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An investigative look into the role of CT-fiber-mediated social touch and insular activity in anorexia nervosa

Suggesting an etiological importance of socio-emotional deficits in conjunction with altered interoception

verfasst von / submitted by

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Abstract

Anorexia nervosa (AN) is an illness that is difficult to investigate due to a multitude of plausible influence factors that play predisposing, triggering, maintaining, and exacerbating roles at its different stages within an intricate network of related psychopathology. In this investigation, several modes of action for AN and a novel perspective on the human social brain, both building upon interoception, are discussed. I argue that early and persistent interoceptive deficits could explain the strikingly broad and eclectic psychopathology that accompanies AN, especially characteristic socio-emotional impediments. To substantiate the claims, an fMRI experimental paradigm is used to measure insular activity of anorexic and healthy females during interoceptively integrated CT-afference, which is then connected to individual eating disorder syndrome severity and levels of alexithymia. A small and non-significantly larger activation was found in the posterior insula of anorexic individuals, while an opposite effect was found in the anterior insula. Small and very small non-significantly positive correlations of anterior and posterior insula activations were found with eating disorder syndrome severity and alexithymia levels. The results are understood as an implication of a disturbed integration of interoceptive afference in the anorexic insula. The reader is advised to shift focus on the summary and synthesis of etiological approaches incorporating interoceptive deficits, as well as the prospective orientation of the discussion, guiding future research.

1. Introduction

1.1 Anorexia Nervosa and the Intricacies of its Comorbidities

AN is a clinical condition that is characterized by “deliberate weight loss, induced and sustained by the patient” (World Health Organization, 2016). Secondary effects of long-term malnutrition have been hypothesized to perpetuate the illness in a vicious cycle, with dysfunction in bio-, psycho-, and social observation levels understood as cause and effect, to a varying extent. For a concise summary of proposed etiological factors, see Treasure et al. (2015; fig. 1). The illness especially affects adolescent and young females and is accompanied by the highest mortality rate of any psychiatric illness (Jacquemot & Park, 2020); this is in part due to the direct effects of prolonged starvation and in part, due to suicide (Pompili et al., 2004). Comorbidities include depression, personality disorders, anxiety disorders, self-harm, obsessive compulsive disorder, social phobia, and autistic traits

in terms of repetitive and stereotyped behavior (Nilsson et al., 1999; Franko et al., 2004; Kaye et al., 2004; Pooni et al., 2012; Allen et al., 2013). Also, sub-clinical conditions such as general cognitive rigidity, diminished social cognition and Alexithymia (Jacquemot & Park, 2020), which is found in up to 77% of anorexic individuals, accompany AN above chance and are thought of as risk and maintenance factors (Bourke et al., 1992; Jacquemot & Park, 2020). Restrictive eating behavior has enduringly been understood as a coping mechanism that reduces stress and distressing emotions (American Psychiatric Association, 2013; World Health Organization, 2016; Fairburn, 2008). Due to the striking specificity of age and gender, I propose heightened attention towards sociocultural factors and snowballing effects of early socio-emotional developmental aberration.

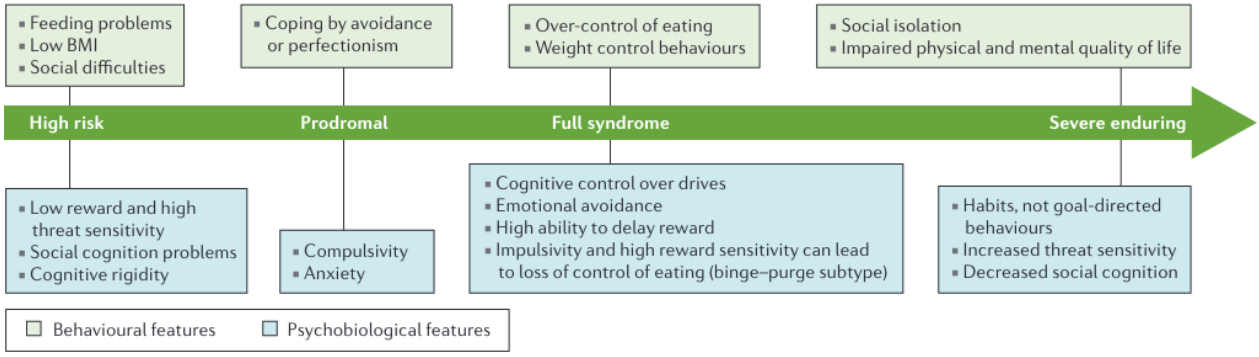


Fig. 1. *Underpinning behaviors and psychobiological factors of AN, as proposed in Treasure et al. (2015). Several could be connected to an underlying interoceptive impediment.*

Among the many clinical and sub-clinical comorbidities of AN, causal relationships suggest themselves but are extremely intricate to investigate due to their interwoven nature. An additional hardship is added by the cross-domain nature of currently respected models of etiology that suggest an interconnected pattern of predisposing, triggering, maintaining and exacerbating factors that incorporate social, cultural, developmental, behavioral, cognitive and neurobiological viewpoints (Treasure et al., 2015). Research is also impeded by the context of developmental trajectories that complicate the definition of deviation from the norm (Treasure & Schmidt, 2013), as well as by the limited realizability of longitudinal investigations that are needed for credible causal assumptions.

Considering these hardships, a major step substantiating existing assumptions of causality is finding support for a common denominator within the intricacies of AN's symptomatology and its comorbidities. The here presented investigation aims at strengthening an assumed

central role of aberrant insular activity and concurrent interoceptive deficits for AN (Jacquemot & Parker, 2020). Mechanisms reviewed in Jacquemot & Parker (2020) and a number of theories connecting interoception and the perception of emotion will be discussed and linked to a novel perspective on the emergence of a social brain as presented by Atzil et al. (2018). Neuroimaging will be used in conjunction with a social touch experimental paradigm and a clinical assessment to corroborate theoretical speculations on the role of altered interoception for AN.

1.2 The Insula and Interoception

The insula has been shown to play a major role in anxiety (Paulus & Stein, 2010), depression (Drevets et al., 2008), addiction (Naqvi & Bechara, 2009) and eating disorders (Wagner et al., 2008; Khalsa et al., 2015) and is seen as the central hub for receiving and integrating sensory information from different organs, the term interoception describing the perception of these visceral signals (Critchley et al., 2004; Menon & Uddin, 2010). It is also involved in regulating autonomic functions, and, as will be highlighted later, cognitive processes and emotions (Craig, 2009; Menon & Uddin, 2010). Anorexic individuals have been shown to experience disturbed interoception, with emerging discord about the roles of interoceptive sensitivity (IS) and interoceptive awareness (IA), stemming from ambiguity about the concept of interoception itself. While IS refers specifically to the accuracy of detecting and perceiving bodily sensations, IA encompasses a broader set of processes that involve the integration of those sensations with other cognitive and emotional processes (Garfinkel et al., 2015). As will be shown in the following section, interoceptive impediments are hypothesized to affect anorexic individuals through a multitude of effects.

1.3 Explanatory Models Linking Interoceptive Aberration to Anorexia Nervosa

Most viewpoints that are presented in Jacquemot & Parker (2020) share a central relevance of interoception as a means of monitoring the allostatic state of the body, thus seeing it as the key input that enables efficient allostasis in healthy individuals. Apart from this commonality, theoretical explanations link interoception to a strikingly diverse array of impediments. This prominent eclecticism of explanatory models and comorbidities, combined with the convincing hypotheses about their linkage to interoceptive deficits, suggests a central role of interoception and thus, the insula, for AN.

Hunger and satiety can be seen as the most direct and intuitively comprehensible dysfunctional aspects of AN that have been linked to interoceptive deficits. Nevertheless, research on this topic seems to have not reached a clear consensus. Anorexic patients report increased and prolonged satiety in subjective questionnaires and visual analog scale (VAS) ratings (Robinson, 1989; Bluemel et al., 2017). Also, Kurth et al. (2010) found that one in three AN patients reports fullness and no hunger even when the stomach is empty. A study with very limited generalizability due to its small sample size showed altered interoceptive gastric sensitivity in AN after administering food directly into the stomach (Coddington & Bruch, 1970), providing a rare objective measure. On the other hand, a more recent study found that individuals with AN did not differ from healthy controls in their ability to detect changes in stomach fullness (Khalsa et al., 2015) and another study found that individuals with AN were able to accurately perceive their own heartbeats, suggesting that interoceptive deficits may be specific to certain bodily signals and not a generalized impairment in interoceptive processing (Pollatos et al., 2016). Possibly, much of the uncertainty in this field of research results from the challenging distinction and operationalization of IS and IA along a gradient of cognitive involvement (Critchley & Garfinkel, 2017), and the failure to consider its importance in many experimental designs. Also, the hardship of experimentally inducing hunger, satiety, and interoceptive sensations in general becomes evident – much of the variation of effects might be attributed to different stimuli relying on interoceptive signaling to varying extents.

Body dysmorphia has been shown to predictably maintain negative eating behaviors, as reviewed in Jacquemot & Park (2020). The authors postulate that interoceptive impairment hampers the perception of physical changes that accompany weight loss, “leading to perpetual body image dissatisfaction and an increased tendency to self-objectify due to increased reliance on exteroceptive signals”. Disturbed interoceptive sensitivity is associated with the malleability of body representation, as has been shown in an experiment by Tsakiris et al. (2011) that found a stronger illusion of ownership in the right-hand illusion task in healthy individuals with low scores on a heartbeat tracking task (HBT), thus suggesting a heightened reliance on exteroceptive percepts. In anorexic patients, as well as in recovered individuals, “poor IS is associated with an over-evaluation of self-image despite normal perception of others” (Zucker et al., 2013; Sachdev et al., 2008). Interestingly, a similarly

external orientation also characterizes the thinking style of anorexic (Treasure et al., 2015) and alexithymic individuals (Bagby et al., 1994), discussed in 1.4.

Risk prediction errors (RPEs) are an important type of prediction error within the framework of predictive coding that, if disturbed, can have significant impacts on behavior and decision-making. Preuschoff et al. (2008), used a gambling task with changing risk to link risk prediction errors in healthy individuals to activity in the insula. Palminteri et al. (2015) support the insula as playing an important role in adaptive decision making and Seymour et al. (2007) tie the insula to the affective valence of risk prediction errors. Additionally to disturbances in AN (Holsen et al., 2012; O'Hara et al., 2015), risk prediction errors have been postulated to play a role in anxiety and addiction (Paulus & Stein, 2010). Jacquemot and Park (2020) postulate that "abnormal mapping of interoceptive signals in AN results in erroneous judgements about the internal state of the body, therefore causing a mismatch between expected and actual outcomes. This produces an interoceptive prediction error and negative affective state which may precipitate or propagate abnormal eating behaviors." Linking diminished accuracy of prediction errors and negative effects of erroneous prediction to AN establishes it as an overarching mechanism to be considered as playing a causal role. Limiting this train of thought, the framework of predictive coding postulates such a fundamental role to human cognition that defective functioning could play a major role in virtually any instance of altered psychological perception and behavior in mental illness. Therefore it should be considered an important cognitive perspective, rather than a separate mode of action. Since interoceptive signals are interdependently linked to risk prediction errors as their visceral basis (Seymour et al., 2007; Gu & Fitzgerald, 2014), a similarly far-reaching role can be attributed to interoceptive deficits as a fundamental disturbance in feedback signaling that shapes cognitive and behavioral aberrancy in mental illness. This idea is elaborated on in Atzil et al. (2018) and summarized in 1.5.

1.4 Alexithymia in Anorexic Individuals – An Interoceptive Deficit?

Through longitudinal follow-up studies it could be shown that socio-emotional problems lead to adverse outcome (Herpertz-Dahlmann et al., 2001, Zipfel et al., 2000), and hinder therapeutical treatment in AN by negatively affecting the likelihood to apply and tendency to adhere to treatment (Speranza et al., 2007). In fact, focusing on socio-emotional deficits has become a treatment focus for anorexic patients (Fairburn et al., 2003, McIntosh et al., 2000,

Schmidt and Treasure, 2006, Wildes and Marcus, 2010). Due to the central role of socio-emotional pathology, and the before-established relevance of interoceptive deficits for AN, disturbed emotion appears to be of special interest.

Emotional awareness is diminished in AN (Bourke et al., 1992; Jacquemot & Park, 2020). This phenomenon is known as Alexithymia, a sub-clinical condition with a prevalence of 6.7% in the healthy female population and up to 77.1% in anorexic female individuals (Bourke et al., 1992). Alexithymia has been defined as a "difficulty in identifying and describing emotional states" (Vuillier et al., 2020) and is also connected to Obsessive-Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), Autism Spectrum Disorder (ASD), and Schizophrenia (Westwood et al., 2017). A relatively high variance when estimating its prevalence might stem from heterogenous samples and varyingly conservative approaches to isolating AN, in the context of multi-layered psychopathology. The conjunction of socio-emotional deficits and AN is reviewed in Hatch et al. (2010) and Oldershaw et al. (2011). A mediating role of depression is discussed in Torres et al. (2015).

As an emotional deficit, alexithymia stands vis-à-vis the relevance of altered cognition for AN, as has been described in the previous section, while also being empirically linked to impaired interoceptive signaling (Brewer et al., 2016; Bornemann & Singer, 2017). This commonality disputes the notion of emotion and cognition as independent constructs and leads onto the quagmire of theories of emotion. Interestingly, research has shown Alexithymia to be multi-faceted, with postulated impediments dispersing along a gradient from rudimentary visceral percepts (Brewer et al., 2016) to cognitive interpretation and verbalization of emotion (Herbert et al., 2011; Gaggero et al., 2021), thus reflecting an interesting uncertainty about the relationship of cognition, emotion and interoception. Whereas cognitive deficits in alexithymic individuals advocate cognitive theories of emotion, support for aberrant interoception and insular activity in alexithymia endorses more physiological theories. The reader is reminded that, similarly to the congruent functioning of RPEs and interoceptive signaling, both standpoints may be describing aspects of the same mode of action – possibly conjoined by the here contemplated basal role of interoceptive input.

Theories of emotion regularly stress the importance of interoceptive signaling, reaching as far back as the historic theories of James and Lange (Lang, 1994). Often, rudimentary visceral

signals are postulated to be cognitively integrated, thus forming emotional percepts. Newer approaches have been brought forward by Damásio (1994) and, explicitly incorporating insular activity and interoception while focusing on heightened fear and anxiety in AN, Craig (2002) and Paulus and Stein (2006). The latter have been empirically backed and discussed in the context of AN by Kerr et al. (2015). The Somatovisceral Afference Model of Emotion (SAME; Cacioppo, 1992) and the younger "Theory of Constructed Emotion" (TCE; Barrett, 2017) also build upon interoceptive afferents and have been linked to interoceptively processed social touch (see 1.6) by Burleson & Quigley (2021).

The commonly used TAS-26 (Toronto Alexithymia Scale; Bagby et al., 1994) gives detailed insight into the discrete defining characteristics of an individual's Alexithymia by dividing it into three dimensions. The questionnaire was constructed following professional appraisal and empirical knowledge about the etiology of Alexithymia and now shapes consensus about the definition of this sub-clinical condition through its status as a standard tool. Therefore it is now used to illustrate the central aspects of Alexithymia and its respective consequences for affected individuals: Problems with the "identification of feelings" represent the combined effect of possible interoceptive deficits and a diminished ability to interpret these percepts / emotions in general; in an extreme case, an individual is not able to tell apart physiological percepts from emotional percepts. Problems with the "description of feelings" are naturally connected to all the beforementioned scale assesses, but are more reliant on problems with the verbalization and nonverbal expression of possibly adequately perceived emotions. It is linked to communicative and interpersonal problems that arise in affected individuals, endorsing the notion of emotion as an important communicative tool (Emotions as Social Information Model / EASI; Van Kleef, 2009). This perspective gains considerable relevance for this research endeavor when considering the predominantly socio-emotional clinical picture of AN (see 1.1). The third dimension, assessing an "external oriented thinking style", gives insight into a divergent operational thinking ("pensée opératoire"; Marty & de M'Uzan, 1978), that is described as mechanistic and automated. Individuals tend to have a repetitive and superficial approach to problem-solving and a diminished interest in analytic thinking – this is hypothesized to lead to problems in adaptation, as seen in the context of cognitive learning theories (Kupfer, et al., 2000). Interestingly, rigid cognitive functioning has also been proposed to lead to overly strict adherence to once established beliefs about body weight, shape, and formed habits such as eating behavior in AN (Treasure et al., 2015). As has been mentioned in 1.3, reliance on external cues also plays a role in body dysmorphia

(Jacquemot & Park, 2020). In general, cognitive rigidity and the concurrent problems with adaptation are connected to far-reaching and cascading troubles when facing developmental tasks (Havighurst, 1953; Seiffge-Krenke & Gelhaar, 2008) – a perspective that is given a central role in AN (Bradley & Pauzé, 2008).

Summing up the detailed inspection undertaken in 1.3 and 1.4, connections of interoceptive deficits and AN's defining symptoms and comorbidities are well established, even though the pivotal mode of action may be hidden from the eye of empirical research within the black box of human cognition. A question that arises recurrently pertains to the role of interoceptive signaling for disturbed emotion and cognitive functioning, especially to which extent this triangular dynamic relies on basal interoceptive sensations. I expect interoceptive deficits to play a decisive role for AN by shaping its distinctly socio-emotional pathology, without dismissing an additional role of other modes of action that have been presented before. Considering the crucial developmental steps during the mean age of incipience and its predictive power, the development of pathological socio-emotional functioning might be understood as a tipping point, with other impediments then adding to the likelihood of developing the full syndrome and entering the severe enduring phase.

1.5 Synthesis - Anorexia Nervosa and the "Growing of a Social Brain"

Given the far-reaching impact of interoceptive aberration, potentially explained through a notably eclectic multitude of proposed modes of action exerting their effect on various stages and domains of the disease (see Treasure et al., 2015; fig. 1), it becomes self-evident to see interoceptive aberration in a developmental context, thus giving it the potential to explain the assumed cascading effects that are suggested in this investigation.

Atzil et al. (2018) argue that the human brain does not have an innate system for sociality – which would be of central interest in AN. Instead, they put allostasis at the center of all human behavior and postulate that the human brain evolves into a social brain solely because of its efficiency in achieving homeostatic regulation through social interaction, social touch being the evolutionary most rudimentary form of "social allostasis" (Schulkin, 2011; Atzil et al., 2018). To exemplify, our social brain evolves from a crying child's to an adult's that is capable of wit, flirtation, and all the other innumerable facets of human sociality. Whereas a

child cries out to seek it's mother's alleviating caress, an adult's required input to maintain homeostasis equally increases in complexity.

With this perspective, Atzil et al. (2018) give rise to the assumption that interoceptive deficits and, subsequently, disturbed social allostasis, explain the symptomatology and broad network of socio-emotional comorbidities of AN through snowballing effects on the development of a social brain. Due to the cascading nature of human development and the all-encompassing nature of the perspective presented in Atzil et al. (2018), the basal social input of social touch gains decisive relevance for the investigation of interoception and disturbances of the social brain. Also, the conception of emotion as a plane of communication (Van Kleef, 2009) that is conspicuously affected in the anorexic psyche (Bourke et al., 1992; Jacquemot & Park, 2020) aligns coherently with the perspective of Atzil et al. (2018). Especially considering the prominent notion of interoceptive signals as the basis for emotion, alexithymia and AN are expected to both be connected to interoceptive deficits.

1.6 The Informative Value of CT-Touch as an Experimental Stimulus

The affective quality of social touch is thought to be relayed by so-called C-tactile afferents / CT-fibers that are mainly found in hairy skin and activated by slow, light touch (≤10 cm/s; Löken et al., 2009), such as gentle stroking by a peer (e.g. a mother's caress, as described in 1.5). In contrast to the myelinated and fast-conducting A-β-fibers that rely tactile information, the unmyelinated CT-fibers are slow and not useful for conveying temporally and spatially precise information (Croy et al., 2022). Stroking at CT-optimal velocities has been observed in social animals (allogrooming; Sparks, 1967; Burleson & Quigley, 2018) and is known to have heightened alleviating qualities, compared to other types of touch (Morrison, 2016). Interestingly, despite its external origin, CT-touch is often understood as interoceptive as the fibers project to brain areas known for their role in interoception (brain stem and insula; Craig, 2015) where they are integrated with visceral inputs from within the body. Due to this interoceptive quality CT-touch has been called "social interoception" by Burleson & Quigley (2021) who deliver a comprehensive review of the topic.

Anorexic individuals have been shown to rate CT-optimal touch as less pleasant than healthy controls, while not differing when rating the pleasantness of CT-non-optimal touch (Crucianelli et al., 2016). Anorexic individuals also show less "wanting" of CT-touch when

compared to healthy individuals, with higher alexithymia and lower interoceptive sensibility predicting lower “wanting” and “liking” measures (Crucianelli et al., 2021).

Atzil et al. (2018), along with a substantial body of research within the last decade (Fotopoulou & Tsakiris, 2017; Cascio et al., 2019; Croy et al., 2022) assign central relevance for the early development of the human brain to social touch, and especially to CT-touch. For Atzil et al. (2018) it is the basal form of social allostasis, thus having immense importance due to its cascading effects on an individual’s ontogenetic development. In its essence resembling Atzil et al. (2018), but restricting themselves to a behavioral mode of action, Croy et al. (2022) deliver a comprehensive review that sees CT stimulation as a reinforcer that “contributes to the development of newborns into social beings by means of conditioning”. Importantly, CT-touch also has great phylogenetic importance as it is likely to have played an important role in the evolutionary molding of the human social brain (Croy et al, 2022). It is therefore useful to draw credible inferences about the functional mapping of social allostasis onto concurrent brain systems. Inferences assuming direct external validity outside of the neuroanatomical context are to be made with caution.

1.7 Anatomical and Functional Subdivisions of the Insula

Through the relationship of anatomy and function of the insula, it is hoped to clarify the functional impediments of the anorexic brain during CT-afference. For this, the anatomy and function of the insula are briefly presented here and discussed more thoroughly in 4.2.2.

Though numerous differing approaches to sub-partitioning have been proposed (between 2 and 13; Uddin et al., 2017), the insula is often segmented, following primarily anatomical reasoning, into an anterior area (AI) and a posterior area (PI; Kurth et al., 2010). The two regions are divided by the central sulcus of the insula (fig. 2). The insula is understood as a complex network hub that coordinates and integrates “information within and across cognitive, affective, visual, and sensorimotor networks” (Uddin et al., 2017). The central role of the insula for psychological aberration has been shortly presented in 1.2, highlighting the domains of interoception (homeostatic / allostatic function) and emotion, as well as altered cognition (all hypothesized to play roles in AN).

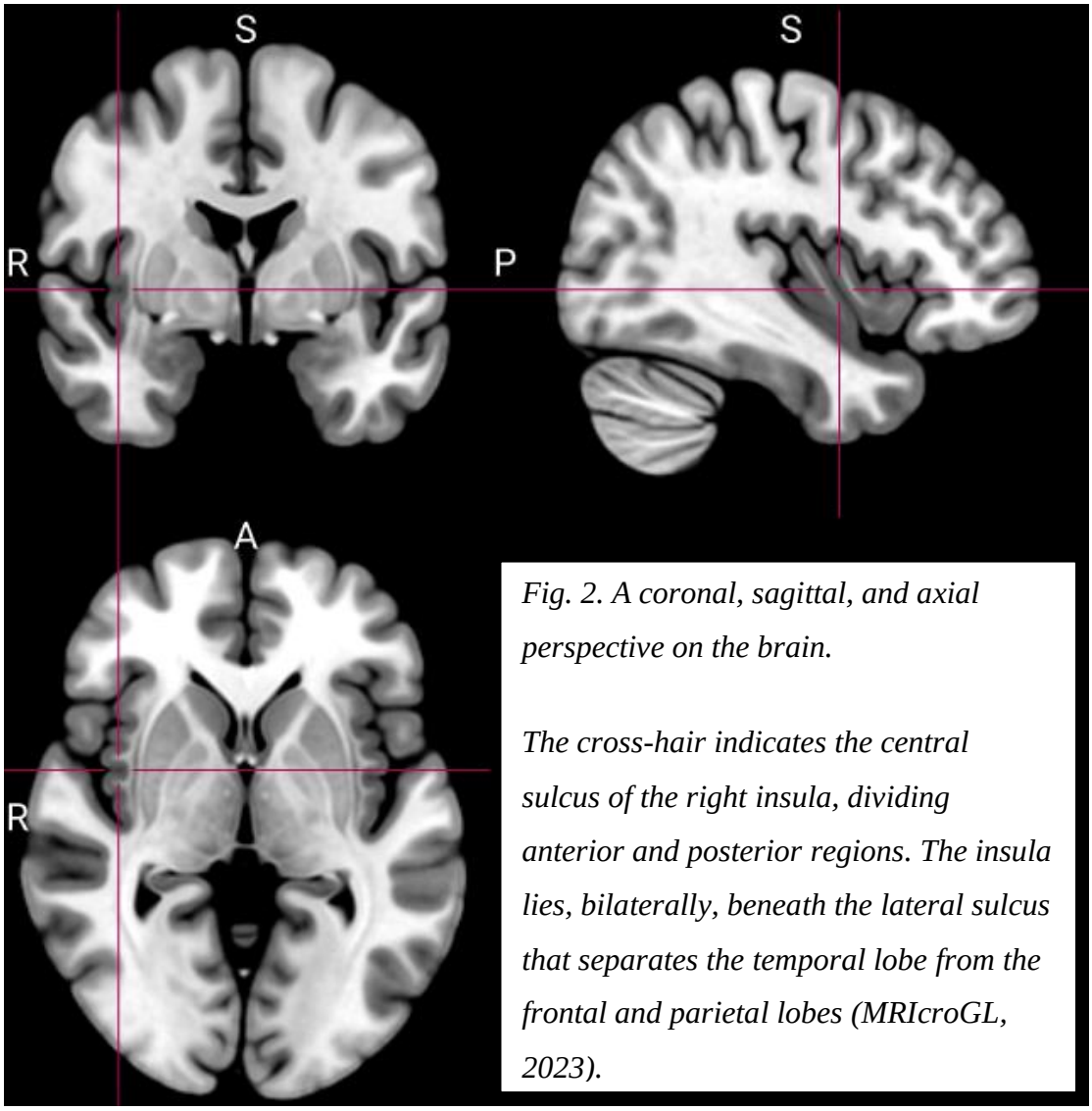


Fig. 2. A coronal, sagittal, and axial perspective on the brain.

The cross-hair indicates the central sulcus of the right insula, dividing anterior and posterior regions. The insula lies, bilaterally, beneath the lateral sulcus that separates the temporal lobe from the frontal and parietal lobes (MRIcroGL, 2023).

Connectivity tracer studies in macaque monkeys show a greater connectivity of the anterior insula (AI) to the frontal cortex (cognition), whereas the posterior insula (PI) is more connected to cingulate (emotion, cognition and social cognition) and parietal cortices (sensory and sensorimotor functions), as well es the olfactory cortex (smell and taste). The findings could be replicated in humans, using diffusion imaging, unraveling a transitioning of connections along an AI-PI-gradient. Using resting state MRI, the ventral anterior insula (vAI) proved to be connected to limbic areas and is involved in affective processes. The dorsal anterior insula (dAI) is connected to frontal, anterior cingulate, and parietal areas and is involved in cognitive control processes. The mid to posterior insula shows heightened connectivity with brain regions for sensorimotor processing. Together, the 3 just-described areas form a network hub that is hypothesized to coordinate multiple functions flexibly (Uddin et al, 2017). Connected to its role in processing visceral information and interoception

(see 1.4), especially the anterior insula is “thought to play a crucial role in emotional experience and subjective feelings” (Tayah et al., 2013). As becomes evident, much of the functional specialization does not clearly relate to simple anatomical sub-partitioning. This problem will be discussed in 4.2.2 and 5.2.

According to Duerden et al. (2013) a lateralization towards the left (anterior and mid) insula accompanies positive emotional stimuli. A functional lateralization of the insula (also towards the left) is hypothesized to play a role in language processing in Ardila et al. (2016) – the researchers propose the insula as coordinating between understanding and producing functions of Wernicke and Broca areas. Surprisingly little research could be found pertaining to possible insular lateralization effects in general.

1.8 Specifying the Spatial Resolution of Interoceptive Impediments and the Functional Role of the Insula in Anorexia Nervosa – Research Gap and Knowledge Gain

The informative value of this investigation lies in providing novel support for insular aberration in AN and in mapping a deviating reaction to an interoceptive percept onto the insula *(a)*. Combining this anatomical specification with existing knowledge about the anatomical-functional relationship of insular subdivisions allows for drawing conclusions about the specific functional aberrancy of the anorexic brain during the integration of interoceptive percepts *(b)*. Utilizing this knowledge gain and linking insular aberration to individual eating disorder severity, the in 1.3 presented modes of action can be corroborated or disputed with functional neuroimaging data *(c)*. Furthermore, the relationship of insular aberrancy with levels of alexithymia within the AN sample is understood as an empirical (though correlative) basis for the theory of 1.5 and 1.6 that could explain an important mode of action in AN *(d)*. Note that the here listed levels of insight build upon an increasingly unstable amount of necessary theoretical assumptions and conclusions to allow inference, from *a* to *d* - the reader is advised to understand the presented insight accordingly.

A central research gap consists in a lacking consensus about the role of interoception for AN (pertaining to *c*, see 1.3 and 1.4), mostly due to the hardships of inducing a (standardized) interoceptive percept and the underlying definition of interoception itself (see 1.2). Additionally, varying approaches at defining who is deemed anorexic (see 2.2) and the

arbitrariness of understanding comorbid psychopathology as part of AN or a factor to be controlled for diminish the comparability of studies on this topic tremendously. Fundamentally, the understanding of interoceptive deficits (in AN) as a higher cognitive impediment or a problem of basal integration of percepts can be illuminated with the here used experimental paradigm (utilizing knowledge about the anatomical-functional relationship of insular activity). A similar research gap, resulting from uncertainty about the involvement of higher cognition versus basal visceral percepts, applies to the question of the emergence of emotion. Again, knowledge about the anatomy and function of the insular can be linked to the interoceptive stimulus and potentially illuminate alexithymia in AN as a basally visceral impediment.

Comparable data is acutely needed to investigate how strongly AN and alexithymia are connected to interoceptive aberration, and thus, to be contemplated as having a common ontogenetic cause. Affirmative findings could consequently shift a causal focus towards insular activity and interoception in AN. Also, a common cause of AN symptoms and alexithymia would give them an empirical proximity that should be considered in etiological models and therapeutic interventions alike.

1.9 Research Question and Hypotheses

Research Question: *Is the clinical picture of anorexia nervosa associated with an altered processing of C-tactile afference in the insula?*

H1: *Anorexic participants will show aberrant insular activity compared to healthy controls during C-tactile afference.*

H2: *Individual levels of alexithymia, as operationalized through the overall-score of the TAS-26, will positively correlate with the extent of insular aberrancy within the anorexic subsample*

H3*: Individual levels of eating disorder syndrome severity, as operationalized through the overall-score of the EDI-2, will positively correlate with the extent of insular aberrancy within the anorexic subsample*

2. Methods

2.1 Organizational Framework and Aim of the Research Project

This investigation is part of a 3-year co-operation between the Univerity of Vienna (Universität Wien) and the Medical University Vienna (Medizinische Universität Wien) under the name “A translational psychiatric approach to adolescent anorexia nervosa - from genes to brain systems and behaviors”. The study is currently ongoing and will continue until 2024, resulting in a multitude of theses investigating different aspects of AN. The data acquisition is conducted by the clinical and social neuroscience (CSN) unit of the University of Vienna at the Vienna General Hospital, under the supervision of Assoz. Prof. Giorgia Silani, Privatdoz. PhD, in close communication with Univ.-Prof. Dr. med. univ. Andreas Karwautz, MD. Adhering to a translational approach, the project aims at exploring a reward-based mechanistic model of AN in the human brain in order to develop more precise therapeutic interventions. This is done by investigating the ‘wanting’ (motivational component) and ‘liking’ (hedonic component) of food (food administration) and social rewards (touch stimuli) in anorexic patients versus healthy controls.

2.2 Participants and Recruiting

The final sample size for the project is expected to reach N = 100 participants (50 healthy controls, 50 anorexic individuals) in 2024. Due to AN mostly affecting young women by a large margin, only female participants are recruited. The age of healthy controls is at all times intended to ideally correspond to the current mean age of the experimental group. Patients from 13 up to 29 years of age are accepted into the study. Anorexic participants are contacted through doctors of the Wiener Allgemeines Krankenhaus (AKH), healthy controls through the recruiting efforts of the research team. Instagram, Facebook, and TikTok as well as lectures in schools, flyers and parent notification letters are in use and function as publicity generators for self-reliant outreach by potential participants via e-mail. A reward of 70€ in form of retail vouchers is given after the completion of the experiment. Before the experiment, online questionnaires are to be filled out, primarily to check for exclusion criteria. Eligible subjects are then contacted via phone call and a date for the experiment is arranged. Additionally, participants are instructed to fast for 4 hours before arriving to the study.

Participants are excluded from the study following criteria that otherwise might have a systematically confounding effect on the data or potentially endanger the participant - diabetes, food allergies, forearm skin conditions (= problems with stimuli), metallic implants, claustrophobia (= problems with fMRI-scanning). Prospective controls are excluded when having a history of psychiatric illness or mentionable dieting to ensure their role as healthy on domains of interest. Additionally, a pre-screening assesses whether or not the participants like the presented stimuli. This latter information is disregarded because of its redundance in the case of food stimuli and due to controlling for categories of preference being deemed a more precise option for isolating the explanatory power of the touch stimuli (see 2.4.5).

The sample initially deemed eligible for the here presented investigation (N = 48) is subdivided in anorexic in-patients (N = 5), anorexic out-patients (N = 14), fully remitted (N= 7) or partially remitted out-patients (N = 9) and healthy controls (N = 13). Participants are considered anorexic when they fulfill criteria A (low body weight), B (intense fear of gaining weight or becoming fat or behaviour that interferes with weight gain) and C (disturbances in self-perception of weight and shape), as described in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013). Remitted participants either fulfill none (fully remitted) or only criterion B and / or C (partially remitted) after previously having fulfilled the full criteria. Due to the small number of currently deemed anorexic patients and the proposed ontogenetic role of early and enduring neural aberration, all in- and out-patients were grouped together as “anorexic” for the analysis (N = 38). Also, the binge-purging subtype of AN (N = 4; 1 currently anorexic in-patient and 3 currently anorexic out-patients) was not examined separately as the underlying catalysts are expected to be widely similar.

11 participants were excluded from the H1 analysis due to having received the stimulus of interest too seldom to promise statistically reliable estimates in the level 1 analysis. One additional participant had to be excluded due to artefacts in the neuroimaging data, caused by dental braces. The resulting sample in the H1 analysis (N = 36) thus consisted of 5 anorexic in-patients, 9 anorexic out-patients, 6 fully and 8 partially remitted out-patients (experimental group; N = 28) and 8 healthy controls (control group; N = 8). H2 and H3 focused on the experimental group alone. Here, 3 additional participants were excluded due to missing

clinical data (1 fully remitted outpatient, 2 anorexic in-patients; N = 25).

The mean age of the H1 experimental group (17.179 years; SD = 2.48) is significantly lower than the mean age of the H1 control group (19.375 years; SD = 2.504), due to difficulties with recruiting very young participants without a direct contact to the AKH (t = -2.205, df = 34, p = 0.334). The mean age of the anorexic sample used in H2 and H3 is 17.16 years (SD = 2.528).

Estimates of statistical power are problematic in neuroscientific research since a significant amount of variance is dependent on technicalities of neuroimaging (low signal-to-noise ratio), the problem of multiple comparisons and concurrent corrections, high interindividual variability, and the unpredictability of brain functioning. This research endeavor therefore aimed at including a maximum number of participants, respecting the beforementioned considerations about potential confounders. However, the nested structure of the data called for a trade-off ensuring maximum accuracy of measures within individual participants (level 1) and when investigating group effects (level 2), simultaneously. Participants were excluded when having received the stimulus of interest < 9 times because this ensured a maximum number of participants being included while also maintaining a necessary number of stimulus administrations to estimate effects within participants.

2.3 Materials

2.3.1 Materials: Experimental Paradigm

The study implements a newly developed and validated experimental paradigm that is designed to assess the anticipatory (“wanting“) and consummatory (“liking”) responses to food (food administration) and social reward (touch administration) on different levels of assessment (Chiappini, Silani, & Korb, 2022). Subjective ratings for “wanting” and “liking” (= explicit “wanting” and “liking”) are supplemented by exerted force measured through a hand-dynamometer (= implicit “wanting”) after a reward announcement. In addition, EMG-technology is used as a supplementary implicit measure (= implicit “liking”), as well as fMRI, to lay open neural correlates in detail. The here presented research utilizes only one sub-modality of a stimulus (the slowest social touch option) administered in the experimental paradigm and solely focuses on concurrent fMRI data within the insula. However, every

participant included in the analysis passed through the entire sequence, as described in detail in 2.4. The final analysis disregards all food stimuli, all behavioral measures and all measures pertaining to "wanting".

2.3.2 Materials: Stimuli

Food and social (touch) stimuli are administered in this experiment; since the food stimuli are of no interest in this investigation they will be omitted except where necessary (for detailed information, see Chiappini et al., 2022). The stimulus of interest is a gentle stroking administered to a 9 cm section of the hairy skin of a participant's right forearm, right below the wrist joint, for 7 seconds. The section is highlighted by an accordingly placed adhesive tape. The research assistant uses the index- and middle fingers to repeatedly stroke up and down the forearm with a velocity of 6 cm/s (faster conditions: 21 cm/s or 27 cm/s), as indicated by a repeated beeping noise that is transmitted through headphones. It is designed to ensure optimal conditions for the activation of C-tactile afferents; for more information on considerations behind these details, see section 1.5 and Chiappini et al. (2022). The stimulus is administered by a same-sex research assistant for heterosexual participants and a different-sex research assistant for homosexual participants in order to prevent possible sexual attraction from confounding the data. To minimize all other possible effects that relate to interpersonal relationship, social interaction before and during the experiment is reduced to a necessary minimum. The complete procedure is presented in 2.4.1 and 2.4.2.

2.3.3 Materials: Data Acquisition Technology

The participants' reaction to the stimuli is measured using functional magnetic resonance imaging (fMRI); (insular) blood oxygen level-dependent (BOLD) activity is recorded via a Siemens 3T Magnetom Prisma whole body MRI scanner (Siemens, 2013) with a 64-channel head / neck coil at the Exzellenzzentrum Hochfeld MR center of the Medical University of Vienna. The functional imaging utilizes a T2-weighted single-band echo-planar image (EPI) sequence. Parameters of interest are specified as: echo time (TE) = 36 ms, repetition time (TR) = 2.5 s, flip angle = 66°, 44 axial slices coplanar to the anterior-posterior commissure connecting line, FoV (Field-of-View) = 140 x 140 x 132 mm, matrix size 96 x 96, voxel size = 1.45 x 1.45 x 3 mm, interslice gap = 3 mm.

The obtained data was processed, analyzed and visualized using Matlab (The MathWorks Inc., 2022) and SPM12 (Friston et al., 2020).

2.3.4 Materials: Assessment of Constructs

The TAS-26 (Toronto Alexithymia Scale; Bagby et al., 1994) is a scale investigating facets of Alexithymia that are of interest in current research and are discussed in 1.4. It is used internationally in research and therapeutic settings alike. Participants rate their affirmation with statements from "does not apply at all" to "fully applies" on a 5-point Likert-Scale. It was administered in its German translation (Kupfer et al., 2000) that consists of an overall-score and 3 subscales that assess the following dimensions:

Difficulty Identifying Feelings (Schwierigkeiten bei der Identifikation von Gefühlen), Difficulty Describing Feelings (Schwierigkeiten bei der Beschreibung von Gefühlen), External Oriented Thinking (Extern Orientierter Denkstil).

Kupfer et al. (2000) validated their translation using a representative sample of N = 2047 Germans from ages 14 to 95, virtually replicating the factor structure of Kirmayer & Robbins (1993). Providing a measure of construct validity, they found a highly positive correlation of the first two subscales (Difficulty Identifying Feelings and Difficulty Describing Feelings) and an independence of the third subscale (External Oriented Thinking). A fourth subscale of the original questionnaire (Reduced Daydreaming) was excluded from the German translation due to negative correlation with the other scales and the overall-score. Pertaining to reliability, Kupfer et al. (2000) ensure a satisfactory internal consistency (Cronbach's α: r = .67 to r = .84) for all scales and the overall-score. The values are practically independent from effects of age, sex, and income but show a linear relation with levels of education in all scales and the overall-score, with lower education predicting higher levels of Alexithymia (see table 4 in Kupfer et al., 2000). Kupfer et al. (2000) recommend a cut-off of ≥ 54 (raw value, overall-score) to declare an individual as alexithymic. This distinction will play no role in the here presented investigation since I understand alexithymia as a sub-clinical condition that should be illuminated in its full spectrum.

The EDI-2 (Eating Disorder Inventory-2; Garner, 1991) is a questionnaire investigating the multidimensional individual psychopathology of patients with AN, bulimia nervosa (BN),

and other eating disorders. It is considered standard practice on an international level and is widely used in a therapeutic setting and research. It was administered in its German translation (Rathner & Waldherr, 1997). Participants rate their affirmation with statements from “never” to “always” on a 6-point Likert-Scale. It consists of an overall-score and 11 sub-scales that assess the following dimensions:

Drive for Thinness (DT; Schlankheitsstreben), Bulimia, (B; Bulimie), Body Dissatisfaction (BD; Unzufriedenheit mit der Figur), Ineffectiveness (I; Minderwertigkeitsgefühle), Perfectionism (P; Perfektionismus), Interpersonal Distrust (ID; Misstrauen gegenüber anderen), Interoceptive Awareness (IA; Unsicherheit in der Wahrnehmung von Gefühlen), Maturity Fears (MF; Angst vor dem Erwachsenwerden), Ascetisism (A; Askese), Impulse Regulation (IR; Impulsregulierung), Social Insecurity (SI; Soziale Unsicherheit).

Rathner and Waldherr (1997) validated their translation by comparing a sample of 40 Austrian females aged 11 to 19 with an AN diagnosis following the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1991) with a representative sample of 1660 female and male Austrian students. Schools were evenly distributed in rural and urban districts of Lower Austria but skewed to include more females by excluding higher technical schools.

The internal consistency of subscales 1 to 8 proved to lie between .70 and .94 for female patients and between .57 and .93 for female students. The three additional scales (A, IR, SI) were found to have an internal consistency of .79 and .85 for female patients and .41 and .75 for female students. The internal consistency of the whole questionnaire is provided with .98 for female patients and .93 for female students. A comparison of healthy and anorexic females substantiated a satisfactory criterion validity by yielding significant differences for 9 of the 11 subscales. The validation also showed that almost all scales are influenced by age (positive correlation for BD; negative correlation for I, MF, A, SI) and weight (positive correlation for DT, B, BD, I). The influencing factors show a satisfactory transcultural congruence with the US-American sample.

2.4 Procedure

2.4.1 Procedure: Pre-Experimental Protocol / Assessments

The study is divided into two parts. At first participants undergo a clinical assessment (~2h) and then the main experimental fMRI task (~2h). The clinical part is performed by a research assistant at the Department of Psychiatry and Psychotherapy of the AKH, incorporating several questionnaires, scales and (semi-) structured interviews screening for symptoms of eating disorders and assessing other psychiatric illnesses, sub-clinical conditions and traits that bear importance for assumed underlying processes of AN (most common psychiatric disorders based on DSM-5, depression, state and trait anxiety, obsessive-compulsive disorder, traumatization and PTSD, cognitive flexibility, central coherence, health-related quality of life, Cloninger's biopsychosocial model of personality, gastrointestinal complaints, attitudes towards social touch, health and taste attitudes). In addition, sociodemographic data, disease course, therapeutic interventions and BMI (body mass index) are assessed. Apart from the previously presented screening for eating disorder symptoms (EDI-2; Garner, 1991) and the assessment of alexithymia (TAS-26; Bagby et al., 1994), this thesis will not go into detail about the clinical assessment as this data will largely be disregarded. Please note that, to ensure readability and coherence, all provisions and detail pertaining to food stimuli will be omitted from this section.

The experimental part follows the clinical part without a major break, at the MR center of the Medical University at the AKH. Participants sign an informed consent form, dress in scrubs and are instructed to remove any piercings or metal jewelry and asked to go to the toilet. Due to the potentially severe psychiatric condition of participants and the stressing effects of expecting to be repeatedly administered an aversive stimulus in a confined space, a guiding research assistant establishes a comforting ambiance by speaking in a low and relaxed tone, utilizing casual small-talk and repeatedly indicating the option to call the experiment off when experiencing distress. During the experiment in the fMRI-scanner, participants can either communicate to the experimenters via intercom or stop the experiment at all times by pressing a rubber ball. Five electrodes are placed on the participants' face to record EMG data (implicit "liking"). There will be no further reference to this as the EMG data will be disregarded in the analysis and discussion.

The participant is lead into the scanner room and the sequence of the upcoming experiment is explained, including a prior maximum hand dynamometer press force assessment, a stimulus

preference assessment, and one test run for each condition (food / touch) before the launch of the actual experiment. The maximum hand dynamometer press force assessment and assessment of stimulus preference are explained in detail with the help of an explanatory sheet. As the participant lies down, the necessary equipment is explained; a button box with three buttons (placed in left hand, three middle fingers on buttons; explicit "wanting") and a hand dynamometer (placed in right hand, fist grip; implicit "wanting") are placed on the participant's abdomen with her forearms in parallel, and an arm angle of 90°, to ensure reachability for the administration of the touch stimulus. A second research assistant, trained to administer the touch stimulus, briefly introduces herself / himself and puts a piece of adhesive tape on the participant's forearm to ensure stroking the intended section.

The participant is placed inside the scanner, viewing instructions, pictograms and visualizations via a mirror that is attached to the head coil, reflecting a screen at the head end of the scanner. First, the stimuli are ranked. Each participant receives all touch and food stimuli options once, in a pseudo-randomized order, in two separate blocks. Respectively, three stimuli are administered consecutively, and then ranked (high subjective "liking", low subjective "liking", very low subjective "liking"). Each stimulus is associated with one pictogram (fig. 3) during its announcement and the ranking, in order to teach the participant which stimulus to expect after an announcement during the experimental task. The individual rankings are used as categories from then on, ensuring individual preferences are reflected in the main task.

Fig. 3. Pictograms indicating "slow" (A; 6 cm/s), "fast" (B; 21 cm/s) and "very fast" (C; 27 cm/s) touch options (Chiappini et al., 2022).

Following this, the hand dynamometer is calibrated by three presses, following instructions to squeeze it as much as possible for a respective duration of three seconds. The instructions are

visible through a mirror extension on the head coil that reflects what is presented on a screen at the head end of the scanner. The peak force reached across the three trials is recorded as the individual maximum voluntary contraction (MVC) in Newtons (N) and is subsequently used as a reference point to calculate a percentage value of force exerted in the experiment, relative to the individual maximum force. This procedure is also repeated after the end of the experiment to check for muscle fatigue.

The participant is then taken out of the scanner again and the experimental task is explained with a second explanatory sheet. The participant is asked whether she wants to use the bathroom again and whether or not she felt at ease inside the scanner. Following a test run for each condition (food / touch), it is checked whether or not the recorded data aligns coherently with the participant's intended indications and if the participant feels comfortable with and has understood the hand dynamometer and button box use accordingly. After an inquiry about the patients well-being through the intercom, the experiment commences.

2.4.2 Procedure: Experimental Task Protocol

While lying on the scanner bed inside the scanner, the task instructions are again displayed on a screen at the head end of the scanner, visible through a mirror extension of the head coil. A trial run is illustrated in fig. 4. The start of each trial is marked by the presentation of a fixation cross, jittered between 2 and 4 seconds. Following this, a 2 second visual cue indicates the possible reward (exclusively options ranked as high or low before; see .4.1) that can be attained in contingency on the sufficient exerted force in the following task (= anticipation phase pre-effort). The participant is then instructed to rate within 4 seconds how much she wants to receive the anticipated reward, choosing a value ranging from "not at all" to "very much" on visual analogue scale (VAS), using the button box. Next, the participant is instructed to exert effort according to her desire to receive the reward (4 seconds), by squeezing the hand dynamometer. She simultaneously receives visual feedback through a growth bar, rising proportional to the force currently exerted. The amount of strength predicts the probability of receiving the announced reward linearly – the actual delivery either being the announced option (high or low) or the lowest alternative (very low) when not having exerted sufficient force. After a visual cue (2 seconds), announcing the obtained reward (= anticipation phase post-effort), the participant is asked to prepare for the administration (6 seconds) and is administered the stimulus (7 seconds), by a research assistant reaching inside

the scanner with one arm, touching nothing but the designated area, as described in 2.3.2 (= delivery phase). After the delivery, the participant is given time to relax (6 seconds) and is then asked to rate how much she liked the just-received stimulus on an identical VAS scale as when rating the "wanting" (4 seconds).

Fig. 4. Trial sequence as described above (Chiappini et al., 2022).

The experiment consists of 4 blocks that each consist of 16 trials (2 food blocks, 2 touch blocks, ABAB or BABA order). Respectively, a "high" reward can be obtained in 8 trials, whereas in the other 8 trials of a block, a "low" reward can be obtained when exerting enough force. Each block lasts approximately 11 minutes, with touch trials lasting ~38 seconds and food trials lasting ~50 seconds. Taken together, the main task takes up approximately 50 minutes of the study. After each block, the intercom is used to ask the participant about her well-being and if she needs a break. She is also informed about the remaining blocks to be completed.

2.4.3 Procedure: Data Collection and Research Design

The data used in this investigation was generated using a cross-sectional experimental between-subjects design, with participants subdivided into an "anorexic" experimental group and a healthy control group. For details on this classification, see 2.2.

In H1 (level 1 / within-subjects), the independent variable (IV) is an interoceptively felt component of the social touch stimulus (CT afference). The dependent variable (DV) is the temporally concurrent insular brain activity (average activation within a pre-defined region of interest; ROI), understood as reactive to the IV. In H1 (level 2 / between-subjects), the IV is the group variable. The DV is again insular brain activity that is understood as resulting from CT afference.

In H2 and H3, incorporating only the experimental group, the IV is a respective overall-score or score of a sub-scale. The DV is the individual extent of aberrancy of insular brain activity when compared with the control group.

In order to isolate the interoceptively felt qualities of CT-optimal touch, the IV was created by calculating a level 1 contrast between individual insular brain activity patterns during the slowest touch option (6 cm/s) and the aggregated activity pattern representing the two faster touch options (21 cm/s and 27 cm/s). This way, all reaction to touch that is common in CT-optimal and CT-non-optimal touch is filtered out, and activity patterns result that are understood as representing an individual's brain activity in response to what is assumed to be unique to CT-optimal touch – interoceptively felt signals, transmitted via C-tactile afferents and integrated via the insula (see 1.6).

Palliative changes had to be applied to this planned analysis after non-significant H1 findings. The alternative analysis will be explained thoroughly in the following section.

2.4.4 Procedure: Data Analysis

H1 Analysis (Level 1)

All data preprocessing was performed utilizing a MATLAB script implementing a preprocessing pipeline. The primary associations of IV (stimulus condition; 3-step within-subjects factor) and DV (brain activity) were estimated using all social touch trial runs performed by a respective participant and the temporally concurrent neuroimaging data. For this, a MATLAB script was used that incorporated the calculation of level 1 contrasts. The level 1 analysis thus resulted in smoothed contrast images that visualize the individual brain activity patterns resulting from a contrast between the slowest (6 cm/s) and the two faster touch stimulus conditions (21 cm/s and 27 cm/s; see 2.4.3).

H1 Analysis (Level 2)

Using the smoothed contrast images from the level 1 analysis as a DV, a two-tailed independent samples t-test was performed in SPM12, comparing the control- and experimental groups, while controlling for "age" and "preference level" (1 = high liking, 2 =

low liking, 3 = very low liking; see 2.4.1). An intracranial volume (ICV) mask was applied to restrict the analysis to voxels inside the brain. Contrasts were defined by dummy coding "AN" and "HC", as well as "age" and "preference group" (main effect: 1 1 0 0; AN: 0 1 0 0; HC: 1 0 0 0; HC>AN: 1 -1 0 0; AN>HC -1 1 0 0). Using a familywise error correction (FWE) to adaptively correct for multiple comparisons and a significance level of 0.001 did not yield significant results. Therefore the significance threshold was iteratively lowered to $\alpha = 0.05$ and it was abstained from correcting for FWE. Subsequently, a whole insula mask (left and right insula) was added to restrict the analysis to the area of interest. Since no significant activations were found within the insula, even with a liberal significance threshold and no correction for an expected type I error (FWE / multiple comparisons problem), the original analysis plan for H2 and H3 had to be discarded (defining an ROI based on resulting significant voxels and extracting averaged individual beta values for further analysis in H2 and H3).

H1 (Alternative Exploratory Approach) Analysis

An alternative exploratory analysis was decided on to facilitate the investigation of H2 and H3. After having inspected the results from the level 2 t-test, a cluster of activity in the anterior insula was deemed promising and chosen as an interest point. Individual averaged beta values (resulting from the basal level 1 contrast) were extracted from 7 ROIs (conjoined left and right / whole insula, LR-I; left insula, L-I; right insula, R-I; left anterior insula, L-AI; right anterior insula, R-AI; left posterior insula, L-PI; right posterior insula, R-PI), using the image extraction tool rex in SPM12. Following this, a repeated measures ANOVA was performed incorporating the between-subjects factor "group" with levels "AN" and "HC", as well as the between-subject covariates "age" and "preference group"; the latter as an ordinal variable (1 = "high liking", 2 = "low liking", 3 = "very low liking"). Additionally, the within-subject variables "hemisphere" (levels "left" and "right") and "partition" (levels "anterior" and "posterior") were included in order to enable an exploratory analysis of individual insular beta values (DV), guided by an anatomical sub-partitioning. This was done to enhance the likelihood of finding significant group effects (interaction terms with the group factor and anatomical partitioning) that could then be used in H2 and H3. Furthermore an anatomical subdivision of the insula was deemed a beneficial guidance for interpretation by enabling convenient references to a substantial body of research) about insular subdivisions (see 1.7, 4). Also, the beforementioned problem of multiple comparisons and the concurrent need for

the conservative FWE correction could be reduced by focusing on averaged values per ROI instead of individual voxels; nevertheless Bonferroni corrections was performed (post-hoc tests) when interpreting significant results in order to abstain from type I error. Ultimately, using an omnibus test (ANOVA) was deemed an economic and convenient way to explore the multiple associations within the data, given the expectation of minimal effects. All findings of statistical significance and theoretical importance are reported in 3 and discussed in 4.

H2 / H3 Analysis

As a reaction to finding minimal effects in H1, the original plan for H2 and H3 was heavily simplified. Instead of investigating the relation of all TAS-26 and EDI-2 sub-scales to the extent of insular aberrancy within a significant cluster (and draw precise theoretical inference from these associations), sole focus was placed on the 2 respective sum scores. A planned stepwise inclusion of multiple sub-scales with theoretical considerations or an exploratory factor analysis approach were deemed neither feasible nor reliable considering minimal size and significance of H1 effects and the concurrent limited expectation of statistically significant associations in H2 and H3.

Anatomically, it was decided to restrict the analysis to the two sub-divisions of the insula that had shown the most convincing associations with the factor “GROUP” in H1, despite the lack of its significance. The posterior and anterior insula (see 3; fig. 7, fig. 8) were chosen as two ROIs over which to average the beta values of the level 1 contrast. The beta values of the left and right PI / the left and right AI were averaged and included in a correlation matrix with the sum-scores of the TAS-26 and EDI-2, as well as the participants’ age and preference rating. Since no effects of interest showed relevant effect sizes or significances it was abstained from further investigating the interrelations of factors in a regression analysis.

3. Results

3.1 H1 Results

The effect of the between-subjects factor “group” (levels “AN” and “HC”), controlling for “age” and “preference”, on the averaged level 1 contrast beta values within the conjoined left

and right / whole insula mask ("LR") yielded no significant result when using $\alpha = 0.05$; $F(1, 32) = 0.076$, $p = 0.784$. This means that, speaking of the whole insula, anorexic individuals do not show significantly different insular activity when processing CT-afference. H0 cannot be rejected.

ANCOVA – LR

Cases	Sum of Squares	df	Mean Square	F	p
Preference	0.112	1	0.112	0.417	0.523
GROUP	0.020	1	0.020	0.076	0.784
Age	0.360	1	0.360	1.347	0.254
Residuals	8.560	32	0.267		

Note. Type III Sum of Squares

Fig. 5. ANCOVA results; effect of "group" on averaged beta values within the whole insula, controlling for "age" and "preference".

This finding is not to be interpreted as the insula not playing a significant role in processing C-tactile afference; additionally to general limitations such as the very small control group, the whole insula mask is too large to make possible activations in anatomically smaller sub-divisions appear significant. Therefore it was decided to focus on anatomical sub-partitioning in an alternative exploratory procedure.

3.2 H1 (Alternative Exploratory Approach) Results

In the following section, all significant factors and factor interactions obtained from the repeated-measures ANOVA will be presented. 4 factors or factor combinations reached significance. Subordinately, all non-significant factors and interactions of theoretical importance, as well as additional associations will be discussed where they add meaning or are necessary for the interpretation of findings. A significance threshold of $\alpha = 0.05$ was employed for interpreting the results. In order to abstain from type I error, significant effects were additionally investigated with Bonferroni-corrected post-hoc comparisons.

Within Subjects Effects ▼

Cases	Sum of Squares	df	Mean Square	F	p
Hemisphere	0.399	1	0.399	5.813	0.022
Hemisphere ✻ GROUP	0.120	1	0.120	1.745	0.196
Hemisphere ✻ Age	0.411	1	0.411	5.983	0.020
Hemisphere ✻ Preference	7.595×10^{-5}	1	7.595×10^{-5}	0.001	0.974
Residuals	2.197	32	0.069		
Partition	0.014	1	0.014	0.356	0.555
Partition ✻ GROUP	0.313	1	0.313	8.232	0.007
Partition ✻ Age	0.050	1	0.050	1.326	0.258
Partition ✻ Preference	0.235	1	0.235	6.197	0.018
Residuals	1.216	32	0.038		
Hemisphere ✻ Partition	0.053	1	0.053	2.390	0.132
Hemisphere ✻ Partition ✻ GROUP	0.007	1	0.007	0.326	0.572
Hemisphere ✻ Partition ✻ Age	0.049	1	0.049	2.244	0.144
Hemisphere ✻ Partition ✻ Preference	0.001	1	0.001	0.056	0.814
Residuals	0.705	32	0.022		

Note. Type III Sum of Squares

Fig. 6. Repeated-measures ANOVA results. Especially interactions of anatomical sub-partitions with "GROUP" are of interest as they represent the essential preposition of H1.

Hemisphere (F = 5.813, df = 1, 32, p = 0.022)

The factor "hemisphere" (L>R) has a significant impact on the level 1 beta values, when controlling for age and preference. This means that, ignoring possible group differences, participants showed a higher average activation within the left insula. Since the interaction Hemisphere*GROUP is not significant (F = 1.745, df = 1, 32, p = 0.196), this effect is neither significantly connected to group differences between healthy and anorexic individuals, nor is the observed effect of the factor "hemisphere" due to one group being significantly larger and dominating the analysis.

Following the Bonferroni-correction of a post-hoc comparison, the effect did not maintain its significance (mean diff. = 0.057, SE = 0.054, t = 1.061, Cohen's d = 0.109, p = 0.297, Bonf-corr.).

Hemisphere*Age (F = 5.983, df = 1, 32, p = 0.020)

A significant interaction was found between the factors “hemisphere” (L>R) and “age”, when controlling for “preference”. Caution is advised since this interaction does not control for the effect of the factor “GROUP”. While age does significantly differ between groups (t = -2.205, df = 34, p = 0.334; see 2.2), the interaction of “GROUP” and “hemisphere” is not significant (F = 1.745, df = 1, 32, p = 0.196).

In order to perform a post-hoc comparison with an adequate Bonferroni correction, “age” had to be included into the repeated-measures ANOVA model as a factor, while controlling for “GROUP” as a covariate. “Preference” was kept as a covariate. To adhere to model assumptions, the group factor was dummy coded (HC = 0, AN = 1) and the factor “age” was included as a dummy coded variable (younger = 0/ older = 1), following a median split (median age = 17.5). Controlling for “GROUP” was deemed necessary since a misbalance was evident between age groups (younger: 2 HCs / 6 ANs; older: 12 HCs / 16 ANs). Through these changes, the effect of the interaction was altered (F = 4.808, df = 1, 32; p = 0.036).

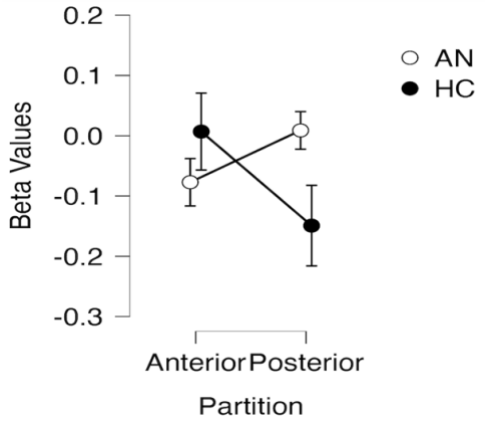
No comparison remained significant within $\alpha \leq 0.05$, following the Bonferroni correction. Only one comparison resulted in a p < 1, Bonf.-corr. (younger/L>younger/R; mean diff. = 0.149, SE = 0.076, t = 1.95, Cohen's d = 0.278, p = 0.36, Bonf.-corr.). This comparison shows a stronger lateralization to the left than to the right insula for younger participants. A potential reason for the extreme Bonferroni-corrected p-values in post-hoc tests of interaction effects is explained using the following interaction.

Partition*GROUP (F = 5.983, df = 1, 32, p = 0.020)

A significant interaction was found between the factors “partition” (AI>PI) and “GROUP”, when controlling for “age” and “preference”. Considering that the main effect of “partition” (F = 0.356, df = 1, 32, p = 0.555) did not reach statistical significance on its own (no significantly different extent of activity between anterior and posterior insula when ignoring possible group differences), it can be concluded that the group factor has decisive explanatory power. This is of special relevance since it is the most prominent effect of the group factor on an anatomical sub-partitioning of the insula in this analysis. To more easily grasp the meaning of the effect, a descriptive plot is provided (fig. 7). To evaluate which

interrelation of the two two-step variables plays a key role in the significance of the interaction, Bonferroni-corrected post-hoc tests are necessary (fig. 7).

Fig. 7.
Note the error bars indicating the respective standard error (SE); an overlap in the AI condition indicates a non-significant difference between groups. Be aware that the plot visualizes results before having undergone a Bonferroni-correction.



Post Hoc Comparisons - GROUP ✻ Partition

		Mean Difference	SE	t	Cohen's d	p_{bonf}
AN, Anterior	HC, Anterior	−0.146	0.219	−0.668	−0.278	1.000
	AN, Posterior	−0.086	0.038	−2.297	−0.164	0.170
	HC, Posterior	0.011	0.219	0.049	0.020	1.000
HC, Anterior	AN, Posterior	0.060	0.219	0.275	0.114	1.000
	HC, Posterior	0.157	0.073	2.135	0.299	0.243
AN, Posterior	HC, Posterior	0.097	0.219	0.443	0.184	1.000

Note. P-value adjusted for comparing a family of 6
Note. Results are averaged over the levels of: Hemisphere

*Fig. 8. Only comparisons that share exactly one factor level are of relevance in the interpretation (AN/**AI**>HC/**AI**, AN/**PI**>HC/**PI** and **AN**/AI>**AN**/PI, **HC**/AI>**HC**/PI).*

When investigating the post hoc results (fig. 8) one might become aware of a relative superfluity of reporting all 4 combinations of 2x2 combinations of factor levels due to their interdependency when included in one statistical model – this could explain the Bonferroni-corrected p-values (= 1) for two of the four comparisons of interest (indicating their de facto emission from the model). Using the descriptive plot in fig. 7 as a visualization, formulating an effect using the slope / beta coefficient (AN/AI>AN/PI, HC/AI>HC/PI) conveys a similar message as referring to a difference between points on the y-axis (AN/AI>HC/AI, AN/PI>HC/PI). Deeming the interaction significant because anorexic participant show more activity in the posterior insula than healthy controls (fixed effect: “partition”, variation: “GROUP”) or because the anorexic participants show higher activity in the anterior insula

than they do in the posterior insula (fixed effect: “GROUP”, variation: “partition”) essentially contains overlapping explanatory power.

The two resulting comparisons of interest did not maintain significance after the Bonferroni-correction (AN/AI>AN/PI; mean diff. = -0.086, SE = 0.038, t = -2.297, Cohen's d = -0.164, p = 0.170, Bonf.-corr. and HC/AI>HC/PI; mean diff. = 0.157, SE = 0.073, t = 2.135, Cohen's d = 0.299, p = 0.243, Bonf.-corr.). The resulting knowledge gain can in its principle be visualized with fig. 7 - more activity in the posterior insula than in the anterior insula in anorexic participants (significant before Bonferroni correction), as well as more activity in the anterior insula than in the posterior insula in healthy controls (not significant) both contribute partially to the group effect that is observed at a $p < 0.05$ but lose all significance after a Bonferroni correction. Acknowledging weak effects and low significances, the data has to be understood as preliminary; anorexic individuals might show more posterior insular activity and less anterior insular activity during CT-afference than healthy controls.

Due to this interaction being the most convincing group effect in H1, the averaged beta values of the posterior insula and the anterior insula (regardless of hemisphere) will be used as a variable in the analysis of H2 and H3.

Partition*Preference (F = 6.197, df = 1, 32, p = 0.018)

A significant interaction was found between the factors “partition” (AI>PI) and “preference”, when controlling for “age”. To ensure the validity of this interaction, an independence of “GROUP” and “preference” must be assumed because the comparison does not control for the effects of “GROUP”. Especially considering that “partition” and “GROUP” were significantly related in the repeated-measures ANOVA and that theoretical considerations about anorexic participants’ reaction towards the stimulus of interest suggest a connectedness of “GROUP” and “preference”, an independent samples t-test was performed. No statistically significant relationship could be found between “GROUP” and “preference” (t = -0.989, df = 34, p = 0.330). It is therefore concluded that “preference” and “group” are both associated with the insular partitioning of the effect. Having assigned a higher preference to the stimulus of interest was associated with less anterior insula activity / higher posterior insula activity.

Post Hoc Comparisons - Preference ✻ Partition

		Mean Difference	SE	t	Cohen's d	p_{bonf}
Preference1, Anterior	Preference2, Anterior	−0.188	0.273	−0.690	−0.357	1.000
	Preference3, Anterior	−0.210	0.216	−0.970	−0.397	1.000
	Preference1, Posterior	−0.092	0.044	−2.096	−0.173	0.661
	Preference2, Posterior	−0.184	0.273	−0.674	−0.349	1.000
	Preference3, Posterior	−0.051	0.216	−0.235	−0.096	1.000
Preference2, Anterior	Preference3, Anterior	−0.022	0.318	−0.068	−0.041	1.000
	Preference1, Posterior	0.097	0.273	0.354	0.183	1.000
	Preference2, Posterior	0.004	0.110	0.038	0.008	1.000
	Preference3, Posterior	0.137	0.318	0.432	0.260	1.000
Preference3, Anterior	Preference1, Posterior	0.118	0.216	0.547	0.224	1.000
	Preference2, Posterior	0.026	0.318	0.081	0.049	1.000
	Preference3, Posterior	0.159	0.083	1.923	0.301	0.952
Preference1, Posterior	Preference2, Posterior	−0.092	0.273	−0.339	−0.175	1.000
	Preference3, Posterior	0.041	0.216	0.188	0.077	1.000
Preference2, Posterior	Preference3, Posterior	0.133	0.318	0.418	0.252	1.000

Note. P-value adjusted for comparing a family of 15
Note. Results are averaged over the levels of: Hemisphere

Fig. 9. No comparison remains significant following the Bonferroni correction.

As can be seen in fig. 9 no effect remained significant following a Bonferroni-correction when calculating post-hoc comparisons. A similar effect as described regarding the "partition" and "GROUP" interaction might have led to several of the p = 1 values.

Exploratory Results Summary

It was abstained from reporting results that reached a Bonferroni-corrected $p > 0.5$ in this summary. No result remained significance within a conventionally respected significance threshold ($\alpha \leq 0.05$), following a Bonferroni-correction. Nevertheless, the most prominent associations may serve a preliminary purpose. The following findings will be integrated into the theoretical background in 4. Since no a priori hypotheses exist pertaining to the effects of Hemisphere and Hemisphere*Age, they will only be discussed briefly.

Hemisphere; left>right
mean diff. = 0.057, SE = 0.054, t = 1.061, Cohen's d = 0.109, p = 0.297, Bonf.-corr.

Hemisphere*Age; younger/left>younger/right:
mean diff. = 0.149, SE = 0.076, t = 1.95, Cohen's d = 0.278, p = 0.36, Bonf.-corr.

Partition*GROUP; AN/AI>AN/PI**:**

mean diff. = -0.086, SE = 0.038, t = -2.297, Cohen's d = -0.164, p = 0.170, Bonf.-corr.

Partition*GROUP; HC/AI>HC/PI:

mean diff. = 0.157, SE = 0.073, t = 2.135, Cohen's d = 0.299, p = 0.243, Bonf.-corr.

3.3 H2 / H3 Results

Pearson's Correlations

Variable		LR-AI	LR-PI	EDI	TAS	Age	Preference
1. LR-AI	Pearson's r	—					
	p-value	—					
2. LR-PI	Pearson's r	0.964***	—				
	p-value	< .001	—				
3. EDI	Pearson's r	0.286	0.177	—			
	p-value	0.166	0.397	—			
4. TAS	Pearson's r	0.095	0.009	0.755***	—		
	p-value	0.657	0.967	< .001	—		
5. Age	Pearson's r	−0.172	−0.204	−0.272	−0.072	—	
	p-value	0.412	0.327	0.189	0.738	—	
6. Preference	Pearson's r	−0.100	−0.190	0.276	0.244	−0.084	—
	p-value	0.634	0.364	0.182	0.251	0.690	—

* p < .05, ** p < .01, *** p < .001

Fig. 10. The correlation matrix summarizing all correlations between factors of interest (EDI and TAS) and AI / PI beta values. Also note the non-significant relation of potential confounders (Age and Preference) to AI / PI and to the factors of interest.

Apart from an expected highly significant and very large correlation of alexithymia (TAS-26) and eating disorder severity (EDI-2; Pearson's r = 0.755, p < 0.001), no correlation yielded significant results. Moreover, the direction of effects for the EDI-AI and TAS-AI correlations (within the anorexic sub-sample) is opposite to what could have been expected from the H1 results (group effect; lower AI activity in ANs). Both effects could hold true simultaneously due to an obviously very large difference in eating disorder symptom severity and alexithymia levels between groups and the assumed complexity of insular functioning. Nevertheless the finding is surprising and is discussed in 4.2.3. Also, it has to be

acknowledged that the correlation is severely underpowered with an N = 25 and not equipped to accurately ($\alpha = 0.05$) detect even large effects ($r = 0.5$; required $N > 41$; G*power). Additionally, the non-significance and small size of effects in H1 (see 3.2) might be attributable, not only to statistical artefacts, but also to the actual non-existence of noteworthy true effects. In this line of argumentation, the validity of H2 / H3 is criticized since the posterior / anterior insula would then not operationalize interoceptive deficits as assumed (see 5.1). It was considered to exclude outliers, but upon investigation they were deemed legitimate and thus potentially distorting if excluded.

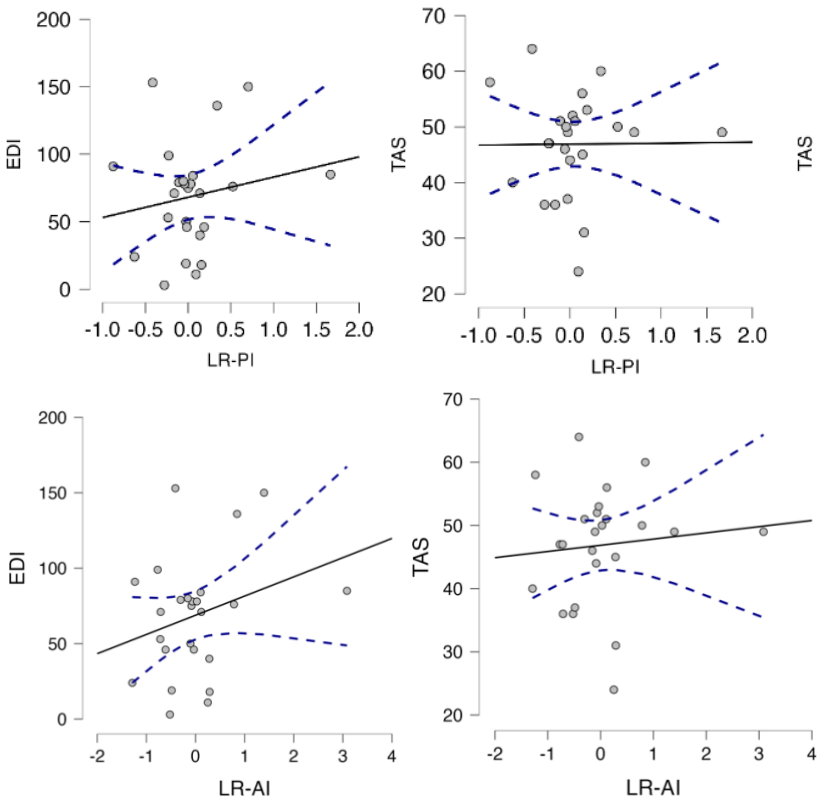


Fig. 11. Scatter plots visualizing the correlations of EDI-PI, TAS-PI, EDI-AI, TAS-AI and TAS-EDI.

Note the wide confidence intervals (95%), indicating great uncertainty about the true population values for the EDI-PI, TAS-PI, EDI-AI and TAS-AI relationships.

4. Discussion

4.1 Interpretational Frame

When empirically investigating correlational linkages in cross-sectional studies and discussing causal assumptions within developmental trajectories, an immense simplification accompanies the required abstraction of a respective topic. The resulting distortion should be limited to a minimum, nevertheless it is inevitable. To regain the required holistic perspective

that is needed to integrate the specific findings of this investigation into existing models of etiology and modes of action within AN, I find it necessary to discuss two approaches to abstracting AN – one understanding it as caused by triggering burdens *(a)*, the other focusing on the clinical picture as a whole *(b)*. With this I want to highlight AN as a stage-to-stage developmental aberration and stress the need for elaborate longitudinal studies to dissect it correspondingly.

Restrictive eating behavior is mostly understood as a coping mechanism that follows an otherwise unbearable load of pre-existing conditions in anorexic individuals *(a)*; implicitly, a causal role is thus attributed to a specific set of psychopathological burdens that could wrongfully be understood as inevitably leading to AN. One might expect the sole reason for restrictive eating behavior to be sufficiently summarized by factors that are connected to its comorbidities (for example the assumed central role of interoceptive deficits). However, this understanding leaves out of the equation that some people develop AN, while others don't, despite comparable burden. Reasons for a tendency to adopt restrictive eating as a coping strategy (= the mechanism that is in effect understood as AN itself) are to be considered as a separate reactive mechanism with, presumably, separate determining factors that are not necessarily expressed through detectable comorbidities. In other words, not all factors that cause restrictive eating behavior exert their effect through other clinically or sub-clinically ascertainable constructs.

The here presented investigation (H1), focuses on the role of insular aberration, as a possible factor of importance, for AN as a holistic construct *(b)*, including its clouding comorbid conditions and ignoring developmental trajectories. On its own, this approach is distorting; a factor's relative contribution to possibly triggering pre-existing conditions or tendencies towards maladaptive coping strategies lies beyond its scope, due to the limitations of statistical inference in cross-sectional studies. The reader has to understand this investigation as establishing correlative associations (H2 and H3) that pertain to a holistic construct, while at all times being aware of AN as a stage-wise developmental aberration with a multitude of modes of action to be considered in different phases – especially when understanding restrictive eating as reactive. Ignoring temporal processes is this study's greatest conceptual limitation and provokes this discussion's character as a speculative synthesis of empirical data and existing theories about modes of action.

4.2 Integrating Empirical Data

Unfortunately, the consistently non-significant results allow no confident backing of the presented theories as they do not allow inferences onto the population. Nevertheless, they will be discussed in order to motivate further research.

4.2.1 Discussing H1 Results

No significant group differences during CT-afference were found when focusing on the insula as a whole. Due to considerations in 5.1 and 3.1, this should also not be understood as there not being a true difference between groups. The original assumption of a general insular aberration cannot be evidenced – therefore, a more explorative look into insular aberration in AN is undertaken.

4.2.2 Discussing H1 (Alternative Exploratory Approach) Results

No significant differences in activity were found in any of the anatomically predefined sub-divisions of the insula (see 2.4.4) when comparing AN and HC groups during CT-afference. This cannot be understood as there being no true differences between groups during CT-afference.

When trying to integrate the preliminary spatial insight into insular aberrancy in AN, the complexity of the current state of research pertaining to insular functioning becomes apparent. Unfortunately, “the insula is one of the least understood brain regions”, due to its impractical spatial position for research and the very small number of naturally occurring lesions (Uddin et al., 2017). This makes it hard to draw specific conclusions from simply connecting CT-afference to activity differences in a specific brain region (AI/PI) between groups. Also, insular subdivisions are known to function not only independently, but also cooperatively if needed (= the insula as an integrative hub; see 1.7). This adds further impotence to the here discussed findings as a singular averaged beta score does not convey information about the temporal integration of afference or the sequential connectivity of insular subdivisions. The interpretational reach is thus restricted to linking distinct activity to the broad functional domain of the area in which it was observed (considering the direction of effects).

Result: Hemisphere / Hemisphere*Age

A significant lateralization to the left, independent of the group factor, was detected but lost significance after a Bonferroni correction (Cohen's d = 0.109, p = 0.297, Bonf.-corr.). Why could this effect have been observed? It is deemed very probable that this lateralization is due to participants being touched exclusively on their right forearm, therefore predominantly representing the insula's functional connectivity with (contralaterally functioning) sensorimotor areas (Otte et al., 2015). Additionally, as mentioned in 1.7, positive emotional stimuli are hypothesized to be connected to a lateralization effect towards the left insula (Duerden et al. (2013). Since CT-touch is generally deemed emotionally positive (see 1.5 and 1.6), CT-afference is made partially responsible for this effect. Even though the sample consists of many more anorexic participants than controls, this conclusion is still deemed plausible – even if ANs were to enjoy CT-touch less than HCs, it could still be perceived as more positive than baseline activity. Also, language processing and generation are hypothesized to evoke lateralized insular activity (Ardila et al., 2016), evoking thoughts about a possible confounding due to written instructions or communication with the experimenter. This however is not deemed a plausible explanation, since the level 1 effects result from a contrast between the slow and the two faster touch conditions. There is no reason for expecting more language processing or production, uniquely during CT-optimal touch.

Additionally, an interaction effect of hemisphere and age was found, indicating a stronger lateralization to the left for younger individuals, but lost significance following a Bonferroni correction (Cohen's d = 0.278, p = 0.36, Bonf.-corr.). Why could this effect have been observed? Due to the specificity of this interaction, and the surprisingly small amount of research on insular lateralization effects, not much but speculation can be added to this already inconclusive finding. To abstain from too far-reaching conclusions and due to the relative irrelevance to the research question, this discussion will now shift focus on the (preliminary) core finding.

Result: Partition*GROUP

The interaction effect of group and partition was the primary hope for an empirical knowledge gain, before losing significance following a Bonferroni correction when

formulating post-hoc comparisons (AN/AI>AN/PI; Cohen's d = -0.164, p = 0.170, Bonf.-corr.; HC/AI>HC/PI; Cohen's d = 0.299, p = 0.243, Bonf.-corr.). This means that ANs showed more activity in the PI than in the AI, while HCs showed the opposite pattern. Why could this effect have been observed?

Referring to the functional-anatomical associations of the insula that are addressed in 1.7, anorexic participants showed *(a)* more activity in the insular sub-division (PI) that is connected to cingulate (emotion, cognition and social cognition) and parietal (sensory and sensorimotor functions), as well as the olfactory cortices (smell and taste). It is connected with sensorimotor processing brain regions and integrates bodily sensations, such as pain, temperature, and touch and is involved in representing and perceiving bodily states (Uddin et al., 2017). Interestingly, the PI is also connected to social anxiety, as could be shown by Wang et al. (2019) – using a Cyberball paradigm, the researchers found significantly higher PI activity in socially highly anxious individuals during self-initiated contact, compared to less socially anxious participants. Possibly, the group effect can be partially explained through ANs being more socially anxious (Godart et al., 2002), when understanding CT-afference as social input (see 1.5 and 1.6). Concurrently, anorexic participants showed *(b)* less activity in an insular sub-division (AI) that is connected to the frontal cortex (cognition), frontal, anterior cingulate and parietal areas (cognitive control processes), limbic areas (emotion, motivation, memory, anxiety) and plays a major role in affective processes, emotional experience and subjective feelings (Uddin et al., 2017). It has also been hypothesized to be involved in empathy, self-reflection, and conscious awareness (Craig et al., 2009).

A thus concluded impeded emotional functioning (AI) of the anorexic insula during CT-afference, though preliminary, is seen as the central knowledge gain of this investigation. In line with 1.4, seeing CT-touch as a general interoceptive stimulus, it could substantiate alexithymia in AN as indeed resulting from a basal impediment during the integration of visceral afference (as opposed to more cognitive approaches). Attention is shifted towards the connectivity of the AI to other parts of the limbic system, possibly pinning down the insula as the dysfunctional junction that impedes an accurate emergence of emotion in AN. The preliminary finding is also in line with the more speculative argumentation of 1.5., understanding CT-touch as “social interoception” (Burleson & Quigley, 2019); since CT-afferents are thought to convey the affective quality of touch, much of its central allostatic

function is dependent on an adequate reactive emotional functioning of the insula, which seems to be disturbed in AN. Cascading effects on the development of the human social brain could contribute crucially to the AN syndrome.

Focusing now on the proposed modes of action in 1.3, a heightened sensory functioning of the insula (PI) could concurrently lead to increased satiety responses to stomach fullness. Combined with impeded self-reflective functioning and a lower conscious awareness (AI) during CT-touch, the here demonstrated insular dysfunction could also explain body dysmorphia and self-objectification through a diminished feeling of embodiment and an externally oriented thinking style through diminished interospective abilities. It is noted that these are predominantly post-hoc interpretations and that many of the modes of action of 1.3 originally relate to a more fundamental interoceptive impediment (more sensory function / PI) that cannot be supported in the light of the here discussed findings. Possibly, this uncertainty is exemplative of the insula's complex integrative functioning that links immediate sensory and more interospective qualities (Craig, 2009).

Conclusively, it has to be stressed that many of the just discussed functions are similar or overlapping and often attributed to both here used insular sub-divisions (AI/PI). It is concluded that the macroscopic and anatomical (instead of a-priori functional) sub-division of the insular, in combination with the presented analysis approach, is ill-equipped for the complexity of insular functioning. Possibly, the prominently used sub-division into dAI, vAI, and PI (see 1.7) would have resulted in more precise and interpretable data, better untangling cognitive and emotional functioning. Uddin et al. (2017) is recommended as a comprehensive review of the complexity and our still limited understanding of insular functioning. As Craig (2011) proposes, temporal processes are central when investigating the insular reaction to an (interoceptive) stimulus. He speaks of an "ascending sensory pathway" that terminates in the posterior insula before being re-represented in the mid- and then anterior insula while being connected to subjective feelings from the body and all emotional feelings, simultaneously. Future research could consider investigating this "posterior-to-anterior sequence of increasingly homeostatically efficient representations" and its relation to AN since it matches several aspects of the here proposed theory very well while comprehensively explaining the hypothesized insular functioning (integrating visceral percepts and linking them to emotion). Craig (2011) ultimately relates his ideas to human awareness and subjectivity, which are higher order brain functions that relate to AN via body dysmorphia and external oriented

thinking (1.3 / beforementioned when discussing heightened PI activity). This auspicious perspective on the AN syndrome has not sufficiently been focused on in this investigation and should be investigated more thoroughly, especially in conjunction with insular aberration. In addition to respecting temporal processes, it is advised to rely on functional connectivity in future investigations, doing justice to the insula's complex functional role as an integrative network hub. Especially connectivity between AI and anterior cingulate cortex (ACC) has been linked to "all subjective feelings" in numerous imaging studies (Craig, 2009) and could thus have illuminated here discussed research topic more thoroughly. A connectivity analysis was for example used to untangle the role of the insula in ASD by Ebisch et al. (2011) - since ASD and AN bear resemblance with regards to diminished emotional awareness, extensive social impediments, altered self-awareness and basal interoceptive impediments, the results could prove to be of relevance for the here discussed insular dysfunction in AN. A similar approach is deemed promising for future research endeavours investigating AN and altered insular functioning.

4.2.3 Discussing H2 / H3 Results

Even though it was not implemented into this research endeavor as a hypothesis (but more as a basal assumption to build upon), the correlation of EDI-2 scores indicating eating disorder severity and the sum scores of the TAS-26 (alexithymia) showed a very large and significant effect (Pearson's $r = 0.755$, $p < 0.001$). This does not provide novel insight into AN or alexithymia but it corroborates the connection once more. Future research should further investigate the reasons for this prominent connection.

Limiting the preliminary results of H1 to a certain extent, the EDI-2 and TAS-26 showed low and very low non-significant positive connections, not only with the PI beta values (EDI-PI: Pearson's $r = 0.177$, $p = 0.397$; TAS-PI: Pearson's $r = 0.009$, $p = 0.967$) but also with the AI beta values (EDI-AI: Pearson's $r = 0.286$, $p = 0.166$; TAS-AI: Pearson's $r = 0.095$, $p = 0.657$). Most notably, the positive relationship of the EDI-2 scores and AI activity is puzzling since the group comparison (AN/AI>AN/PI; Cohen's $d = -0.164$, $p = 0.170$, Bonf.-corr.; HC/AI>HC/PI; Cohen's $d = 0.299$, $p = 0.243$, Bonf.-corr.), showing an opposite pattern, was expected to unravel group differences that are interpreted as *(a)* due to a higher eating disorder symptom severity and *(b)* higher levels of alexithymia in the AN group. Why could this effect have been observed?

Theoretically assuming no other limitations being attributable, this contradictory finding would shift the attention to latent group differences that were neither detected by the EDI-2 nor the TAS-26, but still define the difference between healthy and anorexic individuals on a neural level. Keeping in mind the introductory interpretational frame (4.1), a low AI activity during CT-touch (H1 finding) might indicate a clinically non-detectable proneness to develop AN, while not having the same discriminatory power in the more severe syndrome (H2 and H3 finding).

Linked to this train of thought, it has to be stressed that H1 focuses on the difference between anorexic participants (high eating disorder symptom severity and high alexithymia levels) and a normative sample (explicitly intended to display zero clinical anomaly). H2 and H3 investigate differences within the experimental group. Thus, a relative homogeneity exists within the experimental group, not promptly being comparable to the much larger difference between groups. This must not only lead to a quantitively ascertainable difference, but also to a difference in qualitative nature - comparing fast and slow runners differs greatly from comparing a slow runner to a man in a wheelchair. It is possible that AI involvement changes functionally over the course and severity of the disease. Further research is needed to substantiate these speculations.

Admitting limitations, it is very likely that the incongruence of H1 and H2/H3 findings again mirrors the narrow scope of the anatomical-functional reasoning and a macroscopic a-priori anatomical sub-division of the insula. As stated in 4.2.2, more sophisticated functional connectivity approaches are needed to dissect insular functioning in AN accordingly.

5. Limitations

The explanatory power of the empirical investigation is very limited as the reader should not draw inferences about the population from non-significant results. It is therefore recommended to prioritize the knowledge gain that can be drawn from the introduction and the self-reflective hindsight of the discussion.. The following limitations are arranged in an order of importance, within their respective sub-section.

5.1 Sample & Methodological Aspects

This investigation is severely underpowered, mostly due to its small control group (N = 8). This diminishes the empirical basis needed to yield significant effects within a respected significance threshold ($\alpha > 0.05$).

This limitation is propelled by the disadvantageous hierarchical hypothesis structure – assuming that true H1 effects could not be detected due to a lack of power, the resulting lack of significant results in H2 and H3 could very well be traced back to an underpowered H1 analysis. The same logic also applies to the reliance of level 2 results on significant level 1 effects in H1 (see 2.2). It does also result in limitations that weaken the validity of inference; H2 and H3 depending on H1 relays all inferences through the assumption of insular aberration during CT-afference having being assessed validly.

The palliative evasion to an exploratory analysis with anatomically predefined ROIs is not optimal to explore differences between groups since *(a)* peaks and clusters of voxels can "slip through the cracks" of the predefined ROI masks (a mask might include a cluster of significant voxels but many more non-significant voxels that even out the effect when reporting the averaged results). Ideally, a higher number of healthy controls could have unraveled significant clusters in H1 that would have represented the neural footprint of AN much more precisely; not only from a statistical viewpoint, but also in light of theoretical considerations, this would have made the DV in H2 and H3 more valid. Also, *(b)* it became evident that a primarily anatomical sub-division of the insula was less appropriate for the hypotheses than a functionally defined ROI could have been, due to the intricacies of insular functioning. As is explained in the discussion *(5.2)* the functional imaging approach would have needed to implement *(c)* temporal resolution during stimulus administration and a *(d)* connectivity analysis to allow for an adequate insight into a possibly altered functionality of the insula (Wiener-Granger causality approach, Bressler & Seth, 2011). Due to the complex functioning of the insula as an integrative network hub, it is of major interest how afference passes through a functionally connected network – the here used approach is very limited in the inferences it allows.

Additionally, the anorexic group that was used in the H2 and H3 analysis (N = 25) is too small to yield significant results for the expected (small) effect size, even without the snowballing nature of underpowering.

The definition of who is deemed "anorexic" (and thus included in the experimental group) followed pragmatic considerations of feasibility, not exclusively theoretical certainty about the construct. When reading studies about AN it became evident that no clear consensus exists about which factors must be present in an individual in order allow a researcher to draw valid inferences about AN (once again stressing the need to understand AN as a stage-wise developmental aberration). On the one hand, including only currently anorexic in-patients (N = 5) seemed like a clean-cut definition of AN, on the other hand it seemed like distorting the holistic picture of the illness by focusing on currently extremely malnourished participants in acute psychiatric care. It was to decide between seeing the peculiarities of severe cases as *(a)* characteristic of AN and profiting from the more extreme group comparison or *(b)* seeing the conservative selection as potentially distorting inferences about an averagely more moderate syndrome. Nullifying the applicability of these considerations, an N = 5 could not yield significant results. Unfortunately, even adding all anorexic out-patients (N = 9) would not have added enough to the group to enable a meaningful analysis. Finally, all non-HC participants (including partially and fully remitted out-patients) were added as a compromise between group heterogeneity and sufficient sample size. The resulting limitation lies in a heterogeneous group hindering convenient generalizability or lowering the validity when drawing inferences about a more conservatively defined anorexic population. This effect was partially compensated by adding the eating disorder syndrome intensity as a factor in H3, intended to provide additional information connected to the intensity of the syndrome.

The control group is considerably older than the experimental group ($t = 2.205$, $df = 34$, $p = 0.334$). Even though it was controlled for "age" in every analysis, a systematic connection of an IV of interest ("group") to a confounder is hard to counter-act effectively. The often-mentioned importance of developmental trajectories amplifies the relevance of potentially clouding effects of age difference on the group factor. Especially since H1 focusses on neuroimaging, the effects of age on adolescent brain development are to be considered as a potential influence factor on the effects, in either direction.

Considering socio-cultural reasons that have been hypothesized to be tied to the female gender role and due to biological differences between sexes, the findings cannot be generalized onto male anorexic individuals.

5.2 Assessment of Constructs and Stimuli

The TAS-26 is a questionnaire that I criticize for building upon circular evidence – as discussed briefly in 1.4, uncertainty exists about what is understood as alexithymia. Since this debate is often not addressed critically in experimental investigations, but avoided by referring to the TAS-26 / TAS-20 as a standard tool, one could impute alexithymia is gradually becoming what is defined by the TAS. Also, the factorial structure of the TAS has undergone many changes and proved to build upon an inconsistent factor structure, especially in translations (Wilhelm et al., 2021). Since the German translation seems to support the here used 3-factor solution, this limitation does not have top priority beyond the general critique of investigating a construct that lies too deep within subjectivity to be adequately assessed through self-report.

An over-arching and amplifying problem that is omnipresent when researching psychopathology is the combined proneness to error of self-reported data and the altered self-referential psyche in psychological illness. The self-reported data (TAS-26 and EDI-2) is expected to be distorted as a function of psychopathological burden – it is thus also expected to be systematically linked to the group factor. This especially confounds the highly significant large correlation presented in 3.3 and 4.2.3. Since alexithymia is in itself a deficit of self-referential awareness, considerable misjudgment is additionally expected of alexithymic individuals.

Since this investigation utilizes data from a larger research project, several aspects of the executed experimental task are of no interest for this thesis. Nevertheless all participants went through the whole procedure as described in 2.4.1 and 2.4.2 – resulting in an unnecessarily long and taxing experiment with unnecessary sources of confounding. Due to the functional role of the insula (among others, negative emotions and fear; Wang et al., 2019, Baur et al., 2013), the repeated consumption of aversive food stimuli might have had a detectable impact on the insula, even during the administration of the other stimulus of interest, social touch, and during what is understood as baseline activity. Both impede the validity of neuroimaging

data in the anorexic group and thus the inferences about the connection of concurrent brain activity and social touch / C-tactile afference.

The same logic also applies when assuming the correctness of interpreting all observed insular activity as reactive to touch, possibly though to a lesser extent. A plethora of theories exist about anorexic individuals' disturbed reaction towards social touch, social interaction in general, problems with physical intimacy, and a disturbed perception of the own body – all proposing a resulting negative emotional state that could cloud inferences (Maier et al., 2019). Since the contrast calculated in H1 (level 1; see 2.4.5) specifies the activity as specific to what differentiates the slowest touch option from the two faster options, this effect can be minimized. Nevertheless the stimulus is assumed to have different validity between groups.

To conclude, many central aspects of the research object are difficult to adequately define and assess (AN, alexithymia, interoception) and thus impede the comparability of results in existing research, as well as the impact of the here presented investigation. Additionally, the insula's complex functional connectivity calls for more sophisticated neuroimaging methods that were not deemed feasible due to my level of experience and ability. Nevertheless, the extensive review and discussion of interoceptive modes of action in AN (1.3 and 1.4), the proposal of a novel theory (1.5) and the established linkages to insular anatomy and function (1.7, 1.8 and 4.2) are deemed profitable for the field of research. The results are seen as preliminary and, in conjunction with the self-reflective hindsight and suggestions of 4 and 5, hope to inspire future research. Especially a more adequate sample size and a connectivity analysis approach are deemed promising for the further investigation of the role of insular and interoceptive aberration in AN.

6. Literature

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7. Abbreviations

A	Ascetisism
AI	Anterior Insula
AKH	Allgemeines Krankenhaus
A	Askese
B	Bulimia
BD	Body Dissatisfaction
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent

CSN	Clinical and Social Neuroscience
df	Degrees of Freedom
dAI	Dorsal Anterior Insula
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DV	Dependent Variable
EASI	Emotion as Social Information Model
EMG	Electromyography
EPI	Echo Planar Image
fMRI	Functional Magnetic Resonance Imaging
FoV	Field of View
FWE	Family Wise Error
HBT	Heartbeat Tracking Task
ICD-10	International Classification of Diseases
ICV	Intracranial Volume
IA	Interoceptive Awareness
ID	Interpersonal Distrust
IR	Impulse Regulation
IV	Independent Variable
L-AI	Left Anterior Insula
L-I	Left Insula
L-PI	Left Posterior Insula
L-RI	Left and Right Insula
MVC	Maximum Voluntary Contraction
MF	Maturity Fears
N	Newtons
OCD	Obsessive Compulsive Disorder
P	Perfectionism
PI	Posterior Insula
PTSD	Post Traumatic Stress Disorder
R-AI	Right Anterior Insula
R-I	Right Insula
R-PI	Right Posterior Insula
RPE	Risk Prediction Error
ROI	Region of Interest

SAME	Somatovisceral Afference Model of Emotion
SE	Standard Error
SI	Social Insecurity
TCE	Theory of Constructed Emotion
TE	Echo Time
TR	Repetition Time
VAS	Visual Analogue Scale
vAI	Ventral Anterior Insula

8. Appendix

Abstract (in German)

Anorexia Nervosa (AN) ist eine Erkrankung, die aufgrund einer Vielzahl plausibler Einflussfaktoren, die in verschiedenen Stadien eine prädisponierende, auslösende, aufrechterhaltende und verschlimmernde Rolle spielen, schwer zu erforschen ist. In dieser Untersuchung werden verschiedene Wirkmechanismen der AN und eine neuartige Perspektive auf das soziale menschliche Gehirn diskutiert, die beide auf Interozeption aufbauen. Ich argumentiere, dass früh auftretende und fortbestehende interozeptive Defizite die erstaunlich breite und vielfältige Psychopathologie erklären könnten die AN begleitet, insbesondere charakteristische sozioemotionale Beeinträchtigungen. Um diese Behauptungen zu untermauern, wird ein fMRT-Experiment durchgeführt, um die Insula-Aktivität von anorektischen und gesunden Frauen während der interozeptiv integrierten CT-Afferenz zu messen, die dann mit der individuellen Intensität des Essstörungssyndroms und dem Ausmaß der Alexithymie in Verbindung gebracht wird. Es wurde eine kleine und nicht signifikant erhöhte Aktivierung in der hinteren Insula bei anorektischen Personen festgestellt, während der entgegengesetzte Effekt in der vorderen Insula beobachtet wurde. Es wurden kleine und sehr kleine positive nicht signifikante Korrelationen zwischen den Insula-Aktivierungen im vorderen und hinteren Bereich mit der Intensität des Essstörungssyndroms und dem Ausmaß der Alexithymie festgestellt. Die Ergebnisse werden als Hinweis auf eine gestörte Integration interozeptiv integrierter Afferenzen in der anorektischen Insula interpretiert. Dem Leser wird empfohlen, den Fokus auf die Zusammenfassung und Synthese ätiologischer Ansätze zu legen, die interozeptive Defizite einbeziehen, sowie auf die prospektive Ausrichtung der Diskussion, die zukünftige Forschung leiten soll.