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Neuroimaging and Neurophysiologic Biomarkers for Mental Health: An Evidence Map

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises 4 ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the Office of Research and Development working group for the Commander John Scott Hannon Veterans Mental Health Care Improvement Act, Public Law 116-171, section 305 (SHA305). The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, and the review team. The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix C for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABBREVIATIONS TABLE

AHRQ EPC	Agency for Healthcare Research and Quality Evidence-based Practice Center
ASL	Arterial spin labeling
BDI	Beck Depression Inventory
CAPS	Clinician Administered PTSD Scale
DAISY	DistillerSR's Artificial Intelligence System
DTI	Diffusion tensor imaging
ECT	Electroconvulsive therapy
EEG	Evoked potentials and electroencephalogram
ESP	Evidence Synthesis Program
fMRI	Functional magnetic resonance imaging
GOSE	Glasgow Outcome Scale-Extended
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
KQ	Key Question
MADRS	Montgomery-Asberg Depression Rating Scale
MEG	Magnetoencephalography
MeSH	Medical Subject Headings
MINI	Mini-International Neuropsychiatric Interview
MRI	Magnetic resonance imaging
OCD	Obsessive compulsive disorder
PCL	PTSD Checklist
PET	Positron emission tomography
PHQ	Patient Health Questionnaire
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
rTMS	Repetitive transcranial magnetic stimulation
SCID	Structured Clinical Interview for DSM
SHA305	Commander John Scott Hannon Veterans Mental Health Care Improvement Act, Public Law 116-171, section 305
SPECT	Single photon emission computed tomography
SUD	Substance use disorder
TBI	Traumatic brain injury
TBS	Theta burst stimulation
tDCS	Transcranial direct current stimulation
US	United States
VA	Department of Veterans Affairs
Y-BOCS	Yale Brown Obsessive Compulsive Scale
YMRS	Young Mania Rating Scale

EXECUTIVE SUMMARY

Key Findings

- Many studies evaluated the use of structural or functional MRI in diagnosis and prognosis of depression, but there were important methodological concerns:
  - Nearly all diagnostic studies were cross-sectional, small in size, and included participants with variable past histories of symptoms and treatments.
  - Prognostic studies mostly focused on response to antidepressants, and were also generally small.
- A substantial number of studies used EEG for diagnosis and prognosis of depression, but these had similar methodological issues as MRI studies.
- Fewer studies examined bipolar disorder, PTSD, TBI, SUD, OCD, and anxiety disorders; they were mostly focused on diagnosis and were cross-sectional and small in size.
- 14 studies included US Veterans, addressing PTSD, TBI, and/or SUD:
  - All 11 diagnostic studies were cross-sectional, 2 prognostic studies were cohorts, and 1 was an RCT.

INTRODUCTION

Mental health conditions and traumatic brain injury (TBI) are common among Veterans and often negatively impact Veterans, their families, and their communities. The Department of Veterans Affairs (VA) devotes considerable resources to treating these conditions and improving diagnosis and treatment outcomes is an ongoing VA priority.

There have been substantial advancements in precision medicine, specifically the use of biomarkers and/or genetics in diagnosis, prognosis, and tailoring treatments for medical conditions. There are also several ongoing large-scale population-based studies to advance precision medicine, including the VA's Million Veterans Program. In the context of mental health, precision medicine has involved assessment of brain structure and functioning, as well as genetics and serum biomarkers. Despite advances in the development and availability of these tools, challenges to precision medicine for mental health conditions remain. These include complex and heterogeneous clinical phenotypes, high cost and technical difficulty of obtaining neuroimaging and neurophysiologic data, and differing assessments of symptoms and treatment response. Although these challenges have contributed to concerns about the reproducibility and validity of findings, results of more recent efforts to systematically collect and examine large neuroimaging datasets have yielded more promising results. Thus, future work in this area may yet produce insights that improve diagnosis and treatment outcomes in mental health.

This evidence review was requested by the VA Working Group to implement the Commander John Scott Hannon Veterans Mental Health Care Improvement Act (P.L. 116-171), Section 305: "Precision Medicine for Veterans Initiative" (SHA305). SHA305 tasks the VA with developing and implementing a precision medicine initiative focused on brain and mental health biomarkers.

To support the VA SHA305 Working Group, we conducted an evidence map to better understand characteristics of existing evidence on relationships between brain structure and functioning, and mental health conditions and TBI. An evidence map is well suited to address a broad scope covering multiple conditions and numerous neuroimaging and neurophysiological techniques, particularly when some of the evidence base may consist of more exploratory studies. An evidence map is also appropriate for meeting the overall goals of informing research policy and potential clinical demonstrations.

In this report, we provide descriptive information about the number and types of studies that address a wide range of neuroimaging and neurophysiologic assessments for diverse mental health conditions and TBI. We also highlight weaknesses and gaps in the evidence, as determined by the volume and characteristics of studies.

METHODS

Key Question (KQ)

KQ: What are the quantity, distribution, and characteristics of evidence assessing the accuracy and utility of neuroimaging and neurophysiologic biomarkers in the diagnosis and clinical management of the following conditions:

a) Depression
b) Anxiety
c) Posttraumatic stress disorder (PTSD)
d) Substance use disorder (SUD)
e) Bipolar disorder
f) Traumatic brain injury

Data Sources and Searches

We searched for peer-reviewed English language articles from January 2010 to April 2022 in MEDLINE and Embase. We used Medical Subject Headings (MeSH) and title/abstract terms for neuroimaging and neurophysiological tests and conditions of interest. We also searched websites for VA ESP and AHRQ EPC programs to identify relevant reviews.

Study Selection

Abstracts were screened with the assistance of DistillerSR's Artificial Intelligence System (DAISY) in 2 separate phases (see Methods section for full details).

For full-text review, we undertook 2 initial pilot rounds in which all reviewers separately determined eligibility for 10–15 articles in each round. We discussed articles to reach consensus on eligibility, with further clarification on operationalization of inclusion and exclusion criteria. Eligibility of remaining articles was determined by 1 reviewer, with ~50% of these also undergoing evaluation by a second reviewer.

Eligible populations included adults with at least 1 of the conditions of interest, as noted in KQ above. Eligible articles evaluated at least 1 neuroimaging or neurophysiological test of interest (*eg*, magnetic resonance imaging [MRI], including functional MRI [fMRI], and evoked potentials and electroencephalogram [EEG]) for diagnostic accuracy, clinical prognosis, and/or treatment response. Exclusion criteria included pediatric populations, evaluation of symptoms or cognitive functioning only in the context of neurodegenerative conditions or intracranial injury. We also excluded studies attempting to evaluate prognosis using exclusively cross-sectional data.

Data Abstraction and Assessment

We abstracted the following data from all eligible studies: population characteristics (*eg*, condition and method of diagnosis, sample size, demographic data (*eg*, mean or median age, proportion of women, focus on Veterans or combat exposure); neuroimaging test and/or EEG being evaluated (and genetic data if used); outcomes addressed (clinical diagnosis and/or prognosis); and study design (*eg*, cross-sectional or cohort, analytic methods used to assess diagnostic or prognostic accuracy). To verify accuracy of abstracted results, data from ~50% of articles were over-read by a second reviewer.

Quality Assessment and Summary of Results

We did not conduct formal quality assessment of eligible studies included in this report. We also did not undertake a formal synthesis of study results. Our results summaries are organized by the conditions of interest and focus on describing the characteristics of study populations, outcomes (clinical diagnosis, prognosis, and/or treatment response), and study designs (including analytic methods) of eligible studies.

RESULTS

Overview

From 50,989 unique search results, we identified 313 primary studies and 30 systematic reviews. At abstract screening, 47,586 results were excluded, with 54% of these based on low scores from a machine-learning algorithm (see Methods). Most eligible primary studies and systematic reviews addressed depression ($k = 236$, 69%), while fewer studies and reviews evaluated other conditions. Only 2 studies evaluated genetic data in addition to neuroimaging or neurophysiologic data. Three-quarters of primary studies used MRI-based imaging techniques ($k = 236$, 75%), while a fifth used EEG data ($k = 68$, 22%). For multiple conditions, there were none or few studies ($k \leq 5$) examining either diagnosis or prognosis.

Most primary studies had small sample sizes, with only 9 having more than 500 participants (range 555–4,541). Two-thirds of primary studies examined diagnosis ($k = 200$), 110 evaluated prognosis, and 3 addressed both diagnosis and prognosis. Most studies included young and middle-aged participants; only 5 studies had participants with mean ages of 65 or older and all of these addressed depression.

Depression

MRI-based Imaging Techniques (Structural and Functional MRI, DTI, and ASL)

Of 104 studies using MRI-based techniques to address diagnosis of depression, most used structural MRI ($k = 49$), fMRI ($k = 48$), or both ($k = 1$). A few studies used other MRI-based

techniques like diffusion tensor imaging (DTI, $k = 6$) and arterial spin labeling (ASL, $k = 2$). Most were cross-sectional ($k = 91$), while those remaining were cohort/longitudinal ($k = 13$). Three-quarters of studies used machine learning methods to develop models ($k = 75$). Nearly all studies assessed diagnostic model accuracy ($k = 100$) and sensitivity/specificity ($k = 93$). Three-quarters also undertook model validation ($k = 77$). Total sample sizes ranged 30–4541; half of the studies had n<100 ($k = 57$) and only 4 had $N > 1000$. Most included healthy controls ($k = 99$), while a quarter also had participants with bipolar disorder ($k = 26$). A third focused particularly on participants not on medications ($k = 34$). A fifth of studies included participants with their first episode of depression ($k = 19$). Most studies had substantial proportions of women ($k = 92$ with women >40%). Most participants were young and middle-aged; only 5 studies reported race. The most common study locations were China ($k = 57$) and the US ($k = 17$). The most frequent measures for determining diagnostic accuracy were standardized clinician assessments (*eg*, $k = 89$ studies used Hamilton Depression Rating Scale [HAM-D]). Clinician interviews were also used, including the Structured Clinical Interview for DSM (SCID; $k = 74$) and Mini-International Neuropsychiatric Interview (MINI; $k = 18$). Fewer studies used patient-reported measures such as the Beck Depression Inventory (BDI; $k = 21$).

Of 59 studies evaluating prognosis, most also used structural MRI ($k = 22$), fMRI ($k = 31$), or both ($k = 2$); few used DTI ($k = 5$). Nearly all studies examined treatment response ($k = 55$), most commonly to antidepressant therapy ($k = 36$). Fewer studies evaluated response to psychotherapy ($k = 6$), electroconvulsive therapy (ECT, $k = 9$), repetitive transcranial magnetic stimulation (rTMS, $k = 5$), transcranial direct current stimulation (tDCS, $k = 1$), theta burst stimulation (TBS, $k = 1$), or inpatient multi-modal treatment ($k = 1$). Two studies evaluated general trajectories over 2 years for middle-aged and older adults with depression. Twenty-two studies applied machine learning approaches and 34 validated predictive models. Most were cohorts/longitudinal observational studies ($k = 52$) and 7 were RCTs. A single study had total n>1000, while half had $N < 100$ ($k = 31$). Studies that focused on medication-free participants defined this variably, including those who had not received treatment for the current depressive episode or had undergone a washout period ($k = 24$). Others focused on treatment-resistant depression ($k = 11$). Only 2 studies distinguished participants in their first episode of depression. A third of studies included healthy controls ($k = 21$), and a few had participants with bipolar disorder ($k = 4$). Studies had relatively young participants, and women were well represented. Demographic information relating to race/ethnicity was reported in 9 studies. The most common locations were the US or Canada ($k = 21$) and China ($k = 12$).

EEG and Evoked Potentials

Of 24 studies evaluating EEG or evoked potentials for diagnosis of depression, most included healthy controls ($k = 23$) and were very small with total $N < 100$ ($k = 21$). All diagnostic studies were cross-sectional. Only 2 studies focused on participants in their first episode of depression. Study participants were young and middle-aged adults (mean age range 20–55), and more than half of studies had >40% women ($k = 17$). The most common study location was China ($k = 7$). Standardized clinician assessments (HAM-D and Montgomery-Asberg Depression Rating Scale [MADRS]) were the most frequently used diagnostic standard ($k = 14$). A majority of studies used machine learning methods ($k = 17$) and undertook model validation ($k = 20$).

Thirty studies examined prognosis in depression; most addressed response after antidepressant therapy ($k = 19$), while fewer evaluated rTMS ($k = 9$) and 1 study each examined acupuncture or

ketamine. Most were cohorts/longitudinal observational (k = 25) and a few used data from RCTs (k = 4). A third included medication-free participants (k = 11), and 8 focused on treatment-resistant participants (variably defined as not responding to sufficient course of antidepressants). No study included only participants with their first episode of depression. Six included participants who were healthy controls. The majority of studies had $N < 100$ (k = 22). Studies were most commonly conducted in the US or Canada (k = 13). Studies most commonly used standardized clinician assessments (HAM-D and MADRS) to define treatment response (k = 25). A third used machine learning (k = 9). Just under half undertook model validation (k = 12).

Other Neuroimaging Techniques (MEG, PET, and SPECT)

Eight eligible studies evaluated magnetoencephalography (MEG) for depression; 7 examined diagnosis and one addressed treatment response to antidepressants. Five studies also used MRI-based imaging techniques. All diagnostic studies had healthy controls as comparators, while one also included individuals with bipolar disorder. All were conducted in China or Taiwan and were very small (total N range 41–108). Participants were young (mean age range 30–37) and women were well represented (37–61% across studies). Six diagnostic studies were cross-sectional in design, and one was a longitudinal cohort. All studies used structured interviews as the gold standard, and 6 also used HAM-D as the standardized clinician assessment. The prognostic study on outcomes with antidepressants also used HAM-D to define response. Three studies used machine learning methods, and 6 validated models.

Four studies evaluated positron emission tomography (PET) for diagnosis (k = 2) or prognosis (k = 2) in depression. Three of these also used structural MRI to improve localization of PET data. Both diagnostic studies were cross-sectional and conducted in the US. Both prognostic studies occurred in Taiwan, with one being an RCT and the other an observational cohort. Studies were very small (N range 36–107 total participants) and included mostly young adults (mean age range 32–43). None of the studies used machine learning methods, and none conducted model validation.

Lastly, 3 eligible studies used single photon emission computed tomography (SPECT) for diagnosis (k = 1) or prognosis (k = 2). The diagnostic study was very large (N = 4,541), conducted in the US, used a structured clinical interview (MINI) as the gold standard, and undertook model validation. Both prognostic studies were conducted by 1 research group in France, evaluated response to rTMS, and also included participants with bipolar disorder. They had small samples (N = 33–58) and used patient-reported outcome (BDI) to determine response. None of the SPECT studies used a machine learning approach.

Bipolar Disorder

Forty-seven eligible studies evaluated diagnosis (k = 41) or prognosis (k = 6) for bipolar disorders. The majority also included participants with depression (k = 27 for diagnostic studies, and all prognostic studies). Nearly all studies examining diagnosis used MRI-based techniques (k = 24 with structural MRI, k = 19 with functional MRI, k = 3 with DTI, and k = 2 with ASL), with one of these also using magnetoencephalography (MEG). One study examined EEG for diagnosis. Half of studies included healthy controls (k = 23), and half were very small with total sample sizes less than 100 (k = 23). Only 3 studies had more than 250 participants (range 251–441). Most study participants were young adults, with only 2 studies having mean ages of 45 or

older. Most studies had at least 40% women (k = 44). Studies were conducted in different regions of the world, with most common locations being China (k = 15) and the US (k = 12).

Most diagnostic studies were cross-sectional in design (k = 31), while 3 were longitudinal (to confirm symptoms and diagnosis over 1–2 years). About half of diagnostic studies used machine learning methods (k = 25) and undertook model validation (k = 24). Less than half of studies used both structured clinical interviews (MINI and/or SCID) and standardized clinician assessments (Young Mania Rating Scale [YMRS]) as the diagnostic standard for bipolar disorder (k = 16). Another 18 studies used only structured interviews, and 3 used only YMRS. All prognostic studies were included above in results for depression.

Posttraumatic Stress Disorder

Thirty eligible articles evaluated PTSD, with the majority focusing on diagnosis (k = 24). Most used MRI-based techniques, including fMRI (k = 11), structural MRI (k = 7), both MRI and fMRI (k = 1), or fMRI and DTI (k = 1). Remaining studies evaluated PET (k = 1), SPECT (k = 2), MEG (k = 1), or EEG (k = 5). The majority were cross-sectional (k = 22), with fewer being longitudinal cohorts (k = 6) or RCT (k = 2). Most were small, with more than half having sample sizes <100 (k = 17). Sample sizes for remaining studies were 116–432 (k = 12) and 2,137 for 1 large database study. Studies were conducted mostly in the US or Canada (k = 18) and China (k = 7); a few were conducted in the Netherlands (k = 2), South Korea (k = 2), and Iran (k = 1). A third included US Veterans or active military (k = 10), with half of these including combat-exposed Veterans or active military (k = 5).

The most common assessments used for diagnostic standard included structured interviews (SCID, k = 12) and clinician assessments (Clinician Administered PTSD Scale [CAPS], k = 13). Many also used patient-reported outcome measures such as the PTSD Checklist (PCL, k = 7). Ten studies using machine learning methods, and 12 undertook model validation.

Studies in Veteran Populations

A total of 13 studies on PTSD were conducted in Veteran populations, the majority (k = 10) with US Veterans, 2 in combat-exposed Veterans from the Netherlands, and one in combat-exposed members of the Canadian Armed Forces. Of the 10 studies of US Veterans, nearly all evaluated diagnostic accuracy (k = 9). Half used MRI-based techniques (k = 5), while remaining used a variety of other methods (SPECT k = 1, MEG k = 2, EEG k = 2). Five studies included participants with co-occurring TBI. Diagnostic standards included SCID, CAPS, and patient-reported measures such as BDI, PCL, or Patient Health Questionnaire (PHQ). Six studies undertook model validation. Sample sizes ranged from 32–196. The single prognostic study used fMRI and clinical data from a small RCT evaluating response to an integrated psychotherapy to treat comorbid PTSD and alcohol use disorder.

Traumatic Brain Injury

Of 12 articles on TBI, most evaluated diagnosis (k = 10) and 2 reported on prognosis of disability. The majority used MRI-based techniques (k = 8), and fewer used EEG (k = 2) or SPECT (k = 2). One of the MRI studies also used MEG. Most were cross-sectional (k = 10), small in size (*eg*, k = 9 with N < 100), and included younger populations (k = 10 with mean age <45). Six studies included PTSD; all of these focused on diagnosis and were cross-sectional.

Both prognostic studies investigated predictive models for global disability at least 1 year after injury, measured using the Glasgow Outcome Scale-Extended (GOSE).

Studies in Veteran Populations

Seven studies included combat-exposed US Veteran populations. Most included participants with co-occurring PTSD and TBI (k = 5), and most evaluated MRI-based techniques (k = 5). One each evaluated EEG, SPECT, or MEG (this study also used MRI). All studies focused on diagnosis and were cross-sectional.

Substance Use Disorders (SUD)

Twenty studies addressed SUD, with 60% evaluating alcohol use disorder (k = 12) and the remaining studies focusing on cocaine use disorder (k = 3), opioid use disorder (k = 2), or methamphetamine use disorder (k = 3). The majority used structural and/or functional MRI (k = 12) or other MRI-based techniques (ASL, k = 2). Eight evaluated EEG or evoked potentials; no studies used other imaging techniques. About half focused on diagnosis (k = 9), while the rest reported on prediction of relapse (k = 6) or treatment response (k = 5). Most evaluated the accuracy of diagnostic or prognostic models (k = 16), and 40% undertook model validation (k = 8). Most studies were very small with total sample sizes <100 (k = 14); 1 study had a total sample size of 1,376. More than half used machine learning methods to develop models (k = 11). The most common locations were the US (k = 10) and China (k = 3).

Studies in Veteran Populations

We identified 3 studies that included US Veterans and all focused on prognosis. All three used structural MRI or fMRI techniques. One was an RCT including Veteran participants with comorbid PTSD and alcohol use disorder and evaluated improvement in PTSD symptoms with psychotherapy. The other 2 were cohort studies including both Veteran and civilian populations. One addressed predictors of relapse with treatment for alcohol use disorder, and the other examined relapse in methamphetamine use after inpatient treatment. None of these studies validated their predictive models.

Obsessive Compulsive Disorder and Anxiety Disorders

Obsessive Compulsive Disorder

Seventeen studies focused on diagnosis of OCD and all were cross-sectional. Two cohort studies evaluated prognosis. Overall, 12 studies used fMRI, 5 used structural MRI, and 1 each applied DTI and EEG. The most commonly used diagnostic standard was the Yale Brown Obsessive Compulsive Scale (Y-BOCS, k = 15), with 11 studies also using SCID. The 2 prognostic studies also used Y-BOCS to define treatment response to psychotherapy and antidepressants, respectively. Eight studies undertook model validation, and 7 used machine learning. All studies had sample sizes <200 and included young adults. Half had 16-40% women participants (k = 10), while 7 included 41–70% women. Most included healthy controls as the comparator (k = 14), and most were conducted in China (k = 14).

Anxiety Disorders

Four studies addressed diagnosis and 6 evaluated prognosis. All used either structural MRI (k = 3), or fMRI (k = 7). All diagnostic studies used the SCID and/or the Hamilton Anxiety Rating

Scale (HAM-A) as the diagnostic standards. Specific disorders examined were general anxiety disorder (k = 7), social anxiety disorder (k = 2), and panic disorder (k = 3). Three studies were cross-sectional, and those remaining were longitudinal cohorts. Most studies undertook model validation (k = 8). Four studies used machine learning. Sample sizes ranged 34–135 and included young adults with substantial representation of women. Most studies were conducted in the US (k = 6) or China (k = 2). Of prognostic studies, 4 addressed response to psychotherapy, 1 evaluated outcomes after antidepressant therapy, and 1 examined response to a computer-based behavioral intervention.

Systematic Reviews

Of 30 eligible systematic reviews**,** 17 addressed depression. Fewer reviews evaluated the remaining conditions: anxiety disorders (k = 3), bipolar disorders (k = 4), PTSD (k = 2), TBI (k = 3), or OCD (k = 1); no eligible reviews addressed SUD or reported on more than 1 condition. Most systematic reviews included MRI-based techniques (k = 16) or a number of neuroimaging or neurophysiologic data (k = 7). Fewer focused on EEG (k = 5), PET (k = 1) or SPECT (k = 1).

About half examined diagnosis (k = 16), 15 addressed response to treatment, and 3 evaluated change in symptoms or functioning. Four reviews reported on both diagnosis and prognosis**.** The number of studies included by reviews varied widely, ranging from 11–352.

DISCUSSION

Summary of Key Findings

To inform next steps for applying precision medicine to Veterans' healthcare and research, we conducted an evidence map of neuroimaging and neurophysiologic biomarkers in mental health and TBI. We identified 313 eligible primary studies and 30 eligible systematic reviews. The majority of the evidence addressed depression, while fewer studies and reviews examined other conditions of interest. Most primary studies used MRI-based neuroimaging techniques and a fifth employed EEG. Two-thirds of primary studies focused on diagnosis for conditions of interest, and nearly all of these were cross-sectional. Half of primary studies employed machine learning to analyze neuroimaging or neurophysiologic data and develop diagnostic or prognostic models. Primary studies generally included young and middle-aged adults, with only 5 studies having participants with mean ages ≥65. Studies were conducted in diverse locations around the world, with the most common being China, the US, or Canada; very few were conducted in more than 1 country. Overall, most of the evidence came from very small studies. Only 14 primary studies included US Veterans or active military service members; 12 addressed PTSD and/or TBI, and 2 evaluated SUD.

Key findings for primary studies include:

- Many studies evaluated structural or functional MRI for diagnosis and prognosis of depression, but there were important methodological concerns:

  - Nearly all diagnostic studies were cross-sectional, small in size, and included participants with variable past histories of symptoms and treatments.
  - Prognostic studies mostly focused on response to antidepressants, and were also generally small.
- A substantial number of studies used EEG for diagnosis and prognosis of depression, but these had similar methodological issues to MRI studies.
- Most studies on bipolar disorder were small and cross-sectional, included participants with depression, and focused on diagnosis.
- Studies evaluating PTSD were small and cross-sectional, and mainly used structural or functional MRI to address diagnosis.
- Studies examining TBI were small and cross-sectional, often included participants with co-occurring PTSD, and mainly used structural or functional MRI to address diagnosis.
- Studies on SUD used structural or functional MRI and EEG, most addressed alcohol use disorder, and half evaluated prediction of relapse or response to treatment.
- Studies on OCD and anxiety disorders were small and cross-sectional, mainly used structural or functional MRI, and focused on diagnosis.
- Fourteen studies included US Veterans, addressing PTSD, TBI, and/or SUD:
  - All 11 diagnostic studies were cross-sectional, 2 prognostic studies were cohorts, and 1 was an RCT.
- None evaluated prediction of adverse or side effects from treatments.

Implications for VA Policy

We found a large number of studies mainly using MRI-based techniques to evaluate diagnosis and prognosis for depression, but there were substantial methodological limitations. Additionally, none of the depression studies were conducted with US Veterans or military service members. Given that neuroimaging tests are costly and time consuming to conduct (and analyze), it is not clear that using such tests adds value in the clinical setting or that they could replace current standards for diagnosis of depression, which involve structured interviews and clinician assessments. Regarding prognosis, neuroimaging techniques may potentially aid in predicting early response and/or selection of appropriate therapies, but most studies included participants with variable histories of symptoms and past treatments. Only 2 studies focused on participants with their first episode of depression. Furthermore, no study evaluated prediction of adverse or side effects of treatments, whereas this is often an important factor in patient and clinician decisions to stop or switch antidepressants. There were fewer studies using EEG to examine depression and this evidence base has similar limitations as that evaluating MRI-based techniques. Thus, it is unclear how these data could be incorporated into current clinical practice to improve diagnosis or treatment selection and/or monitoring. Future systematic reviews focused on these techniques for diagnosis and/or prognosis in depression may also be needed to better characterize their potential utility for clinical care.

We found considerably less evidence addressing other mental health conditions and TBI, and fewer studies using other neuroimaging and neurophysiologic techniques. Although there were some studies on PTSD, TBI, and SUD that included US Veterans or military service members, overall these shared the same methodological limitations noted above. Therefore, it also appears premature to implement MRI (and other neuroimaging and neurophysiologic techniques) in the clinical diagnosis and treatment of these other conditions.

Future Research

While there are a large number of studies examining depression (using MRI or EEG), these were generally small and the majority used cross-sectional data to evaluate diagnosis. Additionally, participants often had variable trajectories of symptoms and treatments preceding data collection. These study design issues contribute to problems with replicability and validity of neuroimaging and neurophysiologic studies in mental health. Whereas most of the identified primary studies had less than 100 participants, current estimates are that thousands of individuals are needed to provide stable and valid results regarding important associations between neuroimaging findings and clinical phenotypes. Furthermore, it may be critical to use comparisons with age-standardized findings (developed from large populations) instead of data from small samples of age-matched controls. Additional considerations include the need for longitudinal data on symptoms and exposures, and transdiagnostic dimensional approaches in understanding clinical phenotypes. Having data before certain exposures may also be particularly important for studies evaluating PTSD and TBI.

The acquisition and analysis of (longitudinal) data from many individuals will likely require large ongoing investments in this research, as well as fundamental changes in research organization and incentives that currently promote competition and inhibit data sharing. Current projects that exemplify the level of resources, organization, and cooperation needed for such efforts include the Adolescent Brain Cognitive Development (ABCD) Study in the US and the UK Biobank.

Therefore, we recommend the following:

- Consider investment in larger studies (thousands of participants) to identify reproducible and precise associations between neuroimaging and neurophysiologic findings and mental health phenotypes.
- Conduct longitudinal studies with data on exposures, symptoms, and neuroimaging and neurophysiologic data over the life course.
- Consider transdiagnostic approaches for describing mental health phenotypes.
- Particularly for addressing Veterans' health and outcomes, develop longitudinal studies with initial data that precede combat and other service-related exposures.

Limitations

We sought to identify and describe the evidence for a broad range of neuroimaging and neurophysiologic tests used to evaluate the diagnosis and prognosis of a large number of mental health conditions and TBI. Therefore, we conducted an evidence map that provides descriptive information about research studies examining these questions and highlights gaps in the existing

evidence. Thus, we did not abstract detailed results for diagnostic or prognostic models using neuroimaging and/or neurophysiologic data. We also did not formally evaluate the quality of included primary studies or systematic reviews. Additionally, we employed machine-learning techniques to assist with the selection of relevant studies and reviews; it is possible that we may have missed some eligible studies. We also limited our search of the evidence to English-language studies and reviews.

Conclusions

Most existing evidence on neuroimaging and neurophysiologic data for mental health conditions evaluated MRI for diagnosis and prognosis in depression. In addition to the lack of evidence on other conditions or using other types of neuroimaging and neurophysiologic data, most existing studies were limited by small sample sizes and cross-sectional designs. These methodological concerns need to be addressed by future research using larger samples with longitudinal data. Existing evidence gaps and limitations indicate that it may be premature to apply neuroimaging and neurophysiologic tests to evaluate and treat mental health conditions and TBI in clinical settings.

EVIDENCE REPORT

INTRODUCTION

Improving diagnosis and treatment outcomes for Veterans with mental health conditions and traumatic brain injury (TBI) continues to be an important priority for the Department of Veterans Affairs (VA). Veterans enrolled in VA healthcare have a high prevalence of these conditions, estimated at 9% for posttraumatic stress disorder (PTSD), 14% for depression, 8% for substance use disorder (SUD), and 5% for anxiety disorders.[1] Compared with previous service eras, Veterans who served in Iraq and/or Afghanistan have higher rates of PTSD, depression, and/or TBI, due in part to increased diagnosis and the changing nature of military service and combat-related injuries.[2] These conditions often have substantial impacts on long-term health and functioning for individuals, as well as broader effects on their families and communities.[3-6] In terms of VA healthcare costs, treatment for mental health conditions accounted for $11 billion or 13% of overall costs in fiscal year 2021 (FY 2021), with estimated annual increases in FY 2022–2024.[7]

In the past several decades, there have been substantial advancements in precision medicine, specifically the use of biomarkers and/or genetics in diagnosis, prognosis, and tailoring treatments for medical conditions. There are currently several ongoing large-scale population-based studies to advance precision medicine, including the VA's Million Veterans Program.[8,9] In certain fields, such as oncology, the use of biomarkers and genetics to inform diagnosis and treatment decisions are now the standard of care.[10,11] However, despite substantial interest in the use of precision medicine techniques in mental health, there has been much more limited progress.[12,13] In the context of mental health, precision medicine has involved assessment of brain structure and functioning, as well as genetics and serum biomarkers. There are multiple challenges that impact advances in precision medicine for mental health conditions. These include complex and heterogeneous clinical phenotypes, high cost and technical difficulty of obtaining neuroimaging and neurophysiologic data, and differing assessments of symptoms and treatment response.[14-17] These challenges have contributed to substantial concerns about the reproducibility and validity of findings that rest largely on cross-sectional studies of small samples that insufficiently represent the demographic and clinical variability of affected populations.[15] Nevertheless, recent efforts to more systematically collect and examine large neuroimaging datasets, including across the lifespan, have yielded more promising results.[15,18] Thus, future work in this area may yet produce insights that improve diagnosis and treatment outcomes in mental health.

This evidence review was requested by the VA Working Group to implement the Commander John Scott Hannon Veterans Mental Health Care Improvement Act, (P.L. 116-171), Section 305: "Precision Medicine for Veterans Initiative" (SHA305). SHA305 tasks the VA with developing and implementing a precision medicine initiative focused on brain and mental health biomarkers.[19] SHA305 specifies that this initiative "shall include brain structure and function measurements, such as functional magnetic resonance imaging and electroencephalogram" and further coordinate with current data collection by the Million Veterans Program. To support the VA SHA305 Working Group, we conducted an evidence map to better understand characteristics of existing evidence on relationships between brain structure and functioning, and mental health conditions and TBI. An evidence map is well suited to address a broad scope covering multiple

conditions and numerous neuroimaging and neurophysiological techniques, particularly when some of the evidence base may consist of more exploratory studies. An evidence map is also appropriate for meeting the overall goals of informing research policy and potential clinical demonstrations.[20,21]

Therefore, in this report, we provide descriptive information about the number and types of studies that address a wide range of neuroimaging and neurophysiologic assessments for diverse mental health conditions and TBI. We also highlight weaknesses and gaps in the evidence, as determined by the volume and characteristics of studies.

METHODS

TOPIC DEVELOPMENT

We worked with our Operational Partners, the VA SHA305 Working Group, to refine the scope and develop the key questions for this evidence report. To meet the broad scope and main objectives of this workgroup, we conducted an evidence map to identify and describe the current state of research (including evidence gaps) involving the use of a wide variety of neuroimaging and neurophysiologic tests in the context of clinical diagnosis and/or prognosis for a number of important mental health conditions and TBI. An evidence map is also well suited for determining the current state of research areas that have mainly more exploratory or early phase studies. The protocol was developed *a priori* and registered with Open Science Framework (registration DOI: https://doi.org/10.17605/OSF.IO/5PHG2).

KEY QUESTION (KQ)

KQ: What are the quantity, distribution, and characteristics of evidence assessing the accuracy and utility of neuroimaging and neurophysiologic biomarkers in the diagnosis and clinical management of the following conditions:

a) Depression

b) Anxiety

c) Posttraumatic stress disorder (PTSD)

d) Substance use disorder (SUD)

e) Bipolar disorder

f) Traumatic brain injury

SEARCH STRATEGY

We searched for peer-reviewed English language articles from January 2010 to April 2022 in the MEDLINE and Embase databases. We used Medical Subject Headings (MeSH) and title/abstract terms for the neuroimaging and neurophysiological tests, and conditions of interest (Appendix A). We also searched websites for the VA ESP and AHRQ EPC programs for relevant reviews.

STUDY SELECTION

After duplicates were removed, citations were uploaded into DistillerSR (Evidence Partners, Ottawa, Canada). Abstracts were screened with the assistance of DistillerSR's Artificial Intelligence System (DAISY) in 2 separate phases. In the first phase, 2 reviewers were required to exclude an abstract at screening (while only 1 reviewer was needed to include for full-text review) until the DAISY-predicted score for likelihood of inclusion was less than 0.4 and the inclusion rate had fallen to less than 5%. Approximately 12,000 abstracts were reviewed in phase 1. In the second phase, for abstracts with DAISY-predicted scores for likelihood of inclusion of 0.2–0.3 ($k \approx$ 7,000 abstracts), 1 reviewer decided on inclusion for full-text review. The remaining abstracts with DAISY-predicted likelihood scores less than 0.2 were not further reviewed for

eligibility (k = 25,912). Based on an inclusion rate of 0.00066 for the last batch of abstracts evaluated during phase 2 (k = 1,526), we conservatively estimate that an additional 17 abstracts may have been potentially included for full-text review, if we had continued with 1-reviewer evaluation of those abstracts with likelihood scores of less than 0.2.

For full-text review, we undertook 2 initial pilot rounds where all reviewers separately determined eligibility for 10–15 articles in each round. We discussed articles to reach consensus on eligibility, with further clarification on operationalization of inclusion and exclusion criteria. Eligibility of remaining articles was determined by 1 reviewer, with ~50% of these also undergoing evaluation by a second reviewer.

Detailed eligibility criteria are provided in Appendix B.

Briefly, eligible populations included adults (≥18 years of age) with at least 1 of the conditions of interest, as noted in KQ above. Eligible articles also evaluated at least 1 neuroimaging or neurophysiological test of interest (*eg*, magnetic resonance imaging [MRI], including functional MRI [fMRI], diffusion tensor imaging [DTI], positron emission tomography [PET], single photon emission computed tomography [SPECT], and evoked potentials and electroencephalogram [EEG]) for diagnostic accuracy, clinical prognosis, and/or treatment response. Exclusion criteria included pediatric populations, evaluation of mental health symptoms or cognitive functioning only in the context of neurodegenerative conditions (*eg*, Alzheimer's dementia or Parkinson's disease) or intracranial injury (*eg*, due to ischemic or hemorrhagic stroke). We also excluded studies attempting to evaluate prognostic patterns using exclusively cross-sectional data (*eg*, comparing current differences in neuroimaging or neurophysiological patterns between patients with depression in remission vs those with treatment-resistant depression). There are very substantial validity concerns with use of cross-sectional data to evaluate predictors of treatment response or general prognosis, which has been noted previously.[22]

DATA ABSTRACTION

We abstracted the following data from all eligible studies: population characteristics (*eg*, condition and method of diagnosis, sample size, demographic data (*eg*, mean or median age, proportion of women, focus on Veterans or combat exposure), neuroimaging test and/or EEG being evaluated (and genetic data if used), outcomes addressed (clinical diagnosis and/or prognosis), and study design (*eg*, cross-sectional or cohort, analytic methods used to assess diagnostic accuracy). To verify accuracy of abstracted results, data from ~50% of articles were over-read by a second reviewer.

QUALITY ASSESSMENT AND SUMMARY OF RESULTS

We did not conduct formal quality assessment of eligible studies included in this report. We also did not undertake a formal synthesis of study results. Our results summaries are organized by the conditions of interest and focus on describing the characteristics of study populations, outcomes (clinical diagnosis, prognosis, and/or treatment response), and study designs (including analytic methods) of eligible studies.

PEER REVIEW

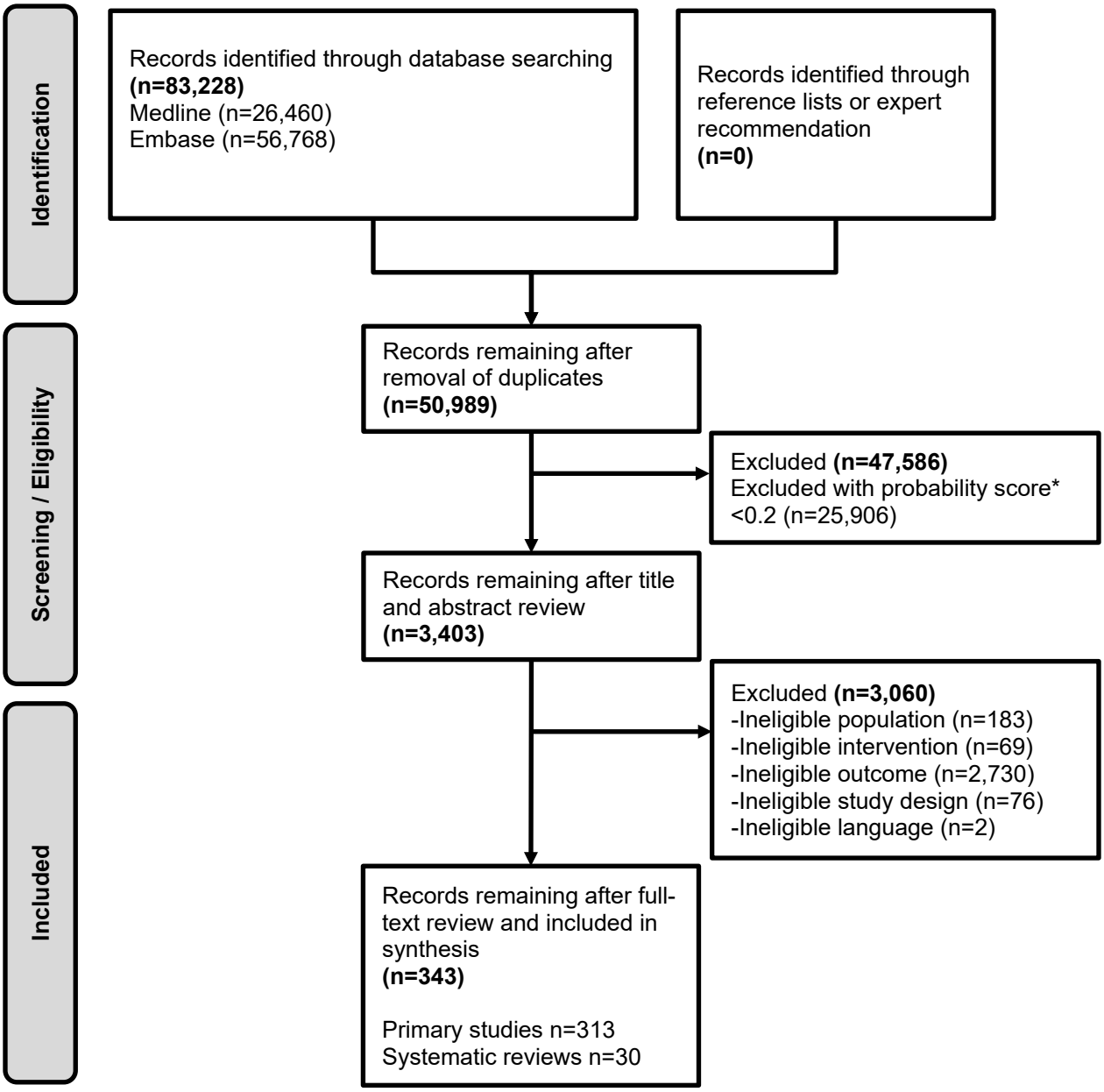
A draft version of this report was reviewed by technical experts as well as clinical leadership. Their comments and our responses are presented in Appendix C.

RESULTS

OVERVIEW

From 50,989 unique search results, we identified 343 eligible articles (Figure 1), consisting of 313 primary studies (Appendix D) and 30 systematic reviews (Appendix E). At abstract screening, 47,586 results were excluded, with 54% of these based on low scores from a machine-learning algorithm (see Methods and Figure 1). A list of references excluded during full-text review (k = 3,060) and reasons for exclusion is available upon request.

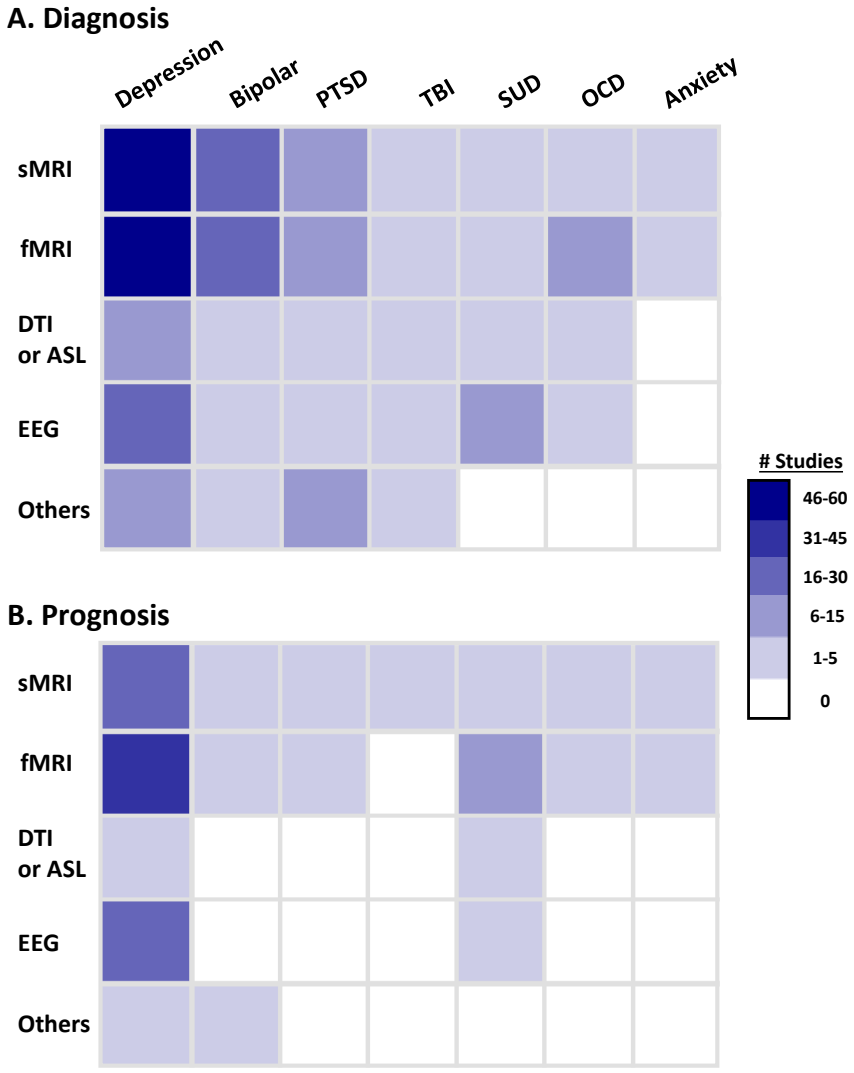
Figure 1. Identification and Selection of Eligible Studies



Notes. * Machine-learning algorithm DAISY on the DistillerSR platform (Evidence Partners).

Most of the eligible primary studies and systematic reviews addressed depression (k = 236, 69%), while fewer studies and reviews evaluated other conditions. Only 2 primary studies evaluated genetic data in addition to neuroimaging or neurophysiologic data. Figure 2 summarizes the distribution of primary studies using various neuroimaging or neurophysiologic data for evaluation of diagnosis or prognosis of each condition of interest. Three-quarters of primary studies used MRI-based imaging techniques (k = 236, 75%), while a fifth used EEG data (k = 68, 22%). For multiple conditions, there were none or few studies ($k \leq 5$) examining either diagnosis or prognosis.

Figure 2. Number of Primary Studies Using Neuroimaging or Neurophysiologic Data to Evaluate Diagnosis (A) or Prognosis (B) for Various Mental Health Conditions



Notes. *Others* category includes positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and magnetoencephalography (MEG).
Abbreviations. ASL=arterial spin labeling; DTI=diffusion tensor imaging; EEG=electroencephalogram; MRI=magnetic resonance imaging (structural or functional); OCD=obsessive compulsive disorder; PTSD=posttraumatic stress disorder; SUD=substance use disorder; TBI=traumatic brain injury.

Table 1 provides more information about study populations and methods for primary studies across the different conditions. Most primary studies had small sample sizes, with only 9 having more than 500 participants (range 555–4541). Two-thirds of primary studies examined diagnosis (k = 200), 110 evaluated prognosis, and 3 addressed both diagnosis and prognosis. Most primary studies included young and middle-aged participants; only 5 studies had participants with mean ages of 65 or older, and all of these addressed depression (with 1 also including participants with bipolar disorder).[23-27] Following Table 1, we present results for primary studies by condition of interest and then describe results for eligible systematic reviews.

Table 1. Summary of Characteristics of Included Primary Studies

	Depression (k = 218)	Bipolar Disorders (k = 47)	PTSD (k = 30)	TBI (k = 12)	SUD (k = 20)	OCD (k = 19)	Anxiety Disorders[a] (k = 10)
Neuroimaging/Neurophysiologic technique							
MRI-based techniques:							
Structural MRI (sMRI)	73	24	8	5	5	5	3
Functional MRI (fMRI)	80	19	13	2	8	12	7
DTI or ASL	12	5	1	2	2	1	—
EEG	54	1	5	2	8	1	—
Others[b]	15	3	5	1	—	—	—
Outcomes							
Diagnosis	130	41	24	10	9	17	4
Prognosis:							
Treatment response[c]	89	6	6		11	2	6
Change in symptoms or functioning	2	—	—	2	—	—	—
Study design & methods							
Cross-sectional	117	38	22	10	9	15	3
Cohort/longitudinal observational	88	9	6	2	10	4	7
Randomized controlled trial	13	—	2	—	1	—	—
Used machine learning	123	28	10	1	11	9	4
Models validated	145	30	12	3	8	7	4
Country							
US/Canada	55	12	18	10	10	1	6
China	84	9	7	—	3	14	2
UK/Europe	33	8	2	—	2	1	1
Others[d]	44	17	3	2	5	3	1
NR	2	1	—	—	—	—	—
Sample sizes (total N)[e]							
30–99	130	23	17	7	13	9	9
100–200	63	19	8	2	6	9	1
201–500	18	5	4	1	—	1	—

	Depression (*k* = 218)	Bipolar Disorders (*k* = 47)	PTSD (*k* = 30)	TBI (*k* = 12)	SUD (*k* = 20)	OCD (*k* = 19)	Anxiety Disorders[a] (*k* = 10)
501–1000	2	—	—	—	—	—	—
>1,000	5	—	1	—	1	—	—
Age (mean or median, years)							
18–25	9	7	2	—	—	4	4
26–44	160	34	22	10	13	14	5
45–64	31	4	3	1	5	—	—
>65	5	1	—	—	—	—	—
NR	13	1	3	1	2	1	1
Type of Veterans included							
US Veterans or active military	—	—	10	7	3	—	—
Non-US Veterans or active military	—	—	3	—	—	—	—

Notes. [a] Includes general anxiety disorder, panic disorder, and social anxiety disorder.
[b] Includes positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and magnetoencephalography (MEG).
[c] For SUD, this was abstinence vs relapse after or during treatment.
[d] Includes other countries not included in categories above, as well as studies done in multiple countries.
[e] Also includes healthy controls if among participants.
Abbreviations. ASL=arterial spin labeling; DTI=diffusion tensor imaging; EEG=electroencephalogram; MRI=magnetic resonance imaging; NR=not reported; OCD=obsessive compulsive disorder; PTSD=posttraumatic stress disorder; SUD=substance use disorder; TBI=traumatic brain injury; UK=United Kingdom; US=United States.

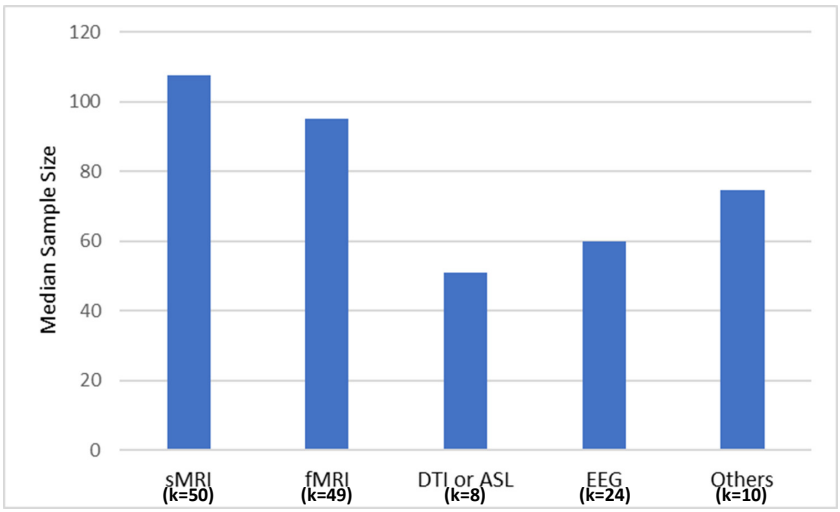
DEPRESSION

Overview

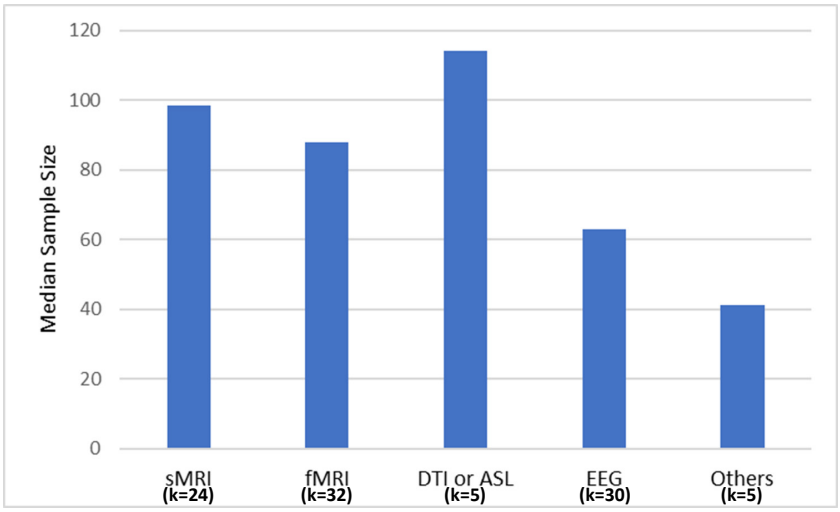
The majority of eligible primary studies evaluated depression (*k* = 218, 70%), and the vast majority of these used structural and/or functional MRI (*k* = 153) (Table 1). Fewer studies employed other MRI-based techniques like DTI (*k* = 10) and arterial spin labeling (ASL, *k* = 2). A quarter of studies addressing depression used EEG or evoked potentials (*k* = 54); others used magnetoencephalography (MEG, *k* = 8), PET (*k* = 4), or SPECT (*k* = 3). Most studies focused on whether neuroimaging tests contributed to diagnosis (*k* = 127). Less than half (*k* = 88) evaluated prognosis, and very few (*k* = 3) addressed both diagnosis and prognosis. About half of studies (*k* = 123) used machine learning methods to develop diagnostic or predictive models, including the selection of imaging features and patterns. Two-thirds of studies undertook model validation (*k* = 144). Most studies were very small with total sample sizes less than 100 (*k* = 130); only 2 studies had 500–1000 participants, and 5 studies had 1000 or more participants. Median sample size for studies using various neuroimaging or neurophysiologic data is shown in Figure 3. Studies were conducted in different regions of the world, with most common locations being the US or Canada (*k* = 55) and China (*k* = 84).

Figure 3. Median Sample Size of Included Studies Evaluating Diagnosis (A) or Prognosis (B) for Depression

A. Diagnosis



B. Prognosis



Notes. Others category includes positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and magnetoencephalography (MEG). Number of included studies is indicated for each type of imaging or neurophysiologic data.
Abbreviations. ASL=arterial spin labeling; DTI=diffusion tensor imaging; EEG=electroencephalogram; MRI=magnetic resonance imaging (structural or functional).

MRI-based Imaging Techniques (Structural and Functional MRI, DTI, and ASL)

Diagnosis

Of 104 studies using MRI-based techniques to address diagnosis of depression, the largest proportion used structural MRI (k = 49), fMRI (k = 48; 39 using resting fMRI and 10 task-specific), or both (k = 1) (Table 2). A few used other MRI-based techniques like DTI (k = 6)[28-32] and ASL (k = 2).[33,34] Most were cross-sectional (k = 91), while those remaining were cohort/longitudinal (k = 13). Three-quarters used machine learning methods to develop models (k = 75). Nearly all studies assessed diagnostic model accuracy (k = 100) and

sensitivity/specificity (k = 93). Three-quarters of the studies also undertook model validation (k = 77).

Total sample sizes ranged 30–4541; half of the studies had $N < 100$ (k = 57) and only 4 had $N >$ 1000. Most included healthy controls (k = 99), while a quarter had participants with bipolar disorder (k = 26). A third focused particularly on participants not on medications (k = 34), with this including those who had not been on any medications and others who were not on medications at the time of the study. A fifth of studies included participants with their first episode of depression (k = 19). Nearly every study had substantial proportions of women (k = 92 with women >40%). Most participants were young and middle-aged; only 5 studies reported race. The most common locations were China (k = 57) and the US (k = 17).

The most frequently used standard for determining diagnostic accuracy was standardized clinician assessments (*eg*, k = 89 studies used Hamilton Depression Rating Scale [HAM-D]). Clinician interviews were also commonly used, including the Structured Clinical Interview for DSM (SCID; k = 74) and Mini-International Neuropsychiatric Interview (MINI; k = 18). Fewer studies used patient-reported measures such as the Beck Depression Inventory (BDI; k = 21).

Table 2. Summary of Characteristics of Included Studies Evaluating MRI-based Imaging Techniques for Diagnosis of Depression

	sMRI (k = 50)	fMRI (k = 49)	Other Techniques[a] (k = 8)
Depression subgroups			
Medication free	14	19	2
First episode	7	12	—
Treatment resistant	1	2	—
Other groups included			
Healthy controls	46	47	6
Bipolar disorder patients	12	12	3
Country			
US	13	6	4
China	26	32	4
UK/Europe	9	8	—
Other[b]	5	3	—
NR	1	—	—
Sample sizes (total N)			
30–99	23	27	7
100–249	21	16	1
250–499	4	3	—
500–999	—	1	—
>1,000	2	2	—

	sMRI (*k* = 50)	fMRI (*k* = 49)	Other Techniques[a] (*k* = 8)
Age (mean or median, years)			
18–25	—	7	1
26–44	45	38	4
45–64	2	3	—
≥65	2	1	1
NR	1	—	2
% Women			
0–15	1	—	—
16–40	3	2	—
41–70	40	41	7
>70	5	6	1
NR	1	—	—
Race reported?	4	—	1
Diagnostic accuracy standard			
Clinician interviews	37	34	5
Clinician assessments	40	35	5
Patient-reported outcomes	8	9	1
Study design			
Cross-sectional	43	43	7
Cohort/longitudinal	6	6	1
Analytic methods			
Sensitivity/specificity	44	45	7
Machine learning	32	40	5
Models validated	47	48	7

Notes. [a] Includes arterial spin labeling (ASL) and diffusion tensor imaging (DTI).
[b] Includes other countries not included in categories above, as well as studies done in multiple countries.
Abbreviations. MRI=magnetic resonance imaging (structural or functional); NR=not reported.

Prognosis & Treatment Response

Among 59 studies evaluating prognosis, most also used structural MRI (*k* = 22), fMRI (*k* = 31; 15 resting fMRI, 14 task-specific, and 2 both resting and task), or both (*k* = 2); 5 studies used DTI. Nearly all studies examined treatment response (*k* = 55), most commonly to antidepressant therapy (*k* = 36). Fewer evaluated response to psychotherapy (*k* = 6), electroconvulsive therapy (ECT, *k* = 9), repetitive transcranial magnetic stimulation (rTMS, *k* = 5), transcranial direct current stimulation (tDCS, *k* = 1), theta burst stimulation (TBS, *k* = 1), or inpatient multi-modal treatment (*k* = 1) (Table 3). Additionally, 2 studies evaluated general trajectories over 2 years for middle-aged[35] and older adults[26] with depression. Twenty-two studies applied machine learning approaches and 34 validated predictive models.

Most studies were cohorts/longitudinal observational (*k* = 49), and 10 were reports of RCTs. Four of these articles[36-39] used data from a single RCT, the international Study to Predict Optimized Treatment in Depression (iSPOT-D).[40] A single study included *N* > 1000,[41] while half had *N* < 100 participants (*k* = 31). Some studies on treatment response only included medication-

free participants, indicating those who had not received treatment for the current depressive episode or had undergone a washout period (k = 24). Others focused on treatment-resistant depression (k = 11). Only 2 studies distinguished participants in their first episode of depression.[42,43] Additionally, a third included healthy controls (k = 21), while a few had participants with bipolar disorder (k = 4). Studies had relatively young participants, and women were well represented. Demographic information relating to race/ethnicity was reported in 9 studies. The most common locations were the US or Canada (k = 21) and China (k = 12).

Table 3. Summary of Characteristics of Included Studies Evaluating MRI-based Techniques for Treatment Response in Depression

	Response to Treatments				
	Antidepressants (k = 36)	**Psychotherapies (k = 6)**	**ECT (k = 9)**	**rTMS (k = 6)**	**Other[a] (k = 3)**
Imaging technique					
sMRI	13	—	7	2	1
fMRI	20	6	3	5	1
DTI	4	—	—	—	1
Depression subgroups					
Medication free	20	3	—	—	2
Treatment resistant	1	—	6	4	—
Other groups included					
Healthy controls	16	3	1	3	—
Bipolar disorder	—	—	4	—	—
Country					
US/Canada	9	5	5	2	1
China	11	—	—	1	—
UK/Europe	5	—	—	—	1
Other[b]	11	1	1	2	1
Sample sizes (total N)					
30–99	18	3	7	4	1
100–249	15	3	2	1	2
250–499	3	—	—	—	—
500–999	—	—	—	—	—
>1,000	—	—	—	1	—
Age (mean or median, years)					
26–44	27	5	4	5	2
45–64	5	—	5	1	1
≥65	2	—	—	—	—
NR	2	1	—	—	—

	Response to Treatments				
	Antidepressants (*k* = 36)	**Psychotherapies (*k* = 6)**	**ECT (*k* = 9)**	**rTMS (*k* = 6)**	**Other[a] (*k* = 3)**
% Women					
0–15	—	0	—	—	—
16–40	3	1	—	1	—
41–70	27	2	6	5	3
>70	4	0	—	—	—
NR	2	3	3	1	—
Race reported?	4	2	2	—	—
Study design					
Cohort/longitudinal	29	5	9	6	2
RCT	7	1	—	—	—
Analytic methods					
ROC (or sensitivity/ specificity)	17	3	2	4	1
Machine learning	12	1	7	3	—
Models validated	22	1	8	4	1

Notes. [a] Includes 1 study on transcranial direct current stimulation (tDCS), 1 study on theta burst stimulation (TBS) vs rTMS, and 1 using multi-modal inpatient treatment.
[b] Includes other countries not included in categories above, as well as studies done in multiple countries.
Abbreviations. DTI=diffusion tensor imaging; ECT=electroconvulsive therapy; MRI=magnetic resonance imaging (structural or functional); NR=not reported; ROC=receiver operating curve; rTMS=repetitive transcranial magnetic stimulation.

EEG and Evoked Potentials

Diagnosis

Of 54 studies evaluating EEG or evoked potentials for depression, 24 examined diagnosis (*k* = 24) (Table 4). Most studies addressing diagnosis included healthy controls (*k* = 23), and most were very small with total sample sizes less than 100 (*k* = 21). Only 2 studies focused on participants in their first episode of depression,[44,45] and only 3 studies had more than 100 participants (range 157–400).[46-48] Study participants were young and middle-aged adults (mean age range 20–55), and more than half of studies had more than 40% women (*k* = 17). Studies were conducted in different regions of the world, with the most common location being China (*k* = 7); 1 study was multi-site, occurring in Japan, the US, and Taiwan.[46]

All diagnostic studies were cross-sectional in design and most used machine learning methods (*k* = 17). Standardized clinician assessments (HAM-D and Montgomery-Asberg Depression Rating Scale [MADRS]) were the most frequently used diagnostic standard (*k* = 14). Most studies undertook model validation (*k* = 20).

Prognosis & Treatment Response

Thirty studies examined EEG or evoked potentials for prognosis in depression. These all examined response to specific treatments; most addressed outcomes after antidepressant therapy (*k* = 19), while fewer evaluated rTMS (*k* = 9) and 1 study each examined acupuncture[49] or

ketamine.[50] A third of prognostic studies included participants who were not on medications (k = 11), and 8 focused on treatment-resistant participants (variably defined as not responding to sufficient course of antidepressants). No study included only participants with their first episode of depression. Six studies included participants who were healthy controls. The majority of studies were small with less than 100 participants (k = 22), while 8 studies included somewhat more participants (range 103–220). Studies most commonly were conducted in the US or Canada (k = 13).

Prognostic studies were most often longitudinal observational (k = 25) but a few used data from RCTs (k = 4).[51-54] A third of prognostic studies used machine learning (k = 9). Studies most commonly used standardized clinician assessments (HAM-D and MADRS) to define treatment response (k = 25). Just under half of studies undertook model validation (k = 12).

Table 4. Characteristics of Included Studies Evaluating Electroencephalogram and Evoked Potentials for Depression

	Diagnosis (Total = 24)	Response to Treatments		
		Antidepressants (Total = 19)	rTMS (Total = 9)	Other[a] (Total = 2)
Depression subgroups				
Medication free	3	8	—	—
Treatment resistant	—	3	1	1
Other groups included				
Healthy controls	23	3	2	1
Bipolar disorder	2	—	—	—
Country				
US/Canada	3	10	3	—
China	7	4	—	1
UK/Europe	5	4	1	—
Other[b]	9	5	3	1
NR	—	—	1	—
Sample sizes (total N)				
30–99	21	13	7	2
100–249	1	6	2	—
250–500	2	—	—	—
Age (mean or median, years)				
18–35	5	3	—	—
36–50	16	14	6	2
51–64	1	—	—	—
NR	2	2	3	—

	Diagnosis (Total = 24)	Response to Treatments		
		Antidepressants (Total = 19)	rTMS (Total = 9)	Other[a] (Total = 2)
% Women				
16–40	1	1	—	—
41–70	14	15	6	1
>70	3	2	—	1
NR	6	1	3	—
Race reported?	—	2	—	—
Diagnosis/prognosis standards				
Clinician interviews	9	—	—	—
Clinician assessments	14	17	7	2
Patient-reported outcomes	7	2	3	—
Study design				
Cross-sectional	24	—	—	—
Cohort/longitudinal observational	—	16	8	2
Randomized controlled trial	—	3	1	—
Analytic methods				
Sensitivity/specificity	23	—	2	—
Machine learning	17	5	3	2
Models validated	20	6	4	2

Notes. [a] Includes 1 study on outcomes after acupuncture and 1 on ketamine.
[b] Includes other countries not included in categories above, as well as studies done in multiple countries.
Abbreviations. NR=not reported; rTMS=repetitive transcranial magnetic stimulation.

Other Neuroimaging Techniques (MEG, PET, and SPECT)

Eight eligible studies evaluated MEG for depression; 7 of these examined diagnosis and 1 addressed treatment response to antidepressants.[55] Five of these studies also used MRI-based imaging techniques. All diagnostic studies had healthy controls as comparators, and 1 also included individuals with bipolar disorder.[56] All studies were conducted in China or Taiwan and were very small (total $N = 41–108$). Participants were young (mean age range 30–37) and women were well represented (37–61% across studies). Six diagnostic studies were cross-sectional, and 1 was a longitudinal cohort.[57] All used structured interviews as the gold standard, and 6 also used HAM-D as the standardized clinician assessment. The prognostic study on outcomes with antidepressants also used HAM-D to define response.[55] Three studies used machine learning methods, and 6 validated models.

We also identified 4 studies that evaluated PET for diagnosis ($k = 2$) or prognosis ($k = 2$) in depression. Three of these also used structural MRI to improve localization of PET data.[53,58,59] Both diagnostic studies were cross-sectional and were conducted in the US.[58,59] Both prognostic studies evaluated response to antidepressants and occurred in Taiwan; 1 was an RCT[53] and the other an observational cohort.[60] All studies were similarly very small (total $N = 36–107$) and included mostly young adults (mean age range 32–43). None of the studies used machine learning methods and none conducted model validation.

Lastly, 3 eligible studies used SPECT for diagnosis (k = 1) or prognosis (k = 2). The diagnostic study was very large (N = 4,541), conducted in the US, used a structured clinical interview (MINI) as the gold standard, and undertook model validation.[61] Both prognostic studies were conducted by one research group in France, evaluated response to rTMS, and also included participants with bipolar disorder.[62,63] They had small samples (total N = 33–58), and used patient-reported outcome (BDI) to determine response. None of the SPECT studies used a machine learning approach.

BIPOLAR DISORDERS

Forty-seven eligible studies evaluated diagnosis (k = 41) or prognosis (k = 6) for bipolar disorders. More than half of studies also included participants with depression (k = 27 for diagnostic studies, and all prognostic studies). Nearly all diagnostic studies used MRI-based techniques (k = 24 for structural MRI, k = 19 fMRI [13 resting and 6 task-specific], k = 3 DTI, and k = 2 ASL), with 1 of these also using MEG.[56] One study examined EEG for diagnosis.[64] Half included healthy controls (k = 23), and half were very small with total N < 100 (k = 23). Only 3 studies had N > 250 (range 251–441).[65-67] Most participants were young adults, with only 2 studies having mean ages of 45 or older.[27,62,68] Most studies had at least 40% women (k = 44). The most common locations were China (k = 15) and the US (k = 12).

Most diagnostic studies were cross-sectional (k = 31), while 3 were longitudinal (to confirm symptoms and diagnosis over 1–2 years).[69-71] About half of diagnostic studies used machine learning methods (k = 25), and undertook model validation (k = 24). Less than half used both structured clinical interviews (MINI and/or SCID) and standardized clinician assessments (Young Mania Rating Scale [YMRS]) as the diagnostic standard for bipolar disorder (k = 16). Another 18 studies used only structured interviews, and 3 used only YMRS. One study did not specifically identify structured interviews or a standardized assessment, indicating only that diagnosis was completed by a psychiatrist.[27]

All prognostic studies were included above in results for depression. Briefly, 4 used MRI-based techniques to evaluate outcomes after ECT[72-75] and 2 used SPECT to examine response to rTMS.[62,63] These were all small studies (total N = 33–122) of middle-aged adults (mean age range 39–56). Three studies used machine learning and validated models.[73-75]

POSTTRAUMATIC STRESS DISORDER

Overview

Thirty eligible articles evaluated PTSD, with most focusing on diagnosis (k = 24) (Table 5). The majority used MRI-based techniques, including fMRI (k = 11), structural MRI (k = 7), both structural MRI and fMRI (k = 1), or fMRI and DTI (k = 1). Remaining studies used PET (k = 1), SPECT (k = 2), MEG (k = 1), or EEG (k = 5). The majority were cross-sectional (k = 22), with fewer being longitudinal cohorts (k = 6) or RCT (k = 2). Most were small, with the majority having N < 100 (k = 17). The remaining sample sizes were 116–432 (k = 12) and 2,137 for 1 large database study.[76] Studies were conducted mostly in the US or Canada (k = 18) and China (k = 7); a few were conducted in the Netherlands (k = 2), South Korea (k = 2), and Iran (k = 1). One third of the studies included US Veterans or active military (k = 10), with half of these including combat-exposed Veterans or active military (k = 5).

Table 5. Summary of Characteristics of Included Studies Addressing Diagnosis of Posttraumatic Stress Disorder

	sMRI (*k* = 6)	fMRI[a] (*k* = 9)	DTI (*k* = 1)	EEG (Total=5)	Others[b] (Total=6)
Population characteristics					
Veteran or active military	2	3	1	2	4
Combat exposed	2	2	1	2	2
Included TBI	1	2	1	1	2
Trauma-exposed controls	5	1	—	—	2
Country					
US/Canada	2	4	1	3	6
China	3	5	—	—	—
Other[c]	1	—	—	2	—
Sample sizes (total N)					
30–99	4	4	1	4	2
100–249	2	4	—	1	3
250–499	—	—	—	—	3
500–999	—	—	—	—	—
>1,000	—	1	—	—	—
Age (mean or median, years)					
26–44	4	7	—	4	5
45–64	2	—	—	1	—
NR	—	1	1	—	—
% Women					
0–15	2	2	—	3	—
16–40	1	1	—	—	3
41–70	3	3	—	1	2
>70	—	2	—	1	—
NR	—	1	1	—	—
Race reported?	1	1	—	—	3
Diagnostic accuracy standard					
Clinician interviews	4	3	—	3	4
Clinician assessments	5	7	1	2	3
Patient-reported outcomes	2	4	1	4	—
Study design					
Cross-sectional	5	8	1	5	6
Cohort/longitudinal	1	1	—	—	—
Analytic methods					
Sensitivity/specificity	3	5	—	5	3
Machine learning	3	4	—	2	2
Models validated	2	4	—	1	2

Notes. [a] All resting fMRI studies.

[b] Includes positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and magnetoencephalography (MEG).
[c] Includes other countries not included in categories above.
Abbreviations. DTI=diffusion tensor imaging; EEG=electroencephalogram; MRI=magnetic resonance imaging (structural or functional); NR=not reported; TBI=traumatic brain injury; US=United States.

MRI-based Techniques (Structural and Functional MRI, and DTI)

Diagnosis

The majority of studies evaluating diagnosis for PTSD used MRI-based techniques (k = 14, Table 5). One of these used both MRI and MEG.[77] Most of these were cross-sectional (k = 12), with only 2 being cohort studies.[78,79] The majority of these studies were small in size, with half having $N < 100$ (k = 7), half with N = 116-217 (k = 6), and 1 large database study with N = 2,137 (this also included multiple mental health disorders).[76] Participants were mostly young adults (mean age range 32–45), and women were variably represented (*eg*, 6 studies with no women). Half were conducted in China (k = 7), with the remaining from the US or Canada (k = 6) and South Korea (k = 1). The most commonly used diagnostic standards included structured interviews (SCID, k = 6) and clinician assessments (Clinician Administered PTSD Scale [CAPS], k = 8). Some also used patient-reported outcome measures such as the PTSD Checklist (PCL, k = 6). Six studies used machine learning to develop their models. All 14 studies addressed the accuracy of their predictive models, and 6 undertook model validation (Table 5). Five studies included US Veterans or active military populations, with 3 of these including combat-exposed persons; more information about these studies is provided in the section below.

Prognosis and Treatment Response

Six studies evaluated predictive models using structural MRI (k = 2)[80,81] or fMRI (k = 4; 2 resting fMRI and 2 task-specific).[82-85] All studies reported on predictive models for response to psychotherapy as treatment for PTSD, using CAPS to assess PTSD severity (Table 6). One study included both psychotherapy and TMS.[85] Two studies were RCTs[82,85] and the remaining were cohorts. Sample sizes ranged from 53–135, with most having $N < 100$ (k = 5). All studies included relatively young adults, with mean ages below 40 years of age. One study used machine learning methods,[84] and 3 assessed model accuracy and validation.[80,84,85] Two studies included combat-exposed Veterans, both conducted in the Netherlands.[80,81]

Table 6. Summary of Characteristics of Studies Evaluating MRI to Predict Response to Psychotherapy for Posttraumatic Stress Disorder

	Response to Psychotherapy (k = 6)
Population characteristics	
Veteran or active military	3[a]
Combat exposed	2[a]
TBI	—
Comorbid alcohol use disorder	1
Country	
US	4
Netherlands	2

	Response to Psychotherapy (*k* = 6)
Sample sizes (total N)	
30–99	5
100–140	1
Age (mean or median, years)	
18–25	1
26–44	4
45–64	—
>65	—
NR	1
% Women	
0–15	3
16-–60	—
61–70	2
NR	1
Race reported?	1
Study design	
Cohort/longitudinal	4
RCT	2
Measures of response or change	
Clinician assessments	6
Patient-reported outcomes	1
Analytic methods	
Machine learning	1
Model accuracy assessed	3
Models validated	2

Notes. [a] Includes 1 non-US Veteran study.
Abbreviations. MRI=magnetic resonance imaging; NR=not reported; RCT=randomized controlled trial; TBI=traumatic brain injury.

EEG and Evoked Potentials

Five studies evaluated EEG for PTSD and all focused on diagnosis (Table 5).[47,86-89] All were cross-sectional and only 1 had $N > 100$ ($N = 157$).[47] Most were conducted in the US ($k = 3$), 1 in South Korea, and 1 in Iran. Most used clinical interviews (SCID [$k = 3$] and/or CAPS [$k = 2$]) as the diagnostic standard ($k = 4$),[47,86,87,89] and 1 used only patient-reported measures.[88] All assessed sensitivity and specificity, but only 1 undertook model validation.[86]

Other Neuroimaging Techniques (MEG, SPECT, PET)

Six studies evaluated other imaging techniques, including MEG ($k = 3$),[77,90,91] SPECT ($k = 2$),[92,93] and PET ($k = 1$)[94]; all of these focused on diagnosis of PTSD and were cross-sectional (Table 5). Most were conducted in the US ($k = 5$), with $N = 44$–397. Three included US Veterans,[90,91,93] and 2 also had participants with TBI.[92,93] All used the SCID and/or CAPS as the diagnostic standard and assessed the accuracy of their models; 2 undertook model validation.[90,91]

Studies in Veteran Populations

Thirteen studies were conducted in Veteran populations, most with US Veterans (k = 10)[76,82,86,89-91,93,95-97], 2 with combat-exposed Veterans from the Netherlands,[80,81] and 1 included combat-exposed members of the Canadian Armed Forces.[77] We focus here on the 10 studies of US Veterans.

Diagnosis

Of the 10 studies in US Veteran populations, most evaluated diagnosis (k = 9)[76,86,89-91,93,95-97]. About half used MRI-based techniques (structural MRI k = 1, fMRI k = 4, DTI k = 1), while fewer used other methods (SPECT k = 1, MEG k = 2, EEG k = 2). Half of studies were conducted in populations who were also diagnosed with TBI (k = 5), all of which also included combat-exposed persons.[76,86,89-91,93,95-97] These were relatively small studies with N = 32–196 and 4 studies with N < 100. The diagnostic standards included the SCID, CAPS, and patient-reported measures such as BDI, PCL, or PHQ. About half undertook model validation (k = 6).

Prognosis and Treatment Response

One small RCT (N = 53), conducted in a comorbid population with PTSD and alcohol use disorder, used fMRI data to predict response to an integrated psychotherapy for both conditions.[82]

TRAUMATIC BRAIN INJURY

Overview

Of 12 articles that addressed TBI, most evaluated diagnosis (k = 10) and the remaining 2 reported on prognosis of disability (Table 7). The majority used MRI-based techniques (k = 8) and fewer used EEG (k = 2), SPECT (k = 2), and MEG (k = 1). Most were cross-sectional (k = 10), small in size (*eg*, 9 studies with N < 100), and included younger populations (mean age <45). Half of the studies included PTSD populations; all of these focused on diagnosis and were cross-sectional, and 5 evaluated combat-exposed US Veterans.

Table 7. Summary of Characteristics of Included Studies Addressing Traumatic Brain Injury

	Diagnosis (*k* = 10)	Prediction of Disability (*k* = 2)
Neuroimaging/neurophysiologic technique		
Structural MRI	3	2
Functional MRI	2	—
DTI	2	—
SPECT	2	—
MEG	1	—
EEG	2	—
Population characteristics		
Veterans and/or active military	7	—
Combat exposed	7	—
PTSD	6	—
Country		
US	10	—
Other[a]	—	2
Sample sizes (total N)		
30–99	5	2
100–199	2	—
>200	1	—
Age (mean or median, years)		
18–25	—	—
26–44	8	2
45–64	1	—
>65	—	—
NR	1	—
% Women		
0–15	6	—
16–40	3	1
NR	1	1
Race reported?	6	—
Diagnosis/prognosis standard		
Clinician interviews	4	—
Clinician assessments	6	2
Patient-reported outcomes	5	—
Hospital records	1	—
Study design		
Cross-sectional	10	—
Cohort/longitudinal	—	2

	Diagnosis (*k* = 10)	Prediction of Disability (*k* = 2)
Analytic methods		
Sensitivity/specificity (or PPV/NPV)	7	—
Machine learning	—	1
Models validated	3	—

Notes. [a] Includes Taiwan and Norway.
Abbreviations. DTI=diffusor tensor imaging; EEG=electroencephalogram; fMRI=functional magnetic resonance imaging; MEG=magnetoencephalography; MRI=magnetic resonance imaging; NPV=negative predictive value; PPV=positive predictive value; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SPECT=single-photon emission computerized tomography.

MRI-based Techniques (Structural and Functional MRI, DTI, and ASL)

Diagnosis

The majority of identified studies evaluating diagnosis for TBI used MRI-based techniques (*k* = 6), including structural MRI (*k* = 3),[95,98,99] fMRI (*k* = 2, both resting fMRI),[96,97] and DTI (*k* = 2).[96,100] One study also included MEG.[99] All were cross-sectional studies conducted in the US. Diagnostic standards included patient-reported measures (*k* = 5), clinician assessments (*k* = 5), and structured clinical interviews (*k* = 1). Half assessed sensitivity and specificity (*k* = 3), and 2 undertook model validation. Most were small, with *N* < 100 (*k* = 5). Most included populations of US combat-exposed Veterans (*k* = 5).

Prognosis and Treatment Response

Both studies evaluating prognosis for TBI used MRI-based techniques. One was conducted in Taiwan[101] and the other in Norway.[102] Both were small cohort studies (*N* = 47–70) and investigated predictive models for global disability at least 1 year after injury, measured using the Glasgow Outcome Scale-Extended (GOSE). None included Veteran or active military populations.

EEG and Other Neuroimaging Techniques

Two cross-sectional US-based studies evaluated EEG and both focused on diagnosis of TBI.[89,103] One used hospital records as the indicator for TBI,[103] and the other used the SCID.[89] Both assessed sensitivity and specificity, but only 1 undertook model validation. Both were very small (*N* = 30–32). Two studies used SPECT to address diagnosis for TBI.[92,93] Both included participants with PTSD, and are described in the PTSD section above.

Studies in Veteran Populations

Seven studies included combat-exposed US Veteran populations.[89,93,95-97,99,100] All focused on diagnosis and were cross-sectional, with most using MRI-based techniques (*k* = 5). One each used EEG, SPECT, or MEG (this study also used MRI).Most of these included participants with co-occurring PTSD and are described above (*k* = 5).[89,93,95-97] The other 2 studies also had small samples (*N* = 84–109) of young and middle-aged adults (mean age 28–48).[99,100]

SUBSTANCE USE DISORDERS

Overview

Twenty studies addressed SUD, with the majority evaluating alcohol use disorder (k = 12) (Table **8**).[82,104-114] Remaining studies focused on cocaine use disorder (k = 3),[115-117] opioid use disorder (k = 2),[118,119] and methamphetamine use disorder (k = 3).[120-122] More than half used structural and/or functional MRI (k = 12) or other MRI-based techniques (ASL, k = 2).[117,121] Eight evaluated EEG or evoked potentials[98-100,102,104,105,110,111]; none used any other imaging techniques. About half focused on diagnosis (k = 9),[105,106,108,110,112,114,118,119,121] while the rest evaluated prediction of relapse (k = 6) or treatment response (k = 5).[82,104,107,109,111,113,115-117,120,122] Most evaluated the accuracy of their diagnostic or prognostic models (k = 16), and nearly half undertook model validation (k = 8). Most studies were very small with $N < 100$ (k = 14); 1 study had a total sample greater than 1000 (N = 1,376).[107] About half used machine learning methods to develop models (k = 11). Studies were most commonly conducted in the US (k = 10) and China (k = 3).

Table 8. Summary of Characteristics of Included Studies Addressing Substance Use Disorder

	Diagnosis (k = 9)	Prognosis	
		Prediction of Relapse (k = 6)	Response to Treatment (k = 5)
Neuroimaging/Neurophysiologic technique			
Structural MRI	2	1	2
Functional MRI	1	3	4
ASL	1	—	1
EEG	6	2	—
Substance			
Alcohol	6	4	2
Opioid	2	—	—
Methamphetamine	1	1	1
Cocaine	—	1	2
Population characteristics			
Veterans and/or active military	—	1	2
Inpatient or residential treatment	4	2	3
Country			
US	2	4	4
China	2	—	1
Europe	—	2	—
Other[a]	5	—	—
Sample sizes (total N)			
30–99	6	4	4
100–200	3	1	1
>1,000	—	1	—

	Diagnosis (*k* = 9)	Prognosis	
		Prediction of Relapse (*k* = 6)	Response to Treatment (*k* = 5)
Age (mean or median, years)			
18–25	—	—	—
26–44	5	5	4
45–64	3	—	1
NR	1	1	—
% Women			
0–15	4	1	2
16–40	1	5	3
41–70	2	—	—
NR	2	—	—
Race reported?	1	—	1
Included information on genetics?	—	1	—
Study design			
Cohort/longitudinal	—	2	1
Cross-sectional	9	—	—
RCT	—	—	1
Analytic methods			
Machine learning	6	4	1
Model accuracy assessed	9	4	3
Models validated	5	2	1

Notes. [a]Includes Turkey, Malaysia and India.
Abbreviations. ASL=arterial spin labeling; EEG= electroencephalogram; MRI=magnetic resonance imaging (structural or functional); NR=not reported; RCT=randomized controlled trial.

MRI-based Techniques (Structural and Functional MRI, and ASL)

Twelve studies used MRI-based techniques for diagnosis of SUD (*k* = 3), or prognosis (*k* = 9) (Table 8). Four used structural MRI,[105,111,115,121] 7 used fMRI (5 resting and 2 task-specific),[82,104,109,114,116,120,122], and 1 used MRI, resting fMRI, and ASL.[117] Six evaluated alcohol use disorder,[82,104,105,109,111,114] 3 addressed methamphetamine use,[120-122] and 3 examined cocaine use.[115-117] Three-quarters evaluated participants in residential or inpatient treatment (*k* = 8). The most common locations were the US (*k* = 8) and China (*k* = 3). All studies were small, with *N* = 45–188. Seven used machine learning and 5 undertook model validation.

EEG and Evoked Potentials

Eight studies used EEG data: 6 for diagnosis of SUD[106,108,110,112,118,119] and 2 for predicting abstinence over a year or more.[107,113] Most studies addressed alcohol use disorder (*k* = 6),[106-108,110,112,113] while the remaining 2 examined opioid use disorder.[118,119] Four studies used machine learning and 3 undertook model validation.

Studies in Veteran Populations

Three studies included US Veteran populations and all focused on prognosis and treatment response. One was an RCT including participants with comorbid PTSD and alcohol use disorder,[82] while the other 2 were cohort studies including both Veteran and civilian populations.[111,122] One of these also addressed alcohol use disorder[111] and the other examined methamphetamine use disorder.[122] All three used structural MRI or fMRI. Two evaluated prediction of relapse[111,122] and 1 focused on response to psychotherapy.[82] None validated their predictive models.

OBSESSIVE COMPULSIVE DISORDER (OCD) AND ANXIETY DISORDERS

Obsessive Compulsive Disorder

Diagnosis

Seventeen studies focused on diagnosis of OCD, with 4 using structural MRI data,[123-126] 11 using resting fMRI,[127-137] and 1 each with DTI[138] and EEG[139] (Table 9). Eleven used SCID as the diagnostic standard,[123-127,131,134-138] while 14 studies used the Yale Brown Obsessive Compulsive Scale (Y-BOCS).[123-132,134,135,137,138] Nearly all studies assessed sensitivity and specificity (k = 14) and evaluated model accuracy (k = 14). Seven studies undertook model validation and 5 used machine learning. All studies had $N < 200$ and included young adults. Half had 16–40% women participants (k = 9), and 6 included 41–70% women. Most included healthy controls as the comparator (k = 14) and were conducted in China (k = 14).

Prognosis & Treatment Response

Only 2 studies evaluated prognosis of OCD; 1 Korean study employed structural MRI to predict response to psychotherapy,[140] and 1 US study used fMRI to examine response to antidepressants (Table 9).[141] Both studies used machine learning analyses and validated models. Total study sample sizes were 42 and 131, and both included young adults and substantial proportions of women (38–52%).

Table 9. Characteristics of Included Studies Addressing Obsessive Compulsive Disorder

	Diagnosis (k = 17)	Treatment Response (k = 2)
Neuroimaging/Neurophysiologic technique		
Structural MRI	5	1
Functional MRI (fMRI)	12	1
DTI	1	—
EEG	1	—
Other groups included		
Healthy controls	14	1
Unmedicated controls	1	—

	Diagnosis (*k* = 17)	Treatment Response (*k* = 2)
Country		
US	—	1
China	14	—
UK/Europe	—	—
Other[a]	3	1
Sample sizes (total N)		
30–99	7	1
100–249	9	1
Age (mean or median, years)		
18–25	3	1
26–44	13	1
NR	1	—
% Women		
16–40	9	1
41–70	7	2
NR	1	—
Race reported?	1	—
Diagnosis/prognosis standards		
Clinician interviews	12	—
Clinician assessments	8	1
Patient-reported outcomes	16	1
Study design		
Cross-sectional	16	—
Cohort/longitudinal observational	1	2
Analytic approach		
Sensitivity/specificity	15	—
Machine learning	7	2
Models validated	8	—

Notes. [a]Includes Turkey, Korea, Japan.
Abbreviations. DTI=diffusion tensor imaging; EEG=electroencephalogram; MRI=magnetic resonance imaging; NR=not reported.

Anxiety Disorders

Diagnosis

Four studies addressed diagnosis of anxiety disorders, all using either structural MRI (k = 1)[142] or fMRI (k = 3; 1 resting and 2 task-specific) (Table 10**)**.[143-145] All studies used the SCID and/or the Hamilton Anxiety Rating Scale (HAM-A) as the diagnostic standards. Three studies were cross-sectional[142-144] and 1 was a cohort.[145] All evaluated the sensitivity, specificity, and accuracy of models, and 3 undertook model validation. Two studies used machine learning. Sample sizes were small (N = 40–93) and included young adults with substantial representation of women.

Prognosis and Treatment Response

Six studies evaluated prognosis in anxiety disorders, with 2 using structural MRI[146,147] and 4 fMRI (all task-specific) [83,148-150] (Table 10). Specific disorders examined were general anxiety disorder (k = 4),[83,146-148] social anxiety disorder (k = 1),[149] and panic disorder (k = 2).[83,150] Four studies addressed response to psychotherapy,[83,147,149,150] 1 evaluated outcomes after antidepressant therapy,[146] and 1 examined response to a computer-based behavioral intervention.[148] Sample sizes ranged from 34–135, most participants were young adults, and most studies had more than 50% women (k = 5). [83,146,148-150] Four studies were conducted in the US,[83,147-149] while the other 2 occurred in Europe.[146,150] Most studies assessed model accuracy and undertook model validation (k = 5).[146-150] Two studies used machine learning.[146,150]

Table 10. Characteristics of Included Studies Addressing Anxiety Disorders

	Diagnosis (k = 4)	Treatment Response (k = 6)
Anxiety disorder		
Generalized anxiety disorder	3	4
Social anxiety disorder	1	1
Panic disorder	1	2
Neuroimaging/neurophysiologic technique		
Structural MRI	1	2
Functional MRI	3	4
Other groups included		
Healthy controls	4	1
Unmedicated controls	—	1
Country		
US	2	4
China	2	—
UK/Europe	—	2
Sample sizes (total N)		
30–99	4	5
100–249	—	1
Age (mean or median, years)		
18–25	2	2
26–44	1	4
NR	1	—
% Women		
16–40	1	1
41–70	2	3
>70	1	1
Race reported?	1	2

	Diagnosis (*k* = 4)	Treatment Response (*k* = 6)
Diagnosis/prognosis standards		
Clinician interviews	3	—
Clinician assessments	3	3
Patient-reported outcomes	3	2
Study design		
Cross-sectional	3	—
Cohort/longitudinal observational	1	6
Analytic approach		
Sensitivity/specificity	4	—
Machine learning	2	2
Models validated	2	5

Abbreviations. MRI=magnetic resonance imaging; NR=not reported.

SYSTEMATIC REVIEWS

We identified 30 eligible systematic reviews. Consistent with our findings for primary studies, the majority of reviews addressed depression (*k* = 17) with fewer evaluating the other conditions: anxiety disorders (*k* = 3), bipolar disorders (*k* = 4), PTSD (*k* = 2), TBI (*k* = 3), or OCD (*k* = 1). No eligible review addressed SUD, and none reported on more than 1 condition (Table 11). Most systematic reviews included MRI-based techniques (*k* = 16) or a number of neuroimaging or neurophysiologic data (*k* = 7). Fewer focused on EEG (*k* = 5), PET (*k* = 1), or SPECT (*k* = 1).

About half of reviews examined diagnosis (*k* = 16), 15 addressed response to treatment, and 3 evaluated change in symptoms or functioning. Four reviews reported on both diagnosis and prognosis (Table 11).[151-154]

The number of studies included by reviews varied widely, ranging from 11–352. Eight reviews included less than 20 primary studies, 10 reviews included 20-49, 10 reviews had 50-99, and 2 reviews included ≥100 primary studies. One was an umbrella review that included 24 other systematic reviews, comprising 352 individual primary studies.[155]

Appendix E provides detailed characteristics of eligible systematic review, including condition studied, outcomes reported, and number of studies included.

Table 11. Summary of Eligible Systematic Reviews

	Depression (*k* = 17)	Bipolar Disorders (*k* = 4)	PTSD (*k* = 2)	TBI (*k* = 3)	OCD (*k* = 1)	Anxiety Disorders (*k* = 3)
Diagnosis	9	3	1	2	1	2
Prognosis						
Response to treatment	11	2	—	—	—	1
Change in symptoms or functioning	1	—	1	1	—	—

Abbreviations. OCD=obsessive compulsive disorder; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury.

DISCUSSION

SUMMARY OF KEY FINDINGS

To assist the VA with determining next steps in the application of precision medicine to Veterans' healthcare and research, we conducted an evidence map of neuroimaging and neurophysiologic biomarkers in mental health and TBI. We identified 313 eligible primary studies and 30 eligible systematic reviews. The majority of primary studies (70%) and reviews (57%) addressed depression, while fewer studies and reviews examined other conditions of interest. Most primary studies used MRI-based neuroimaging techniques (75%) and a fifth employed EEG (22%). Two-thirds of primary studies (64%) focused on diagnosis for conditions of interest, and nearly all of these (91%) were cross-sectional. Half of primary studies (52%) employed machine learning to analyze neuroimaging or neurophysiologic data and develop diagnostic or prognostic models. Primary studies generally included young and middle-aged adults, with only 5 studies having participants with mean ages of 65 or older. Studies were conducted in diverse locations around the world, with the most common being China (35%) and the US or Canada (30%); very few studies (5%) were conducted in more than 1 country. Overall, most of the evidence came from very small studies. For example, among 98 studies using structural and/or functional MRI to address diagnosis for depression, 51% had less than 100 participants, while only 5% had 500 or more participants. Only 14 primary studies included US Veterans or active military service members; 12 addressed PTSD and/or TBI, and 2 evaluated SUD.

Key findings for primary studies include:

- Many studies evaluated the use of structural or functional MRI in diagnosis and prognosis of depression, but there were important methodological concerns:
    - Nearly all diagnostic studies were cross-sectional, small in size, and included participants with variable past histories of symptoms and treatments.
    - Prognostic studies mostly focused on response to antidepressants, and were also generally small.
- A substantial number of studies used EEG for diagnosis and prognosis of depression, but these had similar methodological issues as noted above.
- Most studies on bipolar disorder were small and cross-sectional, included participants with depression, and focused on diagnosis.
- Studies evaluating PTSD were small and cross-sectional, and mainly used structural or functional MRI to address diagnosis.
- Studies examining TBI were small and cross-sectional, often included participants with co-occurring PTSD, and mainly used structural or functional MRI to address diagnosis.
- Studies on SUD used structural or functional MRI and EEG, most addressed alcohol use disorder, and half evaluated prediction of relapse or response to treatment.
- Studies on OCD and anxiety disorders were small and cross-sectional, mainly used structural or functional MRI, and focused on diagnosis.

- Fourteen studies included US Veterans, addressing PTSD and/or TBI, or SUD:
    - All 11 diagnostic studies were cross-sectional, 2 prognostic studies were cohorts, and 1 was an RCT.
- None evaluated prediction of adverse or side effects from treatments.

IMPLICATIONS FOR VA POLICY

We found a large number of studies mainly using MRI-based techniques to evaluate diagnosis and prognosis for depression, but there were substantial methodological limitations for the majority of this evidence. Additionally, none of the depression studies were conducted with US Veterans or military service members. Given that neuroimaging tests are costly and time-consuming to conduct (and analyze), it is not clear that using such tests adds value in the clinical setting or that they could replace current standards for diagnosis of depression, which involve structured interviews and clinician assessments. Regarding prognosis, neuroimaging techniques may potentially aid in predicting early response and/or selection of appropriate therapies, but most studies included participants with variable histories of symptoms and past treatments. Only 2 studies focused on participants with their first episode of depression. Furthermore, no study evaluated prediction of adverse or side effects of treatments, whereas this is often an important factor in patient and clinician decisions to stop or switch antidepressants. There were fewer studies using EEG to examine depression, and this evidence base has similar limitations as that evaluating MRI-based techniques. Thus, it is unclear how these data could be incorporated into current clinical practice to improve diagnosis or treatment selection and/or monitoring for depression. Future systematic reviews focused on these techniques for diagnosis and/or prognosis in depression may also be needed to better characterize their potential utility for clinical care.

We found considerably less evidence addressing other mental health conditions and TBI, and fewer studies using other neuroimaging and neurophysiologic techniques. Although there were some studies on PTSD, TBI, and SUD that included US Veterans or military service members; overall, these shared the same methodological limitations as noted above. Therefore, it also appears premature to implement MRI (and other neuroimaging and neurophysiologic techniques) in the clinical diagnosis and treatment of these other conditions.

GAPS IN EVIDENCE AND FUTURE RESEARCH

As noted above, there are important methodological concerns regarding the evidence on neuroimaging and neurophysiological techniques for evaluating diagnosis and prognosis of mental health conditions and TBI. While there are a large number of studies examining depression (using MRI or EEG), these are largely small in sample size and the majority used cross-sectional data to evaluate diagnosis. Additionally, participants often had variable trajectories of symptoms and treatments preceding data collection. These study design issues have been previously noted as contributing to problems with replicability and validity of neuroimaging and neurophysiologic studies in mental health.[15,18,156] Whereas most of the identified primary studies had less than 100 participants, current estimates are that thousands of individuals are needed to provide stable and valid results regarding important associations between neuroimaging findings and clinical phenotypes.[15] Furthermore, to account for changes in brain structure and functioning over time, current recommendations are to use comparisons

with age-standardized findings (developed from large populations),[18] instead of using data from small samples of age-matched controls. To better understand clinical phenotypes, it is also important to have longitudinal data on symptoms and exposures, in addition to considering transdiagnostic dimensional approaches.[157-159] Having data before certain exposures may be particularly important for studies evaluating PTSD and TBI.

The acquisition and analysis of (longitudinal) data from a large number of individuals will likely require large ongoing investments in this research, as well as fundamental changes in research organization and incentives that currently promote competition and inhibit data sharing.[16,17,160] Current projects that exemplify the level of resources, organization, and cooperation needed for such efforts include the Adolescent Brain Cognitive Development (ABCD) study in the US[161] and the UK Biobank.[162]

Therefore, we recommend the following for future research:

- Consider investment in larger studies (thousands of participants) to identify reproducible and precise associations between neuroimaging and neurophysiologic findings and mental health phenotypes.
- Conduct longitudinal studies with data on exposures, symptoms, and neuroimaging and neurophysiologic data over the life course.
- Consider transdiagnostic approaches for describing mental health phenotypes.
- Particularly for addressing Veterans' health and outcomes, develop longitudinal studies with initial data that precede combat and other service-related exposures.

LIMITATIONS

We sought to identify and describe the evidence for a broad range of neuroimaging and neurophysiologic tests used to evaluate the diagnosis and prognosis of a large number of mental health conditions and TBI. Therefore, we conducted an evidence map that provides descriptive information about research studies examining these questions and highlights gaps in the existing evidence. Thus, we did not abstract detailed results on the factors included, nor performance metrics of, diagnostic or prognostic models using neuroimaging and/or neurophysiologic data. We also did not formally evaluate the quality of included primary studies or systematic reviews. Additionally, we employed machine learning techniques to assist with the selection of relevant studies and reviews; it is possible that we may have missed some eligible studies. We also limited our search of the evidence to English language studies and reviews.

CONCLUSIONS

Most existing evidence on neuroimaging and neurophysiologic data for mental health conditions evaluated use of MRI for diagnosis and prognosis in depression. In addition to the lack of evidence on other conditions or using other types of neuroimaging and neurophysiologic data, existing studies were limited by small sample sizes and cross-sectional designs. These methodological concerns need to be addressed by future research using larger samples with longitudinal data. Existing evidence gaps and limitations indicate that it may be premature to apply neuroimaging and neurophysiologic tests to evaluate and treat mental health conditions and TBI in clinical settings.

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APPENDIX A. SEARCH STRATEGY

OVID MEDLINE AND EMBASE

1	exp Stress Disorders, Post-Traumatic/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
2	exp combat disorder/ or (post* stress dis* or ptsd or combat disord*).kw,tw.
3	exp Depression/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
4	exp Depressive Disorder/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
5	(depress* or dysthymi* or MDD or major-depress* dis* or TRD or TRS).tw,kw.
6	Substance-Related Disorders/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
7	((problem adj2 (alcohol or drink$ or drug$ or substance)) or (substance adj2 abuse) or substance adj2disorder or ((alcohol or drug or tobacco) adj2 (abuse or addiction or disorder))).mp.
8	((Subst* adj2 disorder*) or SUD).kw,tw.
9	Anxiety/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
10	Anxiety Disorders/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
11	(anxiety or anxio* or phobi* or agoraphobi* or panic or neurosis or neuroses or neurotic or psychoneuro* or post-trauma* or stress disorder or obsessi* or compul* or OCD or obsessive compulsive disorde* or generalized anxiety disorder or GAD).tw,kw.
12	Bipolar Disorder/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
13	((bipolar adj2 dis*) or manic-depress*).kw,tw.
14	Brain Injuries, Traumatic/cl, di, dg, rh, th [Classification, Diagnosis, Diagnostic Imaging, Rehabilitation, Therapy]
15	(brain injur* or TBI or concuss* or head injur* or post-concuss*).tw,kw.
16	or/1-15
17	exp Functional Neuroimaging/ or functional neuroimaging.tw,kw.
18	exp Magnetic Resonance Imaging/ or (Magnetic Resonance Imaging or MRI or fMRI).tw,kw.
19	(diffusion tensor imag* or DTI).kw,tw.
20	(voxel-based morphometry or VBM).tw,kw.
21	(tractograph* or tractometr*).kw,tw.
22	(arterial spin label* or ASL).tw,kw.
23	exp tomography, emission-computed/ or ((positron* adj4 tomograph*) or emission-computed or single photon or SPECT).tw,kw.
24	exp magnetic resonance spectroscopy/ or (magnetic resonance spectroscopy or MR spectroscopy or MRS).tw,kw.
25	exp electroencephalography/ or (electroencephalograph* or EEG).tw,kw.
26	exp magnetoencephalography/ or (magnetoencephalograph* or MEG).tw,kw.
27	exp Evoked Potentials/ or (evoked response* or evoked potential*).tw,kw.
28	or/17-27
29	16 and 28

30	((animal or animals or canine* or cat or cats or dog or dogs or feline or goat or hamster* or horse or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.
31	(Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
32	30 or 31
33	29 not 32
34	limit 33 to (english language and yr="2010 - 2022")
35	limit 34 to (addresses or autobiography or bibliography or biography or case reports or comment or dictionary or directory or editorial or interactive tutorial or interview or legal cases or legislation or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or video-audio media or webcasts)
36	34 not 35
37	limit 36 to (juvenile or infan$ or child$)
38	36 not 37

APPENDIX B. INCLUSION AND EXCLUSION CRITERIA

	Inclusion Criteria	Exclusion Criteria
Population	N ≥ 30, ≥ 18 years of age or older, with the following conditions: • Depression • Anxiety (including OCD, phobias and panic disorders) • Posttraumatic stress disorder (PTSD) • Substance use disorder (SUD) • Bipolar disorder • Traumatic brain injury (TBI)	• Pediatric populations or mixed pediatric and adult populations without stratified data • Non-human studies • Stroke patients (CVA) • Multiple sclerosis • Intracranial hemorrhage (intracranial etiology, *eg,* burst aneurysm) • Neurodegenerative conditions (*eg*, dementia, Parkinson's disease) except if assessed as outcomes or subsets of eligible conditions
Test of interest	• Magnetic resonance imaging (MRI) • Functional magnetic resonance imaging (fMRI) • Diffusion tensor imagine (DTI) • Perfusion weighted imaging (PWI) • Magnetic resonance spectroscopy (MRS) • Positron emission tomography (PET) • Single photon emission computed tomography (SPECT) • Arterial spin labeling (ASL) • Magnetoencephalography (MEG) • Evoked potentials and electroencephalogram (EEG) • Paired pulse transcranial magnetic stimulation (ppTMS)	
Outcomes	Diagnostic accuracy compared with: • Validated structured clinical interviews (*eg*, MINI, SCID-5, WHO WMH-CIDI) • Validated clinician reported instruments of symptoms (*eg*, CAPS, HDRS, HAM-A) • Patient-reported measures of mental health symptoms (*eg*, PCL-5, PHQ-9, HADS, BDI, GAD-7, AUDIT) • Measures of cognition, other psychiatric symptoms (*eg*, delusions, hallucinations) Prognosis and treatment response: • Change in symptoms, cognition, functioning (*eg*, SF-36, WHODAS) • Sobriety/abstinence or reduction in substance use (SUD only) • Recurrence or relapse (study must define criteria and use validated measures) • Sensitivity (vs lack of response) to treatment	Only between-group differences (*eg*, in neuroimaging findings) or cross-sectional correlations with symptom severity

	• Self-harm behaviors or suicide risk • Adverse events and side effects	
Timing	Published 2010 or later	Earlier than 2010
Setting	Any	
Study design	Observational studies, trials, and systematic reviews	Study protocols, case reports, abstracts, editorials; for prognosis and treatment response outcomes, cross-sectional studies

APPENDIX C. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	Yes	Thank you.
3	3	Yes	Thank you.
4	4	Yes	Thank you.
5	5	Yes	Thank you.
6	6	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
7	1	No	Thank you.
8	2	No	Thank you.
9	3	No	Thank you.
10	4	No	Thank you.
11	5	No	Thank you.
12	6	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
13	1	No	Thank you.
14	2	No	Thank you.
15	3	No	Thank you.
16	4	No	Thank you.
17	5	No	Thank you.
18	6	No	Thank you.
Additional suggestions or comments can be provided below.			
19	1	On page 9, the sentence should include the public law number: This evidence review was requested by the VA Working Group to implement the Commander John Scott Hannon Veterans Mental Health Care	Thank you, we have updated this in both the evidence summary and main body of the report.

Comment #	Reviewer #	Comment	Author Response
		Improvement Act (P.L. 116-171), Section 305: "Precision Medicine for Veterans Initiative" (SHA305).	
20	3	The authors provide a comprehensive, careful and thoughtful review of studies addressing potential neuroimaging biomarkers for neuropsychiatric conditions.	Thank you.
		This may be in the report, but it is not emphasized: the authors did not assess the various studies for risk of bias since this was not a quantitative review. Therefore, some studies reviewed may provide higher quality data relevant to the questions asked but are treated equally with lower quality studies. I truly don't think this will change the conclusions, but this is an important caveat that should better highlighted.	We have noted this in both the Methods and Discussion (Limitations) sections. We have also added the need for a future systematic review (that would include formal assessment of studies for risk of bias) to the Discussion.
		Given the impracticality of incorporating MRI into clinical practice (unless effect sizes are large, which they aren't), would it be worth encouraging more investment on easier-to-implement imaging methods, such as EEG?	We have added additional comment on the potential utility of EEG to the Discussion. There is a much small evidence base on EEG, and it has the same limitations as MRI-based studies. While the apparatus for obtaining EEG is less costly and more portable, it is probably still quite expensive when added on to the clinical assessments that are currently standard care. As we did not directly include evidence on costs (or cost-effectiveness) of these techniques in clinical settings, we do not further differentiate on this basis when discussing Implications for VA policy. Our recommendations for future studies also mainly focus on sample size and better characterization of participants over time; this would require very substantial financial resources even for EEG-based studies.
		I could have missed this, but does fMRI refer only to resting state fMRI, or did some studies attempt to use task fMRI? This would be helpful to highlight and clarify.	We have added information about use of resting and/or task-specific fMRI to the Results.
		On page 14 of the PDF (pg 11 of the report), lines 9-10: I think one of the words "prognosis" should be diagnosis.	We have corrected this.

Comment #	Reviewer #	Comment	Author Response
21	6	I had a comment/question abut the maturity of evidence for implementing MRI for depression diagnosis/prognosis. I have submitted a copy of report with the comment inserted. Pg 20 Line 42: This statement sounds like there is evidence to implement MRI for depression. Was that the intent? Pg 49 Lines 43/44: Does this mean the evidence is mature enough to start implementing MRI in the clinic for depression diagnosis and prognosis?	We have revised these statements to make sure we were not implying that the evidence supports using MRI in clinical care for depression. We have also clarified the implications specifically for MRI and EEG in depression care.

APPENDIX D. ELIGIBLE PRIMARY STUDIES

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Achalia, 2020[163]		X					
Adinoff, 2015[117]							X
Almeida, 2013[34]	X	X					
Altuglu, 2020[139]				X			
Ambrosi, 2017[164]	X	X					
Amen, 2017[61]	X						
Amen, 2015[92]					X	X	
Arns, 2014[165]	X						
Arns, 2012[166]	X						
Arribas, 2010[167]		X					
Bachmann, 2017[168]	X						
Bailey, 2018[169]	X						
Baranger, 2021[170]	X						
Bares, 2019[171]	X						
Bares, 2017[172]	X						
Bares, 2015[173]	X						
Bartlett, 2018[174]	X						
Baskaran, 2018[175]	X						
Bi, 2019[28]	X						
Bi, 2018[176]	X						
Bi, 2016[31]	X						
Brandt, 2021[177]	X						
Braund, 2022[36]	X						
Brezova, 2014[102]						X	
Bruin, 2021[75]	X	X					
Burger, 2017[178]	X	X					
Camchong, 2021[104]							X
Cash, 2019[179]	X						
Chen, 2022[180]	X						
Chen, 2022[101]						X	
Chen, 2021[123]				X			
Chen, 2020[181]	X						
Chen, 2021[182]	X						
Cheng, 2017[183]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Chin Fatt, 2020[184]	X						
Colle, 2015[185]	X						
Cook, 2020[186]	X						
Cook, 2013[54]	X						
Costafreda, 2011[187]		X					
Crane, 2017[188]	X						
Crowther, 2015[189]	X						
Cui, 2020[137]				X			
Dai, 2021[105]							X
de la Salle, 2020[190]	X						
Deng, 2018[29]	X	X					
Ding, 2019[48]	X						
Drysdale, 2017[41]	X						
Duan, 2020[191]	X						
Dunlop, 2017[192]	X						
Durazzo, 2017[111]							X
Ellard, 2018[193]	X	X					
Erguzel, 2020[118]							X
Erguzel, 2019[119]							X
Erguzel, 2015[194]	X						
Erguzel, 2014[195]	X						
Etkin, 2019[84]					X		
Fan, 2022[49]	X						
Fang, 2012[196]	X						
Farb, 2022[197]	X						
Feder, 2017[198]	X						
Fonzo, 2017[85]					X		
Frangou, 2017[69]	X	X					
Frick, 2020[146]			X				
Gao, 2021[199]	X						
Gao, 2022[200]	X						
Gartner, 2018[201]	X						
Ge, 2020[202]	X						
Ge, 2019[203]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Georgopoulos, 2010[91]					X		
Godlewska, 2018[204]	X						
Godlewska, 2016[205]	X						
Goldstein-Piekarski, 2018[206]	X						
Gong, 2014[207]					X		
Gong, 2014[208]					X		
Gong, 2011[209]	X						
Gosnell, 2019[210]	X						
Gowin, 2015[122]							X
Grieve, 2016[211]	X						
Grotegerd, 2014[212]	X	X					
Guo, 2020[213]	X						
Guo, 2018[214]	X						
Guo, 2012[215]	X						
Guo, 2012[216]	X						
Gyurak, 2016[38]	X						
Hahn, 2015[150]			X				
Hahn, 2011[217]	X						
Hanks, 2019[98]						X	
Hasanzadeh, 2020[218]	X						
Hasanzadeh, 2019[219]	X						
He, 2019[33]	X	X					
Hellewell, 2019[220]	X						
Hopman, 2021[221]	X						
Hou, 2021[222]	X						
Hou, 2018[223]	X						
Hou, 2018[224]	X						
Hou, 2016[225]	X						
Hu, 2019[226]	X						
Hu, 2019[136]				X			
Hu, 2016[126]				X			
Huang, 2015[99]						X	

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Ichikawa, 2020[227]	X						
Im, 2017[79]					X		
Isserles, 2018[51]	X						
James, 2022[90]					X		
Januszko, 2021[113]							X
Jaworska, 2018[52]	X						
Jaworska, 2014[228]	X						
Jaworska, 2013[229]	X						
Jiang, 2021[230]	X						
Jiang, 2020[231]	X						
Jiang, 2018[232]	X						
Kamarajan, 2020[106]							X
Karim, 2018[23]	X						
Kaufman, 2015[59]	X						
Kim, 2020[87]					X		
Kinreich, 2021[107]							X
Kipli, 2015[233]	X						
Klumpp, 2020[83]	X		X		X		
Klumpp, 2017[149]			X				
Koller-Schlaud, 2020[234]	X						
Koo, 2019[235]	X						
Korgaonkar, 2020[37]	X						
Korgaonkar, 2015[236]	X						
Korgaonkar, 2014[237]	X						
Korgaonkar, 2012[32]	X						
Kraus, 2019[238]	X						
Kwak, 2020[132]				X			
Lanka, 2020[76]					X		
Laxminarayan, 2020[86]					X		
Leaver, 2018[239]	X						
Lebedeva, 2017[24]	X						
Lee, 2011[240]	X						
Li, 2021[241]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Li, 2021[242]	X						
Li, 2021[243]	X						
Li, 2020[244]	X						
Li, 2020[245]		X					
Li, 2020[246]	X						
Li, 2019[45]	X						
Li, 2019[121]							X
Li, 2017[247]	X	X					
Li, 2016[53]	X						
Li, 2014[138]				X			
Li, 2021[248]	X						
Liao, 2018[249]	X						
Liu, 2022[44]	X						
Liu, 2021[127]				X			
Liu, 2021[131]				X			
Liu, 2020[124]				X			
Liu, 2020[250]	X						
Liu, 2020[251]	X						
Liu, 2015[252]					X		
Liu, 2015[142]			X				
Liu, 2014[56]	X	X					
Liu, 2012[253]	X						
Lord, 2012[254]	X						
Lu, 2021[255]		X					
Lu, 2013[256]	X						
Luo, 2021[130]				X			
Lv, 2021[128]				X			
Main, 2017[100]						X	
Manelis, 2020[257]	X	X					
Matsuo, 2019[258]	X						
Matsuoka, 2017[259]	X						
McBride, 2013[103]						X	
McHugh, 2014[116]							X
Meng, 2020[260]	X						
Meyer, 2019[261]	X						
Mishra, 2020[108]							X

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Modinos, 2013[262]	X						
Mohammadi, 2015[263]	X						
Mourao-Miranda, 2012[264]	X						
Mulders, 2020[265]	X						
Mumtaz, 2019[266]	X						
Mumtaz, 2018[267]	X						
Mumtaz, 2018[110]							X
Mumtaz, 2018[268]	X						
Mumtaz, 2017[269]	X						
Mumtaz, 2017[112]							X
Mumtaz, 2017[270]	X						
Mwangi, 2016[66]		X					
Neumeister, 2013[94]					X		
Nguyen, 2019[271]	X						
Nicholson, 2019[272]					X		
Niida, 2018[68]		X					
Niida, 2012[27]	X	X					
Nogovitsyn, 2020[273]	X						
Nord, 2019[274]	X						
Olbrich, 2012[275]	X						
Oliveira-Maia, 2017[276]	X						
Palaniyappan, 2022[277]	X						
Pang, 2020[278]	X	X					
Pantazatos, 2014[145]			X				
Patel, 2015[25]	X						
Pillai, 2019[58]	X						
Price, 2018[148]			X				
Qiao, 2017[144]			X				
Qin, 2022[279]	X						
Qin, 2015[280]	X						
Qin, 2014[281]	X						
Qiu, 2014[282]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Rabinoff, 2011[283]	X						
Raji, 2015[93]					X	X	
Rangaprakash, 2018[95]					X	X	
Rangaprakash, 2017[96]					X	X	
Rangaprakash, 2019[97]					X	X	
Redlich, 2014[284]	X	X					
Reggente, 2018[141]				X			
Rentzsch, 2014[285]	X						
Richieri, 2018[62]	X	X					
Richieri, 2011[63]	X	X					
Rive, 2016[286]	X	X					
Rocha-Rego, 2014[287]		X					
Rottstaedt, 2018[288]	X						
Rubin-Falcone, 2018[289]	X	X					
Sacchet, 2015[290]	X	X					
Sadat Shahabi, 2021[291]	X						
Sankar, 2016[292]	X						
Schmaal, 2015[35]	X						
Schnack, 2014[65]		X					
Schnyer, 2017[30]	X						
Schultz, 2018[293]	X						
Sekutowicz, 2019[109]							X
Serpa, 2014[71]	X	X					
Shalbaf, 2018[294]	X						
Shan, 2020[295]		X					
Shan, 2021[296]	X						
Shao, 2019[297]	X	X					
Shi, 2021[298]	X						
Shi, 2018[70]	X	X					
Shim, 2019[47]	X				X		
Shimizu, 2015[299]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Shu, 2014[89]					X	X	
Siegle, 2012[300]	X						
Squarcina, 2019[301]		X					
Stange, 2020[302]	X	X					
Stout, 2021[82]					X		X
Stoyanov, 2019[303]	X						
Sun, 2021[304]	X						
Sun, 2022[305]	X						
Sun, 2022[306]	X	X					
Sun, 2020[73]	X	X					
Suo, 2020[78]					X		
Sverdlov, 2021[307]	X						
Tahmasian, 2017[88]					X		
Takagi, 2017[135]				X			
Tang, 2022[308]	X	X					
Taylor, 2014[26]	X						
Tekin Erguzel, 2015[64]	X	X					
Tenke, 2011[309]	X						
Tian, 2020[43]	X						
Tsolaki, 2021[72]	X	X					
Uyulan, 2022[310]	X						
van Rooij, 2016[81]					X		
van Waarde, 2015[311]	X						
Voineskos, 2019[312]	X						
Wade, 2017[313]	X						
Wade, 2016[74]	X	X					
Wade, 2017[314]	X						
Wang, 2022[55]	X						
Wang, 2021[315]	X						
Wang, 2020[316]		X					
Wang, 2019[133]				X			
Wang, 2019[57]	X						
Wang, 2017[317]	X						
Wang, 2017[318]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Whitfield-Gabrieli, 2016[147]			X				
Williams, 2015[39]	X						
Wu, 2020[319]	X						
Wu, 2021[320]	X						
Wu, 2021[46]	X						
Wu, 2017[321]		X					
Xi, 2022[322]	X	X					
Xiao, 2021[323]	X						
Xing, 2020[143]			X				
Xue, 2021[324]	X						
Yan, 2020[325]	X						
Yan, 2022[326]	X						
Yan, 2021[327]	X						
Yan, 2021[120]							X
Yan, 2021[328]	X						
Yang, 2022[129]				X			
Yang, 2019[134]				X			
Yang, 2018[329]	X						
Yang, 2018[330]	X						
Yang, 2019[331]		X					
Yang, 2016[332]	X						
Yang, 2021[67]	X	X					
Yeh, 2015[60]	X						
Yoshida, 2017[333]	X						
Yu, 2018[334]	X						
Yun, 2015[140]				X			
Zehong, 2019[50]	X						
Zeng, 2012[335]	X						
Zhai, 2021[115]							X
Zhang, 2022[336]	X						
Zhang, 2022[337]	X						
Zhang, 2021[42]	X						
Zhang, 2020[77]					X		
Zhang, 2016[338]					X		
Zhao, 2020[339]	X						

Author, Year	Condition Studied						
	Depression	Bipolar	Anxiety Disorders	OCD	PTSD	TBI	Substance Use Disorders
Zhao, 2017[340]	X	X					
Zhdanov, 2020[341]	X						
Zheng, 2019[342]	X						
Zhong, 2017[343]	X						
Zhou, 2018[125]				X			
Zhu, 2021[344]					X		
Zhu, 2021[345]	X						
Zhu, 2020[346]					X		
Zhu, 2018[114]							X
Zhu, 2018[347]	X						
Zhu, 2019[348]	X						
Zhutovsky, 2019[80]					X		

APPENDIX E. ELIGIBLE SYSTEMATIC REVIEWS

Condition	Author, Year	# Included studies	Diagnosis	Prognosis	
				Response to Treatment	Change in Symptoms or Functioning
Depression	Bruun, 2021[349]	24	X		
	Cohen, 2021[350]	27		X	
	De Crescenzo, 2017[351]	11		X	
	Dichter, 2015[352]	21		X	
	Enneking, 2020[353]	50		X	
	Fu, 2013[354]	20		X	
	Gillett, 2020[355]	21		X	
	Khosla, 2022[152]	132	X	X	
	Levy, 2019[356]	19		X	
	Long, 2020[357]	17		X	
	Masse-Sibille, 2018[358]	58		X	
	Scheepens, 2020[153]	14	X	X	
	Siegel-Ramsay, 2022[359]	88	X		
	Simon, 2021[360]	12	X		
	Sinha, 2020[154]	13	X		X
	van der Vinne, 2017[361]	16	X		
	Widge, 2019[362]	76	X		
Bipolar disorders	Hozer, 2016[151]	63	X	X	
	Librenza-Garcia, 2017[363]	51	X		
	Seeberg, 2018[364]	60		X	
	Whalley, 2012[365]	21	X		
PTSD	Colvonen, 2017[366]	20		X	
	Nelson, 2017[367]	37			X
TBI	Haghbayan, 2017[368]	58			X
	Hulkower, 2013[369]	100	X		
	Raji, 2014[370]	71	X		
OCD	Fullana, 2020[155]	352*	X		
Anxiety disorders	Qing, 2021[371]	11	X		
	Santos, 2019[372]	24		X	
	Xu, 2019[373]	29	X		

Notes. *Umbrella review that identified 24 systematic reviews including 352 primary publications.
Abbreviations. OCD=obsessive compulsive disorder; PTSD=posttraumatic stress disorder; TBI=traumatic brain injury.