> Mental and Behavioural Disorders	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Anxiety disorders are more common in women. It is not clear why but anxiety proneness may be related to imbalances in brain neurotransmitter systems such as the serotonin and dopamine systems. Escitalopram is a selective serotonin reuptake inhibitor and has previously been demonstrated to be effective in patients suffering from anxiety conditions like social anxiety disorder (SAD). SAD is characterized by excessive fear of being observed or scrutinized by unfamiliar persons. An individual with SAD is agonized by the potential risk of performing inadequately or showing overt signs of nervousness with resultant embarrassment or humiliation in social situations, for example when speaking in front of a group. SAD, and other anxiety disorders, can also be treated with psychosocial interventions like cognitive-behavior therapy (CBT). It has recently been demonstrated that CBT can be delivered as a structured self-help program via the internet. It is unclear, however, how effective a combination of drug and psychosocial treatments is. Moreover, it is not known how combined treatments change activity patterns in the brain. The aim of this study is to examine the brain processes underlying anxiety proneness, why anxiety proneness is elevated in women, and what biological processes are related to treatment outcome in patients with SAD.

### Who can participate?

We will recruit 48 medication-free patients (men and women) between 20-65 years of age who fulfill the diagnostic criteria for social anxiety disorder (SAD). For comparison, we will also recruit 48 healthy people.

### What does the study involve?

By use of neuroimaging techniques, this study examines serotonin and dopamine reuptake functions, as well as neural activation patterns during emotional stimulation, in patients diagnosed with SAD, before and after 9 weeks of treatment. Participants will be randomly allocated to receive either escitalopram in combination with Internet-delivered CBT, or a placebo (dummy) drug in combination with CBT. The effects of the treatment on serotonin and dopamine reuptake processes will be studied with positron emission tomography (PET). Moreover, neural activation patterns during emotional stimulation will be studied with

functional magnetic resonance imaging (fMRI). Brain activity will be recorded while patients experience anticipatory anxiety before making a public speech, and while they view images with varying degrees of emotional content. Assessments will be repeated after the 9-week treatment period. A group of healthy controls is also included in the study, for comparison with patients before treatment.

What are the possible benefits and risks of participating?

Escitalopram is usually well tolerated but may cause side effects like nausea for some individuals. Participants may experience discomfort while being assessed with PET or fMRI. During PET assessments short-lived radioactive tracer isotopes are injected. However, the radiation dose is well within established safety limits. We don't expect that participation in this study will lead to negative consequences provided that the safety regulations are followed.

Where is the study run from?

The study will be conducted at the Department of Psychology, Uppsala University, and University Hospital in Uppsala, Sweden.

When is the study starting and how long is it expected to run for?

September 2011 to December 2012

Who is funding the study?

The study is funded by the Swedish Council for Working Life and Social Research, the Swedish Research Council, and the Uppsala University Amersham fund.

Who is the main contact?

Professor Tomas Furmark  
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### **Study website**

<http://www.sofie10.se>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Prof Tomas Furmark

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## **Additional identifiers**

**EudraCT/CTIS number**

2010-023007-10

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**

TF2010

## **Study information**

### **Scientific Title**

A neuroscience perspective on anxiety proneness - sex differences, monoaminergic pathways and treatment response: a randomised controlled trial

### **Study objectives**

1. Serotonin and dopamine reuptake functions are compromised in patients with social anxiety disorder, possibly more so in women than in men
2. Compromised serotonin reuptake functions are restored by successful treatment (escitalopram and CBT)
3. Patients on escitalopram, as compared to placebo, will possibly also demonstrate altered dopamine reuptake functions (due to an increased endogenous dopamine concentration or an effect by the medication on the transporter protein)
4. Serotonin and dopamine related genes affect reuptake functions and treatment success, possibly differently in women and men
5. Networks in the brain that generate and/or attenuate emotion, as measured by functional Magnetic Resonance Imaging (fMRI) during emotional activation, behave differently in women compared to men, and in patients with social anxiety disorder compared to healthy controls
6. Gray matter volume, measured with voxel-based morphometry (VBM), in emotion relevant areas in the brain, differ between women and men, and between patients with social anxiety disorder and healthy controls. That can also be true for white matter nerve fibers, measured with diffusion tensor imaging (DTI)
7. Women and men with social anxiety will differ from healthy controls regarding the extinction of learned (conditioned) fear, and women will demonstrate decreased extinction recall compared to men

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Research Ethics Committee, Uppsala, ref: 2010/226

### **Study design**

Double-blind randomized controlled trial with two arms

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Social anxiety disorder (social phobia)

**Interventions**

1. A group of healthy controls is also included for pretreatment comparisons
2. Patients with social anxiety disorder will be randomized into one of two treatment conditions:
  - 2.1. Either a escitalopram + CBT combination
  - 2.2. Or a placebo + CBT combination
3. Principally, all other therapies will be avoided
4. Administration of escitalopram is based on the accepted recommended dose 10 mg per day during the first week and 20 mg per day for the rest of the treatment period
5. Doses are packaged so that the patients take one capsule per day
6. Placebo is administered with a corresponding capsule without active substances
7. The CBT treatment consists of a previously evaluated self-help manual for social anxiety disorder that is divided into nine modules adapted for use over the Internet
8. Participants are asked to complete one module every week
9. Each module consists of information and exercises (homework assignments) and ends with a short quiz to check adherence
10. The CBT self-help program has been found efficacious in several previous trials

**Intervention Type**

Mixed

**Primary outcome measure**

1. The Liebowitz Social Anxiety Scale (LSAS)
2. The Clinical Global Impression - Improvement (CGI-I) scale
3. Spielberger state-trait anxiety inventory (STAI-S) during anticipatory anxiety in the fMRI-setting

**Secondary outcome measures**

1. Social Interaction Anxiety Scale (SIAS)
2. Social Phobia Scale (SPS)
3. Social Phobia Screening Questionnaire (SPSQ)
4. Montgomery Åsberg Depression Rating Scale (MADRS-S)
5. Beck Anxiety Inventory (BAI)
6. Quality of Life Inventory (QOLI)
7. Karolinska Scale of Personality (KSP)
8. NEO PI-R
9. Spielberger state-trait anxiety inventory (STAI-T)

**Overall study start date**

01/09/2011

**Completion date**

31/12/2012

## **Eligibility**

**Key inclusion criteria**

Patients:

1. Social anxiety disorder (social phobia), according to DSM-IV, must be the main diagnosis as assessed with the structured clinical interview for DSM disorders (SCID)
2. Otherwise somatically healthy
3. Age 18 or older but not postmenopausal
4. Willingness to participate in a symptom provocation brain imaging trial

Healthy controls:

1. No psychiatric diagnosis and otherwise somatically healthy
2. Age 18 or older but not postmenopausal
3. Willingness to participate in a brain imaging trial

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

48 patients with social anxiety disorder, 48 healthy controls

**Key exclusion criteria**

1. Treatment of social anxiety within the three months preceding the study
2. Current serious or dominant psychiatric disorder other than social anxiety disorder (e.g. psychosis, major depressive disorder, bipolar disorder)
3. Suicidal ideation
4. Chronic use of prescribed medication that could influence the results
5. Abuse of alcohol or narcotics
6. Pregnancy or planned pregnancy during the study period
7. Menopause
8. Previous positron emission tomography (PET) examination
9. Contraindications for MRI investigations (e.g. implants or other metal objects in the body, brain and heart operations)

**Date of first enrolment**

01/09/2011

**Date of final enrolment**

31/12/2012

## **Locations**

**Countries of recruitment**

Sweden

**Study participating centre**

**Uppsala University**

Uppsala

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## **Sponsor information**

**Organisation**

Uppsala University (Sweden)

**Sponsor details**

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**Sponsor type**

University/education

**Website**

<http://www.uu.se/en/>

**ROR**

<https://ror.org/048a87296>

## **Funder(s)**

**Funder type**

Research council

**Funder Name**

Forskningsrådet för Arbetsliv och Socialvetenskap

**Alternative Name(s)**

Swedish Council for Working Life and Social Research, FAS

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

Sweden

**Funder Name**

The Uppsala University Amersham Fund (Sweden)

**Funder Name**

Vetenskapsrådet

**Alternative Name(s)**

Swedish Research Council, VR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

Sweden

## Results and Publications

**Publication and dissemination plan**

Not provided at time of registration

**Intention to publish date****Individual participant data (IPD) sharing plan****IPD sharing plan summary**

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	01/09/2016		Yes	No