# Shy parent, shy child ? : delineating psychophysiological endophenotypes of social anxiety disorder

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# Chapter 1

# General introduction

*One of the participants in the Leiden Family Lab study on social anxiety disorder told me she does everyday things, such as going to the hairdresser, in the next village, instead of in her hometown. She does this because she does not know how to react when she would accidently encounter an acquaintance: Should she go over and say hi? Should she just walk by? She really does not know how to behave in this social situation, and thus avoids the situation altogether.*

Of course, everybody feels socially anxious or shy from time to time. Rapee and Spence (2004) propose that social anxiety can be seen as a severity continuum with on the one end people who show no anxiety at all in social situations, and on the other end patients with social anxiety disorder (SAD). SAD is an invalidating psychiatric disorder characterized by extreme fear and avoidance of one or more social situations (APA, 2013). It is diagnosed when this fear persists for more than six months, social situations are avoided or endured with intense fear, and it causes clinically significant distress or impairment in important areas of daily functioning (APA, 2013). Life-time prevalence of SAD is estimated between 5 and 13% in Western societies (De Graaf, Ten Have, Van Gool, & Van Dorsselaer, 2012; Furmark, 2002; Grant et al., 2005; Kessler, Berglund, Demler, Jin, & Walters, 2005; Rapee & Spence, 2004). SAD often co-occurs with other psychiatric disorders, such as other anxiety disorders, depression, and substance abuse (Grant et al., 2005; Rapee & Spence, 2004; Spence & Rapee, 2016). In addition to severe personal, relational, professional, and economic consequences (Acarturk, De Graaf, Van Straten, Ten Have, & Cuijpers, 2008; Dingemans, Van Vliet, Couvee, & Westenberg, 2001; Lampe, Slade, Issakidis, & Andrews, 2003; Wittchen, Stein, & Kessler, 1999), SAD is difficult to treat. For example, cognitive-behavioral therapy is less effective for SAD than for other anxiety disorders, both in children and adults (Hudson, Keers, et al., 2015; Hudson, Rapee, et al., 2015; Norton & Price, 2007; Spence & Rapee, 2016). Strikingly, the mean delay between onset of SAD and seeking treatment ranges from 14 to 28 years (Dingemans et al., 2001; Green, Hunt, & Stain, 2012; Iza et al., 2013). Thus, it is important to gain more insight in the underlying mechanisms of SAD, as this might be used to improve early detection and intervention.

Patients with SAD show information processing biases, such as biases in attention (e.g., hypervigilance, or self-focused attention), interpretation (e.g., evaluating own behavior very critically, or interpreting social situations in a negative way), memory (e.g., selectively retrieving negative information), and imagery (e.g., experiencing images of oneself performing poorly in social situations) (Bögels & Mansell, 2004; Clark & McManus, 2002;

Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013; Wong & Rapee, 2016). Haller, Kadosh, and Lau (2014) suggest that normative brain development could magnify these information processing biases in adolescents and thereby putting them at increased risk for developing SAD. Indeed, SAD usually develops in late childhood or early adolescence (Kessler et al., 2005). Moreover, these information processing biases might accumulate over time, resulting in a persistent cycle. For example, these information processing biases are triggered when the person is confronted with a socially stressful situation, repeated while in the situation, and carried forward in time when anticipating similar future events (Clark & McManus, 2002; Morrison & Heimberg, 2013). These information processing biases play an important role in the development and maintenance of SAD (Bögels & Mansell, 2004; Clark & McManus, 2002; Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013; Wong & Rapee, 2016).

One way to study these information processing biases is by using psychophysiological measures, which provide real-time, objective and direct information with high temporal resolution (Amodio, Bartholow, & Ito, 2014; M. X. Cohen, 2011; Ibanez et al., 2012; Luck, 2005). Psychophysiological measures could be measured before, during and after social situations, and even during resting state. For example, recent studies have focused on frontal alpha asymmetry, delta-beta cross-frequency correlation (further referred to as 'delta-beta correlation'), and heart rate variability during resting state, anticipation of and recovery from stressful social situations (Chalmers, Quintana, Abbott, & Kemp, 2014; Garcia-Rubio, Espin, Hidalgo, Salvador, & Gomez-Amor, 2017; Gerlach, Wilhelm, & Roth, 2003; Grossman, Wilhelm, Kawachi, & Sparrow, 2001; Miskovic & Schmidt, 2012). Most studies on information processing biases during processing of social stimuli have focused on event-related potentials, as they provide the opportunity to differentiate between early and late processing stages (Schulz, Mothes-Lasch, & Straube, 2013; Staugaard, 2010). Faces are often used as social stimuli, but recent studies have also used social evaluative feedback as social stimulus to elicit information processing biases (Cao, Gu, Bi, Zhu, & Wu, 2015; Van der Molen et al., 2014). Recently, studies on processing social evaluative feedback in healthy participants have started to investigate neural oscillatory power. It is suggested that this might give additional information on neural activity that is not phase-locked to social evaluative feedback (Makeig, Debener, Onton, & Delorme, 2004; Van der Molen, Dekkers, Westenberg, Van der Veen, & Van der Molen, 2017). However, this has not been studied in SAD to date.

Taken together, in this dissertation I will focus on psychophysiological measures of information processing biases, to gain more insight in the mechanisms underlying the

development and maintenance of SAD. More specifically, I will focus on frontal alpha asymmetry, delta-beta correlation, and heart rate variability during resting state, anticipation of and recovery from a stressful social situation, and on the N1, feedback-related negativity (FRN), and P3 event-related potentials and theta power in response to social evaluative feedback. The goal of this dissertation is to investigate whether these psychophysiological measures are endophenotypes of SAD.

## Endophenotypes

A promising line of research in psychiatry has focused on delineating endophenotypes (Glahn, Thompson, & Blangero, 2007; Gottesman & Gould, 2003). Endophenotypes are heritable trait markers 'in between' the genotype and the phenotype. Studying endophenotypes could be seen as a first step in unraveling genetic mechanisms underlying psychiatric disorders. That is, psychiatric disorders are caused by a complex interplay between many different genes. Endophenotypes are more specific measures related to the psychiatric disorder, that are supposedly related to fewer genes than these complex psychiatric disorders (Cannon & Keller, 2006; Glahn et al., 2007). Furthermore, endophenotypes could yield a better understanding of the biological mechanisms underlying SAD (Glahn et al., 2007; Iacono, Malone, & Vrieze, 2016; Miller & Rockstroh, 2013), which in turn could help in interpreting genetic findings (Flint, Timpson, & Munafo, 2014). Endophenotypes could be behavioral measures (e.g. task performance, reaction time, or questionnaire data), neural measures (e.g. (f)MRI), or psychophysiological measures (e.g. event-related potentials, neural oscillatory power, heart rate, or heart rate variability) (Gottesman & Gould, 2003). Neural and psychophysiological endophenotypes are presumed to be more closely related to the genotype than behavioral endophenotypes (Cannon & Keller, 2006). Possible endophenotypes of depression, bipolar disorder, or schizophrenia have already been investigated (Bora, Yucel, & Pantelis, 2009; Bramon et al., 2005; Dubin et al., 2012; Glahn et al., 2007; Goldstein & Klein, 2014; Gottesman & Gould, 2003). However, to date no studies have investigated putative endophenotypes of SAD. This is remarkable, given the relatively high heritability of SAD (Distel et al., 2008; Isomura et al., 2015; Kendler, Neale, Kessler, Heath, & Eaves, 1992; Middeldorp et al., 2005; Nelson et al., 2000) and the relatively high life-time prevalence (De Graaf et al., 2012; Furmark, 2002; Grant et al., 2005; Kessler et al., 2005; Rapee & Spence, 2004). Therefore, the goal of this dissertation is to delineate psychophysiological endophenotypes of SAD.

A psychophysiological measure should meet the following criteria to be seen as an endophenotype (Glahn et al., 2007; Gottesman & Gould, 2003):

1) Association with the disorder
2) Co-segregation with the disorder within families
3) Heritability
4) The endophenotypes should be seen in non-affected family members to a higher degree than in the general population
5) State-independence

The association between psychophysiological measures and SAD (first criterion) has already been studied extensively by comparing participants with and without SAD, or high and low socially anxious individuals (Miskovic & Schmidt, 2012; Schulz et al., 2013; Staugaard, 2010). The *second chapter* of this dissertation gives an overview of the most frequently studied EEG measures in social anxiety. The second and third criteria for endophenotypes are based on the observation that psychiatric disorders run in families (Glahn et al., 2007; Gottesman & Gould, 2003). Within these families, the endophenotype should be seen in persons with the disorder. Furthermore, the endophenotype should be heritable. These two criteria could best be studied in extended families instead of in twins or sibling-pairs, because of the many different types of relationships within one family. This increases the power to identify genetic variability and thereby heritability (Gur et al., 2007; Williams & Blangero, 1999). In addition, these families should be selected on two persons with the psychiatric disorder (parent and child), to ensure a focus on a genetic form and to increase the chance that endophenotypes are related to the genetic factors underlying the psychiatric disorder (Fears et al., 2014; Glahn et al., 2010). The *fourth, fifth,* and *sixth chapter* describe the results of the two-generation family study that we conducted to investigate these two criteria for endophenotypes (co-segregation and heritability). The fourth (non-affected versus general population) criterion could eventually be studied by comparing these families with SAD with families without SAD. The last (state-independence) criterion indicates that persons with the disorder should display the endophenotype whether or not the illness is active (Gottesman & Gould, 2003). This could be studied by measuring the endophenotype at different time points within the same individuals.

## Leiden Family Lab study

The goal of our Leiden Family Lab study was to delineate endophenotypes of SAD, by investigating the second (co-segregation) and third (heritability) criteria for endophenotypes. We included 'target participants' with SAD with their partner and children, as well as the siblings of these patients with their partner and children (Figure 1). At least one child of the target participants should have heightened symptoms of SAD. SAD was diagnosed by a psychiatrist or trained clinician based on a clinical interview and the Mini-Plus structured interview (Bauhuis, Jonker, Verdellen, Reynders, & Verbraak, 2013; Sheehan et al., 1998; Sheehan et al., 2010; Van Vliet & De Beurs, 2007). The target participant should be between 25 and 55 years of age, and his/her child with heightened symptoms of SAD should be living at home. Target participants with comorbid disorders other than anxiety or depression were excluded. Inclusion criteria for all family members were good comprehension of Dutch language, and age above 8 years.

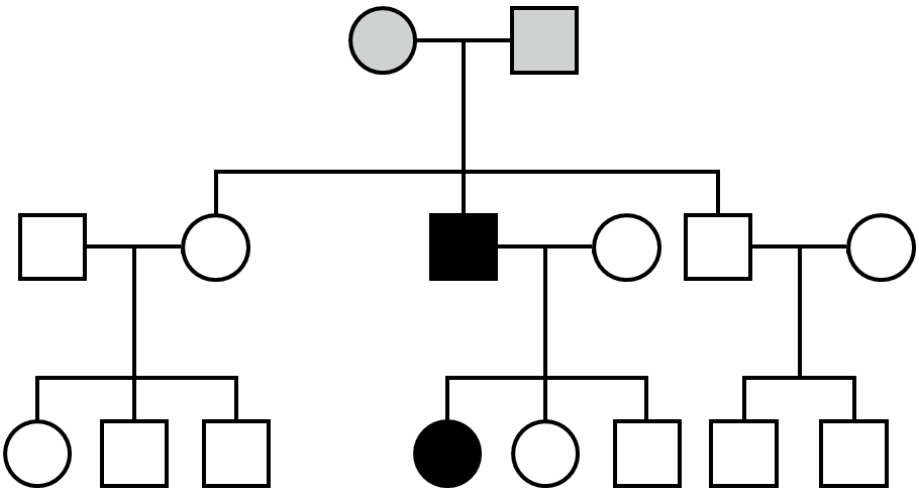

Figure 1. Example of a fictitious family in the Leiden Family Lab study on SAD. Families were selected based on two persons: an adult patient with SAD and his/her child with heightened symptoms of SAD. Grandparents (in grey) were not included.

Family members were asked to participate on one or two testing days in all parts of the Leiden Family Lab study: a clinical interview, an EEG session, an MRI session, questionnaires, and IQ measures (Figure 2). All family members performed the same parts of the family study (as depicted in assessment procedure), but the order of the parts differed

between family members, dependent on their preferences and availability of the labs. Mostly, family members came together to the lab. Eventually, not all family members participated in all parts: some only filled out questionnaires at home, and some were not eligible to take part in the EEG or MRI sessions due to physical constraints, or epilepsy. This dissertation focuses on the EEG session. The MRI data is part of the dissertation of J.M. Bas-Hoogendam.

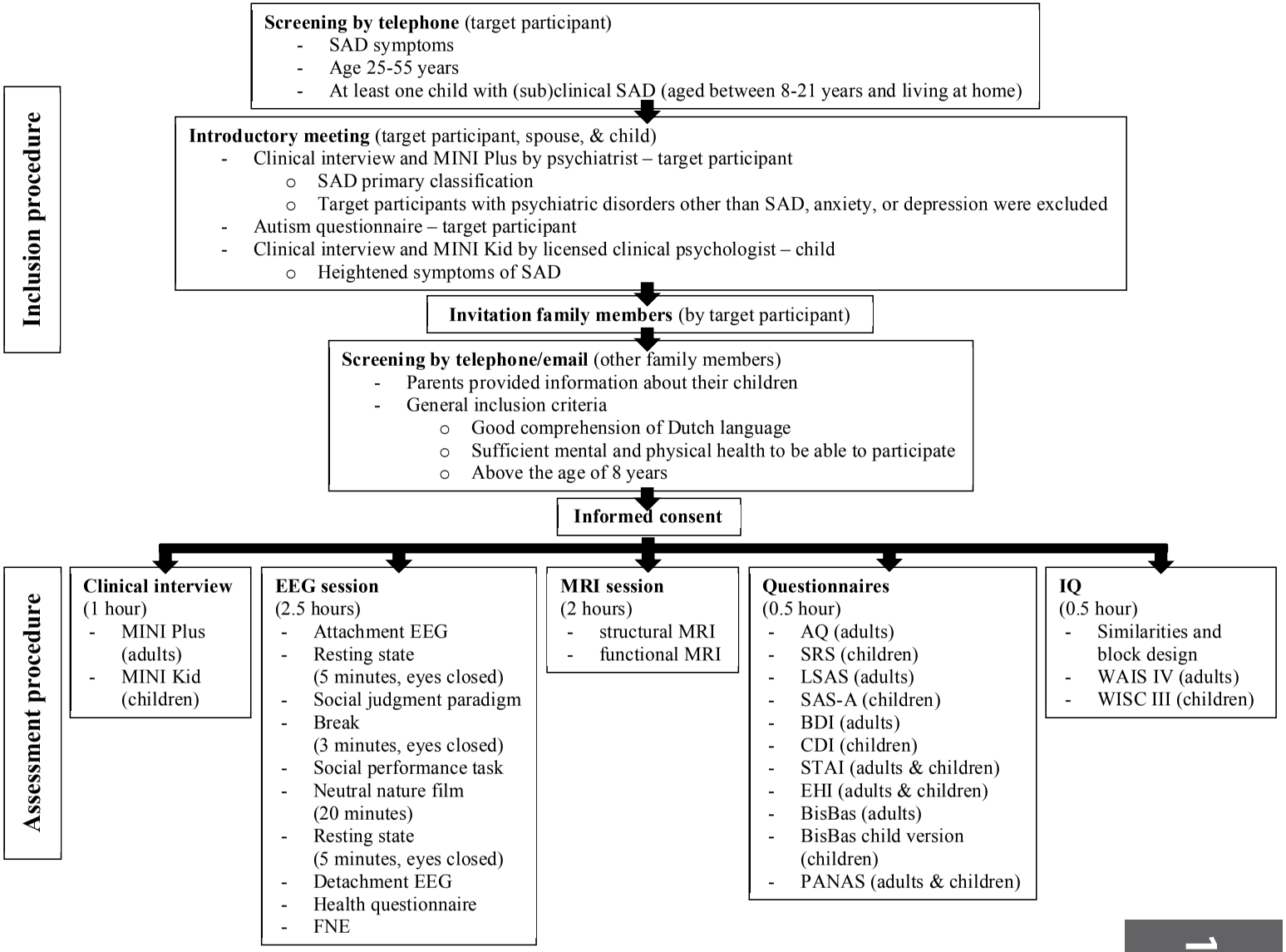
Inclusion procedure
Screening by telephone (target participant)
- SAD symptoms
- Age 25-55 years
- At least one child with (sub)clinical SAD (aged between 8-21 years and living at home)
Introductory meeting (target participant, spouse, & child)
- Clinical interview and MINI Plus by psychiatrist – target participant
o SAD primary classification
o Target participants with psychiatric disorders other than SAD, anxiety, or depression were excluded
- Autism questionnaire – target participant
- Clinical interview and MINI Kid by licensed clinical psychologist – child
o Heightened symptoms of SAD
Invitation family members (by target participant)
Screening by telephone/email (other family members)
- Parents provided information about their children
- General inclusion criteria
o Good comprehension of Dutch language
o Sufficient mental and physical health to be able to participate
o Above the age of 8 years
Informed consent
Assessment procedure
Clinical interview
(1 hour)
- MINI Plus (adults)
- MINI Kid (children)
EEG session
(2.5 hours)
- Attachment EEG
- Resting state (5 minutes, eyes closed)
- Social judgment paradigm
- Break (3 minutes, eyes closed)
- Social performance task
- Neutral nature film (20 minutes)
- Resting state (5 minutes, eyes closed)
- Detachment EEG
- Health questionnaire
- FNE
MRI session
(2 hours)
- structural MRI
- functional MRI
Questionnaires
(0.5 hour)
- AQ (adults)
- SRS (children)
- LSAS (adults)
- SAS-A (children)
- BDI (adults)
- CDI (children)
- STAI (adults & children)
- EHI (adults & children)
- BisBas (adults)
- BisBas child version (children)
- PANAS (adults & children)
IQ
(0.5 hour)
- Similarities and block design
- WAIS IV (adults)
- WISC III (children)

Figure 2. Flow-chart of the inclusion and assessment procedures of the Leiden Family Lab study on SAD.

Note: SAD = social anxiety disorder; MINI Plus = Mini-Plus International Neuropsychiatric Interview (MINI Plus version 5.0.0) (Sheehan et al., 1998; Van Vliet & De Beurs, 2007); MINI Kid = MINI Kid interview (Bauhuis et al., 2013; Sheehan et al., 2010); FNE = Fear of Negative Evaluation (Carleton, McCreary, Norton, & Asmundson, 2006); AQ = Autism-Spectrum Quotient Questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001); SRS = Social Responsiveness Scale (parent-rated) (Constantino et al., 2003); LSAS = Liebowitz Social Anxiety Scale (Liebowitz, 1987); SAS-A = Social Anxiety Scale – adolescents (La Greca & Lopez, 1998); BDI = Beck Depression Inventory (Beck, Steer, Ball, & Ranieri, 1996); CDI = Child Depression Inventory (Kovacs, 1992); STAI = State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); EHI = Edinburgh Handedness Inventory (Oldfield, 1971); BisBas = Behavioral Inhibition and Behavioral Activation Scales (Carver & White, 1994); BisBas child version = Behavioral Inhibition and Behavioral Activation Scales, child version (Muris, Meesters, De Kanter, & Timmerman, 2005); PANAS = Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988); WAIS IV = Wechsler Adult Intelligence Scale IV (Wechsler, Coalson, & Raiford, 2008); WISC III = Wechsler Intelligence Scale for Children III (Wechsler, 1991).

Figure 3 shows an overview of the EEG session of the Leiden Family Lab study. EEG and heart rate were measured during resting state and during two tasks: the social performance task (Harrewijn, Van der Molen, & Westenberg, 2016) and the social judgment paradigm (Van der Molen et al., 2017; Van der Molen et al., 2014). We have chosen these tasks because they focus on one of the core features of SAD: fear of negative evaluation (APA, 2013; Clark & Wells, 1995; Rapee & Heimberg, 1997). In these tasks, feelings of social anxiety are elicited because participants have to give a speech in front of a video camera (social performance task) and because participants receive social feedback (social judgment paradigm). We studied several psychophysiological measures as putative endophenotypes of SAD: frontal alpha asymmetry, delta-beta cross-frequency correlation and heart rate variability during the social performance task, and N1, feedback-related negativity, P3 and theta power during the social judgment paradigm.

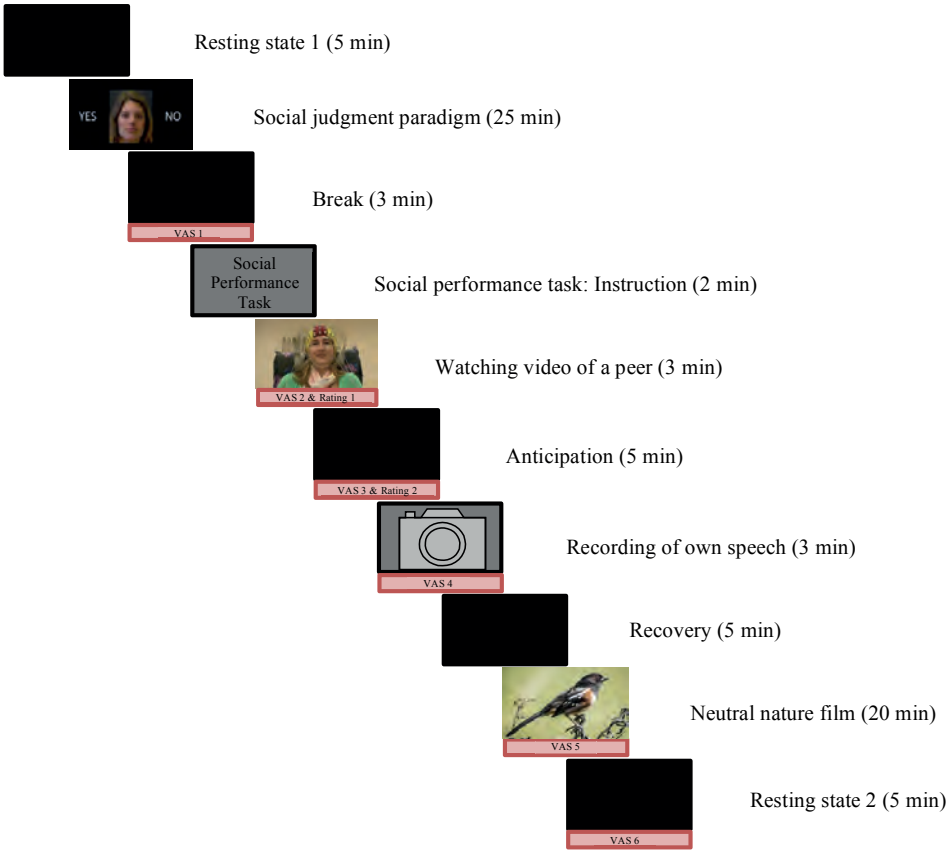


Figure 3. Overview of the EEG session. We asked participants to indicate their nervousness and avoidance at several time points throughout the EEG session on a visual analogue scale (VAS). Participants also evaluated the peer on the video (rating 1), and indicated how they expected to be evaluated (rating 2).

## Outline of this dissertation

The goal of this dissertation was to delineate psychophysiological endophenotypes of SAD, to gain more insight in the mechanisms underlying the development and maintenance of SAD. The *second chapter* focuses on the first criterion (association) for endophenotypes by giving an overview of the most frequently studied EEG measures (both neural oscillatory power and event-related potentials) of information processing biases in SAD. The *third chapter* reports the validation of our newly developed social performance task in high and low socially anxious females. In this chapter we compare two commonly studied EEG measures in this task (frontal alpha asymmetry and delta-beta correlation). The other three chapters focus on

the second (co-segregation) and third (heritability) criteria for endophenotypes and describe the findings of our Leiden Family Lab study on SAD. In the *fourth chapter* we describe whether delta-beta correlation during the social performance task can be seen as a candidate endophenotype of SAD. The *fifth chapter* focuses on heart rate variability during resting state and the social performance task as a candidate endophenotype of SAD. The *sixth chapter* describes whether behavioral (i.e. expectations about social evaluation and corresponding reaction time) and EEG (i.e. N1, feedback-related negativity, P3, and theta power) measures in the social judgment paradigm can be seen as candidate endophenotypes. Finally, in the *seventh chapter* we discuss the results of this dissertation, and describe directions for future research and the clinical implications of these results.