

Distinct Responses to Predictable and Unpredictable Threat in Anxiety Pathologies: Effect of Panic Attack

Supplemental information

Supplemental Methods and Materials

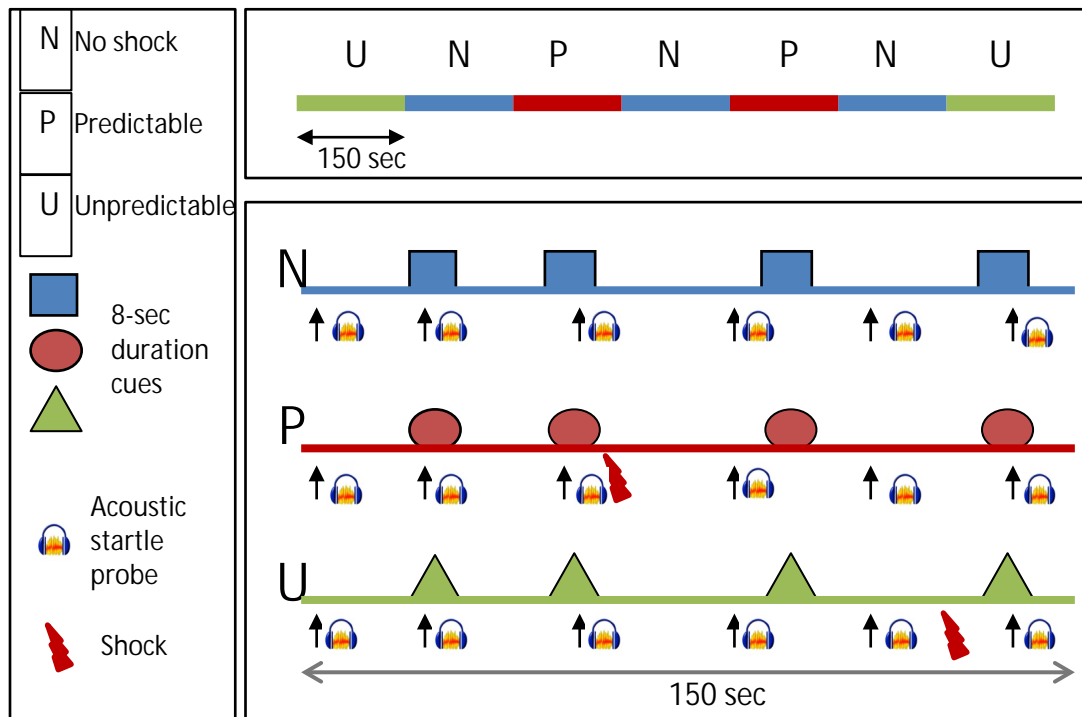


Figure S1. Schematic representation of stimulus presentation during each condition in one block of the NPU-threat test. The upper part of the figure represents a complete block including two P (predictable), two U (unpredictable) and three N (no shock) conditions. The lower part shows examples of each condition, including startle probes, cues (8 s duration) and shocks. Reproduced with permission from Grillon *et al.* (1).

Supplemental Results

Startle

Table S1. Mean (SEM and confidence interval) startle magnitude (μV) across conditions in the controls and anxious patients according to the presence or absence of a history of PAs

	Controls		GAD		SAD		GAD/SAD	
	No PAs (N=72)	PAs (N=2)	No PAs (N=16)	PAs (N=11)	No PAs (N=15)	PAs (N=6)	No PAs (N=17)	PAs (N=7)
Habituation								
Mean	51.3	39.4	87.0	89.8	50.3	69.5	38.6	85.4
(SEM)	(5.2)	(24.8) -	(17.5)	(23.3)	(10.7)	(19.6)	(7.5)	(25.7)
Confidence interval	40.8-61.8	276-355	49.6-124.4	37.7-142.0	10.7-27.5	19.0-120.1	22.7-54.5	22.3-148.4
Pre-test	56.6 (6.3) 43-9-69.3	57.2 (36.0) --400-511	85.7 (11.6) 60.9-110.5	86.1 (19.7) 42.2-130.0	63.7 (12.7) 36.4-91.1	78.7 (27.4) 8.3-149.1	54.5 (9.2) 34.9-74.0	103.1 (40.5) 3.8-202.3
Neutral								
ITI	31.0 (4.1) 22.8-39.3	21.4 (9.6) -101-144	53.7 (11.2) 29.8-77.6	56.9 (20.0) 12.3-101.6	29.2 (5.8) 16.5-41.8	31.7 (8.0) 11.1-52.4	18.5 (3.7) 10.5-26.5	59.4 (17.9) 15.4-103.4
Cue	29.1 (3.8) 21.5-36.7	25.6 (14.5) -158-210	52.4 (10.2) 30.6-74.3	57.2 (19.7) 13.2-101.1	25.7 (5.5) 13.7-37.7	32.1 (9.8) 6.7-57.5	18.3 (3.4) 11.4-26.2	60.0 (19.5) 12.1-107.9
Predictable								
ITI	37.6 (4.2) 29.1-46.2	26.0 (15.0) -165-217	68.1 (13.7) 38.8-97.5	71.7 (20.2) 26.5-116.9	34.0 (7.7) 17.4-50.6	42.1 (13.0) 8.5-75.8	29.1 (4.5) 17.4-40.7	71.7 (19.9) 40.5-159.7
Cue	57.2 (5.7) 45.6-68.7	62.8 (27.2) -283-408	93.5 (17.5) 56.0-130.9	99.5 (23.0) 48.0-150.9	56.1 (8.9) 36.9-75.3	81.4 (13.8) 45.7-117.2	60.0 (9.6) 39.6-80.3	111.9 (26.1) 47.9-175.9

	Controls		GAD		SAD		GAD/SAD	
	No PAs (N=72)	PAs (N=2)	No PAs (N=16)	PAs (N=11)	No PAs (N=15)	PAs (N=6)	No PAs (N=17)	PAs (N=7)
Unpredictable	45.9 (5.2)	46.3 (13.5) -	80.2 (16.2)	86.4 (22.1)	40.5 (7.3)	55.2 (11.3)	36.3 (5.7)	100.0 (24.3)
ITI	35.4- 56.4	125-218	45.6- 114.8	37.0- 135.9	24.8- 56.2	26.0- 84.5	24.2- 48.4	40.5- 159.5
Cue	50.7 (5.7)	63.7 (37.7) -	88.2 (19.1)	92.3 (22.8)	42.2 (7.3)	67.9 (14.6)	36.8 (6.1)	88.7 (22.5)
	39.7- 61.7	416-543	47.5- 128.9	41.3- 143.2	26.5- 57.8	30.3- 105.5	23.8- 49.7	33.6- 143.9

GAD, generalized anxiety disorder; SAD, social anxiety disorder.

Note that fear-potentiated startle = difference startle magnitudes cue/P condition minus ITI/P condition and anxiety-potentiated startle = difference startle magnitudes ITI/U condition minus ITI/N condition.

Table S2. Mean (SEM and confidence interval) startle magnitude (T-scores) across conditions in the controls and anxious patients according to the presence or absence of a history of PAs.

	Controls		GAD		SAD		GAD/SAD	
	No PAs (N=72)	PAs (N=2)	No PAs (N=16)	PAs (N=11)	No PAs (N=15)	PAs (N=6)	No PAs (N=17)	PAs (N=7)
Habituation								
Mean	56.2	48.1	54.5	54.6	52.5	53.7	52.2	50.3
(SEM)	(1.3)	(2.2)	(2.5)	(1.8)	(2.5)	(3.7)	(2.4)	(3.4)
Confidence interval	53.5-59.0	19.8-76.4	49.0-60.0	50.5-58.7	47.1-58.0	44.2-63.2	47.3-57.4	41.9-58.7
Pre-test	577 (1.1)	55.7 (5.4)	55.8 (2.1)	53.6 (3.9)	60.3 (2.6)	55.5 (3.9)	58.4 (3.0)	52.5 (6.9)
	55.5-59.9	-13.6-125	51.1-60.4	44.7-62.5	54.6-66.1	45.3-65.8	51.9-65.0	35.3-69.6
Neutral	43.0 (.4)	41.0 (3.0)	42.3 (1.0)	40.3 (1.0)	43.2 (.6)	42.0 (1.3)	41.8 (.7)	42.4 (.7)
ITI	42.1-43.9	2.6-79.4	40.7-44.6	37.9-42.8	41.9-44.5	38.6-45.4	40.3-43.3	40.5-44.3
	42.0 (.4)	42.5 (1.5)	41.4 (.8)	41.2 (1.0)	41.1 (1.0)	40.7 (1.3)	42.2 (.4)	42.8 (1.4)
Cue	41.2-42.9	28.1-56.9	39.6-43.2	38.8-43.6	38.9-43.2	37.2-44.3	41.1-43.3	39.2-46.4
Predictable	46.7 (.4)	42.6 (1.1)	47.9 (.9)	46.7 (.9)	46.5 (1.4)	44.5 (1.5)	46.8 (.9)	47.3 (1.8)
ITI	45.9-47.5	31.1-54.1	45.9-49.8	44.6-48.8	43.3-49.6	40.5-48.6	44.8-48.7	42.6-51.9
	57.3 (.6)	59.7 (.2)	57.9 (1.1)	58.8 (1.1)	60.3 (1.2)	61.5 (1.7)	61.1 (1.4)	58.6 (1.5)
Cue	56.0-58.3	56.8-62.6	55.5-60.4	56.3-61.2	57.5-63.0	57.0-66.1	58.0-64.3	54.9-62.4
Unpredictable	50.4 (.4)	53.2 (4.4)	51.3 (.9)	54.0 (1.5)	51.1 (1.3)	51.0 (1.3)	51.0 (.9)	56.0 (2.1)
ITI	49.5-51.3	-3.7-110	49.2-53.4	50.6-57.5	49.2-53.4	47.7-54.4	40.0-52.9	50.7-61.2
	53.4 (.6)	58.7 (5.4)	53.7 (1.2)	54.6 (1.1)	51.3 (1.2)	55.2 (1.6)	51.5 (1.4)	51.3 (1.5)
Cue	52.3-54.5	10.8-128	51.0-56.4	52.0-57.1	48.6-54.0	50.9-59.1	48.5-54.5	47.4-55.2

GAD, generalized anxiety disorder; SAD, social anxiety disorder.

Retrospective Ratings

Retrospective ratings are shown in Table S3. The rating from one subject was missing.

Predictable Threat

Ratings during the predictable threat condition were analyzed with a Group (control, GAD, SAD, GAD/SAD) x Stimulus Type (Cue, ITI) rANOVA. Overall fear ratings differed among groups ($F[3, 139]=12.9, p<.0009$), due to higher overall fear rating in the GAD ($p=.001$), SAD ($p=.004$), and GAD/SAD ($p<.0009$) groups compared to control as well as higher fear rating in the GAD/SAD compared to the GAD group ($p<.02$). In addition, subjective fear was higher during the cue compared to ITI in the P condition ($F[1, 139]=200.9, p<.0009$), but this effect did not differ among groups ($F[3, 139]=.9, ns$). When age and sex were used as covariate, the results were similar with the exception that subjective fear was higher in the GAD group compared to the SAD group ($p<.01$).

Rating of fear did not differ among patients with and without a history of PA (PA, $F[1, 66]=.2, ns$; PA x Stimulus Type, $F[1, 66]=1.2, ns$; PA x Diagnostic x Stimulus Type, $F[1, 66]=1.5, ns$).

Unpredictable Condition

Ratings during the unpredictable threat condition were analyzed with a Group (control, GAD, SAD, GAD/SAD) x Condition (neutral ITI, unpredictable ITI) rANOVA. Overall anxiety ratings during the Unpredictable condition differed among groups ($F[3, 139]=13.5, p<.0009$), due to higher overall anxiety rating in each patient group compared to the control group (all $p<.05$). In addition, subjective anxiety during ITI was higher during the Unpredictable condition compared to the Neutral condition ($F[1, 139]=456.5, p<.0009$), an effect that differed among groups ($F[3, 139]=3.9, p=.01$) and was due to greater increased in anxiety from the neutral to the unpredictable condition in the GAD/SAD group compared to controls ($p=.01$). Rating of anxiety

did not differ among patients with and without a history of PA (no significant main effect of PA or interaction with PA).

Table S3. Mean (and SEM) retrospective rating of fear and anxiety during the NPU threat test.

	Controls	GAD	SAD	GAD/SAD
N ITI	1.5 (.1)	2.2 (.2)	2.1 (.2)	2.7 (.3)
Cue	1.6 (.1)	1.9 (.2)	2.0 (.2)	2.6 (.3)
P ITI	3.3 (.2)	4.5 (.3)	4.8 (.4)	5.8 (.4)
Cue	5.1 (.3)	7.0 (.3)	6.8 (.4)	7.9 (.3)
U ITI	5.1 (.3)	6.5 (.3)	7.0 (.5)	7.9 (.4)
Cue	4.5 (.3)	5.8 (.5)	6.4 (.4)	7.1 (.4)

GAD, generalized anxiety disorder; SAD, social anxiety disorder.

Overall anxiety ratings during the Unpredictable condition differed among groups ($F[3, 141]=13.3, p<.0009$), due to higher overall anxiety rating in the GAD ($p<.003$), SAD ($p<.002$), and GAD/SAD ($.0009$) groups compared to control as well as higher anxiety rating in the GAD/SAD compared to the GAD ($p<.02$) and GAD/SAD ($p<.05$) groups. In addition, subjective anxiety during ITI was higher during the Unpredictable condition compared to the Neutral condition ($F[1,141]=462.1, p<.0009$), an effect that differed among groups ($F[3,141]=3.7, p<.03$) and was due to higher anxiety rating in the GAD/SAD group compared to controls ($p<.02$). When age and sex were used as covariate, the results remained the same.

Rating of anxiety did not differ among patients with and without a history of PA (PA, $F[1,66]=.8, ns$; PA x Stimulus Type, $F[1,66]=1.0, ns$; PA x Diagnostic x Stimulus Type, $F[1,66]=.2, ns$).

Supplemental Reference

1. Grillon C, Krimsky M, Charney DR, Vytal K, Ernst M, Cornwell B. (2013): Oxytocin increases anxiety to unpredictable threat *Mol Psychiatry* 18: 958-60.