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**The Leiden Family Lab study on Social Anxiety Disorder:
a multiplex, multigenerational family study on neurocognitive
endophenotypes; *Supporting Information***

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Supporting Information

Pre-registration LFLSAD

Following a pilot phase of the study and upon approval of the Medical Ethical Committee of the LUMC, the background, design, methods and hypotheses of the LFLSAD were pre-registered on the Open Science Framework (osf.io) website

(<https://osf.io/erums/register/564d31db8c5e4a7c9694b2co>).

All components of this pre-registration are publicly available and are listed below.

- Wiki of the project 'Profiling Endophenotypes in Social Anxiety Disorder: a neurocognitive approach': osf.io/q4wx2/
- General Background and Key Question of Project: osf.io/e368h
- Methods: Study Design and Sample: osf.io/aq3sv
- Methods: Diagnostic Measures: osf.io/g9kud
- Hypothesized Endophenotype: Amygdala (MRI): osf.io/erums
- Hypothesized Endophenotype: Prefrontal Cortex (MRI): osf.io/y5m8q
- Hypothesized Endophenotype: Structure and Connectivity (MRI): osf.io/5dgki
- Hypothesized Endophenotype: Resting State (EEG): osf.io/gqnit
- Hypothesized Endophenotype: Social Evaluation (EEG): osf.io/gncf6/
- Hypothesized Endophenotype: Social Performance (EEG): osf.io/ru958

Power analyses

Power was computed by simulation, based on an endophenotype with a heritability of 60% and a correlation of 70% with SAD; prevalence of SAD was set at 10%. Families were generated using linear mixed models and correlations between family members were modeled via normally distributed random effects with a correlation structure of two times the kinship matrix. Only families with at least two affected members in one nuclear family were used for estimation of the power.

Detailed procedure structural and functional MRI measurements

Participants were screened for MRI eligibility and invited for participation in the MRI experiment when they had no contraindications (like, for example, metal implants or pregnancy) for undergoing an MRI scan. Preceding the experimental session, children and adolescents were familiarized with the MRI procedure using a mock scanner (Galván, 2010). All participants received explanation of the MRI paradigms and practiced short versions of the MRI tasks on a laptop before the experiment. They were informed about the safety procedures and they were told that they could refrain from continuing the experiment at any time. State anxiety was assessed before and after the MRI scan by a Dutch-translation of the STAI (Spielberger, Gorsuch, & Lushene, 1970). Scanning was performed using a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands), equipped with a 32-channel Sensitivity Encoding (SENSE) head coil.

The MRI session consisted of a high-resolution T₁ scan, two diffusion tensor imaging (DTI) scans (anterior-to-posterior and posterior-to-anterior direction) and a magnetization transfer ratio (MTR)-scan. In addition, a high-resolution EPI scan and a B₀ field map were acquired for registration purposes. Furthermore, fMRI data were collected during resting-state (eyes closed condition) and during two functional paradigms: an amygdala paradigm investigating amygdala habituation, (based on the work of Blackford, Allen, Cowan, & Avery, 2013; Blackford, Avery, Cowan, Shelton, & Zald, 2011; Schwartz, Wright, Shin, Kagan, Whalen, et al., 2003; Schwartz, Wright, Shin, Kagan, & Rauch, 2003; Wedig, Rauch, Albert, & Wright, 2005) and conditioning (Davis, Johnstone, Mazzulla, Oler, & Whalen, 2010) and the revised social norm processing task (SNPT-R) (Janna Marie Bas-Hoogendam, van Steenbergen, Kreuk, van der Wee, & Westenberg, 2017).

Total duration of the MRI protocol was 55 minutes. After the MRI scan, participants completed the second phase of the SNPT-R on a laptop, and they were debriefed about the amygdala paradigm. Furthermore, they were instructed not to share the details of the MRI session with their family members. Total duration of the MRI session was 2.5 hours.

Detailed procedure EEG measurements

Two weeks before the EEG session, participants were asked to send in a portrait photograph of themselves for a task about first impressions. Participants were informed that a panel of peers would evaluate their photograph. This was a cover story to elicit feelings of social evaluation (Harrewijn, van der Molen, van Vliet, Tissier, & Westenberg, 2018; Van der Molen et al., 2014). Few days before the EEG session, participants were reminded of the EEG session and were asked to come in with clean hair. When participants arrived in the lab, we explained the EEG procedure and attached the electrodes. EEG was recorded using the BioSemi Active Two system (Biosemi, Amsterdam, The Netherlands) with 64 Ag-AgCl electrodes mounted in an electrode cap (10/20 placement) and 8 external electrodes (to measure horizontal/vertical eye movements, heart rate and for offline re-referencing).

The EEG session consisted of several elements. After a resting state measurement (eyes closed), participants performed a social judgment paradigm (Harrewijn et al., 2018; Van der Molen et al., 2014) followed by another resting state measurement (eyes closed). Subsequently, participants were informed about the second EEG task, as they did not know beforehand about this task. EEG data were acquired during a social performance task (Harrewijn, van der Molen, van Vliet, Houwing-Duistermaat, & Westenberg, 2017; Harrewijn, Van der Molen, & Westenberg, 2016), while participants watched a neutral nature movie for 20 minutes (to allow for cortisol measures), and during resting state (eyes closed). Then, the electrodes were detached and participants filled out a questionnaire about their health. Finally, we debriefed all participants and asked them not to tell their family members about the EEG tasks. Total duration of the EEG session was 2.5 hours.

Calculation z-scores

We characterized the LFLSAD sample by comparing the level of social anxiety symptoms (assessed by the LSAS-SR or the SAS-A), the level of fear of negative evaluation (assessed by the BFNE-II-R),

the level of behavioral inhibition (BIS; assessed by the BIS/BAS and BIS/BAS-C) and the level of depressive symptoms (assessed with the BDI or CDI) with those of community samples, by computing z-scores. We used the following reference values (mean \pm SD):

- LSAS-SR: 13.5 ± 12.7 (Fresco et al., 2001);
- SAS-A: 34.7 ± 2.3 (Miers, Blöte, Bögels, & Westenberg, 2008);
- BFNE-II-R: 30.7 ± 9.04 (Carleton, McCreary, Norton, & Asmundson, 2006);
- behavioral inhibition BIS/BAS: 20.0 ± 3.8 (Carver & White, 1994);
- behavioral inhibition BIS/BAS-C: 6.9 ± 3.9 (Muris, Meesters, de Kanter, & Timmerman, 2005);
- BDI-II: 10.6 ± 10.9 (Roelofs et al., 2013);
- CDI: 8.9 ± 5.4 , unpublished data from the study by (Miers et al., 2008).

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