


# BMJ Open Neural and clinical changes of cognitive behavioural therapy versus talking control in patients with major depression: a study protocol for a randomised clinical trial

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## ABSTRACT

**Introduction** While major depression causes substantial distress and impairment for affected individuals and society, the effectiveness of cognitive behavioural therapy (CBT) in treating the condition has been established. However, the therapeutic mechanism underlying the efficacy of CBT remains unknown. This study aimed to describe a protocol for a randomised controlled trial that will measure the CBT-induced clinical and neural changes in patients with non-psychotic major depression.

**Methods and analysis** The current study is a 16-week assessor-blinded, randomised, parallel-group trial with a 12-month follow-up as part of usual depression care at an outpatient clinic. Patients aged 20–69 years with major depressive disorder will be randomly assigned to receive either CBT in addition to their usual treatment or talking control in addition to their usual treatment for 16 weeks. The primary outcome is the functional changes in the brain areas that have been associated with future-oriented thinking at 16 weeks; secondary outcomes include changes in functional brain connectivity, severity and changes in the scores of objective and subjective clinical depression symptoms, proportion of responders and remitters and quality of life. The intention-to-treat analysis will be used.

**Ethics and dissemination** All protocols and the informed consent form are compliant with the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare). Ethical Review Committees at the Keio University School of Medicine have approved the study protocol (version 3, 11 September 2017). We will disseminate research findings to scientific and general audiences through national and international conference presentations as well as lay summaries to the general public, including mental health consumer and publications in international peer-reviewed psychiatry and brain imaging journals.

**Trial registration number** UMIN Clinical Trials Registry (UMIN000018155); Pre-results.

## Strengths and limitations of this study

- This study design is the first to attempt to elucidate the neurobiological underpinnings of future-oriented pessimistic thinking in patients with major depression following the receipt of cognitive behavioural therapy (CBT).
- This study is a prospective, randomised controlled study with blinded assessment.
- This study may provide neurobiological evidence for the efficacy of CBT in the treatment of major depression.
- The study's small sample size and single-site design may affect its generalisability.

## INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder that affects an approximate 300 million people globally.<sup>1</sup> Although progress has been made in the treatment of this disorder, it has been estimated that more than one-third of patients with MDD do not respond satisfactorily to initial and subsequent antidepressant treatments, including combinations of pharmacotherapy and psychotherapy.<sup>2</sup> Thus, there is an urgent need to develop novel and more effective therapeutic strategies.

It has been established that cognitive behavioural therapy (CBT), the most published structured form of psychotherapy developed on the basis of Beck's cognitive theory,<sup>3</sup> is effective in treating depression.<sup>4 5</sup> Numerous randomised controlled studies have shown that CBT is superior to wait-list, non-specific controls and treatment as usual (TAU).<sup>6</sup> Further evidence shows that combining psychotherapy and

pharmacotherapy is more effective than pharmacotherapy alone.<sup>7</sup> Our prior randomised controlled trial showed that patients with pharmacotherapy-resistant depression benefited from supplementing their medication management with CBT.<sup>8</sup>

Patients with depression exhibit hyperactivity in the amygdala and hypoactivity in the prefrontal cortex<sup>9</sup>; it has been hypothesised that pharmacotherapy directly reduces the former (bottom-up effect), while CBT improves the latter and thus mitigates the excess activity of the amygdala (top-down effect).<sup>10</sup> Over the past decade, several published neuroimaging studies have verified the therapeutic effect of CBT. The functional connectivity between brain regions is also associated with differential treatment outcomes for medications and CBT.<sup>11</sup> However, the observed pattern of activation and connectivity in these areas varied among studies, and only one positron-emission tomography study used reliable randomised controlled trials to obtain evidence.<sup>12 13</sup>

Patients with MDD tend to endorse pessimistic thinking due to the difficulty of imagining a positive future; this predisposes them to hopelessness.<sup>14</sup> The Diagnostic and Statistical Manual of Mental Disorders 5th Edition and International Classification of Disease 10th Revision list pessimistic thinking about the future as one of the cardinal symptoms of MDD. Beck proposed that patients with MDD have specific irrational and pessimistic thoughts about future opportunities and prospects and that these negative cognitive biases cause symptoms of depression—not vice versa.<sup>15</sup> This mechanism of symptom onset differentiates MDD from other psychiatric diseases, such as bipolar disorders or schizophrenia. In accordance with Beck's cognitive theory of depression, a recent systematic review of the empirical literature indicated that patients with MDD feature a less adaptive cognitive style, characterised by concrete and specific processing (ie, more maladaptive style characterised by abstract and overly general processing)<sup>16 17</sup> and a reduced ability to imagine possible futures.<sup>18</sup> In the context of cognitive behavioural therapy, improving the patient's ability to imagine possible futures is one of the most important processes, which includes planning and predicting events and outcomes and completing between-session assignments associated with prospective memory.<sup>19</sup> Neuroimaging studies have shown that the medial frontopolar cortex, situated in the medial area of the anterior prefrontal cortex (Brodmann area (BA) 10), plays a key role in future-thinking in healthy individuals.<sup>20–22</sup> It has been proposed that BA10 serves as an integrative centre for higher order emotional, cognitive and social processes.<sup>23 24</sup> In our previous study, we found that patients with MDD were associated with a greater propensity to engage in negative thinking about the distant future and exhibited increased activation in BA10 relative to healthy individuals when imagining the distant future.<sup>25</sup> These observations suggest that patients with MDD engage in pessimistic future thinking and experience difficulty in imagining their distant future, which is associated with abnormal patterns of frontal pole activity.

Dysfunction of the frontal pole during distant future thinking may reflect negative cognition concerning the future and may thus feature potential as a neuromarker for depression as well as indicate the need for interventions, such as CBT, that challenge negative dysfunctional cognition about the future.

Despite its clinical significance, no study has reported the neurobiological underpinnings of future-oriented pessimistic thinking in patients with MDD following the receipt of CBT. We therefore planned a phase II randomised controlled trial to examine the neural and clinical changes regarding future thinking in patients treated for MDD with CBT or talking control (TC). This paper aims to describe the study protocol of the current study.

### Study aims and hypothesis

The primary aim of this study is to compare changes in brain activity underlying shifts in future thinking across 16 weeks of CBT and TC in patients with non-psychotic MDD. The secondary aim of the study is to investigate the effect of CBT on clinical and behavioural changes and shifts in neural functional connectivity relative to those of TC. The tertiary aim of the study is to assess therapy response by means of neurobiological measures.

We hypothesise that patients with MDD who receive CBT will show favourable cerebral haemodynamic changes in brain regions related to future thinking, such as diminished BA10 activity when imagining the distant future and achieve greater improvements in specific domains of cognition than those who receive TC.

## METHODS

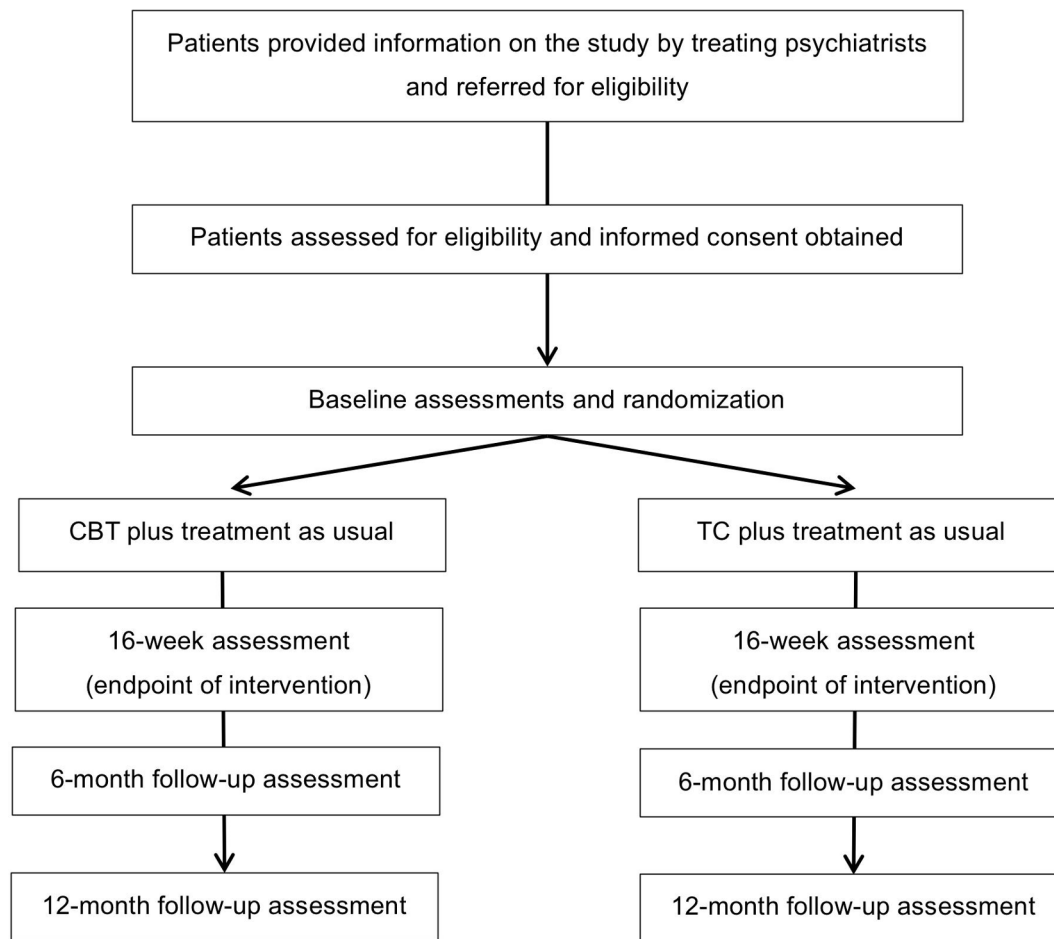
### Study design, setting and approval

The current study is a single-site 16-week assessor-blinded, randomised controlled trial of two parallel groups with a 12-month follow-up period conducted as part of usual depression care at a university teaching hospital outpatient clinic (figure 1). Random treatment allocation will be done at the individual level. Patients will be recruited at the Keio University Hospital, a university teaching hospital located in central Tokyo, Japan.

### Patients

Patients are eligible to be included in the study if they meet the following criteria: (1) outpatients with a diagnosis of MDD, as defined by the DSM 4th Edition (DSM-IV)<sup>26</sup> criteria for single or recurrent MDD without psychotic features, assessed by a trained psychiatrist with the Structured Clinical Interview for DSM-IV (SCID)<sup>27</sup>; (2) aged between 20 and 69 years; (3) experiencing at least moderate-level depression symptoms—at least 16 on the GRID-Hamilton Depression Rating Scale-17 item (GRID-HAMD<sub>17</sub>)<sup>28 29</sup> and (4) competent and able to give informed consent.

Patients will be excluded from the study if they meet the following criteria: (1) have had past or current manic or



**Figure 1** CONSORT diagram of patient flow through the study. CBT, cognitive behavioural therapy; CONSORT, Consolidated Standards of Reporting Trials; TC, talking control.

psychotic episodes; (2) have had a comorbid alcohol or substance use disorder in the 2 years prior to study entry; (3) have had any DSM-IV Axis I disorders other than MDD as the primary diagnosis, as assessed by the Mini-International Neuropsychiatric Interview (MINI)<sup>4 30 31</sup> have antisocial personality disorder; (5) have serious and imminent suicidal ideation; (6) have a serious or unstable medical illness; (7) have had organic brain lesions or major cognitive deficits in the year prior to study entry; (8) have previously completed a full CBT programme; (9) are unlikely to attend more than eight visits during the 16-week trial phase (eg, due to relocation); (10) have MRI-specific contraindications, such as a pace maker or implanted metal. This study targeted patients with MDD in general clinical settings. Because there are limited number facilities that can provide CBT, pharmacotherapy is provided as first-line treatment; patients who do not sufficiently respond to pharmacotherapy alone must seek CBT in the clinical practices equipped to provide the treatment in Japan. In addition, the purpose of this study is to examine the effect of CBT and the difference between pharmacotherapy with CBT and pharmacotherapy with TC in typical medical settings. Therefore, we included patients on concurrent medications and those with any comorbid anxiety disorders, dysthymia,

treatment-resistant depression or any personality disorders—except for antisocial personality disorder, which requires special management in general clinical settings.

## Procedures

### Recruitment

Treating psychiatrists will, during their usual consultations, provide a brochure with information about the study and invite patients to participate. If a patient shows interest in the study and provides contact details to the research team, a face-to-face appointment with a psychiatrist will be scheduled. After obtaining written informed consent, the patient will be assessed by the psychiatrist for eligibility. A diagnosis of MDD will be evaluated with the SCID Axis I Disorders,<sup>27</sup> while other Axis I disorders will be evaluated with MINI.<sup>30 31</sup> Diagnostic interviews will be conducted by the study psychiatrists with extensive training in the administration of semistructured interviews.

### Randomisation

All eligible patients will be randomly assigned to CBT with TAU or TC with TAU after the baseline assessment (1:1 allocation ratio). Block randomisation will be conducted by a computer-generated random number list using a

freeware (<http://www.randomization.com>) prepared by a research assistant with no clinical involvement in the trial. Allocation will be stratified by the severity of the baseline GRID-HAMD<sub>17</sub> score (severe vs non-severe). The cut-off GRID-HAMD<sub>17</sub> score for the randomisation will remain undisclosed until the study termination to ensure concealment.

### Baseline assessment

#### Demographic data

The detailed demographic data will be collected as a part of the baseline assessment at study entry (see online supplementary file for details).

#### Clinical and neurocognitive assessments

Acute psychopathology will be assessed at study entry by the study psychiatrists or psychologists. Objective depressive symptoms will be assessed using the 17-item and 21-item GRID-HAMD. Patients' subjective perception of depression severity will be assessed using the self-reported Beck Depression Inventory-Second Edition (BDI-II)<sup>32 33</sup> and 16-item Quick Inventory of Depressive Symptomatology Self-Reported (QIDS-SR<sub>16</sub>).<sup>34 35</sup> Health-related quality of life will be measured using the European Quality of Life Questionnaire-5 Dimensions (EQ-5D).<sup>36 37</sup> The intensity of dysfunctional attitudes will be measured using the Dysfunctional Attitude Scale (DAS).<sup>38 39</sup> Spontaneous negative self-statements and intrusive cognitions will be assessed using the Automatic Thoughts Questionnaire-Revised (ATQ-R).<sup>40</sup> Neurocognitive functioning will be assessed using the Word Fluency Test (WFT), Digit Symbol Substitution Test (DSST)<sup>41</sup> and Rey Auditory Verbal Learning Test (RAVLT).<sup>42</sup> Assessments will also be conducted at 16 weeks after randomisation as well as at 6 and 12 months after the end of the 16-week intervention.

#### Neuroimaging assessments

Before conducting the functional MRI (fMRI) measurement, all paradigms will be explained to the patients. Images will be acquired on a 3.0T GE Discovery MR750 MRI scanner with a 32-channel receiver coil in the MRI centre at the study hospital. A T2\*-weighted echo planar imaging (EPI) sequence will be made to obtain the structural images necessary to locate functional activation. Functional-task MRI images of blood oxygenation level-dependent signals will be acquired using a T2\*-weighted EPI sequence during a future-thinking task. Patients will also complete a 10 min eyes-open resting-state MRI scan. Detailed anatomical data will be collected using a high-resolution T1-weighted image. The MRI session will last about 40 min. MRI assessment will also be conducted 16 weeks after the randomisation (see online supplementary file for details).

#### Future-thinking task

Based on the Future Thinking Implicit Relations Assessment Procedure developed by Kosnes and colleagues,<sup>43</sup> we will use a modified version of the future-thinking task contextualised and adapted to Japanese culture.<sup>25</sup> The

future-thinking task uses an event design composed of four temporal conditions (distant future, near future, distant past and near past). Each run will last between 10.8 and 12.5 min, depending on the time patients take to identify each event and to press a button in response (see online supplementary file for details).

#### Treatment procedures

Treatment will be conducted in an outpatient consultation room at the study hospital. During study treatment, other depression-specific empirical psychotherapy (ie, interpersonal therapy) and electroconvulsive therapy will be prohibited.

#### Cognitive behavioural therapy

Patients allocated to the CBT group will receive a course of 16 weekly 50 min face-to-face CBT sessions, with up to four additional sessions if deemed clinically appropriate by the study therapist (maximum of 20 sessions, minimum of 8 sessions). Therapists will follow the individual CBT treatment manual for major depression<sup>44</sup>; the manual was developed based on Beck's treatment manual<sup>45</sup> with some adaptation to address the cultural characteristics of Japanese patients, such as a greater emphasis on interpersonal relationships and consideration of family as an essential part of treatment.<sup>46</sup> Problem-solving techniques and specific approaches to address interpersonal issues and cognitive behavioural avoidance are emphasised. Therapists are encouraged to refer to the relevant approaches whenever necessary. Furthermore, the therapists are encouraged to give the patients feedback regarding the case conceptualisation and collaboratively set the treatment goal during the early phase of the programme.

#### Talking control

Patients allocated to the TC group will receive a course of 16 weekly 50-min face-to-face TC sessions, with up to 4 additional sessions if deemed clinically appropriate by the study therapist (maximum of 20 sessions, minimum of 8 sessions). Therapists will follow the individual TC intervention manual for depression developed by Serfaty *et al.*<sup>47</sup> TC will be used as a comparison to evaluate the effectiveness of CBT. The manual specifies nine techniques to be used within a TC session (eg, sessions are client led, the therapist shows enthusiasm and interest towards the client, the therapist is non-judgmental) and 11 suggestions to avoid contaminating TC with other therapeutic techniques (eg, setting an agenda, applying specific cognitive psychotherapeutic and behavioural techniques, setting assignments). During TC sessions, clients will be encouraged to talk about any topic without interruption.

#### Training and supervision of therapists

Six therapists will deliver CBT and TC sessions: a psychiatrist (n=1), a psychiatric nurse (n=1) or master-level or doctoral-level clinical psychologists (n=4). All therapists have received CBT training in the Keio University Cognitive Behavioral Therapy Training and Research Program and will receive supervision throughout the study. To

ensure treatment fidelity, all therapists completed a 2-day workshop and will participate in 1-hour weekly group supervision sessions with other therapists during the study. During the group supervision sessions, therapists will present the case formulation and treatment plan. The group supervision sessions will be led by one of the authors (AN), the board member of trustees of the Japanese Association for Cognitive Therapy, who will encourage discussion of therapeutic difficulties and impasses, facilitate skill acquisition and provide peer support. To assess CBT competency, a random sample of audiotaped sessions will be rated using the Cognitive Therapy Rating Scale.<sup>45 48</sup> All therapists have also participated in 3 hours of role play to master TC techniques. The therapists will be then supervised in 1-hour weekly group supervision sessions by NK, and audiotaped material from therapy sessions will be assessed using a fidelity checklist.

#### *Treatment as usual (usual depression care by psychiatrists)*

Although appropriate flexibility will be allowed for scheduling sessions, patients will typically receive biweekly, 10–15 min consultations with the treating psychiatrist during the treatment phase, with a minimum of eight consultations during the intervention phase. Although there will be no restriction of pharmacotherapy, it should be concordant with major practice guidelines for major depression, such as the American Psychiatric Association practice guideline<sup>5</sup> (see online supplementary file for details).

#### *Follow-up phase treatment procedure*

There will be no restrictions on treatment options for the patients who receive care for their depression from the treating psychiatrists during this phase. Thus, the treating psychiatrists are allowed to refer the patients to appropriate mental health professionals for psychotherapy or electroconvulsive therapy if they deem it clinically appropriate. However, those who receive depression-specific empirical psychotherapy or electroconvulsive therapy will be recorded, and these will be considered deviations from the study protocol. However, the patient will not be considered to have dropped out of the study at this phase and will still receive protocol assessments.

#### *Discontinuations*

If a patient meets any one of the discontinuation criteria, the treating psychiatrist will discontinue the study intervention (see online supplementary file for details).

#### *Outcome measures*

The outcome measures are shown in [table 1](#).

#### *Primary outcome*

The primary outcome is the neural change in functional brain activity, especially in the areas associated with future thinking (eg, the BA10), as measured by fMRI data obtained from baseline (at randomisation) to 16 weeks postrandomisation (the end of the intervention).

#### *Secondary outcomes*

##### *Functional connectivity outcomes*

- ▶ Functional resting-state activity will be recorded. The change of functional connectivity in the brain areas related to future thinking from the baseline to 16 weeks postrandomisation will be assessed.

##### *Behavioral outcomes*

- ▶ All participant responses (yes or no) for each trial during the future-thinking task of the fMRI will be recorded. Change in the ratio of responses with negative valence to the total responses under each temporal condition from baseline to 16 weeks postrandomisation will be calculated.
- ▶ Reaction time (RT) will be calculated from the time at which the sentence is shown on the second slide to the time at which the participant pushes the button to respond. The change in RT to prompts of positive and negative valence under each temporal condition from baseline to 16 weeks postrandomisation will be evaluated.

##### *Clinical outcomes*

Patients will be assessed at four time-points: baseline (at randomisation); 16 weeks postrandomisation and 6 and 12 months after the end of 16-week intervention. All assessors will be blinded.

- ▶ The alleviation of depression symptoms as measured by changes in the total clinician-rated 17-item GRID-HAMD scores. All the assessors (psychiatrists and licensed clinical psychologists) have received extensive GRID-HAMD training and achieved excellent inter-rater reliability (Interclass correlation coefficients (ICC)=0.94–0.98). The GRID-HAMD will be conducted by central assessors by telephone. Patients will be instructed not to disclose their allocated treatment in the periodical assessments.
- ▶ The severity of subjective depression symptoms will be measured using the BDI-II and QIDS-SR<sub>16</sub>.
- ▶ The proportion of responders, defined as those with a 50% or greater reduction on the 17-item and 21-item GRID-HAMD, BDI-II and QIDS-SR<sub>16</sub> relative to baseline will be analysed.
- ▶ The proportion of patients who achieve remission, defined as those with a 17-item GRID-HAMD score of  $\leq 7$ ,<sup>49</sup> BDI-II score of  $\leq 13$ <sup>50</sup> and QIDS-SR<sub>16</sub> of  $\leq 5$ <sup>34</sup> will be analysed.
- ▶ The degree of health-related quality of life will be measured using the EQ-5D.
- ▶ The pattern of automatic thought will be measured using the ATQ-R.
- ▶ The intensity of dysfunctional attitudes will be measured using the DAS.

##### *Neurocognitive evaluation*

- ▶ The level of neuropsychological function of the frontal cortex will be measured using the WFT and DSST.

**Table 1** Schedule of the assessments

Time-point	Enrolment	Baseline/ randomisation	Intervention		Follow-up	
	-1	0	1-15 weeks	16 weeks	After 6 months	After 12 months
<b>Enrolment</b>						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
<b>Interventions</b>						
CBT plus treatment as usual			↔			
TC plus treatment as usual			↔			
<b>Assessments</b>						
Demographic data	X					
<b>Diagnostic assessments</b>						
SCID-I	X					
MINI	X					
Functional MRI		X		X		
<b>Psychopathological assessments</b>						
GRID-HAMD		X		X	X	X
BDI-II		X		X	X	X
QIDS-SR16*		X	X	X	X	X
EQ-5D		X		X	X	X
DAS		X		X	X	X
ATQ-R		X		X	X	X
WFT		X		X	X	X
DSST		X		X	X	X
RAVLT		X		X	X	X

\*QIDS will also be assessed at each visit during the intervention phase.

ATQ-R, Automatic Thoughts Questionnaire-Revised; BDI-II, Beck Depression Inventory-Second Edition; CBT, Cognitive Behavioural Therapy; DAS, Dysfunctional Attitude Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition; DSST, Digit Symbol Substitution Test; EQ-5D, European Quality of Life Questionnaire-5 Dimensions; GRID-HAMD, GRID-Hamilton Depression Rating Scale; M.I.N.I, Mini-International Neuropsychiatric Interview; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology Self-Reported; RAVLT, Rey Auditory Verbal Learning Test; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; TC, talking control; WFT, Word Fluency Test.

- ▶ The level and change in the degree of neuropsychological function of the lateral cortex will be measured using the RAVLT.

### Sample size estimation

This trial is not confirmatory, and the sample size is mainly determined by taking account of feasibility. According to a review of sample size for fMRI studies, at least 12 subjects are required to achieve 80% power at the single-voxel level for typical activations to achieve a liberal threshold of 0.05; after correcting for multiple comparisons, the number of subjects should be larger to maintain this level of power.<sup>51 52</sup> Therefore, we estimated our target number of patients will be 19 per group (a total of 38 patients) in which some exclusions up to 20% are allowed.

### Statistical analysis

#### Task fMRI analysis

All preprocessing and analyses of imaging data will be conducted using the Statistical Parametric Mapping 12

(SPM12) implemented in MATLAB. Preprocessing will be conducted using the standard procedure, including slice-time correction, realignment, coregistration, spatial normalisation and smoothing. First-level analyses will be performed by an event-related model with four condition types: distant future, near future, distant past and near past. A general linear model will be used for statistical parametric maps. Subsequent second-level analyses will be performed on the SPM contrast images of the first-level canonical Hemodynamic Response Function (HRF) responses using paired t-tests. Group, time-point and group-by-time interaction will be included in the model as factors. The compound symmetry will be used as a covariance structure. Kenward-Roger adjustment for the denominator df will be used. P values of <0.001 will be considered statistically significant. Furthermore, region of interest analyses focused on the brain areas related to future thinking will be conducted to correct for multiple comparisons (see online supplementary file for details).

### Resting fMRI analysis

Resting-state fMRIs will be performed to explore functional connectivity in brain regions related to future thinking (see online supplementary file for details).

### Clinical and behavioural data analysis

The analysis population in this study will be the intention-to-treat group, and all randomised patients will be included. For continuous outcomes, the least squares means and their 95% CIs will be estimated using a mixed-effects model for repeated measures to detect changes from the baseline, which contains the treatment group, week and group-by-week interaction as fixed effects with an unstructured covariance matrix among the time-points; Kenward-Roger df adjustment will be used. In addition, the model with stratified factors will be used for a sensitivity analysis. Mean changes for each group at each time-point and mean between-group differences will be estimated using appropriate contrasts in the MMRM which contains baseline value (1 df), the treatment group, week and group-by-week interaction as fixed effects. Notably, missing values will not be inputted. For categorical outcomes, cross-tables between baseline and each time-point will be created for each group. Categorical outcomes will be analysed using the  $\chi^2$  test or Fisher's exact test, and relative risks and their 95% CIs will be calculated. For binary outcomes, we will not use such likelihood-based model because the amount of information is limited with small sample binary data. Summary statistics (means and SD) of patient characteristics will be calculated. When appropriate, a t-test and Mann-Whitney U-test or analysis of covariance will be used to compare baseline continuous outcomes (means). The significance level will be set at 0.05 (two tailed). While the background factors might be controlled by randomisation, subgroup analyses will be conducted to determine whether any factors impacted the outcome. We will also perform per-protocol analyses in addition to the intention-to-treat analyses for primary outcomes to assess the influence of missing data on the results and other reasons accounting for non-conformance to the protocol.

Statistical analyses will be performed using SAS V.9.4 (SAS Institute).

### Data collection and management

Please refer to the online supplementary file for information on data collection and management.

### ETHICS AND DISSEMINATION

Before participation, all subjects will provide voluntary written informed consent after a discussion of the potential benefits and risks of participation (see online supplementary file for more details).

We will disseminate study findings to scientific and general audiences through major national and international medical conference presentations and by submission for publication in international peer-reviewed

psychiatric and brain imaging journals using the International Committee of Medical Journal Editors author guidelines. Professional writers will not be used. The study will be reported according to the Consolidated Standards of Reporting Trials statement. We will also prepare lay summaries of study findings for dissemination to mental health consumer groups and for media release to the general public. We are not permitted to share study data with other individuals for any purpose without specific approval from the relevant data custodians and ethical review committee.

### Patient and public involvement

Patients and the public were not involved in the development of the research questions, selection of outcome measures, study design, patient recruitment or conduction of the study. The burden of intervention was assessed by representatives of patient associations participating in the ethical review committee. As mentioned in the individual consent form, participants may obtain access to the final results of the study through the principal investigator.

### DISCUSSION

The current study aims to provide a means by which to obtain new evidence of the neural and clinical effects of CBT for major depression in general psychiatric care settings. The study design is expected to detect meaningful differences in neural and clinical effectiveness outcomes. This study is distinguished from previous studies in that the design uses TC as a control group to evaluate the effectiveness of CBT, standardises psychiatric interviews to assess depression symptomatology, recruits patients with medium-to-severe depressive symptoms and evaluates the long-term effects of CBT for up to 12 months.

The study is subject to some challenges and limitations. The sample size is small due to the limited MRI machine time. We are aware that the single-site design compromises the generalisability of the results. We will not control for medication which may affect brain activity or connectivity. Although background factors are controlled by randomisation, the results of this study will be interpreted with caution. Nevertheless, this is the first design of a randomised controlled study to attempt to elucidate the neurobiological underpinnings of future-oriented pessimistic thinking using fMRI in patients with MDD following the receipt of CBT. The results of this study will improve the evidence-based knowledge of patients with depression.

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**Contributors** AN and NK conceived and designed the study. NK drafted the protocol manuscript and is organising the study. SU, YT, HT and TK refined the study protocol and study implementation. SU, YT and TA have provided methodological and statistical expertise. AN, NK and TA will conduct the statistical analyses. AN has provided CBT expertise and supervision of the therapists. AN has drafted the grant and is responsible for the implementation of the study. AN has been responsible for study management, staff training and supervision. NK, CK and YS have managed day-to-day study responsibilities, including monitoring recruitment, collecting data and liaising with recruitment sites. CK, DM, SN, SM, MO and YN will provide therapy. DM and NI will conduct data management and study monitoring. MM is the director of the site and provides clinical expertise and on-site management of the study. All authors critically reviewed and approved the final version of the manuscript.

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**Competing interests** AN developed and wrote the Japanese CBT manual for depression and is involved in the National CBT Training and Supervision Project funded by the Japanese Ministry of Health Labour and Welfare.

**Patient consent for publication** Not required.

**Ethics approval** Approval of the study protocol was obtained from the Ethical Review Committee of Keio University School of Medicine (reference number 20150070).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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