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Neural processing of self-touch and other-touch in anorexia nervosa and autism spectrum condition

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ARTICLE INFO

Dedication: This article is dedicated to the memory of our dear colleague Per A. Gustafsson.

Keywords:
Social touch
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ABSTRACT

Introduction: The tactile sense plays a crucial role in the development and maintenance of a functional bodily self. The ability to differentiate between self- and nonself-generated touch contributes to the perception of the bodies' boundaries and more generally to self-other-distinction, both of which are thought be altered in anorexia nervosa (AN) and autism spectrum condition (AS). While it has been suggested that AN and AS are characterized by overlapping symptomatology, they might differ regarding body perception and self-other-distinction.
Methods: Participants with a diagnosis of AN (n = 25), AS (n = 29), and a comparison group without diagnoses (n = 57) performed a self-other-touch task during functional brain imaging. In the experimental conditions, they stroked their own arm or were stroked on the arm by an experimenter.
Results: As shown previously, the CG group showed lower activation or deactivation in response to self-touch compared to social touch from someone else. A main group effect was found in areas including somatosensory cortex, frontal and temporal gyri, insula, and subcortical regions. This was driven by increased activations in participants with AN, while participants in the AS group showed mostly comparable activations to the comparison group.
Conclusions: AN diagnosis was associated with an increased neural activity in response to both self-touch and social touch. Failure to attenuate self-touch might relate to altered predictions regarding the own body and reduced perception of bodily boundaries. Participants with an AS diagnosis were mostly comparable to the comparison group, potentially indicating unaltered tactile self-other-distinction.

1. Introduction

Self-other-distinction is a key contributor to the perception of our own body. The ability to distinguish self-evoked sensations and perceptual outcomes arising due to the activity of other actors is also the foundation of any social interaction. Learning to differentiate self and non-self begins, reflex-based, already in-utero - with fetuses pulling away from tactile stimuli (Hepper, 2015) and orienting movements to touch their own body and others (the wall of the womb or a potential twin) (Castiello et al., 2010). Tactile cues appear to be especially salient early in development (Cascio et al., 2018; Della Longa et al., 2020; McGlone et al., 2014a), and interpersonal touch remains important for the social and bodily self throughout adulthood (Castiello et al., 2010; McIntyre et al., 2019; Schütz-Bosbach et al., 2009). The perception and processing of somatosensory stimuli depend on the current state of the neural and physiological system – e.g. detection of tactile stimuli depends on heartbeat cycle phase (Motyka et al., 2019) –, but can also in turn affect the processing of sensory inputs arising from other sensory modalities (Pleger and Villringer, 2013). The contribution of social touch and self-touch to the bodily self is especially interesting (Boehme and Olausson, 2022), since touch is a sense integrating exteroceptive and interoceptive components (Park and Blanke, 2019): when someone

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touches me, I simultaneously perceive the other person and my own body.

To focus on behaviorally relevant sensations, it has been suggested that the brain attenuates self-generated percepts as they are highly predictable (Boehme et al., 2019). This might be accomplished by an efference copy, which enables the prediction of the somatosensory outcomes of one's own action (Blakemore et al., 1998; Kilteni et al., 2020; Weiskrantz et al., 1971). In short, the original model suggest that a copy of the motor signal (the efference copy) is produced simultaneously with the motor output signal, and is used to predict the evoked sensations related to the action (Von Helmholtz, 1867). If the actual outcomes match the prediction, the perception is attenuated. If the sensation does not match the prediction, a prediction error occurs. The modern elaboration of this model states that the brain always tries to minimize surprise (Friston, 2010). This can be achieved by either integrating prediction errors to optimize future predictions or by altering actions in order to match the prediction more closely (Adams et al., 2015).

The Bayesian brain hypothesis account suggests that the brain combines prior expectations and actual sensory evidence to estimate the cause of an incoming signals. This implies that a highly predictable stimulus could lead to a sharpened sensation (De Lange et al., 2018; Friston, 2012). This would explain studies showing an increase in detection of expected stimuli (Thomas et al., 2022; Yon et al., 2020). The observed reduction in signal during functional imaging of self-produced percepts could within this framework be the consequence of a sharpened signal and lateral inhibition of competing signals derived from noisy sensory input (Yon et al., 2020). However, on the behavioral level, attenuation of self-produced touch has been demonstrated repeatedly using psychophysics (Kilteni and Ehrsson, 2017; Kilteni et al., 2020). The exact mechanism underlying this attenuation continues to be debated. One account suggest that a shift in baseline due to pre-activation could reduce the detectability of the self-produced sensation (instead of a subtraction or inhibition of the incoming sensations), but preserve an advantage of neural processing of self-produced stimuli if no detection is necessary (Roussel et al., 2013). This explanation would also be in line with the hypothesis that self-touch has the function of self-evidencing through continued prediction error minimization of the self-model (Perrykkad and Hohwy, 2020).

A computational simulation has recently suggested that sensory attenuation of self-produced stimuli might be a learned outcome in a system that is based on free-energy-minimization (i.e. aims to reduce surprise) (Idei et al., 2022). This might be the case for human development as well. As a consequence, altered learning of sensorimotor contingencies during development might affect self-touch-attenuation. Such alterations in somatosensory functioning might be associated with alterations in self-related processes in the broader sense (Cascio, 2010) - which are known to play a role in several psychiatric conditions, including autism spectrum condition (AS, (Lombardo et al., 2011; Lombardo et al., 2009)) and anorexia nervosa (AN, (Strober, 1991)).

Both, people with AS and with AN, show alterations in the domains of social functioning (Frost-Karlsson et al., 2019; Rosenblau et al., 2021; Watson et al., 2010), perceptions of the own body (Legrand, 2010b; Mul et al., 2019a; Tordjman et al., 2019), and somatosensory processing (Cascio, 2010; Crucianelli et al., 2016a; Keizer et al., 2012; Zucker et al., 2013). The overlap in symptomatology between these two diagnoses led to the suggestion that they might be two facets of the same underlying alterations (Anckarsater et al., 2012; Baron-Cohen et al., 2013; Brede et al., 2020; Gillberg, 1985; Karjalainen et al., 2018; Kasperek-Zimowska et al., 2016; Kerr-Gaffney et al., 2021; Odent, 2010; Oldershaw et al., 2011; Westwood et al., 2016) – a hypothesis that was already brought up in the 1980's (Gillberg, 1985) and has, in the light of the dimensional approach to psychiatric research, gained attention again (Boltri and Sapuppo, 2021). Indeed, co-occurrence of the two diagnoses is not uncommon (Karjalainen et al., 2016): compared to only 1 % in the general population, between 20 and 35 % of those with AN also meet diagnostic criteria for AS (Brede et al., 2020).

With regard to the bodily self and social function, the processing of social affective touch is of special interest (McGlone et al., 2014b). Affective interpersonal touch is one of the earliest human experiences that evokes self-other-distinction, a perception of the own body's boundaries, and a basic form of social interaction (Boehme and Olausson, 2022; Cascio et al., 2019). While research on social touch in AS is limited, functional and anatomical anomalies have been described in the posterior superior temporal sulcus (pSTS), which is known to be involved in social processing (Kaiser et al., 2015; Perini et al., 2021). Behavioral measures indicate that adults with autism experience affective touch as pleasant, similar to adults without autism (Kaiser et al., 2015). However, the amount of autistic traits both in people with and without a psychiatric diagnosis, relates to altered pleasantness perception of affective touch (Croy et al., 2016). Further evidence showing altered tactile processing comes mainly from clinical and parental observations, while experimental data reports heterogenous findings of both hyper- and hypo-sensitivity (Baron-Cohen et al., 2009).

Regarding AN, reviews of somatosensory processing report alterations in every sensory domain of body perception - including impairments in tactile perception (Gaudio et al., 2014), in interoception (i.e. the sense of signals from within the body; (Kaye et al., 2013)), and in their integration (Teaford et al., 2021). Subjective reports and experimental measures indicate a hypersensitivity to touch which correlates with body image disturbance (Zucker et al., 2013). Those with a current diagnosis of AN (Crucianelli et al., 2016b) perceive affective touch as less pleasant compared to women without an eating disorder. Davidovic et al. (2018) found this lower touch hedonia to be related to decreased activation of the striatum, while somatosensory activation was comparable across groups, which points to an impaired reward pathway. Results regarding those in remission are ambiguous (Bischoff-Grethe et al., 2018; Crucianelli et al., 2021).

Not all theoretical constructs overlap between AN and AS. Accounts based on predictive processing have made some specific, differential suggestions regarding AN and AS, which will be described in the following. AS has been suggested to be associated with an imbalance between prior believes and the precision weighing sensory inputs – favoring sensory evidence over higher-level predictions and potentially resulting in a failure to contextualize sensory percepts (Lawson et al., 2014). The initial consequence would be less attenuation of self-produced sensations. While there is some evidence for this from a task using prediction of external stimuli (mismatch negativity; (Gomot et al., 2011)), a recent study has not found experimental support for a generalized alteration in predictive processing of self-produced sensory inputs in AS (Finnemann et al., 2021). There might be differences in the processing of internal and external inputs that need to be accounted for (DuBois et al., 2016): people with AS pay more attention to internal signals (Garfinkel et al., 2016; Schauder et al., 2015), but detect them with reduced accuracy. Furthermore, the dynamic aspect of predictive models needs to be considered: in adults, high levels of sensory precision throughout the development might eventually (with intact model updating) yield highly accurate model predictions for highly predictable sensory inputs like self-touch, leading to a reduction in prediction errors. Self-touch would then be associated with a highly precise attenuation of the expected sensory outcome. The consequence would be that self-touch would be processed differently from the less predictable touch by others. It has been theorized that people with AS accumulate uncertainty estimations faster (Lawson et al., 2014). This could be an explanation for higher levels of self-stimulation in AS: self-touch could contribute to uncertainty reduction through self-evidencing (Perrykkad and Hohwy, 2020).

For AN, the opposite model has been hypothesized: high precision beliefs about the own body associated with noisy sensory input could lead to a stronger reliance on priors than on sensory evidence. In this case, the brain would try to attenuate the sensory outcomes of self-produced sensations, but based on incorrect predictions (i.e. the non-veridical representation of the own body) - leading to larger

prediction error during self-produced tactile sensations, rendering them more similar to other-produced inputs. In this model, starvation could be understood as an adaptive response to increase interoceptive certainty, when noisy interoceptive signals lead to an incoherent bodily self perception (Barca and Pezzulo, 2020). Similarly, other accounts suggest a lack of integration of interoceptive and exteroceptive signals in AN (Herbert and Pollatos, 2018), which might lead to an allocentric lock state, where the body memory is not updated according to novel (sensory) evidence on the veridical shape of the body (Gadsby and Hohwy, 2019; Riva and Gaudio, 2018). It remains unclear whether poor multisensory integration with the patients' subjective body experience (Legrand, 2010a) can be understood as a causal link as it might as well be a consequence of altered physiology due to starvation (Riva, 2016).

In line with the theoretical accounts and based on symptomatology and experimental observations, a reduced self-other-differentiation has been suggested for AN (Legrand, 2010b; Moncrieff-Boyd et al., 2014; Sugarman et al., 1982), while a sharper self-other-distinction has been hypothesized in AS (Bird et al., 2014; de Guzman et al., 2016; Mul et al., 2019a; Noel et al., 2017). Such a difference between the two groups might specifically explain different observations regarding the bodily self: bodily self-boundaries might be reduced in AN while increased in AS. Experimentally, people with AN demonstrate disturbances in interoception (Bischoff-Grethe et al., 2018; Pollatos et al., 2008) and the sense of body ownership, experiencing more negative self-schemas (Amianto et al., 2016) and overestimating their body size (Dalhoff et al., 2019). Additionally, people with AN more readily incorporate alien body parts into their body schema (e.g., rubber hand illusion (RHI, (Costantini and Haggard, 2007)), simply by looking at them (Keizer et al., 2014), while autistic people are less susceptible to this illusion (Cascio et al., 2012b; Mul et al., 2019a; Paton et al., 2012). Autistic individuals have shown a sharper self-other boundary and perception of a smaller peripersonal space (Cascio et al., 2012a; Mul et al., 2019b; Noel et al., 2017), which could relate to the observed sensory hyperresponsiveness (Boehme et al., 2020; Riquelme et al., 2016; Tomchek and Dunn, 2007).

While there are repeated suggestions of an overlap or even a functional connection between AN and AS, research comparing these two conditions is lacking. We therefore aimed to explore potential similarities and differences between AN and AS in relation to a domain where we had opposing hypotheses for two groups based on previous research and known functional alterations: self-generated touch and social touch, i.e. affective skin-to-skin touch by another person. We obtained neural correlates of self-touch and other-touch from separate groups of young adults with AN and AS and matched comparison groups (CG) with no known psychiatric diagnoses. We hypothesized to find altered touch processing in both clinical groups. We expected a reduced difference between self- and other-touch in AN (reduced deactivation during self-touch and reduced activation during other-touch) and a clearer difference between self- and other-touch in AS (stronger deactivation during self-touch and stronger activation during other-touch; (Boehme et al., 2019; Boehme et al., 2020)). While we had no clear hypotheses about which regions would show a difference between groups, we expected to find differential activations for self-touch and social touch in regions previously shown to be involved including somatosensory cortex, insula, superior temporal gyrus and sulcus (Boehme et al., 2019).

2. Methods

2.1. Participants

Adults (ages 18–35) with a diagnosis of AN or AS and age- and gender-matched comparison groups (CG) of adults with no psychiatric diagnosis were recruited (see details below). The study was approved by the regional ethics board in Linköping (2017/443-31, 2018/444-32, 2019-02821, 2016/360-31). Participants provided written informed consent and completed the Autism Quotient questionnaire (AQ) regarding autistic traits (Baron-Cohen et al., 2001b) and Social Touch Questionnaire (STQ) regarding daily life social touch behaviors (Wilhelm et al., 2001). Participants were informed that they could end their participation at any time without giving any further explanation. Participants received monetary compensation. Demographics are presented in Table 1.

2.1.1. Recruitment and inclusion- AN

Individuals with AN were recruited via the eating-disorder subunit of the specialist services at the Child and Adolescent Psychiatric Clinic (18–24 years) and the Psychiatric clinic (25–25 years) at the University Hospital in the Region of Östergötland. Potential participants were informed about the study by clinical staff. Those interested were contacted by a research nurse who was not involved in the person's treatment, who gave oral and written information about the study, and obtained the written consent.

Inclusion criteria were: DSM-5 diagnosis of anorexia nervosa or atypical anorexia nervosa (restrictive type), at least 18 years of age, BMI $\leq$ 20 kg/m2, and MRI-compatibility. Participants were either free of psychotropic medications or on stable (at least three months on the same dose) medication with antidepressants. On-demand use of mild anxiolytics and hypnotics, treatment with central stimulants (if avoided on MRI day) were also accepted. Further, inclusion depended on the judgement of the physician. Exclusion criteria for the current study were: schizophrenia or psychotic disorder, AS diagnosis, bipolar disorder, alcohol/drug use disorder, ongoing treatment with antipsychotics or tricyclic antidepressants, previous severe head injury, birth before 33 weeks of gestation, hearing impairment, earlier epilepsy or seizure (other than febrile seizures in childhood), claustrophobia, pregnancy, and cognitive disabilities. Twenty-eight participants were recruited, three had to be excluded for AS diagnoses that became apparent only after inclusion. Twenty-five participants were included in the analysis for the AN group.

2.1.2. Recruitment and inclusion- AS

AS were recruited via the Psychiatric clinic in Linköping, Region Östergötland, flyers and online advertisement. People interested in the study were contacted for a phone screening regarding inclusion and exclusion criteria. The phone screening was a standardized interview based of the Modified Mini Screen interview (MMS) (Alexander et al., 2008). Inclusion criteria were: diagnosis of AS, ability to understand verbal and written Swedish and give informed consent, willingness to undergo MRI scanning and to receive skin-to-skin touch on the arm. Diagnosis of AS was ascertained from medical records. Exclusion criteria included co-occurring psychiatric conditions such as but not restricted to attention deficit hyperactivity disorder, severe depression, anxiety, psychotic or bipolar disorder, obsessive compulsive disorder, substance use disorder (regular consumption of any drug/5 or more alcoholic

Table 1
Study population demographics and participants' response to the social touch questionnaire (STQ) and the autism spectrum quotient (AQ).

	AS	CG(AS)	AN	CG(AN)
	N = 29	N = 30	N = 25	N = 27
Sex				
Female	18	17	25	27
Male	11	13	0	0
Age	24.1 (5.3)	24.1 (3.5)	21.3 (2.6)	22.5 (2.3)
BMI	23.85 (5)	23.22 (3)	19.31 (1.3)	21.8 (2.5)
STQ	43.9 (11.0)	22.5 (10.3)	36.9 (14.5)	26.4 (15.7)
AQ	30.5 (9.3)	10.7 (5.9)	17.4 (9.4)	11.9 (8.7)

AS: autism spectrum condition; AN: anorexia nervosa; CG: comparison group. BMI: body mass index, STQ: social touch questionnaire; AQ: autism quotient questionnaire.
Data are presented as mean (SD) for continuous measures, and n for categorical measures.

drinks per week), chronic pain or any other health problems related to touch perception and MRI safety. Prospective participants were also asked questions related to disordered eating and evaluated for exclusion on a case-by-case basis. Medical records were checked for comorbidities. Participants with mild to moderate anxiety disorder or depressive disorder unmedicated or on stable medication (see above) were not excluded. Thirty-two participants were recruited for the AS group. One did not show up to the session, one dropped out when placed in the MRI, and one was excluded due to additional diagnoses that became apparent later. In total, data from 29 participants was used in the analysis. Two of these 29 had missing data from the questionnaires.

2.1.3. Recruitment and inclusion- CG

The study was advertised through posters and through social media (Facebook). Those interested were contacted for a standardized phone screening based on the MMS (Alexander et al., 2008) regarding inclusion and exclusion criteria. Two groups were recruited to match the AS and AN groups with regard to age and gender. Inclusion criteria were: ability to understand verbal and written Swedish, willingness to undergo MRI scanning and to receive skin-to-skin touch on the arm. Exclusion criteria for CG included any psychiatric diagnosis or medication, disordered eating, excessive substance use (regular consumption of any drug/5 or more alcoholic drinks per week during the past 6 months), and chronic pain or any health problems related to touch perception or MRI safety. In total, 57 participants were included (30 in the CG group matched to AS ad 27 in the CG group matched to AN). Two of these 57 had missing data from the STQ questionnaire.

2.2. Touch task

Participants performed a social touch task where they were gently stroked on the arm by a female researcher or touched their own arm in the same manner (Boehme et al., 2019; Boehme et al., 2020). Before entering the MRI scanner, participants were introduced to the task structure and the type of touch, and trained how to stroke their own arm in a slow, affective manner, known to target the C-tactile receptor system (Olausson et al., 2010). In the MRI scanner, participants lay with their left arm across their abdomen and a weighted pillow next to the left arm. The right arm was propped up with pillows and rested on a pillow to require as little movement as possible between stroking conditions. Participants were instructed to only touch the left arm when prompted to do so. Goggles displayed instructions for the different conditions. The three conditions were: 1. Other-touch, in which a trained female researcher slowly stroked the participant's left arm; 2. Self-touch, in which the participant slowly stroked their left arm using their right hand; and 3. Object-touch, in which the participant slowly stroked the pillow using the right hand (non-social control condition). Instructions appeared in white on the goggles screen for three seconds before turning green for twelve seconds, and participants were instructed to perform the condition while the text was green. The texts (in Swedish) read: "Passive, the researcher will stroke your arm"; "Active, stroke your arm"; "Active, stroke the object". Each condition was repeated a total of ten times and lasted twelve seconds, with twelve seconds of rest in between. The trials were performed in randomized order. The task and analysis files for subsequent analysis of the fMRI data (described below) is available here: osf.io/rfy3g. Behavioral and MRI data cannot be made publicly available because participants did not give consent.

2.3. fMRI data collection and preprocessing

A 3.0 Tesla scanner (Prisma; Siemens) with a 64-channel head coil was used to acquire T1-weighted anatomical images (repetition time = 2300 ms; echo time = 2.36 ms; flip angle = 8°; field of view = 288 × 288 mm^2; voxel resolution = 0.87 × 0.87 × 0.90 mm^3) and T2-weighted echo-planar images (EPIs) containing 48 multiband slices (repetition time: 1030 ms; echo time: 30 ms; slice thickness: 3 mm; matrix size: 64 × 64; field of view: 192 × 192 mm^2; in-plane voxel resolution: 3 mm^2; flip angle: 63°). Statistical parametric mapping (SPM12; Wellcome Department of Imaging Neuroscience) in Matlab R2018b (MathWorks) was used to analyze fMRI data. Preprocessing steps included: Correction for motion using SPM's realign-module registering to the mean *EPI* after a first realignment (quality = 0.9, separation = 4, smoothing = 5 full width at half-maximum kernel, interpolation with 4th degree B-Spline), coregistration of the anatomical image and mean *EPI* using normalized mutual information, segmentation of the T1 image using the unified segmentation approach (Ashburner and Friston, 2005), and spatial normalization of T1 and EPIs to the Montreal Neurological Institute T1 template (using forward deformations from the segmentation step, voxel size 2*2*2 for resampling, and 4th Degree B-Spline for interpolation). All functional images were spatially smoothed with an isotropic Gaussian kernel of 6-mm full width at half-maximum.

2.4. Statistical analysis

The general linear model approach was used for analysis of the blood oxygen level dependent (BOLD) response in SPM12. We used the FAST-option (Corbin et al., 2018) due to the short TR; this improves autocorrelation modeling performance (Olszowy et al., 2019). We convolved the hemodynamic response function with the self-, other-, and object-touch conditions. Regressors of no interest modelled the cue phase and the motion after the active conditions (one second when participants moved their right arm back into a resting position). Realignment parameters were added as regressors-of-no-interest to account for variance due to movement. In addition, the first temporal derivative of motion parameters in x,y,z-directions and a regressor censoring volumes with >1 mm volume-to-volume movement (Boehme et al., 2017) were added to the model, to account for the potential of increased movement. Comparison of movement parameters during the three touch-conditions revealed a difference in movement between conditions ($F = 5.2$, $p = 0.006$). There was no difference between groups ($F = 0.27$, $p = 0.76$). The condition effect was driven by the self-touch condition, where movement was lowest compared to the other conditions (mean + -SD [mm]: self = 0.02 + −0.6. object = 0.07 + −0.6, other = 0.08 + −1). However, this calculation included scan-to-scan movements >1 mm which were censored. When excluding these movements, there was no difference between conditions ($F = 0.96$, $p = 0.35$). First-level contrasts of interest were [other-touch – baseline] (referred to as "other-touch" in the following) and [self-touch – object] (in order to control for movement-related activations and activations due to somatosensory input to the touching hand) as well as [self-touch – baseline] (referred to as "self-touch") for replication of our previous analysis. First, using paired t-test, we compared other-touch and self-touch in CG to see if we would replicate our previous findings (Boehme et al., 2019; Boehme et al., 2020). Then, a flexible factorial ANOVA with group as between subject factor (AN, AS, CG) and condition ([other-touch – baseline] and [self-touch – object touch]) as within subject factor was used to test for a main group effect and a group X condition interaction (Gläscher and Gitelman, 2008). We were also interested in the main group effects during other-touch and during [self-touch – object-touch] separately. Family-wise-error (FWE) correction at the voxel level was used to correct for multiple comparisons at the whole-brain level. A minimum clustersize of 10 voxels was applied. For *post-hoc* analyses, groups were compared first with F-test over both conditions, and if there was a difference, then with a T-test per condition (FWE-corrected at the voxel level for the whole brain). Since our samples were unbalanced with regard to the sex of participants (AS contained males, AN did not), we re-ran the analysis with females only in order to test whether observed effects survived or were still present at a more lenient threshold of $p < 0.001$ uncorrected with the same directionality (see supplementary results and Supplementary Table S3). For further statistics, SPSS (IBM Inc.) was used. For graphics, MRIcron was

used.

3. Results

3.1. Demographics and questionnaires

AN and AS did not differ from their respective CG samples regarding age (AN/CG: p = 0.097, AS/CG: p = 0.98, Table 1) and sex (AN/CG: all female, AS/CG: chi-square = 0.18, p = 0.67). They did differ significantly regarding AQ and STQ scores (AN/CG AQ: Mann-Whitney U test Z = −2.1 p = 0.032, STQ: Z = −2.6, p = 0.009; AS/CG AQ: Z = −5.4, p < 0.001, STQ: Z = −5.2, p < 0.001), with AS reporting the highest AQ score, AN intermediate values, and CG the lowest scores (Table 1).

3.2. Self- and Other-Touch related brain activity

First, we compared self-touch and other-touch across all CG, which replicated our previous findings in neurotypical volunteers of a difference in the processing of self- and other-touch in a widespread network of brain regions, including temporal areas, amygdala, and cerebellum (Supplementary Table S1). This difference was driven in part by activations during other-touch and in part by deactivations during self-touch (Fig. 1).

3.3. Main group effect

We compared AN, AS, and CG at the whole brain level including object-touch as a control for potential motor system related differences between groups (Fig. 2). We found a main effect of group in areas including somatosensory cortex, middle and posterior superior temporal sulcus (pSTS), cingulate, and insula (Table 2, Fig. 3 top). There was a group X condition interaction in the claustrum ([24 26 6], F = 16.17, p (FWE-corrected for the whole brain) = 0.028).

When testing the touch-conditions separately, there was a main group effect during other-touch in right somatosensory cortex (S1, [24 −36 58], F = 28.98, clustersize = 41, p(FWE-corrected for the whole brain) <0.001) and in right pSTS ([52 −44 4], F = 28.98, clustersize = 17, p(FWE-corrected for the whole brain) <0.001, Fig. 3 bottom). For the [self-touch - object-touch] condition, there was a main group effect in the claustrum ([24 26 6], F = 33.32, clustersize = 96, p (FWE-corrected for the whole brain) <0.001, Fig. 3 bottom), in the middle temporal gyrus ([58 −40 −10], F = 28.01, clustersize = 140, p (FWE-corrected for the whole brain) <0.001), in the cingulate gyrus ([18 8 42], F = 24.67, clustersize = 121, p(FWE-corrected for the whole brain) <0.001), and further temporal and frontal areas (Table 3, Fig. 3 bottom).

Post-hoc group comparisons were run in order to understand which between-group-effects were driving the main group effects identified at the whole brain level. Using F-test over both conditions revealed a difference between AN and CG, and AN and AS, but not between AS and CG. Therefore, AN was compared to the other groups per condition using T-tests. These *post-hoc* comparisons revealed that higher activations in AN both during self-touch and during other-touch were the main driver (Supplementary Table S2, Fig. 4). Except for a very small cluster in the occipital lobe (for CG > AN, other-touch), there was no region that showed higher activation for CG or AS compared to AN. For self-touch, a significant difference for AN > CG was obtained in the claustrum, cingulate cortex, frontal and temporal areas, S1, striatum, insula, and parahippocampal gyrus. Compared to AS, AN showed higher activity in parahippocampal gyrus, superior and middle temporal gyrus, middle frontal gyrus, cingulate, insula, and putamen. For other-touch, significant differences in S1 and superior temporal gyrus were found for AN > CG and for AN > AS.

4. Discussion

We compared brain activation during both self-touch and social touch between AN, AS, and matched comparison participants with no documented psychiatric or medical conditions. We found main group effects in areas including S1, temporal and frontal gyri, insula, and subcortical areas. This was driven by the AN group showing greater activation than CG in S1 and in pSTS for other-touch condition, and more activation in the claustrum during self-touch. However, against our hypothesis, we did not find support for a reduced self-other-difference in AN. We also did not find strong support for the hypothesis of altered processing of social or self-touch in AS.

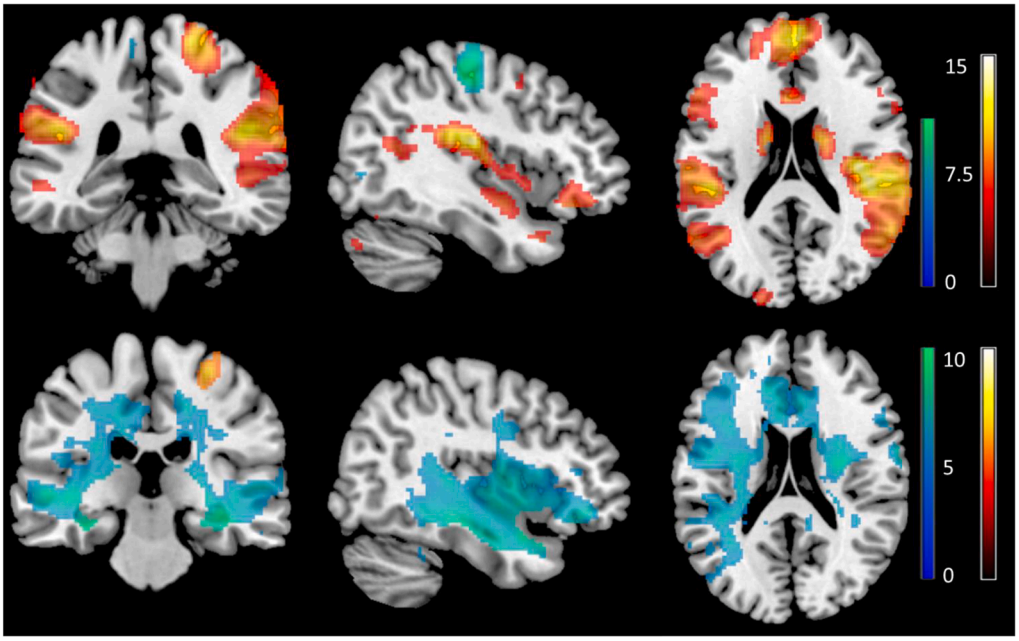

Fig. 1. Activations (red-yellow) and deactivation (blue-green) during other-touch (top row, [40 −35 20]) and [self-touch – object-touch] (bottom row, [40–25 20]) in CG, one sample t-test maps displayed at p(FWE-corrected) <0.05, colorbar displays t-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

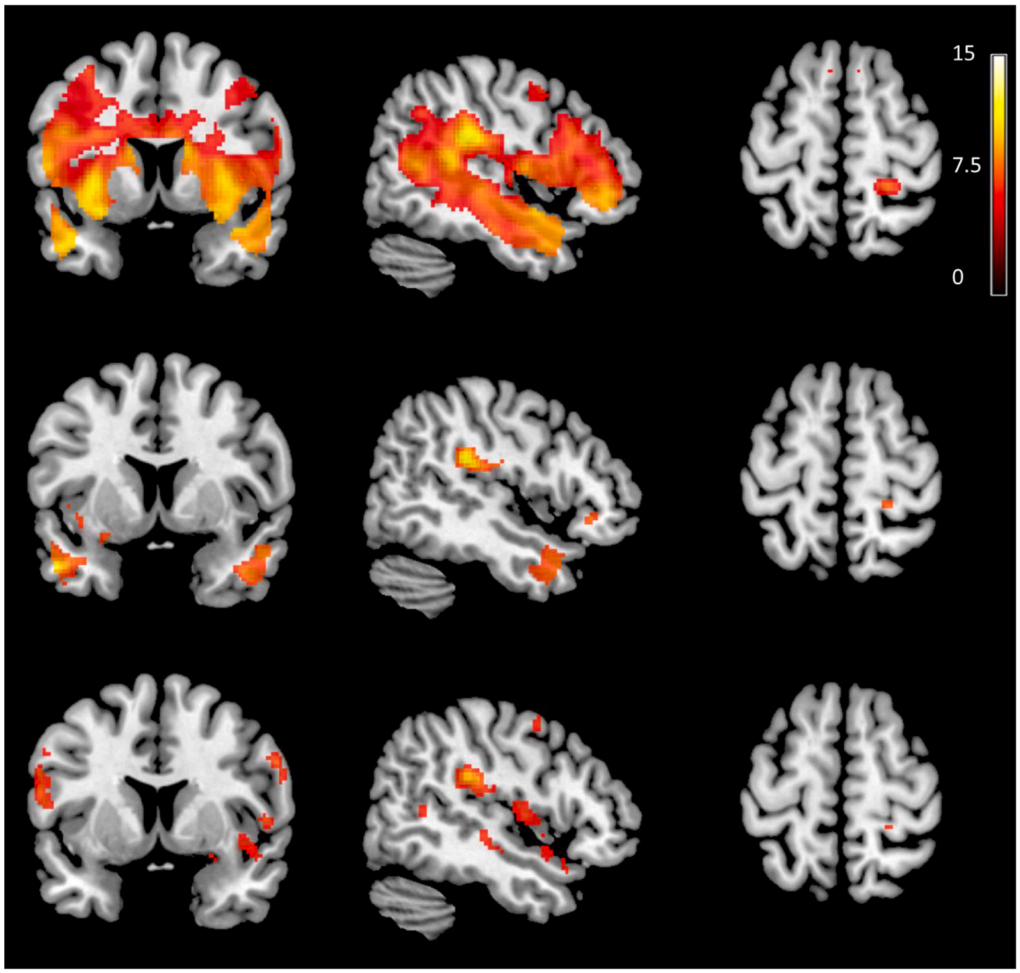

Fig. 2. Areas showing more activation during other-touch than during [self-touch – object-touch] in CG (top), AN (middle), and AS (bottom), paired t-test maps displayed at p(FWE-corrected) <0.05, clustersize >10 voxels, [47 0 56], colorbar displays t-values.

Previous studies found that women with AN rated affective touch delivered by a brush as less pleasant than CG (Crucianelli et al., 2021), and that this type of tactile stimulation evoked reduced activation in AN in the striatum (Davidovic et al., 2018). A higher activation in response to brush-delivered affective touch has previously been shown in women remitted from AN in the insula (Bischoff-Grethe et al., 2018). In our study, which employed skin-to-skin human touch, we found a higher response to touch by others in S1 and in pSTS. The pSTS is implicated in diverse, multimodal social processes including affective touch processing (Beauchamp, 2005; Voos et al., 2012), where its activity has been shown to relate to perceived pleasantness of affective touch (Davidovic et al., 2016). Anatomical differences have been found in pSTS in both AN and AS compared to neurotypical samples (Björnsdotter et al., 2018; Hadjikhani et al., 2006; Pelphrey and Carter, 2008).

AS showed brain activation similar to CG, which is in line with previous findings indicating that adults with and without autism experience touch as equally pleasant (Cascio et al., 2008; Kaiser et al., 2015). We expected to find an even sharper self-other-distinction (stronger deactivation during self-touch and stronger activations during other-touch (Boehme et al., 2020)), which was not supported by our results. These findings also contradict previous studies showing anatomical and functional differences in touch processing in AS compared to controls without autism (Kaiser et al., 2015; Perini et al., 2021). These previous studies used samples consisting of (mainly male) adolescents, and used brushing to deliver affective touch, whereas our sample contained adults who were mostly female and used a skin-to-skin touch paradigm. If the mode of touch delivery or potential sex differences can account for the different results remains to be elucidated. Regarding attenuation of self-produced touch, other studies have also reported no difference between AS and CG participants (Blakemore et al., 2006; Finnemann et al., 2021).

AN and AS participants scored similarly on STQ, and these scores were significantly higher than in CG participants, indicating that both AN and AS experience more aversions to social touch in daily life. Regarding AQ, all three groups were different from one another, with AS reporting most autistic traits and CG reporting lowest levels of autistic traits. As expected, mean AQ scores were significantly higher in the AS sample, well above the cut-off level of 26, but slightly lower than 32 points earlier described in clinical samples (Baron-Cohen et al., 2001a). Both the AN and the CG participants had mean scores indicating no or very low probability of autism in these groups (Ruzich et al., 2015). AN scores were slightly above the population average around 15 (Ruzich et al., 2015), CG scores were lower, possibly due to our sample excluding individuals with autism as well as any mental disorder and including more women, who tend to have lower average AQ scores compared to men (Baron-Cohen et al., 2001a). These behavioral findings are unsurprising and replicate both clinical observations and experimental findings from previous studies.

While AN is a well-defined diagnosis, AS covers a complex and heterogenous group of people with varying symptomatology and functioning, and both clinical and experimental documentation on brain differences is ambiguous. Our findings seem to further support this idea, as the AS group showed behaviorally significant differences from CG on both autistic trait and social touch sensitivity questionnaires, but there were no obvious differences in brain activation.

Table 2
Main group effect over both touch-conditions, clustersize (k) >10 in voxels, FWE-corrected for the whole brain at the voxel level. Peak coordinates of local maxima identified by SPM with a minimum distance of 8 mm within a cluster, sorted by clusters and effect strength, then by identified regions within these clusters.

k	Region		X	Y	Z	F	p(FWE-corr)
279	Postcentral Gyrus	R	24	−36	58	66.60	<0.001
2175	Superior Temporal Gyrus	R	52	−44	2	49.74	<0.001
			66	−18	6	35.80	<0.001
			54	−36	12	33.97	<0.001
			56	−18	2	33.09	<0.001
			58	−14	0	31.28	<0.001
			42	−58	12	28.06	<0.001
	Posterior Cingulate	R	24	−66	6	42.98	<0.001
	Parahippocampal Gyrus	R	26	−48	4	34.78	<0.001
			44	−32	−10	27.82	<0.001
	Insula	R	48	−14	20	31.95	<0.001
			40	−28	14	26.81	<0.001
	Postcentral Gyrus	R	66	−8	20	30.61	<0.001
	Inferior Parietal Lobule	R	56	−34	28	29.27	<0.001
			62	−28	34	27.35	<0.001
	Lingual Gyrus	R	16	−80	4	27.50	<0.001
			18	−46	−2	27.11	<0.001
434	Middle Frontal Gyrus	R	44	0	44	42.18	<0.001
			40	0	60	17.56	0.0109
	Precentral Gyrus	R	46	−6	54	35.53	<0.001
			40	−12	44	25.73	0.0001
120	Insula	R	44	12	18	41.68	<0.001
640	Putamen	R	30	−4	−8	36.19	<0.001
			24	−8	8	24.62	0.0001
			32	−18	−2	23.65	0.0002
			28	−18	6	23.34	0.0003
			34	−20	−6	21.17	0.0010
	Superior Temporal Gyrus	R	46	16	−16	26.34	<0.001
			52	4	−6	21.46	0.0008
			56	10	−8	21.03	0.0011
			54	14	−14	17.22	0.0137
	Amygdala	R	26	0	−14	25.88	0.0001
	Claustrum	R	34	2	−4	20.69	0.0014
			36	−12	−8	19.58	0.0029
	Insula	R	40	2	−6	17.84	0.0090
195	Postcentral Gyrus	L	−22	−38	56	34.53	<0.001
			−32	−40	64	18.88	0.0045
			−20	−40	66	17.66	0.0102
	Paracentral Lobule	L	−20	−42	58	30.99	<0.001
463	Cingulate Gyrus	R	18	8	42	32.19	<0.001
			18	2	50	31.20	<0.001
			14	10	44	25.10	0.0001
			8	8	38	19.16	0.0038
			18	16	32	18.07	0.0078
			16	14	36	17.96	0.0083
	Medial Frontal Gyrus	R	14	14	46	26.98	<0.001
			16	−10	56	23.09	0.0003
			14	8	58	16.77	0.0185
	Superior Frontal Gyrus	R	18	−6	70	22.44	0.0004
	Middle Frontal Gyrus	R	22	−4	66	21.82	0.0007
241	Cingulate Gyrus	L	−10	−4	50	29.80	<0.001
			−12	8	46	19.44	0.0031
	Medial Frontal Gyrus	L	−8	−12	52	21.58	0.0008
			−10	0	62	20.18	0.0019
			−12	−4	60	19.18	0.0037
82	Superior Temporal Gyrus	L	−52	−62	16	26.79	<0.001
87	Caudate	R	22	−10	20	26.19	<0.001
			20	−16	20	20.77	0.0013
	Putamen	R	26	4	20	18.68	0.0052
	Claustrum	R	30	−2	24	17.88	0.0088
	Thalamus	R	24	−18	20	17.27	0.0132
44	Cingulate Gyrus	L	−20	−18	44	23.89	0.0002
	Paracentral Lobule	L	−8	−22	48	15.77	0.0358
23	Inferior Frontal Gyrus	R	58	26	18	23.49	0.0002
23	Superior Temporal Gyrus	L	−50	−8	6	23.26	0.0003
68	Parahippocampal Gyrus	L	−28	−60	4	23.01	0.0003
18	Middle Temporal Gyrus	R	60	−40	−8	22.33	0.0005
12	Inferior Frontal Gyrus	R	50	44	8	21.98	0.0006
27	Middle Frontal Gyrus	L	−20	−20	62	21.64	0.0008
57	Precuneus	R	20	−52	48	21.41	0.0009
11	Precentral Gyrus	L	−60	−12	32	21.08	0.0011
19	Medial Frontal Gyrus	R	6	−12	68	21.00	0.0011
22	Precentral Gyrus	R	60	−8	36	20.93	0.0012
14	Precentral Gyrus	R	30	−16	60	20.67	0.0014
15	Cingulate Gyrus	L	−16	16	34	20.65	0.0014
26	Thalamus	R	26	−32	10	20.47	0.0016
	Hippocampus	R	30	−34	2	16.30	0.0252
17	Insula	R	40	−18	6	20.43	0.0016
25	Middle Frontal Gyrus	R	42	40	12	19.79	0.0025
28	Precentral Gyrus	L	−42	−12	44	19.64	0.0028
23	Superior Temporal Gyrus	R	54	10	4	19.49	0.0031
21	Middle Frontal Gyrus	L	−26	2	44	19.43	0.0032
49	Precentral Gyrus	L	−46	−20	36	19.42	0.0032
12	Superior Temporal Gyrus	L	−58	−42	16	19.23	0.0036
			−66	−44	12	15.99	0.0310
18	Fusiform Gyrus	R	32	−76	−20	19.13	0.0038
11	Paracentral Lobule	R	4	−38	54	17.86	0.0089

Our results further the discussion whether AN and AS might be understood as two facets of the same underlying causes (Odent, 2010), perhaps representing a female and a male variant (Culbert et al., 2008): we did not find comparable brain activation in response to self-touch and social touch between these two conditions. Even though the difference between self-touch and social touch was preserved, an overall increased activation in AN during both touch types could still relate to the symptomatology of a distorted self-body-perception (Legrand, 2010b): altered processing of self-touch, i.e. increased activations compared to the CG group, point to dysfunctional processing of self-produced sensations. This could be, as described in the introduction, explained by incorrect predictions about the own body's shape and about the expected sensations resulting from touching the own body. As a consequence, even if people with AN would rely more on their priors, as suggested by the allocentric lock theory (Riva, 2016), the predictions of their motor system would not be accurately matched with the actually experienced sensations causing increased prediction errors. An intervention to improve somatosensory predictions of self-touch might be a promising tool for increasing the accuracy of the perceived bodily self.

We further found increased activation during self-touch in AN in the claustrum. The function of the claustrum is not fully understood. It has extensive connections with the cortex and limbic areas, and might integrate limbic information such as valence with sensory and motor signals in order to guide attention to salient events (Smith et al., 2020). It was implicated in self-other-touch difference in our previous study in CG, where it showed deactivation during self-touch (Boehme et al., 2019). The here observed claustral activation in AN during self-touch could be associated with the increased activity in S1 and a potential increase of salience of the self-produced tactile sensations. However, while the activation's peak we obtained was localized in the claustrum, it needs to be considered that this is a small structure, and the wider activation cluster appears to potentially include anterior insula and/or the internal capsule at a lowered threshold (Fig. 3, bottom row). These are both areas of interest in AN, as the anterior insula is involved in interoception and perception of the own body (Craig, 2009), and the

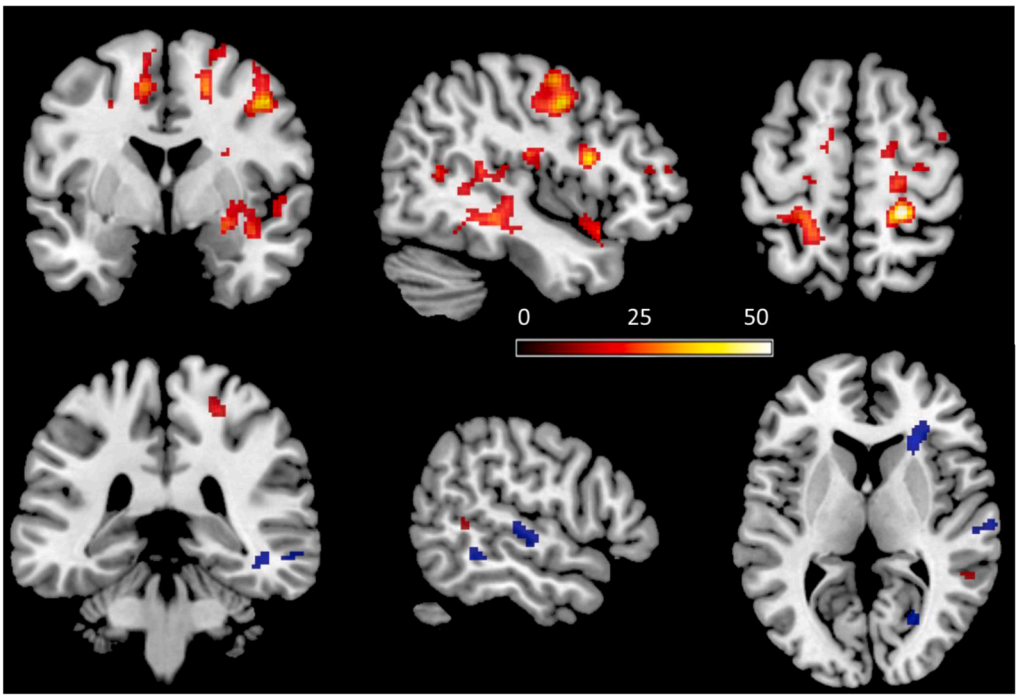

Fig. 3. Areas that showed a significant main effect of group (F-test, p(FWE-corrected) <0.05) over both conditions (top, colorbar indicates F-values), and during other-touch (red, bottom) and self-touch (blue, bottom). For simplification, bottom panel clusters are not scaled by F-value, but indicate location of the clusters at the whole brain threshold p (FWE-corrected) <0.05 (colors are unrelated to effect strength). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Main group effect during self-touch-object-touch, clustersize (k) >10 in voxels, FWE-corrected for the whole brain at the voxel level. Peak coordinates of local maxima identified by SPM with a minimum distance of 8 mm within a cluster, sorted by clusters and effect strength, then by identified regions within these clusters.

k	Region		X	Y	Z	F	p(FWE-corr)
96	Claustrum	R	24	26	6	33.32	<0.001
	Inferior Frontal Gyrus	R	30	32	6	22.35	0.0005
140	Middle Temporal Gyrus	R	58	−40	−10	28.01	<0.001
			52	−40	−10	19.11	0.0039
	Parahippocampal Gyrus	R	44	−32	−12	25.41	0.0001
121	Cingulate Gyrus	R	18	8	42	24.67	0.0001
			18	−4	54	17.04	0.0154
	Medial Frontal Gyrus	R	14	14	46	22.97	0.0003
			16	−10	54	18.73	0.0050
			14	−12	58	17.36	0.0124
36	Posterior Cingulate	R	24	−68	6	24.23	0.0001
15	Medial Frontal Gyrus	R	20	50	−6	23.45	0.0002
33	Anterior Cingulate	R	18	36	18	23.31	0.0003
84	Superior Temporal Gyrus	R	56	−18	2	22.38	0.0005
			66	−18	6	21.46	0.0008
			60	−10	2	17.21	0.0138
24	Putamen	R	24	−6	22	22.02	0.0006
39	Middle Frontal Gyrus	R	44	0	44	21.82	0.0007
25	Medial Frontal Gyrus	R	16	−24	54	21.58	0.0008
40	Cingulate Gyrus	L	−12	−4	52	20.91	0.0012
			−12	2	44	15.90	0.0329
17	Middle Frontal Gyrus	L	−22	−18	60	20.32	0.0018
14	Anterior Cingulate	L	−16	28	18	19.87	0.0024
29	Putamen	R	30	−4	−8	19.56	0.0029
14	Cingulate Gyrus	R	16	14	32	18.83	0.0047
15	Cingulate Gyrus	L	−16	22	34	18.37	0.0064
16	Cingulate Gyrus	R	26	−18	46	18.25	0.0069
14	Precentral Gyrus	R	32	−16	54	18.13	0.0075
11	Cingulate Gyrus	R	20	−2	42	17.69	0.0100

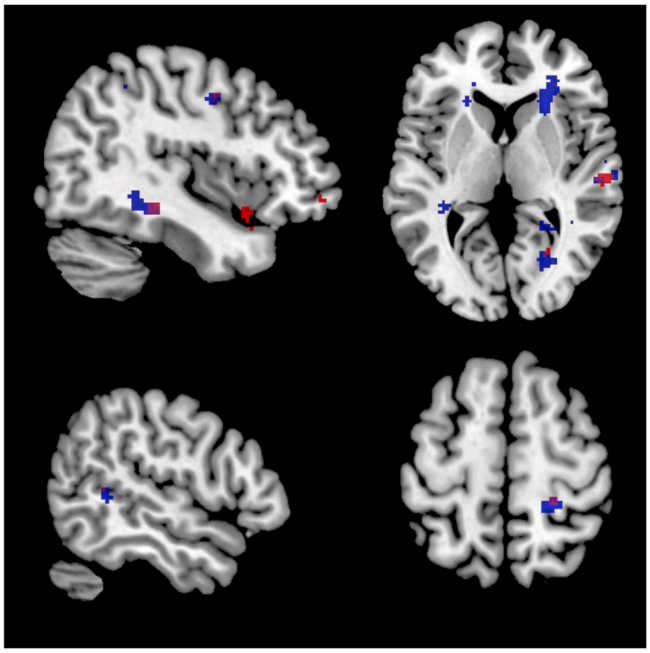

Fig. 4. Significant differences between groups in *post-hoc* comparisons (t-test) for [self-object]-touch (top row: blue = AN > CG, red = AN > AS) and for other-touch (bottom row: blue = AN > CG, red = AN > AS), thresholded at p(FWE-corr.) <0.05 (colors are unrelated to effect strength). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

internal capsule has been reported to show reduced integrity in AN (Shott et al., 2016).

There are several limitations to be considered when interpreting the results of this study. AS is heterogeneous, which is a difficult balance in study design and potential limitations of our study. We wanted to represent the AS population as well as possible without confounding psychiatric and medical comorbidities. By excluding all possible

comorbidities, especially common ones like attention deficit hyperactivity disorder, we ensured an AS group as homogeneous as possible, but this limited generalizability of our findings to independently functioning adults without intellectual disability who can tolerate slow stroking from a stranger- which arguably excludes a large and relevant subpopulation of autistic people. Similarly, we excluded AN participants with an AS diagnosis. This might mean that the results of this study are not generalizable to people with both diagnoses. It is unclear what would be expected in people with both diagnoses, as in the present sample the AS group did not differ from CG. An additional limitation of our recruitment process was that AS and AN groups were not gender-matched (AN contained only females). Since AN is more common in women and AS more common in men, we decided to collect data on both men and women with AS and to check for gender differences during analysis. We did find comparable, yet weaker, results, when only including females. This might of course be due to reduced power because of smaller group sizes – while it might also relate to potential gender differences in AS and even CG groups. It should further be considered that the overall difference between social touch and self-touch was larger in CG (compare visually to the smaller clusters in AS and AN group in Fig. 2). This might be due to the CG sample size, which had to be larger in order to meet the matching criteria for the two neurodiverse samples regarding age and gender. However, this should not affect the main group effect of an ANOVA, which is also supported by the fact that AN but not AS differed from CG, while both AN and AS showed an overall smaller effect for within-subject differences between self- and social touch.

The present study found increased activity in participants with AN: during self-touch in areas including S1, pSTS, frontal, temporal, and subcortical areas, and during social touch in areas including motor cortex, S1, superior, and middle temporal gyrus. Processing of self-touch and social touch in participants with AS appeared comparable to CG - indicating unaltered processing or a failure to detect a difference due to potential limitations of sample size or group heterogeneity. Our results demonstrate differential processing of affective self- and other-touch in AN and AS, indicating potential differences between these two diagnoses regarding the basic neural processing of social touch and self-produced touch sensations implicated in forming the bodily self as well as in social interaction.

CRediT authorship contribution statement

Morgan Frost-Karlsson: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft. **Andrea Johansson Capusan:** Conceptualization, Resources, Supervision, Writing – review & editing. **Irene Perini:** Methodology, Resources, Software, Supervision, Writing – review & editing. **Håkan Olausson:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Maria Zetterqvist:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Per A. Gustafsson:** Conceptualization, Resources, Supervision, Writing – review & editing. **Rebecca Boehme:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosure

AJC has served as consultant and received speakers' fees from Indivior, Camurus Lundbeck, and DNE Pharma all outside the scope of this work. PAG has received speaker fees and scientific advisory board compensation from Lilly and Shire pharmaceutical companies all outside the scope of the current project.

MFK, IP, HO, MZ, RB have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103264.

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