Physical pain recruits the nucleus accumbens during social distress in borderline personality disorder

Supplementary Material

Supplementary Methods

Participant inclusion criteria

All participants were right-handed as assessed by the Edinburgh scale (Oldfield, 1971). Exclusion criteria included a lifetime history of severe neurological illnesses, a lifetime history of schizophrenia, and a history of alcohol or drug abuse or dependence within the past 6 months, use of painkillers within the last month, pregnancy, and presence of counter-indications for MRI scanning (mainly metal in the body and claustrophobia).

Questionnaires

BSL-23 and BSL-Supplement

The Borderline Symptom List short form (BSL-23), French version (Nicastro *et al.*, 2016), is a 23-item self-rated scale which quantitatively assesses symptoms of BPD, based on the DSM-IV (American Psychiatric Association, 2000). This is a unidimensional scale and items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much).

In addition to the BSL-23, participants were also administered the BSL-Supplement which measures the frequency of self-destructive behaviors (e.g. self-harming behaviors, binge eating, substance use, etc.) (Bohus *et al.*, 2007). This questionnaire assesses 11 behaviors rated within last week and ranging from 0 (not at all) to 4 (daily or more often) which are summed to obtain a global score.

RSQ

Griffin and Bartholomew (1994) developed the 30-item Relationship Scales Questionnaire (RSQ) to assess a variety of attachment styles (Griffin and Bartholomew, 1994). It refers to only partners/relationships. The RSQ involves having patients indicate the extent to which (*1= not at all like me, 5 = very much like me*) they believe each of 30 statements best describes their feelings about

close relationships. A recent review (Kurdek, 2002) suggests that avoidance and anxiety emerge as the most reliable factors from the RSQ, organizing a bi-dimensional attachment space.

Experimental design

Modified Cyberball game

Participants were told that they would be playing Cyberball with 4 different players (i.e. players A and B, or players C and D) that would be standing outside of the scanner (Figure 1 main text). To ensure that all participants believed they were playing with "real" other players, before the scanning session they were shown a behavioral testing room filled with computers and told that this would be where the other players would be playing from. Additionally, at the beginning of the scanning session, the experimenter asked, "Player 1, are you ready?" which was followed by pre-recorded messages from 4 distinct female voices saying different variations of "Yes, I am ready/Yep, ready/Yes, let's go".

At the beginning of each block, the following message appeared "You will now be playing with players A and B" or "You will now be playing with players C and D". Unbeknownst to the participants, players A and B represented the "inclusion" players while C and D represented the "exclusion" players. Each block lasted approximately 43 seconds, including 12 throws. Because each block was relatively short, during the exclusion condition, players C and D threw to the participant only 1 to 2 times (in order to maximize the amount of exclusion inflicted) and conversely during the inclusion condition, players A and B threw to each other only 1 to 2 times. The Cyberball and temperature stimuli conditions were presented in pseudorandom order with never more than 2 sequential blocks of either Cyberball condition. In total, each participant played 4 blocks of inclusion followed by a hot thermal stimulation, 4 blocks of inclusion followed by a warm stimulation, 4 blocks of exclusion followed by a hot stimulation, and 4 blocks of exclusion followed by a warm stimulation.

Preselection of thermal stimuli

Individual subjectively hot stimulation temperatures were determined using a multiple random staircase (MRS) algorithm (Gracely *et al.*, 1988). Our MRS procedure consisted of two independent

staircases. Initial thermal stimulations for the two staircases were randomly assigned between 41 to 45°C and participants rated how painful the stimulation was on a 10-point Likert scale. Within each staircase, stimulus temperature increased or decreased with steps of 2°C, while smaller changes of 0.5°C occurred following direction flips in the sequence. The staircases were set to switch around a rating of 7/10 (i.e. 70% subjective pain rating). Participants underwent this thresholding procedure twice. The first threshold was determined outside the scanner (approximately 1 hour before scanning) and required each staircase to have 4 direction flips. A second, shorter thresholding was done inside the scanner, just before the Cyberball game and required only 3 flips. If participants differed by more than 1°C between the two thresholds, we used the mean of the two temperatures during Cyberball scanning. None of our subjects was stimulated at a temperature above 52°C.

The thermal stimuli were delivered in the following way: participants first saw a 1 sec long fixation cross, followed by the text string “Temperature is changing” and concomitant delivery of the heat stimulation. The pain intensity scale was presented just after the 2 sec of plateau stimulation, when the temperature started to return to baseline, and lasted for a maximum of 5 sec.

MRI data acquisition and analysis

ART repair

To account for residual movement artefacts after realignment, Artefact Detection Toolbox (ART; http://web.mit.edu/swg/software.htm) was used. Specifically, an image was defined as an outlier (artefact) image if the head displacement was greater than 0.2 mm in the x, y, or z direction, if the rotational displacement was greater than 0.02 radians, from the previous image, or if the global mean intensity in the image was greater than 9 standard deviations from the mean image intensity for the entire scan. Any image that was identified as an outlier was entered into that participant’s first level SPM model as a regressor of no interest. No participant had more than 5% of total outlier scans.

Participant specific subjective pain threshold as a covariate

In the main fMRI analysis of the manuscript, we added the individual stimulation temperatures as a nuisance regressor to the full factorial GLM model in order to parse out any neural effects due to the fact that BPD patients were stimulated at significantly higher temperatures during the hot stimulations compared to the HCs. In order to check that this manipulation worked, we also created a full-factorial GLM in the exact same way, except that we did not add this covariate. We then compared the differences between the main effect of temperature (i.e. hot>warm) between each model.

The model without temperature regressor revealed that distributed network of regions involved in pain processing (insula, cingulate cortex, somatosensory cortex, and thalamus) was activated. Adding the participant specific subjective pain threshold to the fMRI GLM model captured all the neural differences that were attributed to our hot (vs. warm), painful stimulations. Thus, we can reasonably suggest that group differential activations reported in the main text were due to differences in underlying neural mechanisms independent of the fact that the groups were stimulated at significantly differing temperatures.

Medication load

We computed an index of medication load for each BPD participant based on the summation of the different dosages of each medication. To do so, we first coded the dosage as absent (0), low (1) or high (2) for each medication separately. For antidepressants, we used a previously employed approach (Sackeim, 2001) that differentiates between 4 levels of dosages, which we then converted into low-dose (levels 1 and 2) and high-dose (levels 3 and 4). For antipsychotic treatments, we converted the doses into chlorpromazine dose equivalents, and coded as 0, 1 or 2, for no medication, up to mean effective daily dose, or above the daily dose as defined by Davis and Chen (2004). Anxiolytic (lorazepam and alprazolam) psychostimulant (methylphenidate) doses were similarly coded as 0, 1 or 2, with reference to the midpoint of the Physician's Desk Reference-recommended daily dose range. Finally, we generated a composite measure of total medication load, reflecting dose and variety of

different medications taken, by summing all individual medication codes for each medication category for each individual BPD participant.

To check for any potentially confounding effects of BPD medication status, we entered medication load as a covariate to 2x2 repeated measures ANCOVAs with the within factors 'Cyberball Condition' (inclusion, exclusion) x 'Stimulation Temperature' (hot, warm) in the BPD group using the beta estimates extracted from each of the right NAcc and the left amygdala. Specifically, we were looking for an interaction between medication load and signal change. Both ANCOVAs yielded non-significant results for all 3-way (i.e. Medication Load by Cyberball Condition by Stimulation Temperature) and 2-way interactions (i.e. Medication Load by Cyberball Condition and Medication Load by Stimulation Temperature). All $p>0.34$.

Supplemental Discussion

Comparison with the Bungert et al. (2015) study. Our findings did not replicate those of Bungert et al. (2015) concerning the insula and amygdala activation (see main text). Our paradigm, although quite similar to that used in Bungert et al. (2015), differed in a few key ways. First, we specifically only chose to recruit patients with a documented history of SIBs (discussed in the main text). Additionally, we stimulated our participants at much more painful stimulation temperatures (approximately 3.18^{o} higher), which may more closely approximate the pain of SIBs. Finally, in their fMRI model Bungert et al. did not control for the fact that BPD patients were associated with stronger subjective pain thresholds than HCs. Although this should not be problematic for interpreting those brain responses reflective of subjective pain experiences (comparable between the two-groups), it could lead to biased interpretation for those brain regions who are sensitive to the physical properties of the thermal stimuli. In particular, the posterior insular cortex, which was found to be strongly implicated in BPD pain sensitivity by Bungert et al., is held to be the first cortical output of thalamic nuclei sensitive to thermoception and contribute in processing sensory components of pain (Craig *et al.*, 2000). This opens the possibility that the effects provided by Bungert might be confounded by differential

125 temperatures used for eliciting pain. This is not the case of our study as we added individual
126 stimulation temperature as a covariate to our fMRI model, we demonstrated that it reliably captured
127 neural differences between the stimulation temperatures, including in the insula. Consequently, using
128 this approach, the results from the 3-way interaction that we report throughout the main text are
129 more likely due to underlying neural differences between the groups (BPDs vs. HCs) pertaining to
130 differential processing of painful stimuli in a specific emotional context, rather than to the groups
131 being stimulated at different temperatures.
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Supplemental References

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Supplemental Tables

Table S1: Patient comorbidities and medication list

Patient ID	Currently depressed	Psychiatric comorbidities	Antidepressant (daily dose)	Antipsychotic (dose in chlorpromazine equivalence)	Others (daily dose)	Medication load (antidepressant + antipsychotics + other)
BPD01	No	Bipolar disorder, ADHD, social phobia	Fluoxetine (40)	Olanzapine (100)	Methylphenidate (40)	5 (2+2+1)
BPD02	No	Social phobia				0 (0+0+0)
BPD03	Yes		Venlafaxine (150)	Quetiapine (25)	Oxazepam (1)	5 (2+1+1)
BPD04	Yes	ADHD, panic disorder				0 (0+0+0)
BPD06	Yes	ADHD			Methylphenidate (20)	1 (0+0+1)
BPD07	No	ADHD, social phobia, agoraphobia	Citalopram (10)			1 (1+0+0)
BPD08	Yes	Social phobia	Citalopram (20)			2 (2+0+0)
BPD09	Yes	ADHD, social phobia	Fluoxetine (20)			2 (2+0+0)
BPD10	No	Bipolar disorder, social phobia, panic disorder				0 (0+0+0)
BPD11	No	Bipolar disorder, ADHD, social phobia, agoraphobia, bulimia nervosa	Fluoxetine (20)	Quetiapine (25)	Oxazepam (1)	4 (2+1+1)
BPD12	No	Social phobia				0 (0+0+0)
BPD13	Yes		Fluoxetine (60)		Trazodone (100)	3 (2+0+1)
BPD14	Yes	Panic disorder				0 (0+0+0)
BPD15	No	Social phobia, PTSD	Fluoxetine (40)	Quetiapine (200)	Mirtazapine (7.5)	5 (2+2+1)
BPD17	Yes		Venlafaxine (225)			2 (2+0+0)
BPD20	No	ADHD	Fluoxetine (20)		Oxazepam (1)	3 (2+0+1)
BPD21	No					0 (0+0+0)
BPD22	No	Social phobia	Fluoxetine (20)	Quetiapine (50)		4 (2+2+0)

BPD23	No				Methylphenidate (20)	1 (0+0+1)
BPD24	No		Fluoxetine (20)			2 (2+0+0)
ADHD : Attentional Deficit and Hyperactivity Disorder; PTSD : Post Traumatic Stress Disorder						

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Table S2: Distress scores and pain ratings

	Group			
	BPD (N=20)		**HC (N=23)**	
Need Threat Scale	Mean	SD	Mean	SD
IN distress	9.05	2.60	6.59	1.44
EX distress	14.72	2.27	13.97	1.99
Pain ratings (5-point Likert Scale)				
Pain intensity				
IN hot	3.74	0.65	3.84	0.55
IN warm	1.11	0.25	1.43	0.60
EX hot	3.81	0.79	4.07	0.57
EX warm	1.10	0.25	1.52	0.71
Pain unpleasantness				
IN hot	3.63	1.13	4.04	0.64
IN warm	1.76	0.68	1.79	0.73
EX hot	3.60	1.12	4.29	0.56
EX warm	1.78	0.80	1.73	0.69

BPD=borderline personality disorder; HC=healthy controls; EX=exclusion, IN=inclusion; SD=standard deviation

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Table S3: Right NAcc mediation results

	Consequent Variables																			
	M_1(RSQ Anxiety)					M_2(RSQ Avoidance)					M_3(BDI)					Y (Right NAcc signal [15,8,-14])				
Antecedent Variables		Coeff.	*SE*	*t*	*p*		Coeff.	*SE*	*t*	*p*		Coeff.	*SE*	*t*	*p*		Coeff.	*SE*	*t*	*p*
X (Group)	a_1	10.16	1.16	8.76	<.001	a_2	3.66	1.53	2.39	0.02	a_3	22.99	1.71	13.48	<.001	c'	-0.46	0.77	-0.59	0.56
M_1(RSQ Anxiety)		--	--	--	--		--	--	--	--		--	--	--	--	b_1	0.11	0.04	2.58	0.01
M_2(RSQ Avoidance)		--	--	--	--		--	--	--	--		--	--	--	--	b_2	0.02	0.03	0.66	0.51
M_3(BDI)		--	--	--	--		--	--	--	--		--	--	--	--	b_3	0.00	0.03	0.12	0.91
Constant	i_{M1}	9.39	0.79	11.87	<.001	i_{M2}	20.09	1.05	19.21	<.001	i_{M2}	1.61	1.16	1.38	0.17	i_Y	-1.77	0.78	-2.28	0.03
Path statistics		R^2=0.65					R^2=0.12					R^2=0.82					R^2=0.28			
		F(2,40)=76.66, p<.001					F(2,40)=5.71, p=.02					F(2,40)=181.66, p<.001					F(5,37)=3.61, p=.010			

Indirect effect of X on Y

	Coeff.	SE	LLCI	ULCI
Total	1.24	0.60	0.13	2.53
a_1b_1 (RSQ Anxiety)	1.09	0.57	0.11	2.47
a_2b_2 (RSQ Avoidance)	0.08	0.11	-0.06	0.38
a_3b_3 (BDI)	0.08	0.57	-0.91	1.37

BDI=Beck Depression Inventory, LLCI=lower limit confidence interval, M=mediator, RSQ=Relationship Scales Questionnaire, SE=Standard Error, ULCI=upper limit confidence interval

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Table S4: t-contrasts of whole brain analysis (p<0.05, FWE corrected) of physical pain administered following heightened social distress (elicited via Cyberball)					
Contrasts	Anatomic Region	Cluster size	MNI coordinates		
			x	y	z
Main effects					
Main effect of Cyberball Condition (EX>IN)	L Inferior Parietal	2208	-36	-34	43
			-24	-4	49
			-24	-55	64
	R Inferior Parietal	172	6	2	13
			-3	5	10
			-21	-4	13
	R Superior Parietal	347	21	-64	58
			15	-61	64
			36	-37	43
Main effect of Cyberball Condition (IN>EX)	No significantly activated voxels				
Main effect of Stimulation Temperature (hot>warm)	No significantly activated voxels				
Main effect of Group (BPD>HC)	No significantly activated voxels				
Main effect of Group (HC>BPD)	No significantly activated voxels				
Interactions					
Group x Stimulation Temperature (BPD>HC; Hot>Warm)	No significantly activated voxels				
Group x Stimulation Temperature (HC>BPD; Hot>Warm)	No significantly activated voxels				
Group x Cyberball Condition (BPD>HC; EX>IN)	No significantly activated voxels				
Group x Cyberball Condition (HC>BPD; EX>IN)	No significantly activated voxels				