Profiling endophenotypes in social anxiety disorder: A neurocognitive approach

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The major objective of this pilot study is to delineate SAD endophenotypes by investigating information processing characteristics, brain activity and connectivity, within the two key dimensions relevant to the SAD symptomatology: attention and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anxiety disorders and symptoms
Study type	Observational non invasive

Summary

ID

NL-OMON41397

Source
ToetsingOnline

Brief title
Profiling endophenotypes in social anxiety disorder

Condition

- Anxiety disorders and symptoms

Synonym
social anxiety disorder, social phobia

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Endophenotypes, Family study, Social Anxiety Disorder

Outcome measures

Primary outcome

The main dependent variables are

* Outcomes scores on the questionnaires

* Physiological indices (e.g. heart rate), for example Inter-beat-interval

linked to the onset of a specific event in the neurocognitive paradigm

* Peak amplitude and latency of cortical event-related brain potentials. For

example, P1, FRN, and P3 components of the even-related brain potential

* Brain activity in pre-specified cortical regions (e.g., voxels in fMRI)

averaged in block-design for pre specified (task-related) conditions

* Neural network indices (e.g., graph parameters, tractography). For example,

strength of connectivity between brain areas. In graph theory, functional

connectivity could be indexed by the phase lag index, or the synchronization

likelihood.

* EEG power (e.g., alpha, theta) bands (mean power indices will be used).

* Cognitive bias indices derived from the attentional paradigms. This will be

indexed by the differences in reaction time. For example, longer reaction times

when viewing social (threatening) vs. non-social stimuli.

* Genetic information (acquired with blood samples)

Control variables

Gender, intelligence, and depression are used as control variables

Secondary outcome

N/A

Study description

Background summary

Social anxiety (SA), an intense fear of social interactions and social evaluation, is a relatively common problem. The life-time prevalence of social anxiety disorder (SAD), the severe form of SA including avoidance behavior and disturbance of general functioning, as described in the Diagnostic and Statistical Manual (DSM IV, 1994), is between 7 and 13% in Western societies (Furmark, 2002, Rapee & Spence, 2004). The year prevalence in the Netherlands is 4.8% (Bijl et al., 1997). SA with a sub threshold level below the DSM-IV diagnostic threshold of SAD, with subclinical levels of social anxiety symptoms, shows a life-time prevalence rate up to 25% in the general population (e.g., Davidson et al. 1994, Wittchen et al. 1999; Ruscio et al. 2008).
SAD patients show a high rate of impairment of social functioning, working- and family-life and close relationships (Lampe et al. 2003). In addition, patients with SAD are less likely to be in a relationship or marriage (Dingemans et al 2001). SAD is also associated with early leave of school (Stein & Kean 2000), lower level of education (Dingemans et al., 2001; Wittchen et al., 1999), a higher risk of being unemployed (Dingemans et al., 2001; Lampe et al 2003) and engagement in jobs below the level of qualification (Dingemans et al 2001; Katzelnick & Greist 2001). In addition, the economic costs of SAD are relatively high: about ¤12,000.- per person per year, and about ¤5,000,- for persons with sub threshold social phobia, compared to about ¤3,000,- for persons with other psychological problems (Acaturk, Smit, De Graaf, Van Straten, Ten Have, & Cuijpers, 2009).
Longitudinal studies indicate that SAD grows out of subclinical SA. The growing fear of social interactions and social evaluation often goes unnoticed or is noticed only after a long period of time, because socially anxious individuals shy away from social situations or stay in the background. In contrast with externalizing behavior, socially anxious persons are not an obvious burden on society, another reason why this problem often goes unnoticed. Generally, the age of onset of SAD is during late childhood or adolescence (Rapee and Spence, 2004). SAD is a life-long disease with a low likelihood of spontaneous remission, intervention studies show that SAD is resistant to treatment in comparison with other anxiety disorders. SAD shows a high rate of comorbidity with other anxiety disorders, depression and substance use disorders, in general SAD preceding the other disorders (Merikangas et al. 2002).

In order to reduce the development of SAD, to minimize individual suffering and to reduce the substantial economic costs (as described above), it is imperative to develop preventive interventions (Acaturk et al., 2009). Preventive interventions, focused on subjects with increased SA or subclinical SAD, is called indicated prevention. Until now, such interventions have not been developed and studied in persons with SA, but only in adult populations with subclinical panic attacks (Meulenbeek et al. 2010) and in children with increased anxiety (Kendall, 1990). Insight into the risks and protective factors that play a role in the development and maintenance of SAD form the basis for the development of such preventive interventions.

INTERGENERATIONAL TRANSMISSION OF SAD

Family studies have shown that SAD runs in families. Stein et al. (1998) showed that first-degree relatives of individuals with generalized SAD were 10 times more likely to have SAD than relatives of individuals without SAD. This increased risk of SAD was particularly found for the generalized type of SAD and not for specific SAD (Mannuzza et al., 1995). Furthermore, Lieb et al. (2000) demonstrated that 9.6% of the children of parents with SAD also met the criteria of SAD, whereas 2.1% of the children of parents with no psychiatric disorder had SAD. In contrast, there appears to be no significant association between spouses, indicating a random mating for social anxious persons (Distel et al 2008).

Behavior-genetic research (e.g., twin studies) supports both a hereditary and an environmental contribution to the development of social phobia. Twin studies yield heritability estimates of 20-50% (Distel et al 2008; Kendler et al 1992; Middeldorp et al 2005; Nelson et al., 2000). Investigations of genetics (e.g., Genome Wide Association studies) contributed to the determination of a SAD-specific genetic background (Gelernter, Page, Stein, & Woods (2004), however, it remains unclear which genes are specifically involved in SAD. Likewise, most environmental correlates of SAD seem to be risk factors for internalizing disorders in general (see Rapee & Spence, 2004). Few specific environmental effects have been identified and these effects are rather modest. Recently, several authors have argued that investigations of gene-environment interactions are crucial for a better understanding of the involvement of both genetic and environmental factors in the development of psychopathology (Beauchaine, Neuhaus, Brenner, & Gatzke-Koop, 2008). A special issue of European Archives of Psychiatry and Clinical Neuroscience (2008) emphasized the importance of studying gene-environment interactions in anxiety disorders such as SAD. Our ultimate objective is to conduct investigations of gene-environment interplay in the service of developing preventative interventions. However, to investigate gene-environment interactions it is imperative to understand SAD at the level of its endophenotypes. Allegedly, endophenotypes have a simpler genetic architecture than that of the disorder, and this should enhance the power to discover genes that are specific to the development of SAD (Walters and Owen, 2007). A successful delineation of endophenotypes will facilitate the investigation of gene-environment interactions, which will be the subsequent phase of this research program. Profiling endophenotypes for SAD is the purpose

of the present study

PROFILING ENDOPHENOTYPES OF SAD

The SAD phenotype may be linked to the genotype through endophenotypes, which refer to genetic trait markers of the disorder. Complementary to traditional diagnostics, profiling endophenotypes of SAD will advance our understanding of the genetic architecture of this disorder, and reveal its neurobiological and neurocognitive abnormalities (Ritsner, 2009). The characterization of SAD specific endophenotypes is of both clinical and scientific relevance. Endophenotypes (1) help to improve diagnostic criteria, which are difficult to interpret when signs and symptoms overlap with other disorders; (2) may supplement psychiatric diagnosis solely based on signs and symptoms; (3) are by definition present before the onset of an illness, and can be used to aid in identifying persons who are at elevated risk for becoming ill and for the delivery of preventive interventions; (4) may help to identify a biological subtype of SAD, individualizing treatment and predicting therapeutic response; and (5) may aid in the search for more precise genetic and environmental determinants of the disorder (Ritsner, 2009).

For a marker to be considered an endophenotype, *it has to (1) be associated with the phenotype (formal diagnosis), (2) be independent of clinical state, (3) be highly heritable, and (4) the impairment must co-segregate with the illness within a family, with non-affected family members showing impairment relative to the general population* (Glahn et al., 2007) This calls for a multigenerational family study that examines the affected individual with SAD, his or her siblings and children, as well as the partners of each family member. It is hypothesized that the SAD relevant trait characteristics of the patient will also be observable in family members, however, in a milder form. It is anticipated that these observed SAD traits will not be evident in non-relatives (partners). The proposed family study is the first comprehensive study on SAD endophenotypes.

The key question addressed in this study is whether the psychophysiological and neurocognitive abnormalities often reported in SAD patients are heritable, and can thus be found in family members of the SAD patients. Determination of genetic kinship of these neurocognitive deficiencies is essential for endophenotyping (Ritsner, 2009), and will result in a better understanding of the constellation of trait markers that, together, will determine whether an individual will develop social anxiety.

This study includes paradigms that tap into the two key dimensions relevant to the SAD symptomatology: Attention and Social Cognition (Clark & McManus, 2002; Hirsch & Clark, 2004; Miskovic & Schmidt, 2012a; Rapee & Spence, 2004; Stein & Stein, 2008). The relevance of attention and social cognition to SAD will be outlined below, but shortly, we expect that SAD individuals can be characterized by both vigilance (a biased attentional orienting response) and aberrant inhibitive processes, that is, impaired inhibition of attention to social threatening information and impaired inhibition of negative social cognitions, or rumination.

Study objective

The major objective of this pilot study is to delineate SAD endophenotypes by investigating information processing characteristics, brain activity and connectivity, within the two key dimensions relevant to the SAD symptomatology: attention and social cognitions. To this end, we employ neurocognitive paradigms suitable for measuring event-related brain potentials (EEG) and functional brain activity (functional MRI). The paradigms are discussed in more detail in sections 3 and 6, but see Table 1 for an overview. The included paradigms are representative of a weighted balance between the investigation of both temporal and spatial characteristics of neural abnormalities in the processing of social information (i.e., EEG and fMRI, respectively), attention and social norm processing, as well as network connectivity methods.
The theoretical foundation of the proposed study is derived from the existing literature that has demonstrated its potential to detect robust abnormalities in social information processing corresponding to cognition and behavior (Bokhorst, Westenberg, Oosterlaan, & Heyne, 2008; Miers, Blote, Bogels, & Westenberg, 2008; Miers, Blote, & Westenberg, 2010, 2011; Westenberg, Drewes, Goedhart, Siebelink, & Treffers, 2004; Westenberg, Gullone, Bokhorst, Heyne, & King, 2007), as well as to the brain and network level (Blackford, Avery, Shelton, & Zald, 2009; Blair, et al., 2010; Freitas-Ferrari, et al., 2010; Killgore & Yurgelun-Todd, 2005; Klumpp, Angstadt, & Phan, 2012; Miskovic & Schmidt, 2012b).

Study design

This study is a cross-sectional family study with two generations. Family composition is depicted in Figure 2. Twelve families will be selected provided that one adult (25-55 years of age) has the psychiatric diagnosis of SAD (labeled as *Target* participant hereafter) and that one of the Target*s children has social anxiety symptoms (or SAD). The target*s other children, the target*s spouse, and the target*s siblings and their spouses and children will be included as well. Families are included based on the age of the target*s children: they should be between 8 and 18 years of age. Adolescence appears to be a critical period for the development of clinical levels of SAD. Research shows that SAD is rarely diagnosed below the age of 10 years and that the prevalence increases between 10 and 20 years of age. In addition, retrospective research comprising adult SAD patients indicates that the age at onset is in the mid-teens (DSM-IV, 1994). Hence it is expected that the genotype-endophenotype-phenotype connection is particularly visible in families with children at this vulnerable age.

Due to the complexity of this study we will conduct a pretest and a pilot:
1. Pretest: Before we will recruit the families to participate in this study, we will first recruit a subset of control participants (N = 10, e.g., first year students) for preliminary tests of the procedures and effects (= pretest

phase). For these controls we provide modified informant consent forms and information brochures (please see the attached documents).
2. Pilot: As this is the first time we are recruiting families for research, we will conduct a pilot study in which the protocol discussed below will be administered to 3 families. This pilot study will provide important information about the feasibility of family inclusion, logistics, as well as power to detect endophenotypes with the included paradigms. After testing these 3 families we will evaluate the procedures and report the findings to the METC. Then we will test the remaining 9 families.

Schematic of the test phases
- Protocol will be administered to students (pretest)
- Protocol will be administered to 3 families (pilot)
- Protocol will be administered to the remaining 9 families

After completion of the pilot we will report on the feasibility of the protocol to the Medical Ethics Committee (METC) of the LUMC. Any significant changes made to the protocol will be notified to the METC with amendments. The continuation of the study is dependent on a positive evaluation of the amendment(s) by the METC.

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AMENDMENT March 17 2014
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(please see the research protocol and amendment letter for details)

- Changes to the experimental paradigms. These changes allow for improved sensitivity to detect endophenotypes of social anxiety, without adding significant measurement time or a burden on the participants.

- Debriefing protocol: participants will now be directly debriefed after the EEG test session about the purpose of the social evaluation paradigm.

- Questionnaires: a view questionnaires have been excluded or replaced with more appropriate questionnaires

- Duration of study per participant: due to the proposed amendments to the protocol, the total duration of the experiment per participant has been reduced from 7 hours to 6:30 hours.

- Changes to the "inclusion and screening protocol": Step 1: telephone conversation with potential target and 'screen' for signs of social anxiety. If signs are present, invite person with partner for a interview. Step 2: explain research protocol to the potential target and partner, administer psychiatric standardized interview to the potential target and partner. If potential target meets the inclusion criteria and his/her child(ren) has(have) signs of social anxiety, then the target is asked to invite his/her family members to

participate. After the target discusses the research with his/her family members, we ask for the contact details of the family members . This way we are certain that the target participant meets all inclusion criteria, before (s)he contacts his/her family members about participating in this research (please see page 15 of the protocol for details about inclusion).

- Minor changes to the information letters and informed consent forms.

Study burden and risks

Abnormalities in the MRI and EEG recordings are the only risks anticipated. These negative observations will be communicated to the subject's general practioner (medical doctor) by the neuro-radiologist. Separate consent forms for this a procedure are attachted to this submission

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)

Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Good comprehension of Dutch language (in both speech and writing)
- In good mental and physical health (e.g., appropriate physical mobility to participate in fMRI experiments).
- Aged 25-55 years (adults) and 8-21years (children)
- One of the target's children should be living at home with his/her biological parents
- Children of the brother(s)/sister(s) of the target participant may be older than 21 years
- For the target participants (those with a social anxiety disorder) 'social anxiety disorder' must be the primary classification. Comorbidity with another internalizing disorder (e.g., depression) is allowed
- One of the children of the 'target participant' should show elevated levels of social anxiety (90th percentile) based on social anxiety questionnaires (please see page 16-17 research protocol)

Exclusion criteria

For the target and target's child with social anxiety symptoms, exclusion criteria are: psychiatric disorders other than depression are specifically excluded (e.g., autism, schizophrenia).
For all participants, exclusion criteria are mental and/or physical disabilities that conflict with participation.

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:	Recruiting
Start date (anticipated):	16-05-2013
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO

Date:	11-06-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-03-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL40066.058.12