

BMJ Open Cognitive deficits in treatment-resistant depression: protocol for a systematic review and meta-analysis

Eivind Haga Ronold  ^{1,2} Daniel Jensen  ³ Anders Lillevik L Thorsen  ^{1,4,5} Rune Raudeberg  ¹ Leif Oltedal, ^{2,5} Åsa Hammar, ^{1,6,7} Marco Hirnstein  ¹ Katie Douglas  ^{8,9} Richard Porter  ^{8,9} Maximilian Kiebs  ^{10,11}

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ABSTRACT

Introduction Major depressive disorder (MDD) is a major global healthcare challenge. This is, in part, due to the lack of treatment response and chronic course of MDD. Such a course of illness is often termed treatment-resistant depression (TRD) and is seen in over one-third of people with MDD. Reasons for treatment resistance are not well established, nor is the definition of TRD. Duration and severity of depression, however, are associated with TRD and are also associated with cognitive deficits. Thus, TRD could be particularly prone to cognitive deficits and at heightened risk for neuroprogression. While the cognitive profile of MDD has been investigated in several systematic reviews, no systematic review of cognition in TRD exists to date. The present study will fill this gap in the literature. It is expected that TRD will show more severe cognitive deficits than generally reported in MDD and deficits in all cognitive functions are expected.

Methods and Analysis A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be performed of the databases Embase, Pubmed/MEDLINE, PsychINFO and Cochrane including peer-reviewed studies on humans using standardised cognitive tests. Pilot searching was performed in January 2025 and the full search will be commenced in June 2025, with additional searches following completion. Where sufficient data are reported, a meta-analysis comparing deficits in TRD with MDD and healthy control participants will be performed; alternatively, effects based on norms will be calculated. Meta-regression, subgroup and sensitivity analyses will be conducted to explore moderators that are sufficiently reported in the literature. The quality of studies will be assessed by the Newcastle-Ottawa Scale.

Ethics and dissemination Ethical approval is not necessary to perform the study, and results will be presented at a suitable conference and published in a peer-reviewed journal.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first review focusing on cognitive deficits in treatment-resistant depression (TRD), and by including data from studies with common treatments for TRD, the sample size is increased.
- ⇒ Using normative comparisons for effect size estimates will increase the number of comparisons possible.
- ⇒ The review will investigate the effects of different levels of treatment resistance and available clinical variables on cognitive outcomes.
- ⇒ Focusing on peer-reviewed studies in English might omit grey literature and published studies in other languages.
- ⇒ This meta-analysis depends on the quality of the studies conducted in the field and may be subject to publication bias—which will be examined.

conventional treatments. In their paper, treatment-resistant depression (TRD) was defined as two or more unsuccessful antidepressant treatments, despite adhering to the dose and duration prescribed. The causes and mechanisms of TRD are not well understood, but a recent systematic review found that duration and severity of depression were most frequently associated with TRD.³ Recommended treatments for TRD include pharmacological augmentation (with an additional antidepressant or atypical antipsychotic), electroconvulsive therapy (ECT) and ketamine.² Cognitive deficits occur in MDD⁴ and could be more severely affected in TRD.⁵ Reasons for these more severe cognitive deficits may relate to the cognitive effects of the treatments for TRD such as ECT and polypharmacy,^{6,7} as well as the clinical characteristics of TRD, like duration and severity of MDD.^{4,8–11} Cognitive deficits influence the course of MDD from first onset,^{12–15} and recent findings suggest they could be particularly relevant for TRD.⁵ Deficits present following treatments like ECT could be understood in



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For numbered affiliations see end of article.

Correspondence to
Dr Maximilian Kiebs;
m.kiebs@uol.de

light of deficits present during TRD (eg, difficulties with memory).¹¹ Several studies have also found that cognitive deficits may influence treatment response.^{4 16} A systematic review and meta-analysis of how deficits manifest in TRD is therefore needed.

Cognitive deficits are central symptoms of MDD. Both the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders list difficulty concentrating and making decisions, as well as motor slowing, as symptoms associated with MDD.^{17 18} Previous meta-analyses of neuropsychological test data have found broad, mostly small to medium deficits, in most cognitive functions including processing speed and attention, executive functions and memory.¹⁹⁻²¹ Importantly, these deficits tend to persist in remission and some aspects of cognition are associated with the number of previous episodes of MDD.^{8 11} Indeed, the neuroprogressive aspects of depression,²² entailing gradual worsening of neural and behavioural functioning, are of particular concern,^{4 23} and the links between disability, somatic and neurological conditions and MDD are well established.^{24 25} TRD could be particularly susceptible to this exacerbation,^{2 3} but the nature of this is not known. However, Alzheimer's disease, a condition defined by cognitive and functional impairment, is associated with depressive symptoms, and MDD has recently been declared a preventable risk factor for the condition.²⁶ In addition, residual symptoms are associated with a higher risk of relapse to MDD.²⁷ All this points to significant negative effects of persisting depressive symptoms and the importance of promoting complete remission for as many people as possible. In conclusion, investigating neuropsychological aspects of treatment resistance could be important for understanding and preventing disability and chronic disorders associated with MDD.

Despite several systematic investigations on other aspects of the cognitive profile in MDD, much remains unknown. Roca *et al*²⁸ and Porter *et al*²⁹ reviewed the published meta-analyses on depression and found evidence for broad impairments present from the first onset of MDD, with an indication of more impairment in subtypes of depression (eg, 'melancholic'), and that psychotropic medications could affect cognition. This was supported by two meta-analyses by Zaninotto *et al* who found more cognitive impairments in psychotic depression, and in patients with melancholic depression, compared with patients with MDD.^{30 31} Other meta-analyses find more cognitive deficits in bipolar disorder, particularly bipolar I with psychosis^{32 33} compared with in unipolar depression. Thus, recent meta-analyses point to a severity-impairment relationship between disorders and deficits,⁶ and subtypes with severe MDD are more at risk. Two meta-analyses have found more deficits in older patients,⁹ also with TRD.²⁰ Parkinson *et al*¹⁹ found moderate to large deficits in depressed participants on all the neuropsychological tests examined in their meta-analysis, but that there were significant heterogeneity in most of these tests. Understanding the heterogeneity of cognitive deficits

is important for understanding MDD, and for personalising and improving treatments and interventions for subgroups such as patients with TRD.

A systematic review and meta-analysis are proposed to (a) *describe the cognitive profile in TRD compared with MDD and healthy control participants* and (b) *examine the moderating factors for these differences*. It is expected that TRD will show larger cognitive deficits than MDD in general,¹⁹⁻²¹ more comparable to the previous meta-analyses of psychotic depression,³⁰ melancholic depression³¹ and bipolar disorders.³² Moderate to large deficits in all cognitive domains are expected, with the largest effects on memory.^{11 19} As there is limited consensus on how to define TRD,² studies using different definitions as well as different treatments for TRD will be included, and the identified differences will be used as moderators. Other available clinical and demographic variables will be examined in relation to the cognitive profile in TRD, and deficits are expected to increase with age, number of episodes, severity and duration.

METHODS

This protocol proposes a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^{34 35} The review was preregistered on the International Prospective Register of Systematic Reviews (PROSPERO; record no. CRD42024538898).

Research questions

- ▶ How do MDD patients with TRD differ from MDD patients without TRD and healthy control participants on cognitive measures?
- ▶ How do clinical and demographic factors relate to the different cognitive profile seen in TRD?

Studies included

Peer-reviewed human studies in the English language with cognitive test data in TRD until June 2025 will be included (there is no lower time limit). Studies *in press* will be included. As the majority of published research is in English, the review will be limited to studies in this language. The main outcomes of interest are differences between MDD with and without TRD, as well as TRD and healthy controls, across cognitive domains. Clinical and demographic data will also be collected in order to conduct an exploratory meta-regression, if study numbers permit. Baseline data from studies investigating cognition in common treatments for TRD (ECT, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, (es)ketamine, atypical antipsychotics, serotonergic psychedelics, and other novel antidepressants/ augmentations) will be included. Studies must include at least one standardised and normed clinical neuropsychological or cognitive behavioural test measure. If the same sample was used in several publications, the most complete report (in terms of number of participants

and tests) will be included. Only studies with sufficient results for group analysis will be included; reviews, editorials, conference abstracts and case studies/series will be excluded.

Search strategy

Searches will be done through Embase, MEDLINE, PsycINFO via OVID, and Cochrane Library for papers published until June 2025. A full search strategy including all search terms and limits is available in the (online supplemental file 1). The university librarian at the medical faculty of the University in Bergen was consulted for designing search strategies for the various databases and these terms were piloted by two independent raters in January 2025 (EHR, DJ). Following extraction, the search will be repeated for any potential new papers. Reference lists of relevant papers and meta-analyses will be consulted. The search will be limited to studies investigating humans.

Participants

Adults (≥ 18 years old) diagnosed with MDD (bipolar disorder with a current depression will be allowed) according to any version of The Diagnostic and Statistical Manual of Mental Disorders¹⁷ and the International Classification of Diseases¹⁸ will be included. Patients should be explicitly or implicitly described in the study design as treatment-resistant (>1 unsuccessful treatment) and/or receiving treatments for TRD (eg, ECT/neurostimulation, psychopharmacological/experimental as described above). Comorbid psychiatric disorders will be allowed. Studies recruiting mixed diagnosis samples (eg, schizophrenia/psychosis spectrum) will be contacted to provide data on the mood disorder group only and excluded if this is not provided. Exclusion criteria will be primary diagnoses other than MDD (or bipolar with current MDD), <1 year post-partum depression, populations with somatic and neurological conditions like brain injuries that impair cognition (eg, head trauma <1 year, stroke, epilepsy), and ongoing heavy substance abuse.

Outcomes

Group differences in cognitive functions as measured by clinical neuropsychological and cognitive tests quantified as an effect size will be the main outcomes of this study. For studies with unequal sample size, weighted Hedges g will be calculated. Findings will be categorised into cognitive domains in accordance with standard works in neuropsychology and recent meta-analyses of neuropsychological functioning in MDD including, motor function, processing speed, attention, learning and memory (verbal/visual), executive functions (inhibition, shifting, and updating/working memory), language, general intellectual ability/reasoning, and measures of global cognition.^{8 11 36 37} Differences in variance on cognitive test scores will be investigated in the groups. Effect sizes for individual tests and different outcome measures from individual tests will be presented where sufficient reporting

exists.³⁸ For studies without a control group, normative values will be used to calculate/estimate effect sizes from the most common neuropsychological manuals.^{39 40} Raw scores for calculation will be requested from the study authors.

The association between cognitive function, clinical variables and demographic data in MDD with TRD versus MDD without TRD, and MDD with TRD versus healthy controls will be secondary outcomes. This includes depressive symptoms, polarity, information about treatment (eg, use of ECT), current treatment (eg, psychopharmaceuticals) and other clinical characteristics (eg, onset and length of depression, outpatient status). Demographic characteristics (eg, sex, years of education, age, employment, marital status, ethnicity) will be recorded (used to compare TRD with MDD and/or healthy controls and, might thus, represent risks for TRD). Where this information is not reported, authors of the study will be contacted requesting this information. The implementation of norms of healthy control groups for calculating effect sizes will be explored as a moderator. Types of criteria used for defining TRD will be recorded. Criteria for included studies will be classified according to the Maudsley Staging Method,² where points for treatment, duration and severity are quantified (ranging from 1 to 15, and a mean will be calculated from reported variables where incomplete data exist).

Data collection

Selection process

Abstracts and titles will be screened for inclusion criteria. If insufficient information is reported, the full paper will be consulted. Two of the authors will independently screen for studies (EHR, DJ) and any discrepancies will be resolved by discussion with a third author (MH).

Extraction process

Data will be extracted, duplicates will be removed and the remaining studies will be assessed through specialised software (eg, Rayyan) by two independent raters (EHR, DJ) and Cohen's kappa will be calculated to assess inter-rater reliability. Participants and study characteristics will be recorded in a standardised form where outcomes are organised, including M and SD from cognitive tests, participant characteristics, control conditions (HC/MDD/other clinical group/none), and used to assess clinical and methodological heterogeneity.

Participant characteristics

Participant characteristics will be recorded in the same standardised form as described above: age (M, SD, range), sex (n male/female), ethnicity, years of education (M, SD), TRD definition (explicit/implicit), Maudsley criteria (1–15), symptom severity (eg, MADRS), psychiatric comorbidity (yes/no/not discussed), psychiatric comorbidity type (eg, anxiety/personality/neurodevelopment), somatic comorbidity (yes/no/not discussed), patient status (outpatient/inpatient/mixed), psychotic

depression excluded (yes/no), type of MDD (bipolar/psychotic/melancholic/remitted), medication status (unmedicated/mono/augmentation), previous treatment (eg, ECT), age of onset, number of episodes (n) and duration of illness (n months).

Data synthesis

Data analysis will be conducted using R statistical software with the packages meta and metafor. Alpha values of 95% will be used for assessing significance. Heterogeneity will be tested using Q and I^2 since this is expected to be significant. Hedges g will be used to compare MDD with TRD and MDD without TRD, as well as MDD with TRD and healthy controls (or normative data) on cognitive tests. Weighted Hedges g will be used for groups with unequal sample size. Sensitivity analyses will be performed and meta-regression will be used to explore available participant characteristics where sufficient data are reported. Alternatively, this data will be presented in a table.

Risk of bias

The Newcastle-Ottawa Scale for risk of bias and quality in non-randomised controlled studies will be used to assess for bias and quality of studies.⁴¹ Studies will be rated from low, intermediate to high risk of bias. Sensitivity analyses will be performed.

Patient and public involvement statement

There is no patient or public involvement at the moment. The importance of cognitive deficits for patients has been documented in previous investigations.⁴² Results from the proposed study will be shared in user panels for patients receiving treatment for TRD. It will be used as a basis for designing interventions for improving cognitive function in TRD and following neurostimulation treatments.⁴³

Strengths and limitations

This is the first proposed systematic review of the cognitive profile in TRD. Cognitive functioning in TRD is of clinical importance due to the serious course of illness in this disorder. Since there is no consensus on the definition of TRD, there will likely be heterogeneity in the results. However, statistical measures seeking to control for this will be employed, and the review will contribute to the understanding, management and future treatment of this condition.

ETHICS AND DISSEMINATION

No ethical approval is needed to perform the proposed study. Results will be presented at conferences and published in an international peer-reviewed journal.

Author affiliations

¹Department of Medical and Biological Psychology, University of Bergen Faculty of Psychology, Bergen, Norway

²Mohn Medical Imaging and Visualization Centre, Department of Radiology, Department of Radiology, Haukeland University Hospital, Bergen, Norway

³Betanien Sykehus, Bergen, Norway

⁴Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

⁵Department of Clinical Medicine, University of Bergen, Bergen, Norway

⁶Department of Clinical Sciences Lund Psychiatry, Lund University, Lund, Sweden

⁷Office for Psychiatry and Habilitation, Psychiatry Research Skåne, Skåne, Sweden

⁸Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

⁹Specialist Mental Health Service, Canterbury District Health Board, Christchurch, New Zealand

¹⁰Dept. of Psychiatry and Psychotherapy - School of Medicine and Health Sciences Carl von Ossietzky University of Oldenburg, Oldenburg, Germany

¹¹Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany

X Katie Douglas @KMD_research

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Contributors EHR conceptualised and wrote the draft of the protocol with MK, and EHR is the guarantor. DJ wrote excerpts and commented on draft. ALLT, MH, LO, RP and KD commented on draft and provided ideas for methods. RR, MH and ÅH commented on draft. All authors approved the manuscript for publication.

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ORCID iDs

Eivind Haga Ronold <http://orcid.org/0000-0002-7081-5147>

Daniel Jensen <http://orcid.org/0000-0001-6391-6612>

Anders Lillevik L Thorsen <http://orcid.org/0000-0003-2836-5223>

Rune Raudeberg <http://orcid.org/0000-0003-0919-6479>

Marco Hirnstein <http://orcid.org/0000-0002-6291-0929>

Katie Douglas <http://orcid.org/0000-0002-5344-2959>

Richard Porter <http://orcid.org/0000-0002-8695-3966>

Maximilian Kiebs <http://orcid.org/0000-0002-4216-2679>

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