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Supplemental Information

Human Responses to Visually Evoked Threat

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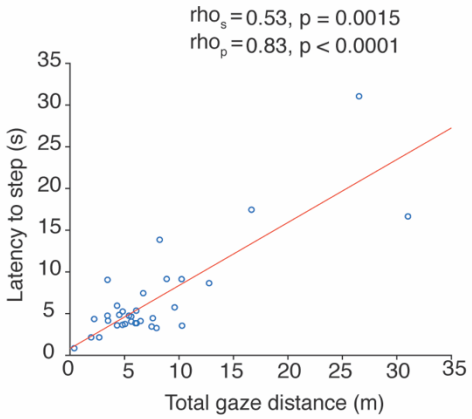
A



B

Linear regression model:

$y \sim 1 + x1 + x2$

x1 = change in SCL in response to heights

x2 = total gaze distance (m)

Estimated Coefficients:

	Estimate	SE	tStat	pValue
(Intercept)	-0.18018	0.93386	-0.19294	0.84835
x1	0.18189	0.067042	2.713	0.011099
x2	0.00071293	8.619e-05	8.2716	4.0495e-09

Number of observations: 32, Error degrees of freedom: 29

Root Mean Squared Error: 3.06

R-squared: 0.748, Adjusted R-Squared 0.73

F-statistic vs. constant model: 43, p-value = 2.11e-09

Figure S1 Increase in arousal and increase in visual scanning both contribute significantly to increased latency to step onto the plank, Related to Figure 1

(A) Scatter plot showing the correlation between latency to step and totally scanning distance. rho_s = Spearman correlation coefficient. rho_p = Pearson correlation coefficient. (B) Generalized linear model statistics that predict latency from a combination of change in SCL and total gaze distance.

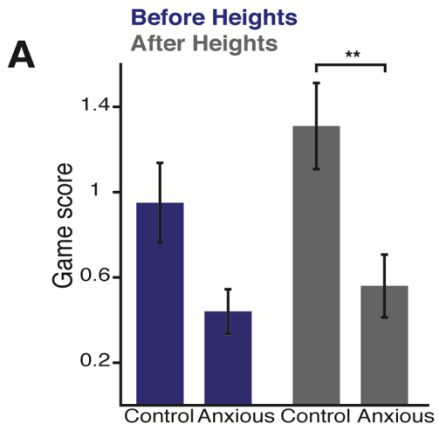


Figure S2 Anxious subjects score lower on the cognitive game than healthy controls after heights exposure, Related to Figure 3

(A) Game score = number of boards completed. p = 0.01, unpaired 2-sided t-test. Error bars = S.E.M. See also Table S2.

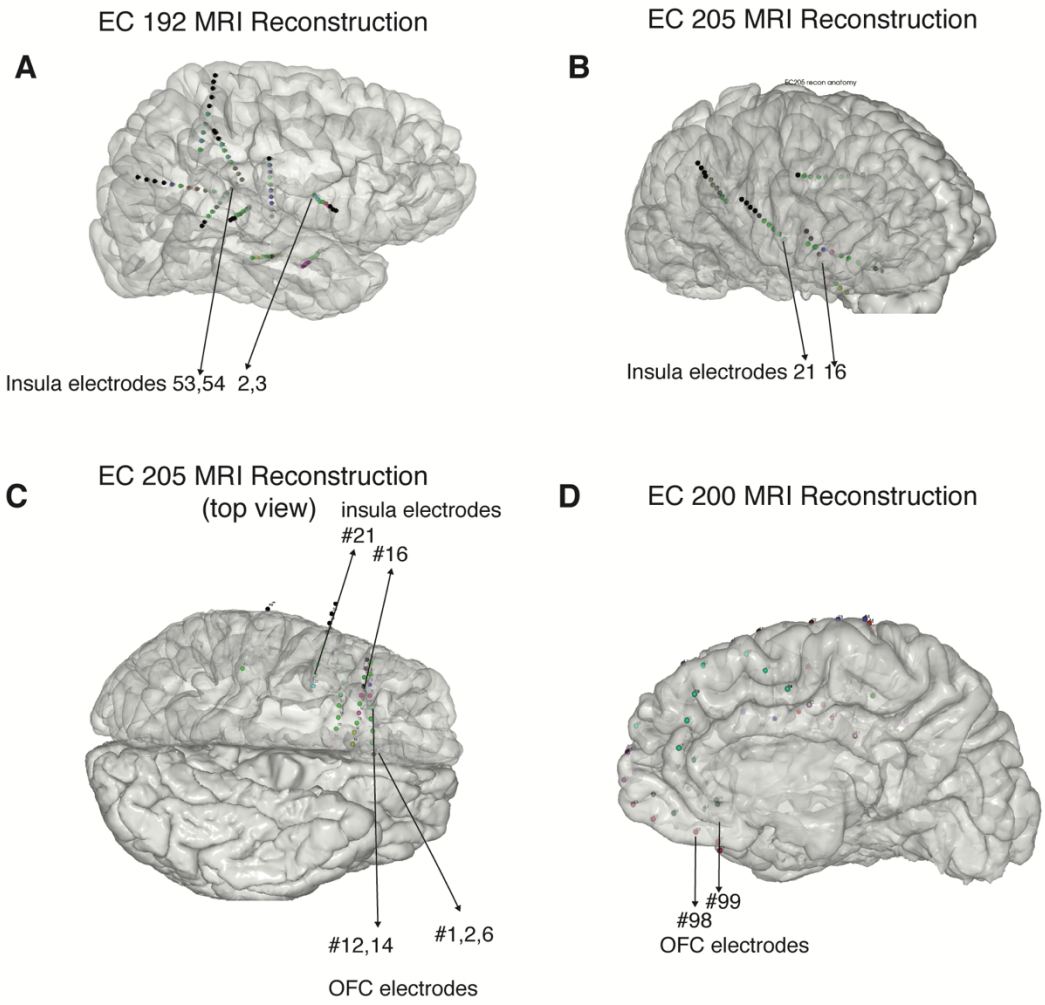
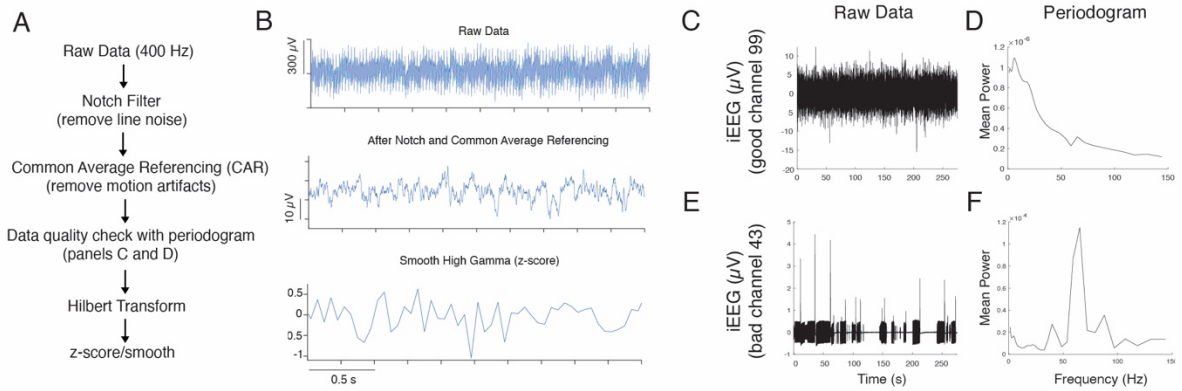
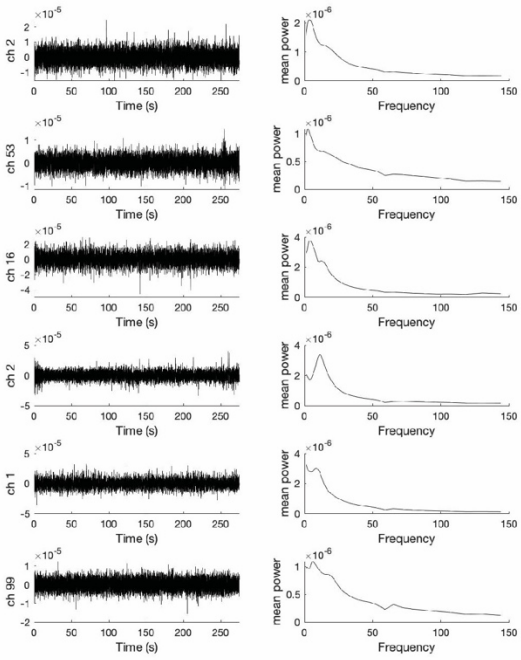


Figure S3 MRI reconstructions with electrode locations from individual epilepsy patients, Related to Figures 5, 6 and 7

Locations of insula and OFC electrodes shown for patient EC 192 (A) and EC 205 (B) and (C) and EC 200 (D).



G Example channels and respective periodograms from all leads included in the analysis (Heights)



H Example channels and respective periodograms from all leads included in the analysis (No Heights)

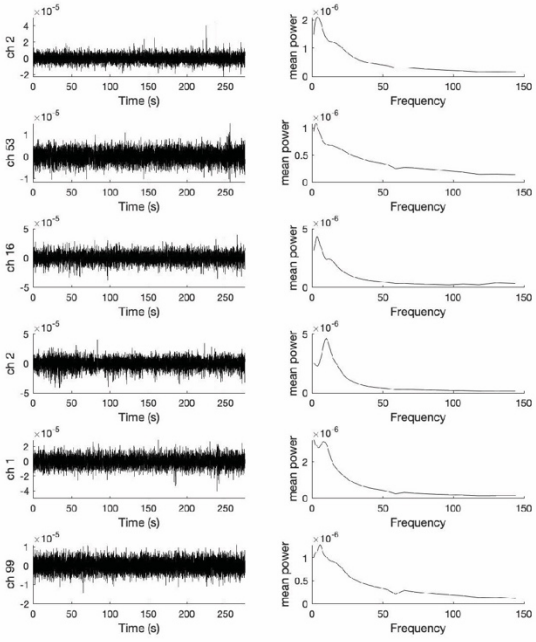


Figure S4 iEEG processing steps for quality control and example periodograms for all included electrode leads, Related to Figures 5, 6 and 7

(A) iEEG data preprocessing steps from raw data to the high gamma signal that gets correlated with the skin response. (B) Example iEEG traces: raw data (top), after notch filtering and common average referencing (middle), smoothed and z-scored high gamma signal (bottom). (C) Examples of raw data from a channel with good data quality (C) and bad data quality (E), and their respective periodograms (D) and (F) showing mean power plotted for each frequency band (5 Hz bins). iEEG traces after common average referencing from one example electrode from each lead during heights (G) and no heights (H) conditions and their respective periodograms.

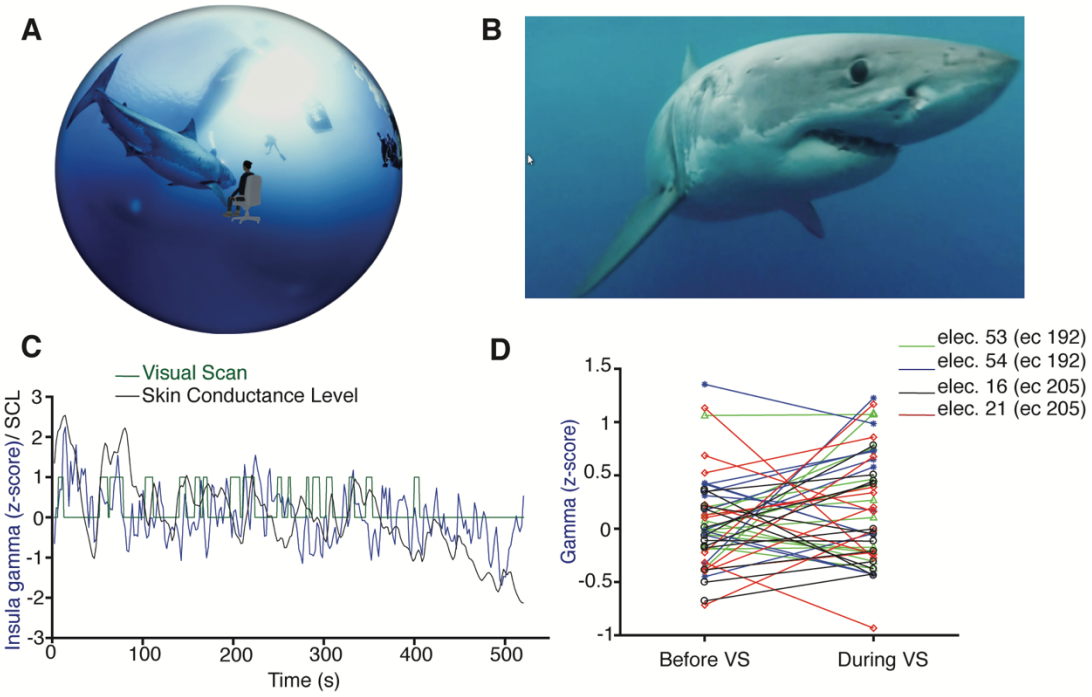

A
B
C
Visual Scan
Skin Conductance Level
Insula gamma (z-score)/ SCL
3
2
1
0
-1
-2
-3
0
100
200
300
400
500
Time (s)
D
elec. 53 (ec 192)
elec. 54 (ec 192)
elec. 16 (ec 205)
elec. 21 (ec 205)
Gamma (z-score)
1.5
1
0.5
0
-0.5
-1
Before VS
During VS

Figure S5 Insula gamma correlates with skin conductance during the 360 shark movie, Related to Figures 5 and 7

(A) An illustration showing the position of the viewer of the 360 shark movie in relationship to the movie which is presented on the inner surface of a virtual sphere. (B) A screen shot from the shark movie. (C) Gamma activity from one electrode (21, EC 205) from the insula superimposed with skin conductance level (SCL) and visual scanning episodes (red) during the sharks stimulus. (D) Gamma activity before and during each visual scanning episode during the shark stimulus. Each line represents data from one electrode during a visual scan. See also Table S2.

Information	Heights		No Heights		Modified Heights Stimulus		
	Healthy	**Anxious**	**Healthy**	**Anxious**	**192**	**200**	**205**
Gender (F, M)	29, 22	27, 10	20, 22	13, 8	M	M	F
Age	35 ± 14	36 ± 15	32 ± 13	36 ± 2	33	23	44
STAI Score (State, Trait)	26 ± 5, 31 ± 7	39 ± 9, 50 ± 11	27 ± 5, 33 ± 11	36 ± 2, 49 ± 3	50, 66	22, 27	24, 26
GAD-7 Score	3± 3	12 ± 4	3 ± 2	13 ± 1	19	3	12

Table S1 Subject information, Related to STAR Methods

- **All values for Heights and No Heights are mean ± s.e.m.**

Figure	Population/Stimulus/Measure	n	Mean	Median	S.e.m.	Test	p - value
1 E	Healthy / Heights / SCL before and after (z-score)	40	7.45	4.61	1.31	Paired t-test	$p < 0.0001$
1 F	Healthy / Heights / HR before and after (z- score)	35	0.84	0.75	0.23	Paired t-test	$p = 0.0077$
1 G	Healthy / Heights / Tidal Volume before before and after (z-score)	34	5.59	3.92	1.53	Paired t-test	$p = 0.0009$
1 J	Healthy / Heights / # of visual scans	34	2.65	2	0.33	N/A	N/A
1 K	Healthy / Heights / scan distance (m)	90	1.57	1.15	0.13	N/A	N/A
2 D	Healthy / Heights vs No Heights / SCL (z-score)	40,32	7.45, 1.85	4.61, 1.85	1.30, 0.35	Unpaired t-test	$p < 0.0001$
2 E	Healthy / Heights vs No Heights / Duration of SCR (s)	40,32	20.78, 8.76	13.85, 9.30	2.46, 0.88	Unpaired t-test	$p < 0.0001$
Text	Healthy / Heights vs No Heights / Heart Rate (z-score)	35, 39	0.84, 0.43	0.75, 0.22	0.30, 0.23	Unpaired t-test	$p = 0.54$
Text	Healthy / Heights vs No Heights /Tidal Volume (z-score)	34,27	5.59, 5.01	3.92, 4.31	1.55, 0.91	Unpaired t-test	$p = 0.76$
2 F	Healthy / No Heights vs Heights /Total scanning distance (m)	40,34	3.64, 7.47	2.55, 5.85	0.84, 1.09	Unpaired t-test	$p = 0.0061$
2 G	Healthy / No Heights vs Heights / # of scans per subject	40,34	1.53, 2.65	1,2	0.28, 0.33	Unpaired t-test	$p = 0.01$
2 H	Healthy / No Heights vs Heights / Avg. distance per each scan (m)	61, 90	1.65, 1.57	1.34, 1.15	0.19, 0.13	Unpaired t-test	$p = 0.73$
2 I	Healthy / No Heights vs Heights / Subjective ‘scary’ rating	38,40	2.18, 3.23	1, 2	0.12, 0.18	Unpaired t-test	$p < 0.0001$
2 I	Healthy / No Heights vs Heights / Subjective ‘real’ rating	38, 40	3.29, 3.26	3, 3	0.15, 0.13	Unpaired t-test	$p = 0.75$
2 J	Healthy / No Heights vs Heights / Latency to step to plank (s)	51, 42	6.34, 2.31	4.70, 2.10	0.72, 0.20	Unpaired t-test	$p < 0.0001$
2 K	Healthy / No Heights vs Heights / %time scanning away from the plank	40, 34	86%, 82%	90%, 86%	2.8%,2.8%	Unpaired t-test	$p = 0.32$
3 C	Healthy control vs Anxious / Before Baseline / Number of SCRs	32, 30	1.51, 2.18	1.43, 2.15	0.19, 0.23	Unpaired t-test	$p = 0.028$
3 D	Healthy control vs Anxious / Heights SCL change (z-score)	40, 24	7.45, 12.86	4.61, 5.55	1.26, 5.58	Unpaired t-test	$p = 0.24$
3 E	Healthy control vs Anxious / Heights SCR duration (s)	40, 24	20.78, 31.07	13.85, 18.79	2.45 ,7.24	Unpaired t-test	$p = 0.11$
3 H	Healthy control vs Anxious / Heights Total scanning distance (m)	34, 33	7.46, 13.85	5.85, 9.43	1.09, 2.51	Unpaired t-test	$p = 0.021$
3 H	Healthy control vs Anxious / No Heights/ Total scanning distance (m)	40, 21	3.64, 3.66	2.55, 3.19	0.84, 0.49	Unpaired t-test	$p = 0.99$
3 H	Healthy control vs Anxious / VR intro/ Total scanning distance (m)	33, 30	6.15, 5.07	5.45, 4.88	0.82, 0.72	Unpaired t-test	$p = 0.33$
3 I	Healthy control vs Anxious / Heights # of scans per subject	34, 33	2.65, 5.37	2, 4	0.32, 0.75	Unpaired t-test	$p = 0.0018$
3 I	Healthy control vs Anxious / No Heights /# of scans per subject	40, 21	1.53, 1.76	1, 2	0.78, 0.21	Unpaired t-test	$p = 0.57$
3 I	Healthy control vs Anxious / VR intro/ # of visual scans per subject	33, 30	2.13, 1.64	2, 1	0.32, 0.23	Unpaired t-test	$p = 0.2124$
3 J	Healthy control vs Anxious / Heights Avg. scan distance for each scan (m)	90, 181	1.57, 1.31	1.54, 1.05	0.14, 0.67	Unpaired t-test	$p = 0.04$
3 J	Healthy control vs Anxious / No Heights /Avg. scan distance for	61, 37	1.65, 1.18	1.34, 1.19	0.19, 0.13	Unpaired t-test	$p = 0.08$

	each scan (m)						
3 J	Healthy control vs Anxious / VR intro/ Avg. scan distance (m)	69, 54	1.20, 1.17	0.80, 0.91	0.15, 0.12	Unpaired t-test	p = 0.85
3 K	Healthy control vs Anxious / Heights/ % time scanning away from the plank	34, 33	82%, 85%	86%, 85%	2.7 %, 1.4	Unpaired t-test	p = 0.39
3 M	Healthy control vs Anxious / No Heights/Latency to step onto the Plank (s)	51, 37	6.34, 13.1	4.7, 8.4	0.72, 2. 28	Unpaired t-test	p = 0.002
3 O	Healthy control vs Anxious / Heights Subjective “scary” rating (1-5)	40, 36	2.17, 2.64	2, 2	0.18, 0.20	Unpaired t-test	p = 0.08
3 O	Healthy control vs Anxious / Heights Subjective “real” rating (1-5)	40, 36	3.24, 3.06	3, 3	0.2, 0.13	Unpaired t-test	p = 0.48
4 A	Control Male vs Anxious Male / Heights Latency to step (s)	22, 10	5.50, 6.91	4.70, 5.20	0.62, 1.28	Unpaired t-test	p = 0.27
4 A	Control Female vs Anxious Female / Latency to step (s)	29, 27	6.98, 15.40	4.60, 9.10	1.18, 2.99	Unpaired t-test	p = 0.009
4 B	Control Male vs Anxious Male / Heights Total gaze distance (m)	16, 9	6.11, 9.05	6.08, 7.44	0.73, 1.52	Unpaired t-test	p = 0.06
4 B	Control Female vs Anxious Female / Total gaze distance (m)	18, 24	8.67, 15.66	5.66, 9.93	1.94, 3.36	Unpaired t-test	p = 0.11
S2 A	Control vs Anxious / Before Heights Cognitive game score	39, 34	0.95, 0.42	0,0	0.19, 0.11	Unpaired Wilcoxon Signed rank test	p = 0.083
S2 A	Control vs Anxious / After Heights Cognitive game score	39, 34	1.31, 0.58	0,1	0.20, 0.15	Unpaired Wilcoxon Signed rank test	p = 0.01
7 C	Mean insula high gamma activity Before and during visual scans/ heights stimulus (z-score)	16	-0.32, 0.57	-0.32, 0.52	0.05, 0.19	Paired t-test	p < 0.0001
S 5 D	Mean insula high gamma activity before and during visual scan (z-score)/sharks	48	0.09, 0.19	-0.01, 0.13	0.07, 0.07	Paired t-test	p = 0.29

Table S2 Descriptive statistics and statistical tests, Related to Figures 1 – 4, 7, S2, S5 and STAR Methods.

Subject ID	GAD-7	Trait Anxiety	Medication	Gender	Age	Co-morbidity
s14	NA	48	None	M	25	None
s53	20	51	Yes / no name	F	71	Current depression, anxiety
s60	14	47	None	M	28	Arachnophobia
s61	10	44	None	F	25	Current GAD, depression, shark phobia, arachnophobia, claustrophobia
s66	9	48	No	F	19	None
s81	20	47	None	F	59	Claustrophobia
s83	10	32	None	F	25	Shark phobia, arachnophobia. Past anxiety, depression, PTSD
s93	10	52	Amlodipine besylate -5 mg	M	54	Current depression, shark phobia
s112	15	38	None	F	23	Current anxiety (GAD), emetophobia, arachnophobia
s116	10	62	Prozac	F	35	Past anxiety. Shark, sharp objects, snakes, airplane phobias
s125	16	66	None	F	26	Current anxiety and depression. Arachnophobia, claustrophobia
s129	15	52	None	F	19	Current anxiety (Panic disorder, SAD). Past depression, shark, snake phobia, arachnophobia
s143	8	59	Wellbutrin-75mg daily Zoloft-100mg daily	F	43	Current depression and PTSD, arachnophobia. Past anxiety (GAD, panic disorder) and addiction
s150	12	42	Lorazepam-0.5 mg and as needed	F	38	Current anxiety (panic disorder), depression, arachnophobia.
S162	13	52	None	F	42	Snake phobia, shark phobia
s170	13	40	None	M	27	None
s174	10	41	None	F	22	Arachnophobia, snakes phobia
s187	18	63	None	F	23	Current anxiety
s194	10	44	None	F	20	Current depression, anxiety (social anxiety), arachnophobia
s198	3	46	Ambien-5mg	F	65	Current depression, past PTSD
s203	3	39	Yes / no name	M	36	None
s209	19	62	None	F	54	Current depression, anxiety, PTSD
s224	8	46	Cymbalta-60 m	F	55	Current depression and anxiety. GAD and SAD. Airplane phobia
s233	13	51	Paxil-50mg, Wellbutrin-50mg	M	33	Current anxiety, depression, PTSD, shark phobia, arachnophobia
s234	12	64	None	F	31	Current anxiety (GAD)
s237	15	25	None	F	50	Current anxiety (GAD), PTSD, snake phobia, past depression.
S240		75	Lexapro-30 mg Mirtazipine-15mg	F	24	Current anxiety (panic, social, agoraphobia)
s241	9	60	Zoloft-200 mg, Wellbutrin-300mg	F	19	Current depression and anxiety (GAD)
s251	10	52	Vyvanse-40mg, Buboprion-300 mg	M	50	Current depression, anxiety, phobia (nonspecific)
s255	5	57	None	F	50	Claustrophobia, airplane phobia

s257	11	51	None	M	34	Current anxiety, social anxiety. Past depression
s265	7	62	None	M	55	Current depression, snake phobia
s266	11	51	None	F	39	Shark phobia, adjustment disorder
s268	13	59	None	F	26	None
s269	19	55	None	M	51	Arachnophobia, migraine
s270	15	62	None	F	21	None
s273	5	46	None	F	25	None
s274	21	68	Yes / no name	M	20	Shark object, snake, shark phobia, claustrophobia

Table S3 Self-reported comorbidity and medication status of anxious subjects, Related to Figure 3

Insula		**No Heights**		**Heights**	
Subject		**192**	**205**	**192**	**205**
	Theta	**-0.153 p= 0.019**	0.08 p = 0.363	**0.274 p < 0.001**	0.091 p = 0.342
	Alpha	-0.085 p = 0.195	0.057 p = 0.533	0.132 p = 0.057	0.143 p = 0.134
	Beta	-0.073 p = 0.270	-0.034 p = 0.707	0.005 p = 0.942	0.003 p = 0.976
	Low gamma	-0.013 p = 0.841	-0.131 p = 0.149	**0.202 p = 0.002**	0.179 p = 0.059
	High gamma	0.078 p = 0.236	**-0.193 p = 0.032**	**0.467 p < 0.001**	**0.304 p = 0.001**
OFC					
Subject		**200**	**205**	**200**	**205**
	Theta	-0.134 p = 0.143	**0.158 p = 0.005**	**-0.364 p < 0.001**	**-0.189 p < 0.001**
	Alpha	**-0.203 p = 0.025**	0.086 p = 0.131	-0.131 p = 0.177	**-0.151 p = 0.012**
	Beta	-0.104 p = 0.253	0.042 p = 0.456	0.155 p = 0.111	0.083 p = 0.166
	Low gamma	**-0.219 p = 0.015**	-0.049 p = 0.383	0.052 p = 0.595	**0.262 p < 0.001**
	High gamma	**-0.338 p < 0.001**	-0.105 p = 0.066	0.137 p = 0.156	**0.267 p < 0.001**

Table S4 Spearman correlations and significance during the modified Heights and No Heights Stimuli, Related to Figures 5 and 6

Significant correlations are in bold.