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Consummatory Brain Responses to Social Touch in Female Adolescents With Anorexia nervosa

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Introduction and Theoretical Background

Anorexia nervosa is considered to be the most lethal among psychiatric disorders, with a mortality rate of 5%, due to consequences of malnutrition and suicide (DGPM & DGKJP, 2018; Herpertz-Dahlmann & Altdorf, 2023; World Health Organisation, 2022). Besides that, the disorder bears a high chronification and comorbidity rate (Herpertz-Dahlmann & Altdorf, 2023; World Health Organisation, 2022). Affected persons endure high amounts of suffering and poor life quality, since socio-emotional and physical wellbeing, as well as functional cognitive abilities can be heavily comprised, which also may result in long-term health impairment (Herpertz-Dahlmann & Altdorf, 2023; Neale & Hudson, 2020; Oldershaw et al., 2011; Treasure et al., 2012), especially in children and adolescents (Olivo et al., 2019).

Epidemiology

In females, current worldwide point prevalence is 0.4 to 0.5% (Fichter, 2022; World Health Organisation, 2022), while measures of lifetime prevalence reach up to 4% (Herpertz-Dahlmann & Altdorf, 2023; Qian et al., 2022; van Eeden et al., 2021; Wälte, 2021) and even 6.3% (Silén & Keski-Rahkonen, 2022). Lifetime prevalence in males is up to 0.3% (Herpertz-Dahlmann & Altdorf, 2023; Silén & Keski-Rahkonen, 2022; van Eeden et al., 2021; Wälte, 2021), but could be underestimated due to a high number of unreported cases. With female to male ratio of 1:10 regarding anorexia nervosa diagnosis, the disorder seems to bear gender-biased attributes. Due to availability, most research on anorexia up to now is based on female samples, but the number of men being diagnosed with anorexia is on the rise. Leaving gender binarity, growing evidence shows that gender diverse populations are at higher risk for eating disorders like anorexia nervosa, compared to their cisgender counterparts (Gordon et al., 2021; Herpertz-Dahlmann & Altdorf, 2023; Nagata et al., 2020; Silén & Keski-Rahkonen, 2022).

Anorexia appears to be not distinctive across cultures, but significant differences in prevalence and symptom presentation of anorexia nervosa among various cultures are seen (DGPM & DGKJP, 2018). Numbers are peaking in post-industrial countries with middle to high income (Phillipou et al., 2019) and

high globalization rate, such as several European nations, the United States, Australia, New Zealand, and Japan. Incidence rates in African and Latin American countries are very low (World Health Organization, 2022), as well as in African American and Latino populations living in the US (Van Dyne et al., 2023; World Health Organisation, 2022), which could be explained by genetic impact or gene-environment interaction (DGPM & DGKJP, 2018). Though, numbers could be biased, as medical services are less frequently accessed by marginalised populations (American Psychiatric Association, 2018).

In Austria, specifically, a 2016 school-based screening study of 3610 adolescents between the ages of 10 to 18 years found alarming evidence of 30.9% of girls and 14.6% of boys being at risk for eating disorders in general (Zeiler et al., 2016). A 2017 study using diagnostic DSM-5 criteria of anorexia nervosa showed a point prevalence of 1.01% (∓ 0.9%) and lifetime prevalence of 1.44% (∓ 1.1%) in their total sample of adolescents, composed of a school sample with point prevalence 0.18% (∓ 0.4%) and lifetime prevalence 0.53% ∓ 0.7%, as well as a clinical sample with point prevalence 26.88% (∓ 9.1%) and 30.11 (∓ 9.4%) (Wagner et al., 2017).

Diagnostic Criteria and Symptoms

DSM-5 (American Psychiatric Association, 2018; Code F50.01, F50.02) and ICD-11 (World Health Organization, 2022; Code 6B80) together sum up following diagnostic criteria of anorexia nervosa:

Significantly low body weight in relation to age, height, gender and developmental stage and history that is not due to any other medical condition or lack of food availability. Body Mass Index (BMI) is a commonly used metric for adults; a BMI of less than 18.5 kg/m2 indicates underweight status. In children, the criterion is met with a BMI below the 5th percentile of age-normative BMI and is more likely associated with weight stagnation than weight loss, since normative development in children and adolescents is associated with weight gain. Rapid weight loss during a short amount of time is also accounted by this criterion, when other criteria are fulfilled. Physical indicators of malnourishment can be: loss of fat and muscle mass, perceived coldness and blueness in the extremities, yellow discoloration of the skin, hair loss, growth of fine, fluffy body hair known as “lanugo hair”, swelling of distal body parts, weakened muscles, absence of

menstruation (in the case of usually menstruating individuals), bone density loss leading to conditions like osteopenia or osteoporosis, a decreased heart rate and reduced blood pressure (World Health Organization, 2022; American Psychiatric Association, 2018).

Extreme fear of weight gain, resulting in a pattern of behaviour to counteract weight gain or induce weight loss, like fasting, opting for low-calorie foods, extremely slow consumption of minimal food portions, concealing or expelling food, along with purging actions like self-inducing vomiting and abusing laxatives, enemas, diuretics, or skipping insulin doses in individuals with diabetes. Alternatively, behaviours might target augmenting energy expenditure through e.g. excessive physical activity, motor agitation, intentional exposure to cold temperatures, and the use of substances that boost energy usage, such as stimulants, weight loss drugs, herbal supplements for weight reduction, and thyroid hormones. In sum, people with anorexia use a wide range of acts aiming at keeping or bringing their weight to the lowest level possible (World Health Organization, 2022; American Psychiatric Association, 2018).

Distorted perception of one's own body shape or weight, where the individual inaccurately views their body weight or shape as normal or possibly even too high/too big. Some individuals may be unaware about the severity of their current low body weight, while others may know, but are lacking awareness regarding medical consequences of their malnourishment (World Health Organization, 2022; American Psychiatric Association, 2018).

And/or: *An intense fixation on body weight or shape*. The individual places excessive importance on being underweight, and it holds a central role in their self-assessment. This preoccupation might be indicated by compulsory-like actions like frequently weighing oneself, regularly assessing body shape with tape measures or in mirrors, persistently tracking calorie intake or seeking weight loss advice, or by extreme avoidance behaviours such as avoiding mirrors at home, shunning tight clothing, or refusing to know one's weight or buy clothes with specified sizes. Often times, individuals view weight loss as a remarkable accomplishment and an indication of exceptional self-control, but weight increase is viewed as an unacceptable lack of self-control (World Health Organization, 2022; American Psychiatric Association, 2018).

ICD-11 and DSM-5 both distinguish 2 types of anorexia nervosa regarding pattern of weight related behaviour. The *restrictive type* (ICD-11: 6B80.x0, DSM: F50.01) is associated with loss/preservation of weight induced by dieting, fasting, and/or excessive physical activity, no bingeing or purging in the 3 months prior to diagnostic assessment. If there is a case of repeated bingeing or purging during the 3 months prior, it would be considered as *binge-eating/purging-type* (ICD-11: 6B80.x1, DSM: F50.02). ICD-11 also includes *unspecified* (6B80.xz) (World Health Organization, 2022; American Psychiatric Association, 2018). Restrictive type is more commonly diagnosed than binge-eating/purging-type, at least in children and adolescents (Jaite et al., 2019).

DSM-5 (American Psychiatric Association, 2018) introduced following specification for underweight status: *light* (BMI ≥17 kg/m²), *moderate* (BMI 16–16,99 kg/m²), *severe* (BMI 15–15,99 kg/m²) and *extreme* (BMI <15 kg/m²). Individuals with *partial remission* no longer fulfil the underweight-criterion for an extended period, but the other 2 criteria still apply to them. *Full remission* is achieved when, for a longer period of time, none of the 3 criteria are met. In ICD-11, specifiers are: *Anorexia nervosa* (AN) *with significantly low body weight* (6B80.0), *AN with dangerously low body weight* (6B80.1), *AN in recovery with normal body weight* (6B80.2), *other specified AN* (6B80.Y), which includes Atypical anorexia nervosa, and *AN, unspecified* (6B80.Z).

Differences between males and females with anorexia are reported in behaviour aiming at losing weight, bodily self-image and age of onset. While females more often use laxatives, excessive exercise and usage of food supplements in combination with a low-caloric diet is more common in men. Regarding self-image, anorexic males are more concerned about muscularity and body fat. Gender differences also can be seen in onset age - females tend to be diagnosed with anorexia at an earlier age than males (World Health Organization, 2022). Symptom presentation also varies cross-cultural, such as, for example, Asian people with anorexia tend to justify decreased food intake with digestive unease or cultural/religious reasons rather than expressing fear of weight gain (World Health Organization, 2022; American Psychiatric Association, 2018).

Onset and Course

Although anorexia occurs across differing age groups (Herpertz-Dahlmann et al., 2024), onset of anorexia nervosa is typically associated with adolescence and young adulthood (World Health Organization, 2022; American Psychiatric Association, 2018) with a peak age of 15.5 years. A meta-analysis on age of onset of mental disorders worldwide found that 18.2% of individuals diagnosed with anorexia dealt with onset prior to the age of 14 years, more than half of the population with anorexia (55.2%) were diagnosed until the age of 18 years, and at 25 years old, 78.7% of this population had received their anorexia diagnosis (Solmi et al., 2022). Accordingly, anorexia is less frequently diagnosed prior to puberty or after the age of 40 (American Psychiatric Association, 2018). However, in the past few years, an increase of incidence in children or teenagers under 15 years could have been observed (Herpertz-Dahlmann & Altdorf, 2023; van Eeden et al., 2021). Lastly, the COVID-19 pandemic and related measures highly affected incident rates (Silén & Keski-Rahkonen, 2023; Herpertz-Dahlmann & Altdorf, 2023), as e.g. German hospitalization rates of female children and adolescents with anorexia nervosa increased with 40%(Herpertz-Dahlmann et al., 2022).

Etiological Perspectives

Concerning etiology of anorexia nervosa, a biopsychosocial approach is widely accepted in the field. On the biological side, first foremost genetics are a major concern (Phillipou et al., 2019). Twin studies suggest that the heritability of anorexia ranges from 48% to 76% (DGPM & DGKJP, 2018; Bulik et al., 2006; Klump et al., 2001; Kortegaard et al., 2001). Female first degree relatives of women with anorexia are 11 times more likely to be also affected by the disorder than women without familial predisposition (DGPM & DGKJP, 2018; Strober et al., 2000). Molecular genetic studies indicate that the development of the diverse phenotypical characteristics of anorexia does not depend on a single gene defect, but a number of genes that contribute with varying degrees (DGPM & DGKJP, 2018; Yilmaz et al., 2015). The first significant locus was found on a region of chromosome 12, where loci of diabetes and autoimmune diseases already had been found, too (DGPM & DGKJP, 2018; Duncan et al., 2017). A newer study found 8 genome-wide significant loci, distributed over chromosomes

1, 2, 3, 5, 10 and 11 and comprising 121 genes that are primarily expressed in the brain. Genetic correlations yielded positive associations between anorexia and obsessive-compulsive disorder, major depressive disorder and depressive symptoms, schizophrenia, anxiety, neuroticism, education level, physical activity and cholesterol, as well as negative associations with various anthropometric traits (e.g. BMI, body fat percentage) and metabolic markers like fasting insulin and leptin (Bulik et al., 2019; Herpertz-Dahlmann et al., 2024; Hirtz et al., 2022; H. J. Watson et al., 2019). To which degree actual metabolic and hormonal functions are antecedent to onset or a consequence of anorexia is uncertain (DGPM & DGKJP, 2018); the same applies to neurobiological factors in terms of brain connectivity, structure and function of brain regions, neurotransmitter and metabolites concentration and function, as well as gut-brain axis and epigenetics (Bulik et al., 2019; DGPM & DGKJP, 2018; Herpertz-Dahlmann et al., 2024; Phillipou et al., 2019).

Moving on to psychological risk factors, older retrospective studies indicated "*increased drive for thinness and restrictive eating, lower self-esteem and a negative self-concept, affective lability and negative affectivity*" (AWMF, 2018, S. 87), neuroticism (Cervera et al., 2003) and an avoidant or obsessive-compulsive personality (Cassin & von Ranson, 2005; DGPM & DGKJP, 2018; Lilenfeld et al., 2006) as being vulnerability factors. (Bulik et al., 2019; Herpertz-Dahlmann et al., 2024; Keel & Forney, 2013; Phillipou et al., 2019)Phillipou et al. (2019) furthermore mention anxiety, stress and trauma (PTSD), body image disturbance and altered response to reward in their latest model of cause and maintenance factors of anorexia. More recent studies reported overall difficulties with expression and processing of socioemotional signals, as well as emotion regulation (Caglar-Nazali et al., 2014; DGPM & DGKJP, 2018; Kothari et al., 2015; Treasure & Schmidt, 2013) as causal and perpetuating factors. Neurocognitive aspects like difficulties with cognitive flexibility, perception, multisensory integration (Phillipou et al., 2019) and central coherence (DGPM & DGKJP, 2018; Lang et al., 2014; Phillipou et al., 2019) are also on the list to be both causing and maintaining factors.

Sociocultural and psychosocial vulnerabilities are summarized within the social approach. Cultural environment and socio-economic status notably shape the risk of developing anorexia (Phillipou et al., 2019), as prevalence is

significantly higher in post-industrialized (“western”) countries with middle – high income (World Health Organization, 2022; Phillipou et al., 2019). Embedded in these societies, thin idealization and social pressure to be thin are pervasive risk factors (DGPM & DGKJP, 2018; Phillipou et al., 2019; Stice & Whitenton, 2002; Bulik et al., 2019; Culbert et al., 2015; Keel & Forney, 2013), and exposition to (social) media representing this ideal leads to increase in body dissatisfaction, especially in risk groups (DGPM & DGKJP, 2018; Hausenblas et al., 2013). Vulnerability factors also can be found in e.g. sports; amateur and professional athletes “*in the esthetically characterized sport types such as gymnastics, ballet and dance, as well as in endurance sports (e.g. distance running) and sports with weight specifications (e.g. boxing, wrestling) can be seen as risk groups for the development of AN*” (AWMF, 2018, S. 86).

In the early days of anorexia etiological theories, dysfunctional familial background of anorexic patients was emphasized (Herpertz-Dahlmann et al., 2011; Minuchin et al., 1975). Nowadays, it is clear that dysfunctional family dynamics are neither the only nor primary cause of eating disorders (Herpertz-Dahlmann et al., 2024; le Grange et al., 2010), but are among other risk factors of the biopsychosocial approach that may contribute to the development of anorexia (Herpertz-Dahlmann et al., 2024; Mensi et al., 2020). DGPM & DGKJP (2018) even state that family dynamics are more associated with severity and chronicity and less etiologically important. Generally, adverse experiences in one’s social environment, like bullying (Copeland et al., 2015; Herpertz-Dahlmann et al., 2024) and negative comments about eating, weight and shape from siblings, peers and coaches or teachers (Herpertz-Dahlmann et al., 2024; Jacobi et al., 2011) may trigger anorexia onset. Also, peer pressure associated with healthy eating, weight and sports can have negative aspects (Bulik et al., 2019; Herpertz-Dahlmann et al., 2024; Keel & Forney, 2013; Phillipou et al., 2019). Furthermore, trauma exposure unrelated to eating also may trigger anorexia onset, but is commonly related to psychiatric disorders in general (Bulik et al., 2019; Jacobi et al., 2004).

Further Pathogenesis

As already mentioned, people with anorexia are detrimentally affected by the condition on a physical and mental level. Starvation is affecting most vital

organs and bodily functions on a micro to macro level, and bears high risk of medical complications, of which some of them are irreversible, even after remission (American Psychiatric Association, 2018; DGPM & DGKJP, 2018; Herpertz-Dahlmann et al., 2011). Physical indicators described along with diagnostic criteria are a result of system malfunction. For example, absence of menstruation in usually menstruating individuals and bone density loss can be traced back to the disturbance of the endocrine system. In children and adolescents, this also implies delay of puberty, stagnation of physical growth and brain maturation (DGPM & DGKJP, 2018; Resmark et al., 2019; Neale & Hudson, 2020).

At an early stage of the illness, individuals may experience positive feelings of ease, control and euphoria, that later turn into "*indirefference, irritability and depressed mood*" (AWMF, 2018, S. 81). "*[…] Rigid thinking, a strong need for control*" (AWMF, 2018, S. 81) (that can turn into obsessive-compulsive thoughts and behaviour), conflict avoidance, social withdrawal, lowered spontaneity, decreased sexual interest, insomnia and difficulties with managing negative affect (especially anger), as well as high psychomotor restlessness is observed in severely underweight individuals (American Psychiatric Association, 2018; DGPM & DGKJP, 2018). Additionally, impact on the individual's social life should not be underestimated. Visible starvation signs often elicit worried reactions from parents, teachers, friends and partners. This heightened social attention may act as a secondary reinforcement of the illness. In chronic cases, the illness becomes part of one's identity and is particularly difficult to "give up". From a lifespan-perspective, anorexia and recovery can consume several years of one's life, and in children and adolescents, this may also result in a delay of education (DGPM & DGKJP, 2018).

While all these factors play a crucial role in the development and maintenance of anorexia, they are also accompanied by significant neurological changes. Advances in neuroimaging have provided a better understanding of structural and functional brain alterations of individuals with anorexia nervosa. Investigating these neurological dissimiliarities can help clarify the relationship between brain structure and function, cognition and behaviour, shedding light on the potential for recovery and the long-term effects of the disorder.

Neuroscience of Anorexia Nervosa

Structural Differences

Whilst unsure whether these changes are pre-existent to the disease or a consequence, neuroimaging data on both anorexic adults and adolescents show a global decrease in grey matter and white matter volume (Bahnsen et al., 2022; King et al., 2018; Seitz et al., 2016; Steinglass et al., 2019; Titova et al., 2013), including cortical thickness and subcortical volumes (de la Cruz et al., 2021; Walton et al., 2022), whilst an increase in cerebrospinal fluid (Seitz et al., 2016; Steinglass et al., 2019; Titova et al., 2013). Alarmingly, global grey matter volume loss is even significantly more pronounced in adolescents than adults (Seitz et al., 2016). According to Seitz et al. (2016), global grey and white matter reductions could be reversed with long time weight recovery in adults, but if the same applies to adolescents is unknown. Bahnsen et al. (2022) and Bernardoni et al. (2016) even found that overall cortical thickness and subcortical volume could be restored during short-term recovery with partial weight regain. However, from the standpoint of regional volume or thickness, the research of Miles et al. (2018) and Castro-Fornieles et al. (2021) demonstrates persistent changes in cortical thickness and subcortical volumes, which may be a long-term consequence of susceptibility or malnourishment. Regional grey matter alterations include both increases and decreases in various loci, but studies differ in their outcome (Steinglass et al., 2019). Cortical and subcortical grey matter areas that are often found to be structurally impacted are frontal (Alfano et al., 2020; King et al., 2018) and parietal areas (Alfano et al., 2020; Phillipou, Rossell, et al., 2018), insula (Alfano et al., 2020), cingulate gyrus (Alfano et al., 2020; King et al., 2018), cerebellum (King et al., 2018; Mishima et al., 2021), striatum (Phillipou et al., 2018; Steinglass et al., 2019), amygdala, hippocampus and thalamus (Steinglass et al., 2019).

Investigation of white matter shows altered fractional anisotropy and mean diffusivity of certain white matter tracts, pointing to the deviance of white matter integrity (Alfano et al., 2020), as well as altered structural connectivity (Frank et al., 2016). Decreases of fractional anisotropy are seen in superior longitudinal fasciculus, corona radiata (Gaudio et al., 2017; Phillipou, Carruthers, et al., 2018), thalamic radiation, corpus callosum (Gaudio et al., 2017; Phillipou, Carruthers, et al., 2018; von Schwanenflug et al., 2019) and fornix (Gaudio et al.,

2017; von Schwanenflug et al., 2019). Structural connectivity is enhanced within pathways linking the insula, orbitofrontal cortex (OFC), and ventral striatum, while showing reduced connectivity between the orbitofrontal cortex, amygdala, and hypothalamus (Frank et al., 2016). Alike grey matter volume, white matter microstructure might normalize with weight restoration in adults (von Schwanenflug et al., 2019). Even in adolescents, there is evidence of partial recovery during weight restoration (Vogel et al., 2016).

Functional Differences

Resting state functional connectivity (rsFC) is altered among various brain networks in both anorexic adolescents and adults. In their work, Lucherini Angeletti et al. (2022) summarized that subcortical-cortical midline structures, "*default mode network (DMN), salience network (SN) and executive control network (ECN)*" (Lucherini Angeletti et al., 2022, S. 2) are of decreased rsFC in anorexia. Subcortical regions showing decreased rsFC with cortical structures are thalamus, putamen, caudate and cerebellum in adolescents, and additionally nucleus accumbens and hippocampus in adults. Intracortical functional connections include insula, medial orbitofrontal cortex, paracentral lobule, right dorsolateral prefrontal cortex , anterior cingulate cortex (ACC) and anterior prefrontal cortex in adolescents, as well as precuneus, somatomotor area, occipital area and dorsolateral ACC in adults. Also, regions of interoceptive self, including insula, thalamus, anterior cingulate cortex, inferior parietal lobule and postcentral gyrus, show reduced rsFC, while task-related activities elicit heightened functional connectivity in those regions (Lucherini Angeletti et al., 2022). Steinglass et al. (2019) also mention rsFC alterations in fronto-parietal and fronto-striatal networks.

With differing research foci, task-based fMRI studies include a variety of stimuli targeting certain aspects of the disease (Frank, 2019; Scharner & Stengel, 2019). Studies on *executive functions* are presenting a pattern of diminished cognitive flexibility, but no differences in working memory and inhibitory control tasks, although more cognitive resources are needed in order to achieve these tasks (Olivo et al., 2019). A study on implicit learning, which is one of the two components of cognitive flexibility, showed decreased activity of ventral thalamic nuclei, associated with impaired implicit learning ability in anorexic adolescents.

Though, this malfunction appears to be reversed with recovery (Firk et al., 2015; Olivo et al., 2019).

Food. In a study from Horndasch et al. (2018), while rating images of high-calorie food as more negatively than controls, anorexic adolescents demonstrate a decrease in cerebellar activity and an increase in the inferior frontal gyrus, medial prefrontal cortex, and anterior insula. Low-calorie food was associated with decreased activity in the medial prefrontal cortex and parietal lobe of anorexic adolescents, with no differences in the ratings of patients and controls. Interestingly, in anorexic adults, both high and low calorie food images mainly elicited heightened activity of cerebellum (Horndasch et al., 2018; Olivo et al., 2019). Other studies based on images of food stimuli further presented heightened activation of posterior cingulate cortex and amygdala, but lowered activation of posterior midcingulate cortex (Gizewski et al., 2010; Joos et al., 2011; Scharner & Stengel, 2019). These differences in processing food images even were found in recovered anorexic patients (Scharner & Stengel, 2019).

Body Image. In healthy controls, normal-weight body images elicit higher activation of ventral striatum, while in anorexic patients, the same cerebral response appears to underweight body images (Fladung et al., 2013; Olivo et al., 2019). When looking at their own bodies, anorexic patients showed decreased activity in inferior parietal lobule, while seeing images of other women led to increased activity in amygdala (Scharner & Stengel, 2019; Vocks et al., 2010). Being confronted with distorted and oversized pictures of themselves, anorexic patients show a pattern of increased activity in the inferior frontal gyrus, middle temporal gyrus and amygdala, and decreased prefrontal cortex activity. On the other hand, looking at images of thin bodies led to heightened activity of the ventral striatum and insula. Furthermore, increased insula activity, alongside higher premotor cortex activation and lower anterior cingulate cortex activity, could be observed when patients compared their own bodies to idealized bodies. Lastly, listening to body-related negative words elicited higher activity of amygdala, medial prefrontal cortex and inferior parietal lobe (Scharner & Stengel, 2019).

Social Cognition. During a theory of mind-task, anorexic adolescents displayed significant decreases in middle and temporal cortex activity, as well as in the medial prefrontal cortex, despite achieving the same task-performance as

healthy controls. Reduced activity in the medial prefrontal cortex was also associated with worse clinical outcome in a 1-year follow-up (Olivo et al., 2019; Scharner & Stengel, 2019; Schulte-Rüther et al., 2012). Hypoactivation of medial prefrontal cortex, again, as well as dorsal anterior cingulate, appeared in anorexic adolescents in connection with social evaluation tasks (Olivo et al., 2019; Xu et al., 2017).

Emotions, Learning and Reward. A meta-analysis from Zhong et al. (2023) found that, during emotion-related tasks, anorexic patients, in contrast to healthy controls, show heightened activation of left cerebellum, but hypoactivity of bilateral striatum, right medial prefrontal cortex, bilateral lingual gyrus, right inferior frontal gyrus and right superior parietal gyrus. They also reported in their meta-analysis that anorexic patients performing reward-related tasks had significantly higher activation of left superior temporal gyrus, left insula, postcentral gyrus, bilateral anterior cingulate cortex, prefrontal cortex and medial cingulate cortex than healthy controls, while no hypoactivation was found. The review from Scharner & Stengel (2019) further mentions increased activity of ventral striatum.

Anorexia Nervosa and the Reward System

Over recent decades, neuroimaging research has revealed that a wide variety of rewards—ranging from food, sex, and drugs to social bonds, music, and art—activate a shared network of brain regions often referred to as the "common currency" reward system. This system can be divided into two interconnected circuits: a ventral bottom-up circuit and a dorsal top-down circuit. The ventral bottom-up circuit, involving regions like the amygdala, anterior insula, anterior ventral striatum, ventral ACC, and OFC, is responsible for recognizing emotionally significant and/or rewarding stimuli and generating affective responses. In contrast, the dorsal top-down circuit, which includes the dorsal caudate, dorsolateral prefrontal cortex, and parietal cortex, plays a role in regulating attention, planning, and controlling emotional states. Together, these circuits work to evaluate the emotional and rewarding significance of stimuli, guide appropriate behavioural responses by considering future consequences, and suppress inappropriate actions (Berridge & Kringelbach, 2015; Boehm et al., 2018; Kaye et al., 2009; Monteleone et al., 2018; Sescousse et al., 2013).

The reward system involves three key processes: ‘liking’, which resembles hedonic impact and conscious pleasure, ‘wanting’, including incentive salience and cognitive incentives, and ‘learning’ (associative and cognitive representations). These processes have distinct neural mechanisms (Anselme & Robinson, 2016; Berridge & Kringelbach, 2015; Berridge & Robinson, 2003) and occur throughout the reward-behaviour cycle. ‘Wanting’ typically dominates the appetitive phase, ‘liking’ the consummatory phase, and ‘learning’ spans the entire cycle (Berridge & Kringelbach, 2015).

Conscious and subconscious aspects of ‘liking’ and ‘wanting’ can diverge. Objective ‘liking’ reactions (neural and behavioural) can occur independently of conscious subjective pleasure and are sometimes distorted by cognitive framing effects. Similarly, a gap between conscious, cognitive ‘wanting’ and subconscious, implicit ‘wanting’ can emerge, and vice versa (Anselme & Robinson, 2016; Berridge, 2018; Berridge & Kringelbach, 2015), due to cognitive (top-down) control abilities including attention shifting and inhibition (Boehm et al., 2018).

There is overwhelming evidence that anorexia is characterized by altered reward system function, particularly within neural circuits such as the mesolimbic pathway and prefrontal regions (Boehm et al., 2018; Ehrlich et al., 2015; King et al., 2016; Wierenga et al., 2015). These neural disruptions not only contribute to maladaptive behaviours like food restriction and excessive exercise but also extend to broader contexts of reward sensitivity, including social domains. To better understand these complex dynamics, several neurocognitive models have been proposed, offering insights into how reward mechanisms influence the development and maintenance of anorexia nervosa. One prominent model suggests that anhedonia, or a diminished ability to experience pleasure, arises from reduced dopaminergic activity within the brain's reward pathways, particularly the striatum and mesolimbic system. This reduced sensitivity to reward may underlie the motivational deficits often observed in individuals with AN (Keating, 2010). In contrast, another model emphasizes excessive ‘top-down’ cognitive control, mediated by dorsal brain regions such as the prefrontal cortex. This control suppresses typical reward responses, enabling the persistent avoidance of food and the formation of restrictive eating habits. Over time, these habits become deeply ingrained, particularly in the restricting subtype of

anorexia, making them resistant to treatment (Steinglass et al., 2019). A third model, termed "reward contamination", offers a paradoxical perspective, proposing that food restriction and purging behaviours may become inherently rewarding due to overlapping neural pathways that simultaneously process both reward and punishment. This creates a maladaptive reinforcement loop, perpetuating these behaviours despite their harmful consequences (Monteleone et al., 2018).

Recent research has proposed that AN is maintained by a dual dynamic: reduced reward from typical experiences and heightened reward from weight-loss behaviours. This cycle reinforces engagement in weight-loss behaviours, which remain rewarding, while prolonged starvation diminishes the capacity to derive pleasure from other stimuli, intensifying reliance on these maladaptive behaviours. This feedback loop further underscores reward system disruptions as a critical treatment target (Haynos et al., 2021; Monteleone et al., 2018; O'Hara et al., 2015; Wierenga et al., 2014).

Social Reward

Social reward – derived from positive interpersonal experiences such as validation, acceptance, or physical touch – is a vital aspect of human relationships, motivation and emotional well-being. Examining social reward in individuals with AN is crucial for understanding how their interpersonal experiences may be impacted by altered reward processing, essentially due to interpersonal difficulties and emotional isolation often observed in individuals with anorexia, further perpetuating the disorder's cycle of maladaptive behaviors and psychological distress (Cardi et al., 2013; Haynos et al., 2021; Kerr-Gaffney et al., 2022; Monteleone et al., 2018; O'Hara et al., 2015; Steinglass & Foerde, 2018; Tchanturia et al., 2012; Via et al., 2015; K. Watson et al., 2010). On the behavioural level, individuals with anorexia display increased attention bias and high sensitivity to social rejection, while being avoidant of positive social stimuli and perceiving social situations as less rewarding than healthy controls (Cardi et al., 2012; Treasure et al., 2012; Treasure & Schmidt, 2013; Via et al., 2015). Neuroimaging shows decreased activity in the dorsomedial prefrontal cortex during social acceptance, and increased activity in visual areas, suggesting heightened sensitivity to negative social stimuli. Moreover, activity in the ventral

striatum during rejection correlates with the severity of the disorder (Via et al., 2015). These findings underscore the importance of focusing on social reward as a distinct, yet interconnected aspect of the broader reward-processing anomalies observed in anorexia nervosa.

Extending this perspective, social touch—a critical component of social reward—warrants focused examination, given its unique role in fostering connection, emotional regulation, and stress relief. Social touch, often mediated through gentle tactile interactions, has been identified as inherently rewarding, engaging neural circuits of the so-called C-tactile nervous system, which are closely tied to affective and reward processing (Dreisoerner et al., 2021; McGlone et al., 2014; McGlone & Reilly, 2010; Olausson et al., 2002; Pawling et al., 2017; Walker et al., 2017). C-tactile (CT) fibers are found in hairy, non-glabrous skin and are activated by soft touching velocities between 1 and 10 cm/s (Olausson et al., 2010; Taneja et al., 2021; Löken et al., 2009) and project to somatosensory and insular cortices (Olausson et al., 2002; Bjornsdotter et al., 2009).

The primary somatosensory cortex (S1), located in the postcentral gyrus, is primarily responsible for processing the basic sensory features of touch, such as pressure, texture, and spatial localization. It receives direct input from the thalamus and is somatotopically organized, meaning different regions of the cortex correspond to specific areas of the body. As such, S1 plays a crucial role in distinguishing where on the body a touch stimulus occurs and in encoding its physical properties. While S1 is mainly involved in the discriminative aspects of touch, the secondary somatosensory cortex (S2), located in the parietal operculum, plays a more integrative role, linking sensory input with cognitive and affective processes. S2 receives input from both S1 and the thalamus and is involved in the perception of touch intensity, the recognition of complex tactile stimuli, and the integration of somatosensory information with other sensory modalities (McGlone et al., 2014; McGlone & Reilly, 2010).

Studies utilizing touch paradigms and self-reported measures have indicated heightened aversion or blunted sensitivity to social touch in AN populations, potentially associated with neurobiological factors, such as changes in sensory processing and altered interoceptive awareness, and psychological factors, including heightened anxiety and distorted body image (Crucianelli et al., 2016, 2021; Teaford et al., 2021). Only a handful of fMRI studies investigated

brain responses to CT-optimal touch in anorexia nervosa, with diverging research foci, study groups and methods. In a study from 2016, Davidovic (2016) performed a comparison between effects of consummatory skin stroking and indentation, provided by a robotic machine using a paint brush, and found no significant activity differences in somatosensory areas and insula between anorexic and healthy participants. Instead, an increase of activity in bilateral lateral occipital cortex in anorexic participants could have been observed. 2 years later, with the same study design, Davidovic et al. (2018) showed a decrease in activity of left caudate nucleus (dorsal striatum) and, again, of bilateral lateral occipital cortex in anorexic participants. Bischoff-Grethe et al. (2018) detected higher activity in the area of right ventral mid-insula extending into superior temporal gyrus, but no significant differences in striatum activity in recovered anorexic participants that received paint brush stroking delivered by trained assistants. Lastly, Frost-Karlsson et al. (2022) investigated consummatory neural responses to CT-optimal self-touch and other-touch provided by an experimenter in participants with a diagnosis of anorexia and autistic participants and revealed higher activations in bilateral somatosensory cortex and right superior temporal gyrus in anorexic participants compared to healthy controls. These findings underscore the complexity and variability of neural responses to CT-optimal touch in individuals with anorexia nervosa, highlighting both regional activation patterns and potential methodological influences.

Research Gap, Research Questions & Hypotheses

Despite the advances described above, critical gaps remain in our understanding of how CT-optimal touch, as a specifically affiliative and emotionally significant sensory modality, is processed within the broader neurocognitive framework of anorexia nervosa. Addressing these gaps is essential for elucidating the interplay between altered social touch perception and the neurobiological underpinnings of the disorder.

The existing literature suggests that individuals with AN exhibit reduced reward sensitivity and heightened cognitive control, as well as atypical somatosensory processing, potentially influencing how social touch is perceived and processed. Results have been heterogeneous and sometimes contradictory,

further underscoring the need for a well-controlled neuroimaging study examining social touch processing in AN.

To address these gaps, the present study seeks to answer the following key research question: What are the differences in consummatory neural responses to CT-optimal touch between individuals with anorexia and healthy controls?

Drawing from existing literature on social touch perception in anorexia, this research is guided by the hypotheses that (1) anorexic participants show reduced activation in brain regions associated with reward processing (striatum, anterior cingulate cortex, ventral tegmental area, and hippocampus; H1) while (2) displaying heightened activity in areas related to sensory processing, cognitive control, and threat detection (primary and secondary somatosensory cortices, prefrontal cortex, posterior insula, amygdala, and superior temporal gyrus; H2).

Methods

Study Design

This study took part in the context of an ongoing bigger project, namely AN-Bel study, which is conceptualized as a cluster project between University of Vienna and Medical University of Vienna under the leadership of Assoc. Prof. Dr. Giorgia Silani, PhD from the University of Vienna, Department of Clinical and Health Psychology, Faculty of Psychology and Univ.-Prof. Dr. med. univ. Andreas Karwautz, FAED from the Medical University of Vienna, Eating Disorders Research Unit, Dept. of Child & Adolescent Psychiatry (Medical University Vienna, n.d.). It corroborates a translational psychiatric approach to adolescent anorexia nervosa with focus on the reward system and combines genetic analyses, (neuro-)psychological assessments, behavioural assessments, as well as structural and functional MRI in combination with facial EMG. The study was approved by the ethics committee of the University of Vienna, was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2024) and started testing in February 2022. For this particular study, base sociodemographic data of participants, current in- or outpatient status and anorexia nervosa subtype of anorexic patients, information about liking (rating) of

the stimuli and structural and functional MRI data was used in a between-subject design.

Participants

The design of the study project was set to include only female participants. At the time of the analysis, the whole sample included 72 female adolescent inpatients or outpatients with a diagnosis of anorexia nervosa that were recruited through Medical University of Vienna/Vienna General Hospital, as well as 26 healthy female controls (HC) that were recruited through personal contacts, schools, youth clubs, flyers that were distributed, displayed or posted up, and advertisement on social media (Facebook, Instagram, Tik Tok). The study was conducted inside Medical University of Vienna/Vienna General Hospital, and it comprised individuals from Vienna and Lower Austria. Testing was usually scheduled once a week with two 5-hour testing slots.

Both groups completed online pre-screening questionnaires to check eligibility. The links to the questionnaires were sent via E-Mail. Pre-screening included questions on contact details, sociodemographic data, eye sight, BMI, psychiatric diagnoses and psychological conditions, medication, physical health and conditions, smoking, addiction, specific diets (veganism etc.), soy allergy, gluten- and lactose intolerance, as well as willingness to drink cow/soy milk or chocolate milk, receive physical touch from an experimenter and facial EMG electrode placement. They also had to answer MRI-specific questions in order to assess any possible safety concerns that could either lead to exclusion or needed further examination, which were: prior MRI experiences, pacemakers, operations, splinters, claustrophobia, kidney problems, tattoos, retainer, permanent make up, piercings, pregnancy, sight and dioptres. Anorexic (AN) participants further completed a questionnaire on their eating disorder symptoms in the past and present that included questions on their diagnosis, treatment, current weight and height, lowest weight, and questions about trying to loose weight or not gain weight in the past 3 and 12 months, influence of their physique and weight on their self-esteem in the past 1, 2 and 3 months, binge eating and usual eating behaviour.

If eligible, participants were contacted to arrange the testing appointment. One week prior to testing, all participants got sent a parcel to their home address

containing consent forms, study information and instructions, a diet protocol and a stool sample tube, which they had to bring with them to their testing appointment.

For this specific study, exclusion criteria for anorexic patients were: diagnosis of different eating disorder or diagnosis of atypical anorexia or full remission or partial remission. In the control group, 1 subject was excluded, because during clinical assessment, the participant was found to be anorexic. In the overall sample, subjects with missing ranking data, trial data or fMRI data or subjects who received less than 7 trials of CT-optimal touch (6cm/s) were excluded. The final sample consisted of 18 controls and 17 anorexic subjects.

All participants partook voluntarily. They were informed about the study procedure and MRI safety prior to testing and gave their written consent. In underage participants, parents gave their written consent. After finishing participation in the study, participants received a voucher worth 70 Euros for a shop of their choice as compensation.

Procedure

Sociodemographic data of all participants, as well as current in- or outpatient status of anorexic patients was assessed during recruitment process. Anorexia subtype had been either already provided or determined during clinical assessment. On testing day, participants individually went through physical assessments and got their blood drawn, as well as completing psychological assessments. Afterwards, participants got transferred to the MRI location. The patient's completed MRI questionnaire was handed to the MRI tech to reassure MRI compatibility. The participants were asked to change into hospital gowns, remove their shoes and any jewellery or body piercings and in cases of long hair, tie their hair together into a low ponytail. A member of the research team (called Experimenter 1 or 2, depending on the time slot) was assigned to be responsible for the participant, giving them information on the procedure and instructions, answering any questions and ensuring the wellbeing of the participant. The same person installed the facial EMG und lead the participant into the scanner room, then explaining the upcoming procedure. Another research team member (called Toucher) entered the room to introduce themselves as the person who was going to deliver the touch stimuli to the participant (as a touch therapist). The Toucher

marked the area where the stimuli were going to be delivered: The outer hairy skin area between the little-finger-sided protruding end of the ulna and a boundary measured 9 cm in proximal direction from the end of the ulna on the right forearm. Boundaries were marked with adhesive medical tape, in order for the research assistants to stay within the given skin area while performing caresses.

Afterwards, Experimenter 1/2 informed the participant to follow the instructions shown on the screen that they are going to see, and that they would already receive small amounts of milk and chocolate milk, as well as water for flushing. When everything was clear, they asked the participant to lay back down on the scanner table, with their head being nearest to the scanner tube and placed on the integrated padded head coil, helped them adjust their position and placed an under-knee cushion. During ranking and testing phase, imagery was displayed on a screen at the head end of the scanner with a video projector. Subjects could see the imagery through a mirror mounted inside the head coil. Experimenter 1/2 installed the external head coil, making sure the mirror was in the right position for the subject to see the display. They then proceeded to tape the plastic tubes delivering the liquid reward onto the external head coil, in a way that the tips were placed inside the participant's mouth laying softly on the tongue. In order to interact with the screen, participants received a button box for the non-dominant (mostly left) hand and a dynamometer press for the dominant hand. Participants' non-dominant index finger, middle finger and ring finger were placed on 3 of the 4 buttons on the button box accordingly to instructions. Subjects were asked to place the hand holding the dynamometer press on the middle of their chest and their hand holding the button box slightly beneath. They were instructed to keep their position this way. An emergency ball was placed and taped in reach for the participant in an event of sudden emergency to immediately stop the procedure. Experimenter 1/2 proceeded to elevate the scanner table and drive it axially into position *Isocentre* with the scanner operation button. The touch therapist then took their position in front of the left side of the scanner in reach of the participant's right arm in order to deliver the touch stimuli. Experimenter 1/2 then left the room. In the following ranking phase, the participant in the scanner (turned off) consecutively received 3 kinds of food and touch stimuli, then were asked to rate their most favourite and their least

favourite out of the 3 with the button box. Whilst delivery, for each stimuli input, the screen showed different symbolic representations. At the end of the ranking, the participants' individual maximum voluntary contraction (MVC) was obtained through dynamometer press, after they were asked via screen to deliver. Duration of ranking and measuring MVC was ~10 minutes.

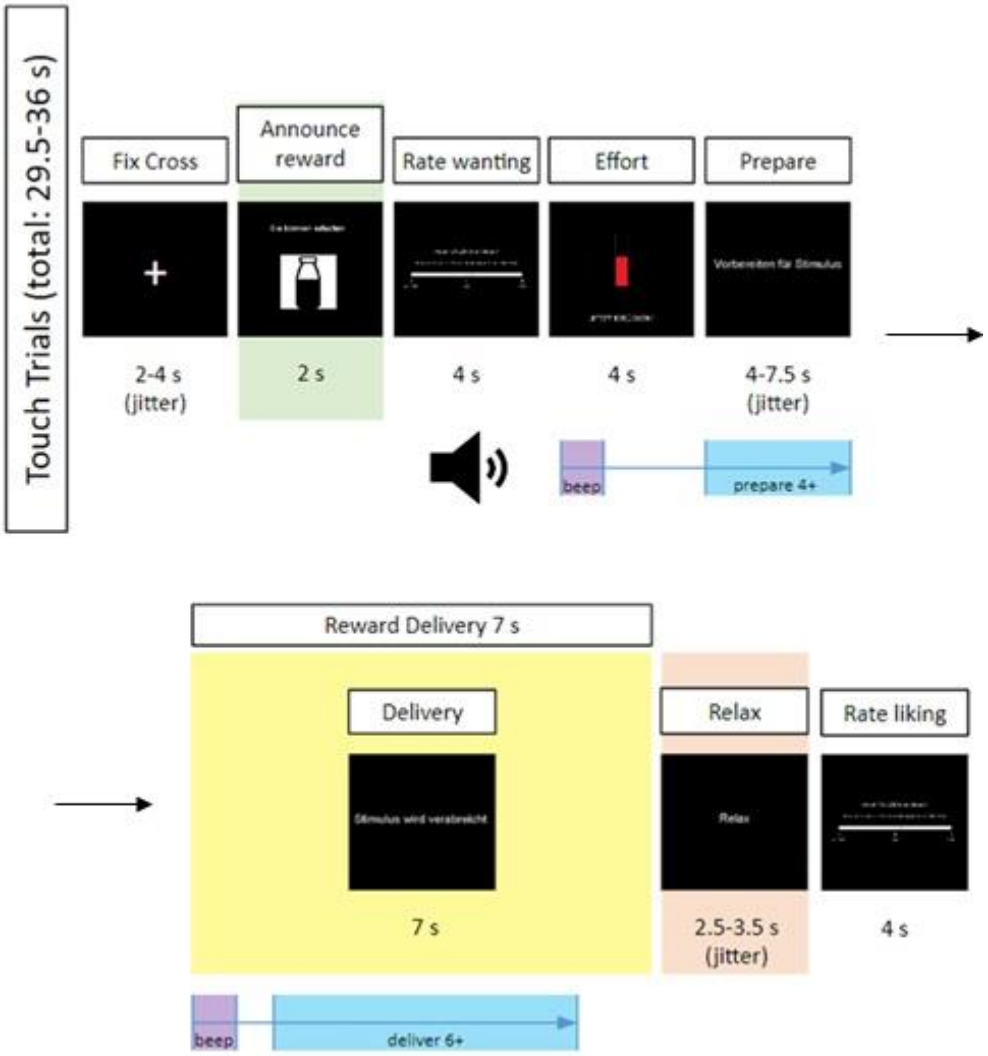
After that, the subject was driven out of the MRI tunnel by Experimenter 1/2, they removed the external head coil with the tubes staying on it, removed the cushion and asked the participant to get up, sitting on the scanner table. They then proceeded to instruct them on the upcoming main procedure that would be going to take ~ 1h 15 min. and made sure that the participant understood their tasks. Experimenter 1/2 also offered a blanket to the participant in order for the participant to not get cold during the session. They explained to the participant that it is very important that the subjects try not to move and stay calm during the whole session. Due to the high volume of the scanner while running, the subjects were given earbuds. They were instructed on how to use them and were told to put them on. The subject was asked to lay back down and Experimenter 1/2 again made sure the participants' body was in the right position, set up the under-knee cushion and blanket when needed, gave the button box and dynamometer back in the participant's hands to place them correctly and installed the emergency button. Pads were placed between the integrated head coil and the left and right ears of the subject, in order to stabilize the head. The external head coil with the tubes was put back on, and the subject was driven back up and into the scanner to position *Isocenter*. EMG cables were connected to its devices. Experimenter 1/2 left the scanner room and immediately spoke to the subject via intercom. After making sure intercom communication was working and the participant was informed about the next step, a practice trial with 3 food tasks, 3 touch tasks and 3 times MVC-measurement got done, with the scanner still off, to check if the task is done properly. The participant's interaction with the screen was on display, and if anything seemed off (e.g. no response), the Experimenter could step back in and talk to the participant via intercom. When done, the Experimenter again told the subject about the next step. MR alignment and T1-weighted MRI imaging took a few minutes. After that, the testing phase started.

Participants went through 4 alternating blocks; 2 food reward blocks and 2 touch reward blocks, each containing 16 trials. In each trial, the stimulus

(symbolic representation) was announced on screen. 8 times the high reward was announced, and 8 times the low reward. The participant then had to rate their desire to receive the stimulus moving a slider on a continuous wanting-scale from *not at all* to *very much*, with *neutral* in the middle, by pressing fingers on the button box as it had been instructed on the screen. Next, subjects could influence the probability of receiving the presented stimulus by increasing or decreasing dynamometer press force. Press force in relation to their MVC was visually presented on the screen with a red bar. Depending on press force and probability, the subject then either received the announced stimulus or one of the other 2 stimuli. The screen than said to relax for 2.5 to 3.5s, before the subject was asked to rate how much they actually liked the stimulus by, again, moving a slider on a scale from *not at all* to *very much*, with *neutral* in the middle, by pressing fingers on the button box. Exact timings of each step in the touch trials is shown in the following image.

Figure 1

fMRI task timings for touch trials



After the last block, MVC at the end of the experiment was measured. The subject was driven out of the scanner, and all equipment were removed from the participant. The participant was led to the former EMG preparation area, where the EMG cap and electrodes were removed. They were asked to perform a debriefing via laptop. After an optional short break, participants were asked one last time to get in the scanner to relax for est. 55 minutes, while resting state MRI, MR spectroscopic imaging, MR-T1 mapping, T2-weighted MR image and MR diffusion tensor imaging was conducted. When finished, the participant was given their voucher and was dismissed after clothing change.

Variables

This study is focused on the differences of neural reactions to consumption of CT-optimal social touch (6 cm/s) in an anorexic and healthy control sample, with the independent variable being the touch stimulus and the dependent variable being the neural reactions. During the functional scans, participants received 2 kinds of stimuli: food reward (3 kinds of milk) and social touch reward, which was operationalized as 3 gentle caresses of different velocities, with 6 cm/s being the CT-optimal touch and 21 cm/s as well as 27cm/s being non-CT optimal, on the right distal forearm, delivered by trained research assistants using their right or left index- and middle finger in a conjoined manner. Heterosexual participants were matched with female Touchers, homosexual participants were matched with male Touchers, and participants with other sexual orientations were matched with female Touchers.

Touching was limited to the outer hairy skin area between the little-finger-sided protruding end of the ulna and 9 cm in proximal direction from the end of the ulna. Boundaries were haptically marked with medical tape to ensure research assistants perform the caresses within the given skin area. During touch blocks, research assistants received auditory input through MRI-safe headphones. They heard short, metronome-like sounds in the speed that they should perform the caresses in order to do so simultaneously, with 3.5s of prelude to be prepared. A ‘beep’-sound signalised when the toucher had to deliver the stimulus for 7 s.

As the dependent variable, neural activation was measured using fMRI. Brain activity was assessed in response to CT-optimal touch conditions. fMRI data were analysed to identify differences in activation levels between the anorexic group and control group across the whole brain.

Technical Data

Structural and functional MRI data was obtained with a 3T (=3 Tesla) Siemens Magnetom Prism Scanner. It has a bore size of 60 cm, system length of 213 cm and system weight of 13 tons while operating, and a magnet length of 198 cm. This MRI scanner is equipped with XR Gradients, featuring a gradient strength of 139 mT/m and a slew rate of 346 T/m/s and features Zero Helium Boil-Off technology (Siemens Healthcare Diagnostics GmbH, n.d.).

fMRI Preprocessing

Preprocessing of the raw fMRI data was mostly conducted by project supervisors using standard practices in neuroimaging analysis and established preprocessing software. Below, the possible steps involved in fMRI pipelines are described to provide context for the processed data used in this analysis.

Preprocessing should always include quality control after every step to visually inspect the images and/or parameters for any artifacts or anomalies that could compromise subsequent analyses. The first step of preprocessing revolves around the structural data, in order to provide a reliable anatomical reference for the functional data. Skull-stripping, which is the term for the removal of the skull, is conducted, ensuring better registration and reducing noise. If the subject's head is tilted, the brain is realigned (reorientation), which also aims at enhancing registration results. Lastly, the various tissue types of the brain – grey matter, white matter, and cerebrospinal fluid – are segmented, creating masks (segmentation) (Crone, 2022/23).

Continuing with the functional data, trimming is applied to remove the initial volumes (est. first 4 timepoints), ensuring that only stable signal data is retained. Next, motion correction and denoising are implemented to account for participant head movements and reduce noise originating from physiological fluctuations. This is followed by distortion correction to reduce geometric distortions typically caused by magnetic field inhomogeneities. Slice timing correction is applied to adjust for temporal differences in slice acquisition, ensuring proper temporal alignment of voxel signals. Subsequently, skull-stripping is performed to remove the skull, analogous to the structural data preprocessing. Spatial smoothing is then applied to enhance the signal-to-noise ratio by averaging signals across neighbouring voxels, which improves statistical power while accounting for inter-subject variability. The data are further subjected to intensity normalization to bring voxel intensities to a consistent scale and temporal filtering to remove frequencies of no interest. Coregistration ensures alignment between functional and structural images, while normalization may be carried out to transform the images into standard space (e.g., MNI space) for inter-subject comparability. Finally, first-level analysis is performed, wherein the preprocessed data is used to generate individual-level statistical maps based on the task or stimulus of interest (Crone, 2022/23).

Software & Analysis Tools

All first-level and second-level analyses were conducted using SPM 12 (Statistical Parametric Mapping, 12th version, Wellcome Trust Centre for Neuroimaging, University College London, UK), a widely used neuroimaging analysis toolbox that operates as a MATLAB-based software (MATLAB version R2023a, MathWorks, Natick, MA, USA). SPM12 uses a General Linear Model (GLM) approach. Second-level analysis output coordinates were assigned to neuroanatomical structures using MRIcron (version 1.0.20190902, Mc Causland Center for Brain Imaging, University of South Carolina, USA) using a standard T1-weighted anatomical template.

First-Level Model Specification & Analysis

A customizable script for the first-level model and analysis was provided by one of the supervisors to automate the process. The functional data consisted of the preprocessed images from both touch blocks during consumption, with a duration of 7 s per trial. Each functional run included a total of 211 volumes, with a repetition time (TR) of 2.5 s. Touch consumption was represented as a parametric modulator with 2 stimulus categories, the first one being the CT-optimal touch (6 cm/s) and the second one being the non-CT optimal touch (21 cm/s and 27 cm/s). T-Contrast images were made for the parametric modulator, main effect of reward delivery (=reward delivery vs. Baseline) and main effect of reward announcement

Second-Level Model Specification & Analysis

A two-sample t-test with groups *AN* and *HC* was conducted using first-level contrast images. First-level contrast images of main effect of reward announcement were included in order to control for anticipatory reactions. Second-level contrasts were defined for AN < HC and AN > HC. Despite this study focusing on group differences, a contrast for main effect was added in order to provide contextual information and ensuring comprehensive interpretation of the data. Statistical significance was set at $p < .05$ using family-wise error (FWE) correction.

Results

Descriptive Analysis

Basic descriptive analysis of the data provided a comprehensive overview of the sample characteristics and trial details. Anorexic participants (*N* = 17) ranged in age from 13 to 22 years (*M* = 16.47, *SD* = 2.61) with 2 cases of anorexia binge-purge type and 15 cases of restrictive type. 6 participants were hospitalized at their testing date, 11 participants were having outpatient treatment. In the anorexic subgroup, minimum of CT optimal touch count per subject was 7, while maximum was 20 (*M* = 12.58, *Md* = 13.5). 64.7% of anorexic participants ranked the CT optimal touch as their high reward. 11 anorexic participants received trials order Food-Touch-Food-Touch (TFTF), and 6 received Touch-Food-Touch-Food (TFTF).

Mean age of participants in the control group was 17.83 - slightly older than in the AN sample – but also ranging from 13 to 22 years (*SD* = 2.36). CT touch count during the trials ranged from 7 to 16 (*M* = 12.17, *Md* = 11.5), hence depicting lower variability than in the AN sample. CT optimal touch was chosen as the highest reward in 83.33% of HCs. Accordingly, quite a higher percentage of healthy controls gave their preference on the CT optimal touch than AN participants. 8 HCs had trial order FTFT, and 10 had TFTF.

Second-Level fMRI Analysis

Primary Analysis (FWE-Corrected)

T-test analysis with settings p= .05 FWE identified significant main effect activations in several brain regions that could be observed on cluster-level and peak-level, but not on set-level. Significant main effect activations are presented in the following table.

Table 1

Main effect activations at p= .05 (FWE)

Cluster-level		Peak-level		MNI-coordinates			Neuroanatomical label
k_E	$P_{FWE\text{-}corr.}$	*T*	$P_{FWE\text{-}corr.}$	x	y	z	
1785	<.001	6.75	<.001	64	-22	80	-*[1] (outside of postcentral gyrus right)
		6.08	<.001	36	-20	54	Precentral gyrus right*[2]
838	<.001	6.29	<.001	18	-88	-10	Right inferior occipital gyrus
1177	<.001	6.29	<.001	-16	-92	-8	Middle occipital gyrus left
4	.037	4.97	.025	4	-112	0	-*[1] (outside of cuneus right)
3	.039	4.88	.035	-20	-66	54	Left superior parietal gyrus
1	.044	4.87	.036	-74	24	52	-*[1] (outside of middle frontal gyrus)

Note. *[1]activation peak in extracerebral space, *[2]non-significant local maxima inside significant cluster (exploratory), k_E = cluster extent, T = T-value derived from T-statistic (effect strength).

For contrast AN > HC, only one cluster in the left cerebellum was found to be significant (MNI: x = -32, y = -78, z = -22, cluster level: $p_{FWEcorr.}$ = .044, k_E = 1, peak level: $p_{FWEcorr.}$ = .044, *T* = 4.81). For contrast AN < HC, no suprathreshold clusters were found.

Exploratory Analysis 1 (Uncorrected, Voxel Extent = 50)

To explore potential activation patterns in contrasts AN > HC and AN < HC that did not survive strict correction, an exploratory analysis was conducted at p =

.001, uncorrected, with a minimum voxel extent of 50. This analysis revealed significant activations regarding contrast AN > HC shown in the table beneath. Again, no suprathreshold clusters were observed in contrast AN < HC.

Table 2

AN > HC with p=.001 (uncorr.), voxel extent = 50

Cluster-level		Peak-level		MNI-coordinates			Neuroanatomical label
k_E	p_{uncorr}	*T*	p_{uncorr}	x	y	z	
		4.81	<.001	-32	-78	-22	Cerebellum left
		4.18	<.001	-50	-28	36	Supramarginal gyrus left
		4	<.001	-8	0	-56	-* (outside of fusiform gyrus left)
		3.99	<.001	6	16	-20	Subgenual ACC right

Note. *activation peak in extracerebral space

Exploratory Analysis 2 (Uncorrected, Voxel Extent = 10)

To further investigate activation patterns, an additional exploratory analysis was conducted using a more lenient voxel extent threshold (10 voxels) while maintaining p=.001, uncorrected. This approach yielded additional activation peaks within contrast AN > HC that could be identified as the left anterior limb of the internal capsule (MNI: x = -18, y = 2, z = 16, $p_{uncorr.} < .001$, $T = 3.58$), right dorsal prefrontal cortex (PFC) (MNI: x = -34, y = 42, z = 10, $p_{uncorr.} < .001$, $T = 3.58$) and right middle occipital gyrus (MNI: x = 10, y = -98, z = 0, $p_{uncorr.} < .001$, $T = 3.56$)

Discussion

Summary of Key Findings

The present study aimed to investigate group differences in consummatory brain responses to CT-optimal social touch between individuals with anorexia nervosa (AN) and healthy controls (HC). Based on previous literature, it was hypothesized that AN patients would exhibit reduced activation in reward-related regions (striatum, anterior cingulate cortex, ventral tegmental area, hippocampus; H1) and heightened activity in regions linked to sensory processing, cognitive control, and threat detection (primary and secondary somatosensory cortices, prefrontal cortex, posterior insula, amygdala, and superior temporal gyrus; H2).

Primary FWE-corrected analysis yielded significant main effects of CT-optimal touch across all participants, confirming neural engagement during social touch processing. However, contrary to H1, no group differences were observed in the core reward-processing regions (striatum, ventral tegmental area, hippocampus) in the primary analysis. The only significant difference between AN and HC was increased activation of the left cerebellum in the AN sample.

Because of FWE-correction possibly being too strict in order to detect smaller effects, exploratory analyses with uncorrected thresholds were conducted. These revealed additional group differences, including heightened activation in the left supramarginal gyrus and right subgenual ACC in AN patients. Applying an even more liberal voxel extent threshold revealed additional activation peaks in the left anterior limb of the internal capsule, right dorsal prefrontal cortex, and right middle occipital gyrus in AN patients.

To summarize, H1 (reduced reward processing in AN) was not supported. No significant differences in core reward-processing areas (striatum, VTA, hippocampus) were observed, even in exploratory analyses. H2 (heightened sensory, cognitive, and threat-related processing in AN) was partially supported. Increased activation in the supramarginal gyrus (sensory processing), dorsal prefrontal cortex (cognitive control), and subgenual ACC (emotion regulation) suggests altered affective and sensorimotor processing in AN.

However, no evidence was found for increased amygdala, insula, or STG activity, which were hypothesized to show heightened responses.

An important methodological challenge in this study was the presence of activation peaks located outside the brain, likely due to spatial normalization errors, preprocessing inaccuracies, or signal noise, that will be discussed later. While neuroanatomical atlases suggested that these peaks were closest to the right postcentral gyrus, right cuneus, middle frontal gyrus, and left fusiform gyrus, these assumptions must be made with extreme caution, as extracerebral activations do not necessarily reflect true neural activity. Examining these findings in the context of the hypotheses brought up that no reward-related structures (striatum, ACC, ventral tegmental area, hippocampus) were implicated in these extracerebral activations. This aligns with the lack of significant findings supporting reduced reward processing in AN.

The proximity of an extracerebral activation peak to the right postcentral gyrus (location of S1) suggests that heightened sensory processing may still be relevant, even though S1 & S2 were not significantly different between groups in primary analysis. This could reflect abnormal tactile processing in AN, aligning with prior evidence of hypersensitivity to bodily sensations in AN (Zucker et al., 2013).

Another extracerebral peak was near the cuneus, a region involved in visual processing and attention (Materna et al., 2008; Palejwala et al., 2021). While not originally hypothesized, this may hint at increased attentional engagement in AN when experiencing social touch, potentially indicating heightened self-monitoring or altered interoceptive awareness.

The left fusiform gyrus, another extracerebral activation site, is a region strongly implicated in face and body perception, as well as emotional salience processing (Kanwisher & Yovel, 2006). Although not a direct part of the hypothesized regions, this could indicate increased visual-tactile integration or heightened sensitivity to social stimuli in AN. Given previous findings of altered body image processing in AN (Scharner & Stengel, 2019), this could reflect an atypical engagement of visual-perceptual networks in response to social touch, warranting further investigation.

Interpretation of Results

Alignment with the Literature on CT-optimal Touch Processing

The finding of increased activation in the left supramarginal gyrus in AN participants aligns with research showing heightened somatosensory activity in AN during social touch. The supramarginal gyrus, part of the somatosensory association cortex, plays a crucial role in body perception, self-other distinction, and the integration of sensory information (Boehme et al., 2019; Dobrushina et al., 2021; Lamp et al., 2019; Silani et al., 2013). This is consistent with findings from Frost-Karlsson et al. (2022), who reported higher bilateral somatosensory cortex activity in AN participants in response to both self-touch and other-touch. Increased supramarginal gyrus activation in AN may reflect heightened sensory awareness of touch, potentially contributing to aversive tactile experiences and discomfort with physical contact observed in this population.

Additionally, results revealed heightened activation in dorsal prefrontal cortex in AN patients, a region implicated in cognitive control and emotion regulation (Kaye et al., 2009). This aligns with Bischoff-Grethe et al. (2018), who found increased activity in the right ventral mid-insula extending into the superior temporal gyrus (STG) in AN participants. Since both the PFC (Olivo et al., 2019; Scharner & Stengel, 2019; Schulte-Rüther et al., 2012; Xu et al., 2017) and STG (Bigler et al., 2007) play roles in higher-order processing of social stimuli , increased activation in these areas may indicate increased cognitive and emotional regulation in response to touch, possibly due to heightened vigilance or discomfort with social touch in AN.

Divergences from previous fMRI Studies on CT-optimal Touch in AN

One notable deviation from previous studies was the lack of significant reward-related activation differences in the striatum, ventral tegmental area (VTA), and hippocampus under both primary and exploratory analyses. While reduced activation in these reward-related regions (H1) was hypothesized, results don’t align with Davidovic et al. (2018), who found reduced left caudate nucleus activity (dorsal striatum) in AN patients during social touch. Though, Bischoff-Grethe et al. (2018) and Davidovic (2016) also found no significant reward-related differences between AN and HC, suggesting that reward-related alterations may not be consistently detected across studies, potentially due to

differences in study paradigms, stimulus modalities (self-touch vs. other-touch), or participant characteristics (acute vs. recovered AN groups).

Similarly, while expecting increased amygdala and insula activity in AN (H2), no significant activations were found in these regions. This contrasts with the findings of Bischoff-Grethe et al. (2018), who reported higher right ventral mid-insula activation in AN participants. One possible explanation is that the whole- brain analysis conducted in this study may have concealed subtle differences in insular activity, which were only evident in previous studies using ROI (region of interest)-based approaches.

Interestingly, exploratory analysis did reveal increased activation in the right subgenual ACC in AN participants, which may reflect altered emotional processing and regulation during social touch. The subgenual ACC is involved in affective modulation and has been implicated in mood disorders (Drevets et al., 2008; Scharnowski et al., 2020). Given the high comorbidity of AN with anxiety and depression, heightened subgenual ACC activation may indicate increased emotional salience or distress associated with social touch, even if insula and amygdala activity were not significantly differing between groups.

Unique Findings: Cerebellar, Occipital Cortex & White Matter Activations

A novel aspect of the findings was the increased activation of the left cerebellum in AN participants, which was significant in both primary and exploratory analyses. While the cerebellum has traditionally been linked to motor coordination, growing evidence suggests its role in affective and sensorimotor integration (Schmahmann, 2019). Similarly, the engagement of the internal capsule, a white matter tract involved in sensorimotor communication, might also reflect altered sensory-motor integration during touch perception (Pryweller et al., 2014).

Additionally, the results revealed heightened right middle occipital gyrus activation in AN participants, similar to Davidovic (2016) and Davidovic et al. (2018), who reported higher activation of the lateral occipital cortex in AN during social touch. This suggests that visual processing regions may be more engaged in AN, possibly due to increased attention to the body during touch or altered multisensory integration of tactile and visual information.

Implications for Anorexia Nervosa Pathogenesis

This study's findings point to the conclusion that anorexia nervosa is characterized by alterations in cognitive control, emotional regulation, and body perception, particularly in the context of social reward processing. Given that social touch is inherently rewarding, engaging the C-tactile system and mesolimbic reward pathways (McGlone et al., 2014; Dreisoerner et al., 2021; Pawling et al., 2017), the atypical neural responses observed in AN may reflect fundamental disruptions in how socially rewarding experiences are processed at the neurobiological level. These disruptions could further contribute to interpersonal difficulties, social withdrawal, and emotional isolation, continuing the cycle of maladaptive behaviors in AN (Cardi et al., 2013; Haynos et al., 2021; Kerr-Gaffney et al., 2022).

Somatosensory/Interoceptive Processing

Interoception, or the ability to perceive and interpret bodily sensations, is thought to be altered in AN, with individuals showing hypersensitivity to certain somatic signals (Crucianelli et al., 2016; Crucianelli et al., 2021). The increased activation in the supramarginal gyrus observed in AN participants in this study suggests heightened sensory awareness during CT-optimal social touch, possibly aligning with previous research showing increased bilateral somatosensory activation in AN (Frost-Karlsson et al., 2022). While heightened somatosensory cortex activation may contribute to aversive responses to social touch, results did not show increased insular activation, which is often implicated in interoceptive awareness and emotional processing of touch (Bjornsdotter et al., 2009). This suggests that while basic sensory processing may be amplified in AN, the affective integration of social touch - typically facilitated by the posterior insula and reward circuits - may be disrupted or de-emphasized, contributing to atypical social touch experiences in AN.

Emotional Regulation and Cognitive Control

The findings also revealed increased activation in the dorsal PFC and subgenual ACC in AN patients, suggesting a role for excessive top-down control over emotional responses to touch. The dorsal PFC is heavily involved in cognitive control, attention shifting, and emotion regulation (Boehm et al., 2018;

Steinglass et al., 2019), and its heightened engagement during social touch may indicate that AN patients are actively regulating their responses to physical contact, possibly to suppress discomfort or distress. Increased activation of subgenual ACC in AN during social touch could reflect heightened affective salience of physical contact, potentially linked to anxiety or social discomfort. This aligns with previous findings showing increased ACC activity in response to social rejection in AN (Via et al., 2015), further supporting the idea that social interactions - including touch - are processed differently in AN, with an exaggerated emotional response or heightened self-monitoring.

Social Reward Processing

The reward system is central to social behavior, and disruptions in social reward processing have been widely documented in AN (Boehm et al., 2018; Monteleone et al., 2018; Kerr-Gaffney et al., 2022). Contrary to hypothesis 1 (H1), no significant reductions in reward-related regions were found. However, results revealed increased activation in cerebellar regions, which have been implicated in reward learning and sensorimotor integration (Schmahmann, 2019), suggesting that alternative circuits may be engaged during social touch in AN, possibly as compensatory mechanisms.

Social reward processing deficits in AN have been linked to diminished dopaminergic signaling in the striatum, reducing the ability to experience pleasure from social interactions (Keating, 2010). This anhedonic response is further compounded by excessive cognitive control from prefrontal regions, suppressing typical reward responses (Steinglass et al., 2019). The finding of dorsal PFC hyperactivation aligns with this model, suggesting that AN patients may not passively experience the rewarding aspects of social touch but rather actively regulate or suppress these sensations, reinforcing avoidant behaviours.

Additionally, heightened occipital cortex activation in AN during social touch, as observed in our study, has been previously reported in Davidovic (2016) and Davidovic et al. (2018). This suggests that individuals with AN may rely more on visual processing strategies when experiencing social interactions, possibly due to difficulties in processing bodily sensations in real-time. Given that previous studies have shown increased visual attention to negative social stimuli in AN (Via et al., 2015), these results may indicate that social touch is evaluated

in a more analytical, externalized way, rather than being processed as an intrinsic affective experience.

Potential Clinical Applications

The findings of this study encourage research-based clinical interventions targeting underlying neural, emotional, and social dimensions of AN. One potential application is the development of interventions that use touch to reduce social avoidance and increase the rewarding value of interpersonal touch. Touch therapy could help retrain the brain to associate social touch with positive emotions. It might include therapist-administered touch, self-touch exercises, or guided social touch with trusted family members, gradually increasing exposure and tolerance to physical contact. Additionally, massage and tactile stimulation therapies, which have been shown to reduce anxiety and improve mood through the release of endorphins and oxytocin (Morhenn et al., 2012) could be incorporated into anorexia nervosa treatment to modulate hypersensitivity to touch, alleviate stress, and promote social bonding. For individuals with significant touch avoidance or social anxiety, haptic feedback devices that simulate CT-optimal touch could serve as tools for gradual exposure therapy.

Emotion regulation training is another important focus, given evidence that individuals with anorexia nervosa show increased activation in the dorsal prefrontal cortex and subgenual anterior cingulate cortex during social touch. This heightened activity suggests excessive cognitive control and emotional salience, which may lead to the suppression of affective responses and contribute to emotional distancing and avoidance behaviour. Mindfulness-based practices, such as interoceptive awareness and body scanning, could help reduce this cognitive control and regulate somatosensory hypersensitivity (Lazzarelli et al., 2024). Compassion-focused therapy might also help patients reinterpret social touch as positive and reassuring rather than threatening.

Another exciting clinical innovation involves neurofeedback-based interventions to modulate neural responses to social touch. For instance, real-time functional MRI neurofeedback could provide patients with immediate feedback on their brain's response to touch stimuli, enabling them to actively regulate their brain activity. Similarly, EEG-based biofeedback could train patients

to reduce excessive cognitive control, such as prefrontal hyperactivation during social interactions, encouraging healthier emotional engagement.

However, given that AN is a heterogeneous disorder with varying degrees of social impairment, sensory sensitivity, and cognitive control biases, future treatment approaches should consider personalized interventions based on individual neural and behavioural profiles. Functional neuroimaging biomarkers could help identify subgroups of AN patients with more pronounced reward deficits, sensory hypersensitivity, or cognitive overcontrol, allowing for tailored interventions. Multimodal approaches integrating behavioural, cognitive, and pharmacological treatments may provide the most comprehensive strategy for improving social functioning and emotional well-being in AN.

Strengths and Limitations

Strengths

This study has several key strengths that contribute to the growing body of research on social touch processing in AN. A distinctive aspect of this study was the use of real human touch rather than mechanical stimulation, such as paintbrushes or robotic devices, to examine consummatory neural responses to CT-optimal touch. One of the main advantages of human-delivered touch is its ecological validity and real-world relevance. Social touch in everyday life typically occurs between humans rather than through mechanical devices, making human-administered touch a more naturalistic representation of interpersonal interactions. This increases the generalizability of the findings and enhances their applicability to understanding social bonding, affect regulation, and physical closeness in AN. Prior research has shown that human touch engages additional brain regions beyond purely tactile processing areas, including social-affective networks involved in social cognition, emotional regulation, and interpersonal bonding (Gordon et al., 2013; Walker et al., 2017). In contrast, mechanical touch delivered by a robotic device or paintbrush may engage somatosensory areas such as S1, S2, and the insula, but may not strongly activate regions associated with higher-order social and emotional processing.

Furthermore, this study used fMRI to investigate patterns of brain activity in response to CT-optimal touch, providing high spatial resolution and the ability to identify specific neural circuits involved in social touch processing. The

application of whole-brain analyses allowed for a comprehensive assessment of group differences. By implementing a strict FWE correction for multiple comparisons in the primary analysis, this study was equipped to ensure that significant results were unlikely to be due to chance. At the same time, exploratory analyses with less conservative thresholds provided additional insights. The voxel extent threshold of k = 50 helped reduce random noise by ensuring that only larger, contiguous clusters of activation were considered. The second exploratory analysis was modified to set voxel extent threshold to 10. This more liberal threshold was used to explore smaller activation clusters, which may be relevant in regions of interest but could have been overlooked due to strict corrections. With k = 10, this analysis was particularly useful for detecting subtle activation patterns in areas associated with social touch processing.

Contributing to existing neurocognitive models of AN, the study provides evidence for heightened prefrontal and subgenual ACC activation in AN associated with excessive top-down control of affective responses to social stimuli. Also, the increased somatosensory and cerebellar activation suggests sensory integration deficits in AN, which may contribute to heightened awareness or discomfort during social touch (Crucianelli et al., 2016). By linking neural findings to established theoretical models, this study helps clarify how reward, sensory, and cognitive control networks interact in AN.

As already implicated, the insights gained from this study propose direct clinical implications, particularly for the development of interventions. Potential applications include touch-based therapies (e.g., CT-optimal touch exposure, massage therapy) to increase tolerance for social touch and enhance positive affective responses, emotion regulation training to help AN patients reduce excessive cognitive control over social experiences and neurofeedback interventions to modulate somatosensory and reward-related brain activity during social interactions. By identifying specific neural alterations in response to social touch, this study contributes to the groundwork for translating neurobiological findings into practical treatment approaches, improving outcomes for individuals with AN.

Finally, the study has broader implications for social and affective neuroscience, particularly in understanding how social touch is processed across psychiatric populations. Given that altered responses to social touch have also

been observed in conditions such as autism spectrum disorder (Frost-Karlsson et al., 2022) and social anxiety disorder (Wilhelm et al., 2001), the findings contribute to a larger discussion on how different psychiatric conditions shape social and affective experiences.

Limitations

While this study provides valuable insights into the neural processing of CT-optimal social touch in AN, several limitations must be acknowledged. One of the primary limitations of this study is its relatively small sample size, which may have limited the statistical power to detect subtle differences in brain activation between AN and HC. Given the heterogeneous nature of AN, a larger sample would allow for more robust subgroup analyses, considering factors such as illness duration, symptom severity, comorbid conditions, and treatment history. Also, selection bias may have influenced the results, as AN participants were recruited from clinical settings, which may not fully represent the broader AN population. Additionally, this study focused on female participants, given the high prevalence of AN in women, but this limits the generalizability to male or non-binary individuals with AN. Future research should aim to include more gender-diverse samples to assess whether similar neural alterations are present across different populations. Other potential confounders include medication use (e.g., SSRIs, atypical antipsychotics), nutritional status, and psychiatric comorbidities (e.g., depression, anxiety, autism spectrum traits), all of which could influence neural responses to social touch. Future studies should aim for more rigorous matching between groups and consider longitudinal designs to assess how neural responses change over time.

Next, interpreting fMRI data in psychiatric populations presents several challenges. One key issue is that brain activation differences may not always reflect the primary pathology of AN, but rather compensatory mechanisms, individual differences in symptom presentation, or effects of prolonged malnutrition. Additionally, psychiatric disorders are often characterized by complex network-level disruptions, meaning that activation in isolated regions may not fully capture the functional connectivity alterations that contribute to AN. Future research should explore functional connectivity analyses to examine how

reward, sensory, and cognitive control networks interact during social touch processing.

Although fMRI provides high spatial resolution, it has limited temporal resolution, making it difficult to capture the precise timing of neural responses to social touch. Additionally, motion artifacts, common in psychiatric populations (Makowski et al., 2019), may have influenced some results, particularly given the potential for heightened anxiety or discomfort during scanning in AN participants. Future studies may benefit from combining fMRI with complementary techniques such as EEG or functional near-infrared spectroscopy (fNIRS), which can provide better temporal resolution and improve ecological validity.

A notable concern in this study is that some activation peaks were located outside the brain, a phenomenon that can arise due to various methodological and technical factors. The process of aligning individual brain scans to a standardized template (e.g., MNI space) can sometimes introduce distortions (Crone, 2022/23), particularly in populations with atypical brain morphology, such as individuals with AN, who often exhibit reduced grey matter volume and structural alterations (Seitz et al., 2014). These errors can cause misalignment of brain regions, leading to apparent activations outside the expected anatomical boundaries. Moreover, even small, involuntary head movements can introduce signal distortions, particularly near the edges of the brain. Motion artifacts can lead to false activations in extracerebral areas, especially in regions near the skull or scalp, despite the use of standard motion correction procedures. Also, MRI signals are sensitive to non-neural physiological fluctuations, such as blood flow in extracerebral vasculature or movement of cerebrospinal fluid (Crone, 2022/23). While these extracerebral activations do not directly impact the primary conclusions, they warrant careful consideration in interpreting the findings and assessing overall study reliability.

Methodological challenges were also faced in this study. In the primary analysis, a significance level of $p = .05$ FWE-corrected was set, ensuring strict control for multiple comparisons and reducing the likelihood of false positives. Given that this study aimed to examine group differences in consummatory brain responses to CT-optimal social touch, this threshold would have provided strong evidence for significant neural effects while minimizing the risk of Type I errors. However, because FWE correction is a strict approach, it may miss subtle but

meaningful effects, especially in regions where activation differences are expected but may be weaker. To address this, additional exploratory analyses using uncorrected thresholds with voxel extent criteria were conducted, but findings from this approach need to be interpreted with caution and are considered preliminary, requiring further validation.

As this study focused on consummatory responses to social touch, it did not examine anticipatory or motivational aspects of social touch processing. Given that reward anticipation and motivation deficits have been widely documented in AN (Keating, 2010; Monteleone et al., 2018), future research should explore whether individuals with AN show reduced approach motivation or heightened avoidance tendencies toward social touch even before physical contact occurs. Additionally, the study design did not include subjective experiences of social touch, meaning it cannot directly link neural responses to participants' affective perceptions of touch. Future studies should integrate self-report measures to better understand the relationship between neural activation patterns and subjective experiences of social touch in AN. Also, use of other implicit measures (eg. EMG, skin conductance, heart rate variability) in combination with neural imaging could provide additional insight.

Future Directions

Upcoming studies should increase sample sizes to improve the reliability and robustness of findings and allow for more detailed subgroup analyses (e.g., comparing AN restricting subtype vs. AN binge/purge subtype). Also, they should include male and gender-diverse participants, as most research on AN has focused on women. Given emerging evidence that AN symptoms may present differently in males (World Health Organization, 2022), it is important to assess whether neural responses to social touch differ by gender. Furthermore, comparing acute vs. recovered AN individuals to determine whether altered social touch processing is a state-dependent effect (linked to malnutrition) or a trait marker (persisting after recovery).

A longitudinal approach would also contribute to clarifying whether altered responses to social touch are an early vulnerability factor, a consequence of starvation, or a residual feature of AN. Upcoming studies should track neural and behavioural changes in social touch processing before, during, and after

treatment to determine whether successful recovery is associated with a normalization of reward responses to social touch, as well as investigating whether altered social touch processing predicts relapse risk, potentially identifying biomarkers for long-term recovery outcomes. The neural mechanisms underlying social touch processing may not be distinctive to AN but could be similar to other psychiatric conditions characterized by social withdrawal, altered interoception, and sensory sensitivity. It would be interesting to compare AN with other psychiatric populations such as autism spectrum disorder, social anxiety disorder and major depressive disorder.

Comparing responses to touch from different sources, such as a close friend, family member, therapist, or an unfamiliar experimenter, could help determine whether familiarity influences neural activation patterns in key sensory, reward, and emotional processing regions. It is possible that touch from a familiar individual may be perceived as more acceptable or comforting, whereas touch from a stranger may elicit heightened vigilance or discomfort. Functional MRI studies could examine whether somatosensory regions (S1, S2, insula), reward-related areas (striatum, orbitofrontal cortex), and emotion regulation circuits (anterior cingulate cortex, amygdala) respond differently depending on the familiarity of the toucher. Additionally, studies could assess whether greater familiarity leads to increased positive affect and reduced avoidance behaviours, providing insight into how interpersonal relationships impact touch perception in AN.

The broader social context in which touch occurs may also play an important role in determining how it is processed in AN. Future studies could compare responses to social touch in different settings, such as a clinical setting (e.g., therapist-administered touch), a social setting (e.g., touch from a peer or family member), or a neutral setting (e.g., touch from an experimenter in a lab environment). These studies could help determine whether touch avoidance in AN is context-dependent and whether certain social environments facilitate more positive responses to touch. If neural and behavioural responses to social touch differ based on context, this could suggest that interpersonal comfort and perceived social safety modulate how individuals with AN experience physical contact.

While fMRI provides important insights into brain activation patterns, future research should adopt a multimodal approach to capture a more comprehensive picture of social touch processing. Self-report questionnaires should be incorporated to assess individuals' subjective experiences of social touch. These may include measures such as pleasantness ratings and touch avoidance scales to gain insights into personal perceptions and attitudes toward touch. Additionally, social interaction tasks should be included to explore how altered responses to touch manifest in real-world behaviour. For instance, tasks could assess an individual’s willingness to engage in physical contact with others, providing valuable data on the practical implications of touch perception. To evaluate stress or relaxation responses during social touch, physiological measures of autonomic nervous system activity should be recorded. These include heart rate variability, skin conductance, and oxytocin release, which can indicate levels of physiological arousal or calmness (Eckstein et al., 2020). Furthermore, electromyography (EMG) should be utilized to measure facial expressions in response to touch. This approach provides objective markers of affective engagement, helping to assess emotional reactions that may not be captured through self-report measures alone.

Future research should go beyond examining regional brain activation and instead focus on analysing functional connectivity between key neural regions. Specifically, the connectivity between somatosensory regions (such as S1, S2, and the insula) and reward-related areas (including the striatum, anterior cingulate cortex, and orbitofrontal cortex) should be investigated to determine whether weaker connectivity is associated with reduced pleasure from social touch. Additionally, the relationship between the prefrontal cortex and limbic regions should be explored to assess whether excessive cognitive control dampens natural emotional responses to touch. Understanding these neural connections could provide deeper insights into the mechanisms underlying social touch processing.

An important step is to translate research findings into clinical applications by designing intervention studies that directly target social touch processing in AN. One sight for investigation is the potential benefits of CT-optimal touch interventions. These approaches could be tested to determine whether they improve social reward sensitivity and reduce avoidance of interpersonal touch in

individuals with AN. Additionally, researchers should assess whether consistent exposure to CT-optimal touch leads to long-term changes in neural activity, particularly within somatosensory and reward-processing regions, which are critical to the perception and enjoyment of social touch. Another potential intervention strategy involves developing training programs aimed at reducing excessive cognitive control over social experiences. This could include mindfulness-based touch therapy. Furthermore, researchers should determine whether such emotion regulation training can normalize the hyperactivation of the prefrontal cortex in response to social touch, thereby improving emotional engagement and reducing avoidance behaviours. Neurofeedback may also serve as a promising therapeutic tool for addressing social touch deficits in AN. Additionally, researchers should investigate whether reinforcing activation in reward-related brain areas, such as the striatum and anterior cingulate cortex (ACC), can help restore typical reward sensitivity to social touch in individuals with AN. If successful, neurofeedback could provide a novel, brain-based approach to improving social reward processing in this population.

Given that social interactions are crucial for recovery from anorexia nervosa (AN), researchers should investigate how different aspects of social support and interpersonal relationships influence social touch processing and overall well-being in individuals with AN. One important area of study is how social touch processing varies between AN patients who have high levels of social support compared to those with low levels. Understanding these differences could provide insights into whether strong social connections serve as a protective factor against touch avoidance and impaired social reward processing. Moreover, it could be explored whether interventions aimed at improving social reward sensitivity—such as group therapy or oxytocin administration—can enhance engagement in interpersonal relationships. By increasing sensitivity to social rewards, these interventions may help individuals with AN develop stronger, more fulfilling social connections. Finally, the potential benefits of family-based interventions that incorporate gentle social touch should be examined. These interventions could use touch as a tool for fostering emotional connection and support within families, potentially helping individuals with AN feel more secure and engaged in their close relationships.

Conclusion

This study provides important insights into the neural processing of CT-optimal social touch in anorexia nervosa, shedding light on how altered sensory integration, cognitive control, and social reward processing contribute to atypical interpersonal experiences in AN. The findings reveal heightened activation in somatosensory and cognitive control regions (supramarginal gyrus, dorsal prefrontal cortex) and altered engagement of emotion regulation circuits (subgenual ACC, cerebellum) in AN participants, suggesting that social touch may be processed with increased sensory awareness, excessive cognitive regulation, and heightened emotional salience.

These findings have broad theoretical and clinical implications. The study supports existing models of AN that emphasize excessive top-down cognitive control and altered somatosensory processing. It also highlights the need for interventions that target social touch processing, such as touch-based therapies, emotion regulation training, and neurofeedback techniques. By improving the understanding of how AN patients experience and process social touch, this research paves the way for novel treatment approaches aimed at restoring positive social interactions and reducing social avoidance behaviours.

Beyond AN, this study contributes to the broader field of social and affective neuroscience, emphasizing the importance of social touch in psychiatric conditions characterized by social dysfunction. Future research should expand on these findings by exploring social touch processing across different psychiatric populations, incorporating multimodal neuroimaging techniques, and developing intervention-based studies that translate neural insights into clinical practice.

Ultimately, findings highlight the critical role of social touch in emotional well-being and interpersonal bonding, emphasizing that understanding its neural basis in AN is essential for developing more effective, socially-focused treatment strategies. By addressing social reward deficits and sensory integration difficulties, this research field has the potential to enhance recovery outcomes and improve the quality of life for individuals affected by AN.

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List of Tables

List of Abbreviations

ACC……....anterior cingulate cortex
AN……..anorexic/anorexia nervosa
CT……C-tactile
FWE…….....family-wise error
HC……..healthy control(s)
MVC……maximum voluntary contraction
OFC……..orbitofrontal cortex
PFC……...prefrontal cortex
ROI……...region of interest
rsFC…….resting state functional connectivity
S1…….primary somatosensory cortex
S2……secondary somatosensory cortex
STG…….…superior temporal gyrus

Appendix

Abstract (EN)

This master thesis examines consummatory neural responses to CT-optimal social touch in female adolescents with anorexia nervosa compared to healthy controls. Using functional magnetic resonance imaging (fMRI), participants underwent trials of CT-optimal and non-optimal touch to investigate differences in social reward processing. Significant neural engagement was observed in response to CT-optimal touch, yet no group differences were found in core reward-related areas, such as the striatum, ventral tegmental area, and hippocampus. However, anorexic participants exhibited increased activation in regions associated with sensory processing (supramarginal gyrus), cognitive control (dorsal prefrontal cortex), and emotion regulation (subgenual anterior cingulate cortex). Furthermore, analysis highlighted additional activation patterns in the cerebellum and occipital regions, suggesting heightened attentional engagement and altered sensory-motor integration. These findings indicate that anorexia is characterized by enhanced sensitivity to sensory and emotional stimuli during social touch, alongside potential disruptions of reward processing due to excessive top-down control. The study contributes to the understanding of interpersonal experiences in AN and its implications for the disorder's maintenance and treatment. Further research is needed to validate these findings and develop targeted interventions for improving social and emotional functioning in AN patients.

Zusammenfassung (DE)

Diese Masterarbeit untersucht die neuronalen Reaktionen auf CT-optimale Berührung bei weiblichen Jugendlichen mit Anorexia nervosa im Vergleich zur gesunden Kontrollgruppe. Mittels funktioneller Magnetresonanztomographie (fMRT) wurden die Reaktionen der Teilnehmerinnen auf CT-optimale und nicht-optimale Berührungen getestet, um Unterschiede in der Belohnungsverarbeitung zu untersuchen. Als Reaktion auf CT-optimale Berührungen wurde eine signifikante neuronale Aktivierung beobachtet, wobei jedoch keine Gruppenunterschiede in zentralen belohnungsbezogenen Bereichen wie dem Striatum, dem ventralen tegmentalen Areal und dem Hippocampus festgestellt wurden. Die anorektischen Studienteilnehmerinnen wiesen jedoch eine erhöhte Aktivierung in Regionen auf, die mit der sensorischen Verarbeitung (supramarginaler Gyrus), der kognitiven Kontrolle (dorsaler präfrontaler Kortex) und der Emotionsregulation (subgenualer anteriorer cingulärer Kortex) in Verbindung gebracht werden. Darüber hinaus zeigte die Analyse zusätzliche Aktivierungsmuster im Kleinhirn und in okzipitalen Regionen auf, die für eine erhöhte Aufmerksamkeit und eine veränderte sensorisch-motorische Integration bei Berührungsreizen sprechen. Diese Ergebnisse könnten darauf hindeuten, dass Anorexie neben möglichen Störungen der Belohnungsverarbeitung aufgrund einer übermäßigen kognitiven Kontrolle durch eine erhöhte Empfindlichkeit gegenüber Berührungsreizen gekennzeichnet ist. Die Studie trägt zum Verständnis der zwischenmenschlichen Erfahrungen bei Anorexie und ihrer Auswirkungen auf die Aufrechterhaltung und Behandlung der Störung bei. Weitere Forschungsarbeiten sind erforderlich, um diese Erkenntnisse zu validieren und gezielte Maßnahmen zur Verbesserung der sozio-emotionalen Probleme von Anorexie-Betroffenen zu entwickeln.