Supplemental Information

Title: Common neural responses to romantic rejection and acceptance in healthy adults

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Contrast	Region	Brodmann	MNI	k _E	t
		Area	coordinates (x.v.z) mm	(voxels)	
Rejection	L Superior Frontal Gyrus	6	-8, 10, 68	240	6.13
-Neutral	L Ventrolateral Prefrontal Cortex	47/12	-42, 22, -4	475	5.46
(Rej-Neu)	(vIPFC) (includes Operculum)				
· · ·	R Superior Frontal Gyrus	9	10, 50, 44	549	5.46
	L Occipital Gyrus	18	-20, -88, -12	60	5.36
	R vIPFC/Anterior Insula (AI)	47/12	28, 18, -12	220	5.28
	R Occipital Gyrus	19	28, - 84, -18	23	4.83
	L Medial Temporal Gyrus	21	-54, -30, -4	154	4.82
	L Medial Frontal Gyrus	6	-44, 0, 52	155	4.77
	R vIPFC	47/12	50, 28, 2	111	4.49
	L Supramarginal Gyrus	39	-56, -50, 30	38	4.37
	L Putamen		-22, 10, 8	19	4.30
	R Superior Frontal Gyrus	6	10, 22, 62	32	4.28
	L Occipital Gyrus	19	-34, -70, -18	22	4.26
	L Precentral Gyrus	6	-46, -2, 36	14	3.96
	L Superior Frontal Gyrus	8	-10, 36, 50	14	3.96
	L Medial Temporal Gyrus	21	-46, -48, 10	18	3.94
	L Caudate		-16, 4, 18	18	3.92
	L Cerebellum		-14, -82, -22	10	3.78
Acceptance	L Occipital Gyrus	19	-30, -78, -12	958	6.72*
-Neutral	L Inferior Frontal Gyrus	45	-48, 22, 8	1303	5.93
(Acc-Neu)	includes L vIPFC (Operculum)	47/12	-42, 20, -2		5.60
	R vIPFC (includes AI)	47/12	40, 24, -6	740	5.58
	R Caudate		8, 8, 2	220	5.48
	L Superior Temporal Gyrus	21	-54, -44, 8	238	5.33
	R Superior Frontal Gyrus	9	8, 54, 24	236	5.12
	L Superior Frontal Gyrus	6	-2, 10, 58	613	5.12
	L Caudate		-14, 12, 6	200	4.92
	L Fusiform Gyrus	37	-38, -46, -16	75	4.82
	R Superior Frontal Gyrus	8	12, 20, 38	15	4.80
	Cerebellum		0, -54, -32	43	4.69
	R Fusiform Gyrus	37	32, -52, -16	95	4.62
	R Occipital Gyrus	18	24, -92, 2	336	4.59
	L Superior Frontal Gyrus	10	-22, 54, 26	58	4.51
	L Caudate		-16, -2, 20	66	4.41
	L Superior Frontal Gyrus	9	-2, 40, 28	151	4.38
	R Superior Temporal Gyrus	22	50, -18, -8	75	4.37
	L Posterior Orbital Gyrus	47	-26, 26, -16	13	4.26

Supplemental Data

	L Superior Frontal Gyrus	8	-14, 40, 48	54	4.16
	L Frontal Operculum	45	-30, 24, 14	11	4.11
	R Precentral Gyrus	6	544. 38	15	3.96
	R Superior Frontal Gyrus	8	8 40 48	15	3 92
	R Precentral Gyrus	44	46 6 26	10	3 91
	L Substantia Nigra		-8 -12 -16	12	3 00
	L Sup Transverse Frontopolar	10	-0, -12, -10	24	2.90
		10	2, 30, 10	24	0.00
	Gylus D. Oscinital Oursus	17	0, -94, 0	24	3.70
		39	-40, -30, 20	14	3.75
	L Superior Temporal Gyrus	6	42, 2, 40	21	3.68
	R Precentral Gyrus		-20, -4, -12	17	3.66
	L Amygdala	6	46, 6, 50	11	3.54
	R Precentral Gyrus				
Neu-Rej	L Precuneus	7	-4, -60, 48	1705	6.41*
•	L Posterior Insula	13	-38, -24, 0	82	5.75
	L Inferior Temporal Gyrus	37	-56566	158	5.51
	L Medial Frontal Gyrus	6	-28, 8, 58	204	5.42
	R Parietooccipital Area	39	46 -72 40	50	4 57
	L Parietooccipital Area	19	-42 -82 26	58	4 43
	R Postcentral Gyrus	1	30 -42 62	33	4 25
	L Parietal Operculum	40	-48 -34 20	63	4.20
	P Medial Temporal Gyrus	37	-0, 0-1, 20 58 -51 -2	27	1 17
		37	50, -5 4 , -2 66 12 10	21 60	4.17
	L Falletal Operculum	41	-00, -12, 10	40	4.10
	R Medial Frontal Gyrus	6	30, 12, 34	12	4.13
	L Panetooccipital Transition Zone	19	-34, -80, 30	12	4.10
	L Paranippocampai Gyrus	36	-32, -42, -8	22	4.05
	L Angular Gyrus	39	-38, -52, 38	10	4.01
	L Occipital Gyrus	18	-12, -68, 24	45	3.95
	R Superior Frontal Gyrus	9	28, 38, 36	20	3.90
	R Superior Frontal Gyrus	31	8, -22, 44	10	3.86
	R Superior Parietal Lobule	7	16, -48, 70	31	3.80
	R Precuneus	31	8, -60, 18	15	3.74
	R Superior Frontal Gyrus	6	18, -6, 68	11	3.74
Neu-Acc	R Precuneus	31	6, -44, 52	17	4.08
	R Superior Frontal Gyrus	6	28, 20, 62	10	3.85
Rej-Acc	No clusters				
Acc-Rei	L Paracentral Lobule	7	-6 -46 66	260	5 21
	R Medial Temporal Gyrus	37	58 -54 -4	36	5.02
	I Parietooccipital Transition Zone	19	-40 -86 24	28	4 82
	L Superior Frontal Gyrus	8	-2 36 30	69	4 77
	L Medial Frontal Cyrus	44	-10 11 28	35	4.62
	P Inferior Frontal Cyrus	44	60 20 12	12	4.60
	R Cinquiato Gyrus	40	6 9 29	15	4.00
	R Ciliguiale Gylus R Intermediate Orbitel Cyrue	24 11	0, -0, 30 20, 42, 12	43	4.50
	R Internetiate Orbital Gyrus	7	20, 42, -12	17	4.52
		1	-10, -42, 02	49	4.42
	L Superior Frontal Gyrus	ð	-24, 34, 40	13	4.38
	Liviediai Frontai Gyrus	6	-28, 8, 58	13	4.34
	L Superior Parietal Lobule	(-6, -72, 52	16	4.32
	L Pretectal Area		-8, -30, -8	19	4.29
	L Cingulate Gyrus	23	-4, -58, 14	110	4.26
	R Cingulate Gyrus	32	6, 8, 34	55	4.25
	L Parietal Operculum	40	-42, -32, 22	37	4.22

L Superior Frontal Gyrus	6	-10, -18, 64	21	4.16
L Fusiform Gyrus	19	-10, -64, -8	24	4.10
L Cerebellum		-10, -50, -22	57	4.09
R Inferior Rostral Gyrus	10	12, 4 8, -10	97	4.08
L Superior Frontal Gyrus	8	-4, 30, 40	34	4.03
L Superior Temporal Gyrus	22	-66, -40, 18	14	4.01
L Precentral Gyrus	8	-34, 2, 32	13	3.99
L Caudate		-8, 14, 0	18	3.95
L Parietooccipital Transition Zone	7	-28, -80, 42	12	3.93
R Superior Frontal Gyrus	6	24, -2, 62	11	3.91
L Cerebellum		-18, -40, -24	13	3.90
L Occipital Gyrus	18	-40, -90, 6	15	3.90
R Frontal Operculum	44	44, 16, 4	14	3.87
R Cerebellum		4, -54, -34	16	3.79
R Cingulate Gyrus	32	10, 18, 36	11	3.77
L Cingulate Gyrus	23	-4, -38, 36	21	3.77
R Frontal Operculum	1	44, -16, 18	17	3.70
L Superior Frontal Gyrus	6	-2, -20, 74	16	3.68

Supplemental Table S1. Activation in the entire brain (no masking) in the entire sample (n = 36). One-sample *t*-tests were performed for each contrast, controlling for sex and age. Whole-brain uncorrected threshold was set at P < 0.001 with minimum extent threshold of $k_E > 10$ voxels. Voxel-wise peaks are listed in MNI standard space (Montreal Neurological Institute). *Whole-brain family-wise error (FWE)-corrected P < 0.05 (2-tailed).



Supplemental Fig. S1. Distribution of neural activation. A) Rej-Neu and B) Acc-Neu contrasts (controlling for sex and age) from Table S1. R, right; Coordinates in Montreal Neurological Institute stereotactic space. Contrast *t* map displayed at P < 0.001 (one-sample *t*-tests, whole-brain uncorrected, no masking), $k_{\rm E} > 10$.



Supplemental Fig. S2. Distribution of neural activation. A) Neu-Rej and B) Acc-Rej contrasts (controlling for sex and age) from Table S1. R, right; Coordinates in Montreal Neurological Institute stereotactic space. Contrast *t* map displayed at P < 0.001 (one-sample *t*-tests, whole-brain uncorrected, no masking), $k_{\rm E} > 10$.

Activation in the precuneus

An exploration of significant whole-brain voxel-wise activation ($k_E > 10$, whole-brain FWEcorrected P < 0.05, two-tailed) yielded an unexpected finding of significant *de*activation in the left precuneus during rejection (Neu-Rej) (t = 6.41, $P_{FWE-whole-brain} = 0.034$; $k_E = 1705$; peak activation: -4, -60, 48; **Table S1**, **Fig. S2C**). Previous work has shown that the precuneus, which is part of the "default mode" network¹, is involved in self-related mental representations during rest² and reflection of one's own personality traits². Thus, it is possible that during Neu blocks, when participants are viewing their own picture plus a picture of a person who had "not completed" their ratings, participants were left with more of an opportunity for selfreflection compared to blocks when they were rejected. Although it is not clear why activation in the precuneus was not found during Neu-Acc, it is possible that being accepted caused more first-person self-reflection similar to Neu, whereas being rejected caused more engagement of goal-directed actions, which is associated with reductions in default mode of brain function¹. Given that the finding in the precuneus was unexpected, and no data on selfreflection was collected, our interpretation of this finding is speculative and requires further study.

Contrast	ROI	MNI coordinates t		k _E	P unadjusted	P adjusted
		(x,y,z) mm		(voxels)	-	-
Rej-Neu	L Dorsal Anterior Cingulate Cortex (dACC)	No clusters				
	R dACC	No clusters				
	L vIPFC	-42, 22, -4	5.46	131	0.0018	0.036*
	R vIPFC	38, 22, -20	5.24	190	0.0032	ns
	LAI	-40, 20, -4	4.91	12	0.0032	ns
	R AI	28, 18, -12	5.28	20	0.0013	0.026*
	L Nucleus Accumbens (NAcc)	No clusters				
	RNAcc	No clusters				
	L Amygdala (AMY)	No clusters				
	R AMY	No clusters				
Acc-Neu	L dACC	-2, 36, 26	3.77	16	0.049	ns
	R dACC	10, 18, 36	3.81	4	0.063	ns
	L vIPFC	-42, 20, -4	5.53	125	0.0016	0.032*
	R vIPFC	40, 24, -6	5.58	299	0.0014	0.028*
	LAI	-40, 20, -2	5.36	59	0.0010	0.020*
	R AI	38, 22, -4	4.36	39	0.0124	ns
	L NAcc	No clusters				
	R NAcc	8, 10, - 2	3.77	6	0.0106	ns
	LAMY	-20, -4, -12	3.66	15	0.037	ns
	R AMY	No clusters				
Neu-Rej	No clusters w	ithin any ROI mask				

Neu-Acc No clusters within any ROI mask

Supplemental Table S2. Activation in individual ROI masks in the entire sample (n = 36). One-sample *t*-tests were performed for each contrast, controlling for sex and age. Whole-brain uncorrected threshold was set at P < 0.001 with minimum extent threshold of $k_E > 10$ voxels, followed by small volume correction for each ROI mask (K_E values in some ROI masks were less than 10 if clusters spread across more than one ROI mask). Voxel-wise peaks are listed in MNI standard space (Montreal Neurological Institute). *P* values (FWE-small volume corrected, SVC) are listed as unadjusted, or Bonferroni-adjusted for a two-tailed test (x2) across 10 ROI masks (x10). *No clusters* indicate no clusters present at the set threshold; *P < 0.05; *ns*, not significant.

Relationship Status

Similar to our previous study³, relationship status was examined by comparing those who were single (n = 24) with those who were in a relationship or married (n = 11). Group-level, voxel-wise two-sample *t*-tests were conducted for each contrast. No significant clusters were found in the ROI mask (threshold $P_{FWE-SVC} < 0.05$), or in the whole brain (threshold $P_{FWE-whole-brain} < 0.05$).

		Region		Brodmann Area	Center of mass, MNI coordinates (<i>x, y, z</i>)	Voxels
L	vIPFC	(includes	Precentral	47/12	-48, 20, 5	385
Operculum)				47/12	49, 27, 4	92
Ŕ	vIPFC	(includes	Precentral	47/12	37, 24, -9	70
Ope	rculum)	·				
R vIPFC (includes AI)						
R Superior Frontal Gyrus				9/10	4, 54, 29	182
L Superior Frontal Gyrus				6/8	-7, 10, 63	177
L Medial Frontal Gyrus				6	-43, -1, 52	105
L Middle and Superior Temporal Gyrus			oral Gyrus	22/21	-51, -36, 1	71
L Occipital Gyrus				18	-23, -86, -11	50
L Superior Frontal Gyrus				8	-10, 48, 44	15

Supplemental Table S3. Conjunction of Rej-Neu & Acc-Neu contrasts controlling for sex and age (whole-brain, no masking).

Contrast	Region		Brodman	Center of mass, MNI	Voxels
Poi Nou	Superior Frental Gyrus			0.51.37	244
Rej-Neu	P vIPEC (includes AI)		9 17/10	0, 07, 07	150
	L Medial Temporal Gyrus		47/1Z 21	-52 -33 -3	83
	L Interior Frontal Cyrus		21 45	-52, -53, -5	64
	L Superior Frontal Cyrus		40	-0 17 61	56
	L Medial Frontal Gyrus		0	-48 4 51	47
	L Superior Temporal Gyrus		30	-57 -48 29	3/
	R Superior Frontal Gyrus		6	9 25 61	31
			0	-21 9 8	18
	R Inferior Frontal Gyrus		45	55 24 5	15
	L Superior Temporal Gyrus		21	-48 -49 11	14
	I vIPEC (includes	Precentral	47/12	-42 23 -9	11
	Operculum)	1 rooontrai	11712	12, 20, 0	
Acc-Neu	L Occipital Gyrus		18	-35, -83, -7	896
	L Precentral Gyrus		44	-45, 9, 25	798
	R vIPFC (includes	Precentral	47/12	43, 27, 1	578
	Operculum)		6	-1, 12, 58	433
	L Superior Frontal Gyrus		18	33, -90, -2	321
	R Occipital Gyrus			10, 11, 6	220
	R Caudate			-9, 5, 6	199
	L Caudate		21	-50, -40, 6	163
	L Superior Temporal Gyrus		32	-4, 39, 25	151
	L Cingulate Gyrus		37	35, -53, -20	95
	R Fusiform Gyrus		37	-38, -50, -17	75
	L Fusiform Gyrus		22	49, -26, -1	75
	R Superior Temporal Gyrus		10	-18, 55, 29	58
	L Superior Frontal Gyrus			-17, 1, 20	55
	L Caudate			1, -53, -35	43
	R Cerebellum		8	-13, 39, 48	33
	L Superior Frontal Gyrus		10	7, 60, 17	27
	R Frontopolar Gyrus		10	-1, 58, 9	24

L Frontopolar Gyrus	17	8, -93, -2	24
R Striate Area	6	42, 4, 40	21
R Precentral Gyrus		-20, -5, -13	17
L Amygdala	8	10, 19, 38	15
R Superior Frontal Gyrus	6	54, -4, 39	15
R Medial Frontal Gyrus	47/12	-26, 27, -15	13
L vIPFC		-7, -14, -16	12
L Substantia Nigra	45	-29, 23, 12	11
L Frontal Operculum	8	48, 7, 50	11
R Medial Frontal Gyrus			

Supplemental Table S4. Non-overlapping clusters of Rej-Neu & Acc-Neu contrasts controlling for sex and age (whole-brain, no masking).

Supplemental Methods

The SFT did not involve deception, however participants were asked to imagine that the profiles they were rating and the feedback they received were real. A previous study showed that social exclusion was aversive even when participants knew that they were being excluded by a computer during Cyberball, or when they knew that others (unseen and unmet) were following a script to exclude them⁴. In several pilot studies, we maximized the emotional impact of the SFT without using deception by 1) having participants pre-select their most-liked profiles, thus personalizing the task for each participant and 2) having participants submit their own photo, which was presented during the task (Fig. 1). These procedures helped to create an immersive experience and made it easy for participants to access genuine emotional responses from the feedback, without using deception. Our manipulation checks (see Results) showed that without deception, the mean response was above "moderately" for all three manipulation check questions, suggesting that the SFT produced emotional responses that were more than moderately similar to real-life situations. The SFT without deception has been used in our previous studies^{3,5–7}. To ensure that participants understood the meaning of the feedback, participants were given the following instructions prior to performing the task:

'You will see a picture of yourself, followed by a picture of someone you liked. Below his/her picture, you will see whether or not s/he likes you, based on your picture and the information that you provided about yourself. His/her answer to the question "Would I like this person?" are categorized as follows:

"very likely no" or "definitely no" = this person does not like you.

"very likely yes" or "definitely yes" = this person likes you.

"not completed" = this person left the study early and did not complete the profile ratings."

References

- 1. Gusnard, D. A., Raichle, M. E. & Raichle, M. E. Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* **2**, 685–694 (2001).
- 2. Cavanna, A. E. & Trimble, M. R. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain J. Neurol.* **129**, 564–583 (2006).
- Hsu, D. T. *et al.* Response of the μ-opioid system to social rejection and acceptance. *Mol. Psychiatry* 18, 1211–1217 (2013).
- Zadro, L., Williams, K. D. & Richardson, R. How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. *J. Exp. Soc. Psychol.* **40**, 560–567 (2004).

- Hsu, D. T. *et al.* It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Mol. Psychiatry* 20, 193–200 (2015).
- 6. Yttredahl, A. A. *et al.* Abnormal emotional and neural responses to romantic rejection and acceptance in depressed women. *J. Affect. Disord.* **234**, 231–238 (2018).
- 7. Sankar, A. *et al.* Dissociable Neural Responses to Monetary and Social Gain and Loss in Women With Major Depressive Disorder. *Front. Behav. Neurosci.* **13**, 149 (2019).