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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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4 1 **Eating Disorder Neuroimaging Initiative (EDNI): a multicenter prospective**
5 2 **cohort study protocol for elucidating the neural effects of cognitive behavioral**
6 3 **therapy for eating disorders**
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8 4

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46 **ABSTRACT**

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

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

62 **Ethics and dissemination:** The study was approved by The Ethical Committee of the
63 National Center of Neurology and Psychiatry (A2019-072). We will obtain informed
64 consent in written form from all patients who participated in the study after they had
65 been fully informed about the study protocol. All the imaging, demographic, and clinical
66 data are shared between the participating sites and will be made publicly available in
67 2024.

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

71 **Strengths and limitations of this study**

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

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3
4 75 ► This should contribute to the early detection and early intervention of eating
5 76 disorders.
6
7 77 ► We will also create a brain imaging database in Japan for those with eating disorders.
8 78 ► The number of people at one site is not very large because the brain imaging
9 79 machines differ across facilities.
10

11 80

12 81 INTRODUCTION

13 82 Eating disorders (EDs) are a psychiatric disorder with a focus on body shape, weight
14 83 and abnormal eating behavior. They are mainly classified as anorexia nervosa (AN),
15 84 bulimia nervosa (BN), and binge-eating disorder (BED).¹ In Japan, the number of
16 85 patients with EDs has increased about 10-fold between the 1980s and 1990s.² Based on
17 86 a meta-analysis including 36 studies, AN was found to have a standardized mortality
18 87 ratio (SMR) of 5.1³ and the highest mortality among mental disorders.⁴⁻⁷ In addition,
19 88 renal function decreases as the duration of AN increases,⁸ and patients often suffer
20 89 from various physical complications associated with prolonged symptoms and low
21 90 weight.⁹⁻¹² The rate of chronicity for patients with AN for up to 10 years is
22 91 approximately 10-20%, and the long-term prognosis is poor.^{13,14} Furthermore, there is
23 92 currently no evidence of treatment for severe cases with chronic AN.¹⁵
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31 93

32 94 Cognitive behavioral therapy (CBT) has been shown to be effective as a psychotherapy
33 95 for EDs,¹⁶⁻¹⁸ and CBT is also recommended in the NICE guidelines.¹⁹ Meta-analyses of
34 96 RCTs that include waitlist controls report that CBT is particularly effective for BN and
35 97 BED.²⁰⁻²⁴ In Japan, there are two reports on the effectiveness and feasibility of CBT for
36 98 BN or BED,^{25,26} and health insurance has covered CBT in Japan since 2018. However,
37 99 according to a meta-analysis of RCTs, the dropout rate for CBT is approximately 24%,²⁷
38 100 and there are large individual differences in treatment responsiveness. To the best of
39 101 our knowledge, there are no reports of neural mechanisms that regulate the effects and
40 102 treatment responses of CBT for EDs. Therefore, accumulating evidence using brain
41 103 imaging and biomarkers of gene expression would further our understanding of CBT
42 104 effectiveness for EDs.
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51 106 Since individuals with EDs show abnormal eating behavior, structural and functional
52 107 brain imaging studies have been conducted to elucidate the neural basis of these
53 108 abnormalities through brain imaging research. There are various reports on brain
54 109 imaging research in ED patients that have revealed abnormal reward systems,²⁸ a
55 110 reductions in gray matter of various brain regions (frontal lobes;²⁹ frontal gyrus;³⁰
56 111 parietal and temporal lobes;³¹ occipital lobe³²), and limited reductions in white matter
57 112 volume.³³ In Japan, the neural basis for the pathogenesis of EDs has been clarified.³⁴⁻³⁷
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4 113 However, brain imaging research for EDs has only been conducted in the form of small
5 114 cross-sectional studies in a single facility, and the reproducibility and validity of these
6 115 results remain questionable. Therefore, research at a larger scale is needed to elucidate
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8 116 the cognitive brain science of ED pathology and progression, and to identify clinically
9
10 117 useful diagnostic and therapeutic markers and prognostic predictors.
11

12
13 119 The ENIGMA-Eating Disorders should be noted as a multicenter study outside of Japan.
14 120 However, it is only registered by researchers in Europe, the United States, and Africa,
15 121 and mainly takes place in Germany. For the time being, they have used methods to
16 122 meta-analyze anatomical images and diffusion tensor-weighted images of AN and BN
17 123 patients that have already been imaged at participating facilities. The ENIGMA-Eating
18 124 Disorders study is expected to build a framework for joint research to be developed in
19
20 125 the future. However, ED brain image multicenter research cannot be confirmed even by
21
22 126 searching the world's major clinical research registration sites such as
23
24 127 ClinicalTrials.gov in the United States and EU register in the EU, and an ED brain image
25
26 128 database has not yet been developed globally.
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28 29 130 **Aims and hypotheses**

30
31 131 We aim to generate neuroscientific evidence for the effect of CBT and contribute to the
32 132 early detection and early intervention for EDs. First, we will collect brain magnetic
33 133 resonance imaging (MRI) images and clinical data as longitudinal observational studies
34
35 134 before and after CBT for EDs. Next, we will identify clinical biomarkers of EDs through
36 135 analytical studies using longitudinal image data before and after CBT for EDs, and
37
38 136 create neural evidence for the effect of CBT. We aim to identify brain image biomarkers
39 137 that can be used as clinical markers (diagnostic markers, therapeutic markers, and
40
41 138 therapeutic response prediction markers) for EDs. Furthermore, the brain image data
42
43 139 collected for this project will be integrated into an international brain database.
44

45 141 **METHODS AND ANALYSIS**

46 142 **Study design**

47
48 143 This is a multisite, observational cohort study. For ED patients who have received
49
50 144 structured CBT, the following will be performed before and after CBT: Brain MRI
51 145 imaging (T1WI, T2WI, resting state functional MRI, DWI); Blood collection for gene
52
53 146 polymorphism and gene expression analysis; and Psychological evaluation. Table 1
54
55 147 shows the study design. In the pre-treatment evaluation, subjects will visit each
56 148 treatment facility, and an outpatient doctor or psychologist (recruiter) will evaluate
57
58 149 eligibility and exclusion criteria for CBT introduction. After obtaining the informed
59
60 150 consent for individuals who meet the criteria for introducing CBT, they will then be

151 registered as subjects of this study. After registration, the schedule for the first session
 152 of CBT will be determined. In principle, brain MRI scans and other tests will be carried
 153 out within 4 weeks before the session date. The post-treatment evaluation is based on
 154 the day when CBT for EDs is completed, and in principle, tests such as brain MRI are
 155 performed within 4 weeks. In addition, a similar assessment one year after treatment
 156 (50+/-8 weeks) will be performed for subjects who are willing.

157

158 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	×	-	×	×

159 *Outpatient /**inpatient

160

161 **Study setting**

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

166

167 **Recruitment**

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

175

176 **Study participants**

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

179

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/m²(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
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180

181 **Patient and Public Involvement**

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

183

184 **Interventions**

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

188

189 **Primary outcome**

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

197

198 **Secondary outcomes**

- 199 1. Remission at the end of treatment (state that does not meet DSM-5 criteria)
- 200 2. Treatment completion rate (completed when 75% or more of 21 to 41 treatment
- 201 sessions are received)
- 202 3. ED specific indicators: Currently BMI; the lowest and highest BMI in the past; history
- 203 of AN and BN
- 204 4. Non-specific psychological indicators: The Mini-International Neuropsychiatric
- 205 Interview (M.I.N.I.)^{41,42} for Comorbidities; Japanese Adult Reading Test(JART)^{43,44} for
- 206 intellectual ability; Beck Depression Inventory-Second Edition (BDI-II)^{45,46} for Severity
- 207 of depressive symptoms; State-Trait Anxiety Inventory (STAI)^{47,48} for anxiety; NEO
- 208 Five-Factor Inventory (NEO-FFI) ^{49,50} for personality scores; 20-Item Toronto
- 209 Alexithymia Scale (TAS-20)^{51,52} for alexithymia; Adult version facial expression
- 210 recognition test⁵³ for adult facial expression recognition ability; Edinburgh handedness
- 211 inventory ^{54,55} for determining objectively whether one is left or right handed;
- 212 Childhood trauma questionnaire (CTQ)^{56,57} for childhood trauma; Posttraumatic
- 213 Diagnostic Scale (PDS)^{58,59} for trauma; Visual Analogue Scale (VAS)⁶⁰ for Expectation to
- 214 treatment; General functioning scale of Family Assessment Device (GF-FAD)^{61,62} for
- 215 family assessment ; Help-seeking preferences⁶³ for attitude to seek help for others;
- 216 Multidimensional Assessment of Interoceptive Awareness (MAIA)^{64,65} for relevant
- 217 dimensions of bodily awareness; Barratt Impulsiveness Scale (BIS-11)^{66,67} for
- 218 impulsivity scale; Maudsley Obsessional Compulsive Inventory (MOCI)^{68,69} for
- 219 Obsessive-compulsive symptoms scale; Autism-Spectrum Quotient (AQ)^{70,71} for Autism
- 220 tendencies; Rosenberg Self-Esteem Scale (SES)^{72,73} for global self-esteem; Tri-axial
- 221 Coping Scale (TAC24)⁷⁴ for evaluation of stress coping strategies; Working Alliance
- 222 Inventory (WAI)⁷⁵ for aspects of the therapeutic alliance; EuroQol-5 Dimension (EQ-
- 223 5D)^{76,77} for Quality of Life; The Generalized Anxiety Disorder Assessment (GAD-7)^{78,79}
- 224 for severity of generalized anxiety disorder; Patient Health Questionnaire (PHQ-9)^{80,81}
- 225 for depression module; The World Health Organization- Five Well-Being Index (WHO-
- 226 5)⁸² for Mental health scale; Socioeconomic status (SES) for Education history; Stanford
- 227 Sleepiness Scale (SSS)⁸³ for subjective sleepiness levels
- 228 5. Brain image data, gene polymorphism / gene expression analysis data

229

230 **Demographic data**

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

234 **Imaging acquisition**

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

249 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

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

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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 Measure ments	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	6/16	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	6/16	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 Measure ments	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	0/16	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).

270 **Biological measures from blood samples**

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

278 **Data logistics**

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

291 **Statistical analysis**

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

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3 308 and BN disease types, and search for cognitive, psychological, and behavioral indicators
4 309 associated with disease type diagnosis. At this time, a comparison with the healthy
5 310 group will also be performed. By comparing these groups, diagnostic markers based on
6 311 conventional diagnoses will be identified (categorical approach). Furthermore, we will
7 312 identify diagnostic markers on searching for psychopathological features in brain
8 313 images, gene polymorphisms and gene expression data related to core disease state
9 314 indicators and other psychological indicators across all disease types (dimensional
10 315 approach); (2) Identification of therapeutic effect (longitudinal data set 40 people): we
11 316 will analyze the relationship between changes in ED symptoms before and after CBT,
12 317 and changes (rates) in brain images, psychology, gene polymorphisms, and gene
13 318 expression data, and identify the therapeutic effects of CBT; (3) Identification of
14 319 therapeutic response markers (longitudinal data set 60): analyzing associations with
15 320 baseline brain images, psychology, gene polymorphisms, and gene expression data to
16 321 predict the completion and remission of EDs before and after CBT, and identify
17 322 treatment predictive markers; (4) In addition to the above, analysis that is judged
18 323 necessary or meaningful at the time of analysis will be performed. In particular, we
19 324 plan to conduct analysis using machine learning techniques. If there are missing values
20 325 in the dataset to be analyzed, they will, in principle, be excluded from the analysis.
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327 **Sample size**

328 The number of cases needed to detect an improvement in ED symptoms, which is the
329 main outcome, was calculated. If calculated based on interpersonal therapy (n=65,
330 Mean=2.37, SD=1.25) vs CBT (n=65, Mean=1.57, SD=1.25) [18], a single group of 27
331 cases is required based on a comparison of average outcomes of two independent
332 samples at the time of post intervention (t-test); two tails, $\alpha=0.05$, $1-\beta=0.80$. Hence, a
333 total of 54 patients is required (27 cases for AN; 27 cases for BN). We plan to complete
334 72 cases among the joint research facilities. For five years, considering the dropout rate
335 of CBT for ED treatment (about 40%) and the consent rate for MRI (about 60%), and
336 differences in CBT for each facility, we plan to recruit 200 patients with EDs who are
337 introduced CBT at all facilities, and we expect 120 cases to obtain consent for MRI
338 examination and 72 cases to complete CBT. Regarding the disease type, the number of
339 patients with AN and BN is expected to be about 1:1 in the end. Tohoku University and
340 Kyoto University have mainly implemented CBT for patients with BN; conversely,
341 Tokyo University, University of Occupational and Environmental Health, Kyushu
342 University have mainly implemented CBT for patients with AN, whereas NCNP and
343 Chiba University have implemented CBT for patients with AN and BN almost equally.
344 Furthermore, we will collect 70 cases of healthy control group data. In particular, in
345 order to verify the effects of low body weight, it collects the data for 30 healthy women
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4 346 with a BMI between 16 and 17.5 (BMI values satisfy one of the diagnoses of AN) and no
5 347 ED pathology.

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8 349 **Trial status**

9 350 The first participant was included in this study on June 16, 2020. The end of the
10 351 recruitment phase is currently scheduled for July 31, 2024.

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14 353 **ETHICS AND DISSEMINATION**

15 354 **Data distribution**

17 355 At the end of the project period, the data will be publicly distributed to researchers
18 356 through public databases. All imaging, demographic, and clinical data are shared
19 357 between the participating sites and will be made publicly available in 2024. To the best
20 358 of our knowledge, this is one of the first multi-site human brain MRI projects
21 359 investigating multiple mental and neurological disorders throughout life. The
22 360 Brain/MINDS Beyond human brain MRI project will help identify common and disease-
23 361 specific pathophysiological features of brain disease and develop imaging biomarkers
24 362 for clinical practice.

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30 364 **Ethical regulation**

31 365 We follow the ethical regulation of the previous study.⁸⁸ Sharing neuropsychiatric
32 366 patient data that can contain information linked to subjects' privacy requires special
33 367 attention⁸⁵. Hence, the Brain/MINDS Beyond project has made NCNP the core site for
34 368 supporting ethical considerations. Before participating in the project, all institutions
35 369 are required to have their research plans approved by their ethical review committee.
36 370 This includes the following points and ethical documentation: (1) MR images and
37 371 clinical data of the participants can be shared within the Brain/MINDS Beyond Project
38 372 or Japanese/international scientific institutions. Anonymized MR images with limited
39 373 clinical data may become publicly available on an open database for research purposes,
40 374 (2) MR images of the participants may be compared with nonhuman primate MRI data,
41 375 and (3) the intellectual property rights derived from the research of the Brain/MINDS
42 376 Beyond project shall be attributed to the researcher's institute, not the participants. All
43 377 participants, after receiving the full description of the experiment, are required to
44 378 provide written informed consent to participate in this project. The Japanese
45 379 regulations for the sharing of personal information used for research purposes require
46 380 attention when handling two types of data: "individual identification codes" and
47 381 "special care-required personal information"
48 382 (<http://www.japaneselawtranslation.go.jp/law/detail/?id=2781&vm=04&re=01>). The
49 383 Individual identification code is a direct identifier and is sufficient to identify a
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4 384 particular individual. Special care-required personal information represents indirect
5 385 identifiers that need special care in handling in order to avoid potential disadvantages
6 386 to the participants. In consideration of these regulations, data accompanied with the
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8 387 MR images are limited in the publicly accessible open database and include only 5-year
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10 388 age bins, sex, diagnostic information, handedness, simple socioeconomic status, clinical
11 389 scale scores, and sleepiness scale scores. In the Brain/MINDS Beyond project, we
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13 390 exclude the datasets of MR images containing facial information from the data in the
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15 391 publicly accessible open database.
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393 Discussion

394 The strengths of this research are listed below. Firstly, to construct a brain image
395 database of EDs using the longitudinal brain imaging scans of ED patients from
396 multiple facilities. To date, brain imaging research for ED has been limited to small-
397 scale cross-sectional studies.³⁴⁻³⁷ For this reason, it is important to establish a brain
398 imaging database of EDs using brain images from ED patients across multiple facilities
399 and longitudinally to identify clinically useful diagnostic and therapeutic markers and
400 prognostic predictors. Secondly, data collected before and after CBT treatment will be
401 collected longitudinally, and treatment responsiveness can be input as a variable. In
402 addition, it is possible to explore the effects of treatment responsiveness by treating
403 childhood trauma as a treatment resistance factor and covariate. Thirdly, the machine
404 learning method can be used to develop into analytical research that leads to an
405 integrated understanding of the pathology of EDs and even neuropsychiatric disorders.
406 Thus far, studies that apply machine learning techniques to brain imaging data from ED
407 patients have begun to gradually appear, but remain limited to cross-sectional studies
408 using samples of 15 to 24 patients in a single group.^{86,87} To date, there remains no
409 longitudinal data from before and after treatment and the association with other
410 clinical markers. Lastly, we apply an omics analysis as a clinical marker of ED. Thus far,
411 previous studies have been reported in Japan addressing the susceptibility gene for
412 feeding regulators: the relationship between Ghrelin polymorphism and BN;⁸⁸ the
413 association with young female dissatisfaction of the body, physique and high-density
414 lipoprotein cholesterol;⁸⁹ and the association with AN and FAAH polymorphism.⁹⁰ A
415 genome-wide correlation analysis (GWAS) using the world's first microsatellite marker
416 for AN was performed, and single nucleotide polymorphisms (SNPs) showing AN
417 sensitivity were identified in at least three gene regions (exon 9 of the CNTN5 gene, the
418 3'-downstream region of the SPATA17 gene, and TOX3 gene).⁹¹ Furthermore, in a
419 GWAS using SNP markers, a previous study has suggested that having the minor 385A
420 allele of the FAAH gene may be protective against restricting AN. Utilizing the
421 knowledge of ED genetic research, it is possible to narrow down the genes targeted in
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4 422 an omics analysis for ED carried out in this research project. Omics research for EDs is
5 423 only a report of a cross-sectional study of few groups for AN,⁹² and no longitudinal
6 424 study before and after treatment including CBT has been conducted. ED omics research
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8 425 is now beginning to gain traction. Based on the above, it is designed to handle
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10 426 multivariates that includes omics analysis results in brain imaging data. We reduce the
11 427 dimensions using deep learning techniques and perform a multiple regression analysis
12 428 using machine learning algorithms. This is expected to generate evidence for clinical
13 429 markers of EDs (diagnostic markers, therapeutic effects, therapeutic response
14 429 prediction markers).
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18 432 This study has some limitations. First, the number of people at one site is not very large
19 433 because the brain imaging machines differ across facilities. Although harmonization is
20 433 made, measurement variability may increase due to the multiple sites. Second, the
21 434 number of brain function image samplings at a resting state is very different depending
22 435 on the facility. Finally, there is a possibility that the image captured by the innovative
23 436 brain is low in reliability and resolution.
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29 439 **FIGURE LEGENDS**

30 440 Figure 1 Data logistics
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33 442 **DECLARATIONS**

34 443 **Acknowledgments**

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40 447 **Author contributions**

41 448 SH and YH participated in the design, drafted and modified the manuscript.
42 448 YH, MI, NK, KY, YM, TA, KY, and YS are the co-investigators of the study who obtained
43 449 funding and significantly contributed to the conception or design. ASu, YE, JT, NN, TT,
44 450 HH, TN, KT, KW, HA, MG, ST, SF, and ES participated in the design and substantially
45 451 contributed to the different stages of the study's development towards its practical
46 452 conduction. ASe is the principal investigator of the study who obtained funding,
47 453 modified the manuscript, and provided substantial contributions to the study
48 454 conception and design. All authors read and approved the final manuscript.
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51 457 **Availability of data and materials**

52 458 Please contact Atsushi Sekiguchi for future proposals and requests to use the data that
53 459 will be obtained from this project.
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3 461 **Competing interests**

4 462 None declared.

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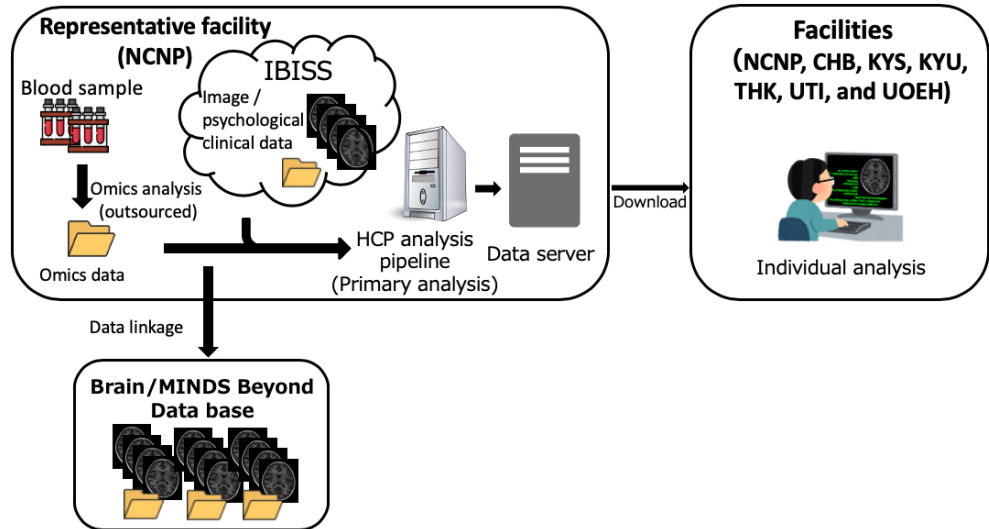


Figure1

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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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Primary Subject	Mental health

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4 1 **Eating Disorder Neuroimaging Initiative (EDNI): a multicenter prospective**
5 2 **cohort study protocol for elucidating the neural effects of cognitive behavioral**
6 3 **therapy for eating disorders**
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46 **ABSTRACT**

47 **Introduction:** Anorexia nervosa is a refractory psychiatric disorder with a mortality
48 rate of 5.9% and standardized mortality ratio of 5.35, which is much higher than other
49 psychiatric disorders. The standardized mortality ratio (SMR) of bulimia nervosa is
50 1.49; however, it is characterised by suicidality resulting in a shorter time to death.

51 While there is no current validated drug treatment for eating disorders in Japan,
52 cognitive behavioural therapy (CBT) is a well-established and commonly used
53 treatment. CBT is also recommended in the Japanese Guidelines for the Treatment of
54 Eating Disorders (2012) and has been covered by insurance since 2018. However, the
55 neural mechanisms responsible for the effect of CBT have not been elucidated, and the
56 use of biomarkers such as neuroimaging data would be beneficial.

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

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

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

72 **Strengths and limitations of this study**

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

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4 76 ► This should contribute to the early detection and early intervention of eating
5 77 disorders.
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7 78 ► We will also create a brain imaging database in Japan for those with eating disorders.
8 79 ► MRI equipment and treatment protocols are not completely unified.
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81 INTRODUCTION

82 Eating disorders (EDs) are a psychiatric disorder with a focus on body shape, weight,
83 and abnormal eating behaviours. They are mainly classified as anorexia nervosa (AN),
84 bulimia nervosa (BN), and binge-eating disorder (BED).¹ In Japan, the number of
85 patients with EDs has increased about 10-fold between the 1980s and 1990s.² Based on
86 a meta-analysis including 36 studies, AN was found to have a standardized mortality
87 ratio (SMR) of 5.1,³ and the highest mortality rate among mental disorders.⁴⁻⁷ In
88 addition, renal function decreases as the duration of AN increases,⁸ and patients often
89 suffer from various physical complications associated with prolonged symptoms and
90 low weight.⁹⁻¹² The rate of chronicity for patients with AN for up to 10 years is
91 approximately 10-20%, and the long-term prognosis is poor.^{13,14} Furthermore, current
92 treatments may not be effective in severe cases of chronic AN.¹⁵ Regarding BN, the SMR
93 is 1.49; however, it is characterised by suicidality resulting in a shorter time to death.³
94 Therefore, early detection and early intervention are important.
95

96 Cognitive behavioural therapy (CBT) is a psychotherapy that aims to improve
97 psychiatric symptoms by focusing on cognitive processes and behavioural patterns.
98 CBT for eating disorders identifies the psychopathology that contributes to the disease
99 while advancing regular eating and weight-regulating behavioural modifications.¹⁶
100 Cognitive styles such as fear of weight gain and adherence to body shape and
101 behavioural patterns such as dietary restrictions and excessive exercise are often seen
102 in eating disorders¹⁷; CBT can be used to address these psychopathologies.¹⁶ CBT has
103 been shown to be effective as a psychotherapy for EDs,¹⁸⁻²⁰ and CBT is also
104 recommended in the NICE guidelines.²¹ Meta-analyses of RCTs that include waitlist
105 controls report that CBT is particularly effective for BN and BED.²²⁻²⁶ In Japan, there are
106 two reports on the effectiveness and feasibility of CBT for BN or BED,^{27,28} and the
107 national health insurance has covered CBT in Japan since 2018. However, according to
108 a meta-analysis of RCTs, the dropout rate for CBT is approximately 24%,²⁹ and there
109 are large individual differences in treatment responsiveness.
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111 To the best of our knowledge, there are no reports of neural mechanisms that regulate
112 the effects and treatment responses of CBT for EDs. Therefore, accumulating evidence
113 using brain imaging and biomarkers of gene expression would further our

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4 114 understanding of CBT effectiveness for EDs. The identification of biomarkers may
5 115 provide clues to the development of diagnostic and therapeutic methods based on the
6 116 elucidation of the pathophysiology and pathogenic mechanism of EDs. It may
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8 117 contribute to social implementation of early detection and early intervention with
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10 118 diagnostic methods using objective indicators
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12 120 Since individuals with EDs show abnormal eating behaviours, structural and functional
13 121 brain imaging studies have been conducted to elucidate the neural basis of these
14 122 abnormalities through brain imaging research. There are various reports on brain
15 123 imaging research in ED patients that have revealed abnormal reward systems,³⁰
16 124 reductions in grey matter of various brain regions (frontal lobes,³¹ frontal gyrus,³²
17 125 parietal and temporal lobes,³³ occipital lobe³⁴), and limited reductions in white matter
18 126 volume.³⁵ In Japan, the neural basis for the pathogenesis of EDs has been studied.³⁶⁻³⁹
19 127 However, brain imaging research for EDs has only been conducted in the form of small
20 128 cross-sectional studies in a single facility, and the reproducibility and validity of these
21 129 results remain questionable. Therefore, research at a larger scale is needed to elucidate
22 130 the cognitive brain science of ED pathology and progression, and to identify clinically
23 131 useful diagnostic and therapeutic markers and prognostic predictors.
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32 133 The ENIGMA-Eating Disorders should be noted as a multicentre study outside of Japan.
33 134 However, it is only registered by researchers in Europe, the United States, and Africa,
34 135 and mainly takes place in Germany. For the time being, they have used methods to
35 136 meta-analyse anatomical images and diffusion tensor-weighted images of AN and BN
36 137 patients that have already been imaged at participating facilities. The ENIGMA-Eating
37 138 Disorders study is expected to build a framework for joint research to be developed in
38 139 the future. However, ED brain image multicentre research has not been found to have
39 140 been conducted, even when searching the world's major clinical research registration
40 141 sites such as ClinicalTrials.gov in the United States and EU register in the EU.
41 142 Furthermore, an ED brain image database has not yet been developed globally.
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144 **Aims and hypotheses**

50 145 We aim to generate neuroscientific evidence for the effect of CBT. First, we will
51 146 longitudinally collect brain magnetic resonance imaging (MRI) images and clinical data
52 147 in observational studies before and after CBT for EDs. Next, we will identify clinical
53 148 biomarkers of EDs through analytical studies using longitudinal image data before and
54 149 after CBT for EDs and create neural evidence for the effect of CBT. We aim to identify
55 150 brain image biomarkers that can be used as clinical markers (diagnostic markers,
56 151 therapeutic markers, and therapeutic response prediction markers) for EDs. We
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4 152 hypothesise the following: 1) characteristic brain circuit abnormalities exist for each
5 153 type of ED; 2) there are brain circuit changes that correlate with changes in severity
6 154 before and after treatment for ED; and 3) there are brain circuit features that define the
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8 155 therapeutic response of CBT for ED. Furthermore, the brain image data collected for
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10 156 this project will be integrated into an international brain database prepared by the
11 157 Japan Agency for Medical Research and Development (AMED). In the future, after the
12 158 AMED Brain / MINDS Beyond human brain MRI database is constructed, it will be
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14 159 possible to access the database. At the moment, the portal site ([https://brainminds-](https://brainminds-beyond.jp/ja/resources/2020/05/amedmri.html)
15 160 [beyond.jp/ja/resources/2020/05/amedmri.html](https://brainminds-beyond.jp/ja/resources/2020/05/amedmri.html)) is being created. (Details of The
16 161 Brain / MINDS Beyond human brain MRI project: koike et al., 2020 preprint).
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20 163 METHODS AND ANALYSIS

21 164 Study design

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23 165 This is a multisite, observational cohort study. For ED patients who have received
24 166 structured CBT, the following will be performed before and after CBT: brain MRI
25 167 imaging (T1WI, T2WI, resting state functional MRI, DWI); blood collection for gene
26 168 polymorphism and gene expression analysis; and psychological evaluation. Table 1
27 169 shows the study design. In the pre-treatment evaluation, subjects will visit each
28 170 treatment facility for treatment, and a doctor or psychologist (recruiter) will evaluate
29 171 eligibility and exclusion criteria for CBT introduction. Among the subjects who meet
30 172 the CBT eligibility criteria, the eligibility criteria and exclusion criteria of this study will
31 173 be evaluated. Subjects who have obtained informed consent for this study will be
32 174 registered as study subjects. After registration, the schedule for the first session of CBT
33 175 will be determined. In principle, brain MRI scans and other tests will be carried out
34 176 within 4 weeks before the session date. The post-treatment evaluation is based on the
35 177 day when CBT for EDs is completed, and in principle, tests such as brain MRI are
36 178 performed within 4 weeks. In addition, a similar assessment 1 year after treatment
37 179 (50+/-8 weeks) will be performed for subjects who are willing.
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47 181 Table 1. Standard protocol items

48 Items	49 Pre	50 Intervention	51 Post	52 Follow Up
53 Time point	54 -4W-0	55 1~21 sessions* 56 or 41 sessions**	57 Within 4 weeks	58 50 +/-8 W
59 Informed consent	60 ×	-	-	-
Demographic data	×	-	-	-
Cognitive and psychological indicators				
EDE 17.0D	×		×	×
EDE-Q	×		×	×

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4	M.I.N.I.	×	×	×
5	JART	×		
6	BDI-II	×	×	×
7	STAI	×	×	×
8	NEO - FFI	×	×	×
9	TAS-20	×	×	×
10	Adult version facial			
11	expression recognition test	×	×	×
12	Edinburgh handedness			
13	inventory	×		
14	CTQ	×		
15	PDS	×	×	×
16	VAS	×	×	×
17	GF-FAD	×	×	×
18	MAIA	×	×	×
19	BIS-11	×	×	×
20	MOCI	×	×	×
21	AQ	×		
22	SES	×	×	×
23	TAC24	×	×	×
24	WAI	×	×	×
25	EQ-5D	×	×	×
26	GAD-7	×	×	×
27	PHQ-9	×	×	×
28	WHO-5	×	×	×
29	SES	×		
30	SSS	×	×	×
31	Brain MRI examination	×	-	×
32	Blood sample (non-fasting period)	×	-	×
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182 *Outpatient /**inpatient

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

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4 191 11:Barratt Impulsiveness Scale; MOCI: Maudsley Obsessional Compulsive Inventory;
5 192 AQ: Autism-Spectrum Quotient ; SES: Rosenberg Self-Esteem Scale; TAC24: Tri-axial
6 193 Coping Scale ; WAI: Working Alliance Inventory; EQ-5D: EuroQol-5 Dimension; GAD-7:
7 194 Generalized Anxiety Disorder assessment ; PHQ-9:Patient Health Questionnaire; WHO-
8 195 5: World Health Organization - Five Well-Being Index; SES: Socioeconomic status; SSS:
9 196 Stanford Sleepiness Scale.

197

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199 **Study setting**

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

204

205 **Recruitment**

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

216

217 **Study participants**

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

220

221 Table 2. Inclusion and exclusion criteria

222 *Eating disorder*

Inclusion criteria	1) Meets the DSM-5 diagnostic criteria for an ED (AN and BN) 2) \geq 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)

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- Exclusion criteria
- 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
 - 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
-

38 *Healthy control*

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- Inclusion criteria
- 1) Those do not meet the diagnostic criteria for EDs (AN and BN) in the DSM-5
 - 2) \geq 18 years of age at the time of informed consent
 - 3) Body Mass Index (BMI) at screening is greater than 16 kg/m² (or standard weight -35%) and < 40.0 kg/m²(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
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221

222 **Patient and Public Involvement**

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

224

225 **Interventions**

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

233

234 **Primary outcome**

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

242

243 **Secondary outcomes**

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

247 3. ED specific indicators: current BMI; the lowest and highest BMI in the past; history of
248 AN and BN.

249 4. Non-specific psychological indicators (see details as a supplemental file): the Mini-
250 International Neuropsychiatric Interview (M.I.N.I.)^{43,44} for comorbidities; Japanese
251 Adult Reading Test (JART)^{45,46} for intellectual ability; Beck Depression Inventory-
252 Second Edition (BDI-II)^{47,48} for severity of depressive symptoms; State-Trait Anxiety
253 Inventory (STAI)^{49,50} for anxiety; NEO Five-Factor Inventory (NEO-FFI)^{51,52} for
254 personality scores; 20-Item Toronto Alexithymia Scale (TAS-20)^{53,54} for alexithymia;
255 adult version facial expression recognition test⁵⁵ for adult facial expression recognition
256 ability; Edinburgh handedness inventory^{56,57} for determining objectively whether one
257 is left or right handed; Childhood Trauma Questionnaire (CTQ)^{58,59} for childhood
258 trauma; Posttraumatic Diagnostic Scale (PDS)^{60,61} for trauma; Visual Analogue Scale
259 (VAS)⁶² for expectation to treatment; General Functioning scale of Family Assessment
260 Device (GF-FAD)^{63,64} for family assessment; help-seeking preferences⁶⁵ for attitude to
261 seek help for others; Multidimensional Assessment of Interoceptive Awareness
262 (MAIA)^{66,67} for relevant dimensions of bodily awareness; Barratt Impulsiveness Scale
263 (BIS-11)^{68,69} for impulsivity scale; Maudsley Obsessional Compulsive Inventory
264 (MOCI)^{70,71} for obsessive-compulsive symptoms scale; Autism-Spectrum Quotient
265 (AQ)^{72,73} for autism tendencies; Rosenberg Self-Esteem Scale (SES)^{74,75} for global self-
266 esteem; Tri-axial Coping Scale (TAC24)⁷⁶ for evaluation of stress coping strategies;
267 Working Alliance Inventory (WAI)⁷⁷ for aspects of the therapeutic alliance; EuroQol-5
268 Dimension (EQ-5D)^{78,79} for quality of Life; the Generalized Anxiety Disorder
269 assessment (GAD-7)^{80,81} for severity of anxiety; Patient Health Questionnaire (PHQ-
270 9)^{82,83} for depression module; the World Health Organization - Five Well-Being Index
271 (WHO-5)⁸⁴ for mental health scale; Socioeconomic status (SES) for education history;
272 Stanford Sleepiness Scale (SSS)⁸⁵ for subjective sleepiness levels.

273 5. Brain image data, gene polymorphism / gene expression analysis data.

274

275 **Demographic data**

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

280

281 **Imaging acquisition**

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

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

293

294 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

295 *Institutions that originally planned for SRPB may replace after HARP was developed.

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

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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 Measure ments	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	6/16	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	6/16	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 Measure ments	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	0/16	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).

312 **Biological measures from blood samples**

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

320 **Data logistics**

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

333 **Statistical analysis**

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

345
346 At the secondary analysis stage, strategies (harmonization) for adjusting inter-facility
347 factors will be considered. At present, we are planning to use corrections based on
348 average values between facilities, or software such as Combat. The ComBat
349 harmonization tool⁸⁸⁻⁹⁰ 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.

377

378 **Machine-learning approach**

379 We are planning to use the python Scikitlearn library (version 0.22.1) to perform
380 Support vector machine (SVM) classification⁹¹. To prevent overfitting (i.e., the classifier
381 works perfectly on the training data, but is poorly generalizable to new data), we will
382 perform a feature relevance evaluation and dimensionality reduction using a tree-
383 based feature selection approach with a nested cross-validation design.⁹²⁻⁹⁴
384 The nested cross-validation consists of an inner loop for model building and parameter
385 estimation, and an outer loop for model testing. Consequently, the dataset will be
386 divided into two parts: a training plus validation subset and a test subset. In the inner
387 loop, SVM models will have been trained with varying SVM hyper-parameters (i.e., cost

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4 388 parameters C and kernel function) based on a grid search, and a feature selection will
5 389 have been performed using classification trees or random forests. The validation set
6 390 will be used to determine the SVM hyper-parameters over the grid of possible values.
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8 391 The performance of the resulting model, with optimized SVM hyper-parameters and
9 392 features, will be subsequently evaluated on the test set in the outer loop. For this outer
10 393 loop, we will use a leave-one-out cross-validation scheme so that each sample will be
11 394 used once as a test set (singleton) while the remaining samples form the
12 395 training/validation set. The training/validation set will be divided into five equally
13 396 sized parts. Four of these will be used as the training set and one as the validation set.
14 397 This process is repeated until all subjects are left out at least once and prediction
15 398 results are aggregated as well as reported.
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22 400 **Sample size**

23 401 The number of cases needed to detect an improvement in ED symptoms, which is the
24 402 main outcome, was calculated. If calculated based on interpersonal therapy (n=65,
25 403 mean=2.37, SD=1.25) vs CBT (n=65, mean=1.57, SD=1.25) [18], a single group of 27
26 404 cases is required based on a comparison of average outcomes of two independent
27 405 samples at the time of post intervention (t-test); two tails, $\alpha=0.05, 1-\beta=0.80$. Hence, a
28 406 total of 54 patients is required (27 cases for AN; 27 cases for BN). We plan to complete
29 407 72 cases among the joint research facilities. For 5 years, considering the dropout rate of
30 408 CBT for ED treatment (about 40%) and the consent rate for MRI (about 60%), and
31 409 differences in CBT for each facility, we plan to recruit 200 patients with EDs who are
32 410 introduced to CBT at all facilities. We expect 120 cases to obtain consent for MRI
33 411 examination and 72 cases to complete CBT. Regarding the disease type, the number of
34 412 patients with AN and BN is expected to be about 1:1 in the end. Tohoku University and
35 413 Kyoto University have mainly implemented CBT for patients with BN; conversely,
36 414 Tokyo University, University of Occupational and Environmental Health, Kyushu
37 415 University have mainly implemented CBT for patients with AN, whereas NCNP and
38 416 Chiba University have implemented CBT for patients with AN and BN almost equally.
39 417 Furthermore, we will collect 70 cases in the healthy control group. In particular, in
40 418 order to verify the effects of low body weight, we will collect data for 30 healthy
41 419 women with a BMI between 16 and 17.5 (BMI values satisfy one of the diagnoses of
42 420 AN) and no ED pathology.
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54 422 **Trial status**

55 423 The first participant was included in this study on June 16, 2020. The end of the
56 424 recruitment phase is currently scheduled for July 31, 2024.
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426 ETHICS AND DISSEMINATION

427 Data distribution

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

437 Ethical regulation

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

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4 463 exclude the datasets of MR images containing facial information from the data in the
5 464 publicly accessible open database.

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8 466 **Discussion**

9 467 The strengths of this research are listed below. Firstly, we aimed to construct a brain
10 468 image database of EDs using the longitudinal brain imaging scans of ED patients from
11 469 multiple facilities. To date, brain imaging research for ED has been limited to small-
12 470 scale cross-sectional studies.³⁶⁻³⁹ For this reason, it is important to establish a brain
13 471 imaging database of EDs using brain images from ED patients across multiple facilities
14 472 and longitudinally to identify clinically useful diagnostic and therapeutic markers and
15 473 prognostic predictors. Secondly, data collected before and after CBT treatment will be
16 474 collected longitudinally, and treatment responsiveness can be input as a variable. In
17 475 addition, it is possible to explore the effects of treatment responsiveness by treating
18 476 childhood trauma as a treatment resistance factor and covariate. Thirdly, the machine
19 477 learning method can be used to develop into analytical research that leads to an
20 478 integrated understanding of the pathology of EDs and even neuropsychiatric disorders.
21 479 Thus far, studies that apply machine learning techniques to brain imaging data from ED
22 480 patients have begun to gradually appear but remain limited to cross-sectional studies
23 481 using samples of 15 to 24 patients in a single group.^{96,97} To date, there remains no
24 482 longitudinal data from before and after treatment and the association with other
25 483 clinical markers. Lastly, we will apply an omics analysis to identify clinical markers of
26 484 ED. Thus far, previous studies have been reported in Japan addressing the
27 485 susceptibility gene for feeding regulators: the relationship between Ghrelin
28 486 polymorphism and BN;⁹⁸ the association with young female dissatisfaction of the body,
29 487 physique and high-density lipoprotein cholesterol;⁹⁹ and the association with AN and
30 488 FAAH polymorphism.¹⁰⁰ A genome-wide correlation analysis (GWAS) using the world's
31 489 first microsatellite marker for AN was performed, and single nucleotide
32 490 polymorphisms (SNPs) showing AN sensitivity were identified in at least three gene
33 491 regions (exon 9 of the CNTN5 gene, the 3'-downstream region of the SPATA17 gene,
34 492 and TOX3 gene).¹⁰¹ Furthermore, in a GWAS using SNP markers, a previous study has
35 493 suggested that having the minor 385A allele of the FAAH gene may be protective
36 494 against restricting AN. Utilizing the knowledge of ED genetic research, it is possible to
37 495 narrow down the genes targeted in an omics analysis for ED carried out in this
38 496 research project. Omics research for EDs has only been reported in a cross-sectional
39 497 study of a few groups for AN,¹⁰² and no longitudinal study before and after treatment
40 498 including CBT has been conducted. ED omics research is now beginning to gain
41 499 traction. Based on the above, it is designed to handle multi-variables that includes omics
50 500 analysis results in brain imaging data. We reduced the dimensions using deep learning

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4 501 techniques and will perform a multiple regression analysis using machine learning
5 502 algorithms. This is expected to generate evidence for clinical markers of EDs
6 503 (diagnostic markers, therapeutic effects, therapeutic response prediction markers).

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8 504 This study has some limitations. First, the number of participants by sites may not be
9 505 uniform depending on the recruitment of patients and other situations. Also, the
10 506 number of total participants is too small, and therefore it is not possible to use machine
11 507 learning approaches to explore appropriate models without overfitting the available
12 508 data. Second, although harmonization is applied, the measurement variability may
13 509 increase because MRI scanners and imaging protocols can differ between
14 510 manufacturers. For example, an image scanned using the SRPB imaging protocol has a
15 511 lower signal-to-noise ratio and resolution compared to an image scanned using HARP.
16 512 Also, because of the presence or absence of the multi-band option, the sampling rate
17 513 can be up to three times different among facilities. Despite these limitations, such
18 514 challenging and exploratory approaches are necessary to construct a brain imaging
19 515 database of patients with eating disorders from multiple institutions as a first step.
20 516 Hopefully, by sharing data between other research teams who are collecting brain
21 517 imaging data on patients with eating disorders, we will be able to collect a sufficient
22 518 amount of data.

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25 521 **FIGURE LEGENDS**

26 522 Figure 1. Data logistics

27 523

28 524 **DECLARATIONS**

29 525 **Acknowledgments**

30 526 We are very grateful to the patients for participating in the trial dissemination. We also
31 527 thank the authors of this study and our colleagues supporting the study.

32 528

33 529 **Author contributions**

34 530 SH, YH and NK participated in the design, drafted and modified the manuscript.
35 531 YH, MI, NK, KY, YM, TA, KY, and YS are the co-investigators of the study who obtained
36 532 funding and significantly contributed to the conception or design. ASu, YE, JT, NN, TT,
37 533 HH, TN, KT, KW, HA, MG, ST, SF, and ES participated in the design and substantially
38 534 contributed to the different stages of the study's development towards its practical
39 535 conduction. ASe is the principal investigator of the study who obtained funding,
40 536 modified the manuscript, and provided substantial contributions to the study
41 537 conception and design. All authors read and approved the final manuscript.

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4 539 **Availability of data and materials**

5 540 Please contact Atsushi Sekiguchi for future proposals and requests to use the data that
6 541 will be obtained from this project.

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9 543 **Competing interests**

10 544 None declared.

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13 546 **FUNDING STATEMENT**

14
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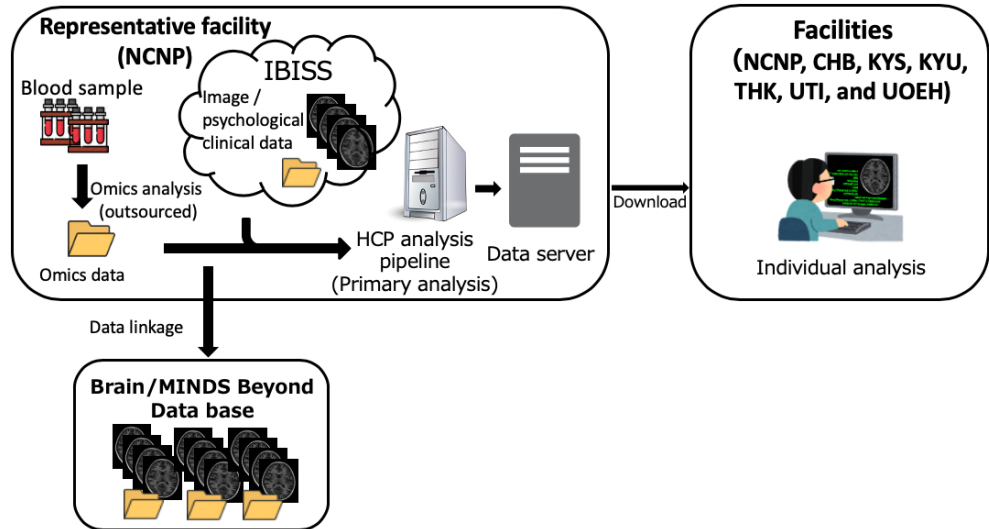


Figure1

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Supplemental table. Non-specific psychological indicators of secondary outcome

Name of psychological indicators	Content	Item questionnaire	Score range		
			Minimum	Maximum	
<i>Semi-structured interview</i>					
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
<i>Self-administered questionnaire</i>					
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

1		CTQ measures childhood trauma and it consists of five				
2	Childhood trauma questionnaire (CTQ) ^{58,59}	subscales (emotional abuse, physical abuse, sexual abuse,	28	5-point Likert	28	140
3		emotional neglect, physical neglect).		scale		
4						
5		The PDS is a self-reported measure that identifies high-				
6	Posttraumatic Diagnostic Scale (PDS) ^{60,61}	risk individuals with PTSD during an evacuation	3	4-point Likert	0	9
7		situation.		scale		
8						
9	Visual Analogue Scale (VAS) ⁶²	VAS assesses expectation to treatment.	1	-	0	100
10						
11	General functioning scale of Family Assessment			4-point Likert		
12	Device (GF-FAD) ^{63,64}	The FAD is a measure assessing family functioning.	12	scale	12	48
13						
14	Help-seeking preferences ⁶⁵	Help-seeking preferences measure attitudes to seek help	11	5-point Likert	11	55
15		for others.		scale		
16						
17		MAIA assesses the relevant dimensions of bodily				
18		awareness. It consists of eight subscales (Noticing, Not-				
19	Multidimensional Assessment of Interoceptive	Distracting, Not-Worrying, Attention Regulation,	32	6-point Likert	0	5
20	Awareness (MAIA) ^{66,67}	Emotional Awareness, Self-Regulation, Body Listening,		scale		
21		and Trusting)				
22						
23		BIS measures impulsivity scale. It consists of three				
24		subscales (attentional impulsiveness, attentional	30	4-point Likert	30	120
25	Barratt Impulsiveness Scale (BIS-11) ^{68,69}	impulsiveness, and non-planning impulsiveness).		scale		
26						
27		MOCI is administered to assess obsessive-compulsive				
28		symptoms. A higher score indicates more severe level of				
29		obsessive-compulsive symptoms. It consists of five	30	2-point Likert	0	30
30	Maudsley Obsessional-Compulsive Inventory	subscales (checking, washing, slowness repetition,		scale		
31	(MOCI) ^{70,71}	doubting conscientiousness, and ruminations).				
32						
33		AQ can use any of the dichotomous evaluations to				
34		measure autistic characteristics. The total score range is				
35		0-50. It consists of five subscales (social skills, attention	50	4-point Likert	0	50
36	Autism Questionnaire (AQ) ^{72,73}	switching, attention to detail, communication, and		scale		
37		imagination).				
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1	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
2						
3		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
4	Tri-axial Coping Scale (TAC24) ⁷⁶					
5						
6		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
7	Working Alliance Inventory (WAI-SF) ⁷⁷					
8						
9		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
10	EuroQol-5 Dimension (EQ-5D-5L) ^{78,79}					
11		The presence and severity of general anxiety was assessed using the GAD-7.	7	4-point Likert scale	0	21
12	The Generalized Anxiety Disorder Assessment (GAD-7) ^{80,81}					
13		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
14	Patient Health Questionnaire (PHQ-9) ^{82,83}					
15		SES assesses educational history. It consists of three subscales (oneself, father, and mother)	2	7-point Likert scale	1	7
16	Socioeconomic status (SES)					
17		WHO-5 is a short self-reported measure of current mental wellbeing.	5	6-point Likert scale	0	25
18	The World Health Organization- Five Well-Being Index (WHO-5) ⁸⁴					
19		SSS assesses the subjective sleepiness levels during fMRI imaging.	1	7-point Likert scale	1	7
20	Stanford Sleepiness Scale (SSS) ⁸⁵					