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Altered Neurobiological Processing of Unintentional Social Norm Violations: A Multiplex, Multigenerational Functional Magnetic Resonance Imaging Study on Social Anxiety Endophenotypes

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ABSTRACT

BACKGROUND: Patients with social anxiety disorder (SAD) fear negative evaluation in social situations. Specifically, previous work indicated that social anxiety is associated with increased medial prefrontal cortex activation in response to unintentional social norm (SN) transgressions, accompanied by increased embarrassment ratings for such SN violations. Here, we used data from the multiplex, multigenerational LFLSAD (Leiden Family Lab study on Social Anxiety Disorder), which involved two generations of families genetically enriched for SAD, and investigated whether these neurobiological and behavioral correlates of unintentional SN processing are SAD endophenotypes. Of four endophenotype criteria, we examined two: first, the cosegregation of these characteristics with social anxiety (SA) within families of SAD probands (criterion 4), and second, the heritability of the candidate endophenotypes (criterion 3).

METHODS: Participants (n = 110, age range 9.0–61.5 years, eight families) performed the revised Social Norm Processing Task; functional magnetic resonance imaging data and behavioral ratings related to this paradigm were used to examine whether brain activation in response to processing unintentional SN violations and ratings of embarrassment were associated with SA levels. Next, heritability of these measurements was estimated.

RESULTS: As expected, voxelwise functional magnetic resonance imaging analyses revealed positive associations between SA levels and brain activation in the medial prefrontal cortex and medial temporal gyrus, superior temporal gyrus, and superior temporal sulcus, and these brain activation levels displayed moderate to moderately high heritability. Furthermore, although SA levels correlated positively with behavioral ratings of embarrassment for SN transgressions, these behavioral characteristics were not heritable.

CONCLUSIONS: These results show, for the first time, that brain responses in the medial prefrontal cortex and medial temporal gyrus, superior temporal gyrus, and superior temporal sulcus, related to processing unintentional SN violations, provide a neurobiological candidate endophenotype of SAD.

Keywords: Endophenotypes, Family study, fMRI, Intentionality, Social anxiety disorder, Social norm processing

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Social anxiety disorder (SAD), a prevalent anxiety disorder, is characterized by an onset during early adolescence, a long-term course, and a high risk of comorbid psychopathology (1–6). Furthermore, treatment for SAD is at present often suboptimal (7). Thereby, this psychiatric condition has a large negative impact on the patients' lives (8,9), as well as on society (10). It is therefore essential to gain a better understanding of the vulnerability for developing SAD to improve preventive and therapeutic interventions (11).

A defining feature of SAD psychopathology is the fear to act in a way that will be embarrassing and humiliating (12). More specifically, it has been postulated that an important fear of SAD patients concerns that they will "unintentionally generate an embarrassing behavioral blunder in a social situation" (13). The neurobiological and behavioral correlates of this fear of negative evaluation, which is out of proportion to the context and actual threat (14), can be assessed using the Social Norm Processing Task (SNPT) (15). In this paradigm, participants read and evaluate three types of stories: stories describing unintentional social norm (SN) violations, stories about intentional SN violations, and stories about neutral social situations. This enables examining the effect of intention on processing SN transgressions.

Two previous studies have used the SNPT to investigate SN processing related to social anxiety (SA), indicating that

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socially anxious people show increased sensitivity to unintentional SN violations. The first study, an imaging study comparing 16 SAD patients with 16 healthy participants (16), revealed increased activation related to unintentional SN violations in the medial prefrontal cortex (mPFC) in SAD patients. Furthermore, patients rated all stories as more inappropriate and more embarrassing, with the most prominent effect for the unintentional SN violations, which SAD patients considered significantly more embarrassing than control subjects did (16). This effect of SA on the embarrassment ratings for unintentional SN violations was recently replicated in a community sample (17). Using a revised version of the SNPT (SNPT-R), which enabled investigating SN processing in children, adolescents, and adults (18), we reproduced the general effect of SA on ratings of inappropriateness and embarrassment, and the specific effect of SA on embarrassment ratings for unintentional SN violations: while participants with low-to-intermediate SA levels rated unintentional SN transgressions as less embarrassing than intentional SN transgressions, participants with higher SA levels rated the unintentional SN violations as equally embarrassing as the intentional SN violations (17). This distinct experience of embarrassment is a critical factor underlying the development and maintenance of SA, as it could lead to negative self-evaluations and to the increased concerns about the judgments of others that are typical of individuals with SAD (19,20).

These results suggest that aberrant processing of unintentional SN transgressions, at both the neurobiological and behavioral levels, reflects an important component of the SAD phenotype. No study has, however, investigated whether these correlates of SN processing are potential endophenotypes of SAD. Endophenotypes are measurable and heritable traits located on the causal pathway from genotype to phenotype and reflect genetically based disease mechanisms (21); this definition distinguishes endophenotypes from biomarkers, which do not necessarily have a genetic basis, and from the intermediate phenotype concept, which is usually used to describe a subclinical form of a serious psychiatric disorder (22). As described in more detail elsewhere (23–25), endophenotypes could advance our insight to the pathways leading to serious psychopathology, could potentially identify individuals at risk, and can be valuable for improvement of therapeutic interventions. An endophenotype is supposed to be associated with the disorder (criterion 1), be state independent and already present in a preclinical state (criterion 2), and be heritable (criterion 3). Furthermore, an endophenotype should cosegregate with the disorder within families of probands, with nonaffected family members showing altered levels of the endophenotype in comparison to the general population (criterion 4) (22,25,26). Given that twin and family studies suggest that genetic factors are involved in the pathogenesis of SAD, by reporting heritability estimates for SAD between 39% and 56% (27–29), as well as a significantly increased risk to develop the disorder in first-degree relatives of SAD patients (30,31), exploring whether the neurobiological and behavioral correlates of SN processing are candidate endophenotypes will provide more insight into the genetic vulnerability for this impairing disorder (23).

Here, we tested the hypothesis that brain activation related to processing unintentional SN violations, as well as behavioral ratings related to such SN transgressions, are candidate SAD endophenotypes [preregistration of hypotheses publicly available at Open Science Framework (32)]. We used data from the LFLSAD (Leiden Family Lab study on Social Anxiety Disorder), a unique multiplex, multigenerational family study (33). This design is especially suitable to investigate candidate endophenotypes of SAD, as it allows for testing two endophenotype criteria in the same sample: cosegregation of the candidate endophenotype with social anxiety within families of probands (criterion 4) and the heritability of the candidate endophenotype (criterion 3). Based on previous findings (16,17), we predicted a positive correlation with brain activation in the mPFC, specifically related to processing unintentional SN violations; furthermore, we hypothesized to find a positive association between SA levels and embarrassment ratings on the unintentional SN violations. Next, as genetic influences on brain activation (34–36), as well as on personality and temperamental and emotional traits (37–39), have been demonstrated, we expected these candidate endophenotypes to be at least moderately ($h^2 \geq 0.20$) heritable.

METHODS AND MATERIALS

Participants

Participants were part of the LFLSAD, including two generations of families genetically enriched for SAD (total sample: $N = 132$, nine families; magnetic resonance imaging (MRI) sample: $n = 110$, eight families) (see the Supplement for details about ethics, recruitment, and exclusion criteria, as well as an a priori power calculation). More information with respect to the background, aims, and methodology of the LFLSAD is provided elsewhere (33); a preregistration is available online (40). The sample consists of nuclear families who were invited for participation based on the combination of parent with a primary diagnosis of SAD (age 25–55 years; "proband") and a child who met criteria for (sub)clinical SAD (age 8–21 years; "proband's SA child"). In addition to these two SAD cases, the proband's partner and other children from this nuclear family (age $\geq$ 8 years), as well as the proband's sibling(s), with their partners and children (age $\geq$ 8 years), were invited. Thereby, the LFLSAD sample consists of family members of two generations (Figure 1). Participants took part in several measurements, including a diagnostic interview, self-report questionnaires, and an MRI scan (33). The LFLSAD was approved by the Medical Ethical Committee of the Leiden University Medical Center, and all participants provided informed consent.

Phenotyping

Family members participated in various measurements to enable extensive phenotyping (33). Here, we focus on the measures of SA (see the Supplement for an extended characterization of the LFLSAD sample). The presence of DSM-IV diagnoses was determined using the Mini-International Neuropsychiatric Interview–Plus version 5.0.0 (41,42) or the Mini-International Neuropsychiatric Interview–Kid interview version 6.0 (43,44). Clinical SAD was established using the DSM-IV-TR criteria for the generalized subtype of SAD, but a clinician verified whether the DSM-5 criteria for SAD were also

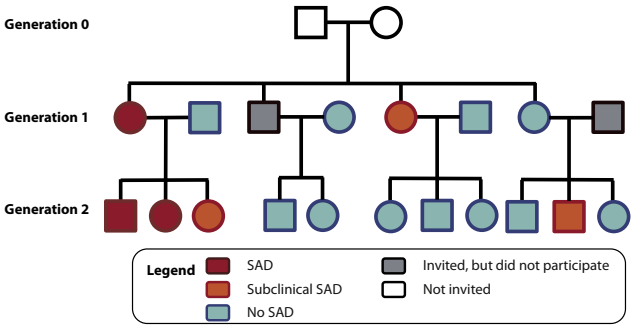

Figure 1. Illustration of family composition within the LFLSAD (Leiden Family Lab study on Social Anxiety Disorder). Families were included in the LFLSAD based on the combination of a parent with social anxiety disorder (SAD) ("proband"; depicted in red) and a proband's child with SAD (red) or (sub)clinical SAD (orange). Furthermore, family members of two generations were invited, independent from the presence of SAD within these family members (no SAD: light blue; did not participate: gray). Grandparents (generation 0; white) were not invited for participation. The details of the family illustrated in the figure are slightly modified to guarantee anonymity; however, the number of family members and the frequency of (sub)clinical SAD are depicted truthfully. Squares and circles represent men and women, respectively. [Reproduced with permission from Bas-Hoogendam *et al.* (33)].

met. A diagnosis of subclinical SAD was established when participants met the DSM-5 criteria for SAD but did not show impairing limitations in important areas of functioning (12). Furthermore, participants completed age-appropriate questionnaires on the level of SA (45,46): the Liebowitz Social Anxiety Scale (45,46) or the Social Anxiety Scale for Adolescents (46). *Z* scores were computed (33) to use these scores over the whole sample.

MRI Experiment

Prior to the MRI scan, participants were informed about the safety procedures, and they were told that they could refrain from continuing the experiment at any time. Children and adolescents were familiarized with the MRI scanner using a mock scanner (47) and all participants received instructions about the task paradigms presented during the scan session. Scanning was performed using a 3T Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands), equipped with a 32-channel Sensitivity Encoding head coil. The MRI experiment (total duration MRI protocol: 54 minutes 47 seconds) consisted of several structural scans (48) and functional task paradigms (33), including the SNPT-R (18). Scan parameters are reported in the Supplement.

Revised Social Norm Processing Task

The SNPT-R (18) consists of a story-reading phase, taking place in the MRI scanner, and an unannounced rating phase on completion of the MRI scan (Figure 2). During the story-reading phase (Figure 2A), short stories written in the second person are presented. Stories consisted of two sentences: a stem sentence (for example: "You are baking an apple pie with friends.") followed by an ending sentence that described a neutral social situation ("You use the amount of sugar the recipe calls for."), a situation in which a social norm was unintentionally transgressed ("You use salt instead of sugar without realizing."), or a situation in which a social norm was intentionally transgressed ("You use salt instead of sugar as a joke."). Stories were suitable for a broad audience and age range. However, because of the second-person form of the stories, small adaptations were made in stories describing age- or gender-specific elements. Therefore, the SNPT-R has four age- and gender-specific versions (boys, girls, men, women). We refer to the dataset on Open Science Framework for all SNPT-R stories (49).

The SNPT-R consists of 26 stem sentences, each combined with the three different types of endings. These 78 stories were divided into two consecutive blocks of 39 stories. Participants were instructed to imagine themselves in the social situations and to press a button after reading the stem sentence of each story to verify participants' task engagement.

After the scan, participants rated all stories on a five-point Likert scale on embarrassment and inappropriateness (Figure 2B). Presentation parameters and scripts are available in the Supplement.

Data Analysis

Sample Characteristics. We replaced incidental missing values on the self-report questionnaires by the average value of the completed items. Differences between participants with and without (sub)clinical SAD were examined by fitting regression models in R (50), with (sub)clinical SAD as the independent variable and the level of self-reported social anxiety (*Z* score) as the dependent variable. Gender and age were included as covariates; genetic correlations between family members were modeled by including random effects.

Imaging Data: General Processing. The functional MRI (fMRI) data were prepreprocessed using FMRIB Software Library, version 5.0.9 (51); next, event-related statistical analysis was performed (details in the Supplement). Briefly, the general linear model included four explanatory variables with their temporal derivatives, representing the presentation of a stem sentence, a neutral ending (EN), an unintentional SN violation ending (EU), and an intentional SN violation ending (EI). Three contrasts were defined: EI > EN, EU > EN, and EU > EI. We verified the main effects of the SNPT-R on brain activation by using contrasts EI > EN and EU > EN (Supplemental Results), while the contrast EU > EI was used for the endophenotype analysis, following previous results (16).

Imaging Data: Neuroimaging Candidate Endophenotypes. The cosegregation between SA and brain activation related to processing unintentional SN violations within the families was investigated using regression models in R (50), with self-reported SA (*Z* score, centered) as independent variable and individual activation level related to the contrast EU > EI as dependent variable. Analyses with (sub)clinical SAD as a discrete predictor are included in the Supplement. Correlations between family members were modeled by including random effects; age (centered) and gender (centered) were included as covariates. Models were run for each voxel separately to determine the effect of SA on a whole-brain voxelwise basis. Results (*Z* scores) were transformed into a NIfTI (Neuroimaging Informatics Technology

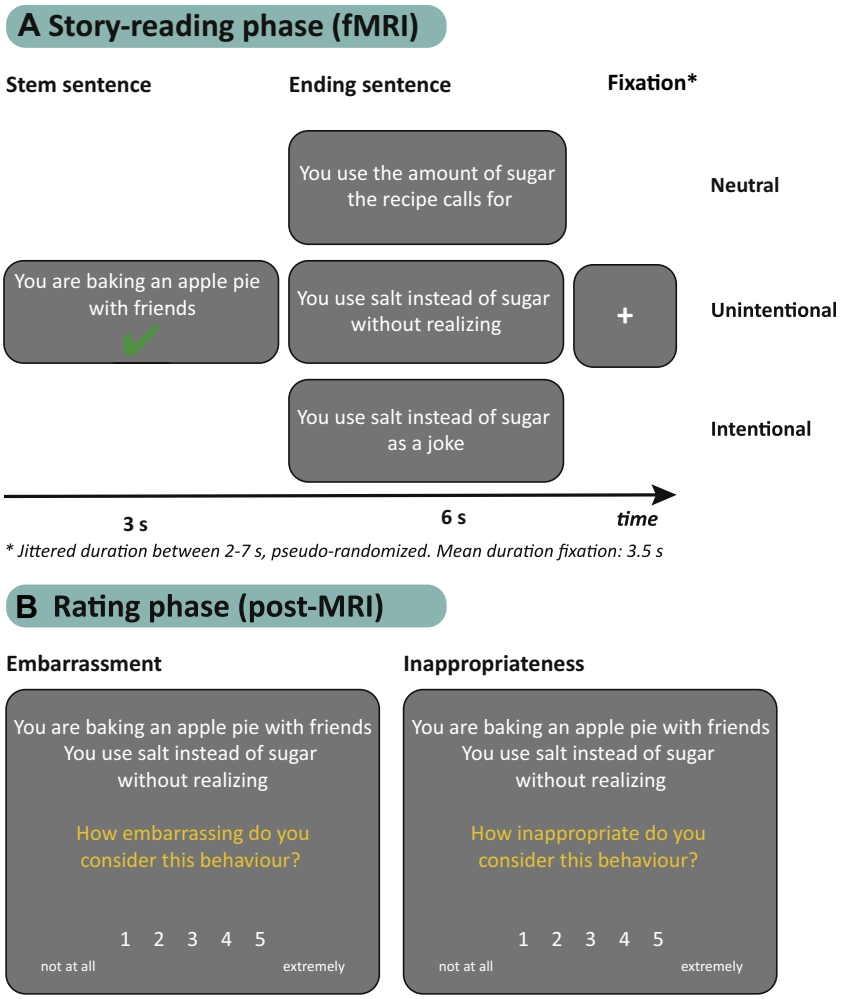

Figure 2. The revised Social Norm Processing Task. **(A)** Story-reading phase. While in the magnetic resonance imaging (MRI) scanner, participants read stories consisting of a stem sentence (duration: 3 seconds) and an ending sentence (duration: 6 seconds), describing a neutral social situation, a situation in which a social norm was unintentionally transgressed, or a situation in which a social norm was violated intentionally. Participants were instructed to imagine themselves in the social situations described and to press a button with their right index finger after reading the stem sentence of each story. A button press within 3 seconds resulted in visual feedback to the participant (a green checkmark presented beneath the sentence). **(B)** Rating phase. Following the MRI session, participants rated all stories on embarrassment and inappropriateness. fMRI, functional MRI. [Reproduced with permission from Bas-Hoogendam *et al.* (18)].

Initiative, National Institutes of Health, Bethesda, MD) image with the same dimensions of the Montreal Neurological Institute T1-template brain. Clusters within this NIfTI image, representing the association between SA and brain activation, were corrected for multiple comparisons at the whole-brain level using the FSL tool easythresh (cluster threshold: $Z > 3.1$, cluster extent threshold $p < .01$) (52). Subsequent sensitivity analyses were performed to investigate whether the results of the association analyses were driven by the severity of depressive symptoms or by (comorbid) psychopathology other than SAD (see the Supplement).

Next, we determined the heritability of brain activation for voxels in the significant clusters. Voxelwise heritability estimates were obtained with a method that takes the ascertainment process into account and incorporates familial relationships (53). Age and gender (both centered) were included as covariates.

Behavioral Data: Responses During Story-Reading Phase. Analysis of the behavioral responses during the story-reading phase confirmed that participants paid attention to the stories (Supplemental Results).

Behavioral Data: Behavioral Candidate Endophenotypes. The cosegregation between SA and the post-MRI SNPT-R ratings within the families was investigated using linear mixed models in R [package: coxme (50)], with self-reported SA (Z score, centered) as predictor of interest. Analyses with (sub)clinical SAD (discrete predictor) are described in the Supplement. Separate models were used to investigate the ratings of embarrassment and inappropriateness. Task condition (intentional, unintentional, neutral), age- and gender-specific task version (modeled using the dummy variables gender and age group [boys/girls vs. men/women]), as well as three interaction terms (condition × gender, condition × age group, condition × SA level) were added as independent variables and tested for significance. Random effects were included to account for genetic correlations between family members and within-subject correlations between task conditions. Interaction terms lacking significance were removed from the final models. Significance level was set at $p < .05$.

Next, we investigated whether the behavioral outcomes were heritable, focusing on the ratings displaying a significant association with SA. We estimated heritability by applying an

Table 1. Characteristics of Participants With and Without (Sub)Clinical SAD

	Behavioral Sample[a]			fMRI Sample[a]		
	(Sub)clinical SAD (n = 39)	No SAD (n = 62)	Statistical Analysis	(Sub)clinical SAD (n = 33)	No SAD (n = 58)	Statistical Analysis
Demographics						
Male/female, n	20/19	30/32	χ^2_1 = 0.08, p = .84	16/17	29/29	χ^2_1 = 0.02, p = 1.00
Generation 1 / generation 2, n	19/20	27/35	χ^2_1 = 0.26, p = .68	19/14	27/31	χ^2_1 = 1.02, p = .39
Age in years, mean ± SD; range	30.3 ± 15.5; 9.2–59.6	31.3 ± 15.2; 9.0–61.5	β (± SE) = −0.9 ± 3.1, p = .76	33.4 ± 14.9; 13.3–59.6	32.7 ± 14.8; 9.6–61.5	β (± SE) = 0.7 ± 3.2, p = .83
Diagnostic Information						
Clinical SAD, n	17	0		15	0	
Self-report Measures						
Social anxiety symptoms, Z score, mean ± SD	3.0 ± 3.3	0.6 ± 1.5	β (± SE) = 2.4 ± 0.5, p < .001	2.9 ± 3.0	0.7 ± 1.3	β (± SE) = 2.4 ± 0.4, p < .001

fMRI, functional magnetic resonance imaging; SAD, social anxiety disorder.
[a]For technical reasons, data on the presence of (sub)clinical SAD were lost for 8 family members. Data from these participants, however, were included in the endophenotype analyses using SA level (Z score) as a predictor (behavioral sample: n = 109; fMRI sample: n = 99).

approach that takes the ascertainment process into account and incorporates familial relationships, by jointly modeling the ratings and phenotype on which the family selection was based and by including random effects (53). Age group and gender were included as possible confounders.

RESULTS

Sample Characteristics

Characteristics of the sample after quality control (n = 109 for the behavioral analyses; n = 99 for the fMRI analyses) (see the Supplement) are summarized in Table 1. Family members with (sub)clinical SAD (n = 22 subclinical SAD; n = 17 clinical SAD) did not differ from family members without SAD (n = 62) with respect to male-to-female ratio and age. However, as expected, family members with (sub)clinical SAD reported higher levels of social anxiety. A detailed characterization of the sample, including clinical diagnoses other than SAD, is available in the Supplement.

Neuroimaging Candidate Endophenotypes

Whole-brain voxelwise regression analyses revealed two clusters in which self-reported SA level was positively associated with brain activation related to the contrast EU > EI (Table 2, Figure 3). The first cluster (6647 voxels, $p = 1.8 \times 10^{-7}$; corrected for multiple comparisons at the whole-brain level) was located in the occipital pole and encompassed the temporal occipital fusiform cortex, lateral occipital cortex, right superior temporal gyrus (STG), right medial temporal gyrus (MTG), superior temporal sulcus (STS), and cuneal cortex. The second cluster (1589 voxels, p = .003; corrected for multiple comparisons at the whole-brain level) comprised the frontal pole, extending to the paracingulate gyrus and mPFC. There were no clusters displaying negative relationships with SA, while visual inspection of the data confirmed the absence of outliers. Follow-up analyses confirmed the specificity of this positive association for processing unintentional SN violations, while sensitivity analyses, taking the effect of depressive symptoms and (comorbid) psychopathology other than SAD into account, further supported our results (see the Supplement).

Subsequent voxelwise heritability analyses within the two clusters indicated that activation within the right MTG, STG, and STS cluster and within the mPFC, paracingulate cortex, and frontal pole was heritable, with 91 voxels (cluster MTG/STG/STS) and 188 voxels (cluster mPFC) showing at least moderate ($h^2 \geq 0.20$) heritability, with some voxels displaying moderately high ($h^2 \geq 0.40$) heritability (Figure S1).

Behavioral Candidate Endophenotypes

Post-MRI SNPT-R ratings are summarized in Table 3; detailed results for each task version (boys, girls, men, women) are included in the Supplement. Analyses revealed significant associations between SA and embarrassment, but no relation with inappropriateness. Follow-up analyses indicated positive relationships between SA and embarrassment in all three conditions (Figure 4), while sensitivity analyses indicated that

Table 2. Effect of Self-reported Social Anxiety on Processing Unintentional Norm Violations[a]

Cluster	Region	Z Score	Peak Coordinates (MNI Space) x	y	z	Cluster Size
1	Temporal occipital fusiform cortex	5.45	32	−60	−18	6647
	Occipital pole	5.29	10	−94	26	
	Superior temporal gyrus, posterior division	4.31	62	−6	−8	
	Medial temporal gyrus, posterior division	3.66	60	−22	−10	
	Cuneal cortex	3.54	20	−76	32	
2	Frontal pole	5.75	−10	56	32	1589
	Frontal pole/frontal medial cortex	3.71	0	58	−4	

EI, intentional social norm violation ending; EU, unintentional social norm violation ending; MNI, Montreal Neurological Institute.
[a]Unintentional norm violations vs. intentional norm violations (EU > EI).

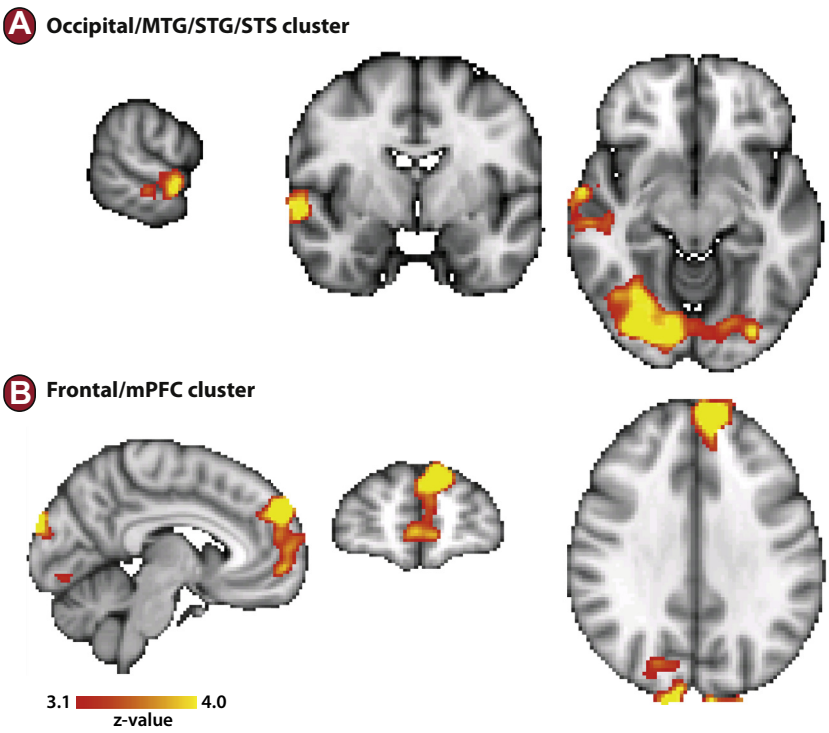

Figure 3. Brain activation (related to processing unintentional social norm violations) cosegregates with social anxiety within families: there were significant positive associations between social anxiety (*Z* scores) and activation related to processing stories on unintentional social norm violations vs. intentional social norm violations. Coordinates of displayed slices (Montreal Neurological Institute, x, y, z): 64, −4, −10 (occipital/medial temporal gyrus/superior temporal gyrus/superior temporal sulcus [MTG/STG/STS] cluster) **(A)** and −6, 56, 32 (frontal/medial prefrontal cortex [mPFC] cluster) **(B)**. Clusters are displayed on the template MNI_T1_152_2 mm_brain (partial brain coverage: inferior parts of the frontal medial cortex, superior parts of the postcentral gyrus as well as parts of the cerebellum are not included). Images are displayed according to radiological convention: right in the image is left in the brain.

these effects were not driven by the clinical SAD cases within the sample (see the Supplement).

Heritability analyses demonstrated that embarrassment ratings on the intentional stories had low heritability (h^2 = 0.17), while embarrassment scores for unintentional and neutral stories were not heritable (Table 3).

DISCUSSION

Here, we provide evidence that brain activation related to processing unintentional SN violations is a neurobiological candidate endophenotype of SAD by using data from LFLSAD (33). This study, with its unique multiplex and multigenerational design, was especially designed to explore SAD endophenotypes (54), and our data revealed that SAD-related neurobiological alterations in processing unintentional SN violations cosegregated with SA within families of probands (n = 99). Next, our data indicated that these aberrant brain activation patterns displayed moderate to moderately high heritability, providing support for the endophenotype criterion of heritability. Thereby, we replicate and extend previous work on the processing of SN violations in SAD, which provided support for the endophenotype criterion of association with the disorder by reporting increased brain activation in the mPFC related to processing unintentional SN violations in SAD patients (16). In addition to these neurobiological alterations, we found positive relationships between SA and ratings of embarrassment within the families, but as these behavioral measures were not heritable, our data do not provide support for these ratings as candidate endophenotypes of SAD.

Level of mPFC and MTG, STG, and STS Activation as a Candidate SAD Endophenotype

The fMRI data revealed a positive relationship between SA level within the families and brain activation in the frontal cortex, including the mPFC, in response to unintentional SN violations (vs. intentional SN violations), as well as an association with activation within the occipital cortex and MTG and STG, including the STS between them (Table 2, Figure 3). Furthermore, activation clusters within the mPFC and MTG/STG/STS displayed moderate to moderately high heritability (maximum h^2 = 0.47) (Figure S1). Thereby, activation within the mPFC and MTG, STG, and STS is a promising neurobiological endophenotype of SAD.

The heightened mPFC reactivity in response to unintentional SN violations confirmed our hypothesis, as this finding is in line with previous work reporting on 16 patients with generalized SAD (16). The mPFC is engaged during social cognitive processing, including self-referential processing (55,56) and as such, the exaggerated mPFC activation during processing unintentional SN violations supports the idea that SAD patients consider these transgressions as extremely self-relevant, probably because these unintentional transgressions relate to their strong fear of unintentionally generating an embarrassing behavioral blunder in a social situation (13,57). The importance of the mPFC in the neurobiological characterization of SAD is further supported by studies indicating increased mPFC activation related to self-referential statements and criticism (58,59), as well as in response to performance feedback (60); see reviews by Miskovic and Schmidt (61) and Brühl *et al.* (62).

Although not a priori hypothesized, the increased activation in the posterior MTG, STG, and STS could concur with

Table 3. Ratings of Inappropriateness and Embarrassment

			Effect of Social Anxiety (*Z* Score)		Heritability
	(Sub)clinical SAD	No SAD	β ± SE	*p*	h^2
Inappropriateness			0.002 ± 0.009	.84	
Intentional stories	4.36 ± 0.40	4.36 ± 0.43	n.i.	n.i.	n.i.
Unintentional stories	2.98 ± 0.73	2.98 ± 0.64	n.i.	n.i.	n.i.
Neutral stories	1.39 ± 0.34	1.31 ± 0.29	n.i.	n.i.	n.i
Embarrassment			0.03 ± 0.01	.003[a]	
Intentional stories	3.92 ± 0.72	3.89 ± 0.58	0.06 ± 0.02	.010[a]	0.17
Unintentional stories	3.45 ± 0.54	3.23 ± 0.51	0.06 ± 0.02	.003[a]	0.01
Neutral stories	1.38 ± 0.38	1.25 ± 0.24	0.03 ± 0.01	.024[a]	0.02

Values represent mean ± SD.
n.i., not investigated; SAD, social anxiety disorder.
[a]Significant at $p < .05$.

the role of this area in social cognition (63–65), including, but not limited to, understanding intentions from other people's actions (66–68). Interestingly, recent work demonstrated that the posterior STS is involved in experiencing embarrassment with another person's mishaps (69), while work on SAD demonstrated increased bilateral STS activation in response to emotional faces (70,71). Furthermore, the STS is functionally connected to the amygdala (72,73). Based on these findings, we cautiously hypothesize that the heightened posterior temporal activation in response to unintentional SN violations could represent the increased affective value that socially anxious people attribute to making an unintentional slip. Furthermore, as these temporal regions are involved in visual processing and visual imagery (74), enhanced activation within these areas could also represent the increased saliency of the social situations for socially anxious participants when they imagine themselves in the hypothetical scenarios.

Embarrassment Cosegregates With SA Within Families

Within the LFLSAD-sample, family members with higher levels of self-reported SA rated all types of stories as more embarrassing (Figure 4). These findings are in line with previous work (16,17) and confirm the notion that feeling embarrassed is an important characteristic of SA. Our results did not, however, support the specific effect of SA on embarrassment in the unintentional condition, which was reported previously, nor did we replicate the effect of SA on the ratings of inappropriateness (16,17), indicating the need for future studies to unravel this complex pattern. Furthermore, heritability of these behavioral endophenotypes was low (intentional condition) or absent (unintentional and neutral condition). So, the present findings reinforce the view that increased reports of embarrassment are associated with SA, but as these embarrassment levels have heritability estimates below our predefined threshold, they do not meet criteria for being a candidate endophenotype.

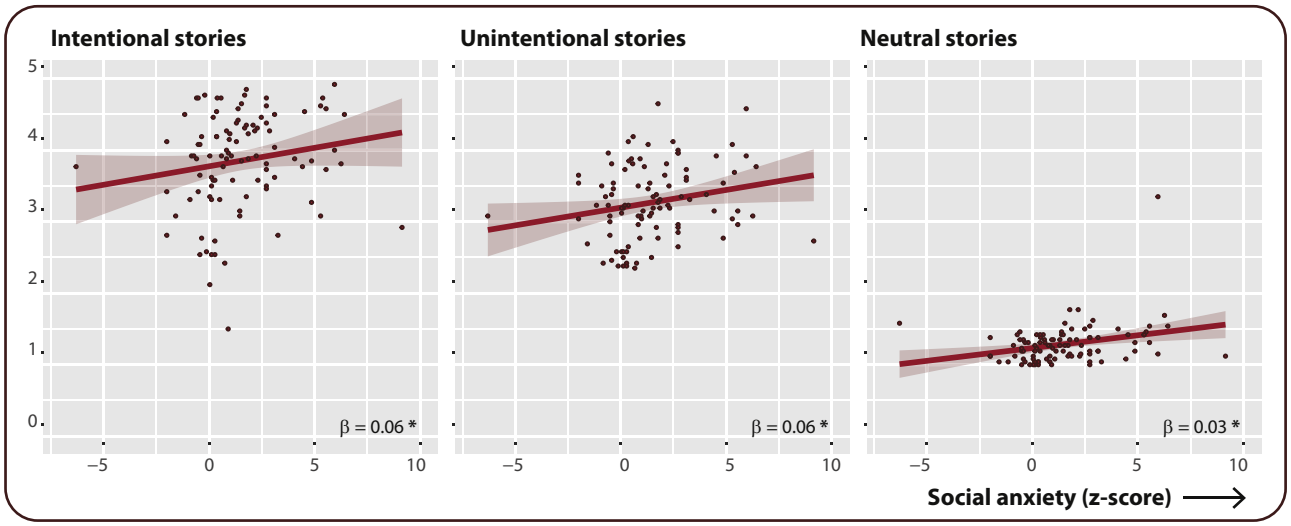

Figure 4. Embarrassment ratings cosegregate with social anxiety within families. Correlation between level of self-reported social anxiety (*Z* score) and ratings of embarrassment. Shaded area represents 95% confidence interval. Asterisks indicate effects of social anxiety at $p < .05$.

Limitations and Directions for Future Research

Although the results presented here, from a unique two-generation neuroimaging family study on SAD that was especially designed to explore two endophenotype criteria (33), provide support for the cosegregation of the candidate endophenotypes with SA within families of probands (criterion 4, first part) and the endophenotype criterion of heritability (criterion 3), the cross-sectional nature of the LFLSAD and the lack of control families do not allow for investigation of the state independency (criterion 2) of the candidate endophenotypes, nor do the data enable assessing whether nonaffected family members show altered levels of the endophenotype in comparison to the general population (criterion 4, second part). Future studies employing a longitudinal design and including control families from the general population are needed to investigate these criteria and to replicate the current findings. In addition, given the heterogeneity in the SAD phenotype (14), future studies could consider using individually tailored stimuli [cf. (75)]. We hypothesize that such stimuli, representing social situations that are most anxiety provoking for participants with SAD, might yield even stronger neurobiological and behavioral responses compared with those of the present study. Furthermore, given the fact that the SNPT-R has age- and gender-adjusted task versions, the present design does not allow for determining effects of age and gender on the candidate endophenotypes.

Another interesting avenue for future research would be to link the altered brain activation observed here to changes in brain structure. In a previous study on the same sample, we found a negative correlation between SA levels and cortical thickness of the left mPFC and bilateral STG (48). In addition, cortical thickness of the left mPFC and left STG displayed moderately high and high heritability (48). However, owing to the complexity of the present association analyses, in which we had to account for the family structure of the data, we were not able to consider the connection between brain structure and brain function on a voxelwise basis. Moreover, it should be noted that a voxel-based morphometry mega-analysis on the largest sample of SAD patients to date did not reveal gray matter differences in frontal and temporal areas (76). Furthermore, the alterations in function are specific to processing unintentional SN violations, while the structural changes are independent of any task condition. Therefore, more research is needed to unravel the complex relationship between brain structure and function (77,78). Besides, longitudinal MRI studies [cf. (79)] could explore the potential of cognitive behavioral therapy enriched with neurofeedback (4) to specifically target the altered brain activation patterns in the mPFC. Finally, as we have not yet considered the genetic data collected within the LFLSAD (33), we are at present not able to relate the alterations in brain activation to genetic variations, which would be a next step to further unravel the genetic susceptibility to SAD.

Conclusions

The findings of this study provide considerable support for increased brain activation in the mPFC and MTG, STG, and STS, related to the processing of unintentional SN violations, as a neurobiological candidate SAD endophenotype. Thereby, these results offer novel insights in the neurobiological pathways leading to SAD.

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