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Touch aversion in patients with interpersonal traumatization

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Abstract

Background: Interpersonal touch is a key aspect of human interaction and a usually very comforting experience. For patients suffering from post-traumatic stress disorders (PTSD) caused by interpersonal traumatization, such touch is affectively ambiguous.

Methods: In two studies, we investigated the experience and neural processing of various types of interpersonal and impersonal touch in patients as compared to healthy controls.

Results: Patients strongly disliked slow, interpersonal skin-to-skin stroking, while controls appreciated this kind of touch. No group differences were observed for ratings of impersonal touch. Similarly, the neural activation differed between groups for interpersonal, but not for impersonal touch. The interpersonal touch aversion in patients was accompanied by enhanced blood-oxygen-level-dependent response in the superior temporal gyrus and by a pronounced reduction of response in the hippocampus. This reduction was significantly correlated to symptoms of negative alterations and arousal within the patients.

Conclusion: We interpret the hippocampal suppression as an attempt to control traumatic memories, evoked by interpersonal touch. This mechanism may maintain the aversion of interpersonal touch in patients with interpersonal trauma-related PTSD.

1 Introduction

Post-traumatic stress disorder (PTSD) is a mental health condition that develops in some individuals who were exposed to exceptionally threatening ordeals such as threatened dead, sexual violence or serious injury assault. Symptoms include alterations in arousal and reactivity, negative alterations in cognitions and mood as well as intrusions. Patients consequently avoid of stimuli that remind them of the traumatic event (American Psychiatric Association, 2013). Being faced with traumatic reminders, patients typically exhibit increased activation in limbic regions such as the amygdala and hippocampus, and decreased activation in the medial prefrontal cortex (Osuch et al., 2001; Patel, Spreng, Shin, & Girard, 2012; Rauch, Shin, & Phelps, 2006; Shin et al., 2004; Shin, Rauch, & Pitman, 2006). Traumatic reminders, which are usually used in studies on PTSD, are auditory and visual cues or verbal script driven imagery (Etkin & Wager, 2007; Frewen et al., 2008; Shin et al., 2004), but there are hardly any studies using triggers involving interpersonal interaction. This is surprising given that physical assault is one of the leading Type-A criteria of PTSD. Among the exceptions is one study using face photographs that either directed gaze towards the participant or not (Steuwe et al., 2014), and another study where women with interpersonal traumatization-related PTSD watched film scenes with threatening and romantic interactions between men and women (Moser et al., 2015). In addition to higher dorsolateral prefrontal activation to mean-acting videos, women with PTSD exhibited higher activity in hippocampal regions to both romantic and mean-acting scenes as compared to neutral stimuli. The authors concluded that any kind of emotional interaction is processed as if it was threatening. Whereas these studies provide important insight into the processing of visual stimuli related to interpersonal interaction, we are not aware of any studies examining the perception of interpersonal touch in interpersonal trauma-related PTSD.

Interpersonal touch is one of the triggers which can prompt the re-experience of traumatic events (Dunmore, Clark, & Ehlers, 1999) and people with a history of severe childhood maltreatment - an etiology which is closely related to PTSD (Heim & Nemeroff, 2001) – consequently report problems with intimacy (Taft, Watkins, Stafford, Street, & Monson, 2011), sexual interactions, and simple casual touching with strangers or friends (Dunmore et al., 1999). This matches our clinical experience: Patients who are traumatized by intentional physical or sexual violence (interpersonal traumatization related PTSD) report an ambiguous relation to interpersonal touch. They avoid touch and strongly mistrust the touch provider's intention, but they also long for being held and caressed.

The longing for touch is a strong drive of behavior (Gallace & Spence, 2010) and the human cutaneous receptor system seems to be wired for touch. Caressing touch is coded by a particular type of so-called C-tactile afferents in the skin (McGlone, Wessberg, & Olausson, 2014). Those fibers constitute a subgroup of the unmyelinated C-fibers and possess responsive characteristics which make them ideal for signaling to interpersonal touch (H. Olausson, Wessberg, McGlone, & Vallbo, 2010). They fire with highest frequency in response to slow stroking stimulation at a velocity of about 1 to 10 cm/s applied with light force (Löken, Wessberg, McGlone, & Olausson, 2009) and are selectively reactive to skin temperature (Ackerley et al., 2014). Slow stroking stimulation of the skin which targets C-tactile fibers is normally perceived as very pleasant (Löken et al., 2009; H. Olausson et al., 2010) and increases parasympathetic activity (Triscoli, Croy, Olausson, & Sailer, 2017; Triscoli, Croy, Steudte-Schmiedgen, Olausson, & Sailer, 2017). The primary projection areas of C-tactile targeted touch involve the somatosensory cortices and the posterior insula, with the latter area being the main cortical target for information from C-tactile afferents (Morrison, Bjornsdotter, & Olausson, 2011; H. W. Olausson et al., 2008). In addition, such touch is processed in the superior temporal gyrus (STG) (Davidovic, Jönsson, Olausson, & Björnsdotter, 2016; Gordon et al., 2013; Sailer et al., 2016), an area involved in social processing and cognition (Uddin, Iacoboni, Lange, & Keenan, 2007), which integrates multimodal social information (Schirmer & Adolphs, 2017). STG activation predicts for instance, how pleasant healthy participants rate stroking (Davidovic et al., 2016).

The aim of the present study was to investigate how individuals with interpersonal traumatization react to touch, both on the level of subjective experience and neural activation. We hypothesized in *experiment one* that patients with interpersonal trauma-related PTSD rate interpersonal, C-tactile targeted touch as aversive. We furthermore assumed that this aversion is more pronounced when patients have no visual control over the stimulation, because such touch leaves more room for interpretation. For impersonal touch, we hypothesized no aversion and hence no difference between patients and controls. In a *second experiment*, we hypothesized that the aversion of interpersonal touch would go along with larger activation in patients than controls in areas that are involved in the processing of fear (amygdala), traumatic memories (hippocampus) and social processing (STG). We furthermore expected that the activation within those areas would be highest for patients, when interpersonal touch is presented with velocities that target C-tactile fibers, and therefore explored the differential impact of the agency of touch (interpersonal vs impersonal) and of C-tactile fiber stimulation in a balanced design.

2 Experiment 1

2.1 Materials and methods

2.1.1. Participants

Thirteen female patients aged between 20 and 55 years (mean age 41.9+/-15.5 years SD) with a history of interpersonal traumatization (related to sexual abuse and physical maltreatment) and a diagnosis of PTSD were examined. The diagnoses and biographical interviews were performed by trained clinicians and confirmed via the structured clinical interview for DSM-IV (SCID, (Wittchen, 1997)) and via self-report in the Childhood Trauma Questionnaire (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). Detailed information about medication and diagnosis is presented in supplementary table 1. The patients were compared to 13 female healthy control participants (aged 30-55 years, mean age 39.8+/-7.8years SD), all of whom were negatively screened for mental disorders using the PHQ questionnaire (Freyberger, Spitzer, & Stieglitz, 1999). None of the patients or controls participated in experiment two.

As part of the clinical routine, all patients answered a number of self-report questionnaires: 1) the Childhood Trauma Questionnaire (CTQ; Bernstein, 1998, German version by Gast et al. 2001), which retrospectively assesses traumatization due to emotional, physical and sexual neglect and abuse during childhood, 2) the PTSD Checklist (PCL; Weathers et al., 2013, German version by Krüger-Gottschalk et al., 2017), a widely-used measure that assesses the presence and severity of PTSD symptoms and 3) the Questionnaire of dissociative symptoms (Freyberger et al., 1999)(in German: Fragebogen dissoziativer Symptome; FDS-20; (Spitzer, Mestel, Klingelhöfer, Gänsicke, & Freyberger, 2004)), which assesses dissociative experiences over the past 14 days. Healthy controls answered those questionnaires after the experiment via online-assessment.

As expected, the patient group reported significantly higher levels of childhood traumatization (CTQ patients: 17.1 +/- 4.5SD, controls: 6.1 +/-0.8SD, $T[24]=8.7$; $p<0.001$), PTSD symptomatology (PCL patients: 47.3 +/- 11.7SD, controls: 7.9 +/-7.8SD, T[24]=10.1; p<0.001) and dissociation severity (FDS (Freyberger et al., 1999)(Freyberger et al., 1999)(Freyberger et al., 1999)(Freyberger et al., 1999)(30)(Freyberger et al., 1999) patients: 21.4 +/- 14.3SD, controls: 11.8 +/-1.4SD, T[24]=2.4; p=0.024).

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the TU Dresden (EK 533122015). All participants gave written informed consent.

2.1.2 Experimental procedure

We implemented five separate stroking conditions in which the subjects were stroked across a distance of 10cm which was marked on their left dorsal forearm. The order of conditions was randomized and three trials were presented in each condition. The conditions varied the interpersonal aspect of stroking, the amount of C-tactile fiber stimulation and in visual control. Interpersonal stroking was defined as stroking with the palm of the female experimenters' (LT) hand, and impersonal stroking as stroking performed using a 50 mm wide flat, soft brush made of fine, soft goat's hair. The five conditions presented were 1) impersonal touch at 30 cm/s (C-tactile suboptimal stroking), 2) impersonal at 3 cm/s (C-tactile-optimal stroking), 3) interpersonal at 3 cm/s and 4) interpersonal visually shielded at 3 cm/s with experimenter and own arm not visible due to a screen in-between participant and experimenter. In condition 5, the participants were asked to "stroke yourself within the marked area as you would normally do" (self-touch). For reasons of brevity, methods of and results from the self-touch condition are not presented here.

Precision of stimulus onset as well as of stroking velocities was guided by a computerized metronome, which was displayed on a screen and was only visible to the experimenter, but not to the participants. As stroking temperature has an influence on C-tactile fiber reactivity

(Ackerley et al., 2014), the experimenter aimed at keeping hand temperature constant by rubbing her hands prior to interpersonal stroking. Prior to the experiment, the experimenter intensively practiced the stroking procedure in order to ensure stability of velocity and force (for detailed description please see supplement: preparation of stroking). Stroking applied with the aforementioned methods is perceived comparable to stroking applied with a robot (Triscoli, Olausson, Sailer, Ignell, & Croy, 2013).

After each trial, the participants were asked to assess both the pleasantness (visual analogue scale scoring from -5 to +5: very unpleasant to very pleasant) and the intensity (visual analogue scale scoring from 0 to +10: not intense at all to extremely intense) of stroking on a tablet.

In order to explore whether the touch caused any flashbacks, we asked the participants after the last condition whether they experienced memories or intrusions during the stroking. In case participants answered with “yes”, they were asked if the memory was negative and during which of the particular touch conditions the memory occurred.

Prior to the experiment, the participants filled in the Positive and Negative Affect Schedule (PANAS, (Watson, Clark, & Tellegen, 1988), and the touch deprivation questionnaire (Punyanunt-Carter & Wrench, 2009), which assesses the existence of a subjectively perceived lack of touch.

A psychology student performed the experiment. The student was instructed how to support the patients in case they showed any sign of discomfort and how to get further help from a supervisor who was present in the same floor. Such additional help was not needed for any of the patients.

2.1.3 Data analysis

Analyses were performed with SPSS 25. Results from the PANAS questionnaire were compared between groups using t-test for independent samples. Pleasantness and intensity ratings were averaged across the three trials for each condition and thereafter, the ratings were separately analyzed with two separate repeated-measures analyses of variance with the between-subjects factor "group" (patient, control) and the within-subjects factor "touch" (impersonal, C-tactile suboptimal, impersonal, C-tactile optimal, interpersonal, C-tactile optimal, interpersonal shielded, C-tactile optimal). Significant interactions were followed up for differences between groups by post-hoc T-tests for independent samples.

2.2 Results

Patients expressed more negative and fewer positive emotions prior to testing than healthy controls (PANAS positive affect: patients: 25.1 +/- 8.1SD, controls: 35.7 +/- 4.3SD, $T[24]=4.2$; $p<0.001$, $d=1.3$; negative affect: patients: 34.2 +/- 5.1SD, controls: 18.5 +/- 4.9SD, $T[24]=8.1$; $p<0.001$, $d=1.7$).

Patients rated all touch conditions as less pleasant than controls did (main effect of group: $F[1,24]=5.1$; $p=.033$; $\eta2=0.18$) and there was a significant interaction between group and touch type ($F(3,72)=10.3$, $p<0.000$; $\eta2=0.30$). Post-hoc tests showed that patients rated the two interpersonal conditions significantly more negative than controls (interpersonal, C-tactile optimal: $T[24]=3.5$; $p=0.002$, $d=1.1$; interpersonal shielded, C-tactile optimal: $T[24]=3.6$; $p=0.001$, d=1,2, Figure 1, while there were no differences for the impersonal conditions T[24]=0.4-0.9, d=0.16-0.35; p=0.381-0,680). For intensity ratings, there was no significant main effect of group ($F[1,24]=0.1$; $p=.72$; $\eta2=0.01$) and no significant "touch type by group" interaction ($F(3,72)=1.2$, $p=0.28$; $\eta2=0.05$) (please see Figure 1).

Five patients and one control participant reported negative memories in response to the touch. All of those memories were related to previous instances of unwanted touch and for three of the patients the memories were directly related to an experienced trauma. All of these memories occurred in the interpersonal shielded touch condition.

2.3 Discussion

In line with our hypothesis, patients with interpersonal trauma-associated PTSD selectively dislike interpersonal touch. Visual control did not further decrease the patients pleasantness ratings. Nevertheless, the shielded touch condition made the occurrence of unwanted memories more likely.

In experiment 2, we aimed at examining the neural basis for the observed touch aversion.

3 Experiment 2

3.1 Materials and methods

3.1.1 Participants

Twenty right-handed patients (19 women, aged between 24 and 58 years, mean age 44.3 ± 10.7 years SD) were examined. Similar to experiment one, all patients reported a history of interpersonal trauma related to sexual abuse and physical maltreatment and were diagnosed with PTSD. None of the subjects from experiment 1 were part of experiment 2. The diagnoses and biographical interviews were performed by trained clinicians and confirmed via the SCID and CTQ (compare supplementary Table 2 for detailed information about medication and diagnosis).

The patients were compared to 20 right-handed age- and sex-matched healthy control participants (19 women, aged between 24 and 58 years, mean age 40.3±14.0 years SD). Current psychiatric/psychotherapeutic treatment and subjective suffering from mental disorders (as screened by BDI-II *(Hautzinger, Keller, & Kühner, 2006) (cut-off of 13 points)* and PHQ (Kroenke, Spitzer, & Williams, 2001)(cut-off of 5 points)), as well as a history of Childhood maltreatement (as screened by the CTQ *(Bernstein et al., 1997)(cut-off: two standard errors above the norm)*) served as exclusion criteria. There was no significant difference between groups in age (p=0.3) or gender distribution (p=0.9). As normal in this population of patients (Christiansen & Hansen, 2015), women were highly overrepresented. We therefore performed the main analysis twice, with the whole sample and under exclusion of the two male participants. As the analysis under exclusion of men did not change any of the behavioral or neural results, we omit from presenting it here.

As expected, the patient group reported significantly higher levels of childhood traumatization (CTQ patients: 24.6 +/- 5.4SD, controls: 6.4 +/-1.2SD, T[38]=8.1; p<0.001, d=5.5). We acquired data regarding current PTSD symptomatology, dissociation severity and depression only from the patients and they reported high symptom load for PTSD (PCL intrusion: 16.6 +/- 3.82SD; avoidance: 5.3 +/- 2.3; negative alterations: 16.9 +/- 5.5SD), dissociation (FDS 28.7 +/- 17.4SD) and symptoms of depression (BDI II (Hautzinger et al., 2006) 33.6 +/- 11.7SD).

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the TU Dresden (EK 533122015). All participants gave written informed consent.

3.1.2 fMRI acquisition and experimental design

Functional magnetic resonance imaging (fMRI) data were acquired on a 3-Tesla MR scanner (Trio; Siemens Medical, Erlangen, Germany) using a protocol with a T2*-weighted gradient-echo, echo-planar imaging sequence (TR = 3s, TE 51ms, flip angle 90°, 25mmx6mm axial slices, 3.6x3.6mm in-plane resolution). A high resolution T1 sequence (3D IR/GR sequence: TR = 3s, 0.7x1mm in-plane resolution) was added for precise anatomical mapping of functional data as well as exclusion of potential brain pathology in all participants. The scanning planes were oriented parallel to the anterior-posterior commissure line and covered the whole brain.

At the day of data collection, participants provided informed consent and then answered questionnaires about their current mood (PANAS) before the scanning procedure began.

Stroking was performed on a 10cm distance marked on the subjects left dorsal forearm in four separate runs, which were designed to modulate both the interpersonal aspect of stroking and the amount of C-tactile fiber stimulation.

Each run consisted of 12 on-off stimulation periods (15 s stimulation followed by 15 s non-stimulation), which resulted in a total of 6 minutes of scanning per run (see Figure 2).

One condition was presented in each run. The agency of the stroking (interpersonal stroking performed by the experimenters' hand vs impersonal stroking performed by a brush) and the velocity of stroking (C-tactile optimal stroking at 3cm/s vs C-tactile suboptimal stroking at 30cm/s) were modulated in a randomized design.

The experimenter (TS) manually stroked participants in a similar way as in experiment one: For the impersonal conditions, stroking was performed using a 50 mm wide flat, soft brush made of fine, soft goat's hair. For the interpersonal conditions, stroking was performed with the palm of the experimenters' hand, which was warmed prior to stroking by rubbing. Precision of stimulus onset and stroking velocities was guided by a computerized metronome, which was displayed on a screen outside the scanning room and which was only visible to the experimenter. The participants could not see the experimenter.

Similar to experiment one, the experimenter intensively practiced the stroking procedure in order to ensure stability of velocity and force prior to the tests (for detailed description please see supplementary information: preparation of stroking).

After each run, the participants were asked to verbally assess the pleasantness of stroking on a 10-point scale from -5 to +5, where -5 corresponded to "very unpleasant" and +5 to "very pleasant". Subsequently, intensity was to be assessed on a 10-point scale from 0 to +10 ("not intense at all" to "extremely intense"). The ratings were given directly to the technical assistant and auditory shielding of the experimenter prevented him from hearing the verbal feedback.

A trained psychologist supervised the scanning. This was done in order to ensure that the patients felt comfortable and safe during the experiment and that they received fast support in case of discomfort. Such support was necessary for three individuals after the experiment.

3.2 Analysis

3.2.1 Mood, touch pleasantness and intensity

Data was analyzed using SPSS v. 25. Results from the PANAS questionnaire were compared between groups using t-test for independent samples. Intensity and pleasantness ratings were separately entered into a general linear model (GLM). Satterthwaite approximation and robust covariance structures were modeled in order to handle the small sample size. Group served as between-subject factor and two within-subject variables were included: agency (interpersonal vs impersonal) and velocity (C-tactile optimal vs C-tactile suboptimal). The main effect of group and the "group by agency" and "group by velocity" interaction were modeled. Post-hoc tests were performed as t-test for dependent samples within each group and were sequentially Bonferroni-Holm-corrected. Effect sizes are presented as η^2 or Cohens d for significant results.

3.2.2 fMRI analysis

The analysis of fMRI time-series data was conducted with a standard GLM approach implemented in SPM12 (Statistical Parametric Mapping; Welcome Department of Imaging Neuroscience, in the Institute of Neurology at University College London [UCL], UK) within Matlab (Matlab 9.1, The MathWorks IncS., Natick, MA). Data preprocessing steps included realignment with 2nd degree B-spline, temporal filtering with high-pass filter cutoff at a period of 128s; normalization using the segmentation procedure implemented in SPM 12 with affine registration to the ICBM space template (MNI space), bias regularization of 0.0001, and spatial smoothing of functional data with a Gaussian kernel with FWHM = 6 x 6 x 6 mm.

For the first-level statistical analysis we compared stimulation blocks (on) to non-stimulation blocks (off) using a boxcar covariate reflecting stimulus on-off cycles convolved with SPM´s canonical hemodynamic response function. Motion-based noise regressors (which were very limited for each participant and run; <2 mm cumulative translation and 1° cumulative rotation) were included in our analysis.

In a full factorial design, we modeled the within-subject effects of velocity and agency and the between-subject effect of group. As the behavioral data showed no touch aversion related to velocity, we decided to merge the data from the C-tactile optimal and C-tactile suboptimal touch conditions in order to enhance power. For reasons of transparency, the velocity related-data is also presented (see supplementary Table 4). We performed all analyses using an assumption-free whole brain analysis in order to not miss any effects in this new investigation. We furthermore tried to use individual pleasantness ratings as regressors of interest for the full factorial design. As we did not observe any result on the whole brain analysis which holds for FWE correction we decided against reporting those results with a more liberal threshold. Activations were localized with the help of the anatomy toolbox (Eickhoff et al., 2005) and the Anatomical Automatic Labeling atlas implemented in the WFU pick atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). In order to reduce type I error, we report FWE-corrected results on peak level with $p<0.05$, as recently suggested (Eklund, Nichols, & Knutsson, 2016) and give the cluster level results in addition.

We first analyzed the touch vs baseline contrasts for the interpersonal and impersonal touch conditions for patients and controls, respectively. To test our hypothesis, we proceeded comparing both groups using independent sample t-tests for the activation in a) all four conditions, b) the two interpersonal conditions and c) the two impersonal conditions. Areas in which activation differed between groups were further examined. We therefore extracted beta coefficients for all four touch versus baseline conditions for each individual from a 6mm sphere around the peak-voxel activation difference (MNI 63, -44, 18) using the Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002). Using SPSS 25, we then related those coefficients to the individual pleasantness rating using linear and quadratic curve regression.

In the next step, we compared the interpersonal to the impersonal touch conditions within the group of patients only using a paired t-test. The significantly different areas were again extracted (6mm sphere around the respective peak-voxel (MNI 31, -40, 4 and MNI -31, -62, 6) and the beta coefficients were extracted for every condition and participant using Marsbar. Those coefficients were averaged over the interpersonal and impersonal stroking conditions. In order to examine whether the neural response in the ROIs was related to the symptomatology, the data were used as target in a forward stepwise regression model with main symptoms related to the group of patients (PTSD symptomatology [PCL with the subscales intrusion, avoidance, arousal, negative alterations]) included as predictors.

3.3 Results

3.3.1 Mood, touch pleasantness and intensity

Relative to healthy controls, patients expressed more negative and fewer positive emotions prior to testing (PANAS positive affects: patients: 21.2 +/- 6.6SD, controls: 36.1 +/- 6.0SD, T[38]=7.5; p<0.001, d=2.4; negative affects: patients: 37.0 +/- 5.7SD, controls: 16.9 +/- 3.9SD, T[38]=12.9; p<0.001, d=4.2).

Patients rated any touch as significantly less pleasant than healthy controls did ($F[1,35]$=37.8; p<0.001; η^2=0.48, Figure 3). A significant agency-by-group interaction ($F[2,55]$=3.8; p=0.029 η^2=0.08) indicated that patients especially disliked interpersonal touch. Controls rated interpersonal and impersonal touch as similarly pleasant (t=1.2, p=0.42), but patients rated interpersonal touch as more aversive than impersonal touch (t=2.5, p=0.042, d=0.53). Accordingly, patients rated the interpersonal touch as significantly less pleasant than controls (t=5.8, p<0.001, d=1.6). Patients also rated the impersonal touch as significantly less pleasant than controls (t=3.2, p=0.005, d=0.92). We also observed a significant velocity-by-group interaction ($F[2,127]$=16.2; p<0.001, η^2=0.12), showing that patients did not differentiate between C-tactile optimal and suboptimal stroking (t=0.1, p=0.9), while the controls significantly preferred C-tactile optimal over suboptimal stroking (t=5.7, p<0.001, d=1,25).

Patients rated tactile stimulation as more intense than controls did ($F[1,35]$=5.0; p=0.038; η^2=0.10, Figure 3). A significant agency-by-group interaction ($F[2,55]$=4.5; p=0.041, η^2=0.11) revealed that controls rated the interpersonal conditions as more intense than the impersonal ones (t=5.9, p<0.001, d=1.3), while ratings of patients did not differ according to agency. A significant velocity-by-group interaction ($F[2,127]$=5.5; p=0.024, η^2=0.13), revealed that controls rated C-tactile suboptimal stroking as significantly more intense than C-tactile optimal stroking (t=2.0, p=0.05, d=0.44), while patients did not differentiate between both velocities of stroking (t=1.6, p=0.1). Please see supplement for detailed information about all post-hoc tests.

After the experiment, three of our participants spontaneously reported the occurrence of traumatic memories during stroking, which they intended to suppress.

3.3.2 Neural responses: group-comparative effects

For each group and each condition, stroking activated the expected touch-responsive regions contralateral to the side of stimulation in somatosensory cortices S1 and S2, extending to the STG (see supplementary Table 4 and Figure 4).

The STG was in tendency more strongly activated in patients than in controls for all types of tactile stimulation compared to baseline ($p_{FWE\ \text{peak level}}$= 0.057; $p_{FWE\ cluster\ \text{level}}$= 0.014; see Table 1). This enhanced STG activation was slightly more pronounced in the interpersonal touch conditions (t=4.51) than in the impersonal touch conditions (t=4.10). The averaged BOLD response within the STG cluster was significantly related to pleasantness ratings and this relationship proved to be quadratic: high and low pleasantness ratings were associated with higher STG activation over all groups and conditions (R^2=0.172, p<0.001, see Figure 6) and the quadratic fit explained more variance than a linear fit (R^2=0.037, p=0.014). Focusing on the interpersonal conditions, the relationship between pleasantness ratings and STG activation increased even more (R^2=0.34, p<0.001), and pleasantness ratings explained 30.6% of the variance of STG activation (quadratic fit, p<0.001). A still significant, but reduced quadratic relation was observed for the impersonal conditions (R^2=0.092, p=0.024).

The activation of the insular cortex unfortunately failed the strict FWE-corrected threshold. This is in contrast to previous research in the domain of social touch (H. Olausson et al., 2002). Nevertheless, with a more liberal threshold of p<.0.001, uncorrected we observe an activation of the insular cortex in the merged C-tactile optimal touch conditions.

3.3.3 Neural responses: distinct activation patterns in patients

Within the group of patients, we found a higher hippocampal activation for impersonal touch compared to the interpersonal touch (p_{FWE} peak level =0.02; p_{FWE} cluster level = *0.0001;* k = 396). This was not driven by a high activation following *impersonal touch vs baseline* but by a pronounced deactivation following *interpersonal touch vs baseline,* which was observed in a cluster encompassing the posterior dorsal parts of the hippocampus reaching into the subiculum and the posterior parts of the thalamus (p_{FWE} peak level =0.003, p_{FWE} cluster level < 0.001; k=559, t=5.59, MNI 31 -40 4) (please see figure 5). In addition, we observed an enhanced activation of the visual cortex (occipital lobe, region hOc2) for impersonal touch compared to the interpersonal touch (p_{FWE} peak level =0.08; p_{FWE} cluster level =*0.004*; k=231). This was also driven by a stronger deactivation of this area during *interpersonal touch vs baseline* as compared to *impersonal touch vs baseline* (compare Table 1). Both of these effects - on hippocampus and area hOc2 - were not observed in the healthy controls.

Furthermore, patients showed a stronger precentral extending to postcentral gyrus activation for interpersonal versus impersonal touch (p_{FWE} peak level < 0.001; p_{FWE} cluster level < 0.001). This finding was, however, not exclusively present in the group of patients: the same effect was observed in the controls (compare Table 1).

3.3.4 Relationship between neural response and current symptomatology in the patients

For the **interpersonal touch conditions**, 35.6% of the variance of the hippocampal response was explained by PTSD symptomatology measured by PCL. Stepwise inclusion revealed two significant predictors: the PCL subscale negative alterations was negatively related to reduced hippocampal activation (F=12.3; p=0.003), and the PCL subscale arousal was positively related to reduced hippocampal activation (F=8.2; p=0.011). No relationship was found between STG or hOc2 response and symptomatology.

For the impersonal conditions, neither the hippocampal nor the STG or hOc2 activation was significantly explained by variance in symptomatology.

4 Discussion

Consistent with our hypothesis and in line with the findings from experiment one, patients with interpersonal-trauma related PTSD rated interpersonal stroking touch as aversive. This was in contrast to controls who appreciated the stimulation. The slightly different touch conditions in experiment one and two allow us to conclude that the interpersonal touch aversion in patients is independent from the sex of the stroker, from whether the stroker can be seen or not and from whether stroking is performed to target C-tactile fibers or not.

For impersonal touch we found conflicting results. Patients showed an aversion for impersonal touch in experiment 2, which was performed in the scanner but not in experiment 1, which was performed in a test room. It is possible that the scanner environment, where participants are lying in a noisy and cramped environment, leads to a generalization of the patients touch aversion to impersonal touch conditions.

On a neural level, the observed touch aversion was related to enhanced hippocampal suppression in the patients and – in tendency - to enhanced activation of the STG. Both brain regions are reviewed in the following paragraphs.

Following the argumentation of Anderson et al (Anderson et al., 2004), we assume that the hippocampal deactivation relates to a voluntary suppression of unwanted memories. Both lower (e.g., (Bremner et al., 1999; Bremner et al., 2003; Hayes et al., 2011) and higher (Moser et al., 2015; Osuch et al., 2001; Patel et al., 2012) hippocampal activation has been reported in patients with PTSD to threat-related (Bremner et al., 1999; Moser et al., 2015; Osuch et al., 2001; Shin et al., 2001; Thomaes et al., 2009) and non-threat-related stimuli (Moser et al., 2015; Werner et al., 2009), depending on the paradigm and on whether patients suppressed unwanted memories. As our patients – who all reported a history of severe and repetitive interpersonal traumatization - perceived the interpersonal stroking conditions as very aversive, we assume that the reduction of hippocampal activity corresponds to an active neural coping mechanism preventing the recollection of traumatic memories. This aligns well with the spontaneous reports of unwanted memories from three patients of experiment two and with experiment one, in which patients reported unwanted memories after interpersonal touch. Alternatively, the reduced activation of the hippocampus could hint towards reduced Default Mode Network-activity in the patients (Peterson, Thome, Frewen, & Lanius, 2014; Shang et al., 2014). We favor the first explanation for two reasons: Firstly, we observed no group differences in any other prominent node of the DMN, such as the ventral medial prefrontal cortex, dorsal medial prefrontal cortex or the posterior cingulate cortex (Raichle, 2015). Secondly, in addition to the reduced hippocampal activity, patients also exhibited reduced activity of the visual cortex, which presumably indicates the attempt to suppress visual recollections. The hippocampal suppression may therefore be the neural correlate of a coping mechanism. This is supported by the observed relation between hippocampal suppression and symptoms of negative alterations and arousal in the group patients.

Compared to controls, patients showed in tendency an enhanced activation in the STG during all touch conditions but especially during interpersonal touch. It seems plausible that this area which tracks social perception (Schirmer & Adolphs, 2017; Uddin et al., 2007) is more alert in those individuals who made traumatic experiences to interpersonal touch. STG activation is known to correlate with the pleasantness of touch (Davidovic et al., 2016). As our study included participants who strongly disliked touch, we were able to extend this finding and observed a u-shaped relation between STG activation and pleasantness ratings, with the smallest activation in those participants who rated the touch rather neutral. This suggests that the STG is involved in salience coding, which accords well with observations from the visual domain showing that STG codes the salience of facial emotions (Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001).

No group differences were observed in the primary or secondary tactile areas. Hence, basal touch processing seems undisturbed in patients with interpersonal-trauma related PTSD.

Contrary to our hypothesis, patients did now show any increased amygdala activation to interpersonal touch. This is somewhat puzzling, as traumatic reminders normally result in enhanced amygdala activation (Rauch et al., 2006; Shin et al., 2004; Shin et al., 2006) and needs to be followed up in further studies.

We need to point the reader's attention to several limitations of this study. First, medication was rather the norm than the exception in the group of patients and we cannot exclude that medication, especially antipsychotic drugs, may have caused a hedonic dampening in patients (Kapur, 2003). Further, we cannot exclude that medication could have impacted the BOLD data (H Roder, Marie Hoogendam, & M van der Veen, 2010). We argue however, that such a dampening would result in more neutral, but not in more negative ratings. Due to the procedure chosen for patient recruitment and informed consent, the experimenter was not blind to the participant's group membership. As stroking was performed by hand, we cannot exclude subtle differences in the pressure and smoothness of the stroking stimulation. We tried to minimize this potential confounder by careful standardization procedures. Another limitation refers to the external validity of the fMRI study: While our design allowed for stimulus control of the different types of touch, interpersonal touch was performed under rather artificial laboratory conditions as a stranger performed the touch in a fMRI scanner. As the rating results were similar in experiment one, we can exclude an effect of the scanning procedure, but still touch processing and perception may differ quite a lot when the touch is not performed by an experimenter but by a trusted partner for instance.

To sum up, our results show that patients with interpersonal trauma-related PTSD have a selective aversion to interpersonal touch. The related suppression of hippocampal activity might be a strategy to control intrusive memories and this mechanism may maintain the aversion of interpersonal touch in patients with interpersonal trauma- related PTSD. In the long run, such reduction may hinder the integration of traumatic events into the biographical memory.

Furthermore, the aversion to interpersonal touch may hinder social interactions and limit the patient's possibilities to seek and enjoy the comforting effect of touch-mediated social support.

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Conflict of Interest

None of the other authors reports any financial disclosures for that study.

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Tables

Condition	Cluster size	T value	MNI coordinates			FWE corrected p value: peak level	FWE corrected p value: cluster level
			x	y	z		
Over all conditions: Patients > Controls							
Right Superior Temporal Gyrus	157	4.86	63	-44	18	0.057	0.014
Over all conditions: Controls > Patients							
No suprathreshold activation							
Interpersonal stroking: Patients > Controls							
Right Superior Temporal Gyrus	100	4.51	63	-44	18	0.19	0.078
Interpersonal stroking: Controls > Patients							
No suprathreshold activation							
Impersonal stroking: Patients > controls							
Right Angular Gyrus	193	4.29	41	-52	22	0.31	0.01
Right Superior Temporal Gyrus	135	4.10	63	-44	22	0.51	0.05
Impersonal stroking: Controls > Patients							
No suprathreshold activation							
C-tactile optimal stroking: Controls > Patients							
No suprathreshold activation							
C-tactile optimal stroking: Patients > Controls							
No suprathreshold activation							
C-tactile suboptimal stroking: Controls > Patients							
No suprathreshold activation							
C-tactile suboptimal stroking: Patients > Controls							
Right Superior Temporal Gyrus	6	5.08	61	-46	20	0.021	0.01
Patients: Impersonal > Interpersonal conditions							
Right Hippocampus	396	5.09	31	-40	4	0.02	0.0001
Left Area hOc2	231	4.73	-31	-62	6	0.08	0.004
Patients: Interpersonal > Impersonal conditions							
Right Precentral Gyrus extending to Right Postcentral Gyrus	296	4.77	33	-26	60	0.065	0.001
Controls: Impersonal > Interpersonal conditions							
No suprathreshold activation							
Controls: Interpersonal > Impersonal conditions							
Right Precentral Gyrus extending to Right Postcentral Gyrus	77	6.72	29	-24	74	<0.001	<0.001

Table 1 - group-comparative neuronal regions and distinct activation within group of patients. Results are reported with a height threshold of p<0.001 and only activations with FWE-corrected p-values of p<0.05 are presented.

Figure Legends

Fig. 1 - Pleasantness of touch conditions in experiment 1. Patients rated the interpersonal touch as significantly less pleasant than the healthy controls. Each dot represents one individual. Mean and Standard Error of the Mean are presented in each condition.

Fig. 2 - Visualization of the functional magnetic resonance imaging (fMRI) design. Each participant underwent four different stroking conditions in four different runs (one per condition) during fMRI scanning in a randomized order. In every run, the stroking touch was applied in a block design with 12 repetitions of “On” and “Off”. After each of the conditions, the participants verbally assessed both pleasantness and intensity of the touch percept.

Fig. 3 - Rating of the touch conditions in patients and controls. In general, patients rated touch as less pleasant and more intense compared to controls. This was especially pronounced in the interpersonal touch conditions. Furthermore, controls rated C-tactile optimal touch as more pleasant than C-tactile suboptimal touch. This effect was not observed in the patients. However, patients rated interpersonal touch as significantly less pleasant than impersonal touch. Mean and Standard Error of the Mean are presented in each condition.

Fig. 4 - Neural response to interpersonal and impersonal touch conditions in patients and controls. Data is presented in a template provided by Marsbar and FWE (peak)-corrected with a height threshold of $p<0.05$. In the left panels, the combined (slow and fast) interpersonal touch conditions vs baseline are displayed; in the right panels, neural response for the combined impersonal conditions is displayed. In comparison to the controls, patients exhibited tendentially enhanced superior temporal gyrus (STG) activation in the interpersonal touch conditions. Furthermore, the patients showed a reduced hippocampal activity in the interpersonal compared to the impersonal conditions.

Fig. 5 – Mean Bold Signal estimation of the right Hippocampus in interpersonal compared to impersonal touch conditions in patients and healthy controls. Averaged data was extracted from a 6mm sphere around the peak activation voxel of the within-patients analysis (MNI: 31 -40 4) for each participant and condition and shows a pronounced reduction of hippocampal deactivation in patients during interpersonal touch (T[40]=2.6; p=0.012, d=0.7), which was not present in the impersonal touch condition (T[40]=1.5; p=0.15, d=0.3). Error bars indicate the Standard Error of the Mean.

Fig. 6 - Neural-response-by-pleasantness scatterplots for interpersonal and impersonal touch conditions in patients and controls. In both conditions, superior temporal gyrus activation exhibits a quadratic relation to pleasantness ratings. This effect was more pronounced for the interpersonal (R^2=0.31) than for the impersonal (R^2=0.092) condition.