Articles Describing Datasets

Brain, behavior, cognition, and physical health in first-onset adolescent anorexia nervosa: The BRAVE Study design and cohort profile

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Background

Anorexia nervosa is a severe psychiatric disorder with a heterogeneous course with one of the highest rates of morbidity and mortality of all psychiatric disorders. Little is known about factors that predict both course and treatment outcomes of this disorder. The BRAVE Study is a longitudinal first-onset anorexia nervosa cohort study focusing on four topics of interest in girls only: (1) behavior, (2) neurobiology, (3) cognitive functions, and (4) physical health.

Objective

The goal of this paper is to introduce the BRAVE Study. The primary aim of the BRAVE Study is to identify predictors of treatment response in a large sample of 12-to-22-year-old females with first-onset typical or atypical anorexia nervosa. The second aim is to longitudinally investigate the association between clinically significant changes in eating disorder symptoms with the underlying behavioral, neurobiological, cognitive and physical health changes. The results of this study will allow us to develop more precise treatment strategies in order to provide more optimal treatment.

Methods and analysis

The BRAVE Study implements a longitudinal case-control design. Study recruitment was designed within a collaborative network of 16 Dutch mental health organizations, each with expertise in the diagnosis and treatment of patients with anorexia nervosa. After obtaining informed consent, assessments were performed at baseline and one-year follow-up. Patients with anorexia nervosa received treatment as usual. The primary outcome measures at one year are restoration of weight and a reduction of eating

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disorder symptomatology. Predictive measures include neurobiological, cognitive, behavioral and physical health measures.

Sample description

In the BRAVE Study 79 girls with anorexia nervosa and 75 typically developing girls were included between May 2017 and October 2021. This period of time partially overlapped with the COVID-19 pandemic. 72% of the girls with anorexia nervosa and 88% of the typically developing girls also completed measurements at follow-up. The mean time between data collections points was 13 months. The groups were comparable in education level of their mothers, neurodevelopmental disorders, and ethnical background. The girls with anorexia nervosa were slightly younger than the typically developing girls.

Conclusion

The BRAVE Study aligns with one of the most important study priorities in the field of anorexia nervosa by examining (i) predictors of treatment response and (ii) investigating how symptoms with eating disorder symptoms track with changes in neurobiological, cognitive, behavorial and physical health functioning. Moreover, the study is innovative by its longitunal case control design, relatively large study sample and broad selection of measures.

INTRODUCTION

Anorexia nervosa (AN) is a debilitating psychiatric disorder that commonly presents during adolescence and primarily affects girls and young women.[1] Characteristic features of AN include malnutrition, an intense fear of weight gain, disturbed body image and behaviors associated with a drive for thinness, such as severe dietary restriction, laxative and diuretic usage, and excessive physical activity.[2] The exact etiology of AN is unknown and it is currently considered multifactorial, involving the interplay between genetic and environmental factors.[3] As is true with many psychiatric disorders, the course of AN is heterogeneous. Some patients have relatively short-term illness and recover quite quickly, while other patients have a prolonged illness with multiple hospitalizations and long-term impairment.[4,5] The mean duration of AN is 4.5 years and 20% of all individuals with AN remain chronically ill.[5] Recovery rates vary depending on the specific criteria used. Generally, weight recovery occurs faster (i.e. 11.3 months) than eating disorder symptomatology (i.e. 22.6 months).[6] Patients with AN, clinicians and researchers have stated that the identification of predictors of treatment outcome and illness duration is one of the highest priorities for research into adolescent AN.[7,8] A range of possible predictors of illness course in AN have been identified. Social-cultural and behavioral predictors for a worse outcome include purging, compulsivity, interpersonal and social problems, rumination, impulsivity, autistic traits, a history of suicide attempts, alcohol and/or drug abuse, earlier specialized treatments, longer duration of inpatient treatment and a longer duration of AN before treatment.[9-16] Also, patients with an illness onset before 17 years-of-age tend to have a better outcome than both patients with an onset in adulthood and patients with a prepubertal onset.[17] Eating disorder characteristics, including a low body mass index (BMI) and body image disturbances, and more social and psychological problems have been shown to predict a worse outcome.[9,10] Two studies reported that greater levels of exercise during treatment or shortly after discharge were associated with relapse,[11,13] while another study did not find an association between exercise and the one-year recovery rate of AN.[18]

Neuroimaging studies help improve our understanding of neurobiological underlying processes of AN and the way brain functions drive behavior in general.[19] Both structural and functioning neuroimaging studies have been used to predict treatment course and outcome in AN.[20,21] In young people with AN, only one study investigated the predictive value of structural imaging data. This study showed that cortical gray matter and (sub)cortical white matter volumes at admission were positively associated with the BMI-Standard Deviation Score (BMI-SDS) at one-year follow-up.[22] While global decreases in grey and white matter have been shown to be associated with malnutrition,[20] the pattern of regional brain differences in restoration appears to predict outcome, as shown by studies investigating the entire age range of AN.[23,24]

No known studies to date have investigated the predictive value of resting state fMRI on eating disorder related features in clinical populations. However, in healthy young adults, Chen and colleagues found that high levels of eating disorder pathology were associated with lower functional connectivity, specifically in the executive control network, the basal ganglia network, and in the default mode network.[25]

Three studies have assessed the predictive value of task-based functional neuroimaging studies on eating disorder related features in young people and found associations between brain activity and different aspects of social and emotional functioning.[26-28] These studies differed in study design, sample characteristics and had paradigms that make it difficult to draw general conclusions.

Several studies have focused on the possible predictive value of different cognitive domains on the severity of AN symptoms. Using a cross-sectional design, Harrison et al.[29] showed that participants with AN who had a greater com-

bination of fragmented perseverative cognitive style, less global flexible cognitive style, and more socio-emotional difficulties had a more chronic and severe form of AN. Moreover, poor set shifting skills were associated with prolonged illness duration.[30]

Results regarding the predictive value of physical health measures on treatment outcome are mixed. A lower BMI at admission and a higher rate of weight loss predict a poorer long-term outcome in patients with AN.[10,31-34] Also eating behavior during the treatment phase was found to be a predictor: high diet energy density and high diet variety were found to positively predict a better one-year treatment outcome.[35] Studies on the endocrine system showed that the presence of endocrine abnormalities, such as hypoglycemia, osteoporosis, irregular menses, amenorrhea, and high serum leptin levels at discharge appeared to increase the risk of a poor clinical outcome.[14,32,36] Moreover, body composition is a significant predictor for treatment outcome according to some studies[37-39] but these results are in contrast with results from others.[31]

Methodological limitations, such as small sample sizes, heterogeneous samples and differences in analysis strategies, make it difficult to draw general conclusions about predictors of the illness course of AN. We expect that measuring multiple predictors simultaneaously in one larger sample will lead to broader, more reliable and potentially more precise findings about factors that predict the illness course of AN. The identification of prognostic factors can not only help with treatment planning, but can also provide important insights into the neurobiological mechanisms of AN. A better understanding of the underlying mechanisms can in turn direct and improve current treatment approaches. Given the importance of the identification of predictive factors of AN, our goal was to capture multiple measurement domains, including physicial health, cognitive functions, neuroimaging, and behavior to best predict outcome in the face of considerable heterogeneity.

THE BRAVE COHORT

Currently, clinicians, relatives, or other individuals involved in the care of someone with AN cannot predict their clinical course. This lack of predictability is distressing for the individual, their relatives, and the clinicians involved. Identifying predictors of treatment response and illness duration is therefore a top research priority in the field of eating disorders.[7,8] It is within this framework that we initiated a first-onset study recruiting girls and young women who fit the broader spectrum of first-onset AN. We also recruited a similar number of typically developing (TD) girls and young women without AN. The aim of the BRAVE study is twofold: 1) To identify predictors of one-year treatment response; 2) To investigate over time the association between clinically significant changes in the symptoms of AN with the underlying behavioral, neurobiological, cognitive and physical health changes. Eating disorder symptoms and BMI-SDS are defined as the primary longitudinal outcomes.

The results of this study will allow us to develop different treatment strategies to help curb what are deeply rooted neurobiological and cognitive processes in girls who require longer-term treatment. Based on what is both known and not known from the AN literature, a wide-array of measurements were selected to cover four specific domains: 1) behavior: general psychopathology, comorbidity (including autism spectrum disorder features, depression, anxiety and obsessive compulsive symptomatology), and eye gaze patterns; 2) neurobiology: structural and functional neuro-imaging; 3) cognitive domains (including intelligence, attentional bias, set shifting abilities, inhibitory control, visual spatial skills and decision making); and 4) physical health measures (including body composition, microbiome, cortisol measure in hair, muscle strength, and biobanking blood for DNA isolation and blood and serum measures). Our approach for the selection of measures was built on previous research, but also is hypothesis-driven to conduct exploratory analyses using advanced techniques, including machine learning. In addition, we will use epidemiological principles of data collection to collect biobanked measures for future use, and we welcome collaboration with other researchers in this field.

The goal of this paper is to provide an overview of the study design, measures, the rationale for the measures selected, and an overview of the collaborative network.

METHODS AND ANALYSIS

STUDY DESIGN AND MANAGEMENT

The BRAVE study is a multisite study initiated within the Erasmus Medical Centre – Sophia Children's hospital (Erasmus MC-Sophia) in Rotterdam, the Netherlands. BRAVE is the abbreviation of the full title of this project 'Brain functions and attention processing in adolescent anorexia nervosa: predictors of its differential course'. The study employed a case control repeated-measures design with a baseline visit and the first follow-up visit taking place one year after intake (see Figure 1 for a schematic overview). We are currently seeking permission from the medical ethics committee to add a third wave to our study design.

The study population consisted of female young people between 12 and 22 years-of-age with a first-onset DSM-5 classification of AN or atypical AN classified in the past 12 months and 12 to 22-year-old TD females. The age range 12-22 years was chosen because AN rarely presents before the age of 11 and rarely appears for the first time in adulthood. 'First-onset' referred to an initial diagnosis of AN obtained within the past 12 months, as confirmed by the involved clinician. Participants were required to fulfill the criteria for active AN at the time of screening and if they had received a diagnosis of AN prior to one year, they were excluded from the study.

Measurements were collected at baseline and at one year follow-up. During the time between baseline and follow-up, participants with AN received treatment as usual (i.e. family based interventions, cognitive behavioral therapy and somatic evaluations).

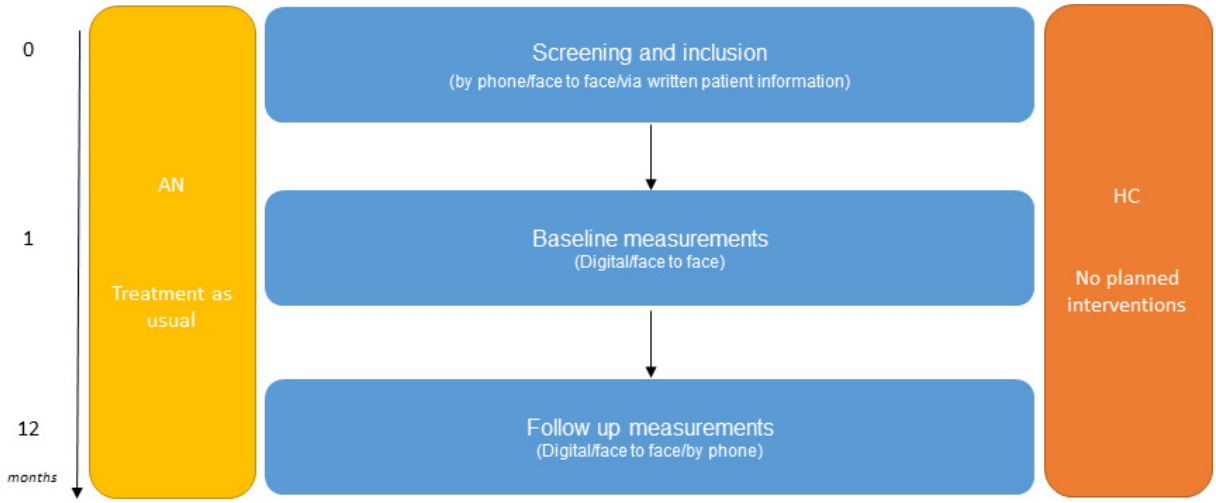

Figure 1. Study design

PARTICIPANT ELIGIBILITY, RECRUITMENT AND ETHICAL ISSUES

To assure that the recruitment of AN participants is representative of the Dutch population, patient recruitment included not only our university-based AN inpatient and outpatient clinics, but we also formed collaborations with a wide network of national partners located in different parts of the Netherlands, both rural and urban settings. The partners included: Altrecht-Rintveld, Bravis Hospital, Curium-LUMC, Elisabeth-TweeSteden hospital, Emergis, GGNet-Amarum, GGZ Delfland, GGZ-Rivierduinen, GGZ-WNB, Franciscus Gasthuis hospital, Franciscus Vlietland Hospital, Ithaka, Reinier de Graaf Gasthuis, Stichting Human Concern, and the Van Weel Bethesda hospital. In addition, patients were recruited though advertisements via patient organizations, relevant websites and social media.

A control group of typically developing (TD) adolescent girls without AN, comparable in age and educational level to the AN group, was also recruited to compare cases versus controls and to adjust for typical developmental trajectories between the TD and AN youth. No additional aims were formulated for the TD group. Recruitment of the TD group was performed by inviting female friends of the young women with AN, advertisements in schools, sports clubs and via social media.

Exclusion criteria for both AN and TD included significant motor or sensory disorder(s), substance related disorders, neurological disorders, schizophrenia or other psychotic disorders, a poor command of the Dutch language, an IQ below 70 as measured by an intelligence test in the past, or the inability to fill in questionnaires independently. Controls were required to have a healthy weight (range BMI-SDS -1.3 to 1.3). Participants with contraindications for MRI scanning or with dental braces were invited to participate in all measures except for the MRI component of the study.

The research protocol and the collaboration with organizations in child and adolescent psychiatry/psychology were approved by the medical ethics committee of the Erasmus Medical Center in Rotterdam (MEC 2016-194/ NL55175.078.16). Informed consent/assent has been obtained from every participant and informed consent was obtained from the parents in cases where the participant was younger than 16 years of age.

RECRUITMENT PROCEDURE

A schematic overview of the recruitment procedure is shown in Figure 1. In Figure 2, the BRAVE Study design is presented. Figure 3 presents a flow chart of the recruitment of the study sample.

Young people with first-onset AN were informed about the BRAVE Study through their care coordinator or clinician, who provided a short explanation about the study. If the study came to their attention via social media, patient organisations, or otherwise, they had the opportunity to ask for further information by returning a reply card or to request additional information via our website (https://www.erasmusmc.nl/nl-nl/sophia/pages/b/brave-onderzoek). Written information about the study was provided to the adolescent and their parents prior to the visit. The TD group learned about the BRAVE Study via our social media site, sportsclubs, or participants with AN (e.g. classmates, friends, acquaintances). If they were interested in receiving more information about the study they could send us an e-mail, fill in their personal details on our website, or by completing a reply card via mail. Shortly thereafter, a member of the BRAVE team contacted the young people or their parents, depending on the age of the adolescent, to check screening criteria. If eligible, written information about the study was sent to the adolescent and her parents at home. This information was comparable to information that was sent to the participants with AN. We contacted each potential participant two weeks after they received

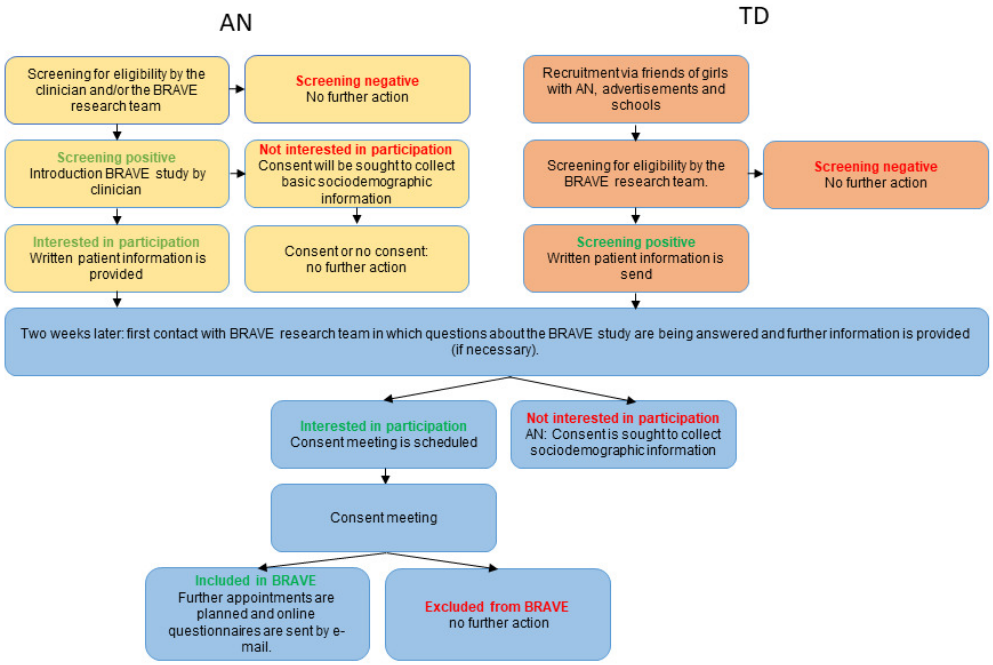

Figure 2. BRAVE recruitment procedure

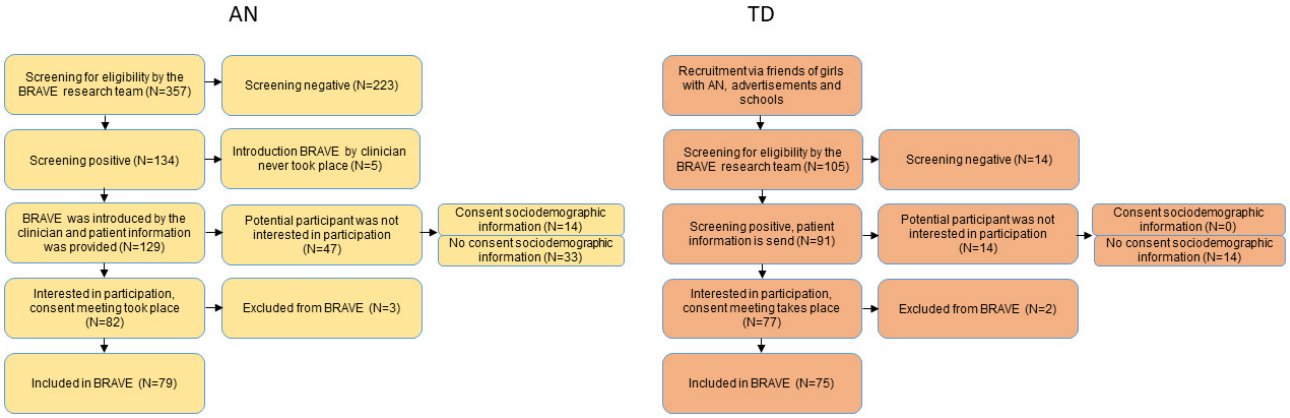

Figure 3. Flow chart recruitment BRAVE Study sample

the written information to answer any questions about the study. If the adolescent was interested in participating, a consent meeting was planned. At the consent meeting, informed consent was obtained and inclusion and exclusion criteria were assessed via diagnostic interviews. If eligible for participation, two additional appointments were planned in random order.

One appointment consisted of the assessment of imaging, eyetracking and physical health measures. In the other appointment cognitive assessments were performed. Questionnaires regarding eating disorder related characteristics, socio-demographic features, psychopathology and quality of life were sent digitally to all participants and to the primary caregiver. In cases of participants with AN, we also sent a digital questionnaire to the mental health professional. If young people said that they were not interested in participation after learning more about the study, we asked if they were willing to provide basic sociodemographic information to be able to assess recruitment bias.

The baseline measurements were repeated at the one-year follow up visit. The interviews that were administered at the consent meeting are repeated approximately one year after the baseline measurement at a time that suited the participants. Our follow-up and retention strategies are presented in supplementary figure 1.

MEASURES

The assessments are obtained both at baseline and repeated a year later in both AN and TD individuals, unless explicitely mentioned otherwise.

BEHAVIORAL MEASURES

In the BRAVE Study, psychiatric symptoms were measured using both interviews and questionnaires. The interviews were performed face to face. When face to face appointments were not possible due to COVID-regulations, interviews were carried out using Microsoft Teams or Skype for Business. At follow up the participants also had the choice to perform the interviews by phone. The questionnaires were filled out by the participant, the caregiver, and/or the clinician digitally on a secured website using Gemstracker (Gemstracker, copyright©, Erasmus MC and Equipe Zorgbedrijven, latest release at 2022, version 1.9.1p7, open source (new BSD licence), https://gemstracker.org). In Table 1 psychometric properties and a description of the measures are presented.

EATING DISORDER RELATED MEASURES

The *Eating Disorder Examination, version 12.0* (EDE) is a semi-structured interview that is considered to be the gold standard for the assessment eating disorder pathology.[56] The participants were interviewed about dieting patterns and the extent to which they worry about food, body shape and weight. The EDE-BRAVE also includes questions about the duration of symptoms in order to gain more information about the onset of the disorder. The *Readiness and Motivation Questionnaire (RMQ-Dutch)*[41] was completed only by the AN participants to gather information about the readiness and motivation to recover from 12 AN symptoms. We translated the RMQ into Dutch, with permission of the original developers, to make it suitable for our participants. The *Eating Disorder Inventory – third edition (EDI-3)*[57] is a self-report questionnaire that was used to assess eating disorder symptoms, i.e. drive for thinness, bulimia and body dissatisfaction, and psychological features of eating disorders, i.e. ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, ascetism, impulse regulation and social insecurity. Lastly, participants filled in the *Body Shape Questionnaire – Dutch version (BSQ-Dutch),* that measured body shape concerns over the previous 4 weeks. With permission, we translated the English version[43] into a Dutch version.

GENERAL PSYCHOPATHOLOGY

We use two versions of the *Mini-International Neuropsychiatric Interview (MINI-KID/MINI-PLUS)* to assess general psychopathology in our participants, based on DSM-IV criteria*.* For those below 18 years-of-age we use the MINI-KID. For participants of 18 years and older we use the MINI-PLUS.

The Achenbach System of Empirically Based Assessment (ASEBA) questionnaires (44, 45) were also used to assess general psychopathology. For participants younger than 18 years-of-age, the Child Behavior Check-List (CBCL) (parent report) and Youth Self Report (YSR) (self-report) were administered. For participants aged 18 years and older, the Adult Behavior Check-List (ABCL) (parent report) and Adult Self Report (ASR) (self-report) were used.

AUTISM

The *Social Responsiveness Scale* (SRS)[58] is a parent-reported questionnaire that obtains information about autistic traits. We used the SRS-2 for participants younger than 18 years old. For participants ages 18 years and older we used the SRS-A.

ANXIETY

The *Screen for Child Anxiety Related Disorders – Dutch (SCARED-NL)*[50,59] assesses anxiety symptomatology. We used both the child and the parent version of the SCARED-NL for all participants, irrespective of their age.

OBSESSIVE COMPULSIVE BEHAVIORS AND THOUGHTS

The (Children's) Yale-Brown Obsessive Compulsive Scale ((C)Y-BOCS)[51,60,61] is a semi-structured interview that assesses obsessive compulsive behaviors and thoughts in adults. We used the Y-BOCS in participants aged 18 years and older. For participants aged 17 years and younger we used the CY-BOCS.

DEPRESSION

The *Beck Depression Inventory-II NL (BDI-II NL)*[53,62] is a self-report questionnaire that measures depressive symptomatology. It is one of the most widely used tests for measuring the severity of depression. The BDI-II NL was suitable for the entire age group of our participants.

QUALITY OF LIFE

The *KIDSCREEN-27*[63,64] is a parent and self-report questionnaire that assesses the quality of life of our participants in general and on several domains

EYE GAZE PATTERNS

A Tobii 120 eyetracker (Tobii Technology, Danderyd, Sweden) was used to investigate eye gaze patterns in our participants, while they performed a free viewing and a dot probe task, both described below. The paradigms were programmed in E-prime (version 2.0.10.252, including extensions for Tobii, Psychology software tools, Pittsburgh, PA, USA).

NEUROBIOLOGICAL MEASURES

We used multimodal neuroimaging that included structural MRI, diffusion tensor imaging (DTI), and both task and resting state fMRI. The imaging procedure took place at Erasmus MC-Sophia. An overview of the sequences and parameters is shown in Table 2.

NEUROIMAGING MEASURES AND PROCEDURE

Magnet resonance imaging (MRI) was conducted using a GE Discovery 750w 3.0 Tesla system (GE Healthcare, Milwaukee, WI, USA) using an 8-channel head coil. The imaging

Table 1. Behavioral Measures

Construct	Instrument	Psychometrics	Description
Eating disorder related measures	Eating Disorder Examination-Questionnaire –BRAVE (EDE-BRAVE)	The EDE has sufficient reliability an validity to assess eating disorder symptoms[40]	The EDE exists of 34 items, 23 of which form the following 4 subscales: dieting, worrying about food, worrying about body shape and worrying about weight. Most of the items have categorical answer categories. Items that assess symptom duration have an open response possibility, as well as questions about length and weight. An increasing total or subscale score indicates more eating disorder symptomatology
	Readiness and Motivation Questionnaire – Dutch version (RMQ-Dutch)	The RMQ has demonstrated fair test-retest reliability and good convergent and discriminant validity.[41] The psychometric properties of the RMQ-Dutch have not been investigated yet.	Respondents answer to what extent a certain item applies to her on a 10 point Likert scale. It yields total (averages across all 12 symptoms) and symptom-specific (restriction, cognitive bingeing, and compensatory strategies) scores for the following categories: precontemplation, action, internality and confidence.
	Eating Disorder Inventory-3 (EDI-3)	The EDI-3 has excellent reliability and adequate convergent and discriminant validity.[42]	Participants respond on a 6-point Likert scale on 91 items, which yields composite scores on the following domains: eating disorder risk, ineffectiveness, interpersonal problems, affective problems, overcontrol and general psychological maladjustment. A higher score indicates that a psychological feature is more typical for the respondent as opposed to lower scores.
	Body Shape Questionnaire (BSQ-Dutch)	Both the concurrent and discriminant validity have been shown to be good in the English version of the BSQ.[43] The Dutch version, which was developed by us with permission of the original developers, has not been validated yet.	The BSQ consists of 34 items. The respondent answers the items on a 6-point Likert scale. The items yield a total score in which higher scores reflect more concerns about the body shape.
General psycho-pathology	Mini-International Neuropsychiatric Interview (MINI-KID/MINI-PLUS)	The sensitivity and specificity of the MINI are rated as good to excellent.[44,45]	The MINI-KID contains 23 modules and the MINI PLUS contains 26 modules. Each module corresponds to a diagnostic category. All modules start with one or more screening questions. If the respondent notifies that she suffers from a certain symptom, detailed questions about the psychiatric disorder are addressed; if the responses on the screening questions are negative, the researcher goes on to the next module (diagnostic category). Both versions of the MINI yield DSM-IV diagnoses.
	The Achenbach System of Empirically Based Assessment (ASEBA) questionnaires (CBCL, ABCL, YSR, ASR)	The ASEBA instruments (83, 84) have been used extensively in different contexts and have shown excellent psychometric properties.[46]	The questionnaires consist of 113 items each that are answered on a three point Likert scale. Higher scores indicate that the item is true for the participant. The items yield a total score and scores on the following domains: aggressive behavior, anxious/ depressed, attention problems, rule-breaking behavior, somatic complaints, social problems, thought problems, withdrawn/ depressed.
Autism	Social Responsiveness Scale	The SRS has good psychometric properties[47,48]	The SRS-2 consists of 65 and the SRS-A of 64 items that are answered on a 4-point Likert Scale. Both the SRS-A and SRS-2 version yield information about the level of 1) social communication and interaction and 2) restricted interests and repetitive behavior.
Anxiety	Screen for Child Anxiety Related Disorders – Dutch (SCARED-	The SCARED was found reliable in terms of internal consistency, test-	The self-report consists of 41 items and the parent version consists of 69 items that are answered on a 3-point Likert scale. A total score on both questionnaires is obtained, in which higher scores indicate more anxiety psychopathology in the participant.

	NL)	retest reliability[49] and has good convergent[50] and discriminant validity.[49]	Also the following scale scores are yielded: separation anxiety, panic disorder, specific phobia (animal, medical and situational type), social phobia, obsessive compulsive disorder, posttraumatic and acute stress disorder, generalized anxiety.
Obsessive compulsive behaviors and thoughts	(Children's) Yale-Brown Obsessive Compulsive Scale ((C)Y-BOCS)	The Y-BOCS and CY-BOCS demonstrate good convergent and divergent validity, as well as high internal consistency and inter-rater reliability[51,52]	Both versions of the interview consist of 10 items. The items are scored on a 4-point scale and yield a total score between 0 and 40, in which a higher score indicates more obsessive compulsive behaviors and thoughts. A score of 16 is set as the clinical cut-off score.
Depression	Beck Depression Inventory-II NL (BDI-II-NL)	The test has good psychometric properties.[53]	The BDI-II NL has 21 items that are scored on a three point scale. A higher total score indicates more depressive symptomatology.
Quality of life	KIDSCREEN-27	The KIDSCREEN is a valid and reliable tool to assess quality of life measures.[54]	All 27 items are answered on a 5 point Likert scale and yield a total score which resembles a general quality of life estimate. Subscale scores are obtained on the domains physical wellbeing, psychological wellbeing, autonomy and parent relation, peers and social support and school environment.
Eye gaze patterns	Tobi 120 eyetracker, E-prime software	The Tobii 120 eyetracker has been used more often in eating disorder research, but also in other fields such as autism research[55]	At the start of the procedure, the participant is seated in a fixed chair, approximately 60 cm in front of the computer screen. A five-point calibrating procedure takes place to determine the eye position before the execution of both paradigms. The examiner evaluates the calibration and, if necessary, the calibration routine is repeated in case of unsatisfactory data. Then, the participant is instructed to read the instructions on the computer screen and use the response box to respond to the cues. The execution of the DPT and free viewing task follows. For each participant and each stimulus, the locations and durations of the fixation are measured.

YPAN: Young People Anorexia Nervosa; YPHC: Young People Healthy Controls; PCAN: Parent/Caregiver of a participant with Anorexia Nervosa; PCHC: Parent/caregiver of a healthy control participant; CBCL: Child Behavior Check List; ABCL: Adult behavior Check List; YSR: Youth Self Report; ASR: Adult Self Report

protocol and sequences were harmonized with those obtained in the Generation R Study,[65] which is a Dutch longitudinal prospective cohort study (See reference 52 for an overview of the imaging protocol and sequence parameters).

Researchers involved in neuroimaging data collection underwent an extensive safety-training course to become certified to work in the MRI setting. These researchers also underwent intensive training to master operating the GE Discovery 750w MR system.

The MRI scanning procedure was performed as follows. Prior to entering the MRI environment, all participants completed a MRI contra-indication form (including their parents of participants younger than 16 years old if they wanted to accompany their child into the control or MRI room). For those without contra-indications, a check was performed to assure that they were safe to go into the MRI (i.e., lack of jewelry, anything in their pockets, metal in their clothing, history of surgeries, etc.). If the participant was excluded from MRI scanning for any reason, the participant was still able to undergo the cognitive, behavioral and physical health measurements of the study.

Following the MRI, all scans were evaluated for both data quality (see Figure 4 for the quality assessment ratings and Table 3 for movement parameters of the BRAVE MRI data) and incidental findings, initially performed by trained PhD students (see[66] and[67] for a decription of the quality rating procedures). If abnormalities were identified, the findings were then discussed with a neuroradiologist. If clinically relevant, the participant (and parents if the participant was younger than 16 years of age) was informed about these findings and the participant was referred for follow-up

COGNITIVE MEASURES

Cognitive tasks were performed face to face with using testing materials, including a laptop, two-button (yellow/blue) Curdes response box, computer mouse, keyboard, a pencil, and a stopwatch.

The dot probe, go/no go and set shifting tasks were programmed in E-prime and practice trials were performed prior to the execution of the experimental trials to ensure that the tasks were understood by the participants. The paradigms that were performed in the MRI were practiced on a laptop with the same two-button response box as used in the MRI, approximately 20 minutes before MRI scanning. In all practice trials, each paradigm ended automatically when the participant reached a correct response rate of 80%. The same timing characteristics were applied in the practice trials as in the experimental tasks, but different stimuli were used to keep the testing effect as small as possible.

In Table 4, a description of the measures and their psychometrics are shown.

Table 2. Neurobiological measures

MRI sequences													
	Paradigms	*TR/TE/ T1 (ms)*	*Flip angle (°)*	*Field of view*	*Acquisition matrix*	*Slice thickness*	*In-plane resolution (mm)*	*R*	*Bandwidth (kHz)*	*Fat saturation*	*Frequency encoding direction*	*Phase encoding direction*	*Volume*
IR-FSPGR	-	8.77/ 3.4/600	10	220x220	220x220	1.0/230	1.0 mm^2	2	25	Yes	S/I	R/L	200
DTI	-	12,500/ 72.8	-	240x240	120x120	2.0/65	2.0 mm^2	2	250	Yes	R/L	P/A	38
RS-fMRI	-	1760/ 30	85	230x230	64 x 64	4.0/36	3.4 mm^2	2	250	None	R/L	P/A	200
fMRI Passive	Passive information processing	1760/ 30	85	230x230	64 x 64	4.0/36	3.4 mm^2	2	250	None	S/I	P/A	214
fMRI go no go	Inhibition skills using body stimuli	1760/ 30	85	230x230	64 x 64	4.0/36	3.4 mm^2	2	250	None	S/I	P/A	277
fMRI set shifting	Set shifting skills using food stimuli	1760/ 30	85	230x230	64 x 64	4.0/36	3.4 mm^2	2	250	None	S/I	P/A	210
fMRI dot probe	Attention bias for food	1836/ 30	85	230x230	64 x 64	4.0/36	3.4 mm^2	2	250	None	S/I	P/A	277

IR-FSPGR, Inversion Recovery Fast Spoiled Gradient Recalles, T1-weighted image; DTI, Diffusion Tensor Imaging, RS-fMRI, resting-state functional magnetic resonance imaging; fMRI passive, a 7-minute functional magnetic resonance imaging sequence in which participants are faced with varying stimuli; fMRI go no go, a functional magnetic resonance imaging sequence in which inhibition skills using images of bodies with either a very low or very high BMI are measured; fMRI set shifting, a functional magnetic resonance imaging sequence in which set shifting skills are assessed with images of high and low caloric food; fMRI dot probe, a functional magnetic resonance imaging sequence in which attentional bias for food is measured; TR, Repetition Time; TE, Echo Time; TI, Inversion Time; R, Acceleration

Table 3. Functional MRI Movement Parameters for Baseline and One-year Follow-up for the BRAVE Study Participants

	Baseline					
	AN			HC		
Sequence	*N*	*Median TR to TR movement (IQR)*	*Median maximum movement (IQR)*	*N*	*Median TR to TR movement (IQR)*	*Median maximum movement (IQR)*
fMRI-resting state	57	0.03 (0.02, 0.06)	0.78 (0.60, 1.16)	64	0.04 (0.02, 0.05)	0.78 (0.62, 1.20)
fMRI-passive task	57	0.04 (0.02, 0.05)	1.47 (1.26, 1.71)	63	0.03 (0.02, 0.05)	1.47 (1.16, 1.70)
fMRI-set-shifting task	54	0.04 (0.02, 0.05)	1.50 (1.25, 1.93)	59	0.04 (0.02, 0.06)	1.58 (1.29, 1.98)
fMRI-dot probe task	54	0.03 (0.02, 0.05)	1.82 (1.44, 2.52)	59	0.03 (0.02, 0.05)	1.60 (1.29, 2.05)
fMRI-go nogo task	54	0.03 (0.02, 0.05)	1.55 (1.30, 1.91)	61	0.03 (0.02, 0.06)	1.67 (1.41, 2.20)
	One-year-follow-up					
	AN			HC		
Sequence	*N*	*Median TR to TR movement (IQR)*	*Median maximum movement (IQR)*	*N*	*Median TR to TR movement (IQR)*	*Median maximum movement (IQR)*
fMRI-resting state	45	0.04 (0.02, 0.06)	0.71 (0.55, 0.90)	50	0.03 (0.02, 0.06)	0.84 (0.69, 1.13)
fMRI-passive task	42	0.04 (0.02, 0.08)	1.50 (1.15, 1.94)	49	0.03 (0.02, 0.05)	1.45 (1.15, 1.72)
fMRI-set-shifting task	39	0.05 (0.02, 0.08)	1.75 (1.34, 3.08)	49	0.03 (0.02, 0.05)	1.59 (1.27, 2.28)
fMRI-dot probe task	40	0.03 (0.02, 0.07)	1.54 (1.28, 2.66)	48	0.03 (0.02, 0.06)	1.61 (1.27, 2.15)
fMRI-go nogo task	41	0.04 (0.03, 0.07)	1.66 (1.25, 2.54)	49	0.04 (0.03, 0.05)	1.66 (1.25, 2.54)

Note: AN=anorexia nervosa; HC=healthy controls; TR=repetition time; fMRI=functional magnetic resonance imaging; IQR=Interquartile range.

INTELLIGENCE

Measures of Intelligence are obtained with the Wechsler Abbreviated Scale of Intelligence-II, Dutch version (WASI-II NL).[91] With this test we gained measures of verbal, non-verbal and general cognitive abilities.

ATTENTION BIAS

The Dot Probe Task (DPT) is a broadly used paradigm to assess attention bias. Originally, it was developed by MacLeod and colleagues.[92] Our DPT was based on the version of Werthmann and colleagues.[93] In the BRAVE Study, two DPTs were developed, with both containing images of food and neutral stimuli. One of the paradigms was administered during fMRI scanning and the other during eyetracking. See Supplementary figure 2 for the timing characteristics of both DPTs.

VISUAL SPATIAL ABILITIES

We used three tasks to assess visuo-spatial abilities in our participants: 1) The *Rey Complex Figure test* (RCFT)[94] measures visual spatial organization, visual spatial memory and visual spatial recognition. 2) The *Motor free visual perception test, 4th edition (MVPT-4)*[76] assesses visual-perceptual abilities 3) The *Navon task* is a computerized paradigm that assesses global versus local processing of visual stimuli. Our Navon Task was based on the original version as developed by Navon,[95] with adaptions implemented by Stoet.[96]

SET SHIFTING

We used three versions of the same set shifting task to obtain measures of set shifting abilities. In the first set shifting task, neutral stimuli were used. In a second version, rather than neutral stimuli, we used images with individu-

Figure 4a. Systematic Quality Assessment Rating Scale for Structural MRI scans

Structure	Areas of Interest	Rating Scale
Cerebellum	Folia	0 = Crystal clear 1 = Most GM/WM folia good 2 = Some GM/WM folia good 3 = No diffferentation of GM/WM in folia
Axial waves	Anterior and posterior	0 = No waves 1 = Minor waves (anterior or posterior) 2 = Multiple waves (anterior and posterior) 3 = Large waves
GM/WM interface	Anterior and posterior	0 = Crystal clear 1 = Some blurring 2 = Sig. blurring but some differentiation 3 = No differentiation of GM/WM
Subcortical (caudate and putamen)	Axial	0 = Crystal clear 1 = Some minor blurring, but still traceable 2 = Significant blurring, can trace some aspects 3 = Not traceable

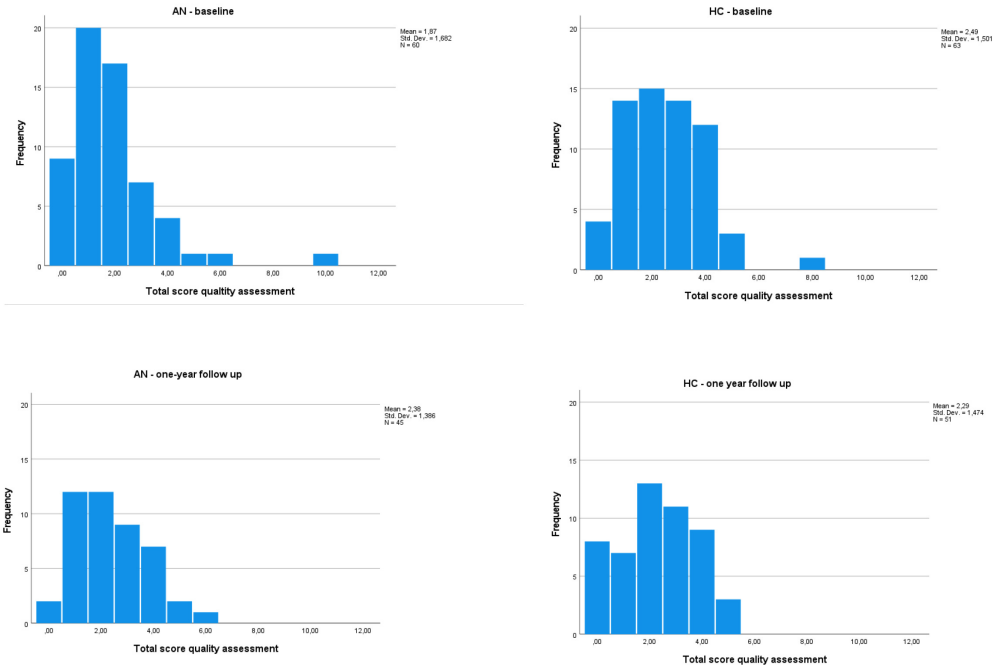

Figure 4b. Distribution of scan quality ratings using the Systematic Quality Assessment Rating Scale for Structural MRI scans at baseline and one-year-follow-up, split by groups.

Note: AN=anorexia nervosa; HC=healthy controls

als participating in physical exercise; and in the third version, which was performed in the MRI, food stimuli were used. The paradigms were based on the plus-minus task as described by Miyake and colleagues[97] and the category switch paradigm of Wolf and colleagues.[78] Similar tasks have been used by Van Autreve and colleagues[98,99] in patients with AN. A schematic overview of the paradigms is shown in Supplementary figure 3.

INHIBITORY CONTROL

We programmed three *go/no go* paradigms in order to measure proactive inhibition, i.e. the ability to suppress or interrupt motor responses.[100,101] A version with neutral stimuli was performed on a laptop. A second version in which stimuli of female bodies with a normal BMI was performed during eyetracking and a third version with stimuli of female bodies with a very low and very high BMI was performed during fMRI. Our paradigms were based on the go no go task as used by Wolf and colleagues.[78] See Supplementary figure 4 for a schematic overview of our paradigms.

DECISION MAKING

Three computerized paradigms were used to measure decision making, which were a *Balloon Analogue Risk Task*

Table 4. Cognitive measures

Construct	Instrument	Psychometrics	Description
Intelligence	Wechsler Abbreviated Scale of Intelligence, second version, Dutch edition (WASI-II NL)	The Dutch version of the WASI-II NL has not been validated yet, but the Dutch version of the WASI has been previously used in autism research.[68]	The WASI-II NL consists of two verbal (Vocabulary and Similarities) and two non-verbal tasks (Block design and Matrix Reasoning). For a description of the subtests of the WASI-II we refer to the WASI-II manual.[69] Items are scores on a two (0/1) or three point scale (0/1/2). The raw scores of every subtest are converted to standard scores and thereafter converted to scale and total scores.
Attention bias	Dot probe task (DPT)	The DPT has shown to be sensitive to detect attentional biases.[70] The psychometric properties of the paradigm for the AN group with the use of food stimuli have not been validated yet.[71]	Both our DPTs consist of two blocks with 60 trials. The paradigm starts with a fixation cross after which a pair with two stimuli (one of which is a food image and the other is a neutral stimulus, similar in shape and color) follows. Then, an asterix (i.e. probe) appears at the location of one of these stimuli. The participant has to press the left or right button on a two-button response box to indicate the location of the asterix. Reaction time and accuracy are measured for every trial. Differences between incongruent and congruent trial are studied.
Visual spatial abilities	Rey Complex Figure Test (RCFT)	The RCFT has good psychometric properties for the standard scoring systems[72] as proposed by Osterrieth[73]	The participant has to draw a complex figure, first by copying the figure from an example and then after 3 and 30 minutes from memory. Lastly, the participant performs a recognition task in which she has to indicate which elements among alternatives were shown in the original figure. Every element is scored on a 4-point (2/1/0.5/0). For the recognition trial scoring takes place on a 2-point scale (0/1). Raw scores are converted to standard scores. Additionally, we apply a slightly modified version of the Booth scoring method[74] as formerly used by Lang and colleagues[75] to obtain measures of local versus global processing.
	Motor-free Visual Perception Task- fourth edition (MVPT-4)	The MVPT-4 is a valid and reliable instrument to assess visuo-spatial abilities without using a motor response[76]	The test consists of different tasks in which the respondent as to point to the correct answer among alternatives. All of the 45 items are scored as true[1] or false (0). We gain measures of visual discrimination abilities, the ability to distinguish an object from its background (visual figure ground), visual memory skills, visual closure abilities and visual spatial relationships. Also a total raw score is yielded. Ray scores are converted to standard scores and an age equivalent.
	Navon task	The Navon task is a widely used task to assess global versus local processing, although the construct validity is questioned since local-global visual processing is not supposed to be a unitary construct.[77] Therefore the interpretation of the results should be done with caution	The participant looks at figures in the shape of a letter, which is build up from small letters. The participant has to indicate by pressing a key on a laptop whether an H or an O is presented in the stimulus, which demands the participant to examine the figure globally and locally. The stimuli is shown until response. Measures of accuracy and reaction times are obtained per trial. Differences between consistent and inconsistent stimuli are studied.

Set shifting skills	Set shifting neutral	The psychometric properties of the used paradigms have not been assessed yet, but the set up of our paradigms is similar to the category switch paradigm of Wolf and colleagues.[78]	Each paradigm has two blocks that consists of 32 trials. In the first version we use neutral stimuli and in the second version stimuli of sports/leisure activities are shown The neutral and sports/leisure activity stimuli are collected via Google search. In the third paradigm high caloric and low caloric food stimuli are shown. The stimuli are obtained from Blechtert's food image database.[79] The neutral and activity paradigms are executed on a laptop and the food paradigm is performed during fMRI scanning. All paradigms start with a cue that indicates what task has to be executed. Thereafter a stimulus is presented and the task, indicated by the cue, has to be executed as quickly as possible. When the cue changes, it demands from the participant to switch strategies. The outcome measure for each task is the switch cost, calculated as the inverse efficiency scores (IESs[80,81]) by dividing the mean response time (RT) of correct responses by the proportion of correct responses (RT/[1 – ER]). Thus, participants with lower shifting competencies obtained higher scores in these tasks.
	Set shifting food		
	Set shifting active		
Inhibition skills	Go no go-neutral	The go no go paradigm is a widely used paradigm to assess inhibition skills. The psychometric properties of these particular paradigms have not been assessed yet, but the set up is similar to the go no go task as used by Wolf and colleagues.[78]	Each paradigm contains a go-block, consisting of 120 trials and a no-go block that also consists of 120 trials. In the first paradigm (neutral version, executed on a laptop) the participant has to press the button when dots are presented horizontally; when the dots are placed vertically they have to withhold their response. In the second and third paradigm, we used images of bodies, developed by Mousally and colleagues,[82] with a normal weight (second version, executed on a laptop) and bodies with a very low and very high weight (third version, executed during fMRI scanning). The instruction for both paradigms is to press the button on the response box when the body is in standing position. The participants have to withhold their response when the body is in a sitting position. The outcome measure for these tasks are the IES, calculated as the mean RT for correct go trials divided by the proportion of correct responses on no-go trials. Thus, participants with lower inhibiting capacities obtain higher scores.
	Go no go-normal		
	Go no go-highlow		
Decision making	Balloon Analogue Risk Task (BART)	The BART evidenced sound experimental properties and is supposed to be a useful tool in the assessment of risk taking .[83]	In this task the participant has to pump a balloon by pressing a button on the keyboard. With each pump the participant earns points. However, when the balloon collapses, the participant loses all points. This set up and analysis of the paradigm is described extensively elsewhere.[84] Reaction time and number of pumps per trial are obtained per trial. For a detailed description of the analysis of the BART we refer to Pleskac and Wershbale's paper[84]
	Iowa Gambling Task (IGT)	Evidence provides support for the use of the IGT to detect decision making deficits in clinical populations, although data regarding reliability of the IGT are lacking[85]	The participant needs to choose one out of four card decks. The participant wins or loses money with each card they pick. Two out of four desks yield little money, but the participant doesn't lose a lot of money either. The other two desks yield lots of money, but the participant is at risk to lose a lot of money as well. The number of choices from each deck during each trial are added up. We also calculate the number of "good" and "bad" desks .
	Probabilistic reversal learning paradigm (PRLT)	Probabilistic reversal learning tasks have been applied in AN studies previously	The participant has to choose between a yellow or a blue square. Every time the participant receives feedback about whether this choice was right or wrong. The participant is instructed to gain as many right responses as possible. This PRLT has three conditions: in the first condition the participant receives positive feedback in 90% of the cases, in the second condition this was 80% of the cases and in the third condition 100% of the cases.

		e.g.[86,87] The paradigm as used in BRAVE has previously been used by Hooper[88]	The average number of trials to criterion (defined as the total trials for a discrimination or reversal minus the randomly determined criterion) is calculated separately for the different conditions. Errors (choosing the current "bad" color) are coded as: failures to maintain set, perseverative, or other.
Passive information processing	Passive task Free viewing	As these paradigms are newly developed for this study, the psychometric properties are not evaluated yet.	The fMRI data analyses procedures are described elsewhere.[89] The eyetracking procedure has been described in Table 1.
Executive functioning	The Behavior Rating Inventory of Executive Function (BRIEF)	The internal consistency of the Dutch BRIEF has appeared to be very high and has a high test-retest stability. The Dutch BRIEF is supposed to be a reliable measure of executive functioning.[90]	The 86 items of the BRIEF are answered on a 5 point Likert scale. The questionnaire provides a total score and two index scores (Behavioral regulation and Metacognition), which are derived from the following eight subscales: Inhibition, Shifting, Emotional control, Initiation, Working memory, Planning and organization, Organization of materials and Monitoring. Raw scores are converted to standardized subscale scores, index scores and a total score.

(BART), the *Iowa Gambling Task* (IGT) and a *Probabilistic Reversal Learning Task* (PRLT). The BART task has previously been used previously in studies by Pleskac and collegues.[84] The IGT was developed by Bechara and collegues.[102] Our PRLT was adopted from Hooper and colleagues.[88]

PASSIVE INFORMATION PROCESSING

We developed two computerized paradigms in which the participated was instructed to passively view a computer screen that presented a wide array of varying stimuli (e.g. bodies, food, eating situations, emotions (pleasant and scary), flashing checkerboard, video and sound of hands playing the piano, visual versus serial search, memory for faces). The participants performed this paradigm during fMRI scanning (passive task) and another version during eyetracking (free viewing task). The goal of this task was to actively drive different brain networks, including the shifts between networks. The passive task was also performed during the eyetracking session.

EXECUTIVE FUNCTIONING

The *Behavior Rating Inventory of Executive Function* (BRIEF)[103] (self-report and parent/informant report) examines executive functioning of the participant. The BRIEF was used for participants younger than 18 years old and the BRIEF-A was used for participants aged 18 years and older.

PHYSICAL HEALTH MEASURES

The measurements in this section included height, weight, and other measures of physical health and were collected in the Erasmus MC-Sophia Children's Hospital. Table 5 provides a complete description of the measures and the data collection procedure.

BODY MATERIAL

Four *blood tubes* were collected at baseline and at follow-up to gain insight in the biological changes in AN with regard to the DNA profile/methylation patterns, hormonal assays, liver, kidney function, glucose levels and hematology abnormalities (leukocytes and thrombocytes). These data have been biobanked with the goal to engange or participate in large consortia, making it possible to perform large (i.e., GWAS, EWAS, etc.) studies in which large sample sizes are needed to draw meaningful conclusions. A *hair sample* was collected for cortisol analysis. Also participants provided a *stool sample,* collected at home with the goal to analyze intestinal flora (microbiome).

BODY COMPOSITION

Body composition was assessed by using the BODPOD (COSMED, the Metabolic Company, Italy), which is a a safe and non-invasive Body Composition Tracking System that provides measures of total body mass, fat mass (grams), fat-free mass (grams) and total body fat (%).

Table 5. Physical health measures

Domain	Method	Description
Body material	Venipuncture	Four blood tubes are taken by a trained nurse or doctor to collect DNA, hormones, liver-, and kidney functions, glucose levels and hematology abnormalities (leukocytes and thrombocytes) of our participants. Dutch age and sex equivalent reference norms are used to interpret results.[104] Rest material will be stored for possible additional analyses.
	Hair sample	A small tuft of hair (about 300 hairs) is cut as close as possible to the scalp at the height of the posterior vertex position using fine scissors by a member of our research team. The hairs are stored in an envelope and later on send to the department general clinical chemistry for cortisol analysis
	Stool sample	Participants receive material for stool collection in the initial visit of the BRAVE study, They are requested to take a stool sample at home and send it to our gastroenterology laboratory for intestinal flora analysis.
Body composition	BOD POD	The BODPOD is an air-displacement plethysmography, which measures body volume by detecting a difference in air pressure between the test chamber and the reference chamber.[105] The participant is asked to sit in the BOD POD wearing a tight shirt, fitted pants and a cap, provided by the examiner. In two minutes, the BOD POD measures body composition. The total measurement takes about 5 minutes.
Weight, length and BMI-SDS	BMI-SDS Calculator	Data on weight is derived from the BOD POD (COSMED, the Metabolic Company, Italy). If the participants don't undergo the BOD POD measurement, weight is measured with a scale where the participant is wearing lightweight clothes. In an interview the participant is asked about her heighest weight before weight loss and her weight in the 6 consecutive weeks before the interview.Length is measured from head to foot in every participant using a measuring staff (Seca 222). The participants stand on their bare feet whilst the measurement is performed. A Dutch calculating tool is used to obtain BMI-SDS scores (https://tnochildhealthstatistics.shinyapps.io/JGZRichtlijnLengtegroei/)
Muscle strength	JAMAR®-plus+ Digital Hand Dynamometer	The participants are asked to squeeze the instrument as hard as possible. To obtain valid grip force measures we assess grip force 3 times per hand. Average grip forces are calculated per hand.
	Measurement tape	The upper arm circumference of both bare arms is measured using a measuring tape (Seca 201).
General physical health	Interview	Data are digitalized into our electronic database and saved until further analysis.

MUSCLE STRENGTH

Muscle strength was measured with a *hand grip instrument* JAMAR®-plus+ Digital Hand Dynamometer (Patterson Medical ®, Warrenville, IL, USA and Sammons Preston ®, Bolingbrook, IL, USA). The circumference of the upper arm of the participant was measured using a *measurement tape* (Seca 201).

BMI-SDS

The BMI-SDS uses the body mass index, defined by the equation BMI=weight/length^2 (kg/m^2), with a further adjustment for age and sex. For the BMI-SDS measure, the growth curves of the Dutch Organization of Applied Research (TNO) were used.[106]

GENERAL PHYSICAL HEALTH

The physical health interview was perfomed on each participant, the caregiver and/or the clinician. Data regarding current and past physical health including history of diseases, smoking and drinking behavior, medication and vitamin supplement usage was collected. Also information regarding prior mental health treatment. We also collected information on the use of tube feeding tubes.

ADDITIONAL MEASURES

An overview of additional measures collected is provided in Table 6.

PREDICTION

We developed a short questionnaire that was filled in digitally by the clinician of a participant with AN at baseline and follow-up to asses their predicted treatment duration, types of treatment(s) needed, and treatment response.

SOCIO-DEMOGRAPHIC CHARACTERISTICS

In this questionnaires socio-demographic features such as native language, national origin, family characteristics, socio-economic status, including education level of the parents and the participant, were collected.

APPETITE

Before the MRI scanning and eyetracking sessions, the participant filled out a questionnaire about their current appetite and the timing of their previous and next meal. She was asked to give an indication of the time of day she was

Table 6. Other

Domain	Method	Description
Feelings of hunger	Appetite	The Hunger scale exists of 4 items that investigate feelings of hunger at this moment (on a 7 point scale), how much of their favorite food they would like to eat right now (on a 6 point scale), the last time that the participant had a meal and at what time the participant is planning to have her next meal. Data are digitalized into our electronic database and saved until further analysis.
Prediction	Questionnaire	The prognosis questionnaire exists of is filled in by the clinician. The clinician is asked to indicate how long the participant will be needed treatment, what kind of treatment methods will be needed and on what assumption this indication was made.
Socio-demographic characteristics	Questionnaire	Categorical answers are collected.

planning to have her next meal and the time of day she had her last meal.

SAMPLE DESCRIPTION AND DESCRIPTIVE ANALYSES OF THE MEAN VARIABLES

The data collection has been finalized. The inclusion period lasted from 3 May 2017 to 14 October 2021.

The follow up data were completed on 16 January 2023. A total of 79 females with AN (typical=93.67%; atypical=6.33%) and 75 TD girls were included in the study. The retainment rate at time 2 was 72% (n=57) for the AN group and 88% (n=66) for the TD group. To investigate a possible selection bias in both the AN and TD groups, we compared the dropouts from the participants who also fulfilled data point 2 on the following variables: age, mother's ethnicity, BMI-SDS, eating disorder characteristics (EDE and BSQ). The drop-outs in the AN group did not differ in sociodemographic and main variables from the AN participants who fulfilled both data collection points. In the TD-group, the drop-outs were slightly older compared to the TD girls who also fulfilled the measurements at time 2. The mean time between the two data collection points (reference BMI-SDS measurement) was 13.48 (SD=3.72) months for the AN group and 13.03 (SD=1.64) months for the TD group. Part of the data collection took place during the COVID-19 pandemic. Of the participants with AN, 49 were enrolled pre-pandemic and 30 peri-pandemic. For the TD group, 38 participants were enrolled pre-pandemic and 37 peri-pandemic. Enrolment was lower than expected during the pandemic and we did not reach our target goal of 90 participants per group. However, we did achieve a substantial sample size that exceeded most studies in this area.

The baseline characteristics of our sample are presented in Table 7.Compared to the TD girls, the girls with AN were younger in age (Mean Difference (MD)=0.82, (t=2.28, (df)=152, p=0.02). By definition, they had a lower BMI-SDS (MD=1.72, t=9.36, df=129.92, $p<0.001$), had more general eating disorder symptomatology (Mann-Whitney U (W)=193.0, Z=-10,01, $p<0.001$), showed more restrictive eating behavior (W=248.0, Z=-10.86, $p<0.001$) and worried more about food (W=34.0, Z=-10.86, $p<0.001$), weight (W=160.5, Z=-10.2, $p<0.001$) and body shape (EDE subscale body shape concerns: W=105.0, Z=-10.35, $p<0.001$); BSQ total score: W=125.5, Z=-9.65, $p<0.001$). They also fulfilled more DSM-IV criteria for comorbid psychiatric disorders than the TD group (total number of DSM-IV classifications: *Chi-square* (χ^2)=56.24, df=5, p<0.001; eating disorders: χ^2=70.69, df=1, p<0.001; OCD χ^2=15.2, df=1, p<0.001; mood disorders: χ^2=38.87, df=1, p<0.001; anxiety disorders: χ^2=21.72, df=1, p<0.001). There were no group differences in race or background, highest education level of the mother, or in the number of developmental disorders, i.e. ADHD and ASD.

Correlations between sociodemographic and main variables are presented in Supplementary Tables 1 and 2.

DATA MANAGEMENT, ANALYSES AND SHARING

All research data are stored under a de-identified Research ID and visit number (T1/T2) on a secure server within Erasmus MC. A link between research ID and personal details is only made in our Trial Master file, which is only accessible to key members of the research team and can be made available to the Dutch Public Health Inspectorate.

Blood samples were also stored using the Research ID and visit number. Written informed consent forms were scanned into electronic database and stored on protected servers seperate from the clinical report forms (CRFs). CRFs are manually entered into an electronic database. Questionnaires are administered online and stored in an electronic database. (f)MRI data are transferred to two separate dicom servers, one being archived by the department of radiology and the other a secure XNAT server within the department. Eyetracking data and neuropsychological computer tasks were stored on the testing laptop and back-ups were made on two separate storage devices. Blood samples and feces were biobanked within the Erasmus MC awaiting further analyses.

For data analysis, we will examine whether our four potential predictive domains can predict BMI-length/weight SDS and AN symptomatology after one year of treatment. Additionally, we aim to assess the association between clinically significant alterations and changes in these four predictive domains during the initial year of treatment, contrasting individuals with (atypical) AN against TD participants. To accomplish this, we will conduct linear mixed-model analyses. Access to data and requests for collaboration are welcome and will be conducted under the rubric of the European Union's General Data Protection Regulation (GDPR).

Table 7. Baseline characteristics of BRAVE participants included in this study

Characteristics	Participants with (atypical) AN			Typically developing participants		
	N	*Statistic*	*Percentage, median (IQR) or mean (SD)* †	*N*	*Statistic*	*Percentage, median (IQR) or mean (SD)* †
Age at time of inclusion (years)*	79	Mean, SD	16.42 (2.23)	75	Mean, SD	17.24 (2.24)
Ethnicity	76	Percentage	100	73	Percentage	100
Dutch	72	Percentage	94.7	71	Percentage	97.3
Western	1	Percentage	1.3	0	Percentage	0
Non-Western	3	Percentage	3.9	2	Percentage	2.7
Education level of the mother, ‡	76	Percentage	100	71	Percentage	97.3
Low	13	Percentage	17.1	5	Percentage	6.8
Middle	24	Percentage	31.6	24	Percentage	32.9
High	39	Percentage	51.3	42	Percentage	57.5
Handedness (right)	60	Percentage	86.7	61	Percentage	90.2
BMI-SDS**	71	Mean, SD	-1.27 (1.24)	72	Mean, SD	0.45 (0.93)
Body shape satisfaction (BSQ)**	69	Median, IQR	141 (113, 159)	70	Median, IQR	50 (39.75, 65)
EDE – total score**	79	Median, IQR	3.73 (2.82, 4.54)	75	Median, IQR	0.16 (0.06, 0.46)
EDE – restrictive eating behavior	79	Median, IQR	3.40 (2.00, 4.40)	75	Median, IQR	0.00 (0.00, 0,4)
EDE – worrying about food**	79	Mean, SD	2.76 (1.12)	75	Median, IQR	0.00 (0.00, 2.00)
EDE – worrying about weight**	79	Median, IQR	4.00 (2.3, 5.2)	75	Median, IQR	0.2 (0.00, 0.4)
EDE – worrying about body shape**	79	Median, IQR	4.75 (3.5, 5.38)	75	Median, IQR	0.25 (0.00, 0.63)
Time since AN diagnosis at the time of inclusion (years)	71	Median, IQR	0.32 (0.19, 0.66)	NA	NA	NA
Number of DSM-IV classifications (MINI-interviews) (max 7)**	78	Percentage	100	74	Percentage	100
0	5	Percentage	6.4	58	Percentage	78.4
1	27	Percentage	34.6	12	Percentage	16.2
2	20	Percentage	25.6	3	Percentage	4.1
3	15	Percentage	19.2	0	Percentage	0
4	10	Percentage	12.8	1	Percentage	0
6	1	Percentage	1.3	0	Percentage	1.4
Any eating disorder**	78	Percentage	64.1	74	Percentage	0
Any mood disorder**	78	Percentage	62.8	74	Percentage	13.5
Any anxiety disorder**	78	Percentage	44.9	74	Percentage	10.8
Any OCD**	78	Percentage	21.8	74	Percentage	1.4
Any behavior disorder	78	Percentage	3.8	74	Percentage	0
Any ADHD	78	Percentage	5.1	74	Percentage	4.1
Any ASD	78	Percentage	0	74	Percentage	0

** Siginificant difference between girls with (atypical) AN and typically developing girls (p<0.05)*

*** Significant difference between girls with (atypical) AN and typically developing girls (p<0.01)*

† Values are percentages for categorical variables, medians (interquartile range (IQR)) for continuous non-normally

> distributed variables and means (standard deviation (SD)) for continuous normally distributed variables, derived from the imputed dataset.

‡ High: higher vocational secondary education and higher academic education; Medium: higher general secondary education; Low: primary education and lower general secondary education

BMI-SDS=Body Mass Index-Standard Deviation Score; EDE=Eating Disorder Examination; OCD=Obsessive Compulsive Disorder; ASD=Autism Spectrum Disorder; ADHD=Attention Deficit Hyperactivity Disorder

STRENGTHS AND LIMITATIONS

The study has several strengths, including the use of objective measures in addition to self-report data, a longitudinal design, and a matched reference group based on age, gender, and education. The study also had several limitations. First, the BRAVE Study was not pre-registered, since as when the study was set up, preregistration was not a common practice in the Netherlands. Second, it's noteworthy that this study encountered a slightly higer dropout rate among participants with AN during follow-up compared to those in the TD group. The dropout rate observed aligns with rates documented in other longitudinal studies focusing on AN.[5] There are no indications for a selective drop out in the AN group. However, it remains unclear whether individuals who discontinued participation exhibited a more favorable or severe disease trajectory compared to those who continued, given the available follow-up data. The dropouts in the TD group were older compared to those who also fulfilled the measurements at time 2. No other disparities in sociodemographic or clinical variables were discerned between TD participants with and without follow-up data at the time of enrollment.

Third, considerable data were collected as a part of the BRAVE Study, and thus there is the potential of Type I errors resulting from different statistical analyses. To mitigate the risk of false positives, pre-registration of papers will be implemented, when possible, and the correction for multiple testing (i.e. by using the Benjamini-Hochberg approach) will be applied.

CONCLUSION

The duration of illness of AN varies from several months to life-long, with an average treatment course of 4.5 years and 20% remaining chronically ill.[5] At the moment, clinicians are unable to predict treatment outcome and illness duration for an individual patient, which is confusing and difficult to understand for the patients, caregivers and involved clinicians. Identifying predictors of treatment response has therefore been set as one of the most important priorities in eating disorder.,[7,8] but also since greater symptom reduction during the early stages of treatment is an important goal for achieving better treatment response, especially in young people. Moreover failure to treatment response early may be a risk factor for less favorable long-term outcomes.[107,108] Within this framework, we have set up the BRAVE Study with the primary goal to identify predictors of (immediate and long-term) treatment response in young women with AN. The goal is that we will be able to identify predictive patterns for treatment response within the heterogeneous presentation of symptoms of AN and comorbid symptoms of psychopathology in adolescent girls. By recruiting young people who have recently been diagnosed with AN, we envision we might be able to better detect the specific underlying mechanisms

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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SUPPLEMENTARY MATERIALS

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