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Abnormal brain processing of gentle touch in anorexia nervosa

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ABSTRACT

Body image disturbance is a core symptom in anorexia nervosa (AN). Recent research suggests that abnormalities in touch perception may contribute to the disease mechanisms in AN. Here, we used functional magnetic resonance imaging (fMRI) to study possible abnormalities in cortical processing of affective touch in AN. Gentle skin strokes were applied to the right forearm during fMRI scanning in women diagnosed with AN (n = 25) and in matched healthy controls (HC; n = 25). Blocks of skin stroking were alternated with blocks of static skin indentation. Participants provided ratings of the pleasantness of skin stroking stimulation. AN participants perceived skin stroking as significantly less pleasant than HC. We observed no group differences for the contrast between skin stroking and skin indentation in primary tactile regions. We did find, however, significantly less activity in the AN group in areas including left caudate nucleus. Also, we found less activity in the AN group in bilateral lateral occipital cortex for the main effect of skin stroking. Our results suggest that abnormal functioning of the dorsal striatum could affect evaluation of pleasant tactile stimuli, and that abnormal functioning of the lateral occipital cortex might be related to disturbed body image perception.

1. Introduction

Anorexia nervosa (AN) is characterized by preoccupation with control of eating and an intensive fear of gaining weight. One of the central diagnostic criteria for AN is body image disturbance, which is considered to be a key factor in the development, maintenance, and relapse in AN (American Psychiatric Association, 2000). Body image disturbance is a complex phenomenon, including features such as overestimation of body size and weight, body dissatisfaction, and body weight control. AN thus comprises cognitive, affective and perceptual disturbances pertinent to body experience (Gaudio and Quattrocchi, 2012). These components, in turn, are associated with specific brain abnormalities, such as alterations of the precuneus and the inferior parietal lobe in relation to perceptual disturbances, and prefrontal and insular alterations related to affective processing (Gaudio and Quattrocchi, 2012). In this context, both 'bottom-up' sensory input (e.g. visual and tactile stimuli), and 'top-down' processes (e.g. affectively laden expectations) are employed in constructing the mental body representation (Blanke, 2012). Following this view, it has been hypothesized that body image disturbance in AN may result from an inability to integrate subjective experience of body appearance with objective multimodal appraisal of the body (Legrand, 2010).

A sensory modality with particular relevance to AN is touch (Gaudio et al., 2014). The processing of tactile information starts on the skin. Mechanical stimuli activate myelinated (A-beta) mechanoreceptors, which convey information to the spinal cord and then to the thalamus. From the thalamus this signal is projected to the somatosensory cortices, where the primary representation of the tactile stimulus occurs. This bottom-up input information, however, is subjected to the modulation by higher-level cognitive and affective brain regions (i.e. top-down processing) (Ellingsen et al., 2013). These processes provide us not only with the information about the external world but also about the body itself.

Several psychophysical studies have investigated touch perception in AN (Gaudio et al., 2014). Testing for two-point discrimination shows that patients with AN overestimate distances between tactile stimuli on

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Table 1
Demographic, clinical and behavioral data for healthy controls and women diagnosed with AN.

	Healthy controls (HC, $n = 25$)		Anorexia nervosa (AN, $n = 25$)		
Characteristic	Mean	SD	Mean	SD	p
Age	21.2	2.1	20.3	2.2	n.s.
Age of onset	–	–	16.3	2.7	–
Duration of illness			4.1	3.5	–
Years of education	13.7	1.4	12.2	1.5	n.s.
Body mass index (BMI)	21.1	2.3	16.3	1	<0.001
Depression score (BDI)	7.0	7.5	27.2	13.2	<0.001
Skin stroking pleasantness rating	1.5	1.6	0.4	1.7	0.03

both the arm and abdomen. In the same experiment, patients visually overestimated the images of their bodies (Keizer et al., 2012, 2011). Another study tested the perception of tactile stimuli applied with different orientations along the body axis in AN (Spitoni et al., 2015), and showed that the AN patients judged horizontal tactile stimuli significantly wider than the same stimuli oriented vertically. Together these studies support the view that body image disturbance in AN is linked with abnormal high-level processing of sensory information.

Recently, it was also found that affective aspects of touch are altered in AN: AN patients perceive gentle skin stroking touch as less pleasant relative to healthy controls (HC) (Crucianelli et al., 2016). Specifically, Crucianelli et al. show that gentle slow skin stroking, which activates a special group of unmyelinated afferents called C tactiles (CT) (Löken et al., 2009), is perceived as less pleasant by AN patients. The finding is consistent with the hypothesized role of CT afferents in contributing to pleasant experiences, such as during caresses (Löken et al., 2009).

In the current study, we sought to determine the neural correlates of abnormal affective touch processing in AN. Specifically, gentle skin stroking is tightly coupled with processing supported by insular cortex (Björnsdotter et al., 2009; Morrison et al., 2011; Olausson et al., 2002). Posterior insula receives primary input from thinly myelinated and unmyelinated tactile afferents while the higher level processing of the same input takes place in the anterior insula (Craig, 2002). The insula is also important for the processing of taste (Avery et al., 2015), pain (Henderson et al., 2007), reward (Wang et al., 2015), and interoceptive processing (Craig, 2002; Critchley et al., 2004); all vital aspects of the AN disease process (Nunn et al., 2011). Indeed, the insular cortex has emerged as a key region involved in the pathophysiology of AN (Gaudio and Quattrocchi, 2012; Kaye et al., 2013).

In light of these observations, we posited that altered affective touch perception in AN is related to abnormal insula-mediated touch processing. Specifically, we hypothesized that (i) AN patients perceive skin stroking as less pleasant than HC, and (ii) insular responses are reduced in AN relative to HC. To test these hypotheses, we examined behavioral and brain responses to robot-controlled light skin stroking in AN and HC participants during brain imaging.

2. Materials and Methods

2.1. Participants

The study was conducted in accordance with the Declaration of Helsinki, after approval by the *Regional Ethical Review Board* at the University of Gothenburg, Sweden (Dnr 007-14). All subjects participated voluntarily, after giving informed consent, and received a compensation of 400 Swedish crowns.

Women with AN were recruited consecutively from an in- and outpatient specialist unit, the Anorexia–Bulimia unit at the Queen Silvia Children's University Hospital in Gothenburg, Sweden. A total of 38 patients were asked to participate, 13 of whom declined, leaving 25 patients to be included in the study (all female, age range 16–25; Table 1). At first assessment, all patients were diagnosed with AN according to the DSM-IV (American Psychiatric Association, 2000) by a psychiatrist using SCID I (First et al., 2002). All had body mass indices (BMI) ≤ 17.5 kg/m^2, as measured at the unit. All patients were medically stable and followed an advised meal plan at the time of scanning. One of them was hospitalized in the psychiatric ward at the time of data collection. Twelve patients were not receiving psychotropic medication, and the remaining 13 patients used psychoactive medication: fluoxetine ($n = 6$), sertraline ($n = 4$), olanzapine ($n = 2$), quetiapine ($n = 1$), venlafaxine ($n = 1$), propiomazin (4), lamotrigin (1) and lisdexametafin (1). Four patients had a binge-eating/purging type of AN, and the remaining had a restrictive type of AN.

HC participants were recruited from the universities and high schools in Gothenburg, Sweden. This group included 25 healthy women (age range 17–25 years; Table 1). All healthy participants were asked to report neurological disorders, ongoing diseases and medications through a written questionnaire. In addition, ongoing eating disorders were assessed through the SCID-I. Inclusion criteria for matched control participants were no ongoing eating disorders, no neurological disorders, no ongoing diseases, and no psychotropic medication.

As comorbid depression is widespread in AN (Gillberg and Råstam, 1992), we assessed levels of depression with Beck Depression Inventory (BDI) (Beck et al., 1996) in all participants. We assessed handedness using the Edinburgh Handedness Inventory (EHI) (Caplan and Mendoza, 2011), which showed that three of the HC participants were left-handed. EHI values ranged from -100 to 100, where -100 corresponded to complete sinistrality and 100 to complete dextrality. We subsequently used EHI values as covariates of no interest in the group analyses of fMRI data.

2.2. Stimuli and imaging paradigms

Each subject completed one resting-state, one anatomical (T_1-weighted), and four task sessions (in this order). Here, we report the

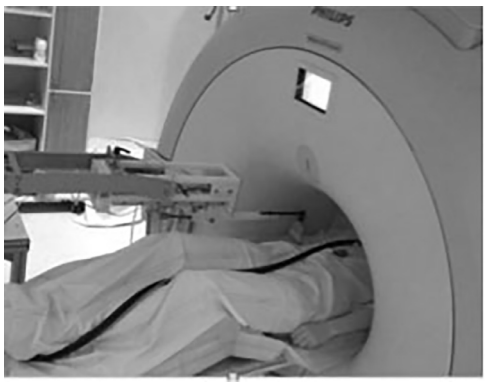

Fig. 1. Linear tactile stimulator for high-precision brush stroking on the right forearm. Movement velocity 2 cm/s, indentation force 0.5 N.

results from the four tactile stimulation task scans. Cortical thickness data are presented elsewhere (Björnsdotter et al., 2017).

To reduce experimenter confounds, we used a custom-built robotic linear tactile stimulator (Dancer Design, St Helens, UK; Fig. 1) designed to deliver high-precision tactile stimuli, identical to all participants. Skin strokes were delivered by means of a 9 cm wide artist's goat-hair brush attached to the robotic stimulator. Strokes were applied at a velocity of 2 cm/s to the skin of the right dorsal forearm, in the center portion between the wrist and the elbow. The brush was applied linearly in a proximal-distal direction for 8 s (*'brush move'* skin stroking condition), went up-back-down to the starting position in 4 s (*'no touch'* or rest period) and then stayed at the starting position gently touching the skin but not moving (*'brush rest'* condition with static skin indentation) for 8 s. Both skin stroking and static touch were applied with the same indentation force of 0.5 N. One task session consisted of 10 cycles of *'brush move'* and *'brush rest'*, lasting 3 min and 20 s. Participants were instructed to lie still with their eyes closed, and to focus on how pleasant/unpleasant the tactile sensation felt.

After each of the four tactile sessions, participants were asked to verbally rate their subjective percept of the stroking sensation on a scale ranging from −5 ('extremely unpleasant') to +5 ('extremely pleasant'). In addition to providing a behavioral response to the stroking, the rating ensured that participants focused on the affective qualities of the tactile sensations. The ratings were averaged across all four skin stroking sessions and this value was used for further analysis.

2.3. Data acquisition

MRI was performed on a Philips Gyroscan 3T Achieva, software release 3.2 (Philips, Eindhoven, The Netherlands). The scanner's two-channel parallel transmit coil was used for improved signal homogeneity over the field of view. To reduce motion and improve comfort, the subject's head was firmly supported with cushions in the head coil (32 channel SENSE, same manufacturer as the scanner). A high-resolution T1-weighted scan (3D T1-TFE) was performed for anatomical reference (parameters: flip angle 8°, TE = 4.0 ms, TR = 8.4 ms, SENSE factor 2.7, TFE factor 240, 170 sagittal slices with scan resolution 1.0 × 1.0 × 1.0 mm^3). Task scans comprised 100 whole-brain acquisitions (parameters: single shot gradient echo, echo planar imaging with flip angle 90°, TE = 35 ms, TR = 2000 ms, SENSE factor 1.8, 33 axial slices without slice gap and with in-plane scan resolution 2.8 × 2.8 mm^2, slice thickness 4 mm).

2.4. Pre-processing

Pre-processing and statistical analysis of anatomical and functional images were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Anatomical images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) images. GM images were used to determine the 12-parameter affine transformation into standard stereotactic space (Montreal Neurological Institute, MNI). Transformed GM images of all participants were used to calculate an average GM image, which was used as a mask in the analysis of functional images. Visual inspection of this image confirmed that all GM structures were preserved and only major WM tracts and ventricles were left out. In addition, a single average anatomical image was calculated using spatially normalized anatomical images from all participants; this image was used as an underlay for presenting functional results.

Preprocessing of functional images included slice time correction, realignment to the first volume of the first run using a rigid translation and rotation spatial transform, co-registration to anatomical images, transformation to MNI space using translation, rotation, scaling and shearing obtained from transformation of gray matter images, resampling to voxels 2 × 2 × 2 mm and spatial smoothing with a 6-mm full width at half maximum Gaussian kernel. In addition, motion artifacts were examined using the Artifact Detection Toolbox (ART; http://www.nitrc.org/). Volumes in which the global signal deviated more than two standard deviations from the mean signal or in which the difference in position between two neighboring volumes exceeded 1 mm (across rotational or translation directions) were marked as outlier volumes. One regressor of no interest was added for each outlier to the design matrix in the first level analysis. Using this procedure reduced the effect of outliers on the data analysis. Smoothed functional images were temporally filtered with a 128 s high pass filter.

2.5. Task fMRI analyses

We performed a whole-brain group-level general linear model random effect analysis of the tactile task-fMRI data. Regressors with the duration of 8 s were modeled using a boxcar function with 1 during the *'brush move'* and *'brush rest'* conditions, and 0 otherwise, convolved with the SPM's canonical hemodynamic response function. For the first level analysis, the motion parameters and outlier volumes were included as regressors of no interest, and beta values were estimated for both conditions. Parameter estimates for the main effect of *'brush move'* condition (i.e. *'brush* move' versus baseline) and the contrast *'brush move > brush rest'* were moved to the second level, and group level analyses were performed. Since three of the HC participants were left-handed and none of the AN participants were, we added EHI values to the design matrix as effect of no interest.

We performed two analyses of primary interest to the study. First, we conducted a whole brain analysis of group-level effects and group differences in the main effect of *'brush move'* condition. Here, we asked whether there were any overall group differences in the brain processing of somatosensory information. Additionally, we conducted detailed examination of the brain responses in somatosensory processing areas, i.e. left S1 (contralateral to the stroking side), bilateral S2 and left posterior insular cortex (PostIC) by extracting regional beta values using MarsBar toolbox (http://marsbar.sourceforge.net/). Coordinates for these areas were estimated from the peak values for *'brush move'* condition in the HC group. Values were extracted using spheres with the radius 6 mm centered at these coordinates. Second, we conducted a whole brain analysis of the contrast *'brush move > brush rest'*, for each group separately and for the group difference. Here, we asked whether there were any group differences specifically in the affective touch component. We also extracted beta values for both conditions at the coordinates that showed significant group difference for this contrast (presented in Supplementary Material). In addition, we investigated correlations between neural responses to the affective component of touch (*'brush move > brush rest'* contrast) and pleasantness ratings in these areas.

2.6. Thresholding

All maps were masked with the average GM mask obtained in the preprocessing of the anatomical images and the threshold was set to $p < 0.001$. We performed cluster level multiple comparison correction using Monte Carlo simulations implemented in Matlab (Song et al., 2011), which estimated that cluster size of 37 voxels controls for the threshold $\alpha < 0.05$.

3. Results

3.1. Behavioral responses

AN patients rated skin stroking as significantly less pleasant than matched healthy participants (unpaired two-tailed *t*-test $p = 0.03$, Table 1). The standard deviations of the ratings were largely similar in AN patients and HC. In the AN group, SD was 3.3 for one AN patient, and between 0 and 1.91 for the remaining patients. In the HC group, SD ranged between 0 and 1.77. Pleasantness ratings did not correlate with

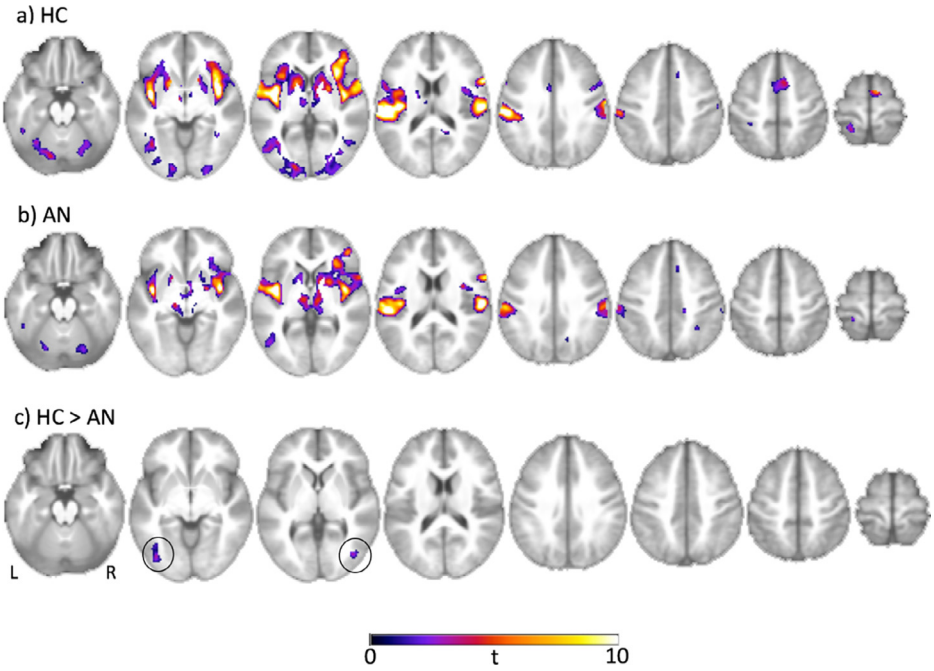

Fig. 2. Whole brain results for main effect of 'brush move' condition for healthy controls (HC), anorexia nervosa patients (AN) and contrast between the two groups. All three maps were thresholded at $p < 0.001$ and cluster size > 37. Images are presented at *z*: −20, −6, 2, 16, 36, 44, 52, 68. In circles: left and right lateral occipital cortex.

Table 2
Whole brain results for group difference, for main effect of 'brush move' condition: *t*-values, MNI coordinates and cluster sizes (ks). Threshold: $p < 0.001$ and cluster size > 37.

Region	*t*-value	*x*	*y*	*z*	ks
L lateral occipital cortex	4,4	−38	−76	−4	103
R lateral occipital cortex	4,3	40	−74	2	54

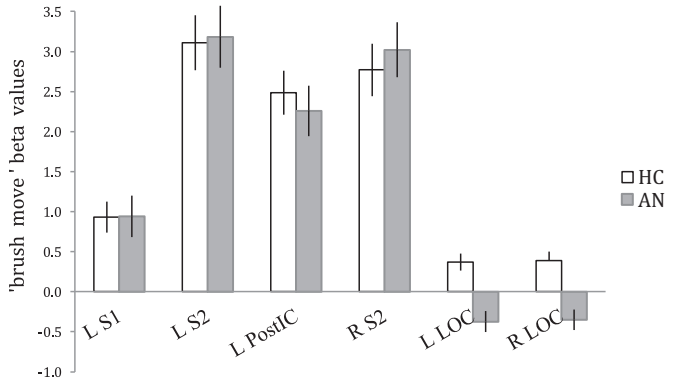

Fig. 3. Extracted beta values for the main effect of 'brush move' condition, for healthy controls (HC) and anorexia nervosa (AN) patients. Coordinates for regions: left S1 (L S1) = −22, −40,64; left S2 (L S2) = −52, −28, 16; left posterior insula cortex (L PostIC) = −38, −18, 12; right S2 (R S2) = 58, −20, 16; left lateral occipital cortex (L LOC) = −38, −76, −4; right lateral occipital cortex (R LOC) = 40 −74,2. Error bars show SEM.

BDI, BMI or duration of illness (all $p > 0.1$). (See also Supplementary Material and figures S1 and S2).

3.2. Task-fMRI results

3.2.1. Main effect of 'brush move' condition

In a whole-brain analyses for main effect of *'brush move'* condition, both HC and AN showed significantly increased activity in a range of areas, including somatosensory areas (S1 and S2) and bilateral insula (Fig. 2a–b). We found, however, no significant group differences in neural response in S1, S2, and bilateral insula (Fig. 2c). Unexpectedly, we found significant group differences in bilateral lateral occipital cortex (LOC) for the group difference HC > AN (Fig. 2c, Table 2).

We extracted beta values corresponding to the main effect of *'brush move'* condition from left (contralateral to the stimulated arm) S1, left and right S2, left PostIC, and left and right LOC for participants from both groups (Fig. 3). AN showed strong, significant activations in S1, S2 and PostIC (all one-sample *t*-test $p < 0.001$). Moreover, there was no significant difference between the two groups in these areas (all two-sample *t*-tests $p > 0.1$). The LOC group difference in Fig. 2c was a consequence of increased activity for HC (one-sample-*t*-test $p = 0.002$ and $p = 0.003$ for left and right LOC, respectively) and decreased activity for AN (one-sample-*t*-test $p = 0.009$ and $p = 0.011$ for left and right LOC, respectively).

3.2.2. Contrast 'brush move > brush rest'

Whole brain results for the contrast *'brush move > brush rest'* showed significant differences in left caudate nucleus, bilateral frontal pole (right middle orbital gyrus and left middle frontal gyrus), bilateral precuneus and right temporal pole for the group difference HC > AN (Fig. 4 and Table 3).

We investigated in detail responses in the areas that showed significant group difference by extracting the values for main effects of *'brush move'* and *'brush rest'* at the MNI coordinates presented in the Table 3 (Supplementary material, Figures S3 and S4) and performing one-sample-t-tests with the significance level set to $p < 0.001$. In the left caudate nucleus (MNI −18, 18, 14), the main effect was significantly positive only for *'brush move'* condition in HC group. In the right precuneus (MNI 12, −72, 36), left precuneus (MNI −4, −72, 38) and right temporal pole (MNI 58, 8, 0) the responses were significantly positive for both main effects and in both groups. In the right middle orbital gyrus (MNI 42, 52, 0), the main effect for *'brush rest'* condition was significantly negative in HC group and not significantly different from zero for *'brush move'* condition in both groups. In right posterior cingulate gyrus (MNI 10, −20, 30) the main effect for *'brush move'* condition was significantly positive in HC group while the main effect for *'brush rest'* condition was significantly positive in AN group. In the left middle frontal gyrus (MNI −36, 44, 8) the main effects were not significantly different from zero in both groups.

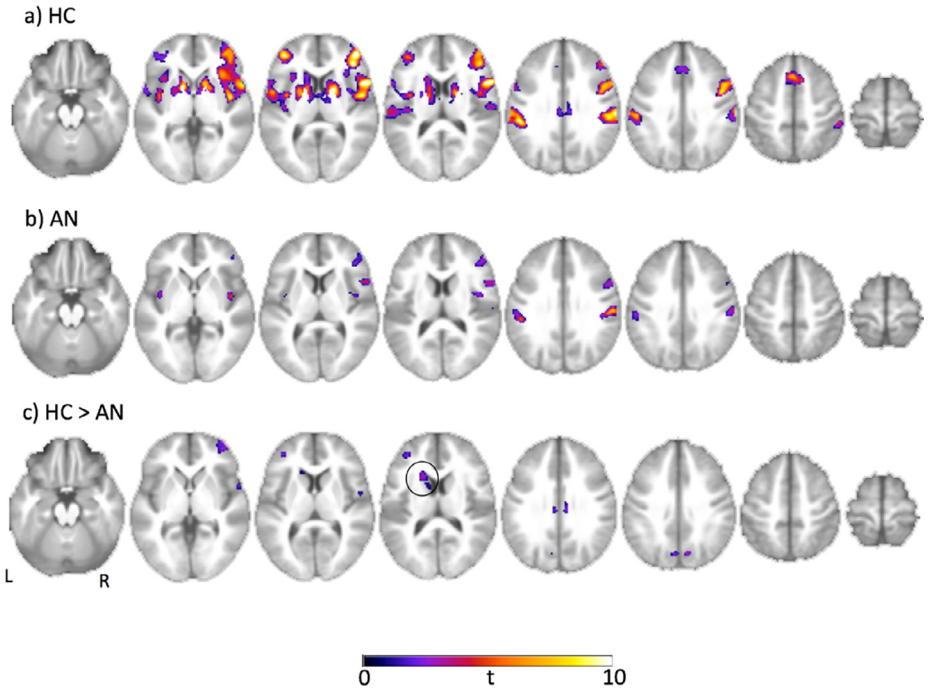

Fig. 4. Whole brain results for the contrast 'brush move > brush rest' for healthy controls (HC), anorexia nervosa patients (AN), and contrast between the two groups. All three maps were thresholded at $p < 0.001$ and cluster size >37. Images are presented at *z*: −20, −6, 0, 8, 14, 30, 36, 52, 68. In circle: left caudate nucleus (caput).

Table 3
Whole brain results for group differences for the contrast 'brush move > brush rest': *t*-values, MNI coordinates and cluster sizes (ks). Threshold: $p < 0.001$ and ks > 37.

Region	*t*-value	*x*	*y*	*Z*	ks
L caudate nucleus	4,5	−18	18	14	107
R precuneus	4,3	12	−72	36	55
R middle orbital gyrus	4,2	42	52	0	176
R posterior cingulate gyrus	4,1	10	−20	30	122
L middle frontal gyrus	4,1	−36	44	8	78
L precuneus	4,0	−4	−72	38	82
R temporal pole	3,8	58	8	0	63

We also investigated responses in the area that showed highest group difference, i.e. left caudate nucleus. Extracted values for contrast '*brush move > brush rest*' at the MNI coordinate (−18,18,14) were significantly positive in HC group (mean 0.23, SD 0.27, one-sample-*t*-test $p < 0.001$) but were not different from zero in AN group (mean −0.13, SD 0.37, one-sample-*t*-test $p = 0.09$). No significant correlations were found between the extracted values and pleasantness ratings, BMI or BDI (tested for each group separately), neither in HC nor AN group (all $p > 0.1$).

To examine effects of medication on the results in left caudate nucleus we tested separately the medicated group of AN (13 subjects) and non-medicated group of AN (12 subjects), and found no significant difference in the extracted values (two-sample *t*-test $p = 0.8$). The extracted values remained significantly different from HC group (two-sample *t*-test $p > 0.1$ for both medicated and non-medicated group).

3.2.3. Handedness

Since three HC subjects were left-handed, we used EHI values as covariates of no interest in the whole brain analyses presented above. We repeated both whole brain analyses with three left-handed subjects excluded. For the main effect of '*brush move*' we obtained significant group difference in same areas as presented in Table 2 with minor decreases in *t*-values and cluster sizes, probably due to the decrease in power. For the contrast '*brush move > brush rest*' we obtained significant group difference in same areas as presented in Table 3 with minor changes in *t*-values and cluster sizes, and in addition in an area in right thalamus (MNI 8, −14, 20; $t = 39$; ks = 53). We concluded that the main findings obtained in the analyses which included all 50 subjects were not importantly affected by the inclusion of left-handed subjects.

4. Discussion

We examined the hypotheses that AN patients perceive skin stroking as less pleasant than HC, and that insular responses to stroking are reduced in AN relative to HC. The results showed that AN patients rated skin stroking as significantly less pleasant than matched healthy participants. Contrary to the hypothesis, however, we found no significant group differences in neural response in the insular cortex, or any other region linked to somatosensory processing. Instead, a whole-brain analysis revealed significantly less activation in the AN group in left caudate nucleus, bilateral frontal pole, bilateral precuneus, and right temporal pole for the contrast between skin stroking and skin indentation, and bilateral LOC for the main effect of skin stroking.

The lack of group differences in somatosensory brain areas suggested that neural processing of tactile sensations mediated through thick, myelinated A-beta afferents are largely intact in AN. These results are consistent with (Pauls et al., 1991). We found unexpected group differences for the main effect of skin stroking between HC participants and AN patients in the LOC, an area not typically involved in tactile processing. Instead, LOC is critically involved in the processing of images of human bodies (Cazzato et al., 2014; Downing et al., 2001; Peelen and Downing, 2007) and in self-representation (Cazzato et al., 2014). Several studies of visual perception of human bodies show alterations in LOC processing in AN. For instance, responses in this area are reduced in participants with eating disorders compared to the healthy controls when watching line drawings of female bodies of different sizes (Uher et al., 2005). In addition, LOC exhibits altered functional connectivity in AN: resting state connectivity shows a disruption in the ventral visual network, which includes LOC, in AN patients (Favaro et al., 2012). We suggest that the observed LOC difference might be related to dysfunctions in the body perception network in AN.

Confirming previous results (Crucianelli et al., 2016), the AN group rated skin stroking as less pleasant. Skin stroking is an effective means

of CT stimulation which entails a strong affective component (Löken et al., 2009) whereas static skin indentation mainly activates slowly adapting A-beta mechanoreceptors important for discriminative touch (McGlone and Reilly, 2010). Thus, we predicted that the decrease in the pleasantness ratings for skin stroking could be related to altered insular processing of the input from CT afferents. The examined contrast *'brush move > brush rest'* may have revealed alterations in the processing of affective CT-mediated touch. Contrary to our hypothesis, we did not observe any significant group difference in the insular cortex for this contrast. Instead, we found the most robust group difference in the left caudate nucleus.

The caudate nucleus is a part of the striatum, a subcortical structure richly supplied by inputs from dopaminergic neurons. The ventral striatum (including nucleus accumbens) receives its main dopaminergic input from the ventral tegmental area and is a central hub in the circuit that evaluates the hedonic value of a presented stimulus (i.e. 'liking') (Berridge et al., 2010). The dorsal striatum (including the caudate nucleus) receives its main dopaminergic input from substantia nigra (Palmiter, 2007) and is a part of the larger network that shapes the response to the stimulus through learning about actions and their reward consequences (i.e. 'wanting') (Balleine et al., 2007). Together these structures have a central role in brain reward processing by linking 'liking' and 'wanting', and disturbances in this system have been associated with addiction (Hyman and Malenka, 2001), depression (Nestler and Carlezon, 2006), and eating disorders (Kaye et al., 2009; Treasure et al., 2015).

In most of the research on eating disorders, food is the primary rewarding stimulus. Animal experiments show that the 'liking' circuit generates hedonic pleasure associated with intake of food while the 'wanting' network is involved in eating behavior and motivation to eat (for review see (Berridge et al., 2010)). In food-deprived healthy subjects presentation of food stimuli increases levels of extracellular dopamine in dorsal but not ventral striatum demonstrating that dopamine in dorsal striatum is involved in food motivation in humans (Volkow et al., 2002). Crucial evidence of the importance of dorsal striatum in the development of altered eating behavior in AN comes from an fMRI experiment in which AN patients performed food-choice tasks (Foerde et al., 2015). AN patients choose high-fat food at much lower frequency than HC, and their food choice correlates with activities in dorsal striatum for AN but not for HC. This demonstrates the importance of dorsal striatum in the shaping of maladaptive eating behavior in AN. Moreover, dysfunction in the brain reward system in AN persists after recovery and spans functions that go beyond eating behavior. For example, both acute and recovered AN show altered dorsal striatal responses to reward and punishment in monetary task paradigms (Bischoff-Grethe et al., 2013; Wagner et al., 2007).

It has been recognized previously that dorsal striatum is involved in the processing of affective touch stimuli. A feedback-based tactile paradigm with different stroking velocities in which participants could choose to repeat the stroking in the previous trial or to change it shows that activation in dorsal striatum is associated with choosing to repeat trials, reflecting the role of this structure in behavioral preferences ('wanting') for pleasant stroking (Perini et al., 2015). Another experiment investigated prolonged pleasant skin stroking and showed that the activation levels in dorsal striatum correlates with the perceived pleasantness of skin stroking (Sailer et al., 2016). Further, in the present experiment, we observed significant increase in the level of activity in dorsal striatum for stroking touch in HC. The absence of this increase in AN patients could be a consequence of their general diminished response in the 'wanting' network to positively valued stimuli.

Being caressed is a basic human need. It not only brings a pleasurable feeling but can also be soothing, diminish pain, reduce anxiety, and is important in social communication and forging of social bonds (Davidovic et al., 2016; Ellingsen et al., 2013; Krahé et al., 2016; Liljencrantz et al., 2017; Mohr et al., 2017; Morrison, 2016). However, body image disturbance may lead to feelings of discomfort from social touch. We therefore speculate that the effects on the behavioral as well as brain levels may be stronger for human, instead of robotic, touch.

4.1. Limitations

Starvation, independent of what causes it, can potentially affect the brain both by decreasing the brain's mass and by affecting levels of neurotransmitters (Titova et al., 2013). The predicted direction of the effects on BOLD differs depending on the brain cells affected. Loss of glutamatergic neurons, for example, should result in reduced BOLD signal whereas loss of astrocytes responsible for clearing glutamate from synapses should lead to increased BOLD signal (Bednařík et al., 2015). In our study, however, the BOLD differences occurred relative to a control condition. Since the effects of starvation on BOLD are likely tonic in nature the control condition should 'subtract out' the malnutrition effect.

The study included medicated patients. We tested the effect of medication by comparing the activity levels in dorsal striatum between medicated and non-medicated patients and found no difference between these groups.

The prevalence of psychiatric comorbidity is usually high in individuals with AN. A shortcoming in the present study is that we did not assess comorbid psychiatric disorders and personality disorders. The study included patients with high BDI scores, and major depressive disorder is one of the most common comorbid diagnoses in AN (Godart et al., 2007; Kaye, 2008). Therefore, it could be argued that the decreased pleasantness rating for skin stroking in AN could be a consequence of anhedonia. Studies investigating anhedonia in depression, however, point to the ventral and not dorsal striatum as the critical structure (Hahn et al., 2014; Robinson et al., 2012). Importantly, we found no correlation between pleasantness ratings, levels of activity in caudate nucleus, and BDI in the AN group. Even though the confounding effects of anhedonia cannot be completely ruled out, we found group differences for touch evoked activation in the dorsal striatum suggesting that decreased pleasantness perception in AN may be a consequence of alterations in the brain's reward system.

5. Summary

AN patients had reduced tactile evoked activation when skin stroking was contrasted with static skin indentation in the caudate nucleus which might be related to their blunted affective touch perception. AN patients also had abnormal LOC response for the main effect for the skin stroking condition, which might be related to their disturbed body image perception.

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Author contributions

All authors participated in the design of the study. M Davidovic and L Karjalainen collected the data and performed scanning in the magnet camera. M Davidovic analyzed the data and drafted the article, which all authors critically reviewed. All authors approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.08.007.

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