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Eating Disorder Neuroimaging Initiative (EDNI): a multicenter prospective cohort study protocol for elucidating the neural effects of cognitive behavioral therapy for eating disorders

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ABSTRACT

Introduction: Anorexia nervosa is a refractory psychiatric disorder with a mortality rate of 5.9% and standardized mortality ratio of 5.35, which is much higher than other psychiatric disorders. Currently, while there is no validated drug treatment for eating disorders in Japan, cognitive behavioral therapy (CBT) is a well-established and commonly used treatment. CBT is also recommended in the Japanese Guidelines for the Treatment of Eating Disorders (2012) and has been covered by insurance since 2018. However, the neural mechanisms responsible for the effect of CBT have not been elucidated, and the use of biomarkers such as neuroimaging data would be beneficial.

Methods and analysis: The Eating Disorder Neuroimaging Initiative (EDNI) is a multisite prospective cohort study. We will collect data from 72 patients with anorexia nervosa and controls longitudinally. Data will be collected at baseline, after 21-41 sessions of CBT, and 12 months later. We will assess longitudinal changes in neural circuit function, clinical data, gene expression, and psychological measures by therapeutic intervention, and analyze the relationship among them using machine learning methods.

Ethics and dissemination: The study was approved by The Ethical Committee of the National Center of Neurology and Psychiatry (A2019-072). We will obtain informed consent in written form from all patients who participated in the study after they had been fully informed about the study protocol. All the imaging, demographic, and clinical data are shared between the participating sites and will be made publicly available in 2024.

Trial registration: UMIN000039841. Registered 18th March 2020, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000045438

Strengths and limitations of this study

►The research project will seek to clarify diagnostic and therapeutic markers, and identify predictive markers of treatment response in patients with eating disorders using a longitudinal approach.

► This should contribute to the early detection and early intervention of eating disorders.
► We will also create a brain imaging database in Japan for those with eating disorders.
► The number of people at one site is not very large because the brain imaging machines differ across facilities.

INTRODUCTION

Eating disorders (EDs) are a psychiatric disorder with a focus on body shape, weight and abnormal eating behavior. They are mainly classified as anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED).[1] In Japan, the number of patients with EDs has increased about 10-fold between the 1980s and 1990s.[2] Based on a meta-analysis including 36 studies, AN was found to have a standardized mortality ratio (SMR) of 5.1 [3] and the highest mortality among mental disorders.[4-7] In addition, renal function decreases as the duration of AN increases,[8] and patients often suffer from various physical complications associated with prolonged symptoms and low weight.[9-12] The rate of chronicity for patients with AN for up to 10 years is approximately 10-20%, and the long-term prognosis is poor.[13,14] Furthermore, there is currently no evidence of treatment for severe cases with chronic AN.[15]

Cognitive behavioral therapy (CBT) has been shown to be effective as a psychotherapy for EDs, [16-18] and CBT is also recommended in the NICE guidelines.[19] Meta-analyses of RCTs that include waitlist controls report that CBT is particularly effective for BN and BED.[20-24] In Japan, there are two reports on the effectiveness and feasibility of CBT for BN or BED,[25,26] and health insurance has covered CBT in Japan since 2018. However, according to a meta-analysis of RCTs, the dropout rate for CBT is approximately 24%,[27] and there are large individual differences in treatment responsiveness. To the best of our knowledge, there are no reports of neural mechanisms that regulate the effects and treatment responses of CBT for EDs. Therefore, accumulating evidence using brain imaging and biomarkers of gene expression would further our understanding of CBT effectiveness for EDs.

Since individuals with EDs show abnormal eating behavior, structural and functional brain imaging studies have been conducted to elucidate the neural basis of these abnormalities through brain imaging research. There are various reports on brain imaging research in ED patients that have revealed abnormal reward systems,[28] a reductions in gray matter of various brain regions (frontal lobes;[29] frontal gyrus;[30] parietal and temporal lobes;[31] occipital lobe[32]), and limited reductions in white matter volume.[33] In Japan, the neural basis for the pathogenesis of EDs has been clarified.[34-37]

However, brain imaging research for EDs has only been conducted in the form of small cross-sectional studies in a single facility, and the reproducibility and validity of these results remain questionable. Therefore, research at a larger scale is needed to elucidate the cognitive brain science of ED pathology and progression, and to identify clinically useful diagnostic and therapeutic markers and prognostic predictors.

The ENIGMA-Eating Disorders should be noted as a multicenter study outside of Japan. However, it is only registered by researchers in Europe, the United States, and Africa, and mainly takes place in Germany. For the time being, they have used methods to meta-analyze anatomical images and diffusion tensor-weighted images of AN and BN patients that have already been imaged at participating facilities. The ENIGMA-Eating Disorders study is expected to build a framework for joint research to be developed in the future. However, ED brain image multicenter research cannot be confirmed even by searching the world's major clinical research registration sites such as ClinicalTrials.gov in the United States and EU register in the EU, and an ED brain image database has not yet been developed globally.

Aims and hypotheses

We aim to generate neuroscientific evidence for the effect of CBT and contribute to the early detection and early intervention for EDs. First, we will collect brain magnetic resonance imaging (MRI) images and clinical data as longitudinal observational studies before and after CBT for EDs. Next, we will identify clinical biomarkers of EDs through analytical studies using longitudinal image data before and after CBT for EDs, and create neural evidence for the effect of CBT. We aim to identify brain image biomarkers that can be used as clinical markers (diagnostic markers, therapeutic markers, and therapeutic response prediction markers) for EDs. Furthermore, the brain image data collected for this project will be integrated into an international brain database.

METHODS AND ANALYSIS

Study design

This is a multisite, observational cohort study. For ED patients who have received structured CBT, the following will be performed before and after CBT: Brain MRI imaging (T1WI, T2WI, resting state functional MRI, DWI); Blood collection for gene polymorphism and gene expression analysis; and Psychological evaluation. Table 1 shows the study design. In the pre-treatment evaluation, subjects will visit each treatment facility, and an outpatient doctor or psychologist (recruiter) will evaluate eligibility and exclusion criteria for CBT introduction. After obtaining the informed consent for individuals who meet the criteria for introducing CBT, they will then be

registered as subjects of this study. After registration, the schedule for the first session of CBT will be determined. In principle, brain MRI scans and other tests will be carried out within 4 weeks before the session date. The post-treatment evaluation is based on the day when CBT for EDs is completed, and in principle, tests such as brain MRI are performed within 4 weeks. In addition, a similar assessment one year after treatment (50+/-8 weeks) will be performed for subjects who are willing.

Table 1 Standard protocol items

Items	Pre	Intervention	Post	Follow Up
Time point	-4W-0	1～21 sessions* /41 sessions**	Within 4 weeks	50 +/-8 W
Informed consent	×	-	-	-
Demographic data	×	-	-	-
Cognitive and psychological indicators	×	-	×	×
Brain MRI examination	×	-	×	×
Blood sample	×	-	×	×

*Outpatient /**inpatient

Study setting

This trial will be conducted by seven facilities (National Center of Neurology and Psychiatry (NCNP), Chiba University, Tohoku University, Tokyo University, Kyoto University, Kyushu University, and University of Occupational and Environmental Health) in Japan.

Recruitment

Those who wish to participate in the study will visit the NCNP, Chiba University, Tohoku University, Tokyo University, Kyoto University, Kyushu University, and University of Occupational or Environmental Health. The outpatient doctor or psychologist (recruiter) evaluates the eligibility criteria and exclusion criteria for CBT introduction. After obtaining the informed consent for this study from individuals who meet the criteria for receiving CBT, individuals will be registered as such as study subjects.

Study participants

Patients will be enrolled in the study if they meet the following selection criteria without meeting the exclusion criteria (see Table 2).

Table 2 Inclusion and exclusion criteria

Eating disorder	
Inclusion criteria	1) Meets the DSM-5 diagnostic criteria for an ED (AN, BN, BED) 2) ≧ 18 years of age at the time of informed consent 3) Body Mass Index (BMI) ≤ 15 kg/m^2 (or Standard weight-35%)> 40.0 kg/m^2 (Cases with lower weight are allowed when performed in inpatient) 4) Those who live in Japan and have the ability to read and write Japanese equivalent to the level of native speakers of Japanese 5) A person who understands the purpose and content of this research and has obtained written informed consent to participate in the research
Exclusion criteria	1) If you are physically severe (impaired consciousness, advanced liver dysfunction, advanced electrolyte abnormalities, etc.) and require advanced physical treatment 2) Mental illness (schizophrenia, bipolar disorder, alcohol abuse/dependence, autism) preceding the history of EDs 3) Persons with intellectual disabilities 4) Imminent risk of suicide 5) Risk of MRI examination (body surface/internal body metal, pregnancy or possibility of pregnancy, claustrophobia, dark phobia, etc.) 6) Those who are expected to have difficulty in coming to the hospital according to the research schedule and receiving evaluation 7) Otherwise, persons who are deemed inappropriate by the principal investigator
Healthy control	
Inclusion criteria	1) Those do not meet the diagnostic criteria for EDs (AN, BN, BED) in the DSM-5 2) ≧ 18 years of age at the time of informed consent 3) Body Mass Index (BMI) at screening is greater than 16 kg/m^2 (or standard weight -35%) and less than 40.0

	kg/m^2(those who do not meet the diagnosis of EDs and mental illness also tolerate lower weight) 4) Those who live in Japan and have the ability to read and write Japanese equivalent to the level of native speakers of Japanese 5) A person who understands the purpose and content of this research and has obtained written informed consent to participate in the research
Exclusion criteria	1) History of EDs 2) Persons with mental illness (schizophrenia, bipolar disorder, alcohol abuse/dependence, autism) 3) Persons with intellectual disabilities 4) Imminent risk of suicide 5) Risk of MRI examination (body surface/internal body metal, pregnancy or possibility of pregnancy, claustrophobia, dark phobia, etc.) 6) Those who are expected to have difficulty in coming to the hospital according to the research schedule and receiving evaluation 7) Otherwise, persons who are deemed inappropriate by the principal investigator

Patient and Public Involvement

Patients and public were not involved in the design of this study.

Interventions

In principle, CBT "improved version" (Fairburn) for EDs, 20-40 session version will be implemented. However, structured CBT performed at each treatment facility is acceptable.

Primary outcome

The primary outcome was ED symptoms and severity assessed by the Eating Disorder Examination Edition 16.0D (EDE 16D) [38,39] or Eating Disorders Examination Questionnaire (EDE-Q). [40,39] The EDE16D is a semi-structured interview, whereas the EDE-Q is a self-contained, 28-item questionnaire derived from the EDE. The EDE-Q is scored on a 7-point Likert scale (0–6) on which a score of ≥4 indicates a clinical range. The global score on the EDE-Q is the sum of the four subscale scores (for restraint, eating concern, shape concern, and weight concern) divided by 4.

Secondary outcomes

1. Remission at the end of treatment (state that does not meet DSM-5 criteria)
2. Treatment completion rate (completed when 75% or more of 21 to 41 treatment sessions are received)
3. ED specific indicators: Currently BMI; the lowest and highest BMI in the past; history of AN and BN
4. Non-specific psychological indicators: The Mini-International Neuropsychiatric Interview (M.I.N.I.)[41,42] for Comorbidities; Japanese Adult Reading Test(JART)[43,44] for intellectual ability; Beck Depression Inventory-Second Edition (BDI-II)[45,46] for Severity of depressive symptoms; State-Trait Anxiety Inventory (STAI)[47,48] for anxiety; NEO Five-Factor Inventory (NEO-FFI) [49,50] for personality scores; 20-Item Toronto Alexithymia Scale (TAS-20)[51,52] for alexithymia; Adult version facial expression recognition test[53] for adult facial expression recognition ability; Edinburgh handedness inventory [54,55] for determining objectively whether one is left or right handed; Childhood trauma questionnaire (CTQ)[56,57] for childhood trauma; Posttraumatic Diagnostic Scale (PDS)[58,59] for trauma; Visual Analogue Scale (VAS)[60] for Expectation to treatment; General functioning scale of Family Assessment Device（GF-FAD)[61,62] for family assessment ; Help-seeking preferences[63] for attitude to seek help for others; Multidimensional Assessment of Interoceptive Awareness (MAIA)[64,65] for relevant dimensions of bodily awareness; Barratt Impulsiveness Scale (BIS-11)[66,67] for impulsivity scale; Maudsley Obsessional Compulsive Inventory (MOCI)[68,69] for Obsessive-compulsive symptoms scale; Autism-Spectrum Quotient (AQ)[70,71] for Autism tendencies; Rosenberg Self-Esteem Scale (SES)[72,73] for global self-esteem; Tri-axial Coping Scale (TAC24)[74] for evaluation of stress coping strategies; Working Alliance Inventory (WAI)[75] for aspects of the therapeutic alliance; EuroQol-5 Dimension (EQ-5D)[76,77] for Quality of Life; The Generalized Anxiety Disorder Assessment (GAD-7)[78,79] for severity of generalized anxiety disorder; Patient Health Questionnaire (PHQ-9)[80,81] for depression module; The World Health Organization- Five Well-Being Index (WHO-5)[82] for Mental health scale; Socioeconomic status (SES) for Education history; Stanford Sleepiness Scale (SSS)[83] for subjective sleepiness levels
5. Brain image data, gene polymorphism / gene expression analysis data

Demographic data

Age, final educational background, marital status, cohabitation/family/partner presence, hospital history, age of onset, medical history, comorbidities, family history, medication content

Imaging acquisition

MRI scans will be obtained in all participants on 3 Tesla scanners: Siemens MAGNETOM Prisma (University of Tokyo), Skyrafit (NCNP), Verio (Kyoto University); GE Discovery MR750 3.0T (Chiba University), Premier (University of Occupational and Environmental Health); Phillips Ingenia 3.0T CX (Tohoku University and Kyushu University). The brain MRI examination takes T1-weighted images, T2-weighted images, resting-state fMRI, and diffusion tensor-weighted images. The imaging protocol is according to Harmonized Protocol (HARP)[84] for Clinical MRI studies in Brain/MINDS-beyond when multi-band echo-planer-imaging option is enabled in each site. If not, imaging protocol will be adopted based on Strategic Research Program for Brain Science (SRPB) protocol. Resting-state fMRI will be acquired with open-eye condition. MRI model, coil, and imaging parameters were shown in Table 3 and 4.

Table 3. 3T MRI specification and imaging protocols

Institution	THK	CHB	TKY	NCNP	KYU	UOEH	KYS
MRI Site	IDAC	CHB2	UTI2	NCNP2	KRC2	OEH	KYS
MRI scanner	Philips Ingenia 3.0T CX	GE Discovery MR750 3.0T	Siemens MAGNETOM Prisma	Siemens MAGNETOM Skyrafit	Siemens MAGNETOM Verio	GE SIGNA Premier	Philips Ingenia 3.0T CX
Number of channels per coil	20	32	32	32	32	48	20
Imaging protocol	SRPB, HARP	HARP	HARP	HARP	HARP	SRPB	SRPB

Abbreviations: THK, Tohoku University, IDAC, Institute of Development, Aging and Cancer; CHB, Chiba University; UTI, The University of Tokyo IRCN; NCNP, National Center of Neurology and Psychiatry; KYU, University of Kyoto; KRC, Kokoro Research Center; UOEH/OEH, University of Occupational and Environmental Health; KYS, Kyushu University, HARP; HARmonized protocol, SRPB: Strategic Research Program for Brain Science

Table 4. Scanning parameters for HARP and SRPB

HARP (Siemens Skyrafit*)	Imaging direction	Phase encoding direction	Matrix	Slices	FOV (mm)	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip angle (deg)	Parallel Imaging	Multiband Acceleration	Phase partial Fourier	No. of Measurements	b-values	Diffusion directions	Scan time
T1WI	Sagittal	AP	320×300	224	256×240	0.8×0.8×0.8	2500	2.18	1000	8	2×	Off	6/8	N/A	N/A	N/A	05:22
T2WI	Sagittal	AP	320×300	224	256×240	0.8×0.8×0.8	3200	564	N/A	Variable	2×	Off	Allowed	N/A	N/A	N/A	05:31
fMRI	Axial	AP, PA	86×86	60	206×206	2.4×2.4×2.4	800	34.4	N/A	52	Off	6	Off	375	N/A	N/A	05:08
DTI	Axial	AP, PA	120×120	84	204×204	1.7×1.7×1.7	3600	89	N/A	90	2×	3	6/8	N/A	0, 700, 2000	7, 20, 40 (AP) 8, 20, 40 (PA)	4:42 (AP), 4:46 (PA)
SRPB (Philips)	Imaging direction	Phase encoding direction	Matrix	Slices	FOV (mm)	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip angle (deg)	Parallel Imaging	Multiband Acceleration	Phase partial Fourier	No. of Measurements	b-values	Diffusion directions	Scan time
T1WI	Sagittal	AP	256×240	170	256×240	1.0×1.0×1.2	6.8	3.1	845.9	9	Off	N/A	15/16	N/A	N/A	N/A	10:56
fMRI#	Axial	AP	64×64	40	212×212	3.3×3.3×4.0	2500	30	N/A	80	Off	Off	Off	240	N/A	N/A	10:10
DTI	Axial	AP	112×112	75	224×224	2.0×2.0×2.0	13000	81	N/A	90	2×	Off	0.709	N/A	0, 1000	2, 32	8:41

*HARP for GE and Philips is under development.

Participants will be instructed to keep their eyes open and look at a fixation cross during resting-state fMRI.

GRAPPA for Siemens and SENSE for GE and Philips were employed as parallel imaging method.

#Scan orders were ascending for Philips and interleaved ascending for Siemens and GE.

Number of acquisitions was one for all the protocols.

Diffusion directions for Siemens Prisma will be set to 5, 16, 32 (AP) and 6, 16, 32 (PA).

Biological measures from blood samples

For blood tests, approximately 20 mL of blood will be collected at a time, for a total of approximately 60 mL during the study period. For shock symptoms due to vasovagal reactions, physical condition will be checked on the day of blood collection, and patients will be closely observed for 5 minutes after the start of blood collection when this reaction is likely to occur. Blood samples will include blood plasma, serum, blood sampling for DNA methylome, and blood sampling for RNA transcriptomics.

Data logistics

The brain imaging data collected at all facilities will be anonymized at each facility and then aggregated in the NCNP through Integrative Brain Imaging Support System (IBISS). The primary analysis will be performed in the NCNP. The results of the primary analysis will be shared by all facilities. Blood samples collected at all facilities will be anonymized; and all samples for gene polymorphism / gene expression analysis will be sent to NCNP where the samples will be extracted and stored in a -80 ° C freezer. As soon as approximately 20 cases are collected, the gene expression analysis will be outsourced to a contractor. In addition, psychological and clinical data will be anonymized at each institution and then shared by all institutes (see the Figure 1). The correspondence table for all data will be managed at the facility where the data was collected.

Statistical analysis

Brain imaging data collected at all facilities are subjected to a primary analysis by the analysis pipeline from NCNP. From the brain images of each individual, the data representing brain gray matter mass, white matter integrity, and resting functional connection of the region of interest will be extracted. In addition, we will evaluate functional connectivity in various intracerebral networks and between networks such as the default mode network, salience network, dorsal attention network, cognitive control network, and affective network in resting brain activity. At the secondary analysis stage, strategies (harmonization) for adjusting inter-facility factors will be considered. At present, we are planning to use corrections based on average values between facilities, or software such as Combat; however, as new harmonization strategies are developed, they will be tested as appropriate. At the time when about 20 longitudinal data are collected, the data will be fixed after being integrated with psychological/clinical data other than brain images, gene polymorphism/gene expression analysis results, and the following analysis will begin: (1) Identification of diagnostic markers (baseline data 20 people): compare clinical symptoms and brain images, psychology, gene polymorphism, and gene expression data at baseline in AN

and BN disease types, and search for cognitive, psychological, and behavioral indicators associated with disease type diagnosis. At this time, a comparison with the healthy group will also be performed. By comparing these groups, diagnostic markers based on conventional diagnoses will be identified (categorical approach). Furthermore, we will identify diagnostic markers on searching for psychopathological features in brain images, gene polymorphisms and gene expression data related to core disease state indicators and other psychological indicators across all disease types (dimensional approach); (2) Identification of therapeutic effect (longitudinal data set 40 people): we will analyze the relationship between changes in ED symptoms before and after CBT, and changes (rates) in brain images, psychology, gene polymorphisms, and gene expression data, and identify the therapeutic effects of CBT; (3) Identification of therapeutic response markers (longitudinal data set 60): analyzing associations with baseline brain images, psychology, gene polymorphisms, and gene expression data to predict the completion and remission of EDs before and after CBT, and identify treatment predictive markers; (4) In addition to the above, analysis that is judged necessary or meaningful at the time of analysis will be performed. In particular, we plan to conduct analysis using machine learning techniques. If there are missing values in the dataset to be analyzed, they will, in principle, be excluded from the analysis.

Sample size

The number of cases needed to detect an improvement in ED symptoms, which is the main outcome, was calculated. If calculated based on interpersonal therapy (n=65, Mean=2.37, SD=1.25) vs CBT (n=65, Mean=1.57, SD=1.25) [18], a single group of 27 cases is required based on a comparison of average outcomes of two independent samples at the time of post intervention (t-test); two tails, α=0.05,1-β=0.80. Hence, a total of 54 patients is required (27 cases for AN; 27 cases for BN). We plan to complete 72 cases among the joint research facilities. For five years, considering the dropout rate of CBT for ED treatment (about 40%) and the consent rate for MRI (about 60%), and differences in CBT for each facility, we plan to recruit 200 patients with EDs who are introduced CBT at all facilities, and we expect 120 cases to obtain consent for MRI examination and 72 cases to complete CBT. Regarding the disease type, the number of patients with AN and BN is expected to be about 1:1 in the end. Tohoku University and Kyoto University have mainly implemented CBT for patients with BN; conversely, Tokyo University, University of Occupational and Environmental Health, Kyushu University have mainly implemented CBT for patients with AN, whereas NCNP and Chiba University have implemented CBT for patients with AN and BN almost equally. Furthermore, we will collect 70 cases of healthy control group data. In particular, in order to verify the effects of low body weight, it collects the data for 30 healthy women

with a BMI between 16 and 17.5 (BMI values satisfy one of the diagnoses of AN) and no ED pathology.

Trial status

The first participant was included in this study on June 16, 2020. The end of the recruitment phase is currently scheduled for July 31, 2024.

ETHICS AND DISSEMINATION

Data distribution

At the end of the project period, the data will be publicly distributed to researchers through public databases. All imaging, demographic, and clinical data are shared between the participating sites and will be made publicly available in 2024. To the best of our knowledge, this is one of the first multi-site human brain MRI projects investigating multiple mental and neurological disorders throughout life. The Brain/MINDS Beyond human brain MRI project will help identify common and disease-specific pathophysiological features of brain disease and develop imaging biomarkers for clinical practice.

Ethical regulation

We follow the ethical regulation of the previous study.[88] Sharing neuropsychiatric patient data that can contain information linked to subjects' privacy requires special attention[85]. Hence, the Brain/MINDS Beyond project has made NCNP the core site for supporting ethical considerations. Before participating in the project, all institutions are required to have their research plans approved by their ethical review committee. This includes the following points and ethical documentation: (1) MR images and clinical data of the participants can be shared within the Brain/MINDS Beyond Project or Japanese/international scientific institutions. Anonymized MR images with limited clinical data may become publicly available on an open database for research purposes, (2) MR images of the participants may be compared with nonhuman primate MRI data, and (3) the intellectual property rights derived from the research of the Brain/MINDS Beyond project shall be attributed to the researcher's institute, not the participants. All participants, after receiving the full description of the experiment, are required to provide written informed consent to participate in this project. The Japanese regulations for the sharing of personal information used for research purposes require attention when handling two types of data: "individual identification codes" and "special care-required personal information" (http://www.japaneselawtranslation.go.jp/law/detail/?id=2781&vm=04&re=01). The Individual identification code is a direct identifier and is sufficient to identify a

particular individual. Special care-required personal information represents indirect identifiers that need special care in handling in order to avoid potential disadvantages to the participants. In consideration of these regulations, data accompanied with the MR images are limited in the publicly accessible open database and include only 5-year age bins, sex, diagnostic information, handedness, simple socioeconomic status, clinical scale scores, and sleepiness scale scores. In the Brain/MINDS Beyond project, we exclude the datasets of MR images containing facial information from the data in the publicly accessible open database.

Discussion

The strengths of this research are listed below. Firstly, to construct a brain image database of EDs using the longitudinal brain imaging scans of ED patients from multiple facilities. To date, brain imaging research for ED has been limited to small-scale cross-sectional studies.[34-37] For this reason, it is important to establish a brain imaging database of EDs using brain images from ED patients across multiple facilities and longitudinally to identify clinically useful diagnostic and therapeutic markers and prognostic predictors. Secondly, data collected before and after CBT treatment will be collected longitudinally, and treatment responsiveness can be input as a variable. In addition, it is possible to explore the effects of treatment responsiveness by treating childhood trauma as a treatment resistance factor and covariate. Thirdly, the machine learning method can be used to develop into analytical research that leads to an integrated understanding of the pathology of EDs and even neuropsychiatric disorders. Thus far, studies that apply machine learning techniques to brain imaging data from ED patients have begun to gradually appear, but remain limited to cross-sectional studies using samples of 15 to 24 patients in a single group.[86,87] To date, there remains no longitudinal data from before and after treatment and the association with other clinical markers. Lastly, we apply an omics analysis as a clinical marker of ED. Thus far, previous studies have been reported in Japan addressing the susceptibility gene for feeding regulators: the relationship between Ghrelin polymorphism and BN;[88] the association with young female dissatisfaction of the body, physique and high-density lipoprotein cholesterol;[89] and the association with AN and FAAH polymorphism.[90] A genome-wide correlation analysis (GWAS) using the world's first microsatellite marker for AN was performed, and single nucleotide polymorphisms (SNPs) showing AN sensitivity were identified in at least three gene regions (exon 9 of the CNTN5 gene, the 3'-downstream region of the SPATA17 gene, and TOX3 gene).[91] Furthermore, in a GWAS using SNP markers, a previous study has suggested that having the minor 385A allele of the FAAH gene may be protective against restricting AN. Utilizing the knowledge of ED genetic research, it is possible to narrow down the genes targeted in

an omics analysis for ED carried out in this research project. Omics research for EDs is only a report of a cross-sectional study of few groups for AN,[92] and no longitudinal study before and after treatment including CBT has been conducted. ED omics research is now beginning to gain traction. Based on the above, it is designed to handle multivariates that includes omics analysis results in brain imaging data. We reduce the dimensions using deep learning techniques and perform a multiple regression analysis using machine learning algorithms. This is expected to generate evidence for clinical markers of EDs (diagnostic markers, therapeutic effects, therapeutic response prediction markers).

This study has some limitations. First, the number of people at one site is not very large because the brain imaging machines differ across facilities. Although harmonization is made, measurement variability may increase due to the multiple sites. Second, the number of brain function image samplings at a resting state is very different depending on the facility. Finally, there is a possibility that the image captured by the innovative brain is low in reliability and resolution.

FIGURE LEGENDS

Figure 1 Data logistics

DECLARATIONS

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Author contributions

SH and YH participated in the design, drafted and modified the manuscript.
YH, MI, NK, KY, YM, TA, KY, and YS are the co-investigators of the study who obtained funding and significantly contributed to the conception or design. ASu, YE, JT, NN, TT, HH, TN, KT, KW, HA, MG, ST, SF, and ES participated in the design and substantially contributed to the different stages of the study's development towards its practical conduction. ASe is the principal investigator of the study who obtained funding, modified the manuscript, and provided substantial contributions to the study conception and design. All authors read and approved the final manuscript.

Availability of data and materials

Please contact Atsushi Sekiguchi for future proposals and requests to use the data that will be obtained from this project.

Competing interests

None declared.

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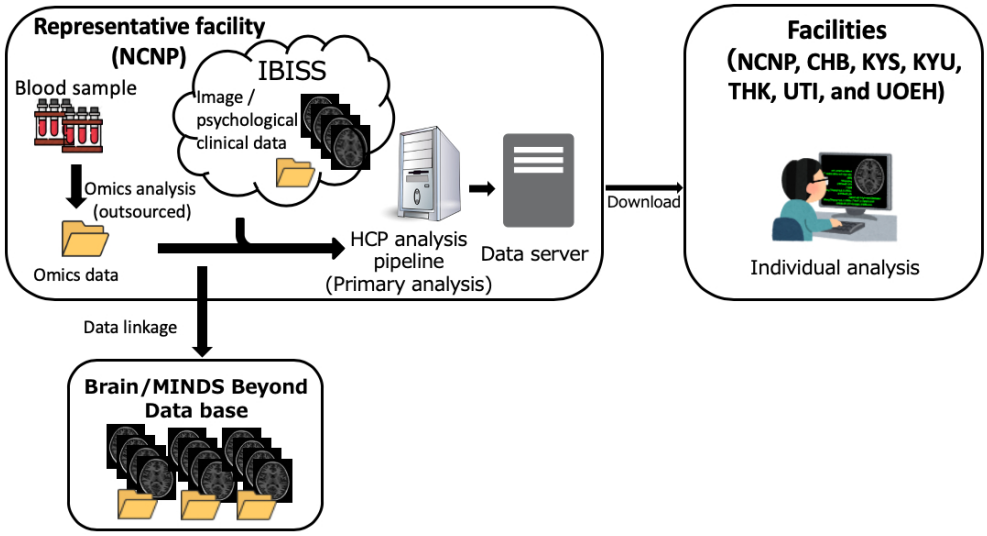

Figure1

385x212mm (72 x 72 DPI)

BMJ Open

Eating Disorder Neuroimaging Initiative (EDNI): a multicenter prospective cohort study protocol for elucidating the neural effects of cognitive behavioral therapy for eating disorders

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Eating Disorder Neuroimaging Initiative (EDNI): a multicenter prospective cohort study protocol for elucidating the neural effects of cognitive behavioral therapy for eating disorders

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ABSTRACT

Introduction: Anorexia nervosa is a refractory psychiatric disorder with a mortality rate of 5.9% and standardized mortality ratio of 5.35, which is much higher than other psychiatric disorders. The standardized mortality ratio (SMR) of bulimia nervosa is 1.49; however, it is characterised by suicidality resulting in a shorter time to death. While there is no current validated drug treatment for eating disorders in Japan, cognitive behavioural therapy (CBT) is a well-established and commonly used treatment. CBT is also recommended in the Japanese Guidelines for the Treatment of Eating Disorders (2012) and has been covered by insurance since 2018. However, the neural mechanisms responsible for the effect of CBT have not been elucidated, and the use of biomarkers such as neuroimaging data would be beneficial.

Methods and analysis: The Eating Disorder Neuroimaging Initiative (EDNI) is a multisite prospective cohort study. We will longitudinally collect data from 72 patients with eating disorders (anorexia nervosa and bulimia nervosa) and 70 controls. Data will be collected at baseline, after 21-41 sessions of CBT, and 12 months later. We will assess longitudinal changes in neural circuit function, clinical data, gene expression, and psychological measures by therapeutic intervention, and analyse the relationship among them using machine learning methods.

Ethics and dissemination: The study was approved by The Ethical Committee of the National Center of Neurology and Psychiatry (A2019-072). We will obtain written informed consent from all patients who participate in the study after they had been fully informed about the study protocol. All imaging, demographic, and clinical data are shared between the participating sites and will be made publicly available in 2024.

Trial registration: UMIN000039841. Registered 18th March 2020, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000045438

Strengths and limitations of this study

►The research project will seek to clarify diagnostic and therapeutic markers and identify predictive markers of treatment response in patients with eating disorders using a longitudinal approach.

► This should contribute to the early detection and early intervention of eating disorders.
► We will also create a brain imaging database in Japan for those with eating disorders.
► MRI equipment and treatment protocols are not completely unified.

INTRODUCTION

Eating disorders (EDs) are a psychiatric disorder with a focus on body shape, weight, and abnormal eating behaviours. They are mainly classified as anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED).[1] In Japan, the number of patients with EDs has increased about 10-fold between the 1980s and 1990s.[2] Based on a meta-analysis including 36 studies, AN was found to have a standardized mortality ratio (SMR) of 5.1,[3] and the highest mortality rate among mental disorders.[4-7] In addition, renal function decreases as the duration of AN increases,[8] and patients often suffer from various physical complications associated with prolonged symptoms and low weight.[9-12] The rate of chronicity for patients with AN for up to 10 years is approximately 10-20%, and the long-term prognosis is poor.[13,14] Furthermore, current treatments may not be effective in severe cases of chronic AN.[15] Regarding BN, the SMR is 1.49; however, it is characterised by suicidality resulting in a shorter time to death.[3] Therefore, early detection and early intervention are important.

Cognitive behavioural therapy (CBT) is a psychotherapy that aims to improve psychiatric symptoms by focusing on cognitive processes and behavioural patterns. CBT for eating disorders identifies the psychopathology that contributes to the disease while advancing regular eating and weight-regulating behavioural modifications.[16] Cognitive styles such as fear of weight gain and adherence to body shape and behavioural patterns such as dietary restrictions and excessive exercise are often seen in eating disorders[17]; CBT can be used to address these psychopathologies.[16] CBT has been shown to be effective as a psychotherapy for EDs,[18-20] and CBT is also recommended in the NICE guidelines.[21] Meta-analyses of RCTs that include waitlist controls report that CBT is particularly effective for BN and BED.[22-26] In Japan, there are two reports on the effectiveness and feasibility of CBT for BN or BED,[27,28] and the national health insurance has covered CBT in Japan since 2018. However, according to a meta-analysis of RCTs, the dropout rate for CBT is approximately 24%,[29] and there are large individual differences in treatment responsiveness.

To the best of our knowledge, there are no reports of neural mechanisms that regulate the effects and treatment responses of CBT for EDs. Therefore, accumulating evidence using brain imaging and biomarkers of gene expression would further our

understanding of CBT effectiveness for EDs. The identification of biomarkers may provide clues to the development of diagnostic and therapeutic methods based on the elucidation of the pathophysiology and pathogenic mechanism of EDs. It may contribute to social implementation of early detection and early intervention with diagnostic methods using objective indicators

Since individuals with EDs show abnormal eating behaviours, structural and functional brain imaging studies have been conducted to elucidate the neural basis of these abnormalities through brain imaging research. There are various reports on brain imaging research in ED patients that have revealed abnormal reward systems,[30] reductions in grey matter of various brain regions (frontal lobes,[31] frontal gyrus,[32] parietal and temporal lobes,[33] occipital lobe[34]), and limited reductions in white matter volume.[35] In Japan, the neural basis for the pathogenesis of EDs has been studied.[36-39] However, brain imaging research for EDs has only been conducted in the form of small cross-sectional studies in a single facility, and the reproducibility and validity of these results remain questionable. Therefore, research at a larger scale is needed to elucidate the cognitive brain science of ED pathology and progression, and to identify clinically useful diagnostic and therapeutic markers and prognostic predictors.

The ENIGMA-Eating Disorders should be noted as a multicentre study outside of Japan. However, it is only registered by researchers in Europe, the United States, and Africa, and mainly takes place in Germany. For the time being, they have used methods to meta-analyse anatomical images and diffusion tensor-weighted images of AN and BN patients that have already been imaged at participating facilities. The ENIGMA-Eating Disorders study is expected to build a framework for joint research to be developed in the future. However, ED brain image multicentre research has not been found to have been conducted, even when searching the world's major clinical research registration sites such as ClinicalTrials.gov in the United States and EU register in the EU. Furthermore, an ED brain image database has not yet been developed globally.

Aims and hypotheses

We aim to generate neuroscientific evidence for the effect of CBT. First, we will longitudinally collect brain magnetic resonance imaging (MRI) images and clinical data in observational studies before and after CBT for EDs. Next, we will identify clinical biomarkers of EDs through analytical studies using longitudinal image data before and after CBT for EDs and create neural evidence for the effect of CBT. We aim to identify brain image biomarkers that can be used as clinical markers (diagnostic markers, therapeutic markers, and therapeutic response prediction markers) for EDs. We

hypothesise the following: 1) characteristic brain circuit abnormalities exist for each type of ED; 2) there are brain circuit changes that correlate with changes in severity before and after treatment for ED; and 3) there are brain circuit features that define the therapeutic response of CBT for ED. Furthermore, the brain image data collected for this project will be integrated into an international brain database prepared by the Japan Agency for Medical Research and Development (AMED). In the future, after the AMED Brain / MINDS Beyond human brain MRI database is constructed, it will be possible to access the database. At the moment, the portal site (https://brainminds-beyond.jp/ja/resources/2020/05/amedmri.html) is being created. (Details of The Brain / MINDS Beyond human brain MRI project: koike et al., 2020 preprint).

METHODS AND ANALYSIS

Study design

This is a multisite, observational cohort study. For ED patients who have received structured CBT, the following will be performed before and after CBT: brain MRI imaging (T1WI, T2WI, resting state functional MRI, DWI); blood collection for gene polymorphism and gene expression analysis; and psychological evaluation. Table 1 shows the study design. In the pre-treatment evaluation, subjects will visit each treatment facility for treatment, and a doctor or psychologist (recruiter) will evaluate eligibility and exclusion criteria for CBT introduction. Among the subjects who meet the CBT eligibility criteria, the eligibility criteria and exclusion criteria of this study will be evaluated. Subjects who have obtained informed consent for this study will be registered as study subjects. After registration, the schedule for the first session of CBT will be determined. In principle, brain MRI scans and other tests will be carried out within 4 weeks before the session date. The post-treatment evaluation is based on the day when CBT for EDs is completed, and in principle, tests such as brain MRI are performed within 4 weeks. In addition, a similar assessment 1 year after treatment (50+/-8 weeks) will be performed for subjects who are willing.

Table 1. Standard protocol items

Items	Pre	Intervention	Post	Follow Up
Time point	-4W-0	1～21 sessions* or 41 sessions**	Within 4 weeks	50 +/-8 W
Informed consent	×	-	-	-
Demographic data	×	-	-	-
Cognitive and psychological indicators				
EDE 17.0D	×		×	×
EDE-Q	×		×	×

	M.I.N.I.	×		×	×
	JART	×			
	BDI-II	×		×	×
	STAI	×		×	×
	NEO - FFI	×		×	×
	TAS-20	×		×	×
	Adult version facial expression recognition test	×		×	×
	Edinburgh handedness inventory	×			
	CTQ	×			
	PDS	×		×	×
	VAS	×		×	×
	GF-FAD	×		×	×
	MAIA	×		×	×
	BIS-11	×		×	×
	MOCI	×		×	×
	AQ	×			
	SES	×		×	×
	TAC24	×		×	×
	WAI	×		×	×
	EQ-5D	×		×	×
	GAD-7	×		×	×
	PHQ-9	×		×	×
	WHO-5	×		×	×
	SES	×			
	SSS	×		×	×
Brain MRI examination		×	-	×	×
Blood sample (non-fasting period)		×	-	×	×

*Outpatient /**inpatient

Abbreviations: EDE 17.0D: Eating Disorder Examination Edition 17.0D; EDE-Q: Eating Disorders Examination Questionnaire; M.I.N.I. :Mini-International Neuropsychiatric Interview JART: Japanese Adult Reading Test; BDI-II: Beck Depression Inventory-Second Edition; STAI: State-Trait Anxiety Inventory; NEO-FFI: NEO Five-Factor Inventory; TAS-20: 20-Item Toronto Alexithymia Scale; CTQ: Childhood Trauma Questionnaire for childhood trauma; PDS: Posttraumatic Diagnostic Scale for trauma; Vas: Visual Analogue Scale; GF-FAD: General Functioning scale of Family Assessment Device; MAIA: Multidimensional Assessment of Interoceptive Awareness; BIS-

11:Barratt Impulsiveness Scale; MOCI: Maudsley Obsessional Compulsive Inventory; AQ: Autism-Spectrum Quotient ; SES: Rosenberg Self-Esteem Scale; TAC24: Tri-axial Coping Scale ; WAI: Working Alliance Inventory; EQ-5D: EuroQol-5 Dimension; GAD-7: Generalized Anxiety Disorder assessment ; PHQ-9:Patient Health Questionnaire; WHO-5: World Health Organization - Five Well-Being Index; SES: Socioeconomic status; SSS: Stanford Sleepiness Scale.

Study setting

This trial will be conducted by seven facilities (National Center of Neurology and Psychiatry (NCNP), Chiba University, Tohoku University, Tokyo University, Kyoto University, Kyushu University, and University of Occupational and Environmental Health) in Japan.

Recruitment

Those who wish to participate in the study will visit the NCNP, Chiba University, Tohoku University, Tokyo University, Kyoto University, Kyushu University, and University of Occupational or Environmental Health. The study participants will be recruited through posters and leaflets placed, through the official Web-based advertisements, and by referrals from their primary care doctors or psychiatrists to receive CBT treatment. The doctor or psychologist (recruiter) evaluates the eligibility criteria and exclusion criteria for CBT introduction. Among the subjects who meet the CBT eligibility criteria, the eligibility criteria and exclusion criteria of this study will be evaluated. Subjects who have obtained informed consent for this study will be registered as subjects for this study.

Study participants

Patients will be enrolled in the study if they meet the following selection criteria without meeting the exclusion criteria (see Table 2).

Table 2. Inclusion and exclusion criteria

Eating disorder	
Inclusion criteria	1) Meets the DSM-5 diagnostic criteria for an ED (AN and BN) 2) ≧ 18 years of age at the time of informed consent 3) Body Mass Index (BMI) >15 kg/m^2 (or Standard weight-35%) <40.0 kg/m^2 (Cases with lower weight are allowed when performed in inpatient)

	4) Those who live in Japan and have the ability to read and write Japanese equivalent to the level of native speakers of Japanese 5) A person who understands the purpose and content of this research and has obtained written informed consent to participate in the research
Exclusion criteria	1) If you are physically severe (impaired consciousness, advanced liver dysfunction, advanced electrolyte abnormalities, etc.) and require advanced physical treatment 2) Mental illness (schizophrenia, bipolar disorder, alcohol abuse/dependence, autism) preceding the history of EDs 3) Persons with intellectual disabilities 4) Imminent risk of suicide 5) Risk of MRI examination (body surface/internal body metal, pregnancy or possibility of pregnancy, claustrophobia, dark phobia, etc.) 6) Those who are expected to have difficulty in coming to the hospital according to the research schedule and receiving evaluation 7) Otherwise, persons who are deemed inappropriate by the principal investigator
Healthy control	
Inclusion criteria	1) Those do not meet the diagnostic criteria for EDs (AN and BN) in the DSM-5 2) ≧ 18 years of age at the time of informed consent 3) Body Mass Index (BMI) at screening is greater than 16 kg/m^2 (or standard weight -35%) and < 40.0 kg/m^2(those who do not meet the diagnosis of EDs and mental illness also tolerate lower weight) 4) Those who live in Japan and have the ability to read and write Japanese equivalent to the level of native speakers of Japanese 5) A person who understands the purpose and content of this research and has obtained written informed consent to participate in the research
Exclusion criteria	1) History of EDs

2) Persons with mental illness (schizophrenia, bipolar disorder, alcohol abuse/dependence, autism)
3) Persons with intellectual disabilities
4) Imminent risk of suicide
5) Risk of MRI examination (body surface/internal body metal, pregnancy or possibility of pregnancy, claustrophobia, dark phobia, etc.)
6) Those who are expected to have difficulty in coming to the hospital according to the research schedule and receiving evaluation
7) Otherwise, persons who are deemed inappropriate by the principal investigator

Patient and Public Involvement

Patients and public were not involved in the design of this study.

Interventions

In principle, CBT "improved version" [20] for EDs, 20-40 session version will be implemented (UMIN000031625). However, structured CBT performed at each treatment facility is acceptable (UMIN000039485; UMIN000036825 etc). Therapists are specialists (psychiatrists, certified public psychologists) who have attended workshops and have been trained in conducting CBT. In addition, each CBT is manualized and structured. Treatment compliance / fidelity is basically maintained by each therapist receiving supervision and following manuals.

Primary outcome

The primary outcome was ED symptoms and severity assessed by the Eating Disorder Examination Edition 17.0D (EDE 17D)[40,41] or Eating Disorders Examination Questionnaire (EDE-Q).[42,41] The EDE17D is a semi-structured interview, whereas the EDE-Q is a self-contained, 28-item questionnaire derived from the EDE. The EDE-Q is scored on a 7-point Likert scale (0–6) on which a score of ≥4 indicates a clinical range. The global score on the EDE-Q is the sum of the four subscale scores (for restraint, eating concern, shape concern, and weight concern) divided by 4.

Secondary outcomes

1. Remission at the end of treatment (state that does not meet DSM-5 criteria).
2. Treatment completion rate (completed when 75% or more of 21 to 41 treatment sessions are received).

3. ED specific indicators: current BMI; the lowest and highest BMI in the past; history of AN and BN.
4. Non-specific psychological indicators (see details as a supplemental file): the Mini-International Neuropsychiatric Interview (M.I.N.I.)[43,44] for comorbidities; Japanese Adult Reading Test (JART)[45,46] for intellectual ability; Beck Depression Inventory-Second Edition (BDI-II)[47,48] for severity of depressive symptoms; State-Trait Anxiety Inventory (STAI)[49,50] for anxiety; NEO Five-Factor Inventory (NEO-FFI) [51,52] for personality scores; 20-Item Toronto Alexithymia Scale (TAS-20)[53,54] for alexithymia; adult version facial expression recognition test[55] for adult facial expression recognition ability; Edinburgh handedness inventory[56,57] for determining objectively whether one is left or right handed; Childhood Trauma Questionnaire (CTQ)[58,59] for childhood trauma; Posttraumatic Diagnostic Scale (PDS)[60,61] for trauma; Visual Analogue Scale (VAS)[62] for expectation to treatment; General Functioning scale of Family Assessment Device（GF-FAD)[63,64] for family assessment; help-seeking preferences[65] for attitude to seek help for others; Multidimensional Assessment of Interoceptive Awareness (MAIA)[66,67] for relevant dimensions of bodily awareness; Barratt Impulsiveness Scale (BIS-11)[68,69] for impulsivity scale; Maudsley Obsessional Compulsive Inventory (MOCI)[70,71] for obsessive-compulsive symptoms scale; Autism-Spectrum Quotient (AQ)[72,73] for autism tendencies; Rosenberg Self-Esteem Scale (SES)[74,75] for global self-esteem; Tri-axial Coping Scale (TAC24)[76] for evaluation of stress coping strategies; Working Alliance Inventory (WAI)[77] for aspects of the therapeutic alliance; EuroQol-5 Dimension (EQ-5D)[78,79] for quality of Life; the Generalized Anxiety Disorder assessment (GAD-7)[80,81] for severity of anxiety; Patient Health Questionnaire (PHQ-9)[82,83] for depression module; the World Health Organization - Five Well-Being Index (WHO-5)[84] for mental health scale; Socioeconomic status (SES) for education history; Stanford Sleepiness Scale (SSS)[85] for subjective sleepiness levels.
5. Brain image data, gene polymorphism / gene expression analysis data.

Demographic data

At the time of pre-CBT, we will collect the following demographic data: age, educational background, marital status, cohabitation/family/presence of partner, hospitalization history, age of onset, medical history, comorbidities, family history, and medication content.

Imaging acquisition

MRI scans will be obtained in all participants on 3 Tesla scanners: Siemens MAGNETOM Prisma (University of Tokyo), Skyrafit (NCNP), Verio (Kyoto University); GE Discovery MR750 3.0T (Chiba University), Premier (University of Occupational and

Environmental Health); Phillips Ingenia 3.0T CX (Tohoku University and Kyushu University). The brain MRI examination takes T1WI, T2WI, resting-state fMRI, and diffusion tensor-weighted images. The imaging protocol is according to Harmonized Protocol (HARP)[86] for Clinical MRI studies in Brain/MINDS-beyond when multi-band echo-planer-imaging option is enabled in each site. If not, the imaging protocol will be adopted based on the Strategic Research Program for Brain Science (SRPB) protocol. Resting-state fMRI will be acquired in ab open-eye condition. MRI model, coil, and imaging parameters are shown in Table 3 and 4.

Table 3. 3T MRI specification and imaging protocols

Institution	THK	CHB	TKY	NCNP	KYU	UOEH	KYS
MRI Site	IDAC	CHB2	UTI2	NCNP2	KRC2	OEH	KYS
MRI scanner	Philips Ingenia 3.0T CX	GE Discovery MR750 3.0T	Siemens MAGNETOM Prisma	Siemens MAGNETOM Skyrafit	Siemens MAGNETOM Verio	GE SIGNA Premier	Philips Ingenia 3.0T CX
Number of channels per coil	20	32	32	32	32	48	20
Imaging protocol	SRPB	SRPB	HARP	HARP	HARP	SRPB	SRPB

*Institutions that originally planned for SRPB may replace after HARP was developed.
Abbreviations: THK, Tohoku University, IDAC, Institute of Development, Aging and Cancer; CHB, Chiba University; UTI, The University of Tokyo IRCN; NCNP, National Center of Neurology and Psychiatry; KYU, University of Kyoto; KRC, Kokoro Research Center; UOEH/OEH, University of Occupational and Environmental Health; KYS, Kyushu University, HARP; HARmonized protocol, SRPB: Strategic Research Program for Brain Science

Table 4. Scanning parameters for HARP and SRPB

HARP (Siemens Skyrafit)	Imaging direction	Phase encoding direction	Matrix	Slices	FOV (mm)	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip angle (deg)	Parallel Imaging	Multiband Acceleration	Phase partial Fourier	No. of Measurements	b-values	Diffusion directions	Scan time
T1WI	Sagittal	AP	320×300	224	256×240	0.8×0.8×0.8	2500	2.18	1000	8	2×	Off	6/8	N/A	N/A	N/A	05:22
T2WI	Sagittal	AP	320×300	224	256×240	0.8×0.8×0.8	3200	564	N/A	Variable	2×	Off	Allowed	N/A	N/A	N/A	05:31
fMRI	Axial	AP, PA	86×86	60	206×206	2.4×2.4×2.4	800	34.4	N/A	52	Off	6	Off	375	N/A	N/A	05:08
DTI	Axial	AP, PA	120×120	84	204×204	1.7×1.7×1.7	3600	89	N/A	90	2×	3	6/8	N/A	0, 700, 2000	7, 20, 40 (AP) 8, 20, 40 (PA)	4:42 (AP), 4:46 (PA)
SRPB (Philips)	Imaging direction	Phase encoding direction	Matrix	Slices	FOV (mm)	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip angle (deg)	Parallel Imaging	Multiband Acceleration	Phase partial Fourier	No. of Measurements	b-values	Diffusion directions	Scan time
T1WI	Sagittal	AP	256×240	170	256×240	1.0×1.0×1.2	6.8	3.1	845.9	9	Off	N/A	15/16	N/A	N/A	N/A	10:56
fMRI[#]	Axial	AP	64×64	40	212×212	3.3×3.3×4.0	2500	30	N/A	80	Off	Off	Off	240	N/A	N/A	10:10
DTI	Axial	AP	112×112	75	224×224	2.0×2.0×2.0	13000	81	N/A	90	2×	Off	0.709	N/A	0, 1000	2, 32	8:41

Participants will be instructed to keep their eyes open and look at a fixation cross during resting-state fMRI.

GRAPPA for Siemens and SENSE for GE and Philips were employed as parallel imaging method.

#Scan orders were ascending for Philips and interleaved ascending for Siemens and GE.

Number of acquisitions was one for all the protocols.

Diffusion directions for Siemens Prisma will be set to 5, 16, 32 (AP) and 6, 16, 32 (PA).

Biological measures from blood samples

For blood tests, approximately 20 mL of blood will be collected at a time, with a total of approximately 60 mL during the study period. For shock symptoms due to vasovagal reactions, physical condition will be checked on the day of blood collection, and patients will be closely observed for 5 minutes after the start of blood collection when this reaction is likely to occur. Blood samples will include blood plasma, serum, blood sampling for DNA methylome, and blood sampling for RNA transcriptomics.

Data logistics

The brain imaging data collected at all facilities will be anonymized at each facility and then aggregated in the NCNP through the Integrative Brain Imaging Support System (IBISS). The primary analysis will be performed in the NCNP. The results of the primary analysis will be shared by all facilities. Blood samples collected at all facilities will be anonymized; and all samples for gene polymorphism / gene expression analysis will be sent to NCNP where the samples will be extracted and stored in a -80°C freezer. As soon as approximately 20 cases are collected, the gene expression analysis will be outsourced to a contractor. In addition, psychological and clinical data will be anonymized at each institution and then shared by all institutes (see the Figure 1). The correspondence table for all data will be managed at the facility where the data was collected.

Statistical analysis

Brain imaging data collected at all facilities are subjected to a primary analysis by the analysis pipeline from NCNP. From the brain images of each individual, the data representing brain grey matter mass, white matter integrity, and resting functional connection of the region of interest will be extracted. In addition, we will evaluate functional connectivity in various intracerebral networks and between networks such as the default mode network, salience network, dorsal attention network, cognitive control network, and affective network in resting brain activity. For example, we plan to perform seed-based analysis with CONN toolbox (www.nitrc.org/projects/conn)[87]. We plan to verify the presence or absence of network abnormalities using the orbitofrontal cortex and anterior cingulate cortex, which have been pointed out as seeds in ED, and whether these network abnormalities have changed after CBT.

At the secondary analysis stage, strategies (harmonization) for adjusting inter-facility factors will be considered. At present, we are planning to use corrections based on average values between facilities, or software such as Combat. The ComBat harmonization tool[88-90] uses Bayesian regression to find systematic differences among

multiple data collected using different scanners. The tool performs additive and multiplicative corrections to produce distortions that eliminate these systematic differences from the data; however, as new harmonization strategies are developed, they will be tested as appropriate. At the time when about 20 longitudinal data are collected, the data will be fixed after being integrated with psychological/clinical data other than brain images, gene polymorphism/gene expression analysis results, and the following analysis will begin: (1) Identification of diagnostic markers (baseline data 20 people): compare clinical symptoms and brain images, psychology, gene polymorphism, and gene expression data at baseline in AN and BN disease types, and search for cognitive, psychological, and behavioural indicators associated with disease type diagnosis. At this time, a comparison with the healthy group will also be performed. By comparing these groups, diagnostic markers based on conventional diagnoses will be identified (categorical approach). Furthermore, we will identify diagnostic markers on searching for psychopathological features in brain images, gene polymorphisms, and gene expression data related to core disease state indicators and other psychological indicators across all disease types (dimensional approach); (2) Identification of therapeutic effect (longitudinal data set 40 people): we will analyse the relationship between changes in ED symptoms before and after CBT, and changes (rates) in brain images, psychology, gene polymorphisms, and gene expression data, and identify the therapeutic effects of CBT; (3) Identification of therapeutic response markers (longitudinal data set 60): analysing associations with baseline brain images, psychology, gene polymorphisms, and gene expression data to predict the completion and remission of EDs before and after CBT, and identify treatment predictive markers; (4) In addition to the above, analysis that is judged necessary or meaningful at the time of analysis will be performed. In particular, we plan to conduct analysis using machine learning techniques. If there are missing values in the dataset to be analysed, they will, in principle, be excluded from the analysis.

Machine-learning approach

We are planning to use the python Scikitlearn library (version 0.22.1) to perform Support vector machine (SVM) classification[91]. To prevent overfitting (i.e., the classifier works perfectly on the training data, but is poorly generalizable to new data), we will perform a feature relevance evaluation and dimensionality reduction using a tree-based feature selection approach with a nested cross-validation design.[92-94]

The nested cross-validation consists of an inner loop for model building and parameter estimation, and an outer loop for model testing. Consequently, the dataset will be divided into two parts: a training plus validation subset and a test subset. In the inner loop, SVM models will have been trained with varying SVM hyper-parameters (i.e., cost

parameters C and kernel function) based on a grid search, and a feature selection will have been performed using classification trees or random forests. The validation set will be used to determine the SVM hyper-parameters over the grid of possible values. The performance of the resulting model, with optimized SVM hyper-parameters and features, will be subsequently evaluated on the test set in the outer loop. For this outer loop, we will use a leave-one-out cross-validation scheme so that each sample will be used once as a test set (singleton) while the remaining samples form the training/validation set. The training/validation set will be divided into five equally sized parts. Four of these will be used as the training set and one as the validation set. This process is repeated until all subjects are left out at least once and prediction results are aggregated as well as reported.

Sample size

The number of cases needed to detect an improvement in ED symptoms, which is the main outcome, was calculated. If calculated based on interpersonal therapy (n=65, mean=2.37, SD=1.25) vs CBT (n=65, mean=1.57, SD=1.25) [18], a single group of 27 cases is required based on a comparison of average outcomes of two independent samples at the time of post intervention (t-test); two tails, α=0.05,1-β=0.80. Hence, a total of 54 patients is required (27 cases for AN; 27 cases for BN). We plan to complete 72 cases among the joint research facilities. For 5 years, considering the dropout rate of CBT for ED treatment (about 40%) and the consent rate for MRI (about 60%), and differences in CBT for each facility, we plan to recruit 200 patients with EDs who are introduced to CBT at all facilities. We expect 120 cases to obtain consent for MRI examination and 72 cases to complete CBT. Regarding the disease type, the number of patients with AN and BN is expected to be about 1:1 in the end. Tohoku University and Kyoto University have mainly implemented CBT for patients with BN; conversely, Tokyo University, University of Occupational and Environmental Health, Kyushu University have mainly implemented CBT for patients with AN, whereas NCNP and Chiba University have implemented CBT for patients with AN and BN almost equally. Furthermore, we will collect 70 cases in the healthy control group. In particular, in order to verify the effects of low body weight, we will collect data for 30 healthy women with a BMI between 16 and 17.5 (BMI values satisfy one of the diagnoses of AN) and no ED pathology.

Trial status

The first participant was included in this study on June 16, 2020. The end of the recruitment phase is currently scheduled for July 31, 2024.

ETHICS AND DISSEMINATION

Data distribution

At the end of the project period, the data will be publicly distributed to researchers through public databases. All imaging, demographic, and clinical data are shared between the participating sites and will be made publicly available in 2024. To the best of our knowledge, this is one of the first multi-site human brain MRI projects investigating multiple mental and neurological disorders throughout life. The Brain/MINDS Beyond human brain MRI project will help identify common and disease-specific pathophysiological features of brain disease and develop imaging biomarkers for clinical practice.

Ethical regulation

We follow the ethical regulation of the previous study.[86] Sharing neuropsychiatric patient data that can contain information linked to subjects' privacy requires special attention.[95] Hence, the Brain/MINDS Beyond project has made NCNP the core site for supporting ethical considerations. Before participating in the project, all institutions are required to have their research plans approved by their ethical review committee. This includes the following points and ethical documentation: (1) MR images and clinical data of the participants can be shared within the Brain/MINDS Beyond Project or Japanese/international scientific institutions. Anonymized MR images with limited clinical data may become publicly available on an open database for research purposes, (2) MR images of the participants may be compared with nonhuman primate MRI data, and (3) the intellectual property rights derived from the research of the Brain/MINDS Beyond project shall be attributed to the researcher's institute, not the participants. All participants, after receiving the full description of the experiment, are required to provide written informed consent to participate in this project. The Japanese regulations for the sharing of personal information used for research purposes require attention when handling two types of data: "individual identification codes" and "special care-required personal information" (http://www.japaneselawtranslation.go.jp/law/detail/?id=2781&vm=04&re=01). The individual identification code is a direct identifier and is sufficient to identify a particular individual. Special care-required personal information represents indirect identifiers that need special care in handling in order to avoid potential disadvantages to the participants. In consideration of these regulations, data accompanied with the MR images are limited in the publicly accessible open database and include only 5-year age bins, sex, diagnostic information, handedness, simple socioeconomic status, clinical scale scores, and sleepiness scale scores. In the Brain/MINDS Beyond project, we

exclude the datasets of MR images containing facial information from the data in the publicly accessible open database.

Discussion

The strengths of this research are listed below. Firstly, we aimed to construct a brain image database of EDs using the longitudinal brain imaging scans of ED patients from multiple facilities. To date, brain imaging research for ED has been limited to small-scale cross-sectional studies.[36-39] For this reason, it is important to establish a brain imaging database of EDs using brain images from ED patients across multiple facilities and longitudinally to identify clinically useful diagnostic and therapeutic markers and prognostic predictors. Secondly, data collected before and after CBT treatment will be collected longitudinally, and treatment responsiveness can be input as a variable. In addition, it is possible to explore the effects of treatment responsiveness by treating childhood trauma as a treatment resistance factor and covariate. Thirdly, the machine learning method can be used to develop into analytical research that leads to an integrated understanding of the pathology of EDs and even neuropsychiatric disorders. Thus far, studies that apply machine learning techniques to brain imaging data from ED patients have begun to gradually appear but remain limited to cross-sectional studies using samples of 15 to 24 patients in a single group.[96,97] To date, there remains no longitudinal data from before and after treatment and the association with other clinical markers. Lastly, we will apply an omics analysis to identify clinical markers of ED. Thus far, previous studies have been reported in Japan addressing the susceptibility gene for feeding regulators: the relationship between Ghrelin polymorphism and BN;[98] the association with young female dissatisfaction of the body, physique and high-density lipoprotein cholesterol;[99] and the association with AN and FAAH polymorphism.[100] A genome-wide correlation analysis (GWAS) using the world's first microsatellite marker for AN was performed, and single nucleotide polymorphisms (SNPs) showing AN sensitivity were identified in at least three gene regions (exon 9 of the CNTN5 gene, the 3'-downstream region of the SPATA17 gene, and TOX3 gene).[101] Furthermore, in a GWAS using SNP markers, a previous study has suggested that having the minor 385A allele of the FAAH gene may be protective against restricting AN. Utilizing the knowledge of ED genetic research, it is possible to narrow down the genes targeted in an omics analysis for ED carried out in this research project. Omics research for EDs has only been reported in a cross-sectional study of a few groups for AN,[102] and no longitudinal study before and after treatment including CBT has been conducted. ED omics research is now beginning to gain traction. Based on the above, it is designed to handle multi-variates that includes omics analysis results in brain imaging data. We reduced the dimensions using deep learning

techniques and will perform a multiple regression analysis using machine learning algorithms. This is expected to generate evidence for clinical markers of EDs (diagnostic markers, therapeutic effects, therapeutic response prediction markers).

This study has some limitations. First, the number of participants by sites may not be uniform depending on the recruitment of patients and other situations. Also, the number of total participants is too small, and therefore it is not possible to use machine learning approaches to explore appropriate models without overfitting the available data. Second, although harmonization is applied, the measurement variability may increase because MRI scanners and imaging protocols can differ between manufacturers. For example, an image scanned using the SRPB imaging protocol has a lower signal-to-noise ratio and resolution compared to an image scanned using HARP. Also, because of the presence or absence of the multi-band option, the sampling rate can be up to three times different among facilities. Despite these limitations, such challenging and exploratory approaches are necessary to construct a brain imaging database of patients with eating disorders from multiple institutions as a first step. Hopefully, by sharing data between other research teams who are collecting brain imaging data on patients with eating disorders, we will be able to collect a sufficient amount of data.

FIGURE LEGENDS

Figure 1. Data logistics

DECLARATIONS

Acknowledgments

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Author contributions

SH, YH and NK participated in the design, drafted and modified the manuscript. YH, MI, NK, KY, YM, TA, KY, and YS are the co-investigators of the study who obtained funding and significantly contributed to the conception or design. ASu, YE, JT, NN, TT, HH, TN, KT, KW, HA, MG, ST, SF, and ES participated in the design and substantially contributed to the different stages of the study's development towards its practical conduction. ASe is the principal investigator of the study who obtained funding, modified the manuscript, and provided substantial contributions to the study conception and design. All authors read and approved the final manuscript.

Availability of data and materials

Please contact Atsushi Sekiguchi for future proposals and requests to use the data that will be obtained from this project.

Competing interests

None declared.

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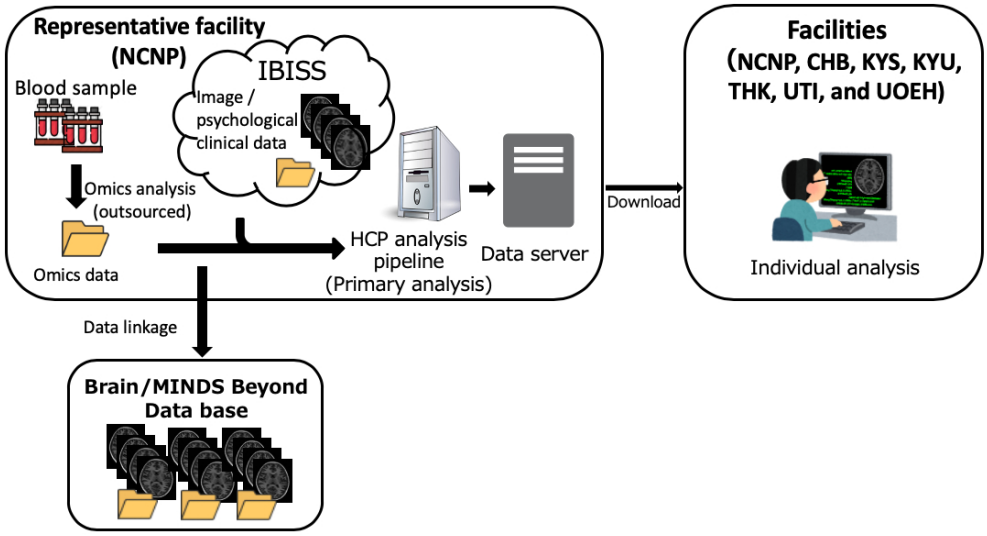

Figure1

385x212mm (72 x 72 DPI)

Supplemental table. Non-specific psychological indicators of secondary outcome

Name of psychological indicators	Content	Item questionnaire		Score range	
				Minimum	Maximum
Semi-structured interview					
The Mini-International Neuropsychiatric Interview (M.I.N.I.)[43,44]	M.I.N.I. is a brief diagnostic interview that follows DSM-IV compliant criteria for general mental status.	-	-	-	-
Japanese Adult Reading Test (JART)[45,46]	JART estimates the premorbid intellectual ability by assessing the ability of reading Chinese characters.	25	-	69	120
Self-administered questionnaire					
Beck Depression Inventory-Second Edition (BDI-II)[47,48]	BDI-II is used to assess the severity of depression. A higher score represents a more severe level of depression.	21	4-point Likert scale	0	63
State-Trait Anxiety Inventory (STAI)[49,50]	STAI evaluates state and trait anxiety. A higher score indicates a higher level of anxiety.	40	4-point Likert scale	0	60
NEO Five-Factor Inventory (NEO-FFI)[51,52]	NEO FFI is a personality inventory that examines a person's Big Five personality traits (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness).	60	5-point Likert scale	0	48
Toronto Alexithymia Scale-20 (TAS-20)[53,54]	TAS-20 is aimed to evaluate alexithymia. It consists of three subscales (difficulty describing feelings subscale, difficulty identifying feeling subscale, and externally-oriented Thinking subscale).	20	5-point Likert scale	20	100
Adult version facial expression recognition test[55]	This scale measures facial expression recognition ability for adults' face.	32	4-point Likert scale	0	32
Edinburgh handedness inventory[56,57]	To determine objectively whether one is left- or right-handed.	10	5-point Likert scale	-100	100

Childhood trauma questionnaire (CTQ)[58,59]	CTQ measures childhood trauma and it consists of five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect).	28	5-point Likert scale	28	140
Posttraumatic Diagnostic Scale (PDS)[60,61]	The PDS is a self-reported measure that identifies high-risk individuals with PTSD during an evacuation situation.	3	4-point Likert scale	0	9
Visual Analogue Scale (VAS)[62]	VAS assesses expectation to treatment.	1	-	0	100
General functioning scale of Family Assessment Device (GF-FAD)[63,64]	The FAD is a measure assessing family functioning.	12	4-point Likert scale	12	48
Help-seeking preferences[65]	Help-seeking preferences measure attitudes to seek help for others.	11	5-point Likert scale	11	55
Multidimensional Assessment of Interoceptive Awareness (MAIA)[66,67]	MAIA assesses the relevant dimensions of bodily awareness. It consists of eight subscales (Noticing, Not-Distracting, Not-Worrying, Attention Regulation, Emotional Awareness, Self-Regulation, Body Listening, and Trusting)	32	6-point Likert scale	0	5
Barratt Impulsiveness Scale (BIS-11)[68,69]	BIS measures impulsivity scale. It consists of three subscales (attentional impulsiveness, attentional impulsiveness, and non-planning impulsiveness).	30	4-point Likert scale	30	120
Maudsley Obsessional-Compulsive Inventory (MOCI)[70,71]	MOCI is administered to assess obsessive–compulsive symptoms. A higher score indicates more severe level of obsessive–compulsive symptoms. It consists of five subscales (checking, washing, slowness repetition, doubting conscientiousness, and ruminations).	30	2-point Likert scale	0	30
Autism Questionnaire (AQ)[72,73]	AQ can use any of the dichotomous evaluations to measure autistic characteristics. The total score range is 0-50. It consists of five subscales (social skills, attention switching, attention to detail, communication, and imagination).	50	4-point Likert scale	0	50

Rosenberg Self-Esteem Scale (SES)[74,75]	SES measures global self-esteem related to overall feelings of self-worth or self-acceptance.	10	5-point Likert scale	1	7
Tri-axial Coping Scale (TAC24)[76]	TAC24 evaluates stress coping strategies. The scale consists of eight subscales (Planning, Information, Cognitive reappraisal, Catharsis, Abandonment, Responsibility shifting Cognitive distancing, and Distraction).	24	5-point Likert scale	0	120
Working Alliance Inventory (WAI-SF)[77]	The strength of the therapeutic alliance was assessed using the WAI-SF. It consists of three subscales (agreement on the task of treatment, agreement on the goal of treatment, and a bond between the therapist and patient).	12	7-point Likert scale	12	84
EuroQol-5 Dimension (EQ-5D-5L)[78,79]	Quality of life is measured using the EQ-5D-5L questionnaire. The EQ-5D-5L are scored from 0 (death) to 1 (in good health).	5	5-point Likert scale	-0.025	1
The Generalized Anxiety Disorder Assessment (GAD-7)[80,81]	The presence and severity of general anxiety was assessed using the GAD-7.	7	4-point Likert scale	0	21
Patient Health Questionnaire (PHQ-9)[82,83]	The presence and severity of symptoms of depression experienced in the previous 2 weeks was evaluated using the PHQ-9.	9	4-point Likert scale	0	27
Socioeconomic status (SES)	SES assesses educational history. It consists of three subscales (oneself, father, and mother)	2	7-point Likert scale	1	7
The World Health Organization- Five Well-Being Index (WHO-5)84	WHO-5 is a short self-reported measure of current mental wellbeing.	5	6-point Likert scale	0	25
Stanford Sleepiness Scale (SSS)[85]	SSS assesses the subjective sleepiness levels during fMRI imaging.	1	7-point Likert scale	1	7