Appendix 1

Table S1. Clinical sample description for the 4 groups emerging from the factors social anxiety disorder and early-life adversity.

	Ce	CE	Se	SE
Total participants	34	24	21	21
Diagnosis				
Current depression (mild-moderate)	0	0	2	2
Dysthymia	0	0	2	4
Alcohol abuse	1	1	0	2 (past)
Panic disorder	0	0	4	4
Agoraphobia	0	0	4	2
Specific phobia	2	2	5	4
Obsessive–compulsive disorder	0	0	0	2
Generalized anxiety disorder	0	0	3	1
Post-traumatic stress disorder	0	0	0	0
Medication				
Benzodiazepines	0	0	2*	0
Antidepressants	0	0	2**	2***

Ce: control participants with low levels of early-life adversity, CE: control participants with high levels of early-life adversity, Se: participants with social anxiety disorder and low levels of early-life adversity, SE: participants with social anxiety disorder and high levels of early-life adversity
* infrequent use as needed
** Escitalopram, Opipramol
*** Escitalopram, Citalopram

Stimuli and task design

Word stimuli originated from previous studies and were matched for numbers of letters and syllables, familiarity, and frequency in spoken and written language using the COSMAS II database (http://www.ids-mannheim.de/cosmas2) [1-7]. The experimental design was closely adapted from Dresler et al. (2012) [1]. Stimulus presentation was randomized and stimulus events were interspersed with 10% null events. For each trial, participants were instructed to indicate as fast and accurately as possible the number of word repetitions with an MRI compatible response pad using their right index, middle or ring finger. The order of the assigned buttons was balanced between the participants, i.e., whether the index or ring finger was assigned to 2 or 4 word repetitions. The mean inter-trial-interval was 6 s (range: 4.5 s – 7.5 s) jittered in steps of 375 ms (= 1/4 TR) relative to stimulus onset. For each trial, a white fixation cross on gray background was presented first, followed by a stimulus presentation for 500 ms.

Image acquisition – complete parameters

MRI data were acquired using a 3 Tesla scanner (PRISMA, Siemens, Erlangen, Germany). Structural MP-RAGE T_1-weighted images were recorded using the following parameters: 208 slices, repetition time (TR) of 2400 ms, echo time (TE) of 2.22 ms, voxel size: $0.8 \times 0.8 \times 0.8$ mm^3, field of view (FoV) of 256×256 mm^2, flip angle 8°. For functional imaging, multiband echo-planar imaging (EPI) sequences were used with the following parameters: 72 slices, 2 mm thickness, TR = 1500 ms, TE = 34 ms, multiband acceleration factor: 3, voxel size: $2 \times 2 \times 2$ mm^3, FoV = 192×192 mm^2, flip angle 70°, 850 volumes. A field map was acquired with the following parameters: 36 slices, 3 mm slice thickness, TR = 400 ms, TE[1] = 5.19, TE[2] = 7.65 ms, flip angle 60°.
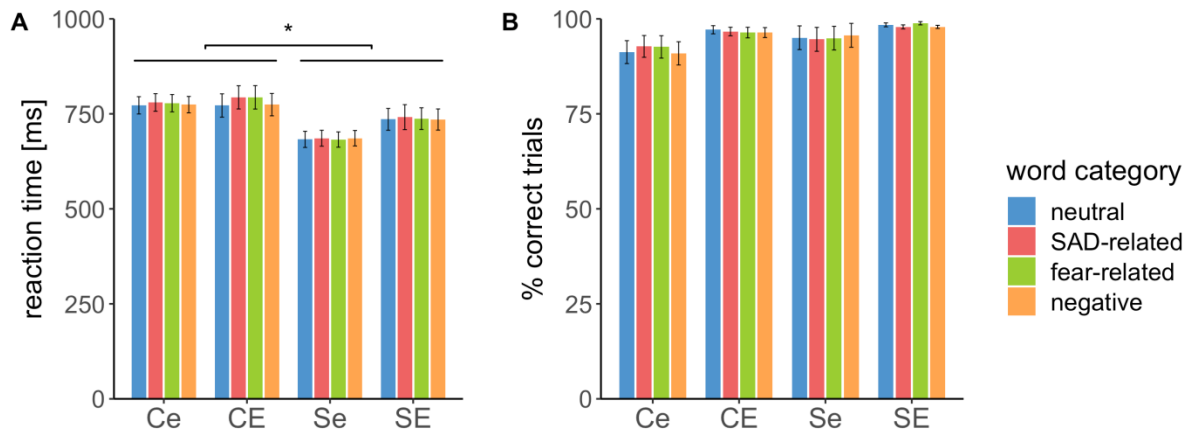
Emotional interference

Figure S1. Emotional interference. A: Mean reaction times ± standard error for each group and each word category. B: Mean number of correctly answered trials ± standard error for each group and each word category. Ce: control participants with low levels of early-life adversity, CE: control participants with high levels of early-life adversity, Se: participants with social anxiety disorder and low levels of early-life adversity, SE: participants with social anxiety disorder and high levels of early-life adversity, SAD: social anxiety disorder, asterisk mark $p < 0.05$.
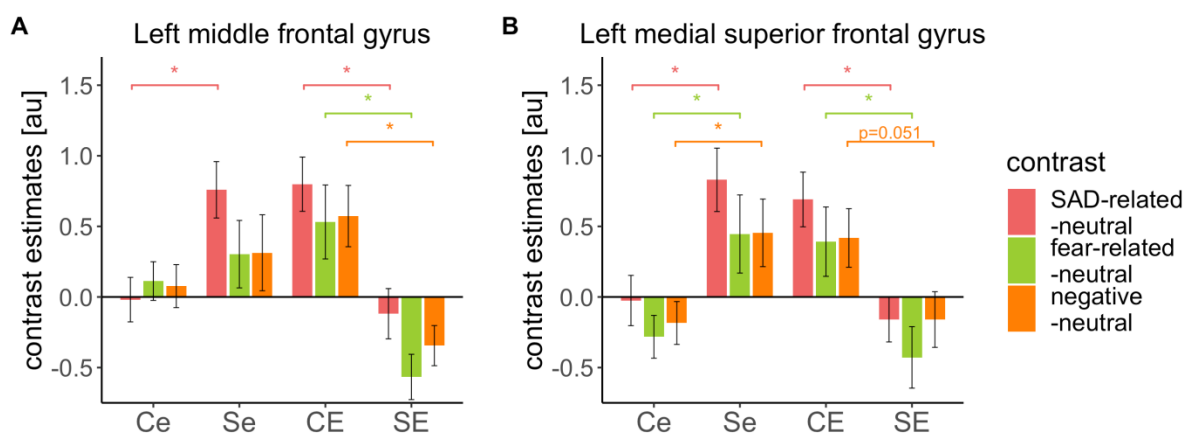
Functional MRI data

Figure S2. Cerebral correlates of the contrast 'SAD-related versus neutral words', 'fear-related versus neutral words' and 'negative versus neutral words' in the identified clusters. Mean contrast estimates for each group extracted from the significant clusters identified in the region-of-interest analysis. Clusters were located within the left middle frontal gyrus (A) and the left medial superior frontal gyrus (B). Ce: control participants with low levels

of early-life adversity, CE: control participants with high levels of early-life adversity, Se: participants with social anxiety disorder and low levels of early-life adversity, SE: participants with social anxiety disorder and high levels of early-life adversity. Error bars depict standard errors of the mean, asterisks mark p < 0.05.

Functional MRI data: controlling for depression, general anxiety and alcohol abuse

To make sure that the observed interaction effect between social anxiety disorder and early-life adversity in the MFG and mSFG is not driven by differences in depression (as indicated by Beck Depression Inventory II scores), general anxiety (as indicated by State-Trait Anxiety Inventory state and trait scores) or alcohol abuse, we included the corresponding values as covariates in our model. Post-hoc tests showed that the interaction effect of social anxiety disorder and early-life adversity remained significant for both clusters when including the Beck Depression Inventory II score (MFG: $F_{(1,93)} = 20.25$, $p < 0.001$, mSFG: $F_{(1,93)} = 18.22$, $p < 0.001$), the State-Trait Anxiety Inventory state and trait scores (MFG: $F_{(1,92)} = 20.38$, $p < 0.001$, mSFG: $F_{(1,92)} = 17.93$, $p < 0.001$) or alcohol abuse as covariates (MFG: $F_{(1,93)} = 20.77$, $p < 0.001$, mSFG: $F_{(1,93)} = 18.70$, $p < 0.001$).
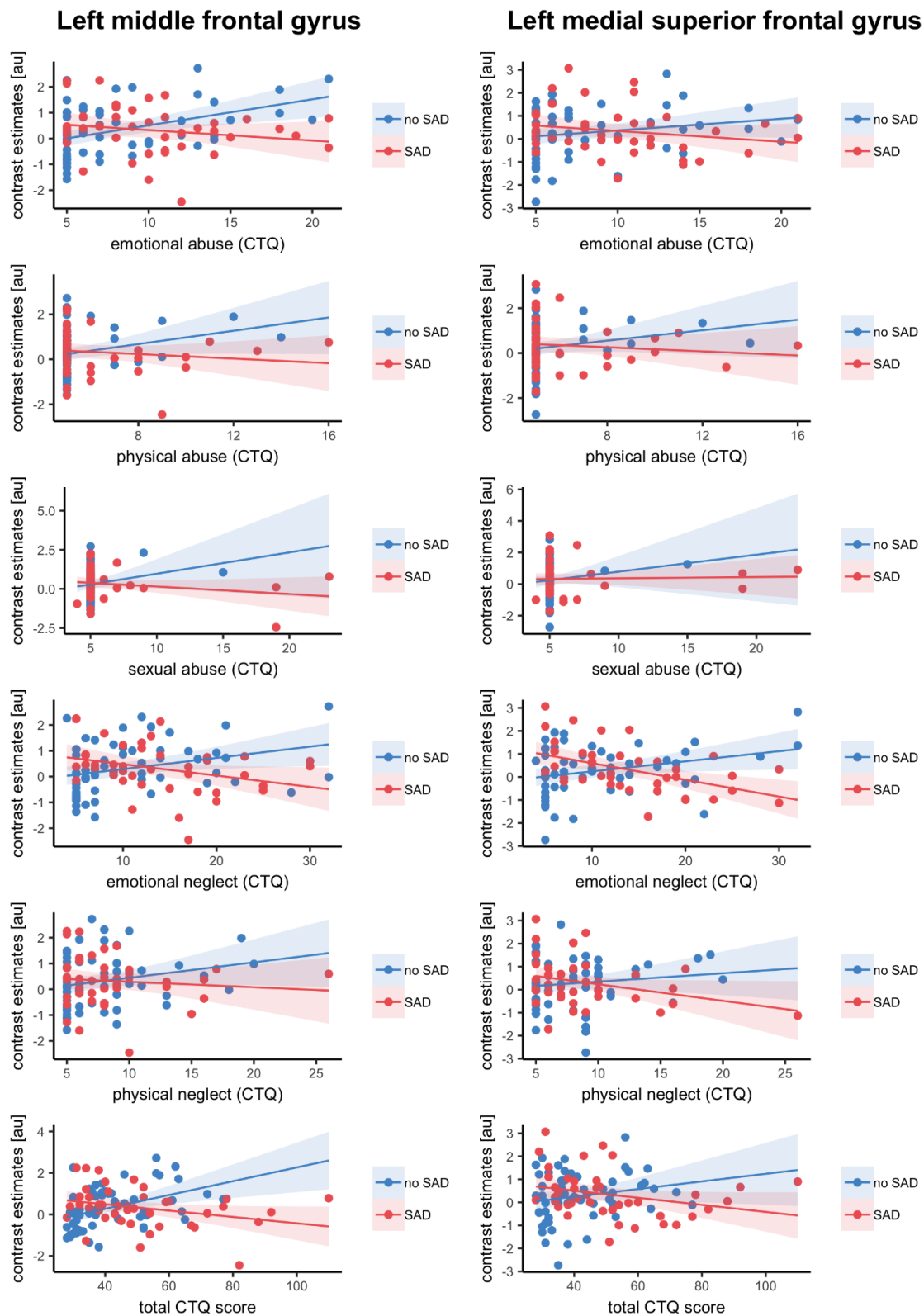
Figure S3. Correlation of mean contrast estimates ('social anxiety disorder-related versus neutral words') extracted from the identified clusters and Childhood Trauma

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Questionnaire scales. Separate regression lines with 0.95 confidence intervals for control individuals and participants with social anxiety disorder. CTQ: Childhood Trauma Questionnaire, SAD: social anxiety disorder.

Table S2. DNA methylation levels at the 74 CpG sites located within the *NR3C1* gene.

CpG site	Mean	SD
cg00294552	94.75%	0.82%
cg00407401	96.65%	0.60%
cg01294526	94.44%	1.20%
cg01751279	91.78%	1.58%
cg01967637	5.48%	0.85%
cg03746860	97.05%	0.51%
cg03857453	79.71%	2.05%
cg03906910	20.75%	1.88%
cg04457787	97.32%	0.49%
cg05483455	98.60%	0.21%
cg05900547	93.73%	1.08%
cg06613263	92.84%	1.40%
cg06952416	7.75%	0.71%
cg06968181	4.99%	0.41%
cg07515400	2.28%	0.63%
cg07528216	98.41%	0.21%
cg07589972	96.99%	0.41%
cg07715663	97.56%	0.36%
cg07733851	32.85%	2.39%
cg07742588	90.55%	2.10%
cg08423118	84.72%	6.09%
cg08695103	38.32%	3.88%
cg08818984	1.77%	0.21%
cg08845721	96.84%	0.76%
cg12466613	98.33%	0.23%
cg12741214	98.07%	0.37%
cg12888360	16.32%	2.97%
cg12969488	74.23%	1.72%
cg13514002	96.92%	0.57%
cg13648501	2.72%	0.34%
cg13764763	92.87%	2.08%
cg14438279	89.47%	2.52%
cg14621978	97.25%	0.36%
cg14939152	2.20%	0.13%
cg15115787	25.16%	1.69%
cg15910486	6.26%	0.69%
cg16219186	96.09%	0.69%
cg16224829	87.32%	1.92%

cg16535116	91.34%	1.47%
cg16586394	96.96%	0.51%
cg16594263	97.96%	0.37%
cg17342132	88.72%	1.99%
cg17349736	95.65%	0.69%
cg18146873	2.21%	0.34%
cg18484679	94.39%	0.90%
cg18718518	59.88%	2.18%
cg18849621	2.27%	0.30%
cg18998365	56.10%	3.18%
cg19135245	3.88%	0.35%
cg19176661	97.19%	0.41%
cg19432243	87.64%	2.34%
cg19457823	94.89%	0.98%
cg19645279	61.20%	2.43%
cg19820298	89.19%	2.15%
cg20598211	97.74%	0.46%
cg20728768	28.95%	2.13%
cg20753294	5.91%	0.46%
cg21209684	2.23%	0.15%
cg21979215	90.03%	1.97%
cg22233604	80.95%	1.82%
cg22402730	1.57%	0.19%
cg23273257	98.86%	0.16%
cg23430507	72.56%	1.51%
cg23776787	3.26%	0.45%
cg24052866	71.86%	1.78%
cg24801588	96.49%	0.48%
cg25535999	96.22%	0.53%
cg25579735	97.83%	0.44%
cg25708981	92.32%	1.59%
cg26081259	98.19%	0.33%
cg26464411	5.83%	0.78%
cg27107893	90.41%	6.10%
cg27122725	6.32%	0.65%
cg27345592	98.39%	0.24%

SD: standard deviation

References

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