**Supplementary Material for**

**Altered reward network responses to social touch in major depression**

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**Supplementary Methods**

*Participants*

Patients between 18 and 60 years of age who fulfilled criteria for unipolar major depressive disorder for at least four weeks were eligible for inclusion. Physiological exclusion criteria were metal in the brain or the skull, a cardiac pacemaker or intracardiac lines, medication infusion devices, heart or brain surgery, pregnancy, or any condition resulting in increased intracranial pressure, traumatic brain injury, a history of epilepsy, cerebral aneurysms, dementia, Parkinson’s disease, Huntington’s disease, multiple sclerosis, stroke or transient ischemic attack (within the last two years). Psychiatric exclusion criteria included substance-induced depression, a history of substance abuse, psychotic episodes, bipolar disorder, anorexia, posttraumatic stress disorder (current or within the last 12 months), personality disorders, claustrophobia, or previous antidepressant treatment with repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (within the last 3 months), vagus nerve stimulation or deep brain stimulation. All patients received concomitant multimodal treatment according to current MDD guidelines. The majority of patients (N = 47) received pharmacotherapy for the duration of the study: selective serotonin reuptake inhibitors (N = 18), selective serotonin-norepinephrine reuptake inhibitor (N = 15), atypical antidepressants (N = 32), atypical antipsychotics (N = 10), anticonvulsants (N = 11), tricyclic antidepressants (N = 5), levothyroxine (N = 4), antihistamines (N = 2), benzodiazepine (N = 1), lithium (N = 1), monoamine oxidase inhibitor (N = 1), norepinephrine reuptake inhibitor (N = 1). In addition, all patients underwent repetitive transcranial magnetic stimulation (rTMS), group psychotherapy and cognitive training (Strobach & Huestegge, 2017). The data analyzed in this study were acquired as part of a larger clinical trial comparing different rTMS protocols (for further information see (Mielacher et al., 2020)). Patient groups were collapsed for the purpose of the present study. While the present paper uses an adapted version of the social touch paradigm as used by Maier et al. (Maier et al., 2019), independent samples were recruited for both studies.

See Table S1 for a characterization of responders and non-responders.

*fMRI paradigm*

Stimulus presentation and response collection was implemented using Presentation 14 software (Neurobehavioral Systems, Albany, CA), liquid crystal display video goggles (Nordic NeuroLab, Bergen, Norway) and an MRI-compatible response box. After the MRI scan participants were asked to rate their positive and negative affect on the Positive Affect Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988).

*Statistical analysis*

Quantitative data were compared by repeated measures and mixed-design analyses of variance (ANOVA) and dependent and independent *t*-tests. Pearson's product-moment correlation was used for correlation analysis. Partial eta-squared was calculated as measures of effect size. For qualitative variables, Fisher’s exact tests were used. All reported *p*-values are two-tailed and values of *p* < 0.05 were considered significant.

*fMRI analysis*

After the second level ROI analysis, parameter estimates were extracted from peak activation voxels for correlational and moderation analyses as well as display purposes (cf. Figure 2 and Figure 3). We used an in-house MATLAB script to extract parameter estimates from the appropriate first level within-subject contrast maps.

To evaluate the effects of the touch paradigm, we performed a whole-brain analysis in controls using the first level contrasts [Touch > No Touch] and [No Touch > Touch] and one-sample *t*-tests on the second level. A threshold for significance of *p* < .05 was used, family-wise error corrected (FWE) for multiple comparisons. The results of this analysis can be found in Table S2.

To answer the question whether controls exhibit striatal activation during social touch we conducted a region of interest analysis in the bilateral caudate nucleus and nucleus accumbens using the first level contrasts [Touch > No Touch] and one-sample *t*-tests on the second level. The peak-level threshold for significance was set to p < .05, FWE-corrected for multiple comparisons based on the size of each region of interest.

*fMRI baseline analysis*

To corroborate our main findings, we conducted post-hoc analysis of baseline fMRI data. First level contrasts averaged over both speed levels at baseline were analyzed using independent t-tests comparing patients to controls ([patients > controls], [controls > patients]) and responders to non-responders ([responders > non-responders], [non-responders > responders]) using SPM. In accord with our main analysis, we focused on the same set of regions of interest. The peak-level threshold for significance was again set to *p <* .05, FWE-corrected for multiple comparisons based on the size of each region of interest.

*ICC test-retest reliability of fMRI scans*

To assess the test-retest reliability of the fMRI scans, we masked first-level activation maps during touch for pre and post scans with postcentral gyrus, nucleus accumbens and caudate nucleus ROIs and calculated mean parameter estimates for each healthy control, time point and ROI. Then, we computed two-way mixed average score intraclass correlation coefficients using a consistency definition (ICC(3,2)) for the three ROIs (Caceres, Hall, Zelaya, Williams, & Mehta, 2009; Portney & Watkins, 2009).

*Correlational analysis*

For patients, controls, responders and non-responders, Pearson's product-moment correlation was used to test associations between fMRI peak-voxel parameter estimates from the region of interest analysis and comfort ratings, social touch aversion, HDRS-17 baseline scores and HDRS-17 item number 7 as a measure of baseline anhedonia. This item assesses “loss of interest in activities”, “decrease in actual time spent on activities” and “experiencing pleasure” (Hamilton, 1960).

*Moderation analysis*

We conducted a moderation analysis, using the PROCESS macro for SPSS, version 3.1 (Hayes, 2013) to test for the potential confounding influence of age, sex, CTQ and STAI scores as well as anxiety during the MRI scan as measured by the respective item of the PANAS on the effect of group (patients, controls) and clinical response (responders, non-responders) on behavioral ratings, touch aversion and parameter estimates extracted from the fMRI analysis. All potential moderators were assessed individually in separate models. Moderation was assumed when the interaction between the predictor (group or response) and the moderator was significant. Additionally, the Johnson-Neyman technique was applied to determine the conditional threshold of significance for any moderation effects.

**Supplementary Results**

*Clinical results*

When analyzing Hamilton Depression Rating Scale (HDRS) scores separately for responders and non-responders, both groups showed clinical improvement (responders: *F*(2.11, 46.37) = 48.54, *p <* .001, ηp2 = .69; non-responders: *F*(2.13, 61.90) = 8.63, *p <* .001, ηp2 = .23). Planned contrasts revealed continuous weekly improvement for responders (all *p*’s < .001), while non-responders only improved after the first week of treatment (*p =* .018) but not over the following weeks (all *p*’s > .200).

*fMRI results*

In addition to the effects reported in the main text, we found a main effect of time (pre vs. post treatment) in the right anterior insula while comparing patients and controls. Activation to social touch decreased over the three weeks of treatment (peak Montreal Neurological Institute coordinates (x, y, z): 36, 26, −4; *F*(1, 89) = 17.80, *p*FWE = .024, ηp2 = 0.17). We also found main effects of speed in the left nucleus accumbens (MNI: -6, 6, −4; *F*(1, 89) = 12.97, *p*FWE = .030, ηp2 = 0.13) and the left posterior insula (MNI: -34, 2, 12; *F*(1, 89) = 25.94, *p*FWE = .001, ηp2 = 0.22), both with heightened responses to slow touch compared with fast touch. Additionally, a significant main effect of speed in two clusters in the right posterior insula (MNI: 36, -14, 22; *F*(1, 89) = 20.25, *p*FWE = .009, ηp2 = 0.19; MNI: 34, -20, 20; *F*(1, 89) = 17.63, *p*FWE = .025, ηp2 = 0.17) showed an inverted pattern, with increased responses to fast touch compared with slow touch.

For the model comparing responders and non-responders, we found main effects of speed in the left caudate nucleus (MNI: -18, 20, 12; *F*(1, 49) = 19.14, *p*FWE = .029, ηp2 = 0.29) and the left (MNI: -36, 0, 12; *F*(1, 49) = 21.78, *p*FWE = .012, ηp2 = 0.32) and right posterior insula (MNI: 36, -16, 22; *F*(1, 49) = 27.13, *p*FWE = .002, ηp2 = 0.37). While the cluster in the left posterior insula exhibited increased response to slow touch compared with fast touch, the reverse pattern was evident in the clusters in the right posterior insula and the caudate nucleus.

In accord with our main findings, the baseline analysis of the contrast [controls > patients] revealed a significant effect in the bilateral caudate nucleus (MNI: -12, 20, 10; *t*(89) = 3.81, *p*FWE = .041, *d* = 0.80; MNI: 8, 16, 6; *t*(89) = 4.20, *p*FWE = .013, *d* = 0.88). Additionally, we found two significant clusters in the right posterior insula (MNI: 38, -2, 16; *t*(89) = 3.90, *p*FWE = .030, *d* = 0.82; MNI: 42, -8, 4; *t*(89) = 3.79, *p*FWE = .042, *d* = 0.79). However, no significant effect was found for the nucleus accumbens or any of the other regions of interest. Baseline analysis did not reveal any significant effects for the contrast [patients > controls], nor for the comparison of responders and non-responders to antidepressant treatment ([responders > non-responders], [non-responders > responders]).

Controls exhibited increased neural responses to social touch compared to the no touch control condition in two significant clusters in the left (MNI: -18, 18, 8; *t*(39) = 5.23, *p*FWE = .002, *dz* = 0.83; MNI: -20, 0, 20; *t*(39) = 5.11, *p*FWE = .002, *dz* = 0.81) and one in the right caudate nucleus (MNI: 16, 10, 10; *t*(39) = 4.69, *p*FWE = .007, *dz* = 0.74) but not in the nucleus accumbens (Figure S1).

*ICC test-retest reliability*

ICC analysis suggest fair to good test-retest reliability between the fMRI scans in the postcentral gyrus (ICC(3,2) = .56, *F(39,39)* = 2.29, *p* = .006), nucleus accumbens (ICC(3,2) = .60, *F(39,39)* = 2.52, *p* = .002) and caudate nucleus (ICC(3,2) = .59, *F(39,39)* = 2.43, *p* = .003) (Cicchetti, 1994).

*Correlational analysis*

No correlations survived Bonferroni correction.

*Moderation effects*

We found that none of our predictors significantly moderated the effect of group or treatment response on any of our behavioral ratings or touch aversion (all *p*’s > .05). For the moderation analysis of the fMRI results, we found that childhood trauma questionnaire (CTQ) scores had a moderating influence on the effect of group on parameter estimates in the right nucleus accumbens (*t*(89) = 2.17, *p =* .033). The Johnson-Neyman technique revealed that the relationship between group and parameter estimates in the right nucleus accumbens was significant when CTQ scores were less than 30.33. This suggests that the occurrence of clinical depression does not impact the response of the nucleus accumbens to social touch in who have suffered from more severe childhood maltreatment. No significant moderation effects were observed for parameter estimates in any other region.

**Supplementary Figures**

**Figure S1**

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**y = 12**

Fig. S1.Controls exhibited increased neural responses to social touch compared to the no touch control condition in the bilateral caudate nucleus across time (i.e. before and after treatment). Significant clusters are displayed at a peak-level threshold of *p <* .05 uncorrected.

**Supplementary Tables**

**Table S1. Demographic and clinical data for responders and non-responders to treatment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Responders (n = 23) | Non-Responders (n = 30) | *p*-value |
| Sex (male/female) | 12/11 | 15/15 | 1.000 |
| Age (in years) | 43.57 (13.73) | 40.07 (12.60) | 0.340 |
| Education (in years) | 15.39 (3.87) | 16.27 (6.39) | 0.565 |
| Handedness (left/right) | 2/21 | 2/28 | 1.000 |
| Duration current depressive episode (in years) | 4.51 (4.94) | 4.77 (7.60) | 0.889 |
| Number of depressive episodes | 2.36 (2.17) (n = 21)a | 3.79 (3.16) (n = 26)a | 0.084 |
| **HDRS-17** |  |  |  |
| Baseline | 16.48 (5.33) | 17.87 (5.86) | 0.378 |
| After treatment | 5.61 (2.39) | 13.73 (5.09) | < 0.001 |
| Improvement (in percent) | 65.36 (12.14) | 21.26 (22.11) | < 0.001 |
| **BDI-II** |  |  |  |
| Baseline | 32.04 (9.52) | 34.33 (8.14) | 0.350 |
| After treatment | 13.35 (7.31) | 23.83 (10.91) | < 0.001 |
| Improvement (in percent) | 57.96 (18.82) | 29.23 (28.14) | < 0.001 |
| 4 weeks after treatment | 19.13 (12.08) | 24.96 (10.64)  (n = 27)a | 0.076 |
| 8 weeks after treatment | 20.73 (10.43) (n = 22)a | 26.19 (10.65)  (n = 27)a | 0.078 |
| 12 weeks after treatment | 23.77 (8.42) (n = 22)a | 24.92 (11.36)  (n = 24)a | 0.702 |
| CTQ baseline | 42.57 (13.74) | 47.00 (17.95) | 0.330 |
| STAI baseline | 61.96 (7.92) | 65.00 (6.18) | 0.122 |

Values are given as frequencies or as means (SD). The *p*-values report the significance levels reached for independent *t*-tests or Fisher’s exact tests comparing groups or for paired *t*-tests comparing improvement within patients. a Sample size in parentheses indicates number of complete responses. The significance threshold was set at *p <* .05.

**Table S2. Whole-brain activation in healthy controls (Touch vs. No Touch)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Region | Right/left | | Cluster size (voxels) | *t*-score | MNI Coordinates | | | *p*-value |
| x | y | z |
| **Touch > No Touch** | |  |  |  |  |  |  |  |
| Insula | | L | 14977 | 15.30 | -40 | -4 | 8 | < 0.001 |
| Postcentral Gyrus | | L |  | 14.18 | -64 | -22 | 22 | < 0.001 |
| Supramarginal Gyrus | | L |  | 13.72 | -56 | -22 | 18 | < 0.001 |
| Supramarginal Gyrus | | R | 9303 | 13.56 | 52 | -28 | 24 | < 0.001 |
| Supramarginal Gyrus | | R |  | 12.70 | 60 | -24 | 22 | < 0.001 |
| Postcentral Gyrus | | R |  | 12.61 | 18 | -42 | 74 | < 0.001 |
| Middle Temporal Gyrus | | R | 842 | 11.75 | 54 | -60 | 4 | < 0.001 |
| Cerebellum VI | | R | 1669 | 10.53 | 24 | -52 | -22 | < 0.001 |
| Cerebellum VI | | R |  | 8.78 | 18 | -72 | -18 | < 0.001 |
| Cerebellum VI | | R |  | 8.53 | 24 | -64 | -20 | < 0.001 |
| Middle Temporal Gyrus | | L | 609 | 9.15 | -50 | -66 | 6 | < 0.001 |
| Cerebellum VI | | L | 167 | 9.09 | -24 | -62 | -22 | < 0.001 |
| Cerebellum VI | | L |  | 8.84 | -16 | -70 | -20 | < 0.001 |
| Thalamus | | L | 309 | 7.34 | -12 | -16 | 4 | 0.001 |
| Middle Frontal Gyrus | | R | 466 | 7.02 | 44 | 48 | 8 | 0.002 |
|  | |  |  |  |  |  |  |  |
| **No Touch > Touch** | |  |  |  |  |  |  |  |
| Inferior Parietal Gyrus | | L | 906 | 7.52 | -36 | -76 | 42 | < 0.001 |
| Angular Gyrus | | L |  | 7.33 | -36 | -66 | 38 | 0.001 |
| Precuneus | | R | 1131 | 6.69 | 8 | -48 | 40 | 0.005 |
| Middle Cingulate Cortex | | L |  | 6.26 | -2 | -42 | 44 | 0.018 |
| Middle Temporal Gyrus | | L | 629 | 6.39 | -52 | -38 | -2 | 0.012 |
| Middle Temporal Gyrus | | L |  | 6.33 | -62 | -42 | -4 | 0.014 |
| Inferior Occipital Gyrus | | L | 157 | 5.91 | -22 | -92 | -6 | 0.045 |

An initial cluster-forming height threshold of *P* < 0.001 was used. Only clusters with FWE-corrected *P*s < 0.05 on peak level are listed. Abbreviations: MNI, Montreal Neurological Institute



**CONSORT 2010 Flow Diagram**

## Follow-up

## Analysis

## Treatment

Received treatment (n = 53)

Excluded (n = 26)

¨  Not meeting inclusion criteria (n = 19)

¨  Declined to participate (n = 7)

Analysed all data (n = 40)

Excluded from social touch fMRI analysis

* Excessive movement during data acquisition (n = 1)

**CONTROLS**

Assessed for eligibility (n = 67)

**PATIENTS**

Assessed for eligibility (n = 90)

## Enrollment

Excluded (n = 33)

¨  Not meeting inclusion criteria (n = 26)

¨  Declined to participate (n = 7)

Completed follow-up after

* 4 weeks (n = 50)
* 8 weeks (n = 49)
* 12 weeks (n = 46)

Analysed all data (n = 51)

Excluded from social touch fMRI analysis

* Excessive movement during data acquisition (n = 2)

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