TOWARDS AN IMPROVED UNDERSTANDING OF SEVERE AND ENDURING ANOREXIA NERVOSA

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TOWARDS AN IMPROVED UNDERSTANDING OF SEVERE AND ENDURING ANOREXIA NERVOSA

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EDITORIAL
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Editorial: Toward an Improved Understanding of Severe and Enduring Anorexia Nervosa

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Editorial on the Research Topic

Toward an Improved Understanding of Severe and Enduring Anorexia Nervosa

This Special Issue presents a collection of 11 articles addressing a range of issues relevant to current dilemmas in the understanding of severe and enduring anorexia nervosa (SEAN). These are the defining characteristics of SEAN, understanding neurobiological, cognitive, and psychosocial mechanisms of illness persistence, and the treatment evidence base.

DEFINING FEATURES

Hay and Touyz (1) have posited that there are three defining features of SEAN, namely a persistent state of illness, for at least 3 years, and having had access to at least two evidence based treatments with appropriate person-centered understanding or formulation. In this regard, Dapelo et al. in a trans diagnostic clinical sample reported an investigation of such putative defining features. They tested illness duration against ED symptom severity. Whilst this was not significant, delays in care were however related to illness severity. Illness duration was also not significantly associated with prior incidents of treatment, hospital admissions, medical co-morbidity, or current function. Their findings highlight the importance of adequate access to care and that a diagnosis of SEAN (or SE eating disorder) should not be made where treatment has been insufficient. This point is further made by Gutiérrez and Carrera et al. in their historical review of treatments. They argue that in some instances treatment intractability may rather be treatment ineffectiveness.

Smith and Woodside et al. in investigating treatment intractability as a putative defining feature of SEAN found significant relationships between presence of purging and depressive symptoms, but not eating disorder symptom severity or body weight, with multiple readmissions in a clinical sample of people with anorexia nervosa. Duration of illness was not significantly associated with multiple readmissions, although there was a trend and the sample may have been underpowered. This underscores the premise that all three defining features of SEAN, treatment intractability, severity and duration may occur together but may occur apart and more research is needed to delineate this syndrome or syndromes.

UNDERSTANDING ILLNESS PERSISTENCE

In exploring symptom persistence Jacquemot and Park et al. in their Mini Review present the literature around altered interception and a novel neuro-circuitry model of its role in the

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maintenance of symptoms through dysregulation of hunger/satiety cues, interceptive predictive error, negative affect, impaired emotion regulation, and body image disturbance. Het et al. presented preliminary findings showing persisting under-reactive hypothalamus–pituitary–adrenal axis which may present targets for identifying those vulnerable to an eating disorder and possibility thereby of early interventions, preventing the severe and enduring state.

van Elburg et al. pose an "idea to research" in the question is impaired mental capacity, i.e., "the ability to understand and process information on a cognitive and an emotional level" impaired in people with SEAN? If so this could lead to poor decision making and contribute to emotion dysregulation which both may help in understanding persistence of illness and may be remedial with innovative therapies.

Musolino et al. provide a novel socio-anthropological qualitative methodology to understanding the psychological state and symptom meaning making whereby the illness persists. Beyond a sense of loss of identity and sense of self, they found that people may fear symptoms reduction, as losing the illness would impact on their sense of "being-in-the-world" and thus they may experience disembodiment.

REFINING AND DEVELOPING TREATMENTS

Zhu et al. present a Mini Review of psychological therapy studies for the outpatient care. Whilst highlighting the deficits in evidence they point to several promising approaches that have been tested in participant samples that included a large proportion of people with longstanding illness. These address putative maintaining features such as affective disorder comorbidity, impaired adaptive function and quality of life and suggest merit in refining treatment goals. Clausen et al. ventures into the challenging area of the use of involuntary care. Clausen presents the argument for a more compassionate and judicious use of such legal restraints, allowing the person to negotiate different goals and time frames for recovery.

Tchanturia et al. describe a new approach "Pathway for Eating disorders and Autism developed from Clinical Experience (PEACE)" to integrated care for people with this problematic co-morbidity that likely also contributes to the poor outcomes for this group. Kerr-Gaffney et al. further empirically examined associations within this comorbidity using a cross-sectional network analytic design. The strongest bridging symptoms were low self-confidence and anxiety about social eating and public body exposure. They acknowledged a prospective design is needed to determine the direction of associations.

CONCLUSIONS

This Special Issue has highlighted the urgent need for empirical research testing putative defining features of SEAN and building the evidence base for treatments. Also, people with longstanding AN may not actually be "treatment resistant," but rather the treatments delivered to them may not have been adequately tailored to meet their needs. Thus, current treatments are ineffective. On a positive note, the papers also provide promise of new treatment targets through an improved understanding of mechanisms of illness persistence.

AUTHOR CONTRIBUTIONS

PH conceived and wrote this paper. ST, RP, and PH edited and provided intellectual input to the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Psychological Treatments for People With Severe and Enduring Anorexia Nervosa: A Mini Review

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This Mini-Review presents recent research into evidence for psychological treatments for people with severe and enduring anorexia nervosa (SEAN). Two psychological therapies, specialist supportive clinical management (SSCM), and cognitive behavior therapy for anorexia nervosa (CBT-AN) have limited (one randomized controlled study) evidence of efficacy. Both have had adaptations for SEAN, notably with revision of the primary treatment goal of improved quality of life and full weight recovery a secondary goal. A major issue with existing studies is poor definition of SEAN, and the large deficit in research that has used an agreed definition of SEAN. In particular, it may be problematic to extrapolate from studies of people with either severe and/or enduring but not intractable or "resistant" illness. People with longstanding AN who have not received evidence based care should be offered this with an expectation of recovery. Similarly, people with SEAN may be offered care with judicious mitigation of expectations. In the future, trials should include people with SEAN clearly defined. Trials with a subsample of participants likely to have SEAN, if identified at randomisation, are an opportunity for secondary analyses of such participants. This would widen the evidence base for psychological treatments providing hope for people with this devastating illness. Finally, there is an urgent need not only to strengthen our existing knowledge with studies of sufficient power, but also, fundamentally, to derive novel conceptualizations of what "treatment" involves.

Keywords: eating disorder anorexia nervosa, therapy, treatment resistant, longstanding chronic, therapy

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INTRODUCTION

Anorexia nervosa (AN) is a serious mental disorder affecting 1.4% of women and 0.2% of men worldwide in their lifetime (1). A significant number of people with AN remain ill for many years, with treatment becoming increasingly challenging and expensive as the disease progresses and recovery is less likely (2, 3). These individuals have the highest mortality rate of all mental disorders and suffer personal and fiscal impoverishment (4, 5). It is essential to stress that both treatment and recovery may occur decades after onset and that illness should not be regarded as intractable

merely because of a lengthy duration (2, 6). Thus, it is important to approach the assessment of people with AN holistically.

In this paper the proposed criteria for severe and enduring AN (SEAN) [(7), p. 2] will be used. These are the presence of: "(1) a persistent state of dietary restriction, underweight, and overvaluation of weight/shape with functional impairment; 2) duration of > 3 years of anorexia nervosa; and, (3) exposure to at least two evidence based treatments appropriately delivered together with a diagnostic assessment and formulation that incorporates an assessment of the person's eating disorder health literacy and stage of change." One major problem with these criteria is that the mean duration of illness in adults at the time of first presentation is frequently much more than 3 years, and some definitions of SEAN include an illness duration of > 7 years. Notwithstanding this limitation, these criteria capture the concept of SEAN as used in this paper.

Approaches to the care of people with SEAN have to date been based on consensus judgments and "clinical wisdom" with few clinical trials (8). There are mixed views on goals of treatment, with some suggesting these should be modified to aim for improved quality of life as a primary outcome (9, 10) whilst others promote a view that the aim of full weight recovery should remain the primary goal no matter the length or severity of illness (11). When undertaking treatment in those with SEAN, a unique challenge is posed for clinicians as patients are very unwell, often appear poorly motivated, feel very alone and unsupported, and experience an overwhelming sense of hopelessness (12). These people experience unremitting and insistent ruminations on food, shape, and weight and treatments aiming for "complete cure" may have little impact. Singularly offering treatments focused on traditional goals (primarily of weight restoration and amelioration of disordered eating symptoms) and physical and psychological recovery may be inappropriate for such individuals, and this mismatch in clinician and patient goals could further contribute to low retention rates (8).

A systematic review in 2012 (13) of randomized controlled trials (RCTs) highlighted the paucity of evidence based treatment for SEAN. This review included participants with AN and an illness duration of 3 or more years. It identified 11 trials, of which four had a majority of such participants. Findings were very limited and there was an absence of evidence for any psychological treatment to be first line in treatment, in contrast to medication which has generally been found to be non-efficacious or non-feasible as a first-line treatment. It was concluded that there may be an advantage for specialist *vs* non-specialist care and cognitive behavior therapy for AN (CBT-AN) may reduce relapse when used following weight restoration. All studies of any treatments required replication and there was no RCT specifically for treatment of people with SEAN.

The 2012 review (13) did, however, identify several psychological therapies that appeared to address issues relevant to people with SEAN, namely comorbidities of mood intolerance and depression, functional impairments, personality vulnerabilities and interpersonal deficits, low motivation to change, and/or modification of treatment goals towards quality of life. These therapies were: Specialist Supportive Clinical Management [SSCM (10)], CBT-AN (11), the Community Outreach Partnership Program [COPP (14)], Maudsley Model of Anorexia Nervosa Treatment for Adults [MANTRA (15)], and that described by Strober (12). A transdiagnostic CBT enhanced–broad [CBT–Eb (16)] therapy was also included as it widened the components of treatment to add modules addressing comorbidities, interpersonal therapy, clinical perfectionism, and low self-esteem. There are shifts towards more collaborative treatment and aims to improve quality of life, however, all these therapies emphasize the importance of ensuring medical safety and encourage, if not mandate, weight gain. Finally, only SSCM, CBT-AN, MANTRA, and CBT-E have been tested in a RCT against a control (active or inactive) treatment for people with AN.

The lack of evidence based treatments for SEAN may have negative effects and result in loss of hope for both patients and clinicians, leading them to seek alternative and less conventional treatment goals and therapies. Wonderlich et al. (8) stated that these attempts to accommodate treatment for SEAN patients may result in "relatively unfocused, intermittent, supportive interventions, where goals become unclear and monitoring of clinical status becomes impressionistic and imprecise." There is little to guide clinicians in challenging areas such as when to use involuntary treatment and the ethics of, and role of, non-specific medical palliation in these patients (17, 18). Strober (2004) reasoned that the objective of care in patients with SEAN may be to support the patient and make up for the effects of the disease—a palliative, holding management that offers support and comfort to partially alleviate the effects of the disease (12).

Given the challenging nature of SEAN treatment, researchers and clinicians are now exploring novel biological treatments based on a neuroscientific understanding of the disorder (19). These include brain-directed treatments such as neuromodulation with non-invasive (20) and deep brain stimulation (21, 22). Novel medications such as dronabinol, a synthetic cannabinoid (23) have also begun to be investigated. However, even if such experimental adjunctive biological approaches are found to improve patient outcomes, they should always be considered adjunctive strategies, used in combination with evidence based psychological treatments, and in accordance with sound ethical guidelines (24).

Since the 2012 systematic review (13) there have been further RCTs of treatment for people with SEAN and a Cochrane review of psychological therapies is in progress (21). This Mini-Review aims to (1) provide an overview of psychological treatment trials and other studies identified since the 2012 review in the course of a recent literature search (25), and (2) discuss treatment gaps and future research directions. Therapy trials are considered that were either a primary RCT for people with SEAN or included a substantive proportion of people with long-standing illness (e.g., median illness of more than 3 years) who may represent a subgroup of people with SEAN. In this Mini-Review inpatient as well as outpatient trials are considered. An overview included trials is found on **Table 1**.

PSYCHOLOGICAL TREATMENT TRIALS

Primary Trial of SEAN

To our knowledge there has been only one RCT evaluating specific psychological treatment for people with SEAN (9, 10). This trial compared two evidence based treatments for AN that were modified for people with SEAN, namely SSCM (34) and CBT-AN (35). In this study SEAN was defined as having a minimum illness duration of 7 years. In both treatment conditions there was a broadening of treatment goals to focus on quality of life and a lessening of the priority to achieve weight gain. Both therapies also highlighted the importance of collaborative goal setting to address patient preferences, with the aim to improve engagement, motivation, and retention rates. This trial did achieve very high rates of treatment completion—with 76% completing more than 30 weeks of therapy. There were significant improvements in eating disorder symptoms, health related quality of life and weight for all participants, which were sustained to 1-year follow-up. Whilst there were few significant differences between groups in primary or secondary outcomes, those with more severe symptoms, depression, an older age, and who were purging, benefited more from the modified CBT-AN (36). CBT-AN was also superior to SSCM in reducing core eating disorder symptoms at follow-up. For all participants improved eating disorder symptoms and increased weight also predicted a significantly better health related quality of life (10).

Trials That Included Participants With Long-Standing Illness

Dalle-Grave CBT-E Trial

In 2013, Dalle Grave et al. (26) reported the immediate and longer-term effects of CBT-E in focused and broad forms in 80 young adults with severe AN and a median illness duration of 5 years. In this RCT both treatments significantly improved weight, eating disorder and general psychopathology in participants, and whilst deterioration did occur after discharge, it was not marked and only for a short duration. Furthermore, as there were no statistically significant differences between the two therapies, it was suggested that there appears to be no benefit of using the more complex CBT-Eb treatment. Thus, whilst Hay et al. (13) postulated that the broader form of CBT-E would offer benefits over the focused form for people with longer illness duration, this was not supported in this study. This may have been because SEAN encompasses the concept of previous treatment intractability as described above, and not merely longstanding symptoms. This trial was also conducted in an inpatient treatment setting where there was additional nutritional support from dietitians. Interestingly no psychotropic drugs were prescribed.

Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA) Trials

MANTRA has not been evaluated in a SEAN group. However, it employs a motivational interviewing style, has as a model individualized care, and optional modules can include the development of a "non-anorexic" identity that was conceived for patients with enduring illness. (27, 37). MANTRA has been evaluated in two RCTs against SSCM in participants with lengthy (mean 8 and 7 years) illness durations. In these RCTs both therapies resulted in statistically significant improvements in BMI, reductions in ED symptomatology, other psychopathology, and clinical impairment over time. Notably, at 2-year follow-up (37) MANTRA was assessed to be statistically significantly more acceptable and credible by patients at 12 months, with higher treatment completion rates. This is a relevant finding as patients with SEAN have notoriously high attrition rates.

The Anorexia Nervosa Treatment of OutPatients (ANTOP) Trial

A treatment more recently evaluated in RCTs in AN is focal psychodynamic therapy (FPT). FPT is a three-phase treatment that focuses on interpersonal relationships (28). In FPT initially a therapeutic relationship is developed and self-esteem, pro-anoretic behavior, and ego-syntonic beliefs are addressed. Treatment then shifts to target associations between AN behaviors and interpersonal relationships. Finally preparations are made for independent recovery. The Anorexia Nervosa Treatment of OutPatients [ANTOP (28)] study was a large (n = 242) multi center RCT aimed to assess the efficacy of FPT and CBT-E against an optimized treatment as usual (TAU). Ninety-four (39%) of participants had AN for longer than 6 years. At the end of treatment (10 months after start of treatment) all groups had gained weight with no difference in weight gain between groups. All participants also exhibited decreased general and eating disorder-specific psychopathology. At 12-month follow-up, people allocated to FPT had significantly higher full recovery rates compared with those assigned to optimized TAU as usual, but there was no significant difference in recovery rates between the CBT-E and FPT groups. Moreover, CBT-E was found to be more effective in terms of speed of weight gain and improvements in eating disorder psychopathology and appeared to offer an advantage for those with lower baseline weight.

Cognitive Remediation Therapy (CRT)

CRT was initially a form of management for patients with brain lesions and schizophrenia. A modified form of CRT was developed by Tchanturia et al. (38) for AN. It is a focused treatment that targets a patient's cognitive inflexibility, thought to be a factor in both the development and maintenance of the illness. With inefficient cognitive flexibility, patients may exhibit obsessive preoccupations related to body shape, weight, and food as well as ritualistic behaviors. Through improvement of basic neurocognitive functions, it is thought that perseverative behaviors in anorexia nervosa may be addressed. Instead of looking at what a patient thinks, *how* they think is examined and it is thought that the proliferation of neural connections due to CRT training results in more flexible thought and behaviors. In an RCT, Dingemans et al. (29) investigated the effectiveness of 10-session CRT for 82 patients with severe or enduring eating disorders by comparing intensive TAU to CRT plus TAU. Forty-six percent of participants had >7 years of illness duration and 93% had a history of AN. Patients who underwent CRT in addition to TAU improved significantly more in eating disorder-

TABLE 1 | Trials identified in this review of psychological therapies that included a substantive proportion of people with long-standing anorexia nervosa (AN).

Trial	Psychological Therapy/ies	Sample Size (*n*)	Duration of Illness	Randomization	Allocation Concealment	Notes
Touyz (9)*	Cognitive Behavior Therapy (CBT) for Anorexia Nervosa Specialist Supportive Clinical Management (SSCM)—both modified for severe and enduring	63	Mean 16.6 years (SD 8.5)	Adequate Used Ephron's biased coin approach stratified within sites based on subtype of illness (restricting vs binge-purge type) and use of psychiatric medication.	Adequate Central randomization performed by biostatistician independent from intervention sites.	Therapists conducted both forms of treatment to control for no-specific therapist effects. Outcome assessments conducted by assessors masked to treatment allocation.
Dalle Grave (26)	CBT-Enhanced focused, CBT-Enhanced broad	80	Median 5.0 years (Range 0–26)	Adequate Computer-based minimization algorithm used to allocate patients into two programs (balancing age, gender, diagnosis, and BMI). When groups evenly balanced, pre-prepared block randomization list of varying size used to allocate patients.	Adequate Author H.D. (who did the computer-based minimization algorithm) was independent from recruitment.	Therapists conducted both types of treatment. Assessors blind to group.
Schmidt (27)	Maudsley model of Anorexia Nervosa Treatment for Adults (MANTRA), SSCM	72	Mean 80.6 months (SD 71.8)**	Likely adequate but did not specify what type of randomization code was used. Randomized after baseline assessment. Randomization codes from a computerized system were used—stratified by eating disorder severity.	Adequate Researcher independent from trial generated randomization codes. Treatment assignment codes contained in numbered sealed opaque envelopes. Administrator was notified of allocation and letter sent to inform patient.	Outcome assessments conducted by two assessors masked to treatment allocation. Participants reminded not to reveal treatment allocation to assessor. Masking success was tested and deemed successful.
Zipfel (28)	Focal Psychodynamic Therapy for AN, CBT -E, optimized Treatment as Usual (TAU)	242	≤6 years: 148 patients >6 years: 94 patients	Adequate Independent coordination center for clinical trials performed centralized randomization. Used the Rosenburg and Lachin covariate-adaptive randomization procedure. Stratified by center and duration of illness.	Adequate After randomization into groups, independent center faxed trial sites the treatment allocation.	Complete masking not feasible as 1/3 of patients were allocated to TAU.
Dingemans (29)	CRT+TAU, TAU	82	≤7 years: 44 patients >7 years: 38 patients	Adequate Randomization sequence created using SPSS v19, stratified by center and treatment unit with 1:1 allocation using random block sizes of 4. Individual not involved performed randomization.	Adequate Individual not involved in recruitment performed randomization. After assessment, neutral person not involved informed patients their assignment.	Researchers who were not involved in conducting CRT conducted assessments and were blind for condition.
Brockmeyer (30)	Cognitive Remediation Therapy (CRT), Non-specific Neurocognitive Therapy (NNT)	40	CRT (n = 20): *Mean 7.89 years (SD 7.60) NNT (n = 20): *Mean 6.82 years (SD 7.57)	Adequate Treatment assignment determined by independent research coordinator using specific open-source randomization software (RANDI2) stratified by duration of illness.	Adequate	Blinding of patients and therapists not possible.

(Continued)

TABLE 1 | Continued

Trial	Psychological Therapy/ies	Sample Size (*n*)	Duration of Illness	Randomization	Allocation Concealment	Notes
Steinglass (31)	AN-Exposure and response prevention (EXRP), CRT	32	Mean 10 years (SD 8)***	Adequate Used computer generated block randomization procedure.	Unclear Patients informed of assignment after baseline assessments.	All study therapists provided both treatments.
Williams (14)	Community Outreach Partnership Program (COPP)	31	Mean 15.23 years (SD 8.15)	Not applicable	Not applicable	NA
Steinglass (32)	Supportive psychotherapy (SPT), Regulating Emotions and Changing Habits (REaCH)	22	SPT (n = 11): *Mean 12.7 years (SD 10.1) REaCH (n = 11): *Mean 15.5 years (SD 11.4)	Adequate Random assignment made using computer generated block randomization procedure.	Unclear Patients informed of treatment procedure after baseline assessments.	Assessors blind to treatment group.
Weiss (33)	Motivational Interviewing (MI), TAU	32	Mean 10.7 years (SD 8.9)	Adequate Randomized through permuted block randomization.	Unclear	Treatment staff in MI program kept blind to patient group assignment. Outcome assessment not blind to group.

**Trial designed to assess psychological therapy in people with SEAN.*
***Data from 58 of 72 patients.*
****Data from 30 of 32 patients.*

related quality of life at end of treatment and eating disorder psychopathology at follow-up when compared to TAU only patients. Whilst Dingemans et al. (29) confirmed the findings of previous uncontrolled case studies using CRT, it should be noted that this trial was not in SEAN patients only, but rather a mix of severe or enduring eating disorder patients. No studies have been conducted with CRT in exclusively SEAN patients.

Brockmeyer et al. (30) also have investigated CRT in a small pilot RCT of people with AN with mean illness duration > 6 years. They only examined outcomes in the 25 participants who completed treatment and only reported on neurocognitive findings. CRT was compared with a non-specific neuro cognitive therapy that focused solely on attention, memory, and deductive reasoning, and not flexibility. The primary outcome was cognitive set-switching which was superior at end of treatment in the CRT group.

Exposure and Response Prevention for Anorexia Nervosa

Exposure and Response Prevention for AN (AN-EXRP) is a manualized method of treatment that was formed to focus on eating-related anxieties and alter dysfunctional eating behaviors through encouraging the confrontation of fears. (31) AN-EXRP modifies these strategies to target eating-related symptoms with particular focus on exposure and ritual prevention. Patients are progressed through a hierarchy of provocative eating situations and attention is brought to stopping ritualistic behaviors and the eventual dissipation of anxiety. Steinglass et al. (31) performed an RCT to evaluate AN-EXRP as an adjunctive strategy to improve eating behavior during weight restoration and compared it with CRT. This study was conducted with participants with AN and a mean illness duration of 10 years. Participants randomized to AN-EXRP had significantly better change in food intake in a test meal than CRT (i.e. average intake increased by approximately 50 kcal compared to a decrease of 77 kcal in the CRT group). Whilst these findings could suggest that AN-EXRP may support continuation of healthy behaviors, a key limitation of the study was that the intervention was delivered adjunct to an intensive treatment and so results cannot be attributed to AN-EXRP alone.

Community Outreach Partnership Program (COPP)

COPP was developed as an outpatient, multidisciplinary form of treatment that differed to traditional approaches in that its goals were improving quality of life instead of targeting the eating disorder. (14) Patient autonomy and self-esteem are improved through skill building and problem solving, and support systems that favor community supports instead of traditional health care providers and hospitals, are developed. A harm reduction model is utilized, where there is collaboration between patient and therapist in an attempt to minimize consequences that may arise from disordered eating behaviors. The program employs strategies from psychosocial rehabilitation and motivational interviewing. Preliminary outcome results have been reported from a small uncontrolled study by Williams et al. (14) in patients with eating disorders (mean duration of eating disorder 15.23 years), 15 (48%) of which were patients with

AN. Positive findings suggested that COPP merits further evaluation in RCTs as an alternative model of care for individuals with long-standing eating disorders.

Regulating Emotions and Changing Habits (REaCH)

REaCH is a behavioral treatment focused on prompts for disordered eating behaviors and was based upon treatments that have seen success in complex behaviors such as habit reversal therapy for Tourette's syndrome. (32) It has been postulated that patients with AN develop restrictive eating behaviors that eventually grow into entrenched reflex responses to certain cues and thus are considered habits. REaCH is a manualized treatment with four main components including cue-awareness, the development of new routines, the repression of detrimental habits, and emotional regulation. In a proof-of-concept RCT by Steinglass et al. (32) 22 hospitalized patients with AN were randomly assigned to either Supportive Psychotherapy (SPT) or REaCH (mean duration of illness was 12.7 and 15.5 years respectively). Study findings demonstrated that REaCH more effectively altered habit strength of maladaptive routines compared to SPT and was associated with clinically meaningful improvements in eating disorder symptoms and energy intake.

Motivational Interviewing (MI)

Weiss et al. (33) tested a four-session weekly MI therapy prior to an intensive hospital program in 39 eating disorder participants (65% with AN) with mean illness duration >10 years. The primary outcome was program completion which was significantly higher in the MI group than a control (wait list) arm. However, there were no differences in measures of motivation and thus the mechanism of the effect was unclear.

DISCUSSION

Whilst there has been some progress in psychological treatment research in AN there remains a grave paucity of trials, and a total of one only (9) for those with severe enduring illness. The situation is further confused by lack of staging patient's illness. As many trials include participants who may have SEAN there is an opportunity to stratify by presence or absence of SEAN and conduct *post-hoc* sub-group analyses in large trials. However, this rests on an agreed definition of SEAN and it is likely the third suggested criterion of treatment intractability would not be known and/or would have been met, which limits this as a means of advancing knowledge. Indeed, it was not a criterion in the single trial of SEAN (9). There is an urgent need not only to strengthen our existing knowledge through larger RCTs of sufficient power, but also, fundamentally, to derive novel conceptualizations of what "treatment" involves, beyond traditional directive and paternalistic models of the past which all too often render patients institutionalized, traumatized, and/or disempowered.

There needs to be an increased effort in determining how this particular population of patients is best empowered to recover. This should be mindful of respecting patients' preferences which are too often neglected in this area (39). Unanswered research questions include: what are the moderators of specific therapies so we can better manage patients with different presentations; how can we avoid providing ineffective treatment, and thus periods of undernutrition, to patients who are unlikely to respond to a certain treatment; what is the role of new technologies such as transcranial direct current stimulation in delivering psychotherapy and support to these chronic patients; and, might there be a more suitable and accurate way to categorize anorexia nervosa such as the hybrid model of categories and dimensions suggested by Wildes (40)?

In conclusion, advances have been made in bringing to public awareness the distinction between acute presentations of AN and that of the severe and less tractable kind. There are several psychological therapies with an emerging evidence base that can be further tested and adapted for SEAN treatment. Research to date, albeit minimal, provides hope for the emergence of new concepts and a stronger evidence base to guide treatments.

AUTHOR CONTRIBUTIONS

PH, ST, and RP conceived this paper. JZ and PH reviewed the literature. JZ and YY wrote the first draft of the manuscript. JZ, YY, ST, RP, and PH edited and provided intellectual input to the manuscript.

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MINI REVIEW
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The Role of Interoception in the Pathogenesis and Treatment of Anorexia Nervosa: A Narrative Review

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Anorexia nervosa (AN) is a psychiatric illness characterized by extreme overvaluation of weight and disturbed eating. Despite having the highest mortality rate of any psychiatric illness, the etiology and neurobiology of AN are poorly understood. A growing body of research has begun to elucidate the role of reward processing, as well as cognitive and limbic networks, in the symptomology of AN. However, these advances have so far failed to contribute therapeutically, suggesting a new understanding may be necessary. A disturbance in the interoceptive system, involved in perceiving and interpreting the physiological condition of the body, has recently been proposed as a central mechanism of pathology in AN, through links to hunger and satiety, risk prediction errors, emotional awareness, and body dysmorphia. This review summarizes the existing literature in order to clarify possible underlying mechanisms and proposes a novel model of the neuro-circuitry of AN. Detailed neuroanatomical studies and new methods for studying interoception may allow further refinement of this model and the development of improved treatment.

Keywords: anorexia, anorexia nervosa, interoception, pathogenesis, treatment

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INTRODUCTION

Anorexia nervosa (AN) is a psychiatric condition defined by extreme overvaluation of shape and weight and disturbed eating, resulting in clinically significant impairments in health and psychosocial function due to self-starvation (1). The symptoms of AN are compounded by resistance to treatment and severe denial (2), resulting in the highest mortality rate of any psychiatric illness (3). AN is thought to have a complex pathogenesis—genetically-determined trait alterations confer a vulnerability which is exacerbated by premorbid experiences and environmental risk factors (4), with state alterations secondary to malnutrition sustaining or accelerating the illness (2). Nonetheless several hypotheses exist surrounding the neurobiology of AN, supported by a growing body of research (reviewed in Kaye et al. (2). In particular, studies have focused on the dysregulation of monoamine neurotransmitters and reward processing in AN (2), as well as on the imbalance between dorsal (cognitive) and ventral (limbic) networks allowing suppression of intuitive responses to satisfy long-term goals (*e.g.* staying thin) over basic needs (2). While these mechanisms explain much of the symptomology of AN, therapeutic applications

have been limited, suggesting new understanding may be necessary. Emergent evidence suggests deficits in interoception may play a role in the pathogenesis of this enigmatic condition.

Interoception refers to the perception and integration of afferent signals which represent the homeostatic and physiological condition of the body (5). These involve highly resolved feelings including pain, temperature, itch, muscular and visceral sensations, hunger, and thirst (6). Primary interoceptive afferents are thought to be located in lamina I of the spinal cord, constituting a parallel system to sympathetic and parasympathetic afferents (**Figure 1**) (5). Neuroanatomical and functional neuroimaging studies have suggested a central role for the insular cortex in this system, specifically the anterior insula (AI) (5, 7–9). A recent meta-analysis has elaborated on the role of the insular cortex in the integration of perception, emotions, thoughts, and plans. This appears to occur through four functionally distinct regions in the insula mapping onto sensorimotor, cognitive, social–emotional, and olfactory–gustatory networks in the brain. The anterior dorsal insula demonstrates significant overlap of these domains and has therefore been hypothesized to serve as a central multimodal integration region which generates a coherent experience of the world in which interoception plays a key role (10). Interestingly, the mid-dorsal insula which links somato- and viscerosensory stimuli to the anterior insula has been repeatedly shown to be altered in patients with AN (11). In fact, a strong literature of neuroimaging studies have referred to aberrant insular function in AN, specifically in the context of altered interoception.

Altered interoceptive awareness (IA) has long been suggested as a precipitating and reinforcing factor in AN—early clinical descriptions of AN patients by Hilde Bruch in 1962 underlined "a failure of recognizing bodily states as a characteristic" (12). In addition, IA has constituted an integral part of the Eating Disorder Inventory (EDI) since its conception by Garner et al. in 1983 (13), supported by recent prospective studies which validate its use as a diagnostic criterion (14) and risk factor for the development of disordered eating (15). However, IA considers a single aspect of interoception—terminology remains confused in the literature as studies fail to differentiate interoceptive sensitivity (IS), measured by objective tests of interoceptive accuracy, and interoceptive awareness (IA), gaged using self-report questionnaires such as the EDI. A recent paper demonstrated that deficits in IS and IA were in fact not correlated in patients with AN—IA was instead correlated with assessed levels of depression and anxiety (16). The authors therefore suggested that IA is not a measure of visceral sensitivity itself but rather a reflection of disorder-specific dysfunctional thoughts and feelings impacting the *interpretation* of visceral signals. Nonetheless, there is evidence to suggest that both IS and IA are disrupted in AN. This narrative mini review aims to explore the possible role of interoception in the pathogenesis and treatment of AN through exploration of both the symptomatology and neuroanatomical correlates and thereby suggest a novel model of the neuro-circuitry of anorexia.

METHOD

Given the nature of this paper as a narrative mini review, a PubMed literature search was conducted primarily as an overview of the existing literature at the time of writing (2019). MeSH terms included were "anorexia nervosa OR eating disorder OR eating disorders" AND "interoception OR interoceptive". However, given the mixture of terminology in the literature in this field in particular, including the frequent use of synonyms for interoception, after the initial search had been done bibliographies of relevant articles were used to find any other relevant literature.

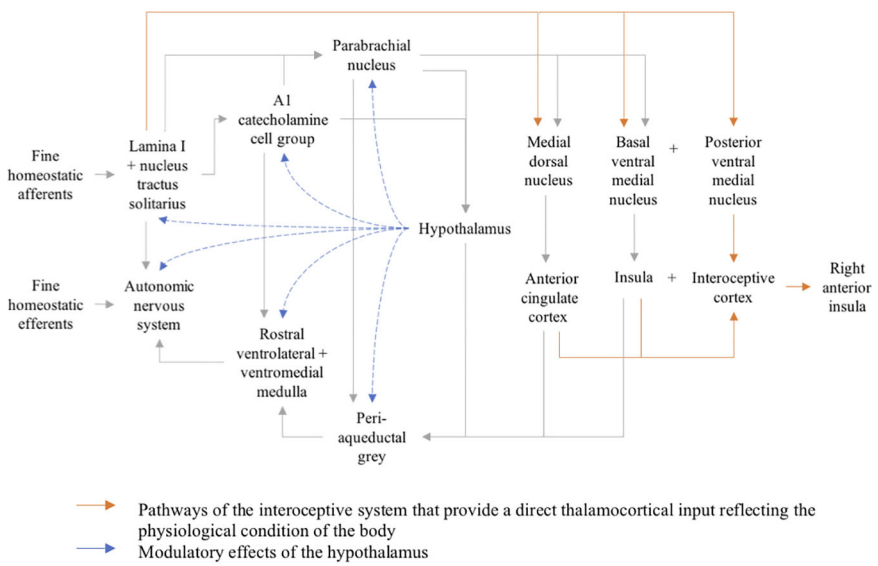

FIGURE 1 | Organizational map of the interoceptive system.

RESULTS

The literature search yielded 259 papers, of which 245 were in English. 229 results remained in searching for only full text articles. 33 were considered most relevant and specific to the contents of this narrative mini review (see **Table 1**).

TABLE 1 | Study characteristics of included papers.

References	Method and sample size
Robinson et al. (17)	Visual analog scale ratings of satiety, n = 22
Bluemel et al. (18)	MRI and 13C lactose ureide breath test, self-reported sensations of satiation, n = 60
Coddington et al. (19)	Direct introduction of liquid into the stomach and self-report questionnaires, n = 3
Nakai et al. (20)	Linear visual analog techniques and hunger ratings, n = 17
Duncan et al. (21)	Genome wide association study, n = 14477
Herbert et al. (22)	Heartbeat perception task, intuitive eating scale and BMI, n = 111
Wang et al. (23)	fMRI and BOLD study during dynamic gastric balloon distension, n = 18
Santel et al. (24)	fMRI study in response to visual food and non-food stimuli, n = 23
Wierenga et al. (25)	Delay discounting monetary decision task and fMRI, n = 40
Geeraerts et al. (26)	Gastric barostat study, n = 14, satiety drinking test and visual analog scale ratings, n = 18
Obendorfer et al. (27)	fMRI and anticipation task, n = 28
Wagner et al (28)	fMRI and sucrose/water administration, n = 32
Strigo et al. (29)	fMRI and painful heat stimuli, n = 22
Frank et al. (30)	fMRI and reward conditioning task, n = 63
Peuschoff et al. (31)	fMRI and gambling task with constantly changing risk, n = 19
Damasio et al. (32)	Neurology book on mind/body dualism
Pollatos et al. (33)	Heartbeat perception task (HPT) and EEG during emotional picture presentation, n = 32
Uher et al. (34)	fMRI and visual and complex gustatory food-related stimuli, n = 18
Terasawa et al. (35)	fMRI and questionnaire on emotional awareness, bodily awareness, and personal possessions, n = 18
Taylor et al. (36)	Toronto Alexithymia Scale (TAS) and the Eating Disorder Inventory, n = 312
Bourke et al. (37)	TAS, n = 78
Herbert et al. (38)	HPT, TAS, BDI-2, n =155
Beadle et al. (39)	TAS, Interpersonal Reactivity Index, Minnesota Multiphasic Personality Inventory-2, n = 42
Rezek et al. (40)	Manipulation of perceived control and questionnaires related to eating and body image = 40
Tsakris et al. (41)	HBT and hand illusion task, n = 46
Zucker et al. (42)	Variety of neuropsychological and self-report measures, n = 59
Sachdev et al. (43)	fMRI and images of self and nonself, n = 20
Eshkevari et al. (44)	Self-report measures of ED psychpathology *e.g.* EDI-3 subscales, DASS-21 and self-objectification questionnaire, n = 167
Cavanna et al. (45)	Review of literature focusing on the structure and function of the precuneus
Devue et al. (46)	fMRI, self and nonself images, n = 20
Boswell et al. (47)	Review of literature focusing on interoceptive exposure as a method of treatment
Fairburn et al. (48)	Review of literature focusing on the use of cognitive behavioral therapy for eating disorders
Khalsa et al. (49)	Ongoing randomized control trial using infusions of isoproterenol to investigate the effectiveness of IE as a treatment for AN

Interoceptive Sensitivity

Objective tests of interoception, otherwise known as measures of interoceptive sensitivity are most commonly heartbeat perception tasks (HPT) in which subjects silently count their heartbeats in a given period of time without taking their pulse or using other forms of manipulation to aid the counting process. Patients with AN generally show a reduction in the ability to accurately perceive their heartbeat compared to controls (16, 50), with no significant improvement over the course of treatment (50). This interoceptive task in an fMRI study was specifically related to greater activity in the right AI in AN patients than healthy controls (11), suggesting problems in interoception occur at the level of the insula rather than primary afferents. Since the insula is known to be at the center of interoception in the brain (5, 7–9), this study also supports the validity of the HPT in detecting processes involved in interoception.

However, HPTs are influenced by attention and motivation as well as subjects' beliefs and expectancies with respect to their heart rates. It has been suggested that a heartbeat detection method, which involves judging whether heartbeat sensations are simultaneous with external stimuli, suffers from fewer confounds than the tracking method (51) but its use in literature is limited. In addition, while these tasks are often used to represent a definite measure of IS, the generalizability of cardiac awareness to other interoceptive processes is unclear (52) with evidence suggesting that accurate detection of bodily sensations across different sensory modalities is not related (53). Since the literature on IS in AN is dominated by HPTs, it is clear that much scope remains for new methods in future research before application to treatment possibilities is considered.

Hunger and Satiety

Hunger and satiety are important examples of interoceptive modalities which are disturbed in AN. Patients are significantly more likely to report satiety in questionnaires and visual analog scale (VAS) ratings following meal consumption, showing not only increased but also prolonged satiety (17, 18) compared to controls. One explanation considers altered interoceptive sensitivity to gastric distension in AN—an early study reported a failure of three individuals with AN to detect small volumes of a liquid milkshake delivered directly into the stomach (19). However, the sample size hinders valid conclusions being drawn from this data, and the invasive nature of the procedure has led to few attempts to replicate these results. Moreover, a recent study using MRI to measure postprandial gastric volumes found that one in three AN patients reported fullness and no hunger even when the stomach is completely empty (18). This implies that satiety disturbances in AN may be due to the interpretation and perception of visceral signals (IA) rather than actual differences in visceral sensitivity. Alternatively, modalities of interoception other than gastric distension may be involved—hunger ratings in AN patients have been shown to paradoxically decrease in response to insulin induced hypoglycaemia (20). In addition, recent genome wide association studies (GWAS) have identified AN-associated loci with correlations to specific metabolic phenotypes (21). While it is still unclear whether these are predisposing genetic risk factors or state-related changes in gene activation, metabolism is a well-established component of interoception and so abnormal

phenotypes may contribute to faulty IA in AN. Irrespective of the affected interoceptive modality, it is unsurprising that problems with perceiving hunger and satiety can result in dysfunctional eating habits, with recent research suggesting this is due to a departure from intuitive eating which would usually serve to maintain a normal weight (22). fMRI studies have shown that self-reports of satiety and fullness are correlated with insular responses (23), lending support to the insula and its role in interoception as a central candidate for the symptoms of AN.

However, it is important to note that a number of factors other than faulty interoception may contribute to problems with hunger and satiety perception in AN. One explanation points to the role of attentional mechanisms in visual areas during hunger and decreased food-related somatosensory processing *e.g.* gustatory perception/imagination of taste in satiety due to weaker inferior parietal activation (24). Indeed, a recent study using a delay discounting monetary decision task found a failure to increase activation of reward circuitry when hungry compounded by an elevated response in cognitive control circuitry independent of metabolic state (25). This strongly supports a role for faulty reward processing and overactive cognitive circuits focused on long term goals in suppressing hunger and promoting satiety. Another explanation could be that higher satiety ratings and reduced reporting of hunger may represent a "secondary gain" in AN patients undergoing weight rehabilitation—attempts by patients to excuse eating less. Anxiety, often comorbid with AN can also influence results through reducing gastric accommodation (26). Nonetheless it is logical that misinterpretation of hunger/satiety signals could generate food avoidance and disturbed eating habits in AN.

Risk Prediction Errors

Dysregulated interoception may also contribute to food avoidance through generation of risk prediction errors in the body; 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. This mechanism is supported by an emerging neuroimaging literature—on exposure to food or its conditioned stimuli, weight restored AN patients exhibit increased insular and cingulate cortex activation as well as intensified interoceptive sensations, relative to healthy controls (27) yet have a decreased insular response to the taste of food stimuli (28). The exaggerated anticipatory neural response but correspondingly dampened reaction to stimulation may represent a deficit in central integration of expected *versus* experienced interoception in the AI. These results have also been replicated with painful thermal skin stimulation (29). In addition, recent research has shown that patients with AN show increased orbitofrontal cortex activation when receiving reward unexpectedly (30), lending further support to an interoceptive mechanism as the OFC has been explicitly linked to risk prediction errors (31).

Emotional Awareness

Since the early 90s, interoception and the physiological state of the body have been thought to play a role in the subjective experience of emotion (32), with recent findings demonstrating that interoceptive sensitivity is positively correlated with the experienced intensity of feelings (33). In addition, internal motivational factors such as hunger and satiety have been shown to modulate the processing of gustatory food related stimuli in the insula (34), with the right anterior insula being specifically activated by both interoceptive and emotional tasks, suggesting these are functionally associated and may underpin subjective experience of the emotional state (35). In AN, faulty interoception may therefore explain difficulties with emotion processing, including high rates of alexithymia characterized by a reduced ability to identify and describe one's feelings, difficulty in distinguishing feelings from the bodily sensations of emotional arousal, and a tendency to focus on external rather than internal events (36). Specifically, rates of alexithymia are almost 77% in AN patients compared with 6.7% in control subjects (37), with IA inversely associated with all features of alexithymia (38). This appears to not be solely state-related as both recovered and currently ill subjects have greater rates of alexithymia, although the difference is exaggerated in currently ill subjects due to high rates of depression (39).

Patients with AN also demonstrate a lowered ability to self-regulate emotions including poor reappraisal (reframing thoughts and emotions in a more positive direction) and high suppression (modifying one's behavioral response to an event) (39). Intense negative affective reactions and sensations of lack of control may therefore be controlled using psychologically unhealthy strategies—strict food restriction and refocusing the attention on weight or figure has been shown to be increased in subjects experiencing experimentally induced low control than those in a high control situation (40). This supports an alternative mechanism by which abnormal interoception may contribute to AN eating behaviors.

Body Dysmorphia

Interoceptive awareness has also been linked to body dysmorphia which predictably maintains negative eating behaviors. When interoception is impaired, subjects cannot rely on internal signals to perceive 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. Much of the research on body image disturbance in AN has examined cognitive components such as body dissatisfaction and perceptual aspects including visual image distortion but has neglected the subjective *experience* of the body. For example, IS can predict the malleability of body representations—a study found that healthy subjects with low scores on an HBT experienced a stronger illusion of ownership in the right-hand illusion task, despite no apparent proprioceptive deficits (41). In AN, poor IS is associated with an over-evaluation of self-image despite normal perception of others (42, 43), which is also seen in recovered patients suggesting this may be a trait which enables

the development of AN rather than a state-related change (44). Recent evidence has emphasized the role of the precuneus in mental self-representations (45) with AN patients showing deactivation of the precuneus when viewing self-images (43), as well as across a number of interoceptive modalities (11). Similarly to studies in the precuneus, evidence also demonstrates a link between the anterior insula and self-recognition (46). This implies the possibility of parallel roles for the AI and the precuneus in linking interoceptive and contextual information to influence emotional experience (35).

Treatment Implications

Despite recent attention towards interoceptive awareness and sensitivity in the eating disorders literature, the application of these principles in treatment has received minimal attention. Interoceptive exposure (IE) is a behavior therapy intervention, originally developed for the treatment of panic disorder, which aims to increase tolerance to the physical symptoms of anxiety through repeated provocation of personally relevant somatic sensation associated with feared outcomes. Given the exaggerated anxiety related to food and eating which contributes to food avoidance in AN (27), as well as the high rates of alexithymia (39), IE has begun to gain support as a transdiagnostic intervention strategy that can be integrated into cognitive–behavioral therapy oriented (CBT) ED treatment (47). This is on the bases of its ability to not only modify interoceptive sensitivity but also improve interoceptive clarity through identification and labeling of emotion (reviewed in Boswell et al.). While strategies such as exposure to hierarchies of "forbidden" foods, supervised meal exposures and body shape/mirror exposure are already well established in ED specific CBT (48), current literature suggests a more explicit integration of IE into these treatment strategies, which may be advantageous. Notably however, controlled trials published to date have failed to show the effectiveness of IE in clinical practice. An ongoing randomized control trial, predicted to be completed in 2022, is considering the use of implementing this approach pharmacologically in patients with AN by using infusions of isoproterenol to repeatedly trigger cardiorespiratory sensations and anxiety during meal anticipation (49). Clearly, further pilot studies and preliminary trials are needed to examine the process and impact of AN-specific IE techniques, which may allow the development of more effective adjunctive treatment methods.

DISCUSSION

Findings

While often under-represented, several lines of evidence suggest interoceptive abnormalities may play a role in the pathophysiology of AN. Specifically, their contributions to abnormal perception of hunger and satiety, body dysmorphia, abnormal emotion processing, and prediction errors have been summarized in **Figure 2**, which proposes a novel model for the neuro-circuitry of AN with interoception at its core.

Clinical Implications

All four of these domains have been shown to contribute to both the symptomatology observed in AN as well as the barriers to treatment. The link between interoceptive deficits and body dysmorphia—leading to over-evaluation of weight and subsequent negative eating behaviors—could potentially be central to the pathology of AN, while altered self-perception due to abnormal emotion processing and perception of hunger and satiety is likely to contribute to lack of recognition, or 'denial' of the severity of starvation, which is one of the fundamental challenges in treating the disorder. It is important nonetheless that the potentially central role for interoception be considered in the context of broader literature on AN. **Figure 2** also summarizes the possible interactions between faulty interoception and other components of AN pathology. Importantly, the authors hypothesize that the role of abnormal emotion processing and prediction errors in creating negative affective states contributes to overactive top-down modulatory influences and subsequent focus on long-term goals rather than short term needs. This is compounded by well-established deficits in reward processing, leading to a reduced reliance on intuitive responses and thereby the perpetuation of negative eating behaviors and intentional denial of illness.

Strengths and Limitations

Neuroimaging studies suggesting the anterior insula as a key multimodal integrative region (5, 7–10) with abnormal structure and function in AN (11, 27–29, 31, 34, 35, 46) further support a role for interoception deficits in the symptomatology of AN. The novel model of neuro-circuitry proposed in this review can be integrated comfortably with this existing literature, adding a further level of understanding to the neurobiological etiology of AN. Nonetheless, the hypothesis offered here does not constitute a systematic review and is hindered by a paucity of guiding literature. Specifically, prospective longitudinal studies looking at differentiating between genetically-determined trait alterations and state alterations secondary to malnutrition are challenging given the age group affected, incidence of AN, and length of follow-up necessary. Because of this, research has focused on recovered AN patients who are not affected by state related changes, thereby limiting the ability to draw conclusions about the acutely ill phase of AN. In addition, research is often confounded by common comorbid diagnoses including depression and anxiety as well as the inclusion of subjects at varying stages of illness or treatment due to the problematic definition of 'recovery' in AN.

Conclusion and Future Research Directions

Future directions will undoubtedly include detailed studies of the neuroanatomical correlates of interoception in AN, aided by development of new methods to explore modalities of visceral sensitivity. In addition, ongoing research with interoception and its neurobiology at its core will allow a better understanding of

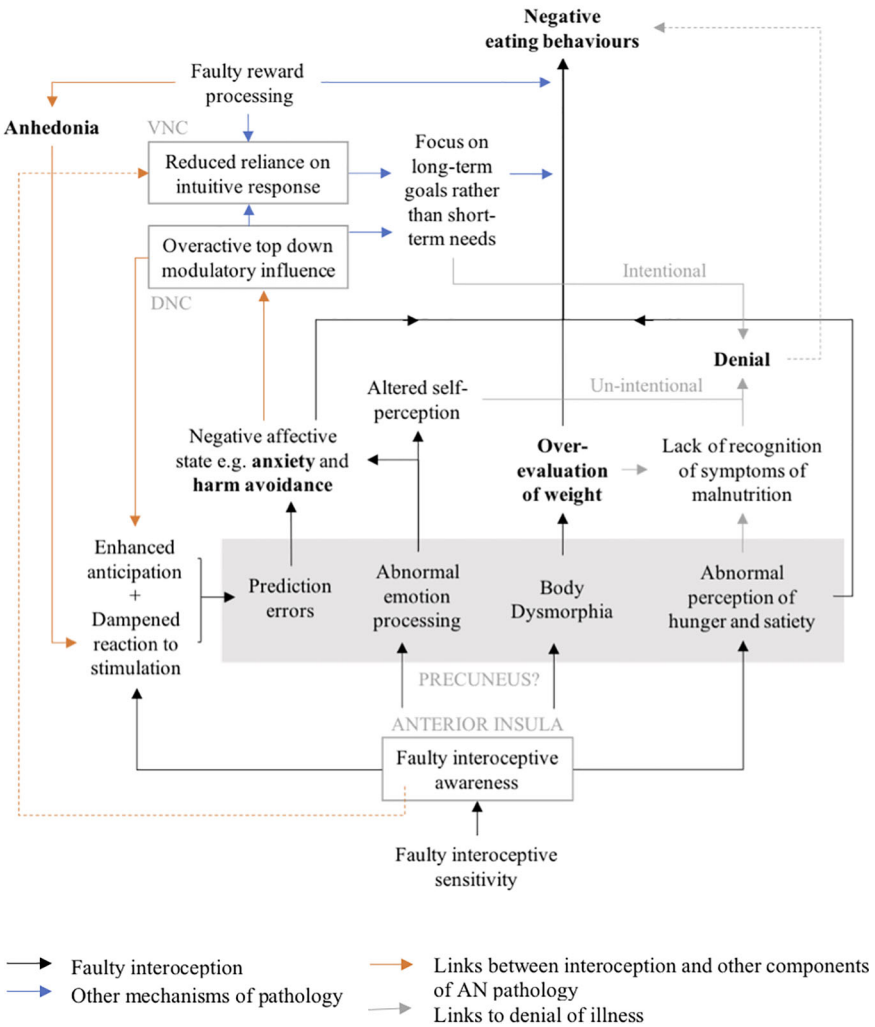

FIGURE 2 | Model for the neuro-circuitry of AN: VNC, ventral (limbic) neuro-circuit—primarily ventral striatum; DNC, dorsal (cognitive) neuro-circuit—primarily dorsolateral prefrontal cortex.

how faulty interoception may contribute to illness denial in AN, which is currently one of the major obstacles to recovery. Given the importance of objective tests of interoception in future research, it is clear that the techniques currently used to measure interoceptive sensitivity (specifically HBTs) must be given due scrutiny, with every effort made to establish more reliable methods of investigating a key component of this devastating illness. Finally, further refinement of the novel model of AN pathology proposed in this review may support the integration of IE techniques into AN-specific CBT or development of more efficacious forms of treatment than those currently available.

AUTHOR CONTRIBUTIONS

AJ was responsible for the conception of the review as well as drafting all versions of the article. RP provided comments and critical revisions during the editing process and both authors were responsible for final approval of the version to be published.

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Exploring Relationships Between Autism Spectrum Disorder Symptoms and Eating Disorder Symptoms in Adults With Anorexia Nervosa: A Network Approach

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Over the past few decades, research has accumulated to suggest a relationship between anorexia nervosa (AN) and autism spectrum disorder (ASD). Elevated ASD traits are present in around one third of those with AN, and there is some evidence to suggest that ASD traits are associated with more severe eating disorder (ED) psychopathology. The current study aimed to examine relationships between ED and ASD symptoms in individuals with a lifetime history of AN using network analysis. One hundred and one participants completed the ED Examination Questionnaire (EDE-Q) and the Social Responsiveness Scale (SRS-2). A regularized partial correlation network was estimated using a graphical least absolute shrinkage and selection operator. Expected influence (EI) and bridge EI values were calculated to identify central and bridge symptoms respectively. Isolation, difficulties with relating to others, and feelings of tension during social situations were most central to the network, while poor self-confidence, concerns over eating around others, and concerns over others seeing one's body were the strongest bridge symptoms. Our findings confirm that interpersonal problems are central to ED psychopathology. They also suggest poor self-confidence and social anxiety-type worries may mediate the relationship between ED and ASD symptoms in those with a lifetime diagnosis of AN. Longitudinal studies examining fluctuations in symptoms over time may be helpful in understanding direction of causality.

Keywords: anorexia nervosa, comorbidity, autism spectrum disorder, self-report, social behavior

INTRODUCTION

Over the past few decades, evidence suggesting a relationship between autism spectrum disorder (ASD) and anorexia nervosa (AN) has accumulated (1, 2). ASD is a neurodevelopmental disorder characterized by difficulties in social communication and interaction, as well as restrictive, repetitive patterns of behavior or interests (3). ASD is a lifelong condition, and is more commonly diagnosed

in males than females (4). On the other hand, AN is a severe eating disorder (ED) associated with persistent restriction of energy intake, fear of weight gain, and disturbances in the way in which one's body shape or weight is experienced (3). AN is more prevalent in females, and peak age of onset is in late adolescence (5, 6).

Despite the apparent differences between the two disorders, empirical research has shown a number of similarities in the phenotypic expressions of AN and ASD. For example, in the socio-emotional domain, considerable research has documented difficulties in emotion recognition (7), empathy (8), and theory of mind (ToM) (9) in individuals with ASD. These difficulties are also seen in those with AN, although are often less pronounced than is seen in ASD (10–12). Furthermore, high levels of alexithymia (13, 14), social anxiety (15, 16), and differences in social attention (17–19) are associated with both disorders. In the neurocognitive domain, both AN and ASD are associated with weak central coherence (20, 21), increased attention to detail (22, 23), and difficulties in set-shifting (24, 25), an executive function that allows for flexible thinking and behavior.

As well as these similarities in socio-emotional and neurocognitive profiles, those with AN show high levels of ASD traits. For example, it is reported that between 4% and 52.5% of individuals with AN score above clinical cut-offs on diagnostic assessment tools for ASD1. It has been suggested that high levels of ASD traits found in a proportion of those with AN may be due to the effects of starvation, and do not represent true ASD (26). However, several studies have found that body mass index (BMI), which is often used as a measure of illness severity, is not associated with ASD traits in individuals with AN (27–33). A few of these studies also examined associations with illness duration, finding that those with high ASD traits had not been ill for a significantly longer period of time than those with low ASD traits (29, 33). Finally, a significant proportion of individuals recovered from AN also show elevated ASD traits compared to HCs (27, 30, 34). Therefore, it seems the association between ASD and AN is not a product of starvation, yet the exact nature of the relationship remains unclear.

However, there is some evidence to suggest that ASD symptoms are positively associated with severity of ED psychopathology in those with AN. For example, in a large sample of inpatients with AN, Tchanturia et al. (31) reported that scores on the Autism Quotient (AQ) (35) were positively associated with scores on the ED Examination Questionnaire (EDE-Q) (36). A similar association between AQ scores and ED symptoms has been reported in nonclinical populations (37, 38). Further, the presence of ASD traits in AN is associated with more frequent and longer inpatient stays (29), less improvement during treatment (39, 40), and poorer outcomes (41–43). Why might a more severe ED presentation be associated with high ASD traits? One possibility is that some of the neurocognitive traits associated with ASD, such as cognitive rigidity, increased attention to detail, and sensitivity to order may perpetuate a narrow focus on food and weight in individuals with AN and make change difficult (44). Indeed, Westwood and colleagues (45) reported that individuals with AN and high ASD traits showed higher levels of cognitive rigidity and set-shifting difficulties than individuals with low ASD traits. As well as a significant proportion of individuals with AN showing high levels of ASD traits on dimensional measures, a number of studies have found that 8%–29% meet full diagnostic criteria for ASD (34, 41, 46–49). Given that social difficulties are an important predictor of poor outcomes in AN (43, 50–52), another possibility is that those with comorbid ASD and AN have particularly poor outcomes due to the social communication difficulties associated with ASD. Yet another possibility is that avoidance of certain foods due to sensory sensitivities in ASD may reinforce food restriction. Such hypotheses remain to be tested empirically.

A potentially useful method for examining the nature of the relationship between AN and ASD symptoms is provided by network theory. Network theories of psychopathology represent psychiatric disorders as constellations of symptoms, activating one another (53). The relationships between symptoms are key to the development and maintenance of psychopathology; symptoms can form feedback loops, eventually producing a set of symptoms that are recognized as a psychiatric disorder. This theory has important implications for understanding comorbidity. Symptoms are often shared among different psychiatric disorders, for example feelings of guilt are common in obsessive compulsive disorder (OCD) and are also a central feature of major depression (3). Because symptoms in a network have causal relationships with one another, clusters of symptoms belonging to one disorder can activate those of another disorder, resulting in diagnostic comorbidity (54).

Psychological networks can be estimated using network analysis. Networks are made up of nodes (symptoms) and edges (relationships between symptoms). It is possible to calculate which nodes or symptoms have most connections in the network (node centrality) and therefore are most important in maintaining psychopathology. Further, it is possible to calculate which symptoms of a given disorder are most connected to symptoms in another disorder cluster (bridge nodes), and therefore may maintain comorbidity. Currently, only a few studies have examined comorbidity using network analysis in individuals with EDs. These studies have most often focussed on comorbidity between anxiety and ED symptoms, finding that avoidance of social eating is an important bridge symptom (55–57). Others have examined depression (55, 58) and OCD symptoms (59), however no study to date has focussed on ASD and ED symptom comorbidity.

The aim of the current study was to examine relationships between ED and ASD symptoms in individuals with AN using network analysis. Because ASD symptoms have been shown to persist in individuals recovered from AN, suggesting independence from clinical state, our sample included those with a current or past diagnosis of AN. We aimed to identify central nodes in order to understand which symptoms may be most important in maintaining the symptom network as a whole. Bridge nodes were also identified in order to detect symptoms most important in explaining potential comorbidity of AN and ASD.

MATERIALS AND METHODS

Participants

The study was cross-sectional. Ethical approval was obtained from the National Health Service (NHS) Research Ethics Committee (Camberwell St Giles, 17/LO/1960). Participants provided their written informed consent to participate in the study. Participants with a lifetime history of AN were recruited from two specialist NHS ED services in London, online advertisements, and through the King's College London university research recruitment email. Participants were required to be between 18 and 55 years old and fluent in English. Exclusion criteria were a history of brain trauma or learning disability. A past or current diagnosis of AN was confirmed using the Structured Clinical Interview for DSM-5 Disorders, research version (SCID-5-RV) Module I "Feeding and Eating Disorders" (60).

Procedure and Materials

Participants attended a testing session as part of a wider study on socio-emotional processing at the Institute of Psychiatry, Psychology & Neuroscience, however where participants were inpatients, testing took place at their place of treatment. Written consent was obtained, and the following measures administered:

The EDE-Q (36) was used to measure severity of ED psychopathology. Twenty-two of the 28 items are rated for frequency during the past 28 days on a seven-point Likert scale, with higher scores indicating more eating, shape, or weight concerns and behaviors. The remaining six items assessing frequency of various behaviors are not included in total or subscale score calculations, as these items can take on any value. The EDE-Q demonstrates good psychometric properties, correlating with measures of similar constructs (61). Cronbach's alpha was 0.91.

The Social Responsiveness Scale-2nd edition, adult self-report form (SRS-2) (62) is a 65-item questionnaire assessing symptoms associated with ASD, with higher scores indicating more autistic symptoms. There are five subscales: social awareness (ability to recognize social cues), social cognition (interpreting social behavior), social communication (reciprocal communication in social situations), social motivation (motivation to participate in social interactions), and restrictive interests and repetitive behavior (circumscribed interests and stereotypy). Respondents indicate their agreement with each item on a four-point Likert scale, rating their behavior over the past six months. The SRS-2 has been used extensively in ASD research, and is also recommended for use in diagnostic assessments in adults with ASD (63). Validation studies have found measurement invariance across the sexes, and few sex, age, or rater effects (64–66). Scores on the SRS-2 have been shown to predict whether individuals with AN score above the clinical cut-off on the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) (67), a "gold-standard" clinical interview measure for ASD (68). Cronbach's alpha was 0.96.

Demographic information was also collected, along with weight and height measurements to calculate BMI (height/weight^2).

Network Analysis

Analyses were performed in R version 3.6.1 (69). R codes are provided in the **Supplementary Information**.

Item Selection

Network analysis assumes that each node in the network represents a distinct construct. Given that some of the questionnaire items are very similar in content, the goldbricker function in R package *networktools* (70) was used to select items to include in the network. Goldbricker compares dependent overlapping correlations (i.e., items with high multicollinearity) for all items in the network. If a certain proportion of correlations between node A and all other nodes do not significantly differ from those between node B and all other nodes (e.g., items share ≥75% of correlations), nodes A and B are assumed to be overlapping items measuring the same construct ("bad pairs"). One of the nodes is subsequently removed. The 22 Likert items from the EDE-Q and all 65 items from the SRS-2 were entered. After dropping the bad pairs, 18 EDE-Q and 55 SRS-2 items were left for inclusion in the network. The full list of EDE-Q and SRS-2 items and those included in the network are provided in the **Supplementary Information**.

Network Estimation and Accuracy

A regularized partial correlation network with weighted edges was estimated using a graphical least absolute shrinkage and selection operator (LASSO) using the *qgraph* R package (71). This method limits the total sum of absolute parameter values and drops edges that are close to zero out of the model, keeping only those that are most robust and likely to represent genuine associations. The tuning parameter (λ) was set to 0.25. This value is typically set between 0 and 0.5, with higher values resulting in simpler models with fewer edges, and lower values favoring discovery but more likely to estimate spurious edges (72).

Accuracy of edge-weights were assessed using nonparametric bootstrapping using the *bootnet* package (73). Bootstrapping involves repeatedly estimating a model under sampled or simulated data and estimating the statistic of interest, in this case, edges. The bootstrapped 95% confidence intervals (CIs) indicate the sampling variation, and the strength of a given edge is difficult to interpret if bootstrapped CIs are wide. Correlation stability (CS) coefficients were calculated to assess the stability of expected influence (EI) and bridge EI. In this case, a case-dropping bootstrap is used to indicate whether the centrality indices remain the same after reestimating the network using only a subset of cases from the sample. The CS coefficient indicates the proportion of the sample that can be dropped to retain a correlation >0.7 with the original sample. It should not be below 0.25, and preferably above 0.5 (73). Finally, bootstrapped difference tests (a = 0.05) were run to test for significant differences in centrality indices between nodes.

Network Interpretation

Central nodes were identified by calculating EI using the *networktools* package. EI is similar to the more commonly used metric, strength, as it is calculated by summing all of the edges a

given node has with all other nodes in a network. However unlike strength, which does not distinguish between positive and negative edges, EI accounts for the direction of associations. This is an important distinction in networks which include psychopathological symptoms of more than one disorder, where some negative relationships are likely (74).

Bridge nodes were identified by calculating bridge EI using the *networktools* package. Both bridge EI one-step (bridge EI1) and bridge EI two-step (bridge EI2) were calculated. Bridge EI1 identifies the strength and directionality of the relationships a node in one cluster has with all nodes of another cluster. Bridge EI2 additionally takes into account the secondary influence of a node *via* the influences of its immediate neighbors. For centrality and bridge indices, higher values represent greater influence. Z-scores are reported throughout for ease of interpretation.

RESULTS

Sample Characteristics

In total, 101 participants took part in the study. Fifty-one were acutely ill with AN, while fifty were recovered. Demographic and clinical information is displayed in **Table 1**. On the SRS-2, 43% of participants scored within the "normal" range, scores within this range are not associated with clinically significant symptoms. Seventeen percent of participants scored within the "mild" range, indicating deficiencies in reciprocal social behavior that are clinically significant and may lead to mild to moderate interference with daily living. A further 21% scored within the "moderate" range, indicating clinically significant difficulties which lead to substantial interference with social behavior. Finally, 19% of participants scored in the "severe" range, indicating severe and enduring difficulties with social behavior. Scores within the moderate and severe range are typical for individuals with a diagnosis of ASD.

Network Estimation and Accuracy

Questionnaire data from three participants contained missing values (representing 0.08% of the total questionnaire data). Given that nodes in our network did not rely on subscale or total score calculations from questionnaires, the rest of the data from these participants was included in analyses. The network structure composed of EDE-Q and SRS-2 symptom scores is displayed in **Figure 1**. Green edges represent positive relationships, while red indicates negative ones. The thicker the edge, the stronger the regularized partial correlation.

Plots displaying the bootstrapped CIs of estimated edge-weights, bootstrapped centrality indices, and bootstrapped differences tests are reported in the **Supplementary Material**. The EI CS coefficient was 0.67, and the bridge EI CS coefficient was 0.59, indicating both EI and bridge EI can be interpreted meaningfully (73).

TABLE 1 | Demographic and clinical information of participants with lifetime anorexia nervosa (AN) (N = 101).

	Mean (SD)	Range
Age (years)	26.95 (8.27)	18.16 – 54.59
% female	95.0	–
BMI	18.39 (3.25)	12.90 – 27.00
Years of education	16.33 (2.89)	10.00 – 27.00
Illness length (years)	6.47 (6.89)	0.50 – 35.00
% on psychiatric medication	43.6	–
EDE-Q total	2.84 (1.75)	0.00 – 5.69
SRS-2 total	77.66 (33.11)	17.00 – 160.00

AN, anorexia nervosa; BMI, body mass index; EDE-Q, eating disorder examination questionnaire; SRS-2, social responsiveness scale; SD, standard deviation.

Centrality

EI is plotted in **Figure 2**. The items with the highest EI were SRS-2 37 "I have difficulty relating to adults outside of my family," SRS-2 57 "I tend to isolate myself," and SRS-64 "I am much more tense in social situations than when I am by myself."

Bridge Nodes

Bridge EI values are plotted in **Figure 3**. For bridge EI1, the strongest ED bridge symptom was EDE-Q 21 "How concerned have you been about other people seeing you eat?", and the strongest ASD bridge symptom was SRS-11 "I have good self-confidence" (reverse coded). For bridge EI2, the strongest ED bridge symptom was EDE-Q 28 "How uncomfortable have you felt about others seeing your shape or figure", and the strongest ASD bridge symptom was again SRS-11 "I have good self-confidence."

DISCUSSION

The current study is the first to examine relationships between ED and ASD symptoms in individuals with past or current AN using network analysis. Constructing a network of partial correlations allowed us to examine connections between symptoms, independent of the effects of other symptoms in the network. Firstly, we aimed to identify core symptoms in the network. The three nodes with the highest centrality in the network were all SRS-2 items: SRS-2 37 "I have difficulty relating to adults outside of my family," SRS-2 57 "I tend to isolate myself", and SRS-64 "I am much more tense in social situations than when I am by myself." The former two items are from the social communication subscale of the SRS-2, while the latter is from the social motivation subscale. These results suggest that difficulties in social communication and isolation may be core symptoms in AN psychopathology, over and above conventional ED symptoms, such as weight and shape concern. However, it must be noted that the inclusion of recovered individuals, some of whom had rather low EDE-Q symptom scores may have influenced these results. Had our sample only included individuals in the acute stage of AN, EDE-Q items might have been more central to the network. Nonetheless, our study is not the first to demonstrate the importance of social difficulties in AN psychopathology. For example, Monteleone and colleagues (58) found that depression and personal alienation were the nodes with highest centrality in their network of symptoms in children and adolescents with AN. Personal alienation, a subscale of the EDs Inventory (EDI), reflects a sense of emotional emptiness, aloneness,

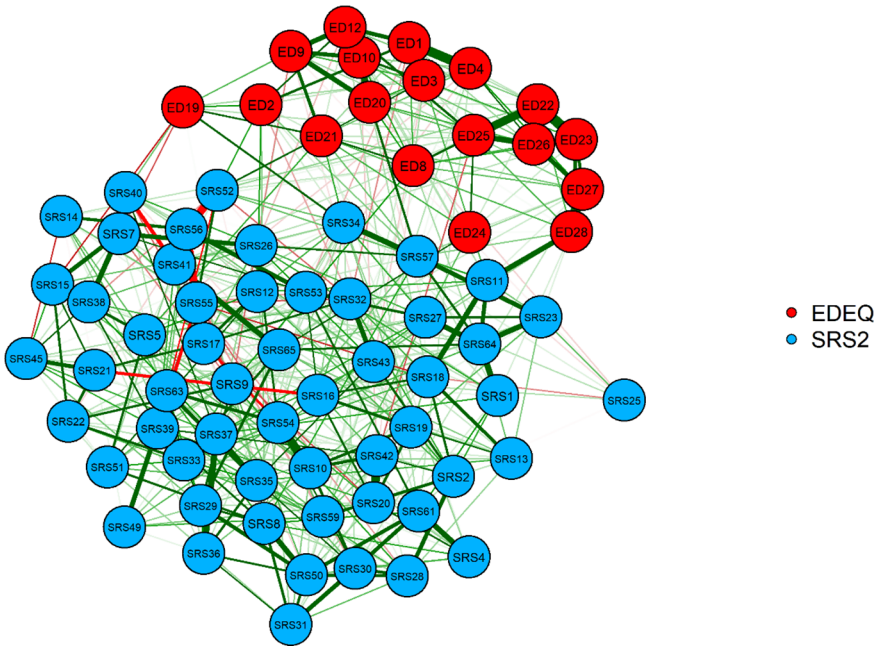

FIGURE 1 | Graphical least absolute shrinkage and selection operator network. Eating Disorder Examination Questionnaire (EDE-Q) items: ED1, limit food; ED2, fasting; ED3, excluding foods; ED4, eating rules; ED8, concentration affected by shape/weight; ED9, fear of loss of control; ED10, fear of weight gain; ED12, desire to lose weight; ED19, eating in secret; ED20, guilt over eating; ED21, concern over other people seeing you eat; ED22, weight overvaluation; ED23, shape overvaluation; ED24, reaction to weighing; ED25, weight dissatisfaction; ED26, shape dissatisfaction; ED27, uncomfortable seeing own body; ED28, uncomfortable over others seeing own body. Social responsiveness scale (SRS-2) items: SRS1, uncomfortable in social situations; SRS2, facial expressions; SRS4, rigid behavior; SRS6, prefer to be alone; SRS7, aware of others feelings; SRS8, strange behavior; SRS9, dependent on others; SRS10, take things literally; SRS11, good self-confidence; SRS12, communicate feelings; SRS13, awkward in turn taking interactions; SRS14, not well coordinated; SRS15, understand change in tone/facial expression; SRS16, avoid/unusual eye contact; SRS17, recognize unfairness; SRS18, difficulty making friends; SRS19, frustrated in conversations; SRS20, sensory interests; SRS21, imitate others'; SRS22, interact appropriately; SR23, avoid social events; SRS25, don't mind being out of step with others; SR26, offer comfort to others; SRS27, avoid starting social interactions; SRS28, think about the same thing over and over; SRS29, regarded as odd; SRS30, upset in situations with lots going on; SRS31, can't get mind off something; SRS32, good personal hygiene; SRS33, socially awkward; SRS34, avoid people who want to be emotionally close to me; SRS35, have trouble keeping up with conversations; SRS36, difficulty relating to family; SRS37, difficulty relating to adults outside family; SRS38, respond to others' moods; SRS39, interested in too few topics; SRS40, imaginative; SRS41, wander aimlessly between activities; SRS42, sensory sensitivity; SRS43, enjoy small talk; SRS45, interested in what others' are attending to; SRS49, do well at intellectual tasks; SRS50, repetitive behaviors; SRS51, difficulty answering questions directly; SRS52, overly loud; SRS53, monotone voice; SRS54, thing about people and objects in the same way; SRS55, invade others' personal space; SRS56, walk between two people; SRS57, isolate myself; SRS59, suspicious; SRS61, inflexible; SRS63, unusual greeting; SRS64, tense in social settings; SRS65, stare into space.

and feeling separated from others. Somewhat similar findings were reported by Somli and colleagues (75), who found that in adolescents and adults with AN, depression, anxiety, interpersonal sensitivity, and ineffectiveness were most central to the network. Interpersonal sensitivity, a subscale of the Symptom Checklist 90 (SCL-90), assesses feelings of inadequacy and inferiority in comparison to others, as well as self-consciousness and discomfort during social interactions.

Our second aim was to identify bridge nodes; those that connect ED and ASD symptom clusters. The strongest ASD bridge symptom was SRS-2 11 "I have good self-confidence" (reverse coded), while the strongest ED bridge symptoms were EDE-Q 21 "How concerned have you been about other people seeing you eat?" (bridge EI1) and EDE-Q 28 "How uncomfortable have you felt about others seeing your shape or figure?" (bridge EI2). The self-confidence item belongs to the social motivation subscale of the SRS-2. Our results suggest that a lack of self-confidence may be important in understanding the link between ED psychopathology and ASD symptoms in those with lifetime AN. However, it must be noted that low self-confidence is a rather nonspecific psychiatric symptom, commonly reported in depression, anxiety, substance abuse disorders, and EDs (76). Interestingly, our finding is very similar to that of Forrest and colleagues (56), who found that the low self-confidence item of the State-Trait Anxiety Inventory (STAI) was the strongest trait anxiety bridge node linked to ED symptoms in a mixed ED sample. It could be that elevated scores on ASD assessments found in individuals with AN are partly due to high anxiety, a symptom shared by both disorders. In an analysis of 18 previously published comorbidity networks, Jones and colleagues (54) observed that several symptoms emerged as bridge symptoms across multiple networks. The networks included several different disorders, including anxiety, bulimia nervosa (BN), OCD, depression, and ASD, and also used a wide variety of symptom scales. This demonstrates that certain symptoms may not only explain comorbidity between two

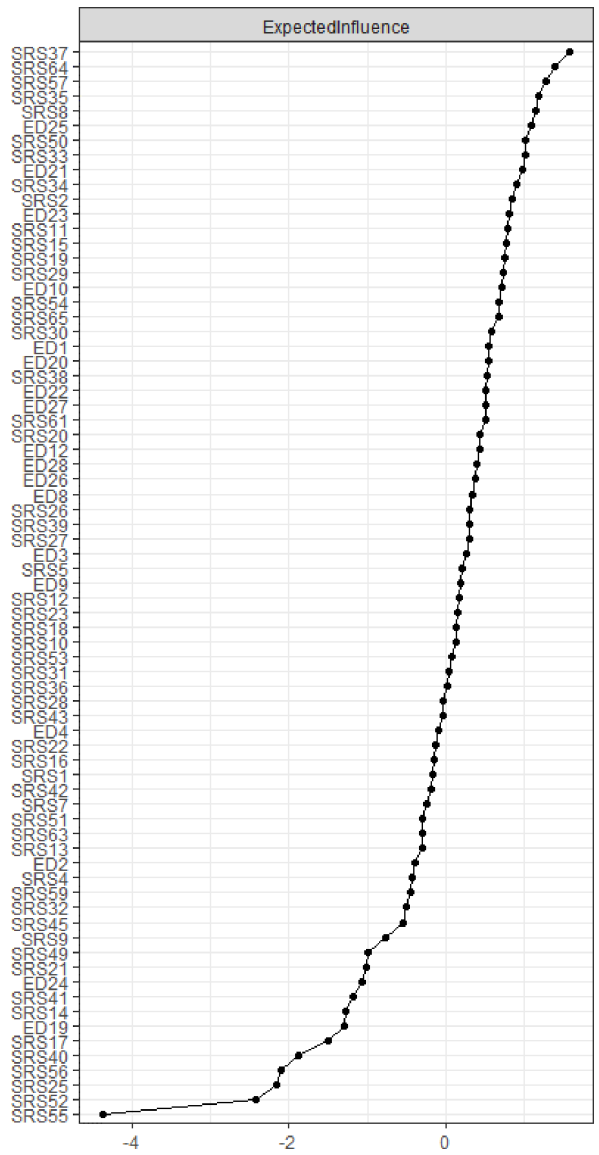

FIGURE 2 | Centrality plot depicting expected influence (EI) of each node. Values are given as Z scores, higher values represent greater centrality in the network.

disorders, but may be important transdiagnostic factors across psychiatric disorders.

Regarding ED bridge nodes, it is notable that both involve concern over being observed by others. The concern over others seeing you eat item has repeatedly been shown to be the strongest ED bridge node connecting ED and anxiety symptoms in those with AN (55) and mixed ED groups (56, 57). High social anxiety is a feature of both ASD (16, 77) and AN (15), and our findings might suggest that social anxiety worries are important in explaining comorbidity between AN and ASD. It has been hypothesized that some of the core symptoms of ASD may increase the risk of developing social anxiety (78, 79). For example, poor social skills or difficulties in recognizing emotions and mental states in others may lead to rejection from peers and isolation during formative years, factors which are implicated in the development of social anxiety disorder (SAD). There is also evidence to suggest that SAD may be a risk factor for the development of AN. In those with both disorders, SAD precedes AN onset in around two thirds of cases (80, 81). Fears around eating in front of others may lead to avoidance of social eating in those with SAD, a potential pathway by which other eating disordered behaviors may form. Qualitative work has also provided some insight into how these factors may interact and contribute to the development of AN. For example, Kinnaird et al. (82) found that participants with AN and ASD felt that their ED had developed as a way of dealing with the social confusion and difficulties relating to other people associated with their ASD. Participants also described how social difficulties, such as dealing with noise and social chat during meal times, made inpatient treatment difficult. Similarly, based on their qualitative study of AN and ASD comorbidity, Brede and colleagues (83) hypothesized that AN may develop through both direct and indirect pathways. In the indirect pathway, ASD-related difficulties are proposed to give rise to negative emotional consequences, and restrictive eating behaviors are employed as an attempt to cope with this. For example, individuals with ASD may have a longstanding history of being bullied and socially ostracized, resulting in low self-esteem and emotional distress. Restricting food intake can provide a sense of control and numbing of strong emotions. Given our study was cross-sectional, hypotheses about the direction of causality between symptoms are preliminary. Future longitudinal research using network analysis could help disentangle interactions between ASD, ED, and social anxiety symptoms.

Our findings have important theoretical and clinical implications. That the symptoms most central to the network all concerned social difficulties provides support for models emphasizing the role of interpersonal problems in the development and maintenance of AN. For example, the cognitive-interpersonal maintenance model of AN proposes that anxious, avoidant, and socio-emotional traits, including sensitivity to stress and negative emotions, anxious and avoidant attachment, and negative self-evaluations are predisposing factors (44). While some interpersonal difficulties are worsened by the ill state, this group of traits are proposed to be present before and after the illness, and often also in family members. Further, our results support the need for therapies to target interpersonal functioning as a key maintaining factor in individuals with AN, such as interpersonal psychotherapy (84), cognitive behavioral therapy (CBT) (85), and the Maudsley model of AN treatment for adults (MANTRA) (86). Secondly, it is of note that none of the items from the restrictive interests and repetitive behavior subscale of the SRS-2 had particularly high EI or bridge EI values. This may suggest that unlike social and communication difficulties, this group of symptoms play a relatively small part in AN and ASD comorbidity. Indeed, previous studies have shown that while social and communication difficulties are often elevated in those with AN, restricted and repetitive behaviors are often less pronounced

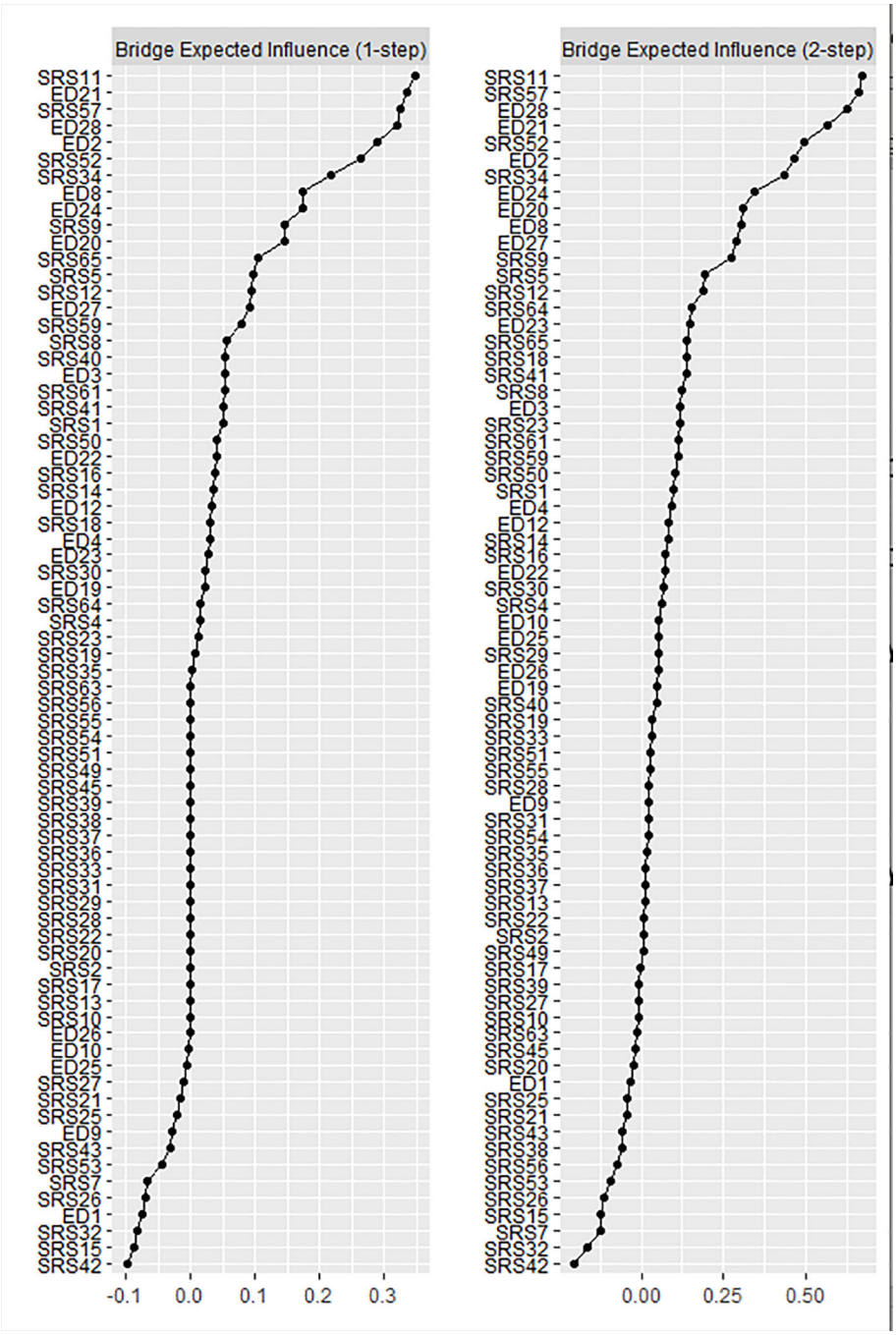

FIGURE 3 | Bridge expected influence (EI) plots. Values are given as Z scores, and higher values indicate more influential nodes in the network.

(33, 49). This might be in part due to AN samples being mostly female, a factor which is associated with lower levels of restricted interests in those with ASD (87). However, there is some evidence to suggest that males and females with ASD show differences in the types of topics they are interested in (e.g., people/animals in females rather than objects/things in males), therefore ASD symptom rating scales may not be sensitive to more female-typical presentations (88) Finally, our study examined relationships between symptoms on a group basis, however an interesting direction for future research would be to construct networks based on an individual basis. It is now possible to examine temporal associations between symptoms within individuals, potentially providing insight into which symptoms may be maintaining psychopathology and therefore

could be targeted during treatment (89). Thus, network analysis could be a useful tool in the move toward more personalized treatments in psychiatry.

Several limitations of the current study should be noted. Our sample size was relatively small given the number of items included in the network, therefore the findings require replications in larger samples. Nonetheless, our stability analyses indicated the centrality indices were stable enough to be interpreted meaningfully. Secondly, only items from self-report questionnaires were considered as nodes in the network. It is likely that vulnerability factors not measured in this study are also important in explaining comorbidity between AN and ASD. For example, given the similarities in neuropsychological profiles, performance on set-shifting or other tests of executive functioning could be included as nodes in comorbidity networks. Although other aspects of psychopathology and social cognition were collected as part of our wider study, these were not included as we wanted to focus on ASD and AN comorbidity specifically, and adding more nodes to the network may have resulted in reductions in the stability and accuracy of the network. Finally, although we confirmed a past or current diagnosis of AN in our sample, we did not confirm whether participants held a diagnosis of ASD. Although scores on the SRS-2 suggested high levels of ASD traits in our sample, there may be qualitative differences in relations between symptoms between individuals with lifetime AN who do and do not have a formal diagnosis of ASD. Previous research suggests around 10% of those with AN meet full diagnostic criteria, and a further 40% display high ASD traits (49). Future studies using a network analytic approach may be useful in establishing which symptoms reflect "true" ASD, and which may be a consequence of starvation.

In conclusion, our results suggest that isolation, difficulties in relating to others, and feelings of tension during social situations may be central symptoms maintaining AN and ASD psychopathology. These symptoms are most strongly connected to other symptoms in the network, and it is suggested that targeting these symptoms in treatment may lead to improvements in the mental health of individuals with past or current AN who also show ASD traits. It must be noted that while central symptoms may be causally influential, longitudinal studies are required to confirm the directionality of relationships between symptoms. We also identified bridge nodes from each disorder cluster; those with the strongest connections to symptoms to the other symptom cluster. Poor self-confidence (ASD cluster), concern around social eating (ED cluster), and concern over other's seeing one's body were (ED cluster) were the strongest bridge symptoms. These symptoms may be important in understanding AN and ASD comorbidity.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NHS Camberwell St Giles Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK-G contributed to the conception and design of the study. JK-G and DH performed the statistical analysis. JK-G wrote the manuscript. DH, AH, and KT contributed to manuscript revision, read and approved the submitted version. KT lead the research group under which the study took place.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00401/full#supplementary-material

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Embodiment as a Paradigm for Understanding and Treating SE-AN: Locating the Self in Culture

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There has been a growing call for sociologically engaged research to better understand the complex processes underpinning Severe and Enduring Anorexia Nervosa (SE-AN). Based on a qualitative study with women in Adelaide, South Australia who were reluctant to seek help for their disordered eating practices, this paper draws on anthropological concepts of embodiment to examine how SE-AN is experienced as culturally grounded. We argue that experiences of SE-AN are culturally informed, and in turn, inform bodily perception and practice in the world. Over time, everyday rituals and routines became part of participants' *habitus'*, experienced as taken-for-granted practices that structured life-worlds. Here, culture and self are not separate, but intimately entangled in and through embodiment. Approaching SE-AN through a paradigm of embodiment has important implications for therapeutic models that attempt to move anorexia nervosa away from the body and separate it from the self in order to achieve recovery. Separating experiences—literally disembodying anorexia nervosa—was described by participants as more than the loss of an identity; it would dismantle their sense of being-in-the-world. Understanding how SE-AN is itself a structure that structures every aspect of daily life, helps us to understand the fear of living differently, and the safety that embodied routines bring. We conclude by asking what therapeutic treatment might look like if we took embodiment as one orientation to SE-AN, and focused on quality of life and harm minimization.

Keywords: Severe and Enduring Anorexia Nervosa, embodiment, culture, *habitus*, qualitative, harm minimization, quality of life

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INTRODUCTION

> When in a rabbit hole, you become largely blind (or nonchalant) to those and the world around you. You are too far down to see them much or properly. And it is all too comfortable, familiar and interesting for you to care otherwise.
> You also become deaf to any voice of opposition. What do they know? You know what you're doing, you have things in hand. Go away, people, and just leave me to it.
> And the older you get and the more times you've been in the rabbit holes, the more they do just leave you to it.

> And for some reason, some small hidden part of you quietly wishes that they wouldn't. - Charlotte's diary entry, 2nd of April, 2013

This diary entry is from a 32-year-old Australian woman who has had severe disordered eating for more than half her life. Charlotte's spatial metaphor of the "rabbit hole" captures the safety and comfort which her "dark home" affords. Having lived in her protective space for many years and not wanting to come out, she is also aware of how hard it is to leave. She has undertaken multiple therapeutic treatments (with minimal success), and each time she has been drawn back down into the familiar rabbit hole of disordered eating. A small part of her wishes people would keep trying to pull her out, but like so many people with enduring eating disorders, her relationship with recovery and help seeking remains highly ambivalent.

While consensus concerning the diagnostic criteria for Severe and Enduring Anorexia Nervosa (SE-AN) remains contentious (1–4), and there are inconsistencies in the definition and labelling of SE-AN in the medical and psychiatric literature (1, 4–7), Charlotte's experiences align with the chronic, severe and enduring nature of this diagnosis. When we met Charlotte in 2013, she had had a previous diagnosis of anorexia nervosa in her late teens, and self-reported 15 plus years of significant eating disorder behaviors. During our research, she admitted herself to a psychiatric service for in-patient care, and otherwise remained living in the community, self-managing myriad, everyday negotiations around food and eating. Charlotte's length of illness duration, her number of previously failed treatment attempts, resistance to traditional treatments, and entrenched and persistent patterns of behavior, correspond to Broomfield et al.'s (1) identification of the most common defining features of SE-AN.

Due to the severity and chronicity of SE-AN, it is not surprising that there is uncertainty around the long-term outlook and whether recovery is possible for everyone. Broomfield et al. (1) note that the term "chronic" (which often implies an incurable illness) is currently the most commonly used adjective in the literature to describe SE-AN. Touyz and Hay (6) certainly argue that most patients with SE-AN are unlikely to fully recover (as defined by clinical criteria), and this is supported in the growing number of long-term clinical studies (8).

There are concerns that current mainstream treatment approaches to SE-AN exacerbate suffering and feelings of failure, and increase resistance to seeking help (1, 5, 9–11). Therefore, many clinicians working with this group over the last decade have been turning to more holistic biopsychosocial approaches to therapeutic care that go beyond symptom reduction, such as harm minimization approaches, and focusing on quality of life and improving general everyday functioning (1, 6, 8, 12–14).

In seeking to understand what quality of life might mean to people with a diagnosis of SE-AN, clinicians and researchers have recently called for more "sociologically engaged" research (6, 15). A number of psychiatric and medical studies have attempted to do this by using traditional qualitative methods of interviews to elevate the voices of people with disordered eating and their carers (13, 16–18). While these studies provide valuable information about people's experiences (e.g., 13, 14, 19), they tend to use what anthropologists call "etic" or "outsider" perspectives, in this case understanding SE-AN through a lens of disease categories and individual psychopathology.

Anthropologists on the other hand, spend time with people in their own environments (often over many months of fieldwork), conducting participant observation and exploring how people navigate particular aspects of their daily lives. This is an explicit focus on "the emic" or insiders' experience that allows the researcher to get close to complex experiences while remaining critical of their own bias. It is through this emic approach that anthropology seeks "to begin with and build upon [peoples] meanings and theories rather than their own" [(20), p.130].

Anthropology not only provides a rigorous and innovative methodological approach (beyond interviews) but seeks to identify the cultural structures that shape and inform mental health. This cultural orientation to mental illness attends to the "cultural making of forms of subjectivity [and intersubjectivity] from the actor's point of view—where the question is how actors enact, resist, or negotiate the world as given, and in so doing, make the world" [(21), p. 9]. In other words, anthropological approaches interrogate the "cultural processes in constructing the experience of illness" [(21), p. 6], and how symptoms (and their meaning and interpretations) are, in turn, shaped by culture.

It is widely acknowledged that eating disorders have a substantial sociocultural component [see, for example, (22–28)], yet this dimension in clinical literature is often absent or reduced to stereotypes of "ethnicity" or "femininity" as a stand-in for culture. A recent edition of *Transcultural Psychiatry*—dedicated to anthropological approaches to eating disorders—demonstrates the value of culture with a series of research papers by anthropologists who examine the "cultural logics that drive eating disordered practices", [showing] how these practices are embodied within everyday, normative milieus and broader cultural patterns [(29), p. 445].

In this paper, we draw on anthropological concepts of embodiment to examine SE-AN within sociocultural contexts, arguing that experiences of SE-AN are culturally informed, and in turn, inform bodily perception and practice in the world. In our study, we found that over time, everyday eating disorder rituals and routines that are enmeshed in cultural worlds became part of participants' *habitus*, experienced as taken-for-granted practices that structured life-worlds. Here, culture and self are not separate, but intimately entangled in and through embodiment.

We begin the paper by outlining the anthropological concept of embodiment, and how this was developed as a critique of Enlightenment dualisms of mind/body. The anthropology of the body has a significant historical relationship with psychiatry, and our analysis begins with Csordas' (30) concept of embodiment as this marked a turning point in theorizing bodies as being-in-the-world, of

experience, perception, sentience, and practice (*habitus*). Following a description of the study, we present three key findings (safety, healthism, and structure) that demonstrate how participants' experiences of anorexia nervosa were culturally situated and embodied. In framing participant experiences as the embodiment of *habitus*, the discussion section argues that these deeply held bodily dispositions are an embodiment of cultural practices. Taking an embodiment approach to SE-AN highlights how models of treatment and recovery which attempt to separate disordered eating from cultural practices and the "self", not only operate within culturally constructed dualisms of the body and mind, but point directly to the profound ambivalence that this group has toward recovery. In the conclusion, we suggest that the paradigm of embodiment can inform harm minimization and quality of life approaches to care in SE-AN.

THE EMBODIMENT OF CULTURAL PRACTICES

Building on a rich history of collaboration and conversation between psychiatry, philosophy, and anthropology (e.g., 31–37), our focus is on anthropological approaches that position cultural practices as central to experiences of bodies, selves, and everyday worlds.

Anthropologists have long been drawn to "the body" (and food), and classic ethnographic work (including cross-cultural research) has illuminated the ways in which understandings of the body vary according to differing historical and cultural contexts [for example, (31, 38–40)]. As a conceptual framing, embodiment came into anthropological writing as a specific critique of and departure from Cartesian dualism. This dominant Enlightenment thinking constructed knowledge as a series of key, hierarchical divisions between nature and culture, the biological and social, sex and gender, the individual and collective, and the body and mind. The mind and body were thus not only conceived as separate entities, but the body was understood to be a passive and fixed entity upon which society inscribed its rules. This ahistorical, acultural, and universal understanding of the body came to underpin the biomedical model in medicine (41).

In rejecting the mind/body dichotomy, Csordas argued that "the body is not an object to be studied in relation to culture, but is to be considered as the subject of culture, or in other words, as the existential ground of culture" [(30), p. 5]. The body is thus not an empirical "thing" that stands in as a backdrop to cultural life, but is an experiencing agent that is intersubjective, relational, dynamic, sentient, and indeterminate in nature (24). For Csordas (42), embodiment was a methodological and analytical tool that bridged dualisms.

Csordas' paradigm of embodiment is key to articulating and theoretically framing the ways in which women with SE-AN in our study inhabited, transformed and reproduced a cultural "logic of practice"—what the French anthropologist Pierre Bourdieu refers to as the *habitus*. The *habitus* is a "system of lasting, transposable dispositions" that provide individuals with a sense of how to act and respond in the course of their everyday lives [(43), p. 95]. It underpins how we experience our bodies, for it is through the body that one learns the taken-for-granted rules of everyday life, such as accents, gestures, and preferences for food, fashion and entertainment [(44), p. 252]. It is through the *habitus* that cultural tastes for certain foods (fried chicken or caviar) and bodily dispositions are socially informed and embodied, in which girls in some cultures are taught to "eat like birds", aspire to culturally constructed bodily ideals, and take up as little space as possible ("cross your legs"). Food and eating are much more than consumption of nutrients; they are deeply engrained in one's *habitus*, displaying elaborate performances of cultural positionings—class distinctions, gender, taste, and identities.

In terms of eating disorders, we have previously argued that a "healthism *habitus*" (26)—the incessant pursuit of "good health" through a plethora of diets and fitness regimes—enables people with disordered eating to readily engage in taken-for-granted cultural norms of "health" that are embodied and structure social worlds. These eating disorder behaviors are not experienced as irrational or bizarre symptoms, but embodied as culturally shaped, highly gendered, and normative practices of health—in other words, part-and-parcel of one's *habitus*.

It's important to highlight that the words "habit" and *habitus* for Bourdieu are not the same; habit is a mechanical behavior, whereas "*habitus*" involves a flexible disposition that entails competence, skill, and know-how (what Bourdieu calls the collective repertoire of practical reason) (43, 45). *Habitus* foregrounds social dimensions that are culturally situated and practiced, whereas "habit" in eating disorder literature follows a different understanding and foregrounds individual compulsive behaviors and stimulus responses [see, for example, (46)].

METHODS

Participants

This paper examines the experiences of a subgroup of women from a larger mixed methods study, including ethnographic fieldwork and psychological evaluation. The purpose of the study was to explore the cultural contexts of disordered eating among women in Adelaide, South Australia with the aim of understanding why they were reluctant to seek help. Data collection occurred over 15 months (January 2013 to March 2014) and involved 28 women ranging in age from 19 to 52. As the project was primarily interested in why women delay seeking help for disordered eating, the criteria for recruitment included women who were over 16 years of age who had not seen a health professional for disordered eating; had not been given an eating disorder diagnosis; had been diagnosed but had delayed seeking treatment; or who did not wish to pursue treatment. Following consent to take part in the Eating Disorder Examination [EDE; (47)], the majority (75%) of study participants met the criteria for a diagnosable eating disorder (48).

The recruitment criteria for the larger study were intentionally broad and we did not purposefully recruit women who fell into a SE-AN category. Here, we focus on five women in the study group (between 27 and 52 years of age) who had been diagnosed and living with anorexia nervosa for more than 10 years (see **Table 1** below). Two key factors contributed to this smaller group of women being retrospectively selected as potentially meeting the criteria for SE-AN out of the overall sample: 1) the five women who were selected had historically received a diagnosis of anorexia nervosa, whereas the other participants had not been clinically diagnosed prior to participating in this study. For the women without a prior diagnosis, it was difficult to establish severity and longevity of their disordered eating; 2) the overall sample were generally younger, ranging from 19 to 30 years of age, and had self-reported disordered eating from 6 months to 10 years. The number of women (5) we thus focus on is entirely consistent with those who develop SE-AN (20% of those diagnosed with anorexia nervosa [(49), p. 314]).

Recruitment

Participants were recruited through purposeful sampling methods from two metropolitan university campuses in Adelaide, South Australia, through South Australian mental health networks and advertising on social media websites such as Facebook groups (South Australian Body Esteem Activists and Supporting Eating Disorders for South Australia). Ethnographic research methods are critical to accessing the everyday practices and private experiences of hard to reach groups such as the population in this study who often did not identify as having a problem, faced social stigma, and were reluctant or too overwhelmed by their situation to engage with services [see (26)]. Therefore, recruitment posters were placed on the backs of toilet doors and pin boards and posed questions such as "Are you continually thinking about your food and your weight?" and "Do you enjoy the feeling of not eating or excessive exercising?"

The study received approval from the University of Adelaide Human Research Ethics Committee (H-2012-069) and the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). Prior to giving consent, all participants were fully informed about the research and the nature of their participation and understood they had the right to withdraw from the study at any time. In agreeing to participate in the study, participants were informed that information gained during the study may be published, and that they would be de-identified in all sources. Participants were provided with a copy of their signed consent form, along with information and resources on available eating disorder services.

TABLE 1 | Participant characteristics.

Participant	Age	Previous diagnosis	EDE Diagnostic results	Self-reported length of disordered eating
Kelly	40	AN	AN	20+ years
Charlotte	32	AN	Did not meet criteria.	15+ years
Michelle	27	AN	EDNOS—weight/BMI not recorded, otherwise psychopathology consistent with AN	10+ years
Sarah	28	AN	AN—Binge-eating/purging type	15+ years
Lorraine	52	AN	AN	30+ years

Data Collection

Author 1 conducted semi-structured interviews and participant observation in people's homes, in interview rooms at one of the universities, in cafes and in public places. Two to three semi-structured interviews, plus the EDE, were conducted with each participant over a number of months. Due to the exploratory nature of qualitative research, the interview schedule was flexible, and interviews varied in length (averaging 1–2 hours). Field notes taken during and after interviews captured observations made during the research meetings, such as non-verbal cues, emotional reactions, appearances, the research setting, as well as conversations outside of the interviews not recorded. The familiar interview settings of homes and the multiple interviews with each participant allowed rapport to build between the researcher and participant and provided opportunities to explore their everyday lives in more detail, not otherwise accessible in clinical settings or in one-off interviews.

In terms of research rigour and our ethical responsibilities, the inclusion of the EDE was important to ascertain if participants might meet psychiatric classifications, to elicit their responses to such evaluations, and to provide them with information about resources and services. We recognize that the language associated with psychiatric diagnostic classifications have value in clinical contexts and the wider community (including policy and practice contexts), but equally that terms such as, "disorder", "illness", "health", and "care" can have different meanings in other contexts, and this was important in engaging a population group reluctant to seek help. For some of the women in this subgroup, they did not identify with the words "illness" and "disorder", despite receiving a clinical diagnosis, but also discussed reluctantly needing to use their diagnosis when accessing the health and social security systems. As the project aimed to explore the denial of eating issues and the delay in seeking treatment, it was not surprising that the women in this study had had varying contact with health providers, and were all resistant to recover (in medical terms).

In addition to the interviews, diary writing was embedded in the ethnographic phase at the end of the interviews for a period of 8 weeks. Participants were invited to record such things as "the everyday moments, activities or events that might support your eating disorder behaviors … your fears, pleasures and desires around food and your body—what are you scared of? What do you need and want"? They could "draw, doodle, write a lot, very little". The collection of diaries also allowed for follow-up questions, including asking about their future help-seeking plans and a debrief of the study. Diaries are widely used in ethnography and social anthropology as a tool of inquiry, and are viewed as a "classic articulation of dailyness" [(50), p. 95]. It is this "everydayness" that the diary writing aimed to capture and helped to overcome problems associated with collecting sensitive

information, allowing participants to jot down their thoughts or feelings as they were happening, providing insights into intimate eating and bodily activities.

Analysis

The research design and methods were guided by grounded theory principles, coupled with thematic techniques of data collection and analysis (51–53). Grounded theory is a qualitative inductive methodology which prioritizes developing analytic categories and themes directly from the data, not from pre-conceived concepts or hypotheses, while also being reflexive of the bias that the researcher brings to the interpretation of the data (51). All interviews (including semi-structured and EDE interviews) were digitally recorded and professionally transcribed, and field notes were written up directly following each interview.

Following a process of open, axial and selective coding, the interview transcripts and field note data were firstly open coded in a Word document, and then through the software programme NVivo by Author 1. Open coding involved reading the transcripts line by line to identify and develop ideas, themes and issues from the data (20). A list of codes and sub codes was developed around dominant themes, for example, "help seeking", "ambivalence", and "lifestyle choice", to then form the basis of the thematic analysis of the interview and diary data. In the research team meetings that followed between Author 1 and 2, axial (secondary) codes were developed. This stage of data analysis involved making comparisons across the data, so that the final stage of selective coding could occur. Selective coding involved taking core themes and positioning these as key theoretical frameworks for analysis, and critically examining them against the wider literature (52). As the participants had written in pen and pencil, the paper diaries were manually coded using the same thematic codes as the interview transcripts.

RESULTS: *HABITUS* AND EMBODIED ROUTINES

Participant Characteristics and Completion Rates of Data Collection

The five women in this study who were identified as meeting characteristics of SE-AN had all previously received a diagnosis of anorexia nervosa from a health care professional, and self-reported 10 to 30 plus years of eating disorder practices. Over their life course, they had experienced different eating disorder and other mental health diagnoses, attempts at recovery, and relapses, ambivalence, and refusal to seek therapeutic help (although they sought help for other mental health and medical conditions). The results of the EDE found that four out of five met the criteria for an eating disorder at the time of the interview. As mentioned in the introduction, while Charlotte did not meet the criteria for an eating disorder when the EDE was conducted[1], she revealed a long history of severe anorexia nervosa that impacted her daily functioning and multiple admissions to in-patient care, locally and internationally. For this reason, and her long-standing struggles with SE-AN, we included her in this analysis.

While the sub-group of women we examine in this paper is small and a limitation of this study, the data is rich. Thirteen semi-structured interviews, 5 EDE interviews, detailed observations, field notes, and four diaries (one of the women declined to participate in the diary writing phase) provide what anthropologists call "thick description"—rich, contextual data describing decades of living with—of the embodiment of—anorexia nervosa.

Safety and Routine

Over time the women described how their eating and body practices came to structure their everyday worlds. Routines brought relief from emotional distress, formed a strategy for coping with daily challenges, a safety net to fall back on and a familiar space to come back to. Kelly, who had lived with anorexia nervosa for over 20 years and described herself as a "healthy anorexic" (26), commented that over time "I think it gets easier and that's one of the hardest things about it - is it gets so easy, it's so natural". Charlotte described how powerful the pull to disordered eating was even when on the road to recovery: "when everything else is crazy in your life it's something to hold on to. It's like a life ring". She further explained, "something big will happen in your life … and it's all feeling too overwhelming. You can actually make a conscious decision to turn around and find that life way, because you need something to hold on to and you know that it's helped in the past". Her disordered eating practices are thus positioned as the logical solution to a challenging situation because of the safety and familiarity that the structure of SE-AN provides.

Just 6 months before our first meeting, Sarah (28) had discharged herself from in-patient care for weight restoration. Physically fragile and reliant on her sister for care, Sarah remained steadfast in her wish not to give up her eating practices. She described the difficulty in trying to re-engage with social circles and study while maintaining her eating disorder routines. An evening education course caused great anxiety because it disrupted her evening eating practices. She would often cancel these classes, stating: "It's such a relief to my system when I cancel. I know my routine will remain intact. I take real comfort in it". Sarah's routine for the past 7 years has been to only eat at night and vomit that meal up afterward. It is the same meal each day and she has rules and rituals which guide her. She chooses food to eat which she knows will be easier and less painful to expunge from her body, prioritizing "a practical sort of selection of foods" which are greasy and soft. There are also rules around eating the lowest calorie food first, preparing

[1] While severity ratings scored high for many of the items in Charlotte's EDE (e.g., fear of weight gain, feelings of fatness, fear of losing control over eating, preoccupation with shape and weight) indicating presence of psychopathology of anorexia nervosa, the majority of Charlotte's frequency data scores (e.g., patterns of eating) did not. In addition, Charlotte was not weighed, opting to tell the interviewer her weight which resulted in a BMI of 19. It is important to note that the EDE only captures behavioral features of eating disorders within a specific time frame (1–3 months), and Charlotte was by her own description, in a "better place" during the EDE.

the food in the same order every time and only allowing "the food to remain in my body" for a set amount of time.

The women in our study spoke of the safety in their home spaces (in which most of the interviews took place) where they performed the majority of their eating and exercise routines. Sarah dreaded being out in public, writing in her diary: "I don't want my physicality on display. I don't want people to see me. I want to be hidden, private, protected". Sarah said she only consumed water when in public and hadn't eaten outside her home in 7 years. When the participants' followed their strict eating and body routines, they spoke of it offering them some safety and protection when entering public spaces.

Eli, in her study of people with eating disorders in Israel, noted that for her study participants, "to engage in eating disordered practice was to transform any space, temporarily, into one's own world" [(28), p. 481]. For Michelle, 27 years of age, "sticking to the regimes that I stick to, it seems to be the only time that I do feel okay about myself" and that "it makes me feel better being in my own skin", especially when under "surveillance" in public and eating with friends and family. There are gendered and moralized norms in Australian culture about eating in public, and for women in particular, what and how much they eat is highly scrutinized and tied to stereotypes of femininity and health status. Participants inhabited and incorporated these cultural norms more intensely – eating a minimal amount or not at all—as a way of feeling safe in public spaces. By following cultural expectations of a gendered *habitus*, Michelle and others were able to more safely engage in relationships and the social world.

For Lorraine, at 52 years of age, who was diagnosed with anorexia nervosa at age 30 and reported having lived with it (and at some points bulimia nervosa) for over 30 years, her practices had become "a script that you just can't shake free of", which felt "safe" and offered "comfort". Lorraine lived with her husband in a beachside suburb and worked part time in the public service, recently stepping down from a leadership position due to worsening mental health. She described seeing psychiatrists for anorexia nervosa on and off from age 30 but not wanting to "give it up". However, at age 50, Lorraine reached out for help, describing her physical health worsening to the point of attempting suicide 6 months previous to the interview. Lorraine stated, "I had no quality of life left" and after the unsuccessful suicide attempt, she decided to engage with psychiatric therapy once again.

Like many people with anorexia nervosa, Lorraine was well aware of the damage that SE-AN was having on her health as she aged (fractures, low bone density, nausea). Prior to our meetings, she had put on some weight (an increase to 46 kg) in an attempt to improve her physical health and quality of life. She felt unsure about these weight changes, telling us that after decades of using anorexia nervosa to navigate the world, "you feel safe if you know what to expect if you stay on this sort of a routine". As the eldest participant in this study, the embodied impacts of SE-AN were striking in Lorraine's presentation and experiential accounts, and improving her physical health and quality of life—but not giving up the anorexia nervosa—was the primary motivation for her recent engagement with psychiatric services.

Sociocultural Elements Which Support and Sustain People's Eating Disorder Practices

In a previous paper, we have described how the women in this study were acutely aware that they lived in a culture that celebrated and equated good health with thinness and restriction (26). This earlier paper explored how the women capitalized on popular health aspects of their *habitus* (such as detox diets, yoga, veganism, and, more recently, fasting diets) and incorporated them into their disordered eating practices and routines, allowing them to engage with dominant gender ideologies of "healthy lifestyles" and "self-care". Positioning their own practices as acts of care and health therefore negated their need for therapeutic care.

Participants sometimes joked about how they shared similar eating and body practices, aspirations, and ideals with those around them who did not have an eating disorder diagnosis. In interviews the women often compared their eating and exercise practices to their friends and family who were overweight or who were regularly on fad diets as justification for rejecting clinical labels of "illness" and "disorder".

Michelle's interaction with her trainer at the gym highlights this positioning of what may be considered by clinicians as eating disorder behaviors, but in sport and gym settings are an admirable demonstration of fitness, control and health:

> I was at the gym the other day and my PT [Personal Trainer] was telling me that she'd been to this weight lifting conference … she talks about, you know "I have [to] really balance my carbs because if I don't get enough carbs then my mood crashes and all this kind of stuff" … like what the hell? But there was this dude there who was talking about his training and was saying that he would deliberately stay up late and deprive himself of sleep because he'd be burning more calories. That's like putting your body through hell to achieve a certain body shape … I did that and I was told I was sick.

LaMarre and Rice (54) examine how women with eating disorders are faced with navigating prescriptions for recovery in a sociocultural context that privileges some bodies and food-related behaviors over others. For example, they argue "following from a 'war on obesity' over the past two decades, fatness is stigmatized, equated with laziness, ill health, ugliness and a lack of restraint and will power" [(54), p. 138]. In her ambivalence toward recovery, Charlotte struggled with resisting these cultural ideals and gendered norms, highlighting that women with anorexia nervosa "continually negotiate culturally dominant understandings of subjectivity, embodiment and health" and in "adopting and disrupting" these norms, demonstrate their active role in their disordered eating [(55), p. 395]. Reflecting on how

she is entangled with these cultural norms Charlotte stated, "we've got a whole society that advocates to have self-control, to be disciplined, to have restraint, you know these are all qualities that we advocate for people to have and this is just one area [anorexia nervosa] that you can put them into but also fits with the societal ideals of you know the slender, waif-like girlfriend".

Toward the end of our data collection, when Authors 1 and 2 visited Charlotte's house to collect her research diary, Charlotte informed us that she had finished and passed a Personal Training course, most of which occurred over the eight week diary writing phase. The diary documents how the Personal Training course became part of her search for a new routine, a way to remain thin and healthy and keep her eating disorder thoughts at bay. Charlotte had "never been much of an exerciser", preferring to restrict her food intake to maintain a low weight, and was enjoying the new sensation of feeling "strong". However, she increasingly struggled with being "triggered" during the course because the central focus of the lessons often ended up being about weight loss and appearance rather than a holistic approach to health and wellbeing. Charlotte then began restricting her diet again, stating she was becoming more "rigid" and "wanting to lose weight", and soon found herself spiralling down the "rabbit hole" once again. In the end, Charlotte decided to put her Personal Trainer ambitions on hold.

The sociocultural *habitus* described above support disordered eating to such an extent that despite the harm caused by long term anorexia nervosa practices, the women transformed this endurance into a moral marker of success.

"It's the Glue" That Holds Everything Together

Would you be reluctant to have to change your food/exercise practices? This was a central question that each participant was asked and which often resulted in a strong response. The women described not having their eating practices as: "a big void in my life", or like "losing the ability to breathe". Kelly responded: "I'm always going to be anorexic, I just have to be able to manage it", and Lorraine "couldn't imagine not thinking about it and acting like I do and doing the things I do … yeah, it's hard as it plays such a big role in my life and [my husband's]". Michelle stated her anorexia nervosa was "the one thing that could almost ground me", and "it became a very tangible thing that I could say, this is my thing, and no one can touch it". Michelle became pregnant during the project, and she viewed her weight gain and increased calorie intake as a temporary measure for the short period of time when her body "was not her own". Following the birth of her baby her goal was to return to her restrictive eating practices and to lose the weight she had gained.

Despite the serious impacts on their health, relationships, and general wellbeing over many years, the women in our project were studying, held down jobs, went on holidays, and were parents, partners, church-goers, and supportive friends. They were highly skilled in managing their eating disorders. It was something that they always came back to, as Kelly described —"it's the glue", that became a "structuring structure" (43) to their everyday worlds. By her late 20s, Michelle had completed an honours degree at university, started a family and worked as a peer support worker at a mental health non-governmental organization (NGO). She had also been "in and out of psych hospitals since [her] early teens", and explained that when she notices herself becoming overwhelmed and spiralling emotionally, she contacts her psychiatrist and asks to be admitted to hospital. When she is discharged the desire for anorexia nervosa has not receded, and she returns to her disordered eating routines. In-patient care had become a necessary and critical tool for Michelle to keep her well enough to continue maintaining her eating and body practices, to go to work, study, and have relationships. However, it was never her intention to stop her practices and despite many near death experiences she explained: "it's like 90% of the time it's just, whatever, like this is just what I'm doing".

Lorraine explained that anorexia nervosa for her is "a lifestyle [in which] everything revolves around not eating or exercise or 'when can I do this' and 'how much did I have here', and weighing yourself and 'how else can I lose weight now'?". "Everything else", she says "is organized around it". Kelly similarly manages and plans her practices, or as she refers to them her "binge ups" and "starve downs", around everyday life circumstances. For example, she is aware that people will treat her coldly at a party if she appears too thin, so she will do things to "plump" herself up in preparation. As she has aged her practices have taken a toll on her body and Kelly has adapted to "starving" more "healthily". Her low blood pressure meant that she had to restrict high intensity forms of exercise, so Kelly took up yoga as a weight maintenance tool instead. She stated that with yoga "I'm allowed to be skinny, and people will say *how are you so muscly and thin?* I do yoga". For these women, their eating disorder practices are normalized and conform to the structures and practices of a dominant, health focused *habitus*.

DISCUSSION: SE-AN IS PROFOUNDLY EMBODIED

In a recent commentary on the self in anorexia nervosa, Aminato et al. (56) outline a theoretical model of eating disorders in which they suggest that the self represents the organizing function of the mind. Referencing and following Hilda Bruch's earlier work (57), these authors argue that "deficits in the self are the basis of eating disorder psychopathology, thus establishing anorexia as a disorder of the self" [(56), p. 849]. Explicitly drawing upon Cartesian metaphors of mind and body, a separation ensues between the person's ability to recognize bodily sensations (such as hunger) and bodies become objectified as a "mere object". In this theoretical model, the self "represents the organizing function of the mind that when disturbed, will lead to and maintain the disorder" [(56), p. 849], and the body sits as a passive backdrop.

As we have argued above, this clinical narrative of self is premised on western philosophical dualisms that split and privilege minds over bodies, insides over outsides. In their

study of a group of women who had recovered from anorexia nervosa, Dawson et al. (13) found that during the illness phase, their participants (who had an average length of illness of 15.5 years) internalized anorexia nervosa and were unable to externalize the illness. As in our study, their participants' perceived anorexia nervosa as "impossible to escape, all-consuming and chronic" (ibid). Recovery [for Dawson (13)] is understood as "externalization of anorexia", or removing anorexia nervosa from the body, putting it outside the body. These culturally and historically constructed "[dualist] metaphors permeate the clinical field, shaping our own understandings and therapeutic practices" [(15), p. 2]. The dominant understanding of anorexia nervosa is thus as "a disorder of the self" (56) and "the self" is frequently the target of interventions for anorexia nervosa (16, 58, 59). However, in exploring recovery narratives, LaMarre and Rice [(54), p. 137] found a great variance in people's understandings and experiences, with many rejecting the clinical ideas "that recovery entails an overcoming and divorcing of self from eating disorder". Indeed, many of the participants in our study rejected the labelling of their practices as "illness" or "disorder", and thus were ambivalent to the proposition that what they were experiencing could be cured or separated from their selves and social worlds.

Taking a different approach, social anthropologists understand "the self as culturally constituted" [(30), p. 5]. A full review of this large body of anthropological scholarship on "the self" is outside the scope of this paper, but the key point is that abstract and disembodied concepts of the self are "held to be outside of time, outside of space, outside of culture and outside of gender" [(60), p. 480]. If we approach SE-AN as the embodiment of cultural practices (situating the self in embodied, cultural contexts), we illuminate "generative schemes and bodily dispositions" that structure and give meaning to people's everyday worlds. Embodiment is a "methodological standpoint in which bodily experience is understood to be the existential ground of *culture and self*" [(42), p. 269, our emphasis]. For people in our study, this generative scheme was not pathological, but a normative, culturally legitimated *habitus*.

To divorce oneself from anorexia nervosa would be to ask participants to not only give up the protective and productive aspects of anorexia nervosa, but also to step outside of culture. While aspects of safety and identity have been documented in eating disorder experiences (14, 24–26, 28, 61–63), framing these experiences through the concept of embodiment broadens how we understand people's experiences and takes us beyond acultural selves. Anthropologist Karin Eli (28), for example, situates the individual experiences of anorexia nervosa within the concept of "social suffering", in which suffering is understood to be "produced relationally, taking shape within networks" from the individual to the political (p. 478). The participants in Eli's study described their daily disordered practices as "surviving", as a way of being-in-the-world that kept them safe from distress caused by interpersonal relationships and structural pressures (such as caring for a family member with a disability and living in poverty). This approach highlights how the self cannot be separated from anorexia nervosa, as the embodiment of eating disorder practices is an individual's response to a much more complex experience of "social suffering" (28). Here, the individual "self" and social structures are relational (not in opposition).

In supporting Eli's arguments, we similarly found that social suffering was a significant component of people's *habitus* in disordered eating. Charlotte's embodiment of anorexia nervosa enabled her to keep safe from the dangers she had experienced as a child. Michelle described the same practices which led her to psychiatric in-patient care many times also helping her to stay alive. She said "sticking to the regime that I have to stick to becomes so overwhelming. But then at the same time it's just such an enticing path to go down, and I'll go down it over and over again … each time I put on weight, so I'm straight down the same path". These pre-worn paths are shaped by an embodied distress which formed a map for being-in-the-world (30). Like Eli's participants, the women's practices went beyond an "expression of a sufferer's distress, but as the manifestation of the broader social and structural configurations that brought this distress into being" [(28), p. 479]:

> embodied distress is not simply relegated to the individual sufferer, but is understood as emerging from and implicating structural constraints and the difficult and sometimes oppressive bonds of social being. Rather than representing maladaptive, idiosyncratic coping mechanisms, when contextualized in the participants' greater narratives, eating disordered practices emerge as grounded in a "logic of practice" [(28, 64), p. 489].

In placing embodiment as a framing approach to SE-AN, the body is not seen as a passive object, but plays an active role in how people inhabit and phenomenologically experience their worlds. The body is not inert or secondary to cognitive processes; participants in our study were highly attuned to bodily sensations, using their bodies as gauges for being-in-the-world. Over many years of what she described as "trial and error", Kelly used feelings of hunger as a barometer to titrate her moods and energy levels:

> You know, … when you don't eat a lot you know how food affects you. You know what foods are going to do what to you and you suddenly know what you need so that you won't need other foods … I find when I'm not eating, if I've gone for periods of time without eating I get really excited and hypo and I buzz around and get really lively … I get excited about being so light.

At 40, Kelly used her hunger as a way to settle into what Wright suggests is "a kind of working anorexia, not careering toward death, but [still] disciplined, self-contained" [(65), p. 172]. Her being-in-the-world was far from disembodied or a "deficit of self", it was profoundly lived and felt in and through her body. Through her continual and fine-tuned awareness of

embodiment, Kelly reveals the key relations between embodied selves and the world.

It may seem anathema to suggest that there is a "logic of practice" to practices which have historically (and continue to be) labelled as "illogical" and pathological. For the women we interviewed (and as many other anthropological analyses of eating disorders also describe), there is a clear cultural logic to eating disorder practices. This logic, as Csordas argues [(30), p. 12], is drawn from the conditions of *habitus*:

> The *habitus* is the universalizing mediation which causes an individual agent's practices, without either explicit reason or signifying intent, to be none the less "sensible" and "reasonable" … the structure which has produced [the *habitus*] governs practice, not by the processes of a mechanical determinism, but through the mediation of the orientations and limits it assigns to the *habitus*' operations in invention. As an acquired system of generative schemes objectively adjusted to the particular conditions in which it is constituted, the *habitus* engenders all the thoughts, all the perceptions, and all the actions consistent with those conditions, and no others [(43), p. 79–95].

The *habitus* is thus a "structuring structure"—a "socialized subjectivity which gives rise to and serves as the classificatory basis for individual and collective practices" [(66), p. 585]. These practices are culturally informed and shaped, and embodied as seemingly "naturalized" ways of thinking, feeling, acting and classifying the social world and [a person's] location within it [(66), p. 586]. For our participants, SE-AN was their embodied *habitus*, their "structuring structure" of their being-in-the-world and could not be separated from their sense of self. This is a position that the Australian author Fiona Wright captures so eloquently in her biographical account of years of anorexia nervosa: "I'm finally accepting that my illness is my normal, that I have to find a way to dwell within and alongside it" [(67), p. 17].

How Does an Embodiment Paradigm Inform Quality of Life Approaches to SE-AN?

While views vary on treatment approaches to SE-AN, the narratives of the women in this study contribute to a growing number of questions about treatment expectations, models, and outcomes. If SE-AN is central to this sub-groups' embodied experiences of being-in-the-world, is it ethical to focus on cure and recovery over quality of life? If recovery is unrealistic and unachievable for this group, how might the goals of treatment be shifted? What are the best models of care to support people with SE-AN?

As discussed in the introduction, there has been a move in eating disorder treatment models for people with SE-AN to include more holistic approaches that focus on improving quality of life rather than understanding recovery only through the medical model of absence of illness. Touyz and Hay [(6), p. 2] suggest "we need to rethink our treatment strategies by drawing upon the patient's strengths and competencies rather than merely paying attention to what is "wrong" with them. Undertaking treatment with a poorly motivated, chronically ill patient where loneliness, despair and an empty sense of self prevail, poses unique challenges for clinicians".

Placing people who have lived with anorexia nervosa for most of their adult lives into standard recovery pathways poses a number of serious harms. People who are fully committed to SE-AN may feel guilty for taking up costly resources for more newly diagnosed and younger patients, or may feel undue pressure to please others by "getting better". Both run a risk of instilling guilt, creating unrealistic pressures to achieve, and compounding treatment failure. Recognizing the unintended consequences of asking too much or pushing too hard doesn't mean giving up (49), it means refocusing treatment toward harm minimization and quality of life. This involves letting go of clinical expectations to restore weight and minimize clinical symptoms, and focusing on the best ways to support people with SE-AN to have a quality of life. Westmoreland and Mehler [(49), p. 316] suggest that the goal of a harm reduction model for people with SE-AN is:

> to assist patients in getting to a reasonable level of functioning that they can then maintain, rather than subjecting them to a full course of treatment, which usually involves a prolonged hospital stay to achieve restoration of ideal body weight. Candidates for this form of treatment are those who have endured multiple previous eating disorder treatments with minimal success, and those for whom full weight restoration has not been sustainable. Patients who undergo a "harm reduction" model of treatment are usually managed as outpatients. They are allowed to remain at a weight that is below their ideal body weight range, but one that is sufficient to enable them to have a reasonable quality of life, even if they cannot work or be fully independent.

Others have outlined how this shift in focus to harm minimization and quality of life includes treatment which prioritizes remaining hopeful, finding meaning and purpose in life, focusing on abilities over disabilities and not setting unrealistic goals of complete symptom resolution (8, 62). If, as we have suggested, SE-AN is seen as an embodied being-in-the-world that structures the everyday through one's *habitus*, treatment that works within and with these practices may offer more hope than current approaches that seek to untether people from their worlds.

CONCLUSION

In this paper, we have argued that the paradigm of embodiment helps to reframe an understanding of SE-AN, thereby allowing treatment approaches to emphasize improved quality of life over full recovery (in medical terms). Embodiment recognizes the protective and productive aspects of the person's eating disorder

practices (safety, comfort, structure) and that eating disorder experiences are supported by and produced in relation to sociocultural contexts. Embodiment is thus not just an individual's pathological reaction to trauma, but a response to a much more complex experience of "social suffering" (28, 62), which informs their understanding of how to be in the world and how to get on in the world.

Approaching SE-AN through a paradigm of embodiment has important implications for therapeutic models that attempt to move anorexia nervosa away from the body and separate it from the self in order to achieve recovery. The medical model trajectory of recovery is based on a clinical narrative that "dualistically separates anorexia nervosa as an illness from its antithetical state of recovery, whereby the person returns to some premorbid state of normality" [(15), p. 2]. This asserts the clinical narrative as the person's reality, rather than other ways in which they understand their everyday worlds and practices. We have argued that separating everyday bodily experiences—literally disembodying anorexia nervosa—is more than the loss of an identity, it would dismantle participants' sense of being-in-the-world. Understanding how SE-AN is itself an embodied structure that structures every aspect of *habitus*, helps us to understand how disordered eating practices contribute to (and simultaneously) impede their quality of life, the fear of living differently [or as Lavis suggests "tasting other ways to live" (62)], and the safety that embodied routines bring. This points to why people persist with such severe and medically dangerous body and eating practices for years and decades. The implication for patient care is that opportunities for harm minimization and improving a person's quality of life may be overlooked because their experiences do not fit the clinical narrative.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Adelaide Human Research Ethics Committee (H-2012-069) and Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MW led the design of the study with input from CM and PG. CM and MW conducted the research and analyzed the data. CM and MW wrote the manuscript with revisions from PG.

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Towards an Improved Understanding of the Anorexia Nervosa and Autism Spectrum Comorbidity: PEACE Pathway Implementation

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This paper describes an eating disorder service development pilot project helping clinicians implement evidence-based research for patients with anorexia nervosa and autism spectrum condition comorbidity. Currently, there are no clear guidelines or recommendations for people who have the developmental condition of autism spectrum condition and a comorbid eating disorder. The Maudsley eating disorder team is pioneering a tailored approach of adaptations for this autism and eating disorder comorbidity to improve and adapt evidenced-based treatments and improve the experience for patients, families, and clinicians involved in their care. This paper aims to support the clinical and research community to implement some of the learning and new strategies developed through the PEACE pathway. The authors aim is to collaborate with teams nationally and internationally to scale up the project to benefit patients with this comorbidity.

Keywords: eating disorders and autism pathway, treatment, implementation, comorbidity, innovation, qualitative study

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PLAN

The Problem

The link between autism spectrum condition and eating disorders is increasingly researched and in recent years has been receiving more clinical attention. With estimates of comorbidity up to 37% (1), extensive research has been conducted on cognitive profiles (2), socio-emotional processing (3), clinical naturalistic studies (4), and epidemiological studies (5, 6). The research in the field has indicated that the overlap in the two disorders seems to be mostly related to high levels of cognitive rigidity, attention to detail (2, 7), sensory sensitivities (8), and poor social functioning (9–11).

Patients with the comorbidity have been found to fare worse in treatment programs, with poorer outcomes, heightened presentation, and longer in-patient admissions (4, 6). From our own internal audit data, we can see that these patients have longer stays in treatment as well and higher percentages are being seen in the more intensive in-patient settings. This evidence leads us to believe

that there is a high percentage of this comorbidity seen in cases of severe and enduring eating disorders and that urgent attention is needed to support this client group, in order to improve their treatment outcomes.

This manuscript summarizes our attempt to translate research evidence into the clinical work we do with patients with comorbid eating disorders. Autism spectrum conditions (preferred term by people with lived experience) are developmental conditions where traits remain stable over lifespans. Recognizing and acknowledging these traits and their stability in eating disorder patients is the first step in educating healthcare professionals in how best to support the unique needs of those on the autism spectrum. Eating disorders, on the other hand, are serious mental health conditions with physical and psychological risks needing treatment. In the clinical pathway development for Autism Spectrum Condition (ASC) and Anorexia Nervosa (AN), we take the view that treatment as usual can be modified to support people with ASC to recover from an eating disorder.

Needs Assessment to Address ASC and Eating Disorder Comorbidity:

Recent interviews with all major stakeholders in supporting the comorbidity effectively (patients themselves, their carers, and their multidisciplinary clinicians), which we refer to as the "stakeholder needs assessment triangle," suggest that there is an urgent need for guidance in this treatment pathway (12–14). These interviews suggest several overlapping themes which all the groups agree on such as: acknowledging a link between the two diagnoses; the need to address neglected sensory sensitivities; that therapeutic engagement takes a longer time to build with therapists; that an individualized and flexible approach needs to be taken in treatment; that there are currently barriers for these patients, namely difficulties in gaining a diagnosis and no clear pathway being available; and finally that clinician training and support around the comorbidity is needed (12–14). In addition, thought needs to be given to ensuring reasonable adjustments are made to outpatient and inpatient treatment areas, to reduce stress levels and support treatment.

There is an urgent need to identify these patients and support their additional needs to ensure patient-centered care and optimal treatment outcomes. With no current guidelines on how to best approach the comorbidity, a novel pathway has been co-produced by patients, clinicians, carers, and researchers within South London and Maudsley NHS Trust Eating Disorders Services. This clinical pathway aims to address all the issues identified within the main stakeholder interviews in order to improve treatment outcomes of the patients with the comorbidity (12–14).

This clinical pathway has been developed using the Institute for Healthcare's Model of Improvement quality improvement methodology, using an iterative Plan, Do, Study, Act (PDSA) format to introduce change and to co-produce the work with people with lived experience and with healthcare professionals. PDSA is implemented in cycles where each development once implemented is continuously assessed and improved in a structured way on a small scale before full-scale implementation. This allows change and feasibility to be assessed in the least disruptive way. We believe this will help define the model and assist with scaling up this program to other eating disorder treatment sites. This article has been structured into the "Plan, Do, Study, Act" template, although retrospectively this information does not slot as easily under the headings as our "Do"-ing and "Study"-ing were taking place alongside each other.

We called the project the project Pathway for Eating disorders and Autism developed from Clinical Experience (PEACE) pathway. This name was chosen by a patient vote as being the most popular of a series of abbreviations. This paper outlines how we have implemented PEACE pathway with the aim of improving care for patients with the ED and ASC comorbidity. We further want to demonstrate that by following our steps and strategies from our experience other clinical teams can "give PEACE a chance".

DO

Clinician Training

As identified in the triangulated stakeholder's interviews, there is a need for clinicians additional training for all members of the multidisciplinary team, and better confidence to manage the ASC and ED comorbidity. This training would not only address this theme, but also others highlighted in the triangulated stakeholder's assessments such as: acknowledging the link, acknowledging atypical sensory profiles, aiding with therapeutic engagement, suggesting ways of working in an individualized and flexible way with each individual. Research suggests that there is a lack of recognition and understanding around the comorbidity and how the two diagnoses interact (15). We have therefore introduced a regular training program for clinicians in South London and Maudsley NHS foundation specialist eating disorder service including inpatient, outpatient, and daycare programs. This training series aims to translate information provided by experts and clinicians in the autism field into applicable adaptations for clinical care on eating disorder wards. Evaluations were taken of each training session providing both qualitative and quantitative feedback. We started with the tools of Assessment of Autism including training in ADOS-2 (Autism Diagnostic Observation Schedule-2) and ADI-R (Autism Diagnostic Interview-Revised). Feedback for these sessions suggested that clinicians gained valuable experience from these two training blocks, most of them commented that interpretation and a good understanding of ASC clinical assessment gave them better insight and understanding of the ASC presentation. Clinical assessment sessions were found most informative in the area of female ASC, where clinicians learned to better understand how females with autism often camouflage their autism symptoms. Furthermore, feedback suggested that the questions such as "how do you differentiate between a friend and colleague" and "How do you feel when you are (insert emotion)" used in the assessments, particularly the ADOS-2,

invited clinicians to think about how to approach certain topics essential to therapy, such as relationships and emotions, and gave a better insight into behaviors of those patients with comorbid autism. Later training sessions focused on adaptations applicable for clinicians. These included various therapeutic modalities and how current clinicians within the autism field adapt to particular patients (CBT, DBT, formulation-based approach, CRT, and CREST training). Further training included learning about specific sensory adaptations for patients and how these would be dealt with in sessions and potential environmental adaptations from experienced occupational therapists working in the ASC field. The knowledge gained from these sessions has allowed our multidisciplinary health professional team of clinicians to build up their "toolbox" of techniques that may help and support individuals, tailoring treatments to the individual and being flexible in their approach as highlighted as a necessity in the triangulated stakeholder interviews.

Clinician confidence and skilling the team up in terms of flexibility and useful adaptations were our main drivers when introducing our PEACE training sessions. Feedback from 100 attendees of these sessions suggests that clinicians' overall confidence in supporting the comorbidity increased from an average of 46/100 to 68/100 (**Figure 1**). In terms of confidence in making adaptations in treatment for patients with the comorbidity, there was a similar increase in confidence from 45/100 to 64/100 (**Figure 1**). Overall, 92% of clinicians agreed that the training sessions equipped them with knowledge, skills, and tools to support patients with the comorbidity and 97% would agree that these training sessions should be recommended to other eating disorder clinicians. The highest confidence changes were after our Formulation adaptation training which saw an average of 35-point increase per person. In addition, the clinical team provided qualitative feedback on the training sessions (e.g. "thanks for recommendation to use more drawing," "I will remember now, less words more visuals," "I will pay more attention to sensory difficulties," "brief sensory assessments will be helpful in my work").

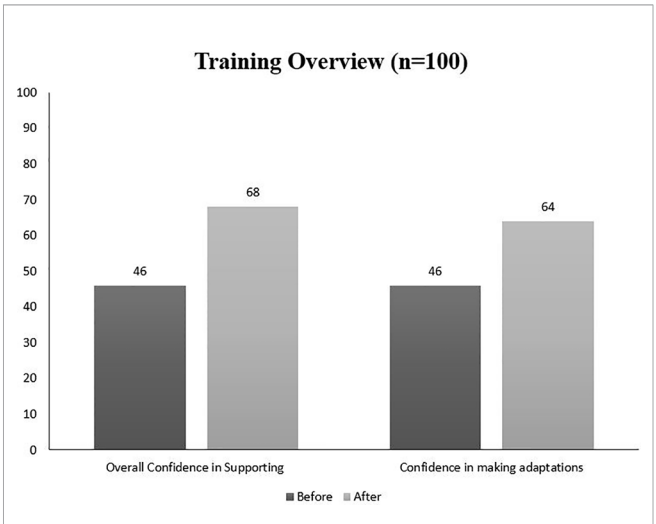

FIGURE 1 | Training feedback graphs.

Clinician Support

As well as introducing autism-specific training, we have also implemented weekly team huddles or "snapshots" which last for 15 min. There is a weekly huddle on the inpatients and step-up unit and one for outpatients and the daycare service. These huddles aim to address many of the themes identified in the triangulated stakeholders needs assessments such as acknowledging the link, offering a clear pathway, supporting clinicians and as a result improving outcomes of treatment adaptations. The purpose of these huddles is to provide support, keep continuity, assess additional needs for the treatment team to improve the quality of the care for the ASC/ED comorbidity. This can be through informal groups supervision, where cases are briefly discussed or formulated as a team. We also think about developments of the PEACE Pathway within these 15 min, either what changes are new or how we can improve current care and treatment plans. The materials we have developed, such as rapport enabling psychoeducation will be discussed and edited by the team in the huddles, ensuring all knowledge developed from clinical experience is collated. Many of these materials along with others are now freely available on our PEACE website. In addition, once a month at each site, we run an extended huddle of one hour where a case study is presented. This will have input from all members of the multidisciplinary team. We observed there were many benefits from these extended huddles for the team including better communication between multiple disciplines involved in the care of the patients (medical doctors, nurses, psychologists, occupational therapists, nurse assistants, admin, and housekeeping staff were also increasingly involved in the huddles particularly with environment adaptations discussed later). As well as this, we found the huddles a useful place for staff to reduce their own stimulus overload, in order for them to be able to do the same for patients.

Patient Identification

Eating disorders are predominantly seen as "female" disorders. In contrast, autism is often seen as a "male" condition. This inevitably creates a bias in the identification of female eating disorder patients with autistic traits, let alone barriers created due to "diagnostic overshadowing" (16). This is where, in our case, the eating disorder and its symptoms would overshadow the autism, often leading to a missed diagnosis. All three stakeholders suggested how difficult it currently is to be identified as autistic and how difficult it is to peruse a diagnosis. Furthermore, clinicians found there was no clear pathway for patients who were identified. As part of our pathway, we have introduced a basic screening measure for all patients starting treatment across our Eating Disorder treatment programs. The AQ10 (Autism Quotient-10) is a ten-question questionnaire which is a shortened version (17) of the AQ50. This measure is not a diagnostic tool but has been found to be an accurate measure in predicting the likelihood of autism. An additional "screener" we used, was clinician's instinct, we updated our admission assessment to highlight the comorbidity to the assessing clinician. Research has shown that clinicians are often very good predictors of autism (18). This instance of high clinician predication came about after the implementation of the pathway, suggesting that initial "instinct" may be lacking and that

after training and open discussions around assessments, clinicians may feel more equipped to recognize autistic people. After the screener, and when potential patients were flagged up, they would often undergo an ADOS-2 assessment. When scoring the ADOS-2, we would always use the updated algorithm (19) as it has been found to have increased sensitivity for females with anorexia (20). This report gave the team a more detailed sense of where this particular individual could be supported, be it in relationships, emotion regulations, or social aspects of daily functioning. For example, if it came to the assessor's attention that the individual particularly struggles with identifying emotions, this would inform clinicians that Cognitive Remediation and Social Skills Training (CREST—more detail in *Psychological Treatments* section) would potentially be a suitable intervention. A further identification tool used was a sensory sensitivity scale which was given to all patients at the start of their treatment. This was a useful tool as the ADOS was not designed to be sensitive to populations who have sensory impairments (21), as sensory atypicality was only recognized formally as being a trait of those with autism in since the assessment was created (22).

Addressing Neglected Sensory Sensitivities

The need to attend to atypical sensory profiles of this patient group was agreed by all parties (patients, clinicians, and families) in our qualitative research studies (12–14). This is of little surprise, as research has shown that treatment settings are often over-stimulating for patients on the autistic spectrum (23). To address this, we worked closely with the National Autism clinical program in our NHS Trust and had consultations with invited experts from the National Autistic Society. We wished to adapt our ward environments to tailor to the sensory needs of the patients with the comorbidity, whilst also balancing the needs of the patients who do not have atypical sensory profiles. Using the co-production nature of our design this was achievable with regular feedback and decisions being made by all patient groups as a whole. For example, all neutral and low stimulating colors were identified for the new color scheme of the ward. All patients then had a say on which neutral color scheme we would select to make the decision inclusive. When implementing the change, one useful thing we found on our inpatient ward was to do this over a weekend. This way, many of the patients were on home leave and there was minimal disruption to the daily routine, especially when refurbishing the dining room. Other necessary environmental adaptations included providing all staff with key-covers for noise reductions, de-cluttering our ward spaces, and "going easy on the walls" (parent quote in [14]).

The sensory screening tool which we developed has been implemented as a pragmatic short assessment to explore over and under-sensitivity in the domains of smell, touch, taste, sight, and sound (24). This tool has been piloted by our patient group over the past year and preliminary findings suggest that 37% of our inpatient clinical group have possible ASC comorbidity. The majority of those with the comorbidity have self-reported problems with touch, and textures when compared to other inpatients without the comorbidity. However, in the domain of taste sensitivity, those with the comorbidity seem to have lower on average taste sensitivity than their other inpatient counterparts. There is also room for expansion on the screener and many patients with ASC have highlighted the preference for bland, soft-textured meals. This information is valuable, especially when taking food choices into account.

In light of sensory information, we have developed a specialized PEACE menu. This was co-produced by dieticians and patients to create a menu that addressed common sensory complexities in patients, whilst also ensuring all nutritional needs were met to ensure proper nourishment of this patient group. Meals on the menu were commonly bland, soft textured and as simple/predictable as possible. The predictability was ensured by having menu items which would not vary much such as mashed potatoes or a cheese sandwich. An example of pathway development within our huddle was just before the implementation of the menu, we brought it to the huddle for discussion and feedback. One of our nursing colleagues suggested we add photographs of each meal as it would be presented to decrease as much anxiety as possible and to increase predictability. This idea was then co-developed by patients who were using the PEACE menu. Sensory sensitivities around food are important to be aware of when supporting autistic people in their eating disorder recovery. We have received positive feedback from our dietetic team about how the PEACE pathway has aided their clinical practice: "As a dietitian, involvement with PEACE increases my understanding of how people with an eating disorder and ASD experience food and eating, and this helps me to better support recovery from the eating disorder."

Further adaptations implemented based on our sensory findings included introducing a sensory box to our ward environments. These boxes include several items requested by the patients with the comorbidities, and as they are often costly items, we suggest it is used as a "try before you buy" box. Items in our box included weighted blankets, ear defenders, and essential oils. Patients are also encouraged to support their own sensory needs in Occupational Therapy by creating their own Sensory "First Aid" Kits. The idea behind these is that in times where sensory stimulation is too much, or not enough, the patient is able to ground themselves on their own. In these boxes, patients are encouraged to collect things that will stimulate different senses, for example dried lavender, some putty or bubbles, etc.

Our Occupational Therapists have also developed a Sensory Group. This group is run over the course of 5 weeks and each week addresses a different sense. The aim of each session is to provide psychoeducation around each sense, allow patients to explore their sensitivity and preference to each sense in a safe, explorative way.

The psychology team further developed a one-off sensory workshop using psychoeducation and experiential content across different eating disorder treatment programs (inpatient, daycare). This workshop is inclusive of all patients, with or without the comorbidity, and is aimed at increasing each participant's knowledge and understanding of their own sensory needs and sensitivities. Using this information, participants are then encouraged to think of the self-soothing nature of meeting these sensory needs and experiential ways of addressing these are suggested and explored together.

Psychological Treatments:

Based on our naturalistic studies we evaluated how patients with AN respond to adjunct therapies based on remediation principles of Cognitive Remediation Therapy (CRT) and Cognitive Remediation and Social Skills Training (CREST) with or without ASC features. In general, we engage patients immediately after admission (regardless of BMI) in psychoeducation and experiential exercise-based cognitive and emotional training programs in individual and group formats. Based on our preliminary findings people with comorbid ASC and AN find these therapies helpful, however self-report and neuropsychological outcomes after therapy significantly change only for individual CRT and CREST. Evaluation of the group versions demonstrated that although there were no statistically significant changes in the self-report questionnaires before and after the group, patients' qualitative feedback was seemingly positive (25–27). Interestingly, qualitative feedback from the patients with high ASC traits suggested that they found CRT and CREST groups safe, easy to attend, and not threatening, suggesting that it might be a helpful setting to begin to tolerate social situations.

Feedback from our clinical team suggests that using classic Motivational Interview techniques for these patients is often extremely challenging, which was reflected in the desire for training and more research in this area is needed. One of the possible explanations could be that motivational interviewing can use open-ended questions, metaphors, choices which is hard to access for people with ASC features due to preference to concrete, specific, simple, and literal language use.

As well as identifying which therapeutic interventions have been successful with this patient group, we have found various individualized strategies can be successful therapeutically (28). Our clinicians have reported that being flexible in various strategies such as the length, pace, and focus of sessions can have a significant impact on outcome and experience for the patient and therapist. For example, someone may have a particularly slow processing speed, who may need slightly longer or more session. On the other hand, someone may have a very short concentration span and may need to have short breaks throughout the session.

In the PEACE pathway we have developed psychoeducation materials for patients, as well as supporting adapted materials. We have adapted and developed an autism-friendly welcome pack for our patients. These are to be sent out pre-admission to make a highly anxiety-provoking situation less anxiety-provoking. This pack includes all information patients being admitted to the ward might need, including what an average bedroom looks like, what an average weekly schedule would be, when they might need to fill their own time and suggestions on what to do in this time, a site map and other information. Communication passports have also been developed for each patient. These communication passports are collaboratively completed so that personal information to do with communication styles, preferences, and goals, are fully understood and accessible to all clinicians involved in the patient's care.

Carers' Support:

The third stakeholder from our stakeholder needs assessment triangle: the carers who have loved ones with the comorbidity. Implementation of carer support is in its infancy, and it is a direction we wish to explore more. We deliver monthly Carers' workshops in our department across the eating disorder program. The purpose of these is to support carers of our patients (e.g. how the brain works when people are malnourished, how to communicate effectively, how to support eating). Our carers' workshop now includes information on the comorbidity, to raise awareness and understanding of carers who attend. Furthermore, the information provided at these workshops and handouts have been made user-friendly, as autism is known to have a heritable aspect and to be considerate to carers who may also have autistic features. Other adaptations to our carers' workshops include the addition of a new "animal" metaphor/s which are used to represent different carers' styles (see (29) for original animal metaphors). In referrals of family therapy across the service (for example, from inpatient to day-care), referrals now explicitly state if a patient has an autism diagnosis or if they or their family members display high ASC. As well as this, clinicians detail any particular adaptations that have been helpful to this patient and their carer/s. Adaptions may include seating positions, lighting, regular appointment times, written information and debriefs, and communication passports. In light of the global pandemic, our PEACE team have also offered virtual coffee mornings to carers to meet and discuss, facilitated by a psychotherapist. Due to its popularity and success, we hope to develop this idea into a more permanent fixture.

Resources for All Stakeholders:

We understand that the stakeholders of the pathway are not only those involved in the South London and Maudsley NHS Foundation Trust, and as a result we have developed materials and resources to share with others based on the learnings of our PDSA "cycle" implementations on what resources where needed for which group of stakeholders. We have a PEACE book currently in publication as well as a newly launched website (www.PEACEpathway.org) which has materials for all three groups of stakeholders freely available. We are hoping to develop this in the future to include a forum to increase our PEACE community-feel.

LEARNING POINTS, FUTURE DIRECTIONS, AND DISSEMINATION

Study

Through implementing this pathway, we have learned a lot about the dynamics and individual contextual challenges of eating disorder clinical service environments at the Maudsley hospital. As part of this development, staff and patients have faced and overcome adversities and as a result learned several important lessons. One thing we found challenging, was that there was some staff resistance. This was mainly due to an increasing perception of workload or "another level" added to their role. In order to successfully implement the changes, a network was established and continues to grow so that the pathway can continue to develop, adapt, and change after the pilot study with its external support. The huddle being open to all staff and sharing case studies

went a long way in obtaining staff buy-in of the need for the pathway. This was done with regular exposure to these patients and their complex cases through case presentations. Discussing these cases as a multidisciplinary team and having all voices heard and valued was essential. Appointing champions (mini project leads) was another important step. Having various champions such as a "sensory champion" and a "dining room champion" has given a sense of belonging and responsibility, without too much-added burden as the load has been spread. We have also increased our forms of communication, to make sure we reach everyone, even those too busy to attend the huddles or those not on the right shift pattern. We have done this through extensive communications amongst busy clinical teams: monthly newsletters, huddles minutes, posters, and ways to recognize us such as pens and badges setting up PEACE twitter. These forms of communication make sure that everyone knows their thoughts and opinions of the pathway are valued and that even if they are not in the meetings they still belong in the pathway. Through these techniques, we have generated interest in our pathway and more staff are becoming actively involved. This has implications for further spread of the model, as each adopting site will have its own individual contextual factors to navigate (30). Each adopting team will need to use the tools developed by the PEACE pathway to develop their local solutions, highlighting the importance of having a core group of interested staff or champions willing to engage in coproduction with patients to make positive reasonable adjustments to service provision and environments.

In terms of patient resistance, this has mainly been from those without the comorbidity. As mentioned previously, although most adaptations are tailored to those with the comorbidity, they benefit all patient groups. Examples of this include the sensory tool kits, where grounding techniques can benefit all patients. The PEACE menu is also available to all patients who are not on the spectrum three times a week. This allows those who may be particularly anxious about a meal or are in need of something predictable, an opportunity to do have this. Involving all patients in decisions has also been very important in ensuring all voices are heard. Regular feedback is also asked for from all patients and focus groups to create meal-support materials included for all patients.

Act

The details of implementation currently focus mainly on two parts of the needs assessment of our original triangle: patients and clinicians. In future adaptation, we will further develop a protocol for carers support. We have outlined above the implementations currently taking place for carers, however, we would like to support this group of carers more. We aim to do that by developing a platform to support and skill up carers. As well as supporting carers, we also hope to look at the comorbidity in young people and to be able to adapt the PEACE pathway for children and adolescents who are also struggling with a lack of individualized and flexible care. We also note that there is emerging evidence for other forms of Eating Disorders such as bulimia nervosa and binge eating disorders being equally comorbid with autism as anorexia nervosa. We would aim for future directions of the pathway to ensure all eating disorder groups are benefited and included.

Dissemination

We hope that with this information other eating disorder services will be able to "give PEACE a chance" and take forward our implementation strategies and improve them, through further testing and iteration of the model. By using a quality improvement approach of implementation, we hope to learn if there are "core" elements to this process that all sites use and map the local adaptations. There is no "correct" way to support this comorbidity group and each implementation step is a learning process which we hope other services will be part of. With new ideas and techniques being introduced we hope to build a supportive, inclusive community.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by South London and Maudsley NHS Trust. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KT is a principal investigator of the PEACE pathway project. KS is a project manager collecting the data and managing day-to-day activities in the project. AB edited and provided coaching for the project implementation. KT developed the study protocol, supervised team. KT and KS wrote the paper. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Treatment-Resistant Blunted HPA Activity, but Reversible Cardiovascular Stress Reactivity in Young Women With Eating Disorders

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Previous research has provided evidence for a reduced neuroendocrine stress response in women with eating disorders (EDs). In the present study female in-patients with Anorexia and Bulimia nervosa were compared to female healthy controls (HC) before and after completing an in-patient treatment program. Salivary cortisol, alpha-amylase (sAA), heart rate response (HR), high-frequency heart rate variability (HF-HRV) and negative affective state were measured before, during and after exposure to the Trier Social Stress Test (TSST) at pre- and post-treatment. Patients with EDs (n = 13) showed significantly less ED symptoms at post-treatment. Compared to HC (n = 22), patients displayed a blunted cortisol stress response combined with overall attenuated sAA levels at pre-treatment. At post-treatment, the blunted cortisol stress response was still observable, while the differences in sAA responses disappeared. HR was attenuated at pre-treatment in patients, also indicated by a stronger HF-HRV throughout the TSST. These cardiovascular differences disappeared at post-treatment. Patients reported in general (pre- and post-treatment) more negative affect compared to HC. This study provides further evidences of a hypo-reactive hypothalamus–pituitary–adrenal axis (HPA) in patients with EDs which persists even after symptom recovery while initial low cardiovascular stress reactivity apparently can be restored by psychotherapy. Given the small sample size the findings have to be considered preliminary.

Keywords: eating disorder, anorexia nervosa, bulimia nervosa, cortisol, hypothalamus–pituitary–adrenal (HPA) axis, stress, Trier Social Stress Test (TSST), alpha amylase

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INTRODUCTION

Psychosocial stress is a potential risk factor for mental disorders (1–4). This includes the development and the maintenance of eating disorders (EDs), such that patients with EDs often experience negative life events or chronic stress before disease onset (5–11). Although not specific to patients with EDs, previous research suggests altered stress responsivity as a risk factor or disorder

sequel (12–14), with ED patients relatively consistently showing sympathetic nervous system (SNS) and hypothalamus–pituitary–adrenal (HPA) axis activity alterations (15).

More specifically, patients with Anorexia nervosa (AN) and Bulimia nervosa (BN) both show a blunted SNS activity compared to healthy controls (HC) under resting [(16), e.g. (17–19)] and acute stress conditions (17, 20–23). Recently, these SNS findings were confirmed by a meta-analysis (24).

In addition, patients with EDs also show dysregulations of the HPA axis, indicated by higher cortisol in urine, serum or saliva in patients with EDs (21, 23, 25–29). Regarding HPA axis reactivity, we previously reported that patients with EDs show a blunted cortisol response to acute psychosocial stress (19).

Only a few studies exist that investigated whether those neuroendocrine deviations normalize after successful treatment. One study compared heart rate and affective responses to a speech tasks in formerly anorectic, adolescent patients (30). The girls reported higher levels of negative affect, but did not show a blunted heart rate response during the stressor, suggesting a restored SNS response after recovery. Another study, investigated the cortisol awakening response (CAR) in underweight and weight-restored women with AN (31). The underweight patients showed an exaggerated CAR, whereas weight-restored patients had a CAR similar to HC, suggesting that weight gain may help to normalize HPA axis activity in patients with AN.

Together, these findings indicate that low cardiovascular activity and exaggerated CAR can be restored by effective treatment, while others (e.g. negative affect) seem to persist even after weight recovery/treatment. We did not find any studies in patients with AN or BN on the HPA axis reactivity after successful treatment. The aim of the present study was to characterize differences in stress responses between ED patients and HC over time. In-patients with AN or BN were investigated with regard to psychological and physiological responses to a standardized laboratory stressor [Trier Social Stress Test: TSST; (32)], before and after a long-term in-patient treatment program. In line with a transdiagnostic perspective (33, 34), which conceptualizes AN and BN as states on a continuum of psychopathology, patients with AN and BN were investigated as one group [cf. (19, 35, 36)].

Based on previous observations (19, 36) we predicted that patients with EDs will show blunted cortisol stress responses at pre-treatment compared to HCs. As described before (19) we suppose a long-term exhaustion of the HPA axis in patients with ED that makes individuals vulnerable for this and other psychological disorders. Therefore we expected that the HPA axis stress reactivity dysfunction persists in patients with ED even after treatment and leads to a blunted cortisol stress responses in patients compared to HC at post-treatment. Additionally, the patients were expected to improve in SNS responses comparable to HCs at post-treatment as already shown earlier [e.g. (30)]. Current studies showed that the HPA does not habituate, if a stress protocol is repeated weeks later or the stress inducing tasks are slightly altered (37–39). However, these studies used special forms of the TSST, protocols similar to the TSST and a time interval of 24 hours or 10 weeks between the first and the second TSST session. Referring to these studies we predicted similar cortisol and SNS stress responses from pre- to post-treatment for the HC. Lastly, since strong responses to negative social feedback appear to persist beyond recovery in with EDs (30, 40, 41), we predicted a stronger negative affect response to the TSST in ED patients compared to HCs both before and after treatment.

METHODS

Participants

For the current report, only patients with AN or BN who completed an in-patient treatment and provided complete pre-treatment and post-treatment data were included. Further, as HPA axis dysfunctions are well-described in post-traumatic-stress disorder, borderline personality disorder, and schizophrenia (42, 43), patients with EDs fulfilling the criteria of at least one of those diagnoses were excluded. Participants with previous TSST exposure and participants who did not refrain from physical exercise or eating one hour before testing were excluded as well. In contrast, smoking (44) and use of oral contraceptives or estrogene–progesterone combination medication to prevent low bone density (45, 46) were permitted. All patients were recruited from the Christoph–Dornier Clinic for Psychotherapy in Münster (Germany) and the Department of Psychosomatic Medicine and Psychotherapy, LWL-University Clinic in Bochum (Germany). Both clinics are specialized in the treatment of EDs. Weight restoration, regaining of normal eating habits, and reduction of bulimic symptoms like vomiting, intensive exercises, or abuse of laxative medication were achieved by an in-patient treatment program according to the national guidelines for the diagnosis and treatment of EDs (47). This treatment program contains elements of cognitive behavioral therapy (CBT) and psychodynamic therapy. It aims to restore healthy eating and reaching a healthy body weight by structuring and accompanying the patients during breakfast, lunch and dinner. A personalized treatment plan was created for each patient based on the processes that appear to be maintaining the eating problem. Information about nutrition, cognitive restructuring, mood regulation, psychodynamic conflicts and relationship problems, social skills, body image concern, self-esteem, and relapse prevention were covered.

Participants of the HC group were physically and mentally healthy, medication-free (except of oral contraceptives) female students with a BMI within the normal range (18.5–26 kg/m^2). They were recruited at the Universities of Bochum and Münster. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Faculty of Psychology, Ruhr University Bochum.

A total of 28 patients (range of age: 15–46) and 26 healthy controls (range of age: 18–37) were recruited (19). For the current study, complete data are available for 13 patients (range of age: 18–29) and 22 healthy controls (range of age:

18–46). In more detail, at pre-treatment, $n = 18$ in-patients with AN and $n = 10$ in-patients with BN were recruited who fulfilled the diagnostic criteria of AN or BN according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000). Ten AN patients and five BN patients terminated the treatment program or their participation in the study before the second assessment and thus had to be excluded from analyses, resulting in a final patient sample of $n = 13$ (AN: $n = 8$, BN: $n = 5$). ED patients were diagnosed on average shortly before entering treatment. Of the initial 26 healthy female control participants, $n = 3$ dropped out of the study and $n = 1$ participant had to be excluded due to weight loss resulting in a BMI <18.5 kg/m^2.

Trier Social Stress Test (TSST)

The TSST was performed before and after the intervention as described by Kirschbaum et al. (32). It has been shown to be effective in eliciting HPA axis and SNS responses and negative affect (48–50). In short, participants were asked to convince a panel of judges that they were the perfect candidate for a job opening in their 'dream occupation'. After a five minute preparation period, participants were asked to talk for a duration of 5 min exclusively about job-relevant personality traits while refraining from reciting application material information. If the participant finished her speech in less than 5 min, pre-formulated questions were asked. During the subsequent 5 min, the participants were asked to count backwards in steps of 17 from 2,043 as fast and as accurately as possible. Whenever the participant made a mistake, she had to start over at 2,043. Both members of the committee were dressed in white lab coats and acted in a neutral manner. All participants had to attend to the TSST before and after treatment. To reduce habituation, the post-treatment TSST was conducted by different panel members and a different subtraction task was used (counting backwards in steps of 27 from 3,074). No other changes were made to the TSST protocol.

Saliva Sampling and Biochemical Analyses

Saliva samples were obtained using Salivette sampling device (Sarstedt, Nümbrecht, Germany) to assess free salivary cortisol and salivary alpha-amylase (sAA) as HPA axis and SNS markers, respectively (51). Samples were collected one minute before (−1) and one (+1), ten (+10) and twenty-five (+25) minutes after each TSST. Cortisol concentrations were measured using a commercially available immunoassay with chemiluminescence-detection (IBL-Hamburg, Germany). Salivary alpha-amylase activity was measured using a quantitative enzyme kinetic method, as described earlier (51). Inter- and intra-assay coefficients of variation were below 10% for both assays.

Autonomic Assessment

HR and HRV were assessed as indicators of autonomic changes using the Polar watch system (RS800CX, Polar, Finland) for heart-beat monitoring. This system has been shown to have high reliability and validity (52, 53). Spectral analysis of HRV was performed with the Polar Pro Trainer 5 Professional Training Software, based on inter-beat intervals (R-R intervals). The software extracts HRV in various frequency bands and expresses it as ms^2. Frequency domain variables were derived from HR measurements during a time span of 5 min before the TSST (baseline) and during the first 5 min of the TSST (54). HRV was assessed for both TSSTs, pre- and post-treatment. We concentrated only on high-frequency HRV (HF-HRV, 0.15–0.4 Hz) as it is thought to reflect cardiac vagal function by representing the respiratory sinus arrhythmia, thus indicating parasympathetic activity.

Assessment of Affect

Participants filled out the *Positive and Negative Affect Schedule* [PANAS; (55, 56)] at arrival at the laboratory, shortly before and immediately after cessation of the TSSTs and 10 and 25 min after the TSSTs. The PANAS is a reliable and valid measure for current affective state (57). It consists of 10 items for positive (e.g., interested, enthusiastic) and negative affect (e.g., upset, ashamed) which are rated on a five-point scale (1 = "very slightly or not at all", 5 = "extremely"). Average scores for positive and negative affect were calculated.

Procedure

All participants underwent a diagnostic examination using the German versions of the *Structured Clinical Interview for DSM-IV, Axis 1* [SCID-I; (58)], the *Beck-Depression-Inventory* [BDI; (59)], the *Symptom-Checklist-90-Revised* [SCL90-R; (60)] and the *Eating Disorder Examination-Questionnaire* [EDE-Q; (61)]. The SCID was administered by trained clinical psychologists. All patients were in-patients and were offered study participation the day of or the day after admission. The patient data were collected after admission to the clinic and before the start of treatment (pre-treatment), and between the end of treatment and before discharge from the clinic (post-treatment). Assessment times for HC were synchronized. The second data collection took place on average 8.47 (SEM: ± 1.8) weeks (range: 2–58 weeks) after the first assessment.

Each assessment involved two days of participation, for a total of four study days. On the first pre-treatment study day, participants provided informed consent as well as information pertaining to their menstrual cycling phase and responses to questionnaires. On the second day, participants were exposed to the TSST in the hospital. The TSST was administered in the afternoon between 2pm and 5pm to minimize between-participant variation in pre-TSST baseline cortisol levels (62). After arrival at the lab, participants were seated in a quiet room. The Polar watch was fitted and started to record HR and HRV continuously until the end of the test day. Additionally, participants answered the PANAS for the first time. Subsequently, a first saliva sample was obtained and the PANAS was answered for the second time. Next, the participants were exposed to the TSST and immediately afterwards, a post-TSST saliva sample (+1 min) and PANAS self-report were collected. Two more (+10 min, +25 min) saliva samples and PANAS self-reports were obtained subsequently. This procedure was repeated at post-treatment, except for omission of informed consent. A debriefing of the TSST was conducted at the end of post-treatment assessment only.

Statistical Analyses

Demographic and descriptive variables were investigated for group differences and changes over time by Pearson's Chi-square test, Student's *t*-test for independent samples and paired-samples *t*-test, respectively. All data were tested for normal distribution with Kolmogorov–Smirnov test (K–S test). In case of a significant K–S test, data were log-transformed and the subsequent statistical analyses were performed with the transformed data. Area under the curve [AUC, (63)] was calculated with respect to increase (AUCi) for the neuroendocrine variables (cortisol and sAA). Cortisol responders to the TSST were defined as showing a 1.5 nmol cortisol increase between baseline and 10-minute post-stress value as recommended (64). Analyses of variance (ANOVA) for repeated measures were performed on cortisol and sAA levels, on PANAS scores, HR, and HRV to reveal possible effects of time (e.g., four cortisol time points), group (ED, HC), treatment (pre-treatment, post-treatment) and the respective 2-way interaction and 3-way interaction. Greenhouse–Geisser adjusted *p*-values are reported in case of violation of the sphericity assumption. Due to potential effects on HPA axis reactivity, analyses pertaining to cortisol indices were repeated controlling for smoking, use of oral contraceptives and disease duration (62), i.e., univariate and repeated-measures ANCOVAs were computed. Statistical analyses were performed using IBM SPSS 25 (Chicago, IL) for Mac OS X. Level of significance was defined as $p < .05$. Effects with $p < .10$ were interpreted as trends.

RESULTS

Sample Characteristics

Sample characteristics are summarized in **Table 1**. Patients with EDs and HC did not differ in age and body height, while BMI was significantly lower in patients both at pre-treatment ($t_{33} = 4.9$, $p < .001$) and post-treatment ($t_{33} = 2.8$, $p = .008$). Comparing pre- and post-treatment BMI and EDE-Q scores in patients only, however, revealed that ED patients showed a significant increase in weight ($t_{12} = 4.8$, $p < .001$) and a significant reduction in ED symptoms ($t_9 = 4.3$, $p = .002$), reflecting treatment success. The two groups did not differ in smoking behavior, average cigarettes per day, average days between pre- and post-treatment testing, menstrual cycle phase, or intake of oral contraceptives (all *p*s >.05).

TABLE 1 | Means and standard error of means for different descriptive variables for each group.

Variable	ED Patients (n = 13)	HC (n = 22)	*t*-test
Age (years)	21 (± 1.3)	23.1 (± 1.1)	$t_{33} = 1.2$, $p = .22$
Height (cm)	165 (± .01)	169 (± .01)	$t_{33} = 1.7$, $p = .10$
Weight (kg):			
pre-treatment*	47.1 (± 2.5)	62.1 (± 1.9)	$t_{33} = 4.8$, $p < .001$
Patients with AN	42.5 (± 2.8)		
Patients with BN	54.5 (± 2.4)		
post-treatment*	53.5 (± 2.0)	62.3 (± 1.9)	$t_{33} = 3.0$, $p = .005$
Patients with AN	51.4 (± 2.7)		
Patients with BN	56.9 (± 2.9)		
BMI (kg/m^2):			
pre-treatment*	17.2 (± .80)	21.9 (± .60)	$t_{33} = 4.9$, $p < .001$
Patients with AN	15.5 (± .75)		
Patients with BN	19.8 (± .48)		
post-treatment*	19.5 (± .52)	21.9 (± .59)	$t_{33} = 2.8$, $p = .008$
Patients with AN	18.7 (± .61)		
Patients with BN	20.8 (± 64)		
EDE-Q:			
pre-treatment*	4.3 (± .29)	.61 (± .11)	$t_{26} = -12.5$, $p < .001$
post-treatment*	2.9 (± .36)	.49 (± .12)	$t_{27} = -8.0$ $p < .001$
Smoking (n):	4	4	$\chi^2_1 = .73$, $p = .40$
cigarettes per day	10.5 (± 2.1)	7.6 (± 6.0)	$t_7 = -.81$, $p = .45$
Days between testing	56.4 (± 16.8)	64.8 (± 18.2)	$t_{32} = .30$, $p = .76$
Weeks between testing	7.7 (± 2.4)	8.91 (± 2.6)	$t_{32} = .30$, $p = .75$
Menstrual cycle (n):			
Pre-treatment	0	2	$\chi^2_1 = .19$, $p = .66$
Follicular	1	10	
Luteal			
Post-treatment			
Follicular	1	6	$\chi^2_1 = .22$, $p = .64$
Luteal	3	10	
Oral Contraception (n)	7	6	$\chi^2_1 = .002$, $p = .97$

Asterisks indicate a significant group difference.

Cortisol Stress Response

Salivary cortisol levels are shown in **Figure 1**. A mixed 2 × 4 × 2-factorial ANOVA for repeated measures with *Treatment* (2) and *Time* (4) as within-subjects factor and *Group* (2) as between-subjects factor revealed a significant effect of Time ($F_{3/99} = 7.1$, $p < .001$) and Group ($F_{1/33} = 2.7$; $p = .10$), as well as a significant Time-by-Group interaction ($F_{3/99} = 5.1$; $p = .004$), reflecting an increase in cortisol levels in response to the TSST in the HC group and a blunted response observed in ED patients. This pattern persisted over time, indicated by a lack of Treatment-related effects (Treatment: $F_{1/33} = 1.5$; $p = .27$; Treatment-by-Time: $F_{3/99} = 1.6$; $p = .19$; Treatment-by-Group: $F_{1/33} = 1.3$; $p = .26$; Treatment-by-Time-by-Group: $F_{3/99} = .51$; $p = .67$). This finding was further corroborated by a mixed 2 × 2-factorial ANOVA for repeated measures on AUCi values with *Treatment* (2) as within-subject factor and *Group* (2) as between-subject factor. This analysis revealed a significant main effect of Group ($F_{1/33} = 5.8$, $p = .02$), indicating higher cortisol output above baseline (AUCi) in response to the TSST in HCs compared to ED patients, and again no treatment-related effects (Treatment: $F_{1/33} = 1.6$, $p = .22$; Treatment-by-Group: $F_{1/33} = .01$; $p = .91$). Of note, the significant Time-by-Group interaction on repeatedly-measured salivary cortisol concentrations was even seen when smoking ($F_{3/96} = 4.2$, $p = .008$), menstrual cycling phase ($F_{3/96} = 4.1$, $p = .008$), comorbidity with depression ($F_{3/93} = 4.2$, $p = .008$), duration of illness in months ($F_{3/93} = 3.8$, $p = .01$) or symptom severity as measured by the EDE-Q ($F_{3/75} = 3.6$, $p = .02$) were considered as covariates or the patients were divided into subgroups according to their differential diagnosis ($F_{6/96} = 2.9$, $p = .01$). Specifically, neither patients with AN nor patients with BN showed a cortisol response to the TSST at pre- and post-treatment.

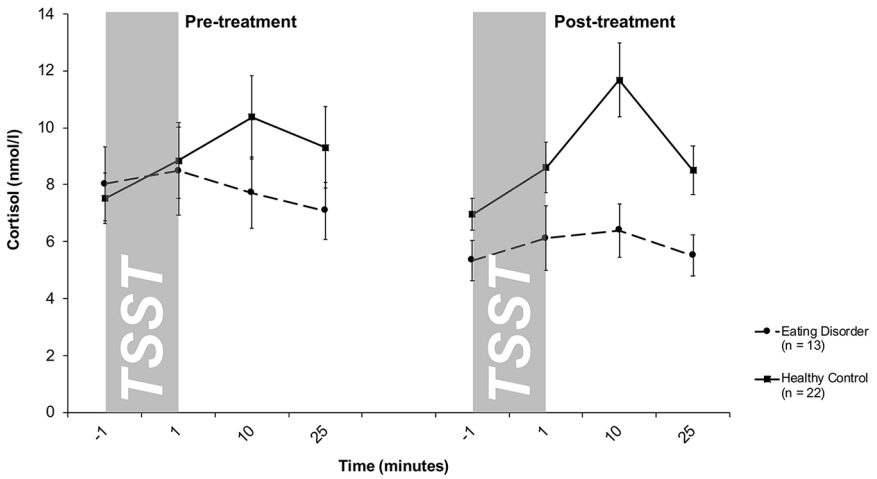

FIGURE 1 | Cortisol stress responses (means and standard errors) pre-treatment (left) and post-treatment (right) in patients with eating disorders and healthy controls (HC). At both pre- and post-treatment, only HC responded to the TSST with increases in salivary cortisol levels.

Alpha Amylase Stress Response

Salivary AA levels are presented in **Figure 2**. The mixed 2 × 4 × 2-factorial ANOVA for repeated measures revealed a significant main effect of Time ($F_{1.4/39.5}$ = 18.3, p <.001) and a significant Treatment-by-Group interaction effect ($F_{1/27}$ = 4.0, p = .05), indicating changes in differences between both groups between pre- and post-treatment. Specifically, at pre-treatment, overall higher sAA levels were obtained in HCs compared to ED patients, while both groups showed comparable sAA responses at post-treatment. There were no further interaction effects (Time-by-Group: $F_{1.4/39.5}$ = 2.2; p = .13; Treatment-by-Time: $F_{3/81}$ = 2.0; p = .12; Treatment-by-Time-by-Group: $F_{3/81}$ = .47; p = .70) as well as no additional main effects (Group: $F_{1/27}$ = 1.0; p = .31; Treatment: $F_{1/27}$ = 2.1; p = .65). This result was confirmed by a mixed 2 × 2-factorial ANOVA for repeated measures on AUCi values with *Treatment* (2) as within-subject factor and *Group* (2) as between-subject factor revealing a main effect of treatment ($F_{1/26}$ = 4.3; p = .04), indicating higher AUC_i in HCs in

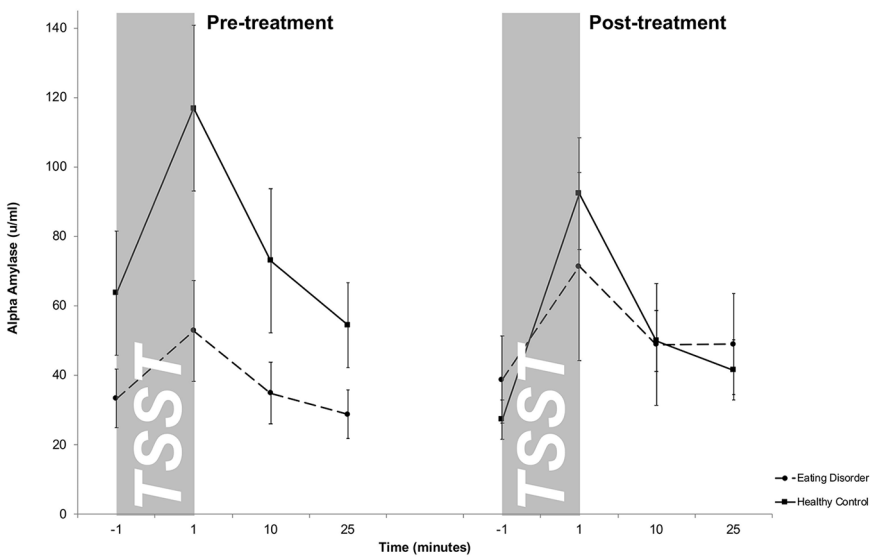

FIGURE 2 | Salivary alpha-amylase (sAA) stress responses (means and standard errors) pre-treatment (left) and post-treatment (right) in patients with eating disorders and healthy controls (HC). While HCs showed an overall stronger salivary alpha amylase output pre-treatment, both groups displayed similar sAA responses post-treatment. For illustrative purposes raw values instead of log-transformed values are shown.

contrast to patients at pre-treatment and a missing group difference at post-treatment. The slight decrease in peak sAA levels from pre- to post treatment within HCs turned out to be not significant ($t_{18} = -1.4$, $p = .17$) on AUCi.

Heart Rate Response and Variability

The descriptive results of HR and HRV are presented in **Table 2**. Using a mixed 2 × 2 × 2 ANOVA for repeated measures with *Treatment*, *Time* and *Group* as factors, we found for HR a significant main effect of Treatment ($F_{1/25} = 7.4$; $p = .01$), Time ($F_{1/25} = 64.8$; $p < .001$), Treatment-by-Group interaction ($F_{1/25} = 7.5$; $p = .01$), Time-by-Group interaction ($F_{1/25} = 5.4$; $p = .03$), and a trend for the Treatment-by-Time-by-Group interaction ($F_{1/25} = 3.7$; $p = .06$). These findings suggest an increase in HR response strength from pre-treatment to post-treatment in patients with EDs, while the HR-responses for the HCs remained stable. Post-hoc analyses confirmed that patients showed lower HR at pre-treatment during baseline ($t_{28} = 4.7$, $p < .001$) and TSST ($t_{28} = 1.7$, $p = .05$) than HC, although the group difference during the TSST failed to reach Bonferroni corrected level of significance ($p = .0125$). During post-treatment, HR results approximated between both groups during baseline ($t_{28} = 1.5$, $p = .15$) as well as during the TSST ($t_{28} = 2.0$, $p = .06$). Additionally, patients with EDs showed overall higher vagal activity as assessed by HF-HRV indicated by a significant Group difference ($F_{1/25} = 4.2$; $p = .05$) and a trend for the Treatment-by-Group interaction effect ($F_{1/25} = 2.9$; $p = .10$). Except of Time ($F_{1/25} = 8.9$; $p < .01$) there was no further effect (all ps > .05).

TABLE 2 | Means and standard error of means and the results of ANOVA for repeated measures of heart rate response and the two components of heart-rate variability (HRV).

Cardiac Marker	Measurement	Eating Disorder	Healthy Control
Heart Rate Response (beats/min)	**Pre-treatment**		
	Baseline	63.5 (± 3.1)	80.4 (± 2.1)
	Stress	90.2 (± 6.0)	100.9 (± 3.5)
	Post-treatment		
	Baseline	75.7 (± 3.8)	81.6 (± 2.1)
	Stress	117.0 (± 10.3)	98.8 (± 3.8)
HF-HRV (ms^2) (vagal activity)	**Pre-treatment**		
	Baseline	2609.4 (± 774.0)	793.7 (± 161.6)
	Stress	1475.2 (± 608.8)	455.3 (± 57.4)
	Post-treatment		
	Baseline	1299.9 (± 611.1)	821.4 (± 196.6)
	Stress	781.9 (± 282.9)	602.8 (± 282.9)

Affective Stress Response

Negative affect scores of the PANAS are shown in **Figure 3**. A 2 × 5 × 2-factorial ANOVA for repeated measures with *Treatment*, *Time*, and *Group* as factors on the negative affect scale of the PANAS showed a significant main effect of Treatment ($F_{2/32} = 13.2$, $p = .001$), Time ($F_{2.1/68.3} = 8.8$, $p < .001$), Group ($F_{1/32} = 18.3$, $p < .001$) and a significant Treatment-by-Time interaction effect ($F_{1.8/56.04)} = 6.6$, $p = .004$) (all other effects p > .05). Together, this suggested that ED patients showed higher negative affect scores both at pre- and post-treatment compared to HCs. Compared to pre-treatment, post-treatment responses were less dynamic in both groups. HCs showed on a trend level a lower increase in negative affect after TSST at post-treatment compared to pre-treatment ($t_{21} = 1.6$, $p = .1$).

DISCUSSION

The present study investigated the neuroendocrine, cardiovascular, and emotional stress response to a psychosocial laboratory stressor in patients with EDs before and after an in-

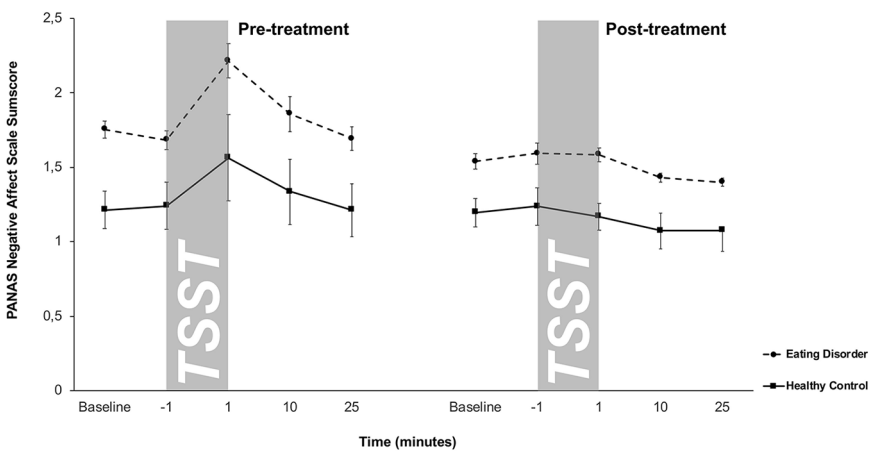

FIGURE 3 | Responses in negative affect to stress (means and standard errors) pre-treatment (left) and post-treatment (right) in patients with eating disorders and healthy controls (HC). Patients with eating disorders showed significantly higher negative affect scores both pre- and post-treatment, while both groups displayed similar blunted negative affect responses at post-treatment.

patient treatment program. To our knowledge, this is the first study in which pre- and post-treatment effects on stress reactivity were investigated in patients with AN and BN and compared to responses in HCs. We observed the following patterns:

1. In-patients with EDs showed a blunted cortisol stress response to the TSST before as well as after a treatment program compared to HCs. There was no evidence for cortisol stress response habituation in HCs.
2. In contrast to HC, patients showed significantly lower sAA levels, lower HR, and higher HF-HRV before treatment. These differences were diminished at the end of the treatment due to increases in patients' response strength and lack of habituation in HCs.
3. Patients with EDs reported overall more negative affect compared to HC. This was during pre-treatment, when all participants showed a significant increase in negative affect responses to the TSST, as well as post-treatment, when responses were blunted in both groups.

Although ED patients gained weight and reported reduced core symptoms of AN and BN after treatment, the blunted cortisol response to the TSST in ED patients observed at pre-treatment persisted after treatment. This indicates that HPA axis dysfunctions in these patients may not recover along with disease symptom reduction which is in line with findings in patients with BED as well (65).

This raises the question whether patients with AN and BN may suffer from a long-term exhaustion of the HPA axis due to rigid fasting being a constant metabolic trigger for cortisol release (66, 67). This exhaustion would then become particularly apparent when a patient's HPA axis is challenged by exposure to a psychosocial stressor. Alternatively, blunted HPA axis reactivity may also precede the development of an ED, i.e., represent a pre-morbid vulnerability factor (16, 17). This would explain why HPA axis reactivity dysfunctions are not affected by treatment. Recently, Monteleone et al. (68) found that childhood trauma-exposed ED patients show significantly reduced stimulated HPA axis activities in contrast to non-trauma-exposed patients, suggesting that early experiences affect the reactivity of the HPA axis in patients with ED. It was also shown in outpatients with AN and BN with an average BMI in the normal range that heightened TSST-induced cortisol secretion is associated with high attachment anxiety or avoidance which might result from childhood trauma (35). Vaz-Leal et al. (36) demonstrated also blunted cortisol stress responses to the TSST in patients with AN and BN (considered as a single group in contrast to HCs) which is in line with our findings. Additionally, they showed that this blunted cortisol response pattern is mainly associated with binge-purging eating behavior as seen typically in BN but sometimes in AN as well. Of note, current studies did not assess long-term effects on HPA axis reactivity. Thus particularly studies in patients for whom treatment success persists over months and years are needed [e.g. (6, 7, 69)]. Such studies would help differentiate between delayed HPA axis recovery and persistence of HPA axis reactivity alterations.

Our results of a blunted cortisol response to the TSST at pre- and post-treatment do not correspond with the results of a recent meta-analysis (24), which showed that patients with EDs and HC do not differ in cortisol stress levels, neither before nor after exposure to an interpersonal laboratory stress task. However, in the meta-analysis, the tests of heterogeneity for cortisol levels before and after a stress task were significant, indicating that the included studies varied markedly in terms of the observed cortisol stress response. These variations might be due to differences between studies with regard of the samples, the methods of cortisol assessment, and in sample sizes. Future studies should use more standardized protocols to measure cortisol responsivity to provide the opportunity for future meta-analyses with more homogeneous studies (50, 70).

Another interesting issue is the response of HC to the second TSST. At post-treatment, the cortisol reactivity of HC was comparable to the results at pre-treatment, i.e. under the conditions of our study there was no habituation to the TSST. This finding is in line with the results of Petrowski et al. (39) who exposed healthy participants to the TSST four times with an interval from 24 h to ten weeks. Although the authors reported decreases in the cortisol responses within 24 h, there were no differences in the HPA response ten weeks later. Other studies using stress protocols similar to the TSST found similar results (37, 38). Usually, it was sufficient if the tasks were slightly altered, e.g. by replacing the committee, changing the topic of the free speech, or the arithmetic task, as we did. These small alterations seem to reduce the predictability of the task and thus, increase the uncontrollability, which, in turn, is a trigger of HPA activity (49). Thus the TSST can be used at different times in the same participants as far as there is a sufficiently long time span between the testing sessions and some alterations in the to be conducted tasks are implemented.

We observed a diminished cardiovascular activity seen at pre-treatment and measured by sAA, HR and HF-HRV in patients with EDs compared to HC. This finding is in line with previous reports of blunted cardiovascular stress reactivity in ED (24). Our data further support the idea that post-treatment, recovered AN and BN patients show a cardiovascular stress reactivity similar to that of HC. As such, our results expand the finding of Miller et al. (30) to include patients with BN. Taken together, it appears that—in contrast to persistent HPA axis dysregulation—blunted cardiovascular stress reactivity can be restored alongside of ED symptom reduction.

As expected, for all assessed cardiovascular parameters, we found no habituation upon second stress exposure in HC. There are studies that used the TSST or TSST-similar stress protocols that showed no significant signs of habituation in salivary alpha-amylase, HR and HRV, if the same protocol is repeated in intervals of three to ten weeks (37, 38, 71). Our data in HC confirm these findings suggesting that the SNS shows uniform activation patterns in response to repeated exposure to psychosocial stress.

Finally, our data show that the higher negative affective state in patients with EDs compared to HC before treatment remained even after significant weight gain and restoration of eating behavior. The meta-analysis of Monteleone et al. (24) also confirmed that patients with EDs have greater negative affect before and after attending a stress protocol. This effect is discussed in light of high attachment anxiety or avoidance (35). Together these observations indicate that the affective response in patients with EDs remains stress-sensitive and negative even after successful treatment.

Interestingly, comparing pre- and post-treatment negative affect independently of group revealed that participants did not show any negative affective response to the TSST at post-treatment. We interpret this result as a sign of psychological habituation to the TSST. Participants were already familiar with this stress protocol at post-treatment and therefore, the test might have lost its surprising effect of novelty and seem to the participants predictable and therefore controllable (38, 49).

To our knowledge, this is the first study that investigated neuroendocrine, cardiovascular and psychological stress responses in patients with EDs before and after an in-patient treatment program and that used the TSST, as already done in other stress related disorders (72–74). The main limitation of our study is the small sample size, especially within the patients group. This threatens the external validity of our study and general conclusions should be drawn cautiously. Our results should be seen as preliminary results and need to be replicated. Indeed, the meta-analysis of Monteleone et al. (24) revealed that studies investigating patients with EDs are often based on small sample sizes. One reason might be the low prevalence of EDs. In Germany a 12-month prevalence of 1.1% for AN and 0.3% for BN in adult women is given (75). This makes it difficult to recruit patients. Beside of this, patients with EDs show a low self-esteem (5). Researchers need to be patient and cautious to motivate these patients to participate in studies with a social evaluation stress task. In sum, future studies are warranted confirming these findings in a larger sample. Additionally, it would be desirable to proof these results across patient groups when separated by ED diagnosis. Further, longitudinal studies with more frequent assessment time-points (e.g. before, during and after treatment) along with expanded assessments until at least 6 months after completion of treatment would provide further valuable insights. To clarify whether the observed HPA changes are a cause or a consequence of the ED, comparable studies are needed in high risk populations (e.g., young women on a diet), ill patients, patients currently under treatment, freshly recovered patients, and long-term recovered patients. Finally, assessment of eating behavior (e.g., daily caloric intake) and gonadal steroids are recommended for future studies to identify potential moderator and mediator variables.

Taken together the present study provided further evidence of a hypo-reactive HPA axis and enhanced negative affect response in patients with AN and BN. It could be demonstrated that both alterations persist even after successful treatment. In contrast, we show that low cardiovascular stress reactivity can be restored in patients with EDs after treatment, suggesting a differential response dynamic of the SNS versus HPA axis. Additionally, it was shown that a repeated TSST presentation is a promising tool to evaluate and detect alterations in stress responsive systems. If further studies confirm our preliminary results and show also that a hypo-reactive HPA axis and an enhanced negative affect stress response are typical patterns or a pre-morbid vulnerability factors for ED, this could help to understand the complex etiology of EDs. This could pave the way to detect high risk individuals and offer them early treatment programs as prophylaxis. Therapeutic interventions that help to restore a normal HPA axis response pattern in these patients need to be developed.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Faculty of Psychology—Ethics committee, Ruhr University Bochum. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SeH: Design, organization and conduction of the study. The paper was written mainly by SeH. SV: Support and recommendations for the design of the study and the recruitment of patients. Additionally SV also read and corrected the final version of the paper. JW: The neuroendocrine data were analyzed in her laboratory. Additionally, JW also read and corrected the final version of the paper especially with regard to the language StH: Support and recommendations for the design of the study and the recruitment of patients. Additionally StH also read and corrected the final version of the paper OW: Financial Support and recommendations for the design of the study. Additionally OW also read and corrected the final version of the paper.

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BRIEF RESEARCH REPORT
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Severity and Endurance in Eating Disorders: An Exploration of a Clinical Sample From Chile

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Introduction: One in five patients with eating disorders (EDs) may take a lasting course. It has been proposed that this enduring group exhibits increased severity, such as low treatment response, severe symptomatology, and poor quality of life. However, there is no consensus defining this group. Moreover, most of the literature comes from high-income societies and may not apply to developing countries.

Aims: This study aimed to evaluate the association between endurance (length of ED) and severity (previous treatments, hospitalizations, medical complications, symptomatology and clinical impairment) in individuals with EDs from Chile. In addition, it aimed to explore the association between endurance and delays seeking specialized treatment.

Methods: Forty-one women with EDs (16 with anorexia nervosa, 11 with bulimia nervosa, 10 with binge eating disorder and 4 with other specified EDs) completed a social-demographic survey, the Eating Disorders Examination Questionnaire, and the Clinical Impairment Assessment. Also, Body Mass Index, length of ED, and complications were retrieved from participants' medical records. Spearman correlation coefficient and linear regression were used to explore the association between length of ED and measures of severity and treatment seeking behavior.

Results: There was no significant association between endurance (length of ED) and measures of severity. There was a significant association between length of ED and delays seeking specialized treatment (r_s=0.72; p<0.01). Regression indicated that for each month in delay visiting a specialized ED treatment team, the ED duration increased by 0.87 months (F(1,38)=75.93; p<0.01; R^2= 0.66).

Discussion: The findings suggest that in developing countries, where specialized treatment access is not widespread, defining SEED solely by the length of illness may not be clinically significant, and other criteria (e.g., timely access to evidence-based treatments) should be considered.

Keywords: severe and enduring eating disorders, chronicity, access to treatment, eating disorder complications, clinical impairment, quality of life

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INTRODUCTION

Eating disorders (EDs) can take a lasting course over time, which is usually associated with higher resistance to usual treatments and a more significant overall impact on individuals who suffer from it. It has been reported that 20% of cases with anorexia nervosa (AN) and 23% of patients with bulimia nervosa (BN) would take this course (1, 2).

There is growing interest in scientific literature to define chronicity in EDs. The first approach to the concept of severe and enduring EDs (SEED) appeared in 1999 when the "severe and enduring" descriptor for mental illness (SEMI) was published by the National Service Framework of the United Kingdom to direct resources to patients suffering from long term severe disorders. It was defined as: "people with recurrent or severe and enduring mental illness, for example, schizophrenia, bipolar affective disorder or organic mental disorder, severe anxiety disorder or severe eating disorder, have complex needs which may require the continuing care of specialist mental health services working effectively with other agencies" (3). Later, it was proposed for EDs, suggesting that a mental disorder that has a mortality rate several times higher than schizophrenia, should not be excluded from disorders carrying the severe and enduring label. Robinson described the term severe and enduring eating disorder (SEED) for patients with severe and prolonged disease in bulimia nervosa with the suffix of BN. and those with anorexia nervosa, SEED-AN (4, 5). However, there is no consensus on how severe or long-lasting the disease should be to be labeled as SEED.

In his systematic review and critical analysis of studies concerning lasting forms of AN, Broomfield found that the duration of the disease was the most common criterion used to define what we understand for SEED (used in 84% of the studies analyzed), with a presentation of an AN for 7 years as the most commonly used duration criterion. The second most common criterion was the number of failed treatment attempts, but most articles did not adequately develop this point. Other criteria that defined severe and prolonged AN were body mass index, the persistence of behavioral or cognitive patterns of AN, alteration of various areas of life, low motivation for recovery, and presence of severe symptoms (6).

Hay and Touyz propose an alternative definition of SEED, using the following criteria: (a) a persistent state of dietary restriction, underweight, and overvaluation of weight/shape with functional impairment, (b) duration of > 3 years of AN and (c) exposure to at least two evidence-based treatments appropriately delivered together with a diagnostic assessment and formulations that incorporates an assessment of the person's eating disorder health literacy and stage of change (7).

Even though most of the research has focused on severe and enduring forms of AN, lasting courses are common in other EDs, such as BN (2). In addition, ED diagnosis is highly unstable, and between 27% and 34% of individuals with AN may crossover to BN within 6 to 7 years (8, 9), and between 15% and 31% of AN may switch to ED not otherwise specified (9). Thus, a more general approach that conceptualizes EDs' course in terms of stages has been developed, proposing that not only AN, but also BN's course (and potentially BED) could be mapped into the following stages: high risk, prodromal, full syndrome, and severe and enduring (10).

The SEED concept assumes that EDs with an enduring course are associated with increased severity (11). In fact, research shows that physical complications are often associated with long-lasting EDs. Almost every organ system can be affected secondary to chronic malnutrition, bingeing, and/or purging behaviors, as well as those individuals with marked overweight or weight fluctuations, with frequent musculoskeletal, endocrine/reproductive, cardiovascular, hematological, gastrointestinal, renal, neurologic, and hydro-electrolyte disturbances, among others (12–15). There is some evidence that this group of patients is more likely to resist change to their ED, though they might be willing to reduce the immediate physical risk. Therefore, the approach to the treatment is crucial, addressing physical needs in the first place, providing compassionate bio (nutritional) psychosocial support (16).

It is common for people with EDs to experience a significant impact of the disorder on their life and close environment (17). In the case of SEED, studies show a more considerable disturbance in the quality of life. Virtually all personal fields are affected, such as physical and psychological integrity, family and social networks, functional level, personal and family economics (11, 18). It is common to observe that there is a variable degree of disability attributable to the disorder and sometimes also to the treatments that have been attempted without success (18).

Most of the literature described above comes from studies carried out in high-income, western societies. However, there is a lack of information about long-lasting forms of EDs coming from other parts of the world. Thus, it is unclear if the current state of the art applies to other societies, such as Latin America. In this context, the study aimed to evaluate the association between endurance, measured as the length of the ED, and clinical characteristics that are usually considered measures of severity, such as the number of previous treatments and hospitalizations for the ED, number of medical complications, ED symptoms and clinical impairment in individuals with ED from Chile. In addition, we explored the association between length of the ED and delays seeking specialized treatment. To our knowledge, this is the first study exploring SEED in the Latino American population.

MATERIALS AND METHODS

Design and Participants

The current research is a cross-sectional exploratory design study of patients who were referred to an Eating Disorder Unit in Santiago, Chile. Participants were recruited from the outpatient specialist eating disorder treatment program. As a part of the routine care, all patients were initially screened by a trained clinician to determine ED symptomatology according to the DSM-5. After completing this clinical interview, they were asked if they wanted to participate in the study. Those who expressed

interest were contacted by a researcher who explained the research further and sought informed consent. Inclusion criteria were being 18 years old or older with a current ED diagnosis. Those who had active substance abuse (information obtained in the clinical interview) were excluded.

Measures

The study was conducted using a set of three self-report measures completed by the participants under the supervision of a researcher (Social-Demographic Survey, EDE-Q, and CIA). Weight, height, and body mass index (BMI= weight (kg)/ [height (m^2)]) were evaluated by one of the authors under a nutritional assessment protocol, at the time of diagnosis. These anthropometric measurements were obtained on calibrated scales with the participants wearing underwear. Information about length of ED and medical complications (specifically, musculoskeletal, cardiovascular, endocrine/reproductive, gastrointestinal, dental, hydroelectrolytic, hematological, renal, and/or vitamin deficiencies) were retrieved by hand from medical records.

Social-Demographic Survey

Data on disease information, marital status, occupation, and educational level were assessed in an investigator-designed demographic survey.

EDE-Q

Eating Disorders Examination Questionnaire [EDE-Q v.6; (19, 20)] The EDE-Q 6th version is a 28-items measure assessing cognitive and behavioral features of ED. It has four subscales (dietary restraint, eating concern, weight concern, and shape concern) and a global score. The Spanish version adapted for Chile was used (Gaete, Lopez, manuscript in preparation). In the study sample, Cronbach's alpha for the global score = 0.95.

CIA

Clinical Impairment Assessment [CIA 3.0; (21)]: The CIA is a 16-item self-report measure designed to assess the ED's impact on psychosocial functioning, specifically on personal, cognitive, and social domains. The CIA has shown good reliability and validity (21). The Spanish version has been adapted to the Chilean population (22, 23). In the current study sample, Cronbach's alpha = 0.95.

Procedure

Patients who expressed interest and met the criteria to participate in the study were contacted by a team researcher and given details of the study. Participants who agreed to take part signed informed consent and completed the study questionnaires in person, in front of one of the researchers. Participants did not receive compensation. The Research Ethics Committee of the Faculty of Medicine of the Catholic University of Chile approved the study.

Statistical Analysis

Descriptive statistics were calculated to characterize the sample regarding demographic and clinical characteristics. Data distributions were inspected using histograms and Kolmogorov-Smirnov test of normality. Since none of the clinical variables exhibited a normal distribution, Spearman rho correlation was used to assess the association between length of ED and clinical variables (Previous treatments, hospitalizations, medical complications, delay visiting specialized ED treatment team, EDE-Q and CIA global scores). Statistical significance was adjusted for multiple testing, according to Bonferroni. Variables that were significantly correlated to length of ED were entered in a linear regression model to assess the extent to which these variables explained variations in length of ED. Bootstrapping based on 1000 bootstrap samples was carried out to obtain 95% confidence intervals for B in the linear regression. All analyses were conducted using SPSS v.26.

RESULTS

Forty-nine individuals with EDs joined the study. In order to reduce heterogeneity, it was decided to remove male participants and those with an uncommon diagnosis. Thus, data from 4 males (3 with other specified ED and 1 with binge eating disorders), 2 women with avoidant restrictive food intake disorder, and 2 women with unspecified ED were removed from the analyses, yielding a final sample of 41 female participants.

In the final sample (n = 41), participants' age ranged from 18 to 51 years (mean = 28.93; SD = 8.31). Most of the participants were single (n = 35; 85.40%), had university-level studies (n = 30; 73.20%), and were not working by the time of the assessment (n = 21; 51.20%). Participants' diagnosis were: anorexia nervosa

TABLE 1 | Participants' clinical characteristics.

	Min–Max	Mean (SD)	Median (IR)
Length of ED in months (n = 41)	12–317	119.27 (93.15)	77.00 (174)
Delay in visiting first specialized ED treatment team in months (n = 40)	0–306	86.40 (88.23)	51.50 (114.00)
Number of previous specialized treatments (n = 35)	0–9	2.00 (2.02)	1.00 (2.00)
Number of hospitalizations for ED (n = 38)	0–5	0.68 (1.17)	0.00 (1.00)
Number of medical complications (n = 41)	0–6	1.37 (1.67)	1.00 (2.00)
EDE-Q Global score (n = 41)	0–6	3.66 (1.48)	4.01 (2.00)
CIA Global score (n = 41)	0–46	30.49 (12.29)	34.00 (18.00)

Min, minimum; max, maximum; SD, standard deviation; IR, interquartile range; n, number of participants with valid data.

(n = 16; 39.00%), bulimia nervosa (n = 11; 26.80%), binge eating disorder (n = 10; 24.40%), and other specified ED (n = 4; 9.80%).

Participants' clinical characteristics are shown in **Table 1**. Length of the ED ranged from 1 to 26 years (specifically, 12.00 to 317.00 months). On average, participants first visited a specialized ED treatment team 7 years after experiencing ED symptoms for the first time (86.40 months), had 2 previous specialized treatments, and 0.68 hospitalizations for the ED. At the time of the assessment, participants showed an average of 1.37 medical complications (i.e., musculoskeletal, cardiovascular, endocrine/reproductive, gastrointestinal, dental, hydroelectrolytic, hematological, renal, and/or vitamin deficiencies), and obtained an average score of 3.66 on the EDE-Q and of 30.49 on CIA.

A significant direct association was found between the length of the ED and the delay in visiting for the first time a specialized ED treatment team ($r_s = 0.72$; $p < 0.01$; adjusted $p < 0.01$). The length of the ED was not significantly associated with the number of previous treatments for ED ($r_s = 0.20$; $p = 0.24$; adjusted $p = 1.00$), number of hospitalizations for ED ($r_s = 0.27$; $p = 0.10$; adjusted $p = 0.58$), number of medical complications ($r_s = 0.07$; $p = 0.65$; adjusted $p = 1.00$), EDE-Q global score ($r_s = 0.21$; $p = 0.20$; adjusted $p = 1.00$), nor with the CIA global score ($r_s = -0.05$; $p = 0.75$; adjusted $p = 1.00$).

Since the only variable showing a significant association with the length of the ED was the delay in visiting for the first time a specialized ED treatment team, only the latter was used as a predictor in the regression analysis. Results from the linear regression indicated that the delay in visiting for the first time a specialized ED treatment team significantly predicted variations in length of the ED ($F(1,38) = 75.93$; $p < 0.01$; $R^2 = 0.66$). Findings showed that the length of the ED increased by 0.87 months for every 1 month of delay in consulting to an ED specialized team ($B = 0.87$; 95% CI = 0.73–1.01; $\beta = 0.82$; $t = 8.66$; $p < 0.01$)[1].

DISCUSSION

By definition, individuals with SEED are thought as having more severe symptoms (11). However, most of the literature comes from studies carried out in high-income western countries, and it is unknown if the profile described for SEED applies to developing societies. In this context, the present study aimed to evaluate the association between endurance, measured as the length of the ED, and clinical characteristics that are usually used to describe severity in a sample of individuals with EDs from Chile. Contrary to our expectations, the study findings showed no significant association between length of the ED and number of previous ED treatments, number of hospitalizations for EDs, number of medical complications, ED symptomatology (assessed through the EDE-Q), and functional impairment (assessed through the CIA).

[1]To explore if the results had been distorted by the inclusion of data from participants with different ED diagnoses, all analyses were repeated in the subgroup with AN (n=16), yielding the same findings (data available upon request).

The findings are not in line with previous research. SEED patients are usually characterized as having multiple previous treatment failures, more physical complications, and poor quality of life (24). In addition, there is evidence of higher scores in global EDE-Q in SE-AN (defined as an AN lasting longer than 3 years), compared to a presentation of fewer than 3 years [Giardini, cited in (25)]. Considering that the most common criterion used to define SEED is based on illness duration, a significant association between length of ED and these variables was expected.

One possible explanation for the discrepant findings may relate to the study participants. Most of the literature in SEED has been carried out in AN. However, our sample includes participants with AN, BN, BED, and other specified ED. Even though we explored the results for AN and were similar to the findings exhibited for the whole sample, this analysis was underpowered, and therefore, it is not possible to be certain that the transdiagnostic approach used in the study did not affect the findings.

There is current discussion regarding the best approach to define SEED, and even though most studies use ED duration as a criterion, there is no consensus regarding a specific threshold to qualify as SEED, and regarding which other criteria should be used in addition to illness length (6). Moreover, the discussion has been largely based on experts' opinion, and empirically driven criteria are needed (26). In fact, findings from a study using empirical techniques to classify SEED suggest that the severity and endurance of the disease may not necessarily be correlated, and that other clinical aspects are essential to consider in the definition (27). This is in line with our findings, highlighting the relevance of avoiding relying solely on ED duration to define SEED, and avoiding assuming its link to severity.

In our study, the only variable that exhibited a significant association to length of the ED was the delay in visiting a specialized ED treatment team. Regression analysis indicated that for each month of delay consulting a specialized team for the first time, since first experiencing symptoms, the length of the ED increases by 0.87 months. This delay obtaining specialized treatment accounted for 66% of the variability in ED duration. It has been described in the literature a delay in specialized treatment for EDs (28). In countries where access to specialists is not widespread, primary care is carried out by non-specialists who may not see as necessary to ask about eating patterns in children, adolescents, or adult patients. In Chile, ED incidence is relatively low compared to other mental health disturbances (29), which has limited the allocation of resources for early detection and treatment. The Chilean health system is mixed, public, and private, with the public system being the one that takes care of the low income, senior citizens, and with a more significant disease burden population. Mental health service provision in Chile still lacks enough resources for addressing high prevalence psychiatric problems (30). EDs have not been adequately visualized as prevalent, severe, and capable of generating disability in young people, mostly because of the lack of studies of prevalence, course, and characterization of the

population suffering from these disorders in our country. In this scenario, people with EDs may find it difficult to access specialized treatment and may experience symptoms for long periods. However, as suggested by the study findings, this group of individuals may not represent a severe group and may not need a specifically tailored treatment.

These results may imply that, at least for countries in which specialized treatment for EDs is not widespread, defining SEED based only on ED duration is not adequate. Other criteria, such as the proposed by Hay and Touyz (7), which include the exposure to at least two evidence-based treatments appropriately delivered, may have more clinical utility.

Limitations

The findings of the study must be taken in the context of its limitations. First, the sample size is small. In addition, even though we removed data from uncommon diagnoses to reduce heterogeneity, participants' diagnoses were still diverse. In particular, it is unclear if the severe and enduring label should be applied to individuals with BED (31), so their inclusion could be questioned. Future studies may aim at having larger sample sizes, and at exploring the long-lasting ED patients' response to evidence-based treatments longitudinally.

CONCLUSION

In conclusion, the study found no evidence for an association between endurance, measured as the length of the ED, and measures of severity, such as the number of previous treatments and hospitalizations for the ED, number of medical complications, ED symptoms, and clinical impairment. The variation in ED duration was better accounted for by the delay in obtaining specialized ED treatment since the onset of symptoms. In a context where mental health treatment is not widely accessible, the finding highlights the need not to assume that endurance and severity are always linked, and to complement the duration criterion with others, such as previous exposure to evidence-based treatment, in order to identify SEED patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The study involved human participants and was reviewed and approved by Research Ethics Committee of the Faculty of Medicine of the Catholic University of Chile. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD, AG, and MV conceived the study. MV obtained ethics approval. MV, AG, and LL recruited participants and obtained data. LL organized the database. MD performed statistical analyses. All authors contributed to the article and approved the submitted version.

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Perspectives on Involuntary Treatment of Anorexia Nervosa

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Involuntary treatment of anorexia nervosa is an option in cases in which the patient's life or other people's lives are at risk or, in some countries, to prevent the deterioration of the illness. Involuntary treatment is often regarded as controversial and has been intensely debated, although typically with few references to documented knowledge. This paper provides a research perspective of the topic by examine data in the field of the involuntary treatment of anorexia nervosa to pinpoint present knowledge as well as areas demanding clinical action or research attention. The prevalence of involuntary treatment in general as well as specific measures is described and possible early markers of patients at risk of involuntary treatment are discussed. Studies including patients' perspectives of involuntary treatment show the complexity of this treatment, its initiation, and its consequences. To qualify future discussions, improve current practice, and minimize involuntary treatment in general as well as on an individual level, at least four areas need attention: (i) the present specific symptoms of anorexia nervosa and their imminent consequences, (ii) illness history, (iii) overall psychiatric symptoms and general functioning, and (iv) contextual sphere of the patient. In particular, the last two require attention from both clinicians and researchers. Furthermore, critical evaluation of the attitudes of both patients and health care professionals toward each other and the treatment is recommended.

Keywords: involuntary treatment, anorexia nervosa, severe and enduring anorexia nervosa, coercion, eating disorders, restraint

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INTRODUCTION

Anorexia nervosa is an illness with an increased mortality rate from both natural and unnatural causes of death (1, 2). The characteristics of anorexia nervosa are self-induced low weight, a disturbed body image, and a fear of weight gain (3). Patients with severe and enduring anorexia nervosa are additionally characterized by being ill for a long time and having significant eating disorder symptoms as well as being resistant or ambivalent toward treatment (4). Hence, these patients are specifically at risk of being treated against their will based on both the dangerous and the deterioration criteria (5).

As described below, involuntary treatment is usually evaluated negatively by patients, professionals, and relatives (6–10). Inpatient care must thus always aim to find alternative strategies and interventions to involuntary treatment, reducing it whenever possible without neglecting its lifesaving purpose and outcome. To do this, up-to-date knowledge on the involuntary treatment of anorexia nervosa is needed.

Prevalence and Predictors

The involuntary treatment of anorexia nervosa, which occurs in 13 to 44% of admissions, is associated with severe psychiatric symptoms, comorbidity, previous admissions, and long illness duration (11, 12).

The significance of preadmissions and illness duration on involuntary treatment are well-established and intuitive as they represent different aspects of illness severity. By contrast, comorbidity and severe psychiatric symptoms are more complex and imprecise terms that are not immediately applicable to clinical practice.

A recent register-based study found that the comorbidity associated with the involuntary treatment is caused by all the main diagnostic groups except intellectual disability. Behavioral and emotional disorders with onset in childhood show a weak association, whereas schizophrenia spectrum disorders, personality disorders, and autism spectrum disorders are the strongest predictors along with age at onset and earlier admissions (13). However, while the association between schizophrenia spectrum disorder and personality disorders and involuntary treatment is well-described within general psychiatry (14–16), the link between autism spectrum disorders and involuntary treatment among psychiatric patients is less clearly examined. However, people with developmental disorders including autism spectrum disorders have been found to have a similar increased risk of involuntary treatment as patients with schizophrenia (16).

Comorbid psychiatric illness is well-described in patients with anorexia nervosa (17) and has been suggested as a defining criterion in severe and enduring anorexia nervosa (18). However, the role of comorbid illness remains unknown. For example, it is unclear whether it raises the risk of involuntary treatment, because (i) comorbidity increases the complexity of overall mental functioning, (ii) the comorbid illness symptoms themselves prompt the involuntary episode, or (iii) the complexity of psychiatric symptoms complicates clinical decisions, thereby increasing the risk of an inexpedient therapeutic response.

Different Involuntary Measures

Involuntary admissions, detentions, and nasogastric tube feeding have been described in relation to anorexia nervosa (19–21). However, one register-based study finds that all involuntary measures are used with patients with anorexia nervosa including medication and mechanical or physical restraint (13). Because the use of these more intrusive involuntary measures not directly relates to the symptoms of anorexia nervosa has been described in relation to compulsory tube feeding in two single case studies of anorexia nervosa (22, 23), we do not expect the results to reflect a country-specific practice. However, it remains relevant to examine whether the use of such measures is common across countries, as legislation on the use of involuntary treatment varies globally and cultural aspects have been shown to affect the frequency and type of involuntary measures (5, 24–27). In addition, questions on the extent to which patient-specific, illness–specific, and contextual factors affect specific involuntary measures need to be answered as well as the impact of these measures on patients.

Attitude Toward Treatment

Attitude toward treatment is an important topic when discussing the involuntary treatment of anorexia nervosa, as these patients often lack the motivation to change or refuse to accept they have a treatment need (28). Their decision-making capacity and their attitudes toward treatment are affected by the ego syntonic nature of the disease (23, 29, 30). At the intrapsychic level, Seed et al. (23) argue that the self is occupied by the illness and Tan et al. (31) describe how patients' value system changes because of anorexia nervosa, resulting in weight-related issues overshadowing other aspects of their life.

Motivation to change and the perception of treatment need have both been found to improve during treatment. Guarda et al. (32) found that 41% of those rejecting an admission need at the time of admission changed their stance after 2 weeks of inpatient treatment and acknowledged a treatment need. Motivation to change has also been shown to increase gradually during admission (33). These changes could reflect an improvement in the decision-making capacity found in a third of patients admitted with anorexia nervosa (29) or patients giving up their resistance to treatment (23). Hence, changes in motivation and the perception of admission need have been a crucial argument for persuading patients into admission. However, the majority of patients with anorexia nervosa, although accepting they are not formerly coerced, state that they do experience a high degree of perceived pressure, informal coercion, and procedural justice (32–34). This has been reported by patients with increased eating disorder psychopathology (34), younger patients, and patients with mild weight loss (33).

Although the use of such informal coercion interventions seems less dramatic or intrusive than formal coercion, it does make the patient feel a loss of autonomy, which is why voluntary and collaborative admission is ideal through therapeutic alliances, transparent dialogue, and motivational interventions whenever possible (35, 36). Furthermore, Seed et al. (23) argue that professionals should take the position of "safe-uncertainty" (37), where several explanations and solutions to a given problem may exist simultaneously, where the therapist is less authoritarian and less of an expert, and where the patient is given a major role in the decision-making process. While this is difficult to uphold in the acute situation where involuntary treatment is deemed necessary and initiated, it does seem important before and after involuntary episodes to prevent future episodes or decrease the negative impact of involuntary treatment on patients, relatives, and professionals. In this way, in addition to the attitude of the patient, the attitude of health-care professionals toward the patient and his/her treatment is crucial if we are to understand and decrease involuntary measures in the future.

Patients' Perception of Involuntary Treatment

Patients' perception of the precursors to or reasons for involuntary episodes augment clinical research that mainly

focuses on patient characteristics and typically overlooks the importance of the attitude and action of health-care professionals, including their use of control, and patients' need to protest (about the treatment or environmental circumstances) (26, 38, 39).

Furthermore, although patients with anorexia nervosa report involuntary treatment interventions as necessary, life-saving, and a sign of caring relations, they mainly see them as actions of punishment and something that should either be short-lasting or even prohibited (23, 40, 41). Some patients argue for the use of involuntary treatment earlier in the illness course, whereas other argue for the right to choose to die from anorexia nervosa (40). Reports of this typically negative perception of involuntary treatment are well-known from general psychiatric patients also (38, 39, 42). The impact of different involuntary measures on these patients seems to vary by measures, with seclusion and restraint having an especially negative impact (6, 39, 42). The subjective implications of nasogastric feeding specifically have in a small qualitative study been reported to increase rebellious behavior as well as involuntary measures such as restraint and forced medication (23).

Hence, studies including patients' perception of involuntary treatment provide information on the relational and contextual factors influencing the risk of involuntary treatment. Such studies are thus warranted to understand the dynamics initiating and escalating involuntary treatment episodes. In addition, clinicians continuously need to be aware of these dynamics if they are to decrease the use of involuntary treatment.

DISCUSSION OF FUTURE DIRECTIONS IN RESEARCH AND TREATMENT

To understand the overall use of involuntary treatment, decrease it, qualify discussions, and improve practice, we must focus on at least four areas. The first area is the present specific anorexia nervosa symptoms of patients, including (i) the somatic status and present physical symptoms of anorexia nervosa, as well as imminent consequences, at least in countries in which involuntary treatment might be initiated to prevent a deterioration of the illness (5) and (ii) the psychopathological aspect of anorexia nervosa, including the value system of patients, insight into their situation, decision-making capacity, and degree to which anorexia nervosa occupy the self.

Second, illness history includes important markers of the risk of involuntary treatment, with a longer duration of illness, older age at first diagnosis, and history of earlier treatment as important predictive factors (11). The association between involuntary treatment and longer duration or number of admissions can be explained as the influence of illness severity as well as the patient's earlier experience and attitude toward treatment. However, the effect of the attitude of health-care professionals must not be neglected as their knowledge of the patient as having a resistant illness may increase their expectations of an involuntary treatment need (10).

The third area to consider is the patient's general functioning and psychiatric symptoms, including self-harm, sexual/physical abuse, and other mental illnesses, especially autism spectrum disorders, schizophrenia and personality disorders (11, 13). These disorders all include some level of basic disturbed and inflexible cognitive and social functioning (43–46) and their coexistence in patients with anorexia nervosa is expected to affect treatment and the relationship with health-care professionals, consequently also impacting on the treatment outcome, including the risk of involuntary treatment. Thus, a thorough assessment of the central comorbid disorders and basic cognitive, communicative, and relational abilities of patients is important in severe anorexia nervosa. Similarly as coexisting psychopathologies affect the relational sphere the match between patient and treatment or therapist might need to be examined, which leads us to the fourth area.

Finally, the contextual area including the exploration of the influence of legislation, systems, relations, and treatment has been found to be associated with involuntary treatment (5, 10, 14). Involuntary episodes might be the manifestation of power over the individual/illness/situation, of powerlessness, or the anxiety of health-care professionals or the patient (23, 38, 39, 47). The expectations of the patient or health-care professionals affect the risk of involuntary admission (10, 48). Therefore, analyzing the build-up to an episode of involuntary measures is an important clinical task to understand and prevent involuntary episodes. Besides intra-clinical factors, examining the influence of the patient's social support and network, which has not thus far been studied in patients with anorexia nervosa, has been found to be an important risk factor of involuntary admissions in acute psychiatry (49).

Lastly, attention must be directed toward the outcome of involuntary treatment. Traditional positive outcome markers such as remission and symptom reduction are insufficient, as involuntary treatment depends upon dangerousness or deterioration criteria, which is why decreased mortality and stable physiology and symptoms might be more relevant markers of outcomes. Unfortunately, research on the effect of involuntary treatment in anorexia nervosa is in its infancy. The findings on the mortality rate are mixed and not applicable as studies compare rates of patients treated involuntary with those treated voluntarily (19, 50) even though involuntary measures can be initiated only when deemed needed in contrast to voluntary treatment.

NEW TREATMENTS AND THE ETHICAL AND LEGAL COMPLEX OF INVOLUNTARY TREATMENT

The exploration of these four areas is complicated by important ethical and legal issues. It is possible to fail the Hippocratic Oath (first, do no harm) both by initiating involuntary treatment and by not initiating it (51, 52). Commitment laws are justified by the caretaking of the patient or society and overrule normal rights to consent to or refuse treatment (5). Substituting the patient's personal right to decide on his/her own life and treatment is controversial, however, the alternative is the loss of life or loss of the right to die. Decisions on use or non-use of involuntary

treatment are extremely complex, hence, studies of legal and ethical issues are important (36, 52–55).

For patients with short-term illnesses, we have to do what we can, even if that includes involuntary treatment in the most severe cases, knowing that anorexia nervosa affects their illness perception and that (early) weight gain is a predictor of improved cognition as well as symptom outcome (56–58). For patients that have been challenged by anorexia nervosa in the long term, with unsuccessful treatment and long-lasting suffering, treatment choice is more complex (59). Studies including established treatments of anorexia nervosa, i.e., Cognitive Behavioral Therapy for Eating Disorders, Maudsley Model of Anorexia Nervosa Treatment for Adults, Specialist Supportive Clinical Management, or modifications of these, have found that symptom outcome improves in some patients with long-term anorexia nervosa (59–61). However, in general new treatments of severe and enduring anorexia nervosa include suggestions to minimize or even dismiss the focus on eating disorder symptoms and instead focus on quality of life (18, 60, 62–64). Palliative care could be considered and admission should in some cases only be initiated with consent and for symptom interruption rather than to normalize weight (51, 65). However, studies evaluating such treatment approaches are still scarce (60, 66) although needed if we are to improve treatment for the most severe patients with increased risk of involuntary treatment.

CONCLUSION

The involuntary treatment of anorexia nervosa is a complex area and further research including quantitative and qualitative studies is needed. Studies focusing on outcomes, patient-specific and contextual factors, and precipitating and processual factors are needed to reduce involuntary treatment, by, for example, the early identification of patients at risk of involuntary treatment and by identification of episodes escalating to include involuntary measures.

Patient characteristics such as severe eating disorder symptoms, psychiatric comorbidity, and illness history are important as involuntary treatment might be more justified in cases with shorter durations and less in cases with long illness duration and years of unsuccessful treatment (23). Understanding the underlying individual psychopathology can thus be vital, including the possible cognitive, communicative, and relational difficulties.

The contextual factors relevant for involuntary treatment are many and often not well-described. A critical examination of how we as therapists contribute or how our clinical culture contributes to the initiation or escalation of involuntary treatment is important. This might lead to new perspectives on episodes of involuntary treatment. Kendall (36) suggests more dialogue with more autonomy and power passed to the patient in the decision-making process, Seed et al. (23) suggest a longer-term recovery approach with a position of more "safe-uncertainty," and several studies suggest focus on quality of life instead of eating disorder symptoms (51, 62, 64). Traditional eating disorder treatment usually focuses on normalizing eating and weight, often with use of non-negotiables (67). However, this might not be the right approach in cases with severe and enduring anorexia nervosa, because this approach might result in disrespecting the patient's wishes and autonomy or exacerbating rigidity and protest behavior, especially in cases with a history of several unsuccessful treatment attempts. Professionals' compassionate care (68) and containment of patients' negative emotions (69) are basic treatment elements that need to be stressed in eating disorder treatment along-side the well-established focus on symptom reduction (57). In cases with several failed treatment attempts, adjustment must be done and clinicians are obliged to search for new approaches, including the right dose of patience, containing and compassion, along with goals for weight gain or stabilization, meal support, guidance and dialogue in the treatment. Finally, individualized approaches tailored to a person's specific characteristics, psychological capacity, treatment history, and social support are important, as the consideration of involuntary treatment guarantees a complex case.

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The author confirms being the sole contributor of this work and has approved it for publication.

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ORIGINAL RESEARCH
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Characterizing Treatment-Resistant Anorexia Nervosa

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Background: The issue of treatment resistance in eating disorder care is controversial. Prior research has identified multiple failed treatment attempts as a common criterion for severe and enduring anorexia nervosa, but little is known about patients who have multiple failed treatment attempts. This study was designed to compare the clinical and demographic characteristics of eating disorder patients with multiple, incomplete inpatient admissions to those with good outcomes. Understanding if these patient populations differ at initial admissions has implications for the prediction and characterization of inpatient eating disorder treatment resistance.

Methods: This study analyzed existing data from a specialist inpatient eating disorder program at a large Canadian teaching hospital collected between 2000 and 2016. Treatment resistance was defined as two or more incomplete admissions and no complete admissions in the study period. Data were available on 37 patients who met this criteria, and 38 patients who had completed their first admission and remained well (defined as a BMI $>$ 18.5 with no binging or purging behavior) 1 year after discharge. Variables of interest included age, weight, diagnoses, duration of illness, eating disorder psychopathology, eating disorder behavioral frequencies and depressive symptoms at the time of index inpatient admissions. Statistical analyses consisted of Mann–Whitney U tests, Chi-square tests, and a logistic regression.

Results: In our main bivariate analyses, patients with multiple incomplete admissions were characterized by more severe eating disorder psychopathology and depressive symptoms at admission as well as an increased prevalence of the binge purge subtype of anorexia nervosa. In our exploratory multivariate analyses controlling for diagnostic subtype and depressive symptoms, severity of eating disorder psychopathology did not remain significant. No statistically significant difference in body mass index (BMI) or frequencies of eating disorder behaviors were found. A trend toward a longer duration of illness did not meet statistical significance.

Conclusions: This study found that patients considered resistant to inpatient eating disorder treatment differ from those with good outcomes at initial admission. These results suggest that while treatment-resistant anorexia nervosa may be related to severe and enduring anorexia nervosa, it may also be a different concept that warrants additional research.

Keywords: anorexia nervosa, eating disorder, inpatient, treatment resistant, premature termination of treatment

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INTRODUCTION

Anorexia nervosa is considered one of the most difficult psychiatric disorders to treat (1). This eating disorder is characterized by severe restriction of food intake resulting in significantly low body weight, an intense fear of gaining weight and undue influence of body weight or shape in self-evaluation (2). Anorexia nervosa often has its onset in childhood or adolescence (3) and despite treatment, 20–25% of patients develop a chronic form of the illness (4, 5).

There has been an increasing focus on potential treatment options for longstanding eating disorders in recent years with a growing body of research on the concepts of chronic eating disorders (6) and severe and enduring anorexia nervosa (SE-AN) (7). These terms are often used interchangeably (6), with a prolonged length of illness (i.e., >7–10 years) as their most common defining criteria (7). Severity itself is defined by the Diagnostic and Statistical Manual of Mental Disorder 5th Edition (DSM-5) in terms of body mass index (BMI), although it allows the inclusion of clinical symptoms, functional disability, and supervision requirements in this assessment (2). There is also a growing body of literature on the concept of treatment resistance, which is often considered another component of severe and enduring anorexia nervosa. A recent review by Broomfield et al. (7) identified a history of multiple failed treatment attempts as the second most common criteria in published definitions of SE-AN, although what constituted a failed treatment attempt, and the number of failed attempts required to meet this criterion, was not clear across studies. Indeed, there is no established definition of treatment-resistant anorexia nervosa (8, 9).

Prior studies on inpatient care have conceptualized treatment resistance as patterns of multiple admissions to hospital (9, 10) or readmissions to specialist eating disorder services (11). For patients who are severely medically compromised or who have not benefitted from outpatient care, inpatient eating disorder care is the most intensive form of treatment available (12). For these patients, inpatient treatment provides a structured environment, supervision, and medical monitoring (13). Many specialist inpatient programs also provide multidisciplinary care and psychotherapy (12). Despite this, inpatient eating disorder programs have high rates of premature termination of treatment, or dropout, ranging from 20% to 51% (14) and rates of readmission ranging from 27% to 42% (15, 16). Prior research at the site of this study reported premature treatment termination rates of 36–51% over time (17–19) with a higher prevalence of the binge-purge subtype diagnosis among patients who did not complete treatment (defined as achieving a BMI of 20 kg/m^2) (17, 19). Studies of potential predictors of premature termination of inpatient treatment at other sites have reported mixed results on the effect of patient diagnoses (18–22), age at admission (19–22), duration of illness (19–22), body mass index at admission (19–22), eating disorder beliefs and cognitions (18–22), eating disorder behavior frequencies (i.e., binging and purging) (19–22), and depressive symptoms (19–22). However, across studies, patients who do not complete inpatient eating disorder treatment consistently have shorter lengths of stay (18, 19, 21) and are discharged at lower body weights than patients who complete treatment (18, 21, 23).

These findings are of high clinical relevance as patients who leave treatment at low body weights are more likely to remain symptomatic after discharge, suffer severe depressive symptoms and be readmitted to specialist inpatient eating disorder care (15). However, almost nothing is known about patients who have multiple incomplete admissions: those who can be considered resistant to specialist inpatient eating disorder care. The purpose of this study was to explore the characteristics of these patients at one specialist inpatient eating disorder unit compared to patients admitted in the same time period who completed treatment and remained well 1 year after discharge.

Research Question and Hypotheses

This study was designed to compare the characteristics of eating disorder patients with anorexia nervosa with multiple incomplete inpatient admissions (two or more) and no complete admissions to patients with good inpatient treatment outcomes in a retrospective study. Drawing from prior research on treatment resistance in inpatient eating disorder care that defined treatment resistance as multiple incomplete (or failed) treatment attempts, we considered patients with two or more incomplete inpatient admissions and no complete admissions as resistant to specialist, inpatient care.

Based on this research, research on premature termination of inpatient eating care and our clinical experience, we defined the following hypotheses: (i) Patients who have multiple incomplete admissions to our specialized inpatient eating disorder unit will have longer lengths of illness than those who have good outcomes, and (ii) Patients who have multiple incomplete admissions to our specialized inpatient eating disorder unit will be more likely than those who have good outcomes to have the binge-purge subtype of anorexia nervosa. As additional variables of interest have yielded mixed results in studies of premature termination of inpatient treatment or readmission, their inclusion was considered exploratory, and no *a priori* hypotheses were established.

METHODS AND MATERIALS

Participants

This study is a secondary analysis of data on 75 patients admitted to the inpatient eating disorder unit at the Toronto General Hospital between January 2001 and December 2015. All patients met the DSM-IV diagnostic criteria for anorexia nervosa according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) at the time of admission and consented to participate in research. Data was collected between August 2000 and August 2016. Data was available on 433 patients with anorexia nervosa who consented to participate in research, of whom 37 (8.5%) had multiple incomplete admissions and no complete admissions, while 38 (8.8%) completed their first admission and remained well and available for follow-up for 1 year (**Figure 1**). Patients were considered to have a good outcome if they remained well at 1-year follow-up, defined as maintaining a BMI >18.5 in the

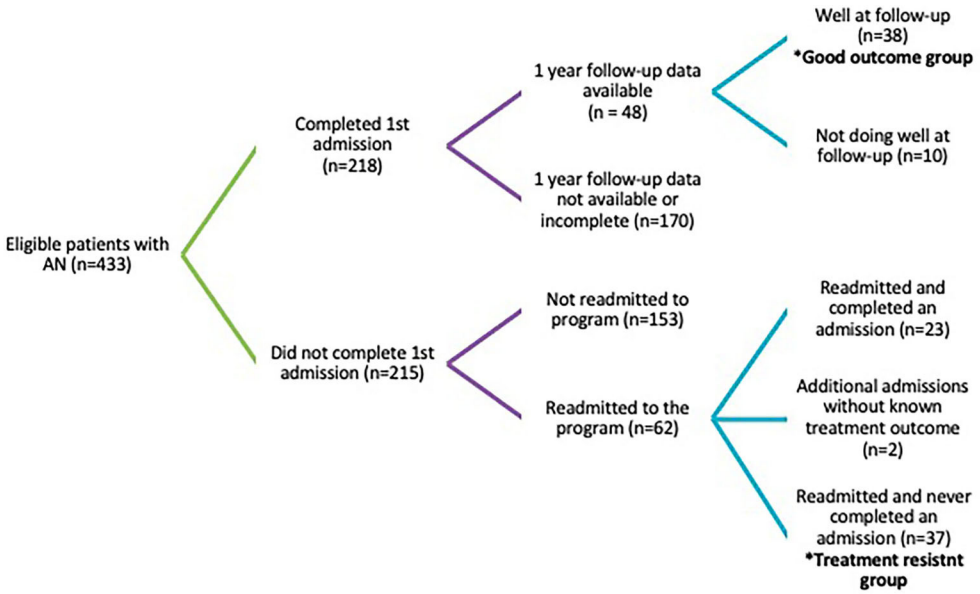

FIGURE 1 | Treatment outcomes of patients admitted to TGH August 2000 to August 2016.

absence of binging or purging in the 3 months preceding. Patients were considered to be treatment resistant if they had had two more incomplete admissions and no complete admissions in the study period. Patients with multiple incomplete admissions as well as admissions without known outcomes were not included in the treatment-resistant group. These two patient subgroups represent the best and worst outcomes observed during the study period. As all patients offered admission to the inpatient program at Toronto General Hospital have serious eating disorders and are often medically unstable, these subgroups were chosen to magnify potential differences in a superficially quite homogenous patient population. All analyses were of admission data from patients' first admission during the study period.

Intervention

During the period these data were collected, the inpatient eating unit program at the Toronto General Hospital was an intensive program that focused on medical stabilization, weight restoration, the normalization of eating behaviors, psychosocial rehabilitation, and group therapy. As it was one of the few specialized adult eating disorder units in its province, it admitted patients from a large geographical area. All patients were admitted voluntarily. Treatment was provided by an interdisciplinary team that included psychiatrists, psychologists, dieticians, social workers, nurses, and occupational therapists. As patients progressed in the program, they were granted more privileges with the goal of transitioning to day attendance. Patients were considered to have completed the inpatient program when they were medically stable and had attained a minimum body mass index (BMI) of 20 kg/m^2. Upon completion of the inpatient program, some patients transitioned to an affiliated day hospital program, while others choose to pursue other forms of outpatient care independently. Inpatient treatment could also be terminated before treatment completion by the patient or treatment team. Patients could choose to discharge themselves from the unit at any time if they were medically stable or they could be discharged by staff for not participating in the program. Staff initiated premature terminations of treatment typically involved long periods of discussion with the patient about their difficulties participating in the program and unsuccessful attempts to modify their behaviors before discharge.

Measures

All patients completed a standardized battery of psychological measures at the time of admission including components of the Eating Disorder Examination (EDE), an Eating Disorder Examination Questionnaire (EDEQ), a Beck Depression Inventory (BDI), and demographic questions. For patients who had multiple admissions in the study period data from their first admission was used for analyses.

The EDE is a semi-structured diagnostic interview that assesses concerns about weight, shape, diet, and the of frequency eating disorder behaviors in the 3 months preceding administration (24). The EDE is a common tool in eating disorder research and has been shown to have good internal consistency (Cronbach α = 0.67–0.79) (25) and interrater reliability (r = 0.69–1.00) (26). In this study, data from the EDE was used to examine the frequency of the eating disorder behaviors of binge eating, self-induced vomiting (purging), and exercise before admission.

The Eating Disorder Examination Questionnaire (EDEQ) is a 28-item self-report questionnaire that is used to assess eating disorder beliefs and cognitions (27). It has four calculated

subscales (shape concern, weight concern, eating concern, and restraint) and a total score. In this study, only the total score was used for analyses given our small sample size. The EDEQ has been shown to have good internal consistency (Cronbach's $\alpha = 0.78–0.93$) and test–test reliability ($r = 0.81–0.94$) (28).

The Beck Depression Inventory (BDI-II) is a 21-item self-report questionnaire of depressive symptoms that has a calculated total score (29). It one of the most commonly used research measures of depression and has been used in prior studies to measure depressive symptoms in eating disorder patients (19–22). The BDI has been shown to have high internal consistency (Cronbach $\alpha > 0.75$) (23).

Height and weight were measured at admission and were used to calculate the body mass index (BMI). Weight was then measured weekly until discharge. This information was used to calculate weight gain in inpatient treatment, rate of weight gain, and BMI at discharge. Duration of illness was self-reported by patients at the time of admission.

Statistical Analyses

Statistical analyses were conducted in SPSS Version 24 (SPSS Inc, Chicago). Chi-square tests were used for categorical variables of interest (gender, diagnostic subtype, living situation, and employment status). Continuous variables of interest (age at admission, duration of illness, BMI at admission, BDI total score at admission, EDEQ total score at admission, frequency of eating disorder behaviors in the 3 months preceding admission, length of inpatient treatment in weeks, weight gain in treatment, rate of weight gain in treatment, and BMI at discharge) were examined for normality. As almost all were not normally distributed, non-parametric Mann–Whitney U tests were used for between-group analyses. A Bonferroni correction was applied to correct for multiple comparisons resulting in an alpha level of 0.003.

Significant variables in the univariate analyses were selected for inclusion in an exploratory binary logistic regression to control for potential confounding. Given the relatively small sample size, the number of variables eligible for inclusion was reduced based on clinical significance to avoid overspecification. Multicolinearity of the final model was assessed using the variance inflation factor with a reference value of four. More complex modeling was not possible due to the small sample size.

RESULTS

All patients ($N = 75$) met the criteria for DSM-IV anorexia nervosa at the time of admission with 46 meeting the criteria for the restricting subtype (AN-R) (61.3%) and 29 meeting the diagnostic criteria for the binge-purge subtype (AN-BP) (38.7%). Patients ranged in age from 17 to 62 years old ($M = 25.92$; SD = 8.35) at admission and had been unwell for an average of 6.70 years (SD = 6.78). Patients' BMIs at admission ranged from 11 to 18 kg/m^2 ($M = 14.83$, SD = 1.73). All patients reported their gender identity, with 97.3% identifying as female and 2.7% identifying as male. Sixty-six patients (88%) reported their employment status, of whom 26 (39.4%) were employed preceding admission, 25 were attending school (37.9%), and 15 were unemployed (22.7%). Sixty-five (86.7%) patients reported their living circumstance of whom 9 lived independently (13.8%), 39 lived with their family of origin (60.0%), 15 lived with partners and/or their children (23.1%), and two lived with roommates (3.1%).

During the study period, 37 patients had two or more incomplete inpatient admissions and no complete admissions. These patients were classified as resistant to inpatient treatment. In this period, 38 patients completed their first admission and remained well (defined as maintaining a BMI >18.5 kg/m^2 without of binging and purging for at least 3 months) at 1-year follow-up. These patients were classified as having good outcomes.

Treatment-resistant patients were more likely to have the binge purge subtype of anorexia nervosa than those who had good outcomes [χ^2 (1, $n = 75$) = 16.99, $p < 0.001$]. Treatment-resistant patients did not differ statistically from patients who had good outcomes in terms of gender, occupation, age, or BMI at admission (**Table 1**). There was a trend of differences in employment status between treatment-resistant patients and those with good outcomes [$\chi^2(2, n = 66) = 6.15$, $p = 0.046$). *Post hoc* testing of residuals showed that this was due to a greater percentage of patients being unemployed in the treatment-resistant group (34.5%) than the good outcome group (10.8%, $p = 0.02$).

Treatment-resistant patients scored significantly higher on the BDI (Mdn = 46.00) than patients who had good outcomes (Mdn = 33.00, $U = 159.00$, $p < 0.001$). Similarly, treatment-resistant patients had significantly higher EDEQ total scores (Mdn = 5.29) than patients who had good outcomes (Mdn = 4.57, $U = 179.00$, $p = 0.003$), although they did not differ significantly in their report of eating disorder behavior frequencies including binge eating, purging, or excessive exercise in the 3 months preceding admission (**Table 1**). There was a trend for treatment-resistant patients to have longer durations of illness (Mdn = 6.84) than those with good outcomes (Mdn = 2.87, $U = 440.50$, $p = 0.068$), but this did not achieve statistical significance.

Treatment-resistant patients had shorter first admissions to the inpatient unit in weeks (Mdn = 4.29) than patients with good outcomes (Mdn = 16.43, $U = 51.00$, $p < 0.001$). They also gained less weight as inpatients (Mdn = 4.50 kg) compared to those with good outcomes (15.25, $U = 48.00$, $p < 0.001$). Thus, treatment-resistant patients were discharged from the program with lower BMIs (Mdn = 16.23) than those with good outcomes (Mdn-20.57, $U = 1.00$, $p < 0.001$), although their weekly rate of weight gain while admitted to the inpatient unit did not differ statistically (Mdn = 0.73) from those with good outcomes (Mdn = 0.90, $U = 585.00$, $p = 0.284$) (**Table 2**).

Independent variables that were significant in bivariate analyses (EDEQ total score, BDI total score, weeks of treatment, weight gain in treatment, and BMI at discharge) were then considered for inclusion in an exploratory logistic regression based on clinical significance. Potential correlations between these variables were assessed using Spearman correlations (**Table 3**). As admission BMIs and rate of weight gain did not differ significantly between groups in bivariate analyses,

TABLE 1 | Demographics of treatment-resistant patients and patients with good outcomes at admission.

Variable	*N*	Treatment resistant % or median (IQR)	Good outcome % or median (IQR)	Test of significance
Diagnosis	75			$x^2(1) = 16.99$, $p < 0.001$
AN-R		37.8%	84.2%	
AN-BP		62.2%	15.8%	
Gender	75			$x^2(1) = 2.00$, $p = 0.157$
Female		100%	94.7%	
Male		0%	5.3%	
Occupation	66			$x^2(2) = 6.15$, $p = 0.046$
Employed		37.9%	40.5%	
Student		27.6%	48.6%	
Unemployed		34.5%	10.8%	
Living Situation	65			$x^2(3) = 0.688$, $p = 0.876$
Independent		13.8%	13.9%	
Parents		55.2%	63.9%	
Partner/children		27.6%	19.4%	
Roommates		3.4%	2.8%	
Age	74	24.00 (21.50, 30.00)	22.00 (20.00, 27.00)	$U = 556.50$, $p = 0.167$
Duration of illness in years	69	6.84 (2.62, 12.32)	2.87 (1.46, 9.43)	$U = 440.50$, $p = 0.068$
BMI in kg/m^2	75	14.36 (13.56, 15.60)	15.59 (13.85, 16.38)	$U = 558.00$, $p = 0.124$
EDEQ total score	55	5.29 (4.76, 5.59)	4.57 (3.35, 5.17)	$U = 179.00$, $p = 0.003$
BDI total score	57	46.00 (34.00, 53.00)	33.00 (21.00, 40.50)	$U = 159.00$, $p < 0.001$
Weekly # days of excessive exercise in 3 months before tx	69	2.80 (0, 6.63)	4.00 (0, 7.00)	$U = 544.50$, $p = 0.553$
Weekly # of binge episodes in 3 months before tx (BP subtype)	23	0.17 (0, 6.67)	0.00 (0, 0.33)	$U = 40.0$, $p = 0.406$
Weekly # of purge episodes in 3 months before tx (BP subtype)	24	7.33 (2.83, 28.08)	5.17 (0, 11.33)	$U = 38.50$, $p = 0.300$

TABLE 2 | Treatment outcomes of treatment-resistant patients and patients with good outcomes.

Variable	*N*	Treatment resistant median (IQR)	Good outcome median (IQR)	Test of significance
Median weeks of treatment received	75	4.29 (3.14, 7.71)	16.43 (14.14, 18.57)	$U = 51.00$, $p < 0.001$
Median BMI at discharge in kg/m^2	74	16.23 (14.80, 17.62)	20.57 (20.36, 21.04)	$U = 1.00$, $p < 0.001$
Median weight gain to discharge in kg	74	4.50 (2.10, 7.65)	15.25 (10.80, 18.60)	$U = 48.00$, $p < 0.001$
Median weekly rate of weight gain from admission to discharge in kg	74	0.73 (0.51, 1.22)	0.90 (0.77, 1.05)	$U = 585.00$, $p = 0.284$

discharge BMI and total weight gain were both considered to be a function of length admission in weeks. To avoid potential overspecification, only BMI at discharge was included in the model in addition to diagnostic subtype, EDEQ total score, and BDI total score.

Analyses of the initial model showed complete separation of data points limiting interpretability. Independent variables were then examined individually, which showed that discharge BMI fully discriminated between groups. To allow the assessment of other independent variables, this variable was removed from the model resulting in a final model with three independent variables associated with group membership (subtype, BDI total score, and EDEQ total score at admission). This model was found to be statistically significant, $\chi^2(3) = 21.70$, $p < 0.001$, with no evidence of multicolinearity. Examination of independent variables within the model showed that the binge purge subtype of anorexia nervosa and higher BDI scores remained statistically significant. Both of these independent variables were associated with higher odds of having an eating disorder resistant to inpatient treatment (**Table 4**). However, having a higher EDEQ total score did not retain statistical significance when controlling for subtype and BDI score.

DISCUSSION

The results of this study show that treatment-resistant patients comprised approximately 10% of the patients treated in our

TABLE 3 | Spearman correlations between significant variables in univariate analyses.

	Diagnostic subtype	Discharge BMI	Weight gain	Weeks in treatment	BDI score (admission)	EDEQ score (admission)
Diagnostic subtype	1.00	−0.45**	−0.41**	−0.40**	0.35**	0.29**
Discharge BMI		1.00	0.82**	0.75**	−0.29*	−0.17
Weight gain			1.00	0.89**	−0.40**	−0.41**
Weeks in treatment				1.00	−0.35**	−0.28*
BDI score at admission					1.00	0.66**
EDEQ score at admission						1.00

*$p < 0.05$; **$p < 0.01$.

TABLE 4 | Patient characteristics associated with multiple, incomplete admissions to inpatient care without any complete admissions in a logistic regression model.

Independent variables	Adjusted OR (95% CI)	Test statistic	*p*-Value
Omnibus Likelihood Ratio		21.70 (3)	$p < 0.001$
Subtype (AN-BP vs. AN-R)	4.60 (1.05, 20.15)	4.09	$p = 0.04$
BDI total score	1.09 (1.01, 1.18)	4.61	$p = 0.03$
EDEQ total score	1.29 (0.47, 3.51)	0.25	$p = 0.62$

specialist, adult inpatient eating disorder program between 2000 and 2016. This finding is concerning as a specialist, inpatient eating disorder treatment is the most intensive form of adult eating disorder treatment available in Canada and patients who are unable to benefit from it have few other options for treatment.

These treatment-resistant eating disorder patients who were not able to complete multiple specialist, inpatient admissions differed from those who were able to complete their first admissions and remain well after treatment. Specifically, eating disorder patients considered resistant to inpatient treatment were more likely to have a diagnosis of anorexia nervosa binge purge subtype, present with more severe depressive symptoms, and endorse more severe eating disorder beliefs and cognitions (psychopathology) despite not presenting at lower body weights or reporting engaging in higher frequencies of specific eating disorder behaviors in bivariate analyses. Patient diagnostic subtype and severity of depressive symptoms remained significant predictors of treatment resistance in an exploratory multivariate model controlling for severity of eating disorder psychopathology as measured by the EDEQ. These findings suggest that it is possible to identify patients at high risk of repeated, incomplete admissions at the time of their initial admission. These findings also represent a novel contribution to eating disorder research as no prior studies have characterized patients with repeated, incomplete admissions to specialist, inpatient care.

Many of the characteristics of patients considered treatment resistant in this study are the same features associated with repeat admissions to inpatient eating disorder care. Specifically, our findings that patients who do not complete inpatient treatment have shorter lengths of stays and are discharged at lower body weights are consistent with prior research on readmission (18, 19, 21). However, our finding in bivariate analyses that treatment-resistant patients differ in their eating disorder cognitions and depressive symptoms compared to those with positive treatment outcomes contrasts the findings of prior research that has compared patients requiring multiple admissions (often defined as two admissions) to inpatient eating disorder care to those singular admissions with mixed results (20–22). This could be explained by our group selection criteria as our definition of treatment resistance, two more incomplete admissions, and no complete admissions, likely magnified group differences and made it possible to detect differences obscured when patients with multiple admissions but differing treatment outcomes were examined as a homogenous group.

Similarly, as our definition of treatment resistance included multiple incomplete inpatient admissions, several of the characteristics that differentiated our treatment-resistant group from those with good outcomes have been previously associated with premature termination of treatment. Specifically, the binge purge subtype of anorexia nervosa (18–20), more severe eating disorder cognitions (18–20), and more severe depressive symptoms (19) have been associated with one episode of premature treatment termination, although these findings have not been consistent across studies of premature termination of treatment (20–22). Again, it is possible that our definition of treatment resistance may have amplified group differences not detectable when patients who completed their admissions were compared to those who terminated only one admission prematurely in prior studies.

In contrast, we did not find that patients with multiple incomplete admissions differed statistically from those with good outcomes in body mass index or frequency of eating disorder behaviors at initial admission. Indeed, at admission, the median BMI in both of our outcome groups fell in the severe or extreme categories of severity in DSM-IV. This is likely a reflection of the patient population served by the inpatient eating disorder at Toronto General Hospital as patients admitted to this specialized program were typically medically very unwell or had not benefitted from outpatient care. Preceding admission, the majority of patients in both outcome groups resided with their families of origin making it unclear whether they were unable to live independently. Similarly, while not statistically significant, a larger proportion of patients in the treatment resistant outcome group were unemployed suggesting that they were not able

to work independently, while a larger proportion of patients in the good outcome group were students prior to admission. These findings may speak to the functional impairment of severe eating disorders and their potential impact on patients' lives.

Statistically, patients in our two outcome groups also did not differ in terms of age at admission, but a trend was seen in the length of illness with patients having two or more incomplete admissions having longer durations of illness than those with positive outcomes. Visual inspection of the median durations of illness in these groups (**Table 1**) suggests that this trend may be clinically significant but did not achieve statistical significance due to our relatively small sample size. This may represent a Type 2 error. If this is the case, then our study would be consistent with prior research that has reported an association between longer durations of illness and poor treatment outcomes (21) as well as definitions of severe and enduring anorexia nervosa that include multiple incomplete or failed treatment approaches (7). If this is not the case, then our findings support the understanding that patients with severe and enduring anorexia nervosa may be a heterogeneous population wherein some patients have had recurrent, incomplete treatment attempts, while others have not. The potential relationship between duration of illness and treatment resistance remains unclear, as many patients may not have had access to specialist eating disorder services or chosen not to seek care preceding their referral to our program. In our study, duration of illness was defined as the length of illness preceding patients' first admission to intensive, inpatient treatment but whether their admission was necessitated by the severity of their symptoms, the failure of outpatient treatment, or both, is unknown. Future research should attempt to quantify what proportion of patients with severe and enduring anorexia nervosa have had recurrent incomplete trials of treatment, and what these specific treatments have consisted of, to inform whether severity of symptoms and length of illness are associated with treatment outcomes when controlling for prior incomplete treatment trials. As prior treatment attempts have not been included in all definitions of severe and enduring anorexia employed in prior studies, it is possible that there are patients in this population who have not had prior trials of intensive treatment for whom such care would still be appropriate to trial.

Interestingly, the results of our exploratory multivariate analyses found that severity of eating disorder cognitions did not predict resistance to inpatient treatment when controlling for the effect of depressive symptoms and diagnostic subtype. One possible interpretation of this finding is that severe depressive symptoms may impede engagement in treatment. It is also possible that patients with more severe depressive symptoms reported more severe eating disorder symptoms as many symptoms of depression such as impaired concentration, excessive guilt, and negative self-evaluation overlap with eating disorder symptomology making it difficult to distinguish their etiology.

Regardless, the findings of this study identify a subset of severely ill eating disorder patients for whom the most intensive form of adult eating disorder treatment, specialist inpatient care is currently not effective in achieving nutritional rehabilitation and weight restoration. Based on prior operational definitions of treatment resistance as multiple incomplete or failed treatment attempts, we have considered these patients resistant to the specialist, inpatient eating disorder program where this study was conducted. It is possible that these patients may have benefitted from a different program or approach. Given the lack of a consistent definition of treatment resistance across treatment settings, we also propose that treatment resistance should be further explored on a program or approach-specific basis in future research to inform the development of a more global and generalizable definition of treatment resistance in eating disorder treatment.

Limitations

Limitations of this study include our relatively small sample size and the selection of our sample. The data used for this study was collected over a 16-year period at one of the few specialized, inpatient eating disorder programs in Canada and one of the largest. In this time, only 37 (8.5%) patients who consented to participate in research had multiple, incomplete admissions and no complete admissions, the worst treatment outcome in this study. It is possible that other patients had subsequent incomplete inpatient admissions to other programs that were not captured. Similarly, of 218 patients who completed their first admission, follow-up data was only available for 48 patients (**Figure 1**). It is possible that other patients were also doing well and either receiving care somewhere other than the Toronto General Hospital or not requiring specialist outpatient care. The implication of this small sample is that we may not have had adequate power to detect relevant significant differences between treatment-resistant patients and those with a good outcome. The limited number of patients in our regression analyses may also explain why severity of eating disorder psychopathology was not significant in multivariate analyses. Furthermore, while the choice to compare patients with multiple incomplete admissions to those with good outcomes was made to magnify potential differences between patient subgroups, our findings may not represent differences between patients with treatment-resistant eating disorders and all patients seeking inpatient eating disorder care. Finally, the patients in this study all required specialized, inpatient treatment, the most intensive form of adult eating treatment available in Canada. While this allowed for a study on resistance to inpatient eating disorder care, results may not be generalizable to patients not requiring such intensive care.

CONCLUSION

Anorexia nervosa remains a difficult illness to treat. Almost 10% of patients treated in our specialist, inpatient eating disorder program for anorexia nervosa over a 15-year period had two or more incomplete admissions and no complete admissions. These treatment-resistant patients represent a severely ill subset of patients who were not able to achieve nutritional rehabilitation and weight restoration in a specialist inpatient treatment and who differed clinically from patients

with good outcomes in the same program. Additional research is required to better characterize the clinical characteristics and health service use of these patients to inform the development of eating disorder treatments that could better meet their needs.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Board, University Health Network. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS and DW contributed to the conception and design of the study. SS completed the literature review, organized the database, completed the statistical analyses under DW's supervision, and wrote the first draft of the manuscript. All authors contributed to the manuscript revisions.

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Severe and Enduring Anorexia Nervosa: Enduring Wrong Assumptions?

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To the extent that severe and lasting anorexia nervosa (SE-AN) is defined in terms of refractoriness to the best treatments available, it is mandatory to scrutinize the proven effectiveness of the treatments offered to patients. The array of so-called current evidence-based treatments for anorexia nervosa (AN) encompasses the entire spectrum of treatments ranging from specialized brand-type treatments to new treatments adapted to the specific characteristics of people suffering from AN. However, after several randomized control trials, parity in efficacy is the characteristic among these treatments. To further complicate the landscape of effective treatments, this "tie score" extends to the treatment originally conceived as control conditions, or treatment as usual conditions. In retrospection, one can understand that treatments considered to be the best treatments available in the past were unaware of their possible iatrogenic effects. Obviously, the same can be said of the theoretical assumptions underpinning such treatments. In either case, if the definition of chronicity mentioned above is applied, it is clear that the responsibility for the chronicity of the disorder says more about the flagrant inefficacy of the treatments and the defective assumptions underpinning them, than the nature of the disorder itself. A historical analysis traces the emergence of the current concept of "typical" AN and Hilde Bruch's contribution to it. It is concluded that today's diagnostic criteria resulting from a long process of acculturation distort rather than capture the essence of the disorder, as well as marginalizing and invalidating patients' perspectives.

Keywords: acculturation, body image disturbances, fat phobia, invalidation, treatment efficacy

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It is the theory that describes what we can observe.
Albert Einstein

INTRODUCTION

The term *severe and enduring anorexia nervosa* (SE-AN) underscores that a substantial number of AN patients are refractory to currents treatments and become chronic (1). As defined by Strober (2), "*Chronicity is refractoriness of illness—permanence of the disease state in spite of repeated exposures to state-of-the-art therapy*." (p. 487). However, as Wonderlich (3) has pointed out, "*There is no hard and fast algorithm, rule, or criteria for designating a patient as having a chronic eating disorder*" (p. 470), but the implicit message is that intractability is due to the inherent complexity of the

essence of AN in these patients. The SE-AN label has been applied to patients with an active disease of 5–10 years in duration (4), meaning most adult patients belong to this category (5).

However, since the aims of any AN treatments are a logical corollary of the current understanding of the disorder, the repeated treatment failures prompt one to consider the possibility that the current conceptualization of AN may be misleading. Therefore, this paper neither intends to review the SE-AN condition, nor recent proposals for managing it (6, 7), but to question misleading assumptions regarding core symptoms capturing the essence of AN, as stated in the second part of the title. From this perspective SE-AN could be the final link of a chain of events that began with the appearance of the body image disturbances (BID) construct[1]. Furthermore, the rapid and widespread acceptance of BID in the 1960s as the cardinal symptom of typical AN has caused a hiatus with previous clinical descriptions of AN spanning almost a 100 years since the work of Marcé (10). Moreover, the BDI construct has created the fallacy that patients who do not spontaneously confirm it are suspected of being outliers or try to confuse doctors by hiding information, telling lies, and being manipulative. Third, there is some evidence that mental health professionals indoctrinate, acculturate, and export the BDI construct to apprehensive adolescents who have to deal with a serious disorder in their transition from adolescence to adulthood. Accordingly, the present work maintains that (a) the intractability of SE-AN ignores the contribution of the cumulative iatrogenic potential effects of successive failed treatments grounded on faulty assumptions and (b) the conception of SE-AN itself could be the result of cross-feedback between misleading assumptions and the increasing iatrogenic effects of failed treatments (11).

THE CREATION OF THE BODY IMAGE DISTURBANCES (BID) MYTH

In his introduction to the Conference on Anorexia Nervosa and Related Disorders held in Swansea (Wales) in September of 1984, Gerald Russell remarked on the increase in the number of scientific publications on anorexia nervosa and bulimia in Medline[2]. Furthermore, Gerald Russell was concerned about the impact of this increased interest on the symptomatic clinical picture of anorexia nervosa, and stated: "*We should also remember that patients may tell us they started to induce vomiting when questioned by their doctors about this practice, or after reading a description in a magazine. This is a sobering thought which should increase our caution when we communicate our research findings, in case they are transmitted widely through the popular press and the media and reach susceptible individuals*" [(12), p. 107].

This call for professional responsibility highlights the configurative role of clinical and research activity on the psychopathological profile of AN patients. As Gerald Russell mentioned regarding BID: "*In recent years there has been a shift in emphasis on the nature of the central psychopathology of anorexia nervosa, with a greater stress on the patient's morbid preoccupation with her body weight and her dread of fatness. Hilde Bruch was probably first in 1962 to refer to a 'disturbance of body image' as part of a more general 'perceptual and conceptual' disturbance" (p. 103)*.

The appearance of the BID construct was a hiatus, rather than an evolution in the conceptualization of self-starvation. In the 1940s, due to the differentiation of AN from Simmond's disease (13–15), there was a return to the foreground of the relevance of psychological factors. This change in the emphasis on the nature of the central psychopathology of anorexia nervosa crystallized in the appearance of BID that is body and shape concerns and fear of fatness in patients with AN as the widespread explanation for their drive toward thinness. This new picture was the culmination of a trend initiated in the 1940s when, according to Casper (16), "*comments indicating concern about the shape of the body are rare in case reports before the forties, but then become the rule*" (p. 3).

This new endeavor was mainly colonized by the clinical descriptions of psychoanalysts after intense psychoanalytic treatment. This aspect is crucial since the golden rule of psychotherapy states that to work together, both patient and therapist must share a common language. Cases of AN are characterized by the stubbornness of teenagers in recognizing their illness, and adult therapists who impose their preferred specialized language on patients in line with their training. However, the therapist's language emanates from an underlying theory that, as Einstein said, not only tells the therapist what to observe[3] but also tells patients the important aspects of their suffering. At variance with what happens in quantum physics, where measurements are no longer considered passive acts of observation but an active interference of the very essence of the object under study, tools for the diagnosis and treatment of mental disorders in general, and anorexia nervosa in particular, are awkward and unsophisticated probes that we stick into the human material. In much the same way as the very act of observation in physics interferes with the subatomic field, our attempts to evaluate symptoms are open to interference, acculturation, and even indoctrination.

[1]In this paper the acronym BID is used to refer to the body image disturbance as a generic construct, much the same as Treasure et al. (8) who listed under the umbrella of body image disturbances "*Weight and shape concerns (e.g., preoccupation with weight, shape, or both); Overvaluation of shape and weight in determination of self-worth; Minimisation or denial of symptom severity; Disturbance in the way body is experienced [and] Intense fear of weight gain, even though underweight*" (p. 584). Other authors, i.e., Fairburn and Brownell (9), group together "*drive for thinness, fear of fatness, shape and weight dissatisfaction, body size misperception, body image disturbance, and fear associated with physical maturity*" (p. 143), as different ways to describe the psychopathology related to weight and shape.

[2]According to data supplied to him by Peter Slade, the 165 publications in 1982 almost tripled as compared to the previous 59 references in 1971. The corresponding numbers for the same search in Pubmed for 2019 yielded more than a thousand references.

[3]An interesting example of the interference of the observer's assumptions was provided by Moulton (17) where her description of the discomfort displayed by an adolescent during nasogastric intubation was seen through the glass of the oral impregnation fantasies theoretical frame: "*For the first five months in the hospital, she was tube-fed daily by different doctors. She said that 'only daddy can put it down without hurting,' and took it with passive disgust, meanwhile making obviously erotic pelvic movements*" (p. 72).

As a result of psychoanalytic delving around the 1940s, the underlying motives of self-starvation began to emerge, as reported by Nicolle (18), who noted: "*In all cases I have seen, behind the trivial excuses offered lurks a fanatical desire to be thin and a dread of obesity. Miss M. said: 'I am terrified of getting fatter or even of not getting thinner.' The psycho-analytic interpretation of this state of mind would regard fatness as the sign of indulgence in the pleasures of the mouth and that the intense guilt associated with these impulses must be penalized by starvation and purgation. Such mechanisms can be brought to light in analytic investigation of these patients, but their restoration to consciousness does not seem to produce an amelioration of the condition as in other compulsive states*" (p. 158). A decade later aspects such as the "*fear of gaining weight and a horror to becoming fat*" [(19), p. 109] were more commonly reported.

Rahman et al. (20) were the first to connect conscious dieting with unconscious motives in their comments on 12 cases: "*the remarks about fatness were utilized as excuses, presumably to avoid touching on more painful topics…* [as intense analysis reveal that]*… In all our cases the reticence about sexual topics was noteworthy. There was no case in which a history of masturbation was elicited. Most of them resented questioning of any kind but especially concerning sex*" (pp. 354–355). This connection was announced in the commentary made by Patterson Brown to the Nicolle's (18) paper read before The Royal Society of Medicine on November 8, 1938, linking superficial dieting to its symbolic function by remarking on how Nicolle had "*related the not eating to a fear of growing fat, and consequently sexually unattractive to the male. This explanation is superficial and inadequate as it does not recognize the active repudiation of sexuality which is going on in these cases and which I should like to stress. At the deeper and more primitive level of the mind where this occurs the ingestion of food symbolizes impregnation and obesity pregnancy*" (p. 162)[4]. On these grounds, Waller et al. (21) launched their theory of the fantasies of oral impregnation[5]. These fantasies of impregnation were soon to be widely reported, for instance, Meyer and Weinroth (24), who were impressed "*by the coincidence of environmental pregnancies with modifications of the clinical history*" (p. 393).

The in-forming capacity of the deep analysis process is well-illustrated in the following paragraph taken from Loeb (23) who notes: "*Fantasy life largely revolved around sexuality, urination, and masturbation, the patient equating masturbation with guilt and dirtiness - masturbation causing a cancer - cancer representing a growth that kills - and a growth as a pregnancy, saying 'people who are thin can't have babies' and 'I lost weight because my stomach looked so big, it looked like I was pregnant*" (p. 448). However, this colonization of the beliefs about oral impregnation fantasies has overlooked Nemiah's question of "*why, since oral impregnation fantasies are common, they so rarely lead to anorexia nervosa*" [(25), p. 263]. A similar inconsistency regarding the discrepancy between the high prevalence of diets and the low incidence of AN shall be examined below.

Nonetheless, it was precisely against this psychoanalytical emphasis on the symbolic significance of food, fears of oral impregnation, and incestuous involvement, and its usefulness for an effective treatment that motivated Bruch's seminal proposal of the core elements of AN. Bruch (26) had no qualms in stating this an instance of adultomorphizing of early behavior[6] "*which needs to be understood in not for what purpose food is used in the psychic economy, but how it has become possible for a body function to be transformed in such a way that it can be misused in the service of non-nutritional needs*" (underlined text were italics in the original, p. 467). Much in the line with the double-bind theory of schizophrenia (27), Bruch focused the lens on the mother-child early interaction process resulting in an incorrect programming of patients' inner awareness during this interaction.

In a later contribution, Bruch (28) launched her conjectural triad of disordered psychological functioning, namely "*disturbance in body image of delusional proportion… disturbance in the accuracy of perception or cognitive interpretation of stimuli arising from the body… and a paralyzing sense of ineffectiveness*[7]*…* [which was based] *on the observations extending over 10 years of 12 patients (3 males and 9 females) whose conditions closely resembled the original image of anorexia nervosa*" [(28), pp. 187–191]. Despite the exiguous number of patients[8], a fact rarely mentioned in the literature [i.e., (31)], Bruch's foresight remained unchanged in a posterior paper (30) where she addressed the differential diagnosis between genuine, pure, true, primary, classical, and typical AN[9], in opposition to secondary, pseudo, non-specific, or atypical AN. In this paper (30), after recruiting 33 more patients, together with the 12 originally described in her previous paper, she performed a debugging task to differentiate the typical anorexia nervosa observed in 30 cases "*characterized by alterations in body image delusional proportions,*" from "*13 cases of refusal to eat in the service of neurotic or schizophrenic conflicts*" (p. 566). Later on, in her book *Eating Disorders: Obesity, Anorexia Nervosa, and the Person Within* (34), Bruch once more increased the sample to 70

[4]Ten years later Moulton (17) interpreted the discomfort displayed by an adolescent during nasogastric intubation through the lens of the oral impregnation fantasies theoretical frame: "*For the first five months in the hospital, she was tube-fed daily by different doctors. She said that 'only daddy can put it down without hurting,' and took it with passive disgust, meanwhile making obviously erotic pelvic movements*" (p. 72).

[5]Within the psychoanalytic formulation, the fantasies of pregnancy were nothing more than the elaboration of the difficulties of adolescents in their transition from adolescence to young adulthood as Rank (22) had pointed out: "*The separation of the growing individual from parental authority it is one of the most necessary achievements, but also one of the most painful of evolution*" (pp. 63–64). In fact Loeb (23) proposed useful "*to conceive of this 'Peter Pan' syndrome as the acting-out of the wish not to grow, to remain always the favored dependent child, unthreatened by the demands of sexuality, of adulthood with its attendant responsibilities*" (p. 450).

[6]She defined adultomorphizing as the "*tendency of interpreting unknown behavior in terms of adult meaning that psychoanalysts have tacitly accepted from Freud*" [(26), p. 3].

[7]Mayer (29) is one of the rare cases that is skeptical of Bruch's third characteristic of a sense of profound ineffectiveness in AN patients; in his experience Mayer stated he "*has not received this impression from the patients he has seen*" (p. 531).

[8]In a posterior paper Bruch (30) introduced certain inconsistencies in stating that the sample of 12 patients included those treated between 1955 and 1959, half the time period cited in the 1962 paper: "I saw only six cases between 1942 and 1954, 12 from 1955 to 1059, and 25 from 1960 to the middle of 1964" [(30), p. 556].

[9]Selvini Palazzoli (32) also added the synonymous essential "*anoressia mentale essenziale*" (p. 29), and more recently Strober (33) still added two more synonyms, *pure* and *prototypic*.

patients (60 females and 10 males), 50 of whom were considered typical AN cases (45 females and 6 males), for whom she maintained the same triad of characteristics mentioned above.

Since its inception, Bruch's proposed key role of BID has been hailed to the Olympus of undisputed psychiatric wisdom *before* any empirical evidence gathering apart from Bruch's theoretical discovery (35). For example, as early as 1966 Daniel Cappon's letter (36) to the editor of the *Journal of the Canadian Medical Association* refuted Farquarson and Hyland's (37) 20 to 30-year follow-up report on 15 patients treated by these authors from 1932 to 1943. In Cappon's letter to the editor[10], he asserted that Farquarson and Hyland's (37) paper was misleading for a number of reasons, among which was the lack of acknowledgment that "*The cardinal aspects of the syndrome are disturbances of body image and concept of physical self, failure to interpret enteroceptive signals, especially those of appetite (often due to a fear of opening the floodgates for eating, sex, etc., and non being able to stop), and denial of fatigue*" (p. 1,062). What triggered Cappon's commentary was Farquarson and Hyland's (37), **Table 1** observation that teasing about being fat in adolescence cannot be taken as the sole origin of the abhorrence and fear of obesity. This same line of reasoning opposing the rarity of the AN, against the epidemic of diets among adolescent girls and young women was expressed more recently by Casper (42).

The caution against excessive generalization referred to by Farquarson and Hyland (37) had already been voiced 30 years earlier by Ryle [(13), see **Table 1**]. In the eight vignettes included in Ryle's (13) paper, five correspond to the youth group (composed of 33 patients, mean age 20 years), and in only one case, case 5, a girl aged 19 "*began to 'bant,' having been told that she was too fat*" (p. 896). In a later paper, Ryle [(39), see **Table 1**] was even more explicit about the error in considering dieting and slimming practices in response to teasing about fat as the sole cause[11]. Furthermore, Berkman [(40), see **Table 1**] highlighted the link teasing-slimming was restricted to a subgroup of young girls (13- to 15-year-olds). Similarly, according to Langdon-Brown [(38), see **Table 1**], slimming was only one of the three reasons upon which patients rationalized their restricted eating. Finally, dieting because "*abhorred fat people or the idea of becoming fat*" was mentioned in less than a third of cases reported by Kay and Leigh (44).

Dieting, however, was soon considered the main road for the relentless pursuit of thinness. What had changed? Obviously, as Bruch pointed out the slimness, conscious society had contributed to a new risk factor: the ubiquitous thin ideal cliché, via its internalization by the pre-anorectic adolescent patient. Actually, it was not Hilde Bruch, but Selvini Palazzoli [(32), see **Table 1**] who first mentioned the cultural ideal of slimness as a factor in the etiology of AN[12].

Nevertheless, the mantra linking social pressure to fit the ideal thinness, and its internalization by vulnerable adolescents, became far more widely accepted than supported either by research or by patients themselves. The assumption that thin internalization is a risk factor in AN has been rebutted by the most extensive study to date involving data from 3 prevention trials involving High-Risk Adolescent Females [(41), see **Table 1**]. Likewise, Striegel-Moore and Bulik (45) lucidly mention that the thin-ideal internalization framework resides more in the minds of clinicians and researchers than in the minds of patients. The idea that media influence is a direct causal agent is so widespread that, as Polivy and Herman (46) pointed out, it would be necessary to explain why the incidence of AN does not have pandemic proportions.

A Brief Overview of Research on the BID Construct

Since the publication of the *DSM-III* (47), the criteria for AN diagnosis have experienced an uneven weakening of signs and symptoms. Thus, in the *DSM-5* (48) two of the three criteria for AN diagnosis involve unobservable symptom complexes, i.e., body image disturbance and fear of fatness. Moreover, the removal of the amenorrhea criterion, the only sign (criterion A) referring to low bodyweight, has progressively become less stringent compared to the demanding clear cut-off point of at least 25% body weight loss in the former *DSM-III*.

Whilst the list of signs has undergone profound changes, in comparison the symptoms that are part of the BDI construct have remained relatively stable. However, despite its status as a core symptom for AN diagnosis, the BDI construct has not obtained sufficient empirical support to dispel the doubts of being an epiphenomenon of the characteristic low weight of these patients. This perspective was already clearly pointed out by Berkman (40), even before the publication of the cognitive, emotional, and behavioral changes of starvation arising from the Minnesota starvation study (49, 50)[13], also mentioned by Dubois (19). According to this view, both somatic symptoms as well as the mental make-up of AN patients would be deemed consequences of starvation.

Nonetheless, the continued presence of symptoms of the BDI construct in the latest *DSM-V* and *ICD-11* (51) would suggest that the accumulated evidence around this construct is irrefutable, which is not so. In fact the evidence on the BDI

[10]It is interesting to note that Cappon quoted not Bruch's (28) original work, but a paper read at the first international symposium on anorexia nervosa in Gottingen in April 1965. Nevertheless, just a few months later, Cappon judged BID was already cardinal.

[11]This list of initiating factors was quite similar to that annotated by Déjerine and Glauckler (43) in cases of true or primary mental anorexia such as "*Grief, disappointment in love, or unhappiness in marriage are very often the emotional source of the most characteristic mental anorexias.*" *In other cases the restriction is at first voluntary and intentional. It is often due to coquetry …* [Dejerine and Glauckler also list] mysticism and poverty where persons "*obliged by the necessities of life to deprive themselves to such a degree that, when the illness or lack of employment which has caused these privations has disappeared, they find it impossible to take food again*" (pp. 4–5).

[12]In addition, Selvini Palazzoli (32) underlined in primary AN "*la necessita di divenire emaciate*" (p. 32), which was over translated into English (32) as a "*desperate need to grow thinner*" (p. 23), perhaps to parallel Bruch's description of primary AN as a relentless pursuit of thinness.

[13]Relevant to Bruch's third characteristic of a sense of profound ineffectiveness in AN patients is the comment on the young men participating in the Minnesota starvation study, "*They became discouraged because of their relative ineffectiveness in daily living. Inability to sustain mental or physical effort contributed much to this feeling of inefficiency*" (p. 33).

TABLE 1 | Relevant opinions regarding being teased as precipitating factors of dieting and slimming practices in AN.

Langdon-Brown (38)	*"Anorexia was rationalized by one of three grounds: (1) humanitarian pleas; (2) slimming, especially if there had been teasing because the young woman had been getting somewhat plump; (4) on religious grounds" (p. 308).*
Ryle (13)	*"Slimming', usually instigated by the ridicule of school friends on account of adolescent plumpness, is generally considered second in importance to these emotional crises. Four cases at least in this group originated in this way" (p. 895).*
Ryle (39)	*"Of initiating or contributory factors, other than slimming in response to teasing on the score of adolescent plumpness (and this can rarely be accepted as a sole cause), love affairs, broken engagements, school attachments and jealousies, home sickness (especially in the case of girls sent abroad), unhappy home life, spoiling by devoted parents, mental shocks, examinations and overwork, and convalescence from a physical illness or operation are all noteworthy" (p. 26).*
Berkman (40)	*"of young girls, 13 to 15 years of age, who during the grade school years…they may realize that they are overweight or may be cruelly reminded of this fact by others. As a result they markedly cut down on their food intake" (p. 682).*
Selvini Palazzoli (32)	*"But to these predisposing generic pathogens we can also add more specific ones: the fashion of being thin and sophisticated, the widespread commercials on diets and drugs to lose weight, the continuous talks on calories and weight loss among family members and friends and, especially, the jokes reserved to women of the type in Rubens's paintings. Nowadays, our cultural environment does not accept the fat woman, doomed to be alone and rejected"* [(32), *p. 58, translated from the original in Italian*].
Farquarson and Hyland (37)	*"It is extremely difficult to learn what the most important precipitating factors in anorexia nervosa may be, for one cannot fathom an adolescent's mind. Abhorrence and fear of obesity loom large in the thinking of many patients. In eight of our patients the onset took place when the patient was subjected to teasing about being fat, or was simply overly conscious of obesity. One cannot accept this as the sole factor, however; otherwise anorexia nervosa would be a common and not a rare disease" (p. 419).*
Stice et al. (41)	*"One striking finding is that low BMI, low dieting, negative affect, and functional impairment predicted onset of AN and a low BMI, whereas the risk factors relating to cultural pressures for thinness and resulting body dissatisfaction and weight control behaviors did not… The fact that thin ideal internalization and body dissatisfaction did not predict AN implies that cultural pressure for thinness do not increase risk for AN" (p. 50).*

construct around the time the *DSM-III* was issued (52) was less than promising with a "*marked inconsistency of findings…* [and] *a fairly consistent finding across studies is greater intersubject variability*" [(53), p. 493]. In the same vein Garner and Garfinkel (54) noted, "*It is unclear whether body image disturbances are pathogenic or strictly a byproduct of a serious eating disorder*" (p. 280).

Although currently BDI is mostly considered a maintenance factor, originally the conception of BDI was the product of an informal fallacy derived from a reasoning error known as the "*post-hoc ergo propter hoc*" fallacy, also known as *"post hoc" fallacy*. This fallacy asserts that if one event occurs after another, the second event is a consequence of the first. In other words, in the acute phase of AN, the "douce indifference" (55) of severely emaciated AN patients shows no concern for their physical appearance, or even claiming they want to stay as they are, or even lose a little more weight, then this apprehensive behavior is the cause of their emaciated state. However, since its discovery by Hilde Bruch likely correlation has been misinterpreted as causation. This flawed form of reasoning was common at the time of the "double bind" hypothesis of schizophrenia (27) that inspired both Bruch (34) and to a greater extent Selvini Palazzoli (32).

The BID construct has two main unsolved problems. The first of them has to do with its multifaceted nature, while the second problem area has to do with its clinical management. The first dissection of the BID construct into its main components was made by Garner and Garfinkel (54). According to these authors, the BDI construct would encompass three types of disorders: perceptual, cognitive, and affective. The first type of disorder has generated extensive research framed under the label of body size distortion, while the study of the last two aspects has been addressed as body dissatisfaction (53). However, in addition to research on the perceptual and cognitive-affective components of the BID construct, Legenbauer et al. (56) remark insufficient attention to other components of BID construct such as dysfunctional body-related behaviors, such as body checking and avoidance behavior. Nevertheless, more than 30 years later, some authors consider BID construct as one of "*the most discussed and controversial symptoms in AN*" [(57), p. 42], and that the "*distinctive features and mechanisms of BID remain unclear, specifically in regards to the contributions of sensory perceptual distortions v. cognitive–affective disturbance*" [(58), p. 642].

Undoubtedly, because BID was originally conceived as a sensory-perceptual deficiency (59) this perceptual aspect, that is, the tendency of patients with AN to overestimate their body size, has been the component of the BID that concentrates greater research efforts. However, this aspect encompasses such a diversity of methodologies (from movable calipers to eye tracking techniques) and stimuli (own body to 3D avatars) and different control groups that a systematic review exceeds the limits of this paper. In addition, to research on the perceptual and cognitive-affective components of the BID construct, Legenbauer et al. (56) remark insufficient attention to other components of BID construct such as dysfunctional body-related behaviors, such as body checking and avoidance behavior. Still, with respect to research of the cognitive-affective component of BID construct, as Eshkevari et al. (60) warn, patients' exteroception has been prioritized in BID research in detriment of BID interoceptive aspects that are an essential source of information for the AN patients' experience of their bodies. However, as is often the case when research activity on a phenomenon is intense, this intensity is often misinterpreted as evidence of proven results. In this regard, as Smeets (61) noted: "*In research on distorted body image, many assumptions have been made. As is often*

the case with assumptions, they have come to have a life of their own and, over time, have acquired the status of established facts" (p. 76).

On the other hand, a second controversial issue is related with the need to address BDI in the treatment of AN. At this respect Bruch (34) stated that correction of the BDI was a "*precondition for recovery*" (p. 90), but evidence accumulated to date is far from clear in this regard. It is almost a convention in any review of the BID literature to mention that the severity of BID predicts long-term outcome in AN patients, and that persistence of BID predicts the rate of relapse (62). However, there is a blatant disproportion between the frequency of these claims and the supporting evidence and most importantly the continuity of the "uniformity myth," which erroneously considers ED as a homogeneous category where the differences between the different disorders are less important than their communalities, as proposed by transdiagnostic theory (62).

Relevant information about the pertinence of targeting BID construct and its relation with treatment outcomes in AN is found in recent work from an Italian team researching focus on body-image concern (BIC), a core construct both in CBT for adults and in CBT-E—an enhanced form of CBT (63) based on the transdiagnostic theory (64). BIC entails three components, namely "Preoccupation with shape/weight," "Fear of weight gain," and "Feeling fat." However, Calugi and Dalle Grave [(65), p. 584] found that "*our data suggest no relationship between the change of BIC components that occurs during treatment and the change in BMI centile over time*." Notwithstanding this shortcoming the authors did not moderate the importance of the core BID construct but they stress that CBT "*works as a whole; in other words, the improvement in body weight seems to be mediated by its overall application rather than its single components*." In a posterior paper Calugi et al. (66) acknowledge that despite CBT-E directly addresses BIC, they concluded that "*the research done to date has not yet clarified whether body-image concern is in fact a core characteristic of eating-disorder psychopathology or merely an epiphenomenon*" (p. 64).

Also relevant to this matter are secondary analyses conducted by members of the Anorexia Nervosa Treatment Outpatient Study (ANTOP). ANTOP is the worldwide largest randomized controlled trial and compared focal psychodynamic therapy (FPT), enhanced cognitive behavioral therapy (CBT-E), and optimized treatment as usual (TAU-O) in adult outpatients with AN (67). These authors documented what they denominate a "*persistency effect*" of BDI remaining high while body weight increased, irrespective of treatment arm (68). Furthermore, they reported that "*The associations of body image perceptions with symptoms of depression and anxiety appeared to increase along the course of treatment despite overall improvement of depression, anxiety, and body image disturbances with treatment duration*" [(69), p. 146]. The apparently contradictory results are commented by the authors in a later publication where body image perceptions predict symptoms of depression and anxiety in the course of outpatient treatment "*which in turn predicts depressive symptoms at the end of therapy which in turn predicts the outcomes body mass index and EDI-2 sum score at 12 months follow-up*" [(68), p. 49]. However, although these authors speculate about the possibility that the relationship of body image self-appraisal and symptoms of depression might be bidirectional, they remark the importance of addressing BDI during AN treatment. However, they caution about probable "*adverse effects of eventually increased stress levels in patients with AN when explicitly focusing on body image self-appraisal during psychotherapeutic intervention…[which] subsequently leads to worsening of affective comorbidities (and not to the intended habituation) and hence to less favorable treatment outcomes*" (p. 56). Still, a recent meta-analysis of randomized controlled trials of body image interventions designed to target body image dissatisfaction among non-clinical populations, including fitness training, self-esteem enhancement, media literacy, and psychoeducation, found "*only a small effect size for improving body image across these interventions*" [(70), p. 163].

Nowadays, a panorama of mixed findings summarizes the state of the art regarding body image-related interventions covering most widely adopted strategies (cognitive restructuring, mirror exposure, video-confrontation, and virtual reality) but without even passing the promising results phase and the absence of replication being a main problem. However, in spite that the two main problem of BDI are unresolved and without promising prospects in the near future still there are proposals for re-classifying AN "*under a new category of body image disorders, together with other mental illnesses in which body image is the dominant feature, such as BN, body dysmorphic disorder (BDD), and muscle dysmorphia (MD)*" [(71), p. 14]. However, with respect to BDI "*We are still living mainly on assumptions*."

A further aspect of the tyranny of the BID construct that should not be overlooked is the bias in the understanding of hyperactivity in AN. Mainstream thinking considers hyperactivity as a mere weight-losing strategy, that is, patients feel fat and want to lose weight because their BID is fuelled by social pressure to be thin. Hyperactivity has been described in anorexia nervosa by clinicians and researchers since the first modern descriptions of the illness (42, 72). Excessive exercise is a characteristic sign in AN with some estimates raising its prevalence as high as 80% (73). Although excessive activity was considered a fundamental clinical feature (74) before the *DSM-III* was released (52), hyperactivity has been traditionally considered a Cinderella among AN signs (75), and accordingly it has been assigned a secondary rank in the *DSM* series, and is conceptualized as a mere calorie burning strategy (76). This conceptualization contradicts research showing that excessive activity often precedes the onset of the disorder (77), as first pointed out by Janet (78) who stated that "*the exaggeration of the movement is sometimes anterior to the refusal of food and therefore precedes all these reasonings*" (p. 501). In the first case of AN described in detail in the literature, Lasègue (79) stressed that in AN the abstinence from food "*tends to increase the aptitude for movement*" (p. 266), and also early in the literature Janet acknowledged the negative impact of excessive activity upon eating when he stated that "*The exaltation of the strength, the feeling of euphoria, as it is known in the ecstatic saints, for instance, does away with the need of eating*" [(80), p. 242]. It was Gull (81) who was the first to acknowledge that this hyperactive profile should "*be controlled, but this is*

often difficult" (p. 25), an observation that is valid for current treatments that consider excessive activity in AN as a voluntary calorie burning strategy at the service, of course, of the BDI construct. This interpretation has been recently challenged in a study (82) where the physical activity of AN patients was significantly modulated by environmental temperature beyond the eventual regulatory function of anxiety, negative affect, body dissatisfaction, and drive for thinness. It is worth noting that this modulation of environmental temperature is similar to the experimental evidence gathered from research with an analogous animal model of AN known as Activity-Based Anorexia (ABA) where ambient temperature (AT) is a critical factor contributing to the expression of excessive running activity. The increase in AT to 32°C completely prevented and fully reversed excessive activity in ABA rats (83, 84). Thus, incorporating warming as an adjunctive treatment for AN patients is a promising alternative to controlling hyperactivity (85, 86), and a heated environment (again at 32°C) reduced post-meal anxiety in AN patients (87).

TYPICAL AN AND ATYPICAL AN: NOT ATYPICAL AN, BUT THE TYPICAL DOCTOR

Though numerous clinicians and researchers since Déjerine and Glauckler (43) have attempted to define AN as a separate nosological entity [i.e., (31, 32, 88–91)], none has had the significance of Hilde Bruch's seminal work. Thus, from the 1960s onwards primary anorexia nervosa was defined in terms of the pathological pursuit of thinness and its association to the disturbed body image (92). The binding association between BID and the typical presentation of AN implicitly entailed all other patients not presenting this characteristic were excluded and assigned to a dubious class of atypical AN. An unintended consequence of Hilde Bruch's use of the term "classical" as a synonym for "typical AN" was the usurpation of this qualifier for all the cases described from the time of Marcé (10), Lasègue (79), and Gull (81). Furthermore, the use of the term "classical" as synonymous to "typical AN," which according to Bruch (28) "*closely resembled the original image of anorexia nervosa*" (p. 187), implied that the triad of characteristics were intrinsic to the very essence of AN. However, given that AN reports in the 60 years prior to Bruch's description, with the exception of the abovementioned antecedents that emerged from the psychoanalytic circle, were mostly devoid of any BID features, we are compelled to examine other alternative explanations. Among these possibilities the most accepted is the one that supports the absence of BID in the psychopathology of AN before Bruch (28), claiming that BID emergence is an evidence of the changing nature of AN. Thus, if the phenomenology of AN had changed, this change would exempt renowned doctors such as Marcé, Lasègue, Gull, Janet, Déjerine, among others, for being blind to Bruch's observations. Russell addressed this point when he said that "*neither Lasègue nor Gull drew attention to the psychological disturbances which appeared so striking lo late observers: the patient's disturbed experience of her own body* (30), *'weight phobia'* (93), or *'morbid fear of fatness'* [(94, 95), p. 7][14]." Russell (12) had previously found that "*these simple observations have only been made in the past fifteen years or so. At the time they were hailed as new discoveries. Yet it would seem surprising that generations of able clinicians should have missed basic and plainly discernible features of the psychopathology*" (pp. 104–105). The explanation put forward by Russell to settle the matter was to state "*psychopathology of anorexia nervosa has changed between 1870s and the 1960s*" [(95), p. 7].

An alternative to the idea of a change in the phenomenology of AN claims that BIDs have always existed, but the absence of BID reports in the medical literature before Hilde Bruch can be explained by the reticence on the part of both patients and doctors. According to the main exponent of this view, Habermas (96), the scarcity of BID reports in the medical literature was due to "*the anorexic's tendency to hide their weight-related motivation, as well as to the corresponding unawareness of most physicians*" (p. 360). But, how could this epidemic of blindness among physicians be overlooked in the face of the obvious? The explanation provided by Habermas (97) illustrates well the role of "*pre-established expectations about what is observed and what is neglected*" by doctors themselves. Therefore, according to this point of view, the selective report and the physicians' BID rely more on membership to "schools of convictions" (98) and the physician's specific training, than on the changing nature of AN. As evidence of his thesis, Habermas (97) mentioned some exceptions to this ignorance in recording the intense fear of being overweight in six of the nineteenth-century case reports and that "*all but one of the authors were French*" and "*most of them were in some way related to the Salpétrière, were Charcot was working and lecturing*" (p. 263). Further on, Habermas adds: "*Once introduced into French psychiatric thinking, other clinicians also discovered the anorexic's fear of obesity, whereas the British and German doctors, not having their attention focused on weight-related fears by a national authority, simply did not see it*" (p. 269)[15].

However, the fact most of these French authors reporting fears related to weight were linked to the Pitié-Salpêtrière Hospital in Paris, where Charcot had worked for 33 years (1862–1893), only implies they were under the influence of Charcot, and not that Charcot was right. Actually, one of Charcot's eminent students, Pierre Janet, criticized him for exaggerating on this matter: "*The authors who have observed such ideas seem to me to be inclined to exaggerate their importance. This is what certainly happened to Charcot, who used to seek everywhere for his rose-colored ribbon and the ideas of obesity*"

[14]Although Bruch (34) acknowledged in her book *Eating Disorders: Obesity, Anorexia Nervosa, and the Person Within,* the characterization of AN in terms of "weight phobia" made by Crisp (93), or the "morbid fear of fatness" by Russell (94), are contributions she could have claimed as her own given that in her 1966 paper she fully addressed the distinction between typical and atypical AN: "*It is of decisive significance whether a patient is preoccupied with its body size, with a relentless pursuit of being thin and a phobic avoidance of being fat*" [(30), p. 555].

[15]In the pre-*DSM* era Crisp (99) made a similar reasoning when he wrote: "*If the physician docs not have the disorder of weight in mind when he is interviewing the patient, he may misdiagnose the patient as having a neurotic adolescent disorder only reflecting whichever of the above behavior patterns and mood states is most evident at the time*" (p. 494).

[(80), pp. 234–235][16]. Nevertheless, Habermas (100) recognized this prescriptive influence of Charcot's observation when he stated: "*This indicates that once an authority had established the legitimate expectation that weight phobia could or even should be found and described in anorexic patients this trait was much more readily identified and reported*" (p. 325). The expression "should be found" goes beyond merely inviting to search and requires a mandatory confirmation. Therefore, the typical and atypical categories are a creation of the typical doctor equipped with a set of fixed expectations and assumptions. This is not only about gathering the fruits of nature, but also sowing them.

Even if Russell's suggestion that the phenomenology of AN had changed were endorsed, the BID requirement for the diagnosis of typical AN still posed a further problem for patients who failed to neatly fit the clinical profile of Bruch's description of typical AN as they were thrown into the catch-all category of an atypical eating disorder in the first *DSM III* (52), "*a residual category for eating disorders that cannot be properly classified in any of the previous categories*" (p. 69).

Soon after the appearance of the *DSM-III* in 1980, the first case reports began to appear that did not meet the newly released *DSM-III* criteria for AN diagnosis, either because they did not meet the weight criteria (101), or the BID criteria (102, 103). Moreover, the role of BID in AN diagnosis was further called into question following the first epidemiological and clinical reports of atypical patients appearing in the Hong Kong area (104), who did not systematically express fears of gaining weight, hence the name non-fat phobic AN patients (NFP-AN). Thus, both weight concerns (105, 106) and body image disturbances (103, 107), two criteria that remain essential elements for the diagnosis of AN under the *DSM-5*, were not endorsed. The first reports from Hong Kong were soon followed by others from other non-Western populations such as Singapore, Malaysia, Ghana, India, Sri Lanka, and Japan, as well as Asian and South Asian patients living in Western countries (108). However, the incidence of these atypical cases was not restricted exclusively to Asian or African populations since the incidence of this type of patient had been estimated to be around 20% of patients treated in Western countries (109). This percentage of up to 20% of NFP-AN cases in Western countries, more specifically in the United States and Europe, is an important nuance when employing Western as a label opposed to East Asian societies. This geographical dichotomy proves to be inappropriate since in countries such as Japan FP-AN cases are more common than NFP-AN cases (110), and there are also high levels of body dissatisfaction and thin ideal internalization, particularly among the population of high school and college-aged women (111).

The first study exploring differences between typical AN, according to *DSM-III*, and atypical patients without the pillars of the BID construct, namely weight phobia and body image disturbance (33), concluded that the classification of patients into typical vs. atypical diagnostic subtypes was "*nosologically valid and clinically useful*" (p. 135). From this study onwards, a second wave of studies explored quantitative differences between NFP-AN and FP-AN patients according to the different cut-off points on the Drive for Thinness Scale in successive versions of the Eating Disorders Inventory [EDI, (112)]. Although the present paper does not seek to undertake an exhaustive in-depth review of existing studies, the results are inconsistent regarding differences in premorbid characteristics, both in eating disorders and in the general psychopathology and outcome of atypical NFP vs. FP typical AN patients[17]. Nonetheless, the overall tendency appears to be less eating-related pathology, less severe psychopathology, and a more favorable course for NFP-AN patients (33, 109, 110, 113–118).

However, the very existence of atypical NFP/AN patients has implications that go far beyond the differences from their typical AN counterparts. First, BID symptoms, supposedly pathognomonic symptoms of AN, seem to be culturally mediated and, in this sense, the current "typical *DSM* AN" is neither purer nor truer than other atypical presentations reported in non-Western and Western cultures. This point has been well-expounded in Steiger's (119) comments on Lee et al.'s study (120), stating that "*Diagnostic conventions dictate that such cases [NFP-AN] should be labeled 'atypical', but this may simply be an invention. Actually, the syndromes characterized by self-imposed wasting can exist quite ubiquitously, although the concept of 'fat phobia' fits many of them bad … anorexia nervosa has a much weaker connection with a Western 'culture of thinness' than previously thought … Western culture can motivate elaborations in which fatness concerns are characteristic, but such expressions do not need to represent defining examples of the syndrome*" (pp. 66–67).

Therefore, according to (120), instead of the "typical AN" designation, the term "conventional AN" would be more appropriate, since it emphasizes that it is the result of a procedure accepted as true or correct by convention. Accordingly, the very essence of AN would be not reflected in what Bruch signaled as prototypic, genuine, pure, classic, primary, or typical, but rather the so-called typical AN picture, as depicted since the *DSM-III*, would be the result of a slow and constant acculturation process spread through the therapeutic milieu and mass media (121). The point is not whether AN can exist without cultural contamination, but rather if there is excessive cultural contamination that is currently sanctioned by the *DSM*, and widely circulated by the mass media. This excessive cultural contamination maintains an unintentional process of indoctrination that formats the patients' experiences and invalidates their own personal experiences. Hence, the successive *DSM*s since the third version could be considered the most active agent in homogenizing what should qualify as typical AN. Probably, as Russell (12) mentioned, the phenomenology of AN has changed, but this change was initiated and maintained by

[16]Janet describes how Charcot, "*while undressing a patient of this kind, he found that the adolescent wore on her skin, fastened very tight around their waist, a rose-colored ribbon. He obtained the following confidence; the ribbon was a measure which the waist was not to exceed. 'I prefer dying of hunger to becoming big as mamma*" [(80), p. 234].

[17]The atypical group is not a homogeneous category according to a recent study conducted in Japan (110). In this study, significant differences were found between a group of patients (NFP-AN) who did not meet Criterion B or Criterion C of the *DSM-IV* criteria, and the AN-NED group not fulfilling criterion C.

mental health professionals who disseminate their expectations among families, patients, public in general, and among other colleagues during conferences, specialist training process, and so on. Obviously, this approach reverses the taken for granted conception that atypical presentations are intrinsically deviations while the current typical AN is natural. Consequently, clinicians and researchers are not passive observers of how culture modulates and colors patients' testimony about their motives for food restriction. On the contrary, they are active agents who handle the brush and the color palette and whose workings, disclosed both through the scientific literature or divulged to non-scientific audiences, are collected and disseminated by the mass media exercising a demand-conforming offer, as Russell (12) has cautioned[18].

One of the aspects supporting the view that atypical AN is the true authentic AN without cultural contamination is the consistency of the clinical picture of AN between those patients described before 1960 and today NFP-AN patients. This means that for almost 100 years since first description by Marcé (10) to the seminal BDI publication by Bruch (28) what is considered today as atypical AN was actually the normal presentation as self-starvation was characterized by the absence of elements of the BID construct as motivating factors. Moreover, as above mentioned the absence of the fear of fatness and body image disturbances are characteristic in patients with NFP-AN in both non-Western countries, and around 20% of AN patients in Western countries.

Twenty-five years ago Russell (95) already expressed his caveat concerning the alleged core role of one of the elements of the BID construct in AN diagnosis by pointing out that "*The dread of fatness is likely to be a modern development in the psychopathology of anorexia nervosa. It need not persist in future generations of anorexic patients. The time may be approaching when it will be advisable to retreat from our cherished diagnostic criteria of anorexia nervosa, as there may be a false precision in the current formulation*" (p. 10). Nonetheless, the most widespread interpretation of the absence of BID in atypical AN is patient denial.

DENIAL AND INVALIDATION: THE RELENTLESS PURSUIT OF FAT PHOBIA

This section refers to the quasi-compulsive need of confirming that patients with AN suffer from fat phobia (a component of BID as explained in footnote[1]). Germane to this, *DSM-5* criterion C has lowered the *DSM-IV* charge of active "*denial of the seriousness of the current low body weight*"[19] by a supposedly more descriptive "*or persistent lack of recognition of the seriousness of the current low body weight*[20]." Despite this subtle change, it is doubtful that the clinicians' lenses are so polished as to discern the subtlety distinguishing active denial from persistent lack of recognition. From the patient's point of view, the transition goes from the experience of being accused of denying, to not wanting to recognize something that the clinician knows is there.

The notion that patients are manipulative, lie, and hide information is certainly old in the literature, but appears precisely when AN patients, previously rescued from the lures of endocrinology (13), were again rescued from the lures of psychoanalytic unconscious motivations. As mentioned above, this release was the merit of two psychoanalysts, Hilde Bruch and Selvini Palazzoli, but the ransom price was the charge of denial and untrustworthiness. Thus; Selvini Palazzoli (32) stated of AN patients: "*They always have excuses ready, they can lie to the point of ridicule*" (p. 27, translated from the original in Italian). Even Selvini-Palazzoli exonerated Gull and Lasègue[21] from not being able to go further in their early description of AN as "*the patients' negative attitude prevented them from communicating their inner experiences to the physician and obstructed all attempts to delve into their psychological motives, the more so as most of them showed a marked lack of introspective powers*" [(32), p. 9]. This is in stark contrast to Lasègue's (79) statement that he was unable to obtain the reasons underlying food avoidance in the patients he consulted as "*None provided me in this retrospective investigation with information other than what I have reported: 'I could not, it was too strong for me, and besides I was well'*" (p. 402, translated from the original in French). The same frustrating experience was reported by Berkman (124) who reported "*On being questioned, most of the patients are unable to express an opinion, or will not do so*" (p. 412).

What numerous clinicians have heard from AN patients has been an unremitting complaint regarding abdominal pain and discomfort: "*dans des douleurs gastriques*" [(79), p. 386]; "*to be troubled with indigestion*" [(125), p. 613]; "*epigastric distress*" [(126), p. 1,085]; "*organic disease of the stomach (ulcer)*" [(127), p. 745]; "*varied gastrointestinal symptoms*" [(128), p. 817]; "*indefinite gastrointestinal disturbance*" [(40), p. 681]; "*abdominal discomfort*" [(19), p. 113]; "*dull or burning pain in the epigastrium*" [(25), p. 256]; "*abdominal discomfort, a common cause of complaint in the early stages of treatment*" [(129), p. 1,771]; "*constipation and minor abdominal disconfort*" [(130), p.

[18]This active role could be an explanation for the unprecedented change in the proportion of typical FP-AN vs. atypical NFP-AN in Hong Kong. While a ratio around 40/60 was documented in the first reports in the first period 1987–1989, in the 2005–2007 period, the proportion had changed to 20/80 (117). How was this change possible?

[19]This change implies a distancing from the position held by Bruch, for whom "*This absolute denial of their starved appearance is pathognomic for primary anorexia nervosa*" [(122), p. 216].

[20]Lack of concern regarding its cachexic appearance has been a feature repeatedly documented in the literature. It was remarked by Berkman, "*they do not express concern over their loss of weight or cachetic appearance*" [(40), p. 681], or by Nemiah, "*especially striking is the lack of concern the patient shows for the seriousness of her physical condition and for her often shocking appearance*" [(25), p. 259]. Recently, a lack of concern and behavioral activation have been postulated as core symptoms of anorexia nervosa (42).

[21]In the same vein, the late Crisp (123) also excused Gull and Lasègue for not having been able to glimpse the fat phobia in their first description of AN disorder because: "*Refusal, in the initial clinical consultation, to recognize or admit to any phobia of normal adult body weight is common enough, especially if the history of initial pursuit of weight reduction has been kept a secret. It is unlikely to have come readily to the attention of those recognizing and struggling to help people with the disorder in the 19th century, when it was first labeled*" (p. 197).

345], "*abdominal tenderness [. . .] and complaints of unbearable abdominal fullness follow the ingestion of even small amounts of food*" [(31), pp. 445–446], "*abdominal pain*" [(131), p. 438], and "*epigastric discomfort*" [(132), p. 594].

Interestingly, the same gastrointestinal complaints have been consistently mentioned by atypical AN patients (94, 101, 103, 108–110, 113, 118, 133). Likewise, a recent study (133) with typical AN patients reported, contrary to expectations, more gastrointestinal symptoms on a Gastrointestinal Dysfunction Scale than a comparison group consisting of NFP-AN patients. Thus, it is plausible to suggest that the absence of reports of gastrointestinal complaints in typical FP-AN patients in the literature was either the result of biased reporting by patients or selectively focused clinical questioning in accordance with diagnostic requirements. This unexpected finding reported by Lee et al. (133) is most interesting as gastrointestinal complaints has been recently identified as a predictor of positive outcome in a 30-year outcome report of the Gothenburg anorexia nervosa study (134).

Nevertheless, digestive discomfort is often seen as an excuse for hiding fear of fatness. This is another example of invalidation of the patient's own experience despite the fact that up to 16% of AN patients have gastric ulcers (135). Perhaps the phenomenology of BDI has changed due to cultural pressure, but this pressure does not seem to have influenced the uninterrupted report of digestive discomfort as an explanation for restrictive eating patterns from the time of Lasegue to recent reports of patients with atypical AN. This continuum deserves to be considered in good faith and not as active concealment and deception. Nonetheless, both past and present interpretations of the absence of BID reports by AN patients still continue to be attributed either to their marked lack of introspective powers (32), or to their defensive reaction, as Crisp (136) claimed: "*Individuals with anorexia nervosa deny their weight phobia, since general awareness of it would lead to their being considered by others as more responsible for their condition than is usually the case and would render them more vulnerable to outside influence by inviting much closer scrutiny of their motives and habits. Thus only a few anorectics are referred with an explicit history of postpubertal concern about their volume and shape, their dieting and weight phobia. The presence of weight phobia or shape or volume phobia and the overriding terror of fatness, within the context of low body weight and its attendant features described above, is pathognomonic of anorexia nervosa*" (p. 687).

However, to unveil these alleged pathognomonic symptoms referred to by Crisp requires substantial collaboration from patients, which leads to the question as to how this task is accomplished. First, during the clinical examination the clinician could attempt resolutely to discover the BID that fueled the patients' relentless pursuit of thinness. Kay and Leigh (44) already stressed how fundamental the psychiatrist's insistence was during the clinical examination when they asserted that "*A history of 'voluntary dieting' probably depends on the intelligence of the patient, her ability to rationalize, and her willingness to discuss her symptoms, no less than on the psychiatrists' zeal in searching out 'motives'*"(p. 413).

Furthermore, in addition, patients are usually required to complete a certain number of paper-and-pencil self-reports in face-to-face interviews where patients are again invited to reveal in writing their beliefs and attitudes (is it that they weren't pathognomonic?), these patients are not prone to disclosing their inner thoughts either verbally or non-verbally.

Nevertheless, if the previous strategies proved to be unsuccessful there was still the option of psychotherapy. These strategies involved reversing the burden of proof where it was almost impossible for patients to prove their innocence under the ubiquitous suspicion of denial.

THE ROLE OF THE BID CONSTRUCT IN THE ACCULTURATION AND INDOCTRINATION OF ANOREXIA NERVOSA

Undoubtedly, it is during treatment, especially when it involves hospitalization in eating disorder clinics, where the therapeutic culture and contagion from other patients push BID into the open. Though the cultural shaping of the treatment context is inevitable, the absence of a clear boundary between education and indoctrination is relevant in anorexia nervosa, particularly in terms of the patient's age, given that in the case of "early onset" or "onset in infancy" patients lack the possibility of critically examining the therapy rationale. In this sense, the term *indoctrination* is not used here in a pejorative sense but to highlight the active role of mental health professionals.

This is well-documented in Thomas et al.'s (137) report on the ultimate acknowledgment of BID in a congenitally blind patient with anorexia nervosa after her third admission to an Eating Disorders Center. The authors noted: "*Even when directly queried about shape and weight concerns during these first two treatment episodes (e.g., during individual therapy sessions and during body image therapy groups), Ms. A minimized their relevance to her long-standing pattern of restrictive eating. It was not until her third admission that Ms. A began to endorse body image disturbance actively*" (p. 17). Moreover, the authors acknowledged that "*It cannot be ruled out that simply hearing other patients talk about their own poor body image or hearing clinicians target body image concerns in both group and individual therapy may have contributed to the initial development or increased salience of such concerns as legitimate rationales for food refusal*" (p. 18). Nonetheless, Thomas et al. (137) concluded that Ms A. "*exhibited such great preoccupation with body image,*" which was contrary to previous case reports (138–141) suggesting body image concerns may not be central to eating pathology among blind individuals. In the same vein, in Yager et al.'s (142) report of the first case of AN in a blind woman, treatment context contagion was mentioned again by the authors "*Psychiatric admission with other anorexic patients preceded the illness*" (p. 506).

More "spontaneous" migrations toward the typical presentation of AN in North America were reported by Woodside and Twose (143) in the following excerpt: "*The most interesting clinical observation that we could add here relates to*

the effect of placing such individuals in a group therapy treatment program primarily attended by women with classical North American anorexia nervosa. The inevitable outcome seems to be that over the course of 2 months the women of Chinese or Indian origin acculturate to the dominant culture of the program, gradually abandoning their original rationale for food avoidance and developing a fear of fatness, a drive for thinness, and body image distortion! It is of course not certain that this represents an improvement, although it does allow for a more homogeneous group" (p. 13).

It appears that in the Eating Disorders Program at the Toronto General Hospital what was typical was not just patients displaying the classical *North American* AN, but also the widespread North American culture inspiring the BID rationale in the treatment of AN patients.

Moreover, white Anglo-Saxon women also experience the acculturation process, as one patient explained: "*I'm still not entirely sure why that is and I could be way off the mark, but I suspect that having significant chunks of my treatment revolve around body image, even when it wasn't currently an issue, may have partly contributed to that faulty line of thought*." This was written by a former AN patient in a blog (Science of Eating Disorders[22]) as a commentary on Ngai et al.'s (144) paper on the variability of phenomenology in AN. In this paper the authors described four cases presenting all possible combinations where the atypical NFP presentation was consistently present (case 1), evolved from (case 2) or toward FP typical AN (case 4), or was absent in a fourth case representing typical FP-AN (case 1).

Ngai et al. (144) quoted Bryant-Waugh and Kaminski's (145) remark that among the 8- to 14-year-old age-group of "early onset" or "Childhood onset," the fact that fat phobia emerges as treatment progresses confirms for these authors the denial of this fear early in the illness. However, it is equally valid to view this emergence as a disclosure subject to demand characteristics.

Zanker (146) was even more critical about the pressure to share the preferred language of treatments she received to rescue her from AN: "*In my 20s and early 30s I was unfortunate to experience the embarrassment and humiliation of 'body image' therapies. I possessed sufficient insight to recognize that my AN was neither caused nor sustained by distorted 'body image', body dissatisfaction or the desire for a very thin body. I did not restrict food and exercise in an obsessive, ritualistic way because I was trying to correct my physical appearance*" (p. 326).

This acculturation process, or perhaps the term *indoctrination* would be more appropriate, appears to have been operative for decades. Thus, Crisp (136) commented on the denial of weight and shape or volume phobia, the overriding terror of fatness of AN patients, and how "o*ften it remains concealed for years and may never be revealed. Only after recovery can anorectics talk more freely about the experiential forces that have been at work in their erstwhile 'illness'*" (p. 687).

Selvini-Palazzoli (32) gave a hint as to the process of turning awkwardness into confidence when she asserted: "*Now it is a well-known fact that anorexics rarely if ever tell the whole truth, except after prolonged and positive psychotherapeutic contacts*" (p. 11). Actually, in the Italian original version of her book there is a final appendix with a table showing demographic and clinical information of the 26 patients she had treated. In 14 of these cases, the duration of psychotherapy varied between 26 and 390 h, and in one case Selvini-Palazoli reported that she had lived with a patient for 4 months.

With regards to denial, determining the amount of pressure that may be reasonably exerted during treatment is a crucial question. In this sense, the case of Lucy, reported by Bruch (147), where at the end of treatment the patient recognized that she had hidden her fat phobia, is paradigmatic. Bruch was probably right[23], and Lucy hid her fears at the beginning of treatment, but as Thomas et al. pointed out (137) the risk is to try to impose treatment justification on patients who actually lack such fears. In this case, the therapist's insistence could lead to the patient deserting, or at least to a weakening in the therapeutic relationship due to discrepancies in the objectives between patient and therapist. The latter scenario was commented by a former AN patient on the Science of Eating Disorders blog. The blogger criticized the findings of two studies in which the evidence of the absence of BID was not considered to be a lack of BID evidence, but evidence of patient denial. In the first case the study by Gailledrat et al. (148) reported, "*a significant proportion of patients seeking treatment for ED had no or only mild concerns with body shape. This could be of surprise as body shape concerns are core symptoms of ED*" (p. 7). However, the authors rule out this finding because denial "*represents the main bias of this type of study and more specifically in patients suffering from AN-R.*" In the second study, Pilecki et al. (149) explored eating disorders in Poland in the context of Westernization and found that the "thin ideal" score items were "*considerably lower for patients with AN-R than for the healthy control group.*"

Instead of acknowledging these results, the authors were again skeptical about the veracity of patient self-reports. As the blogger commenting on these paper stated: "*in both these studies there is a clear issue with invalidation: some of the participants have indicated that body shape concerns or 'thin ideal' pressures are NOT driving their ED – and researchers have refused to believe them. In both studies references are made to authors such as Hilde Bruch or to the DSM definitions to back up claims that the respondents are in denial. They appear to take it for granted that if a participant does not endorse a prevailing social construct theory it is the person living with an ED who is suspect, not the theory. If they are unwilling to accept their participants' responses, you have to question what is the point of even carrying out the research*" (Science of Eating Disorders blog). However, the caution voiced by Russell (12) seems to have been largely ignored, a violation of the wise age-old adage "if the facts don't fit the theory, change the theory," as it's easier to change the facts, or invalidating them due to the lack of witness credibility.

[22]https://www.scienceofeds.org (accessed February 4, 2020).

[23]As reported by Bruch (147), Lucy confessed: "*It is so easy to say you are 'full'–it is a lie- it is only a justification. You have to deny yourself food. You can't say 'I want to be skinny,' not really, so you have to come up with a reason for everybody else. So you say you are full. It is easy to say 'I can't eat that much*'" (p. 81).

APPLYING OCCAM'S RAZOR TO PSYCHOSOCIAL AN TREATMENTS

As we have shown, patient acculturation as mentioned by Woodside and Twose (143) seems to make no difference in terms of patient improvement, although acculturation allows for a more homogeneous group. Furthermore, the patient's resistance to the acculturation process is rated with terms such as denial, active concealment, manipulation, and lying without enough self-criticism of the invalidation that acculturation entails. In any case, acculturation through treatment would be somewhat justified if this process increased the efficacy of the treatment. However, current evidence regarding the efficacy of psychological treatments in AN suggests that this is not the case.

As previously mentioned, SE-AN status refers to the inability of existing treatments to influence the course of the disorder. The space limitations prevent us from reviewing in detail the possible underlying causes of the absence of effective AN treatments [reviewed elsewhere in (150, 151)]. **Table 2** shows four sketches of AN treatment representing two "ancient" proposals and two more "modern" treatment proposals.

As for the first two treatments proposed by Déjerine and Glauckler (43) and Venables (152), both are unsophisticated as compared to the later treatment sketches of Kidd and Wood (31) and the more recent proposal of Attia and Walsh (153). However, there are some common aspects in the treatments proposed by Déjerine and Glauckler (43) and Venables (152); both advocate treatment outside the family[24] with an emphasis on patient education, and there are no excessive details regarding renutrition. Though both treatments insisted physicians should not give up, there are certain differences in the attitude toward the patient, from a firm and energetic attitude including threats in the case of Déjerine and Glauckler to a more patient attitude in the case of Venables (see **Table 2**, "*must be prepared to sit for almost any length of time over a meal . . . , never acknowledge defeat, and must never lose their temper*"). Psychotherapy is secondary, and prolonged and deep analysis is discouraged by Venables[25].

A radical change in AN treatment profile emerges in the 1960s, as described in the excerpts of Kidd and Wood (31). The combination of insulin and chlorpromazine was popularized by staff at the Department of Psychological Medicine at St. Thomas's Hospital, London (154). One of its members, William Sargant, reluctant to continue practicing leukotomies on patients, himself modified the procedure (158), aware of insulin failure at high doses for restoring patient weight "*to have been singularly unsuccessful in most patients, despite the hunger-producing effects of the insulin regime*" (p. 633), and proposed the combination of insulin and chlorpromazine, also at exceedingly high doses (up to 1,000 mg/day). In a later publication, Dally and Sargant (129) reported the supposed beneficial effects of this combination on body weight by reducing hospital stay and relapse after being discharged from hospital. However, these authors recognize themselves in a subsequent report (159), such promising treatment, which also included supportive psychotherapy and bed rest to avoid possible fractures due to hypotension episodes, did not produce a better outcome during follow-up with respect to a group of patients not receiving chlorpromazine, although it caused serious extrapyramidal effects in up to 50% of cases. Since then, there is no antipsychotic, either typical or atypical, that has not been tested in AN. However, the profuse contumacy in the dozens of clinical trials is only comparable to its inability to rule out the null hypothesis, not to mention weakness in its justification in AN.

A comparison of the two oldest treatments with the two most recent ones underscores both the complexification of treatment (31) and the multidisciplinary recruitment of different professionals (153). However, despite the lack of systematic follow-up studies, as far as the literature can be traced, there are no substantial modifications in the outcome of patients with AN since the 1960s. Thus, one of the preeminent studies published in the 1950s involving a 5-year follow-up of 25 of 38 patients concluded that "*Treatment is unsatisfactory*" [(44), p. 428]. The paragraph summarizing treatment is particularly worth quoting: "*The orthodox treatment, by supervised diet, was the one most often used, and was employed at some stage in 60% of the patients. Modified insulin was frequently used as an adjunct to dietary methods. Endocrine preparations of various kinds were given in 30%. Including therapy given in other hospitals, 25% (9 patients) received E.C.T., leucotomy, or insulin shock. 2 of the 3 patients who had leucotomy benefited, but the follow-up periods do not exceed three years. If, as we believe, most of these patients have personality difficulties, good long-term results following leucotomy are not to be expected. One patient gained a stone during a course of E.C.T. In another case, no improvement occurred after 15 deep insulin comas. A few had no treatment, because they either died, or else recovered, too soon. 30% received some form of psychotherapy, excluding simple reassurance and persuasion*" [(160), p. 671, underlined was italics in the original]. In hindsight, it cannot be ruled out that this type of clinical management had significant iatrogenic effects in patients receiving such treatment[26].

Interestingly, and despite their poor results, Kay and Leigh (44) declared that "*The time-honored treatment, by persuasion and meticulous supervision of the patient's diet, practized so success fully by earlier physicians, has in recent reports been found less satisfactory*" (p. 426). What had changed in the space of 20 years for the treatment proposed for example by Venables (152) to be no longer satisfactory? Perhaps the priced payed for the growing

[24] Although Lasègue (79) is generally considered first advocating isolation of patients from his parents ("worst attendants" according to Gull) it was Marcé (10) who stressed this parentectomy in the two cases described in his seminal work on AN.

[25] This recommendation against "*elaborate psychotherapy*" [(156), p. 746], or "*elaborate psychiatric methods*" [(39), p. 737], as well as the most blunt: "*in severe cases of anorexia nervosa it seemed to him almost criminal to waste time in anything like psychoanalytic investigations (however interesting they might be) at the commencement of treatment*" [(157), p. 745] can be found in the discussion following a conference presented on January 24, 1939, by Ryle (39).

[26] For patients receiving this treatment Kay (160) reported a recovery limited to 10–20% of the sample. However, regarding treatments Kay stated: "*As far as we know, the course of the disease is not influenced by endocrine therapy; psychotherapy has given poor results, as have other treatment methods*" (p. 674). It should be noted that this percentage was significantly lower than reported by Theander (91) at six-year follow-up for patients admitted to somatic and psychiatric clinics in southern Sweden for the period 1930–1960, with a recovery rate of 55%.

TABLE 2 | Excerpts showing the evolution of Treatment of Anorexia Nervosa across time.

Déjerine and Glauckler (43)	**Venables (152)**
We do not hesitate to say emphatically that it is impossible to treat mental anorexia in the family circle, and that to attempt it is to run the risk of certain failure of which the patient's death may be the outcome… Therefore, imperative, and in such cases it must be strict isolation. The desire to shorten its duration may sometimes of itself be enough to induce the patient to consent all the sooner to take food. As far as the alimentation itself is concerned, … Among patients who are still vigorous, as are the majority of the primary anorexias, one manages in 3 or 4 days to get to the point where one can give the classic amount to what constitutes overfeeding in a milk diet. If necessary, -that is, if the patient refuses to take the quantity of milk which is prescribed -one should proceed energetically. One may threaten the patient with the feeding-tube, and if necessary, use it. If he makes himself vomit afterward, as often happens, one must simply begin the gavage over again as soon as he is through. The very important thing is not to give in. As a matter of fact, however, when the physician's authority is sufficiently well established, it is very seldom that one is obliged to have recourse to such extreme measures, because, when he feels that he has to do with somebody who is stronger than himself, the patient generally submits. It may happen that, among certain patients who are extremely weak, one is obliged to seek for aid from ordinary medical therapy; one may thus have to give injections of serum, or hypodermics of caffeine, or camphor oil, to warm the patient by artificial means. These are urgent therapeutic measures such as are applied to people in the last stages of starvation and subjects who are at the point of death… In such patients psychotherapy must not be omitted at the start if the patients are strong enough, or if they have passed the most serious point in the disease where the danger of an unfortunate outcome has been avoided; it is necessary then to try to find out, in the different ways that we have indicated, the emotional, moral, or psychical causes of the anorexic conditions. We do not insist on this point… If the patients have really understood the mechanism of their disease, which at some time you must have explained to them, if you have succeeded by an emotional reaction in penetrating sufficiently into their mentality, it is rare if they do not rapidly comprehend your point of view. At first with effort, but later quite naturally, they will eat heartily and in sufficient quantities. Under these conditions one has no need to fear a relapse. It would, however, be almost fatal if after having made your patient gain a certain number of pounds you should leave him without having modified his mentality (pp. 321–322).	Every patient with anorexia nervosa can be persuaded to eat normally. The condition is hysterical, and the diagnosis of hysteria is only justified when the patient is subsequently cured. No patient should remain uncured, and most certainly no patient should be allowed to die. Directly the diagnosis has been made, treatment should be started. A full explanation should be given to the patient as to the condition present. It is useless to ridicule the sensations of which the patient complains. They are real. Discomfort, distension, repugnance to food and nausea-all are real. The patient has become hypersensitive to abdominal sensation. This is explained, and at the same time it is pointed out that in spite of the patient's sensation he can nevertheless eat, and his stomach, which is normal; can accommodate the food as it is of normal size. Anyone starting to treat a case of this type must be prepared to sit for almost any length of time over a meal. He must never acknowledge defeat and he must never lose his temper. The opportunities for annoyance will be many. He must remember that pure obstinacy is the exception; the patient has a real aversion to food in any form. He must be prepared to fight over every mouthful. With each successive meal taken the task generally becomes easier, and it seldom takes more than a week to establish a normal habit, when the patient can be left to take his meals without the presence of the doctor. From the first a full diet must be taken no matter how insufficient the diet has been in preceding months. Psychological causes should never be discussed at first, unless they are so obvious that they cannot be ignored. Even then I should only be in favor of' pointing out to the patient that I fully recognize that there is a cause for the abstention from food, but that the cause is psychological. It will be found that after the symptom of anorexia has been cured without loss of temper on the part of the physician, the patient's confidence has been gained. Then, if necessary, psychological causes become much more readily accessible and discussion becomes fruitful… I am never in favor of prolonged and deep analysis. The immediate cause is seldom hard to find, and a few frank discussions coupled with any necessary adjustment of circumstances should be all that is necessary. This method has been adopted in all the cases described and none have relapsed, nor have other psycho-neurotic symptoms supervened… All cases should be kept in bed, and it is generally necessary for the patient to have a special nurse. Treatment in the patient's home is most undesirable, and anxious parents should be excluded (pp. 225–226).
Kidd and Wood (31)	**Attia and Walsh (153)**
The most successful treatment regime appears to be the joint use of insulin and chlorpromazine or reserpine, given in combination with detailed attention to the patient's nutritional requirements and psychological needs. This regime was described by Dally et al. (154) and by Davison and Nabney (155) and its superiority over other forms of treatment was evidenced first by Dally and Sargant (129). This treatment programme is followed at Aberdeen, as in many other centers in Britain and abroad, with encouraging results. Each patient is confined to bed so that energy is conserved, observation is possible and food intake can be supervised. Chlorpromazine is prescribed in increasing dosage according to tolerance. Soluble insulin is given by intramuscular injection in increasing dosage and the resultant hypoglycemia is terminated when signs of sweating and drowsiness appear. Anabolics, vitamins, and high calorie food supplements are also given. Intubation is avoided as it is psychologically undesirable and rarely required. Throughout the early stages of treatment supportive psychotherapy is employed to provide encouragement, an atmosphere of understanding and to mold the basis of the doctor/patient therapeutic relationship. As the patient improves the drugs are reduced, graduated exercise is allowed and psychotherapy is employed to aid the patient in making the necessary readjustments in her psychological functioning that will both militate against relapse and favor better personality and social integration. Mayer (29) has emphasized rightly that psychotherapy should be directed toward specific aspects of the patient's abnormal emotional characteristics. He has described this as a re-educative procedure whereby the patient must gain the insight to learn, first, "to see herself as others see her, as an abnormally and unaesthetically thin individual"; second, to feel hungry and to want to react to hunger by desiring food; and third, to feel fatigue as others do. In short, psychotherapy here aims to reverse the characteristic triad of denfals. In most cases, psychotherapeutic support or management is required for some time after the patient has fully regained normal nutritional and menstrual functioning (p. 447)	Structured behavioral programs generally use a multidisciplinary treatment team that works to deliver consistently applied interventions that aim to normalize weight and eating behavior. Patients are presented with behavioral expectations, such as eating 100% of their food and achieving a significant rate of weight gain. Priority is given to providing patients with adequate calories to begin weight restoration. Approximately 3,500 kcal over maintenance requirements are required for every pound gained. The eating-disorders program at our institution begins with a prescription of 1,800 kcal per day in solid food. When the patient is medically stable (generally, between 2 and 7 days after admission), the diet is increased by 400 kcal per day every 48–72 h until it reaches 3,800 kcal per day, almost all of which (3,000 kcal) is provided in the form of solid food, with the remainder being provided as a liquid supplement. Patients are weighed three times per week and are expected to gain at least 0.75 lb (0.3 kg) over their previous highest weight each Monday, Wednesday, and Friday morning. An important component of the behavioral approach is that contingencies are established in the event that nutritional goals are not achieved. For example, the level of physical activity that is permitted may be decreased or the amount of supervision increased if a patient's weight does not increase by the recommended amount. Calories may be added (including nasogastric feeding) if weight gain is inadequate. Programs emphasize that such interventions are medically necessary to achieve agreed-upon treatment goals, not punishment for "bad behavior." Opportunities for activity and flexibility within the treatment structure are increased if the expectations are met and reduced if they are not met. Patients participating in behavioral management programs also receive a range of therapeutic interventions from a multidisciplinary team, which may include physicians, psychologists, nurses, nutritionists, clinical social workers, and occupational or recreational therapists. The specific goals of the treatment program include interruption of disordered eating behavior, the reintroduction of "feared" foods, and (especially as normal weight is approached) the practice of normal eating.

specialization was that patience, tact, and gentle understanding succumbed to the maelstrom of advances in technology and resources (antipsychotics, insulin, ECT, leucotomy, and so on) that left in the background essential elements of the doctor-patient relationship, as pointed out by Magendantz and Proger (15): "While *endocrine substitution therapy is being pushed, one should not forget the probable great importance of patience, tact and kind understanding of the patient's personal problems, a therapeutic approach in which the older type of physician seems to have been superior to our highly specialized, modern physician*" (p. 1,983)[27].

Paralleling the absence of efficacy of pharmacotherapy (162–164) the state-of-the-art regarding current evidence-based treatments after several randomized control trials barely exceeds a general "positive care effect"[28] (165, 166). Currently, a "tie score effect" summarizes evidence gathered from comparative efficacy studies as no treatment has shown to be clearly superior to any other. In addition, this result applies to the treatment known as Specialist Supportive Clinical Management [SSCM; (167)]. However, SSCM is a rebranding of a treatment previously referred to as Non-specific Supportive Clinical Management (NSCM), used as an active control condition in randomized controlled trials for AN that ended up being considered an effective therapy in its own right (151). On account of its efficacy, similar to other specialized brand type treatments (enhance cognitive behavior therapy—CBT-E, psychodynamic—PSYCH, interpersonal—ITP), the original authors justified their name change, and recently outlined the properties of SCSCM, despite not being based on any "*theoretical model of causation or theory-driven strategies*" (168). However, despite this apparent shortcoming, SSCM was effective instilling hope (169), and it was indistinguishable from Cognitive Behavioral Therapy for AN (CBT-AN) as "*both treatments were able to promote moderate therapeutic alliance in early treatment, increasing to strong therapeutic alliance in late treatment, to relatively the same degree*" [(170), p. 787].

McIntosh et al.'s (171) study was relevant for an additional reason to the appearance on the scene of SSCM treatment, which has since become the quintessential comparison treatment. Although originally conceived as a non-specific treatment, SSCM worked just as well as the other two treatments, CBT and ITP. This meant, for example, that the focus on weight and shape concerns, a central element of CBT, and the BID construct, made no difference in the outcome. Moreover, the same conclusion holds with respect to the interpersonal assumptions derived from treatments developed for other disorders such as depression, as in the case of ITP.

Moreover, subsequent evidence on the parity of SSCM with respect to two more treatments, the Maudsley model of anorexia nervosa treatment for adults (MANTRA) and enhanced-CBT (E-CBT), merit mention. Thus, SSCM fared equally well to MANTRA (172–174), a modular, research derived treatment based on a cognitive-interpersonal maintenance model of AN (175) that according to their designers "*does not emphasize weight and shape concerns, something that may be surprising to some readers*" [(176), p. 346]. SSCM was also found to be equally efficacious as a new treatment founded on a transdiagnostic model of eating disorders (62). This new version of the treatment added to the original cognitive conception of AN as a "disorder of control" (177) four additional maintenance mechanisms, namely clinical perfectionism, mood intolerance, low self-esteem, and interpersonal difficulties.

There is no simple interpretation of the collective results of clinical trials that have included a treatment such as SSCM, which could be considered of "low therapeutic intensity," compared to conventional psychosocial treatments such as CBT, ITP, MANTRA, and CBT-E. However, it is not far-fetched to say that for both AN in general, and SE-AN in particular, *less is more*, and that when that maxim is not respected, a high drop-out rate is the outcome[29]. Thus, it may also be reasonable to ask to what extent the status of a patient's SE-AN may also depend on the aggressiveness of the acculturation processes inherent to previous treatments. In this sense, SE-AN status is indicative not only of the intrinsic refractoriness due to low motivation of patients with AN but also of the iatrogenic effects of previous treatments. Exposure to treatments that do not respect either the rhythm or the peculiar low motivation of these patients, and focus exclusively on modifying egosyntonic aspects within the precarious equilibrium of the patient, are doomed to failure. The notion of respecting the rhythm of the patient is present in several quotations throughout this paper as manifested by some authors at the beginning of the twentieth century. For example in **Table 2** when Venables states, "Anyone starting to treat a case of this type must be prepared to sit for almost any length of time over a meal. He must never acknowledge defeat and he must never lose his temper." Likewise, Farquharson and Hyland (see text footnote[27]) noted that "the patients can often be helped by kindly support, calm discussion, explanation and persuasion, all entirely free from censure." In the same vein, we can place the "non-interpretive and fact-seeking approach" recommended by Bruch [(34), p. 336], who advised against any authoritarian attitude in therapy, i.e., avoiding telling patients how they should feel and think, as this would further reinforce their sense of profound ineffectiveness. More recently, in order to strength the cooperation with AN patients, Attia and Walsh (179) emphasized shifting the focus toward the ego-dystonic

[27] In the line of the soft treatment exemplified in the excerpt from Venables (152) included in **Table 2**, and the caution concerning deep psychoanalytic treatment, Farquharson and Hyland (161) state that "*Attempts to modify the abnormal attitude by intensive psychotherapy or by psychoanalysis has usually proved ineffective and sometimes worsens the condition. Fortunately, the patients can often be helped by kindly support, calm discussion, explanation and persuasion, all entirely free from censure*" (p. 418).

[28] A general positive effect in which the improvement might not be due to the treatment itself since the effect of spontaneous recovery should be taken into account, as mentioned by Theander (91) 50 years ago in his follow-up study of patients with AN when he said: "*Therefore, in the evaluation of a therapeutic method there is always reason to ask: to what extent are the results reasonably due to the treatment, and to what extent to 'vis medicatrix naturae'. The natural course of the disease should thus always be considered*" (p. 115, underlined was italics in the original).

[29] In this respect, in Touyz et al.'s (178) study the recalibration of aims in both treatments (SSCM and CBT-AN) corresponded with a low dropout rate of SE-AN patients.

consequences of the restrictive eating pattern of patients with AN, such as lack of concentration, anxiety, depression, increased irritability, hair loss, or feeling cold.

Finally, there is a disconcerting aspect in the intrinsic nature of AN, the recovery of a significant number of patients not receiving formal treatment. Though SE-AN is a serious chronic disorder, the spontaneous remission of the disorder was first noted by Lasègue himself (79). Likewise, Farquarson and Hyland (37) pointed that "*Sometimes they improve spontaneously with a change from a stressful environment*" (p. 418), and the majority of AN patients with AN nervosa "*recover with relatively simple treatment*" (p. 419). This affirmation was made after a 20- to 30-year follow-up of 15 AN patients treated between 1932 and 1943, where "*With one exception these patients all made good recoveries from their initial illness*" (p. 418).

More recently, the first paragraph opening a report describing factors associated to AN recovery from a Finnish population-based study Keski-Rahkonen et al. (180) reads: "*A substantial proportion* [of AN patients] *attains complete recovery, even without formal treatment, but about one in five suffers from a chronic disorder that carries a high risk of mortality*" (p. 117). The term *substantial* was probably chosen by these authors as they found in their study that "*The 5-year clinical recovery rates were similar for the detected and undetected cases: 61.8% versus 68.4%, respectively, for DSM-IV anorexia nervosa, and 60.1% versus 69.5%, for broad anorexia nervosa*" [(181), p. 1,263][30]. However, a shortcoming of this study is its retrospective nature (182).

Moreover, in an up-to-date unique controlled, 30-year follow-up study of adolescent onset AN, the Gothenburg anorexia nervosa study (134), the authors reported "*one in four people had never received treatment for an eating disorder. Nonetheless, treatment did not affect the outcome 30 years after the onset of anorexia nervosa*" (p. 5). This finding corroborated a study in Adelaide, Australia, "*where many patients make a good recovery without accessing to specialized treatments of any kind*." In fact, receiving treatment[31] "*did not alter long-term outcome either as predicted by variables gathered at recruitment, or by combination of initial and 6-month variables*" [(183), p. 1,256].

CONCLUSION

As highlighted in the first section of this paper, interference from the clinician's theoretical framework is easily identified in psychoanalytic accounts predating the appearance of the BID construct. This interference is less obvious now that BID is considered a core element in AN diagnosis. In fact, difficulties in getting the patients' acquiescence of BID symptoms required to fulfill diagnostic criteria are conventionally explained as conscious tricks or negations to mislead well-intentioned busy clinicians. However, given the obvious asymmetries in age, power status, and context familiarity between an adolescent and an adult doctor in an unfamiliar hospital ward, or an eating disorders unit, there should be greater awareness about the impact of such asymmetries.

The perpetuation of the symptomatic profile for AN from *DSM-III* to present *DSM-5* gives clinicians the deceptive reassurance that the criteria for AN diagnosis grasp the essence of the disorder, ignoring the issues we have previously addressed (invalidation, acculturation, and indoctrination). It is easy to agree that at a behavioral level AN patients act "as if" they were deeply invested in a relentless pursuit of thinness. Historically, the egosyntonicity of weight loss in AN patients has been documented, as aptly reflected by the German term *magersucht* for anorexia nervosa. However, this commitment to thinness has been equated to other allegedly synonymous actions that go beyond simple avoidance to putting on weight such as weight phobia, fat phobia, or intense fear of gaining weight or becoming fat, as stated by Rieger et al. (184). Thus, from the point of view of BID culture, it is reasonable to view the act of diagnosis itself as the beginning of a process of acculturation and even indoctrination.

We have already seen how difficult it is to justify the lack of clinical expertise by most clinicians from Gull and Lasègue before the advent of Hilde Bruch's proposals regarding the characterization of typical AN in terms of BID construct. On the other hand, we have also reviewed how the current diagnostic criteria that nowadays define a typical AN picture were absent in patients during a period of time (1860/1873–1962) much greater than that elapsed since the original BID formulation until today (1962–2020). Similarly, current conception of typical AN conveys the suspicion of denial and concealment in cases where the patient experience does not conform to the report expected by doctors and researchers. This atmosphere of pressing acculturation is as unrecognized as the responsibility of clinicians and researchers spreading it widely through scientific literature and mass media and thus approaching susceptible people like Russell pointed out (12). Seen from this perspective, bad outcome of SE-AN could result from the interaction between disoriented underweight adolescents who can't help themselves to stop their restrictive eating and excessive activity on one side and ineffective treatments based in rationales that impose a patient's acquiescence of the BID construct on the other side.

Likewise, with hindsight, it is easy to consider that some of the treatments in the past considered the best treatment available (see **Table 2**) were unaware of iatrogenic effects (185)[32]. Evidently, the

[30]Undetected cases amounted for 47% of all *DSM-IV* AN cases, and 59% of all broad AN cases. Cases undetected by the health care system were those never receiving an eating disorder diagnosis from a health professional whereas the other cases were detected by the health care system, although this detection didn't imply they had received treatment for their disorder.

[31]Treatment was categorized according to modality and intensity: "(1) no treatment; (2) minimum treatment (one to three sessions of outpatient treatment after assessment, with no other secondary treatment); (4) extended outpatient treatment (greater than three sessions with any kind of specialist mental health professional, but no inpatient care); (5) short inpatient treatment (<2weeks' inpatient treatment for any mental health disorder, including an eating disorder); and (6) extended inpatient care (>2 weeks' admission for an eating disorder)" (p. 1,254).

[32]Iatrogenic effects due to the etiological uncertainties were sadly mentioned by Magendantz and Proger (15): "*the practical handling of these cases has been difficult and has varied from psychoanalysis to risky, repeated implants of animal pituitary tissue into the omentum of these patients of low resistance. How many of these unfortunate girls have been sent to tuberculosis sanatoriums as was our first patient, who at the outset had no evidence of pulmonary tuberculosis? How many have died in psychiatric institutions classified as schizophrenic or depressive?*" (p. 1,983).

same shortcoming may be said of the theoretical assumptions underpinning such treatments. In both cases, if we apply the definition of chronicity that opens this document, it would be clear that chronicity would have been the result of flagrantly ineffective treatments and faulty assumptions.

As for the state of the art of current treatments, the qualifier "evidence-based" means weak evidence as we are still far from reaching the criterion of strong evidence. The "Dodo Bird" verdict defining the current landscape of psychosocial treatments in AN depicts our repeated failures in the development of an effective treatment for AN (186). We should not discard the possibility that the SE-AN category may be echoing that we have overlooked the Hippocratic dictum *Primum non nocere*. Only time will probably give us the answer. In the meantime, as Freeman Dyson encouraged (187), we should not forget the scientific mandate that any prevailing dogma, as in the case of the BID construct, must be challenged.

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Mental Capacity, Decision-Making and Emotion Dysregulation in Severe Enduring Anorexia Nervosa

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Severe and Enduring Anorexia Nervosa (SE-AN) is a chronic eating disorder characterized by long-term starvation and its physical and psychological sequelae, and severe loss of quality of life. Interactions between neurobiological changes caused by starvation, vulnerability (personality) traits, and eating behaviors play a role. Several other factors, such as increased fear and decreased social cognition, have also been found in relation to SE-AN. With this in mind, we aim to add to the understanding of SE-AN by introducing the concept of mental capacity (MC), which refers to the ability to understand and process information—both on a cognitive and an emotional level—and then make a well-informed choice. MC may be an important construct within the context of SE-AN. Furthermore, we will argue how impaired decision-making processes may underlie, fuel, or contribute to limited MC in SE-AN. We will speculate on the importance of dysfunctional emotion processing and anxiety-related processes (e.g., a high intolerance of uncertainty) and their potential interaction with decision-making. Lastly, we will propose how these aspects, which to our knowledge have previously received little attention, may advise research and treatment or help in dealing with the "want but cannot" situation of life-threatening AN.

Keywords: severe enduring anorexia nervosa, mental capacity, decision-making, intolerance of uncertainty, emotion dysregulation

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INTRODUCTION

Emma is 39 years old. Her anorexia nervosa (AN) started at age 15. After temporary and partial improvement while she was in treatment during adolescence and early adulthood, her AN shows a slow deteriorating course; she is currently "stable" at a body mass index (BMI) of 13. Emma lives alone, is socially isolated, unemployed, and can barely look after herself. Her whole life revolves around her eating disorder. While it is definitely not her wish to die, she is also unable to change her eating habits in a meaningful way: the "want but cannot" situation so often seen. Her treatment team regards her as suffering from a severe and enduring form of AN.

Emma's (fictitious) case illustrates there seems to be a sense of what constitutes a case of severe and enduring anorexia nervosa (SE-AN). However, SE-AN is not an easy term to define. Robinson (1) introduced the term Severe and Enduring Eating Disorders, comparing the persistence of eating-disorder symptoms to other serious mental illnesses such as schizophrenia. He did not

TABLE 1 | Proposed criteria for "Severe and Enduring Anorexia Nervosa" Hay and Touyz (3).

(1) A persistent state of dietary restriction, underweight, and overvaluation of weight/shape with functional impairment
(2) Duration of >3 years of anorexia nervosa; and
(3) Exposure to at least two evidence-based treatments appropriately delivered together with a diagnostic assessment and formulation that incorporates an assessment of the person's eating disorder health literacy and stage of change

define a clear delineation in time, treatment, or severity of symptoms that marked the severe and enduring character. Attempts have been made to develop a staging model (2), and therapists and patients were asked to provide their views on what constitutes chronic AN. Hay & Touyz (3) proposed criteria (**Table 1**) based on duration of illness (more than 3 yrs), two or more not successful treatments, and a persistent state of illness with functional impairment but state there are limitations to these criteria that need empirical testing. Overall, no clear-cut picture emerged, although participants did agree on factors relating to weight, behaviors, and cognitions (4). In one qualitative study (5), patients who suffered from AN for over 20 years described that the eating disorder provided meaning and structure, while at the same time it had robbed them of relationships, family, occupation, etc. Patients may express a desire to change but feel incapable and/or unwilling to translate this desire into actual behavior (6), despite the costs to their lives. We found only one model explaining the progress of AN into SE-AN, by Treasure et al. (7) when they revisited their cognitive interpersonal model for AN and specifically looked at perpetuating factors. They describe how AN can develop into a chronic condition through interaction between behavioral consequences (i.e., increased neuroadaptation, food phobia, and habituation), vulnerability (personality) traits (i.e., rigid and anxious temperament), anorectic behaviors, and interpersonal difficulties (increased fear and frustration, alienation, loneliness, and decreased social cognition), combined with chronic stress (increased allostatic load and inflammation, decreased mood and neurogenesis). The model also highlights the role of heightened anxious and depressive symptomatology and dysfunctional emotion processing (such as problems with emotion recognition and regulation). This type of problem in emotional functioning can have debilitating consequences and, hence, can influence functioning on other levels. For example, it is known that emotions and emotion-related processes are essential for the way people make choices and therefore for our decision-making behaviors. Understanding this seems particularly relevant in the clinical situation of AN where the short- and longer-term consequences of a decision do not align and where a variety of emotions is involved.

This commentary aims to add the concept of mental capacity (MC) to the dialogue about how AN turns into SE-AN. MC refers to the ability to understand and process information both on a cognitive and an emotional level and then make a well-informed choice. MC may be an important construct within the context of SE-AN. We will argue how impaired decision-making processes may underlie, fuel, or contribute to limited MC in SE-AN. We will speculate on the importance of dysfunctional emotion processing and specifically address anxiety-related processes such as a high intolerance of uncertainty (IU) and how they may interact with decision-making. Lastly, we will propose how these findings, which to our knowledge have received little attention until now, may advise treatment or help in dealing with the "want but cannot" situation of life-threatening SE-AN.

MENTAL CAPACITY

When a seriously ill patient refuses a potentially lifesaving intervention, this persons' ability to make an informed decision can be put into question. Clinicians may describe individuals with AN who refuse treatment as having limited MC.

Few studies have been conducted on MC in patients with AN. This is remarkable, as diminished or absent MC is one of the central concepts in the discussion regarding compulsory treatment (CT) (8–16) and the (possible) concept of futility in the treatment of SE-AN (16, 17). MC is a concept that cannot easily be quantified. The way it is conceptualized today derives from legal rulings in the United States in the 1980s. Abilities considered relevant by judges in rulings regarding MC issues were adopted by clinicians in their clinical assessment. The most widely used assessment of MC is the MacCAT-T (18), a semi-structured interview that assesses understanding, reasoning, appreciation, and the ability to express a choice. In the assessment of MC, the clinician assesses the decision-making *process*, rather than the outcome. Since its introduction, the MacCAT-T has emerged as the gold standard in scientific research into MC due to its high interrater reliability, demonstrated concurrent validity with other measures, and extensive testing in a range of patient populations, both medical and psychiatric (13, 19–21). The MacCAT-T was used in two small studies in adolescents with AN (22, 23) and in one larger longitudinal study with severely ill adult patients [mean BMI of 15.5 kg/m^2, mean length of illness of 8.6 years (24, 25)]. The two adolescent studies showed conflicting findings: one (done retrospectively) not showing problems in MC at all, the other showing mild problems with reasoning. In the longitudinal study, patients with diminished MC seemed to do less well in treatment and displayed more fundamental decision-making deficiencies that did not ameliorate with weight gain. Therefore, diminished MC seems a relevant factor to prognosis, in addition to the more obvious factor of BMI. In this study, the MacCAT-T indicated that it was the aspect of appreciation that was driving diminished MC, in line with the findings by Owen and colleagues (2013) (26) in a general psychiatric population. The concept of appreciation refers to the value patients assign to issues such as the illness itself or the proposed treatment. When appreciating adequately, one for instance feels that the issues discussed apply to oneself (e.g., "I do have an eating disorder" or "This risk applies to me") and are therefore relevant in the decision-making process. The question emerges *in what way* MC influences prognosis and thus the development of SE-AN. Considering that MC encompasses the decision-making

processes in the clinical context and diminished MC is mostly related to distorted appreciation, it is important to understand the role of decision-making in a broader sense.

DECISION-MAKING

Decision-making processes of people with AN have been the focus of many studies (27–30). Findings indicate that these processes are disturbed as patients' choices seem more guided by the short-term outcomes (e.g., food intake and weight gain) and less by the longer-term outcomes (improved daily functioning) when compared to people without eating disorders or any other form of psychopathology. Decision-making inherently relies on emotional processes that provide important implicit and explicit knowledge by which the individual is able to make fast and adaptive decisions (31). These emotional processes guide decision-making on several levels, including *via* bioregulatory processes, such as somatic marker signals, and occur both consciously and outside of awareness. One hypothesis is that problems in emotional functioning and processes underlying certain emotional experiences, such as uncertainty tolerance, lead to these disturbances.

EMOTIONAL PROCESSING

AN has frequently been associated with disturbances in emotions and emotional processing. Even more so, emotion dysregulation is suggested to be at the core of AN (32, 33) (**Figure 1**). Problematic emotional functioning of people with AN was shown on various levels (33), for example, frequent and intense emotional experiences, problems recognizing and expressing emotions (34–36), lower ability to regulate emotions, and fewer emotion regulation strategies available (32, 37, 38). To complicate matters further, people with AN are suggested to be on average more emotionally sensitive, to experience emotions longer (the feelings and bodily sensations decline less rapidly) and to be less tolerant of emotional experiences than control participants (39, 40). This can result in so-called secondary emotions such as shame, guilt, anxiety, and (feelings of) depression. It is suggested that eating-disorder-related behaviors are used as coping strategies to reduce, distract from, or even numb emotional experiences as other strategies are lacking or do not result in a reduction of the emotions or unpleasant feelings (33, 41, 42). In **Figure 1**, it reduces the arrow between A and E. A longitudinal study by Racine and Wildes (43) showed that patients with AN who were characterized by high emotion dysregulation reported an increase in AN symptomatology during intensive treatment, and they maintained this high level independent of their low weight over and above their general emotional state. Considering that emotion dysregulation persists with improvement of weight and eating-disorder symptoms, it is regarded as a key factor for relapse and ultimately for chronicity (and thus for the development of SE-AN).

AFFECTIVE STATES AND DECISION-MAKING: INTOLERANCE OF UNCERTAINTY

Indeed, there is initial evidence that emotional processes, more specifically affective states such as anxiety and depression are associated with poorer decision-making in AN (29, 44). This is not surprising and has been recognized much longer in other clinical research fields [for a review on the relation between affective states and decision-making in anxiety and depression, see Paulus & Angela (45)]. This review highlights that an "affect-driven belief system profoundly influences the transformation of action into choices (p. 477)" and proposes that affect in particular plays a role in decision-making that involves uncertainty, which is similar to the type of decision-making mostly studied in AN (24, 29, 30).

We believe uncertainty intolerance to be a potentially important yet currently undervalued concept in the context of SE-AN. For SE-AN patients, certain eating disorder behaviors may function to reduce precisely this uncertainty and the negative emotions associated to uncertainty [see Sternheim et al. (46)]. Quantitative studies confirm elevated levels of IU in both adolescents and adults with AN (47). IU refers to the fear of the unknown (48), a negative response to uncertain situations on emotional, cognitive, and behavioral levels (49). These findings fit well with the revised model by Treasure at al., which includes rigid and anxious personality traits. IU has been found to contribute to abnormalities in the reward system and subsequent decision-making processes (50). We speculate that training patients in tolerating uncertainty and becoming more flexible and less anxious may improve their general quality of life, probably the most important aspect of treatment in SEAN, and may even result in more adaptive decision-making.

DISCUSSION

MC Research

This paper explores the idea that decision-making, and its effect on MC may be important constructs to understand the development of SE-AN. As emotions and emotion regulation play such an important role in decision-making, a focus on these aspects in research regarding MC in AN would be expected. However, the connection to MC in these patients has not yet been thoroughly studied in clinical research, and neither has the relationship between maladaptive decision-making, disturbed emotion processing, and MC. The need to study this relation is supported by the view that MC assessments in general and the MacCAT-T in particular are focusing too much on cognitive and rational functioning, whereas decision-making, as described, is not wholly rational but rather very much influenced by emotional factors (51–55). During a clinical study of the ability to understand and process information both on a cognitive and an emotional level and then make a well-informed choice, we found that it is the aspect of appreciation in MC—the value patients assign to issues such as the illness itself or the proposed

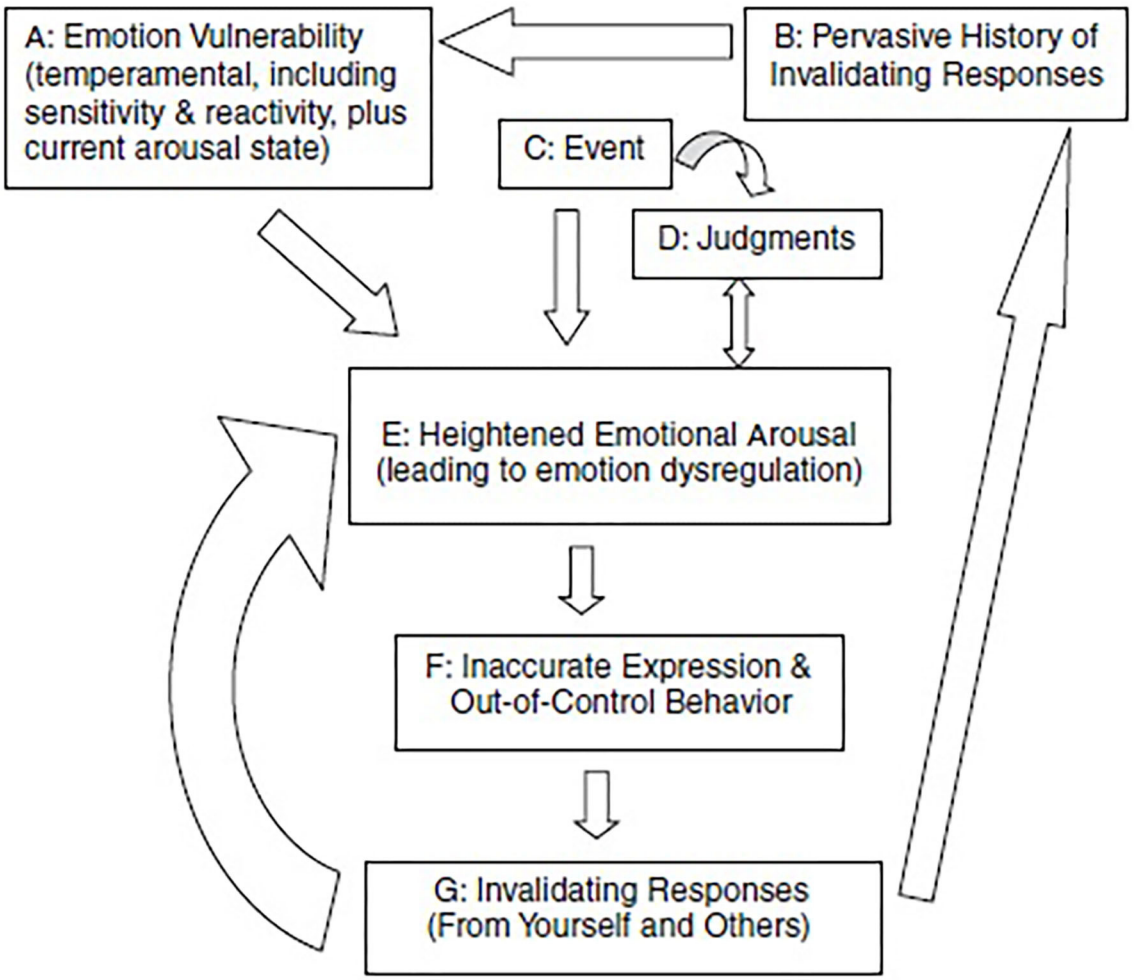

FIGURE 1 | The transactional model of emotion regulation. [Adopted from Haynos and Fruzzetti (33)].

treatment—that can become diminished and underlies the "want but cannot" dilemma of the critically ill patient. Intriguingly, the longitudinal study amongst severely ill patients with AN by Elzakkers et al. (25) showed that patients with diminished MC exhibited persistent maladaptive decision-making over the course of a 2-year follow-up even when controlling for BMI, depression, and alexithymia scores (a direct relationship between these emotional problems and maladaptive decision-making was found). This suggests that the difference between full and diminished MC cannot be fully explained by the variation in emotional problems as measured in this study (depression, anxiety, alexithymia). Presumably, other concepts not measured in this study are also important, such as emotion regulation and the ability to tolerate emotions or uncertainty. Interestingly, appreciation ratings (as measured by the MacCAT-T) of the diminished MC group over time remained inferior to the full MC group, even when gaining weight, linking the concept of more fundamental decision-making (and "gut feeling") to the concept of appreciation in AN. Diminished MC could function as a marker for more severe deficits in decision-making, and underlying disturbed emotional processing, and serve to guide treatment toward implementing a stronger focus on these emotional issues (33, 40).

MC Treatment

On the basis of these findings, we believe clinicians ought to pay more attention to their patient's current MC, especially in SE-AN, when important treatment decisions are to be made. Diminished MC has grave legal consequences in most medico-legal systems and lessens the say patients have regarding their own treatment legally. Even so, we would like to point out that shared decision-making is not by definition impossible in this situation and in fact may help to discuss how to improve their quality of life. Taking patients seriously in their suffering and anxiety and acknowledging their views is still paramount and should remain one of the pillars in the clinical decision-making.

DECISION-MAKING AND DYSFUNCTIONAL EMOTIONAL PROCESSING RESEARCH

Next, we discuss the possibility of underlying dysfunctional emotion processing, such as a high IU, and how this may interact with decision-making (56, 57). A study in healthy individuals and in people with anxiety shows that high IU indeed negatively impacts decision-making (58), and a first study in AN shows that IU contributes to poor social problem solving (59). A number of (cognitive behavioral therapy related) interventions have been validated as successful in reducing IU across emotional disorders (60) and even in treating SE-AN (61). A first study in adolescents with AN showed reductions in IU after an adapted IU intervention (62). Further studies should be conducted to test IU interventions in adults with AN, in particular to explore how reducing IU may result in fewer emotional difficulties and improvements in quality of life and eating disorder pathology.

We argue that decision-making in severely ill patients is driven by a disturbed emotional system, disturbed allocation of reward, and altered values, eventually leading to diminished MC. Haynos and Fruzzetti (33) describe how emotion dysregulation can both be a risk factor and a maintaining factor. To further study this, we need longitudinal and experimental studies in changes over time of emotion regulation, as AN progresses and develops into SE-AN. In one longitudinal study (27) in patients with diminished MC, maladaptive decision-making remained present throughout the treatment period, independent from depression or anxiety. No studies studying the role in AN of emotional factors on MC have yet been published, but research in other areas (borderline personality disorder, depression) (63) has shown a link. Finally, further studies are needed to explore the way in which emotional dysregulation influences decision-making and relates to the development of SE-AN.

TREATMENT

Therapists should be aware of emotional issues at the start of treatment and, when possible, adjust their treatment accordingly. Protocols like CBT-IU (60) or by adding Cognitive Remediation and Emotion Skills Training CREST (64) or MANTRA (65) include attention to emotional problems and IU. It may also be worthwhile to review treatments designed to address a spectrum of difficult-to-treat disorders sharing similar phenotypic and genotypic features associated with maladaptive overcontrol, such as Radically Open-Dialectical Behavior Therapy (66), for people suffering from SE-AN who are in poor physical health.

MEDICO-ETHICAL ASPECTS OF MC

MC can inform us about problems or erroneous decision-making in SE-AN. What to do in case of diminished MC? First and foremost, a good therapeutic relationship is wanted and needed. Even in a patient suffering from SE-AN, we need to discuss what would improve their situation, especially when starvation becomes life-threatening. One of the ultimate clinical implications of diminished MC in critically ill patients is compulsory treatment (CT). CT can be lifesaving and can also lead to positive outcomes, at least in adolescents (67). Patients generally support CT in life-threatening situations, and in their review, Elzakkers et al. (68) report that none of the studies showed a worsening in the therapeutic relationship. However, CT is not the solution for all patients with diminished MC who refuse treatment. In some situations, it may do more harm than good. Data from Denmark (69) show especially in patients with multiple prior treatments that were not separated by a period of good health CT becomes unproductive and sometimes even traumatic for the patient, increasing the likelihood of them refusing future interventions. MC ratings may be of help in the choice for CT, but the warning is, as mentioned earlier, that the MacCat-T is criticized for being too focused on cognitive and rational functioning and therefore misses the effect on decision-making of the underlying emotional dysfunction. Goldberg (70) suggests solving this by adding a narrative coherence (NC) standard to the MC ratings, that is, adding the patient's self-narrative about their illness situation. Miller Tate (71) comments on his paper by stating that SE-AN patients will easily pass this NC based on the "pathological" values that define AN and lead to an egosyntonic experience of their illness. This notion of "pathological" values complicates the discussion and concern is voiced whether the patient's autonomy with regard to MC in such a situation of starvation is not overvalued in SE-AN. By favoring autonomy over the other ethical principles (non-maleficence, beneficence, and justice) in the assessment of MC, the clinician furthermore is in danger of paying too little attention to the patient's relationships, their wishes and care needs, and long-term social context. Bloch and Green (72) propose a combination of this principle-based ethical model with care ethics, with a large role for emotions and interpersonal relationships in moral deliberation besides the issue of MC. In doing so, they underline the findings about emotional dysregulation and its effect on decision-making. In a very recent overview, Wonderlich et al. (73) point out some future directions in research and treatment of SE-AN. The first step being a better diagnostic description of SE-AN and second how best to engage and retain people with SE-AN in treatment, how to support their caretakers and tailor existing treatments or develop new ones. As we see more developments of people suffering from SE-AN being taken into hospices or palliative care, discussions about the medico-ethical aspects of this severe form of AN are needed, and protocols for clinicians, patients, and families to ensure the best interests of the patient are preserved.

CONCLUSION

We need longitudinal and experimental studies in changes over time of emotion regulation, as AN progresses and develops into SE-AN. Moreover, the connection to MC in these patients has not yet been thoroughly studied in clinical research, and neither has the relationship between maladaptive decision-making, disturbed emotion processing, and MC. Finally, we think there is an urgent need for more qualitative studies in patients as well as clinicians to add to this discussion. Patient studies should

aim to specifically address the issue of diminished appreciation, and clinician studies should aim to determine in more detail what it is they estimate when assessing MC.

AUTHOR CONTRIBUTIONS

All authors contributed equally in set up and writing.

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