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Eye-tracking in adult depression: protocol for a systematic review and meta-analysis

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Eye-tracking in adult depression: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: In recent years, eye-tracking has been proposed as a promising tool to identify biomarkers for psychiatric disorders, including major depression. We will conduct an updated systematic review and meta-analysis on eye-tracking research in adults with major depressive disorder or other clinically diagnosed depressive disorders.

Methods and Analysis: This protocol follows all reporting items in the Preferred Reporting Items for Systematic review and Meta-Analysis – Protocol (PRISMA-P) extension. We will conduct a systematic search of PubMed, PsycInfo, Google Scholar, and EMBASE for sources published in the last 50 years (1972–2022). Abstract and full text review will be completed independently by two reviewers. Non-randomized studies utilizing eye-tracking tasks in individuals with a depressive disorder versus controls will be included. Eye-tracking tasks of interest include, but are not limited to, saccade, smooth pursuit, fixation, free-viewing, visual search, and attentional blink tasks. Results will be categorized by eye-tracking task. Risk of bias and confidence in cumulative evidence will be assessed using GRADE criteria.

Ethics and dissemination: Ethics approval is not required due to the nature of the proposed analysis. Results will be disseminated through a journal article, conference presentations, and/or dissertations.

Strengths and Limitations:

- This is the first meta-analysis of eye tracking in depression to include saccade tasks and smooth pursuit
- Inclusion of other depression diagnoses and subthreshold depression, in addition to MDD, will allow us to depict a more comprehensive picture of the population
- Sample size of some tasks, such as the attentional blink task, may be small

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- Due to the large date range, comparability of results may be challenging due to different eye tracking technologies

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BACKGROUND

Major depressive disorder (MDD) is the leading cause of disability worldwide (World Health Organization, 2017). According to the most recent edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), MDD is characterized by having low mood and/or low interest/pleasure all day nearly every day for at least two weeks, as well as having a total of five out of nine listed symptoms (American Psychiatric Association, 2013). The presence of MDD has been found to significantly impact life satisfaction and functioning, with associations with marital dissatisfaction, lower income, more missed work, and cognitive impairments (Kessler, 2012), as well as increased risk for comorbid psychiatric disorders (Hasin et al., 2018). Recurrent depression, in comparison to single major depression episodes, are associated with impaired psychosocial functioning in adulthood, including lower positive and higher negative emotionality, more antisocial behaviour, increased use of mental health services, and increased suicidal ideation (Wilson et al., 2015).

Despite continued efforts to identify biomarkers (e.g., candidate genes, blood-based markers, structural or functional neuroimaging markers, etc.) for depression, research has been unsuccessful at identifying a reliable biomarker to integrate into clinical practice (Kraus et al., 2019). Eye-movements, such as saccades, pupil dilation/constriction, and blinks, have been previously investigated and linked to specific brain structures and networks, and thus may be used to identify impaired functioning in the brain (Habibi et al., 2022; Coe & Munoz, 2017; Wang & Munoz, 2015; Leigh & Zee, 2015). Thus, due to the known relation between eye-tracking tasks and brain areas required for their execution, eye-tracking has emerged as a useful tool for identifying potential biomarkers for neurological and psychiatric disorders. Unlike other biomarker identification methods, such as neuroimaging, eye-tracking is comparatively cost-

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effective and non-invasive, simply requiring the participant to sit in front of a computer screen with their head on a chin rest while an infrared camera tracks their eyes. Thus, eye-tracking is a promising method to identify neural markers for depression, which may lead to early identification in at-risk individuals.

A variety of task paradigms has been utilized in eye-tracking research to probe specific brain functions. Commonly used are saccade tasks, which require participants to make saccades to different areas on a screen. Variations of saccade tasks include the pro-saccade (requiring participants to look towards a visible target), anti-saccade (requiring participants to look away from a visible target), predictive/anticipatory saccade (requiring participants to make a saccade to a location before a target appears), and memory-guided saccade (requiring participants to make a saccade to the remembered position of a target after it has disappeared). Fixation tasks (requiring participants to keep their gaze on one target) and smooth pursuit tasks (requiring participants to keep their eyes on a moving target) have also been employed. Finally, unstructured free-viewing tasks (allowing participants to look wherever they please) of varying stimuli and visual search tasks have become increasingly popular in eye-tracking research. Multiple types of outcomes can be examined from these tasks, including saccade metrics (e.g., saccadic reaction time), pupil metrics (e.g., baseline pupil size), blink metrics (e.g., blink rate), and performance metrics (e.g., error rate).

Eye-tracking research in clinical populations, including in individuals with MDD, has grown substantially in the last decade (Figure 1). To the authors' knowledge, only three reviews exist on eye-tracking in depression. Two of these are systematic reviews and meta-analyses on free-viewing tasks in depression – Suslow and colleagues (2020), which included sixteen studies, and Armstrong and Olatunji (2012), which included nine studies. The third review is a

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systematic review on various eye-tracking tasks in depression, which included 43 studies, and had a broader scope (Carvalho et al., 2015).

In their review, Carvalho and colleagues (2015) identified several differences in eye-movement behaviour between individuals with MDD and controls. In comparison to controls, those with MDD had increased reaction time during the pro and anti-saccade tasks, decreased accuracy in the pro-saccade task, increased error rate during the anti-saccade task. They also had decreased accuracy during the predictive saccade task, decreased reaction time during the memory-guided saccade task, and lower pursuit gain and greater catch-up-saccade rates in smooth pursuit tasks (Carvalho et al., 2015). For free-viewing and visual search tasks, those with MDD, as well as those with bipolar disorder in depressive phase, exhibited increased attention to negative (anger, dysphoric, sadness, anxiety-related, depression-related) stimuli and decreased attention to positive stimuli (Carvalho et al., 2015). Finally, the authors reviewed the effects of medication (such as benzodiazepines, anti-depressants, and anti-psychotic drugs) on oculomotor behaviour, and noted the need for controlling for medication when examining eye-movements in depression and bipolar disorder (Carvalho et al., 2015).

Armstrong & Olatunji (2012) and Suslow and colleagues (2020) also found differences between eye-tracking of attention in those with MDD compared to healthy individuals. Suslow and colleagues' recent meta-analysis found no group differences in initial orientation of attention but found moderate to large effect sizes when looking at maintenance of gaze to various types of stimuli during free viewing of images. Across studies, individuals with depressed individuals looked less at positive images (Hedge's g = -.51) and happy faces (g = -.54) and longer for dysphoric images (g = .66) and sad faces (g = .58) than healthy individuals (Suslow et al., 2020). The previous meta-analysis by Armstrong and Olatunji (2012) reported that, for orientation,

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there was no difference between depressed individuals and healthy participants for threatening (g = -.01) or dysphoric images (g = .18). However, they found individuals with depression oriented less towards positive stimuli (g = -.24; Armstrong & Olatunji, 2012). For maintenance of gaze, there was again no difference for threatening stimuli (g = .08), but an increase in gaze maintenance for depressed individuals for dysphoric stimuli (g = .46) and a decrease in positive stimuli (g = -.80) compared to healthy participants (Armstrong & Olatunji, 2012).

The current systematic review and meta-analysis will discuss and quantify results from eye-tracking literature with a focus on adults with MDD in comparison to healthy controls, as well as other clinically rated depressive disorders (i.e., persistent depressive disorder/dysthymia, dysphoria, bipolar disorder in depressive phase, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, seasonal affective disorder, minor depression, subthreshold depression). Although excluded in prior literature, inclusion of conditions such as subthreshold depression in biomarker research is warranted due to the clinical similarity to MDD (Noyes et al., 2022). Similar to Carvalho et al. (2015), we will include data from saccade, smooth pursuit, fixation, free-viewing, and visual search tasks. Additionally, we will cover tasks not previously examined by other reviews (e.g., attentional blink task). Eye-tracking outcomes include, but are not limited to, saccades (number, rate, types), saccadic amplitude and velocity, reaction time, error rate and accuracy, eye position, fixation count and fixation duration, blinks, and pupil dilation/constriction. As the last systematic review on many of these eye-tracking tasks was published in 2015, an update on adult eye-tracking in depression is necessary given the growth in literature over the past seven years. To the authors' knowledge, this will also be the first meta-analysis to include saccade, smooth pursuit, and fixation tasks, as well as blink and pupil measures, which is important as these tasks implicate different neural networks. As a result, this

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paper may aid in identifying potential eye movement biomarkers for depression and allow for earlier identification of illness.

METHOD

This protocol covers all items outlined under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P; Moher et al., 2015).

ELIGIBILITY CRITERIA:

Types of studies: Experimental studies performed in a controlled laboratory environment will be included. Any experimental sessions, including longitudinal work, that include eye tracking tasks and eye movement outcomes will be included. Case reports and case series will be excluded.

Types of participants: We will review studies involving study participants with a mean age between 18–60 years, and depression symptomatology must be clinically rated or diagnosed (not reliant on self-report measures only). Individuals with a primary diagnosis of major depressive disorder, persistent depressive disorder/dysthymia, dysphoria, disruptive mood dysregulation disorder, seasonal affective disorder, minor/subclinical/subthreshold depression, according to established criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM; any version) or of the International Classification of Diseases (ICD; any version). Studies involving individuals with diagnosed bipolar disorder in depressive phase will be included, and studies involving mixed samples of bipolar phases will be included if depressive phase data can be isolated. Studies will not be included if they utilize experimental mood induction procedures or if participants have a psychotic disorder.

Type of control: Studies must also have a healthy (no psychiatric history) control participant group with a mean age between 18-60 years.

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Types of interventions: The tasks/measures reviewed by Carvalho et al. (2015) will be included: pro-saccades, anti-saccades, predictive saccades, memory-guided saccades, smooth pursuit eye movements, fixation tasks, and free-viewing/search tasks, as well as the attentional blink task (see Table 1 for definitions). Additional tasks that are found not to fit in these categories will be included if sufficient data exist. Tasks must have performance (e.g., reaction time, error rate, accuracy) saccade, pupil, or blink data to be included in analyses.

Task	Definition
Pro-Saccade, Reflexive Saccades, Visually Guided Saccades, Refixation Saccades	Requires participants to look towards a visible stimulus
Anti-Saccade	Requires participants to look away from a visible stimulus
Memory-Guided Saccade	Requires participants to look to a location where a target was previously presented
Predictive Saccade, Oddball Task, Self-Paced Saccade	Requires participants to look to anticipated target location after receiving some warning or cue
Fixation, No Saccade	Requires participants to maintain gaze on a target in the centre of the screen
Free-Viewing	Allows participant to look freely at images or videos that appear
Visual Search	Requires participant to search for stimuli in a scene, or to compare multiple scenes
Smooth Pursuit	Requires participants to track a moving target
Attentional Blink	Requires participants to report two targets that appear one after another

Table 1. Definition of various eye-movement tasks (Leigh & Zee, 2015; Carvalho et al., 2015; Shapiro et al., 1997).

Type of outcomes: eye movement outcomes will include, but are not limited to,

Performance metrics: accuracy, correction factors, error rates, reaction time, response search score

Saccade/fixation metrics: saccade type (back-up, catch-up, corrective, intrusive micro, macro), saccade amplitude, saccade count/rate, saccadic duration, saccadic peak velocity, saccade position error, intersaccadic interval, direction of initial eye movement, eye

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scanning length (mean, total), pursuit (gain, latency), first/initial fixation (location, duration, latency), fixation bias, fixation duration, fixation frequencies, fixation number, percentage of time fixating, scan path length, maintenance of gaze, mean gaze duration, final eye position, root mean square, root mean square error, square wave jerk, time-weight average gain, target waveform

Pupil metrics: baseline pupil size, pupil constriction, pupil dilation

Blink metrics: blink duration, blink rate, inter blink interval

The following outcomes will be prioritized due to their frequency in the literature: task accuracy, error rate, fixation duration/maintenance of gaze, and reaction time. Additionally, we will prioritize pupil and blink outcomes as those have emerged as promising biomarkers in our laboratory.

PICOs Criteria	Determinants
Patient	Individuals with MDD, persistent depressive disorder/dysthymia, dysphoria, disruptive mood dysregulation disorder, seasonal affective disorder, minor/subclinical/subthreshold depression, or bipolar disorder in depressive phase. Mean age of study sample must be between 18-60 years.
Intervention	Any eye tracking tasks (saccade tasks, smooth pursuit tasks, fixation tasks, free-viewing tasks, visual search tasks, attentional blink task)
Comparison	Healthy individuals, mean of study sample between 18-60 years.
Outcome	Task performance and any eye movement outcome (performance, saccade/fixation, pupil, and blink metrics; see above)
Study design	Experimental non-randomized studies

Table 2. PICOs criteria and determinants.

INFORMATION SOURCES:

Journal articles or conference papers in English, French, German, Dutch, and Portuguese published online from the years 1972–2022 will be reviewed. Included studies were not limited by geographic location. The electronic databases searched will include PubMed, PsycInfo, EMBASE and Google Scholar. Reference lists of highly relevant articles will also be examined.

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If full text of papers cannot be accessed, attempts to contact authors will be made. Conference posters, abstracts, and student papers will not be included.

SEARCH STRATEGY:

The following is the utilized search strategy for PubMed. All searches will be completed for Title/Abstract, and filtered for journal articles, full text, and publication years. The same search strategy will be repeated across databases with minor changes to adjust for database search tools.

Search terms:

1. depress OR mood AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
2. dysthymi* AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
3. dysphori* AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
4. seasonal affective disorder AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
5. bipolar AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit

Search strategies for other databases (Appendix 1) were determined via consensus among the authors.

DATA RECORDS AND MANAGEMENT:

Excel spreadsheets will be used to manage records at abstract level, full text review, and data extraction. BKN will perform the initial search and copy relevant information (authors, publication year, title, link to access) from all search hits into an excel spreadsheet and will send the completed spreadsheet to AB. BKN and AB will extract abstracts, screen abstracts for eligibility, and conduct the full-text review independently. Kappa will be used to quantify the level of inter-rater agreement. In the event of discrepancies at abstract or full text review, a third reviewer will make the final decision on inclusion (DPM for discrepancies involving eye tracking methodology, LB for discrepancies involving participants and all other issues).

Data tables will be independently piloted with 10 papers to ensure all necessary information is being extracted. The following data items will be extracted for saccade and smooth pursuit tasks:

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N (by diagnosis)
Mean age and SD
Sex/gender
Ethnicity
Comorbidities
Diagnostic method
Interventions/treatment
Eye-tracking tasks
Eye-movement outcomes
Results

The same data items will be extracted for free-viewing and visual search tasks, with the addition of stimuli (type and emotional valence).

EFFECT MEASURES:

Eye tracking outcome measures between patient groups and healthy controls will primarily be reported as mean differences and their respective standard deviation. We will use mean differences for measures (+/-SD) such as of the number of saccade rate and task error rates, saccade amplitude and velocity, reaction time, fixation count and duration, number of blinks, and pupillometry data.

RISK OF BIAS:

Bias will be assessed by two independent researchers (BKN and AB) and discrepancies will be addressed by LB and DPM. We will investigate in greater detail multiple publications coming out from the same research group and we will assess sample size and sample demographics to check for duplication. In case of overlapping samples/results, the first published reference will be included in the analyses, unless methodology is not sufficiently detailed to be included. Publication bias will be assessed using a funnel plot method (Duval & Tweedie, 2000).

DATA SYNTHESIS:

The PRISMA flowchart will be presented to explain how and the number of articles that were retrieved/selected. Results from included individual studies will be categorized by eye-tracking

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task and expressed both narratively and in data tables. Means, standard deviation, effect sizes, and statistical significance will be reported. It is anticipated that effect sizes will be expressed as Cohen's D. A meta-analysis will be performed if data from three or more studies exist for the same eye-tracking task. It is anticipated that JASP will be used to do the meta-analyses, though other software will be considered at the time of analyses. To assess whether the results are homogenous, the Q statistic will be calculated (Cooper, 2017).

CONFIDENCE IN CUMULATIVE EVIDENCE*:*

BKN and AB will independently assess the strength and quality of evidence using Grading of Recommendations, Assessment, Development and Evaluation (GRADE; Guyatt et al., 2008) approach criteria, a tool for meta-analyses that assesses study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. Strength of evidence will be rated as very low, low, moderate, or high. In the event of discrepancies on GRADE rating, LB and DPM will make the final decision. A quality assessment table will be presented to display which studies were included and which were excluded.

ETHICS AND DISSEMINATION:

Not applicable - **e**thics approval is not required due to the nature of this work. Results will be analyzed and disseminated according to systematic review and meta-analyses protocol and submitted to an academic journal for publication.

PATIENT AND PUBLIC INVOLVEMENT:

Due to the nature of this study, there will be no patient or public involvement.

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DISCUSSION

There is a growing need to identify reliable biomarkers of psychiatric disease, specifically as they relate to depressive disorders, to improve early diagnosis and treatment. Research into psychiatric biomarkers using eye tracking has grown steadily in recent years, as this method offers the ability to use a variety of different task paradigms and is relatively cost-effective. Given the surge in eye tracking-related research for depression biomarkers, it is paramount to summarize these findings to effectively identify potential behavioural biomarkers.

This meta-analysis aims to update the knowledge that has been reported previously by past meta-analyses on attentional tasks in depression (Suslow et al., 2020; Armstrong & Olatunji, 2012), provide the first meta-analyses of saccade, fixation, and smooth pursuit tasks in depression, as well as extend the body of knowledge by including task paradigms and outcomes not previously covered (e.g., attentional blinks). By using methodology as outlined by PRISMA guidelines, this meta-analysis aims to provide a comprehensive overview of current study findings which may help inform future clinical practice in the diagnosis and treatment of depression (and other related disorders). However, while this meta-analysis will attempt to extend the body of knowledge by considering studies using tasks not previously covered by other reviews (e.g., attentional blink task) and those including various depressive disorder populations (i.e., not simply individuals diagnosed with MDD), this may be limited by the number of published studies and their quality.

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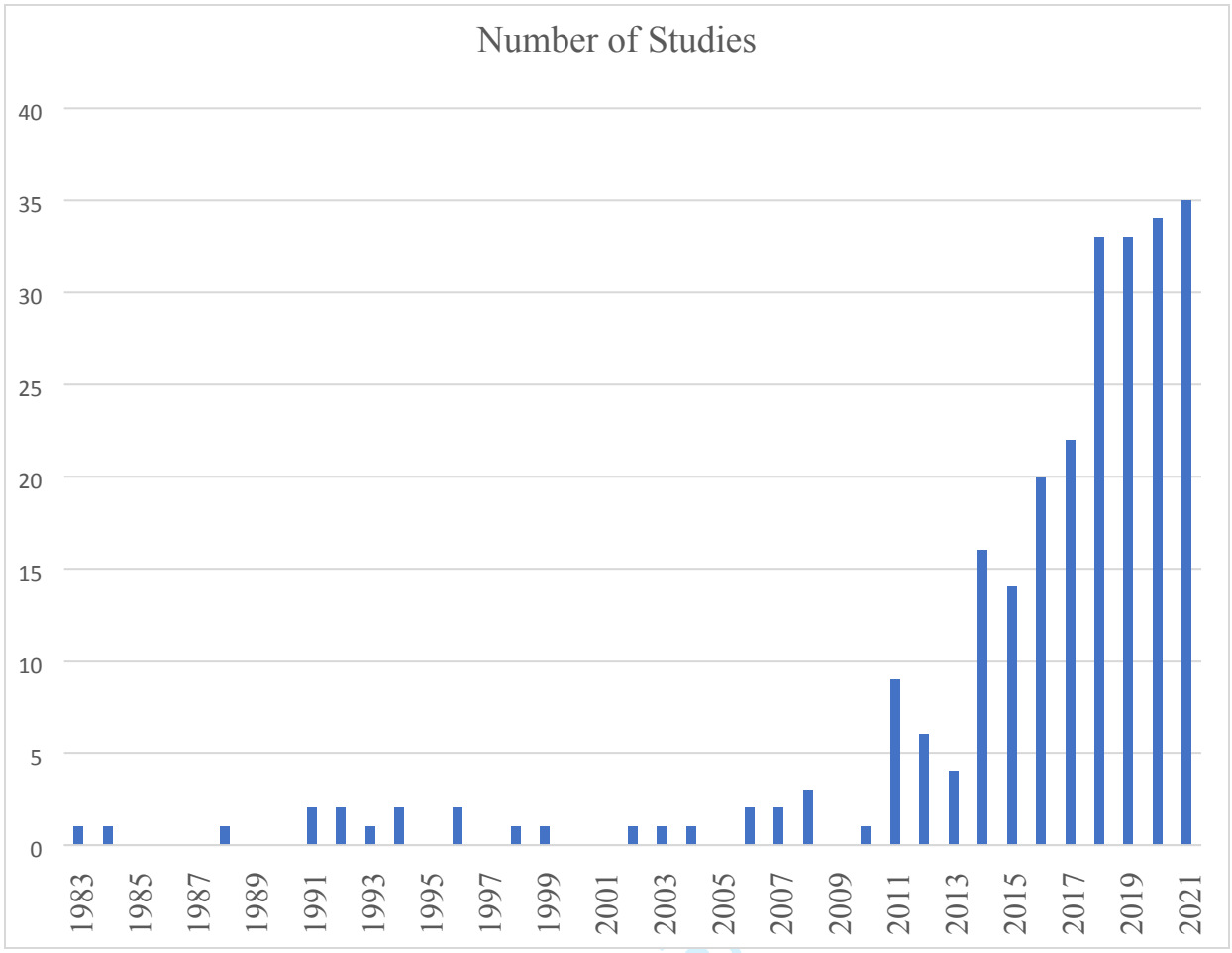
Number of Studies
40
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Eye-tracking in adult depression: protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Research methods
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Neurobiology < NATURAL SCIENCE DISCIPLINES

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Eye-tracking in adult depression: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: In recent years, eye-tracking has been proposed as a promising tool to identify potential biomarkers for mental disorders, including major depression. We will conduct an updated systematic review and meta-analysis on eye-tracking research in adults with major depressive disorder or other clinically diagnosed depressive disorders.

Methods and Analysis: This protocol follows all reporting items in the Preferred Reporting Items for Systematic review and Meta-Analysis – Protocol (PRISMA-P) extension. We will conduct a systematic search of PubMed, PsycInfo, Google Scholar, and EMBASE for sources published up until March 2023. Abstract and full text review will be completed independently by two reviewers. Non-randomized studies utilizing eye movement tasks in individuals with a depressive disorder versus controls will be included. Eye movement tasks of interest include, but are not limited to, saccade, smooth pursuit, fixation, free-viewing, attentional disengagement, visual search, and attentional blink tasks. Results will be categorized by eye movement task. Risk of bias will be assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and confidence in cumulative evidence will be assessed using GRADE criteria.

Ethics and dissemination: Ethics approval is not required due to the nature of the proposed analysis. Results will be disseminated through a journal article, conference presentations, and/or dissertations.

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Strengths and Limitations:

- This is the first meta-analysis of eye-tracking in depression to include saccade tasks and smooth pursuit
- Inclusion of other depression diagnoses and subthreshold depression, in addition to MDD, will allow us to depict a more comprehensive picture of the population
- Sample size of some tasks, such as the attentional blink task, may be small
- Due to the large date range, comparability of results may be challenging due to different eye-tracking technologies and analyses employed

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RATIONALE:

Major depressive disorder (MDD) is the leading cause of disability worldwide.[1] According to the most recent edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5), MDD is characterized by having low mood and/or low interest/pleasure all day nearly every day for at least two weeks, as well as having a total of five out of nine listed symptoms.[2] Similarly, in the latest edition of the International Classification of Diseases (ICD-11), a depressive episode requires a total of five out of ten listed symptoms to be present, with one being either low mood or low interest/pleasure.[3] The presence of MDD has been found to significantly impact life satisfaction and functioning, with associations to marital dissatisfaction, lower income, more missed work, and cognitive impairment,[4] as well as increased risk for comorbid mental disorders.[5] In comparison to single major depressive episodes, recurrent depression is associated with impaired psychosocial functioning in adulthood, including lower positive and higher negative emotionality, more antisocial behaviour, increased use of mental health services, and increased suicidal ideation.[6]

Despite continued efforts to identify biomarkers (e.g., candidate genes, blood-based markers, structural or functional neuroimaging markers, etc.) for depression, research has been unsuccessful at identifying a reliable biomarker to integrate into clinical practice.[7] However, the growing field of eye-tracking in mental disorders may be able to address this issue. Unlike other methods, such as neuroimaging, eye-tracking is comparatively cost-effective and non-invasive, making it an accessible and attractive option for researchers, study participants, and patients. Eye movement behaviour, such as saccades or pupil responses, have been previously investigated and linked to specific brain structures and networks, and therefore may be used to identify impaired functioning in specific brain areas and networks.[8-12] For example, eye

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movement tasks can be designed to target areas responsible motor control, cognitive processes (e.g., inhibitory control), and emotion.[13-14] In mental disorders such as depression, eye-tracking has emerged as a useful tool to understand alterations in cognitive and emotional processes.[15] Thus, eye-tracking is a promising method to improve psychological models of disorders, study progression of illness, and identify neural markers, which may lead to improved interventions and early identification in at-risk individuals.

A variety of tasks or paradigms have been utilized in eye-tracking research to probe specific brain functions. Commonly used are saccade tasks, which require participants to make eye movements to different areas on a computer monitor. Variations of saccade tasks include the pro-saccade (requiring participants to look towards a visible target), anti-saccade (requiring participants to look away from a visible target), predictive/anticipatory saccade (requiring participants to make a saccade to a location before a target appears), and memory-guided saccade (requiring participants to make a saccade to the remembered position of a target after it has disappeared). Fixation tasks (requiring participants to keep their gaze on one target) and smooth pursuit tasks (requiring participants to keep their eyes on a moving target) have also been employed. Finally, unstructured free-viewing tasks (allowing participants to look wherever they please) of varying stimuli, attentional disengagement tasks, and visual search tasks have become increasingly popular in eye-tracking research. Multiple types of outcomes can be examined from these tasks, including saccade metrics (e.g., saccadic reaction time), pupil metrics (e.g., baseline pupil size), blink metrics (e.g., blink rate), and performance metrics (e.g., error rate).

Eye-tracking research in clinical populations, including in individuals with MDD, has grown substantially in the last decade (Figure 1). To the authors' knowledge, only three reviews exist on eye-tracking in depression. Two of these are systematic reviews and meta-analyses on

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free-viewing tasks in depression – Suslow and colleagues[14], which included sixteen studies, and Armstrong and Olatunji[16], which included nine studies. The third review is a systematic review on various eye movement tasks in depression, which included 43 studies, and had a broader scope.[15]

In their review, Carvalho and colleagues[15] identified several differences in eye-movement behaviour between individuals with MDD and controls. In comparison to controls, those with MDD had increased reaction time during the pro and anti-saccade tasks, decreased accuracy in the pro-saccade task, and increased error rate during the anti-saccade task. They also had decreased accuracy during the predictive saccade task, decreased reaction time during the memory-guided saccade task, and lower pursuit gain and greater catch-up-saccade rates in smooth pursuit tasks.[15] For free-viewing and visual search tasks, those with MDD, as well as those with bipolar disorder in depressive phase, exhibited increased attention to negative (anger, dysphoric, sadness, anxiety-related, depression-related) stimuli and decreased attention to positive stimuli.[15] Finally, the authors reviewed the effects of medication (such as benzodiazepines, anti-depressants, and anti-psychotic drugs) on oculomotor behaviour, and noted the need to control for medication when examining eye-movements in depression and bipolar disorder.[15]

In their meta-analyses, Armstrong and Olatunji[16] and Suslow and colleagues[14] quantified differences between eye-tracking of attention in those with MDD compared to healthy individuals. Suslow and colleagues found no group differences in initial orientation of attention but found moderate to large effect sizes when looking at maintenance of gaze to various types of stimuli during free viewing of images. Across studies, individuals with depression looked less at positive images (Hedge's g = -.51) and happy faces (g = -.54) and longer for dysphoric images

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(g = .66) and sad faces (g = .58) than healthy individuals.[14] The previous meta-analysis by Armstrong and Olatunji[16] reported that, for orientation, there was no difference between depressed individuals and healthy participants for threatening (g = -.01) or dysphoric images (g = .18). However, they found individuals with depression oriented less towards positive stimuli (g = -.24).[16] For maintenance of gaze, there was again no difference for threatening stimuli (g = .08), but an increase in gaze maintenance for depressed individuals for dysphoric stimuli (g = .46) and a decrease in positive stimuli (g = -.80) compared to healthy participants.[16]

Although much of the research in this area includes the use of one patient group in comparison to controls, some studies have looked at performance on eye-tracking tasks in relation to differential features of depression. For example, non-melancholic depressed patients have been found to perform more similarly to control participants than melancholic depressed patients for most saccade tasks.[17] Sears and colleagues[18] found that while currently dysphoric participants exhibited initial attention orientation biases for both depression-related and positive images, previously depressed participants only exhibited a bias for depression-related images. This pattern of attention to happy faces was also identified by Isaac and colleagues[19], where currently depressed individuals looked at happy faces less than healthy controls, but there was no difference between individuals with remitted depression and healthy controls in looking time. Severity of depressive scores has also correlated with more abnormal performance on their free-viewing task[20]. Different symptom groupings of depression, patient history, and severity of depression have all been found to impact eye-tracking measures, and thus need to be considered when synthesizing results.

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OBJECTIVES:

The proposed systematic review and meta-analysis will discuss and quantify results from eye-tracking literature with a focus on adults with MDD in comparison to healthy controls, as well as other clinically rated depressive disorders (i.e., persistent depressive disorder/dysthymia, dysphoria, bipolar disorder in depressive phase, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, seasonal affective disorder, minor depression, subthreshold depression). Although excluded in prior literature, inclusion of conditions such as subthreshold depression in research is warranted due to the clinical similarity to MDD.[21] We will include data from saccade, smooth pursuit, fixation, free-viewing, attentional disengagement, and visual search tasks. Additionally, we will cover tasks not previously examined by other reviews (e.g., attentional blink task). Eye-tracking outcomes include, but are not limited to, saccades (number, rate, types), saccadic amplitude and velocity, reaction time, error rate and accuracy (qualitative or quantitative), eye position, fixation count and fixation duration, blinks, and pupil dilation/constriction. As the last systematic review on many of these eye movement tasks was published in 2015, an update on adult eye-tracking in depression is necessary given the growth in literature over the past eight years (see Figure 1). To the authors' knowledge, this will also be the first meta-analysis to include saccade, smooth pursuit, and fixation tasks, as well as blink and pupil measures, which is important as these tasks implicate different neural networks. As a result, this paper may aid in identifying consistent eye movement differences in depression, which may advance the research of biomarker discovery.

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METHOD

This protocol covers all items outlined under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).[22]

ELIGIBILITY CRITERIA:

Types of studies: Experimental studies performed in a controlled laboratory environment will be included. Any experimental sessions, including longitudinal work, that include eye-tracking measures and eye movement outcomes will be included. Case reports and case series will be excluded.

Types of participants: We will review studies involving study participants with a mean age between 18–60 years. Participants must have a confirmed diagnosis via a standardized diagnostic instrument or clinical judgement (not reliant on self-report measures). Individuals with a current or remitted, primary diagnosis of major depressive disorder, persistent depressive disorder/dysthymia, dysphoria, disruptive mood dysregulation disorder, seasonal affective disorder, minor/subclinical/subthreshold depression, according to established criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM; any version) or of the International Classification of Diseases (ICD; any version). Studies involving individuals with diagnosed bipolar disorder in depressive phase will be included, and studies involving mixed samples of bipolar phases will be included if depressive phase data can be isolated. Studies will not be included if they utilize experimental mood induction procedures in otherwise healthy participants.

Type of control: Studies must also have a control participant group with a mean age between 18-60 years. Though screened controls (no history of mental disorders or psychiatric medication

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usage) would be preferred, we will also include studies that do not screen their controls and take this into consideration upon analysis and discussion of results.

Types of interventions: The tasks/measures reviewed by Carvalho et al.[15] will be included: pro-saccades, anti-saccades, predictive saccades, memory-guided saccades, smooth pursuit eye movements, fixation tasks, and free-viewing/attentional disengagement/search tasks, as well as the attentional blink task (see Table 1 for definitions). Additional tasks that are found not to fit in these categories will be included if sufficient data exist. Tasks must have performance (e.g., reaction time, error rate) saccade, pupil, or blink data to be included in analyses.

Task	Definition
Pro-Saccade, Reflexive Saccades, Visually Guided Saccades, Refixation Saccades	Requires participants to look towards a visible stimulus
Anti-Saccade	Requires participants to look away from a visible stimulus
Memory-Guided Saccade	Requires participants to look to a location where a target was previously presented
Predictive Saccade, Oddball Task, Self-Paced Saccade	Requires participants to look to anticipated target location after receiving some warning or cue
Fixation, No Saccade	Requires participants to maintain gaze on a target in the centre of the screen
Free-Viewing	Allows participant to look freely at images or videos that appear
Attentional Disengagement	Requires participants to fixate on a stimulus and then look away when prompted
Visual Search	Requires participant to search for stimuli in a scene, or to compare multiple scenes
Smooth Pursuit	Requires participants to track a moving target
Attentional Blink	Requires participants to report two targets that appear one after another

Table 1. Definition of various eye-movement tasks. [11, 15, 23-24]

Type of outcomes: eye movement outcomes will include, but are not limited to,

Performance metrics: accuracy (qualitative or quantitative), correction factors, error rates, reaction time, response search score

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Saccade/fixation metrics: saccade type (back-up, catch-up, corrective, intrusive micro, macro), saccade amplitude, saccade count/rate, saccadic duration, saccadic peak velocity*, saccade position error, intersaccadic interval, direction of initial eye movement, eye scanning length (mean, total), pursuit (gain, latency), first/initial fixation (location, duration, latency), fixation bias, fixation duration, fixation frequencies, fixation number, percentage of time fixating, scan path length, maintenance of gaze, mean gaze duration, final eye position, root mean square, root mean square error, square wave jerk, time-weight average gain, target waveform

Pupil metrics: baseline pupil size, pupil constriction, pupil dilation

Blink metrics: blink duration, blink rate, inter blink interval

*Because of the saccade main sequence relationship, we will scrutinize any velocity comparisons that are not explicitly amplitude matched.

See Table 2 for an overview of patient, intervention, comparison, outcome, and study design (PICOs) criteria for inclusion.

PICOs Criteria	Determinants
Patient	Individuals with MDD, persistent depressive disorder/dysthymia, dysphoria, disruptive mood dysregulation disorder, seasonal affective disorder, minor/subclinical/subthreshold depression, or bipolar disorder in depressive phase. Mean age of study sample must be between 18-60 years.
Intervention	Any eye movement tasks (saccade tasks, smooth pursuit tasks, fixation tasks, free-viewing tasks, attentional disengagement tasks, visual search tasks, attentional blink tasks)
Comparison	Healthy individuals, mean of study sample between 18-60 years.
Outcome	Task performance and any eye movement outcome (performance, saccade/fixation, pupil, and blink metrics; see above)
Study design	Experimental non-randomized studies

Table 2. PICOs criteria and determinants.

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INFORMATION SOURCES:

Journal articles in English, French, German, Dutch, and Portuguese published online up until March 2023 will be reviewed. Included studies will not be limited by geographic location. The electronic databases searched will include PubMed, PsycInfo, EMBASE and Google Scholar. Reference lists of highly relevant articles will also be examined. If full text of papers cannot be accessed, attempts to contact authors will be made. Conference papers, posters, abstracts, and student theses/dissertations will not be included.

SEARCH STRATEGY:

The following is the utilized search strategy for PubMed. All searches will be completed for Title/Abstract and filtered for journal articles and full text availability. The same search strategy will be repeated across databases with minor changes to adjust for database search tools.

Search terms:

1. depress OR mood AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
2. dysthymi* AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
3. dysphori* AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
4. seasonal affective disorder AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit
5. bipolar AND eye tracking OR saccad* OR pupil OR blink OR smooth pursuit

Search strategies for all databases were determined via consensus among the authors.

STUDY RECORDS:

Data management: Excel spreadsheets will be used to manage records at the level of abstract screening and full text review. BKN will perform the initial search and copy relevant information (authors, publication year, title, link to access) from all search hits and will send the completed spreadsheet to AB.

Selection process: BKN and AB will extract abstracts, screen abstracts for eligibility, and conduct the full-text review independently. Kappa will be used to quantify the level of inter-rater

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agreement. DPM and LB will oversee the selection of articles. DPM will provide input on the eye-tracking (e.g., evaluation of methodology), and LB will provide input on the clinical aspects of the studies. In the event of discrepancies at abstract or full text review, DPM will make the decision for discrepancies involving eye-tracking methodology, and LB for discrepancies involving participants and all other issues.

Data collection process: Once included studies have been determined, RevMan will be utilized for data extraction and analysis. Data will be extracted by two independent reviewers (BKN and AB) in duplicate. Data tables will be independently piloted with 10 papers to ensure all necessary information is being extracted.

Data items: The following data items will be extracted for saccade and smooth pursuit tasks:

N (by diagnosis)
Mean age and SD
Sex/gender
Ethnicity
Comorbidities
Diagnostic method
Interventions/treatment
Eye movement tasks
Eye movement outcomes
Results

The same data items will be extracted for free-viewing, attentional disengagement, and visual search tasks, with the addition of stimuli (type and emotional valence).

OUTCOMES AND PRIOTIZATION:

For a list of eye movement outcomes, see Eligibility Criteria (above). The following outcomes will be prioritized due to their frequency in the literature: task accuracy, error rate, fixation duration/maintenance of gaze, and reaction time. Additionally, we will prioritize pupil and blink outcomes as those have emerged as interesting metrics in our laboratory.

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RISK OF BIAS IN INDIVIDUAL STUDIES:

We will use the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to assess the risk of bias for each study. Bias will be assessed by two independent researchers (BKN and AB) and discrepancies will be addressed by LB and DPM. This information will not be used to exclude studies but will be reported and narratively discussed.

DATA SYNTHESIS:

The PRISMA flowchart will be presented to explain how and the number of articles that were retrieved/selected. Results from included individual studies will be categorized by eye movement task and expressed both narratively and in data tables. Means, standard deviation, effect sizes, and statistical significance will be reported. It is anticipated that effect sizes will be expressed as Cohen's D. A meta-analysis will be performed if data from three or more studies exist for the same eye movement task. Pending the final study sample, we will also analyze dated based on subgroups if three or more studies are available. The proposed subgroups include differential diagnoses (e.g., major depressive disorder versus dysthymia), severity of depressive episode (mild, moderate, severe), and current versus remitted depression. It is anticipated that JASP will be used to do the meta-analyses, though other software will be considered at the time of analyses. To assess whether the results are homogenous, the Q statistic will be calculated.[25] If quantitative synthesis is not appropriate for a subset of data, results will be described narratively.

META-BIASES:

We will investigate in greater detail multiple publications coming out from the same research group and we will assess sample size and sample demographics to check for duplication. In case of overlapping samples/results, the first published reference will be included in the analyses,

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unless methodology is not sufficiently detailed to be included. Publication bias will be assessed using a funnel plot method.[26]

CONFIDENCE IN CUMULATIVE EVIDENCE*:*

BKN and AB will independently assess the strength and quality of evidence using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach criteria, a tool for meta-analyses that assesses study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias.[27] Strength of evidence will be rated as very low, low, moderate, or high. In the event of discrepancies on GRADE rating, LB and DPM will make the final decision. A quality assessment table will be presented to display which studies were included and which were excluded.

ETHICS AND DISSEMINATION:

Ethics approval is not required due to the nature of this work. Results will be analyzed and disseminated according to PRISMA guidelines for systematic review and meta-analyses. We aim to write a scientific publication about the findings. We may also present findings in the form of a poster or oral presentation at one or more scientific conferences.

PATIENT AND PUBLIC INVOLVEMENT:

Due to the nature of this study, there will be no patient or public involvement.

DISCUSSION

There is a growing need to identify reliable biomarkers of mental disorders, specifically as they relate to depressive disorders, to improve early diagnosis and treatment.[28] Research into potential eye movement differences using eye-tracking has grown steadily in recent years, as this method offers the ability to use a variety of different task paradigms and is relatively cost-

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effective. Given the surge in eye-tracking research in depression, it is paramount to summarize these findings to effectively identify potential behavioural biomarkers.

This meta-analysis aims to update the knowledge that has been reported previously by past meta-analyses on attentional tasks in depression,[14, 16] provide the first meta-analyses of saccade, fixation, and smooth pursuit tasks in depression, as well as to extend the body of knowledge by including task paradigms and outcomes not previously covered (e.g., attentional blinks). In doing so, we hope to provide a comprehensive overview of current study findings which may help inform future clinical practice in the diagnosis and treatment of depression (and other related disorders). However, while this meta-analysis will attempt to extend the body of knowledge by considering studies using tasks not previously covered by other reviews (e.g., attentional blink task) and those including various depressive disorder populations (i.e., not simply individuals diagnosed with MDD), this may be limited by the number of published studies and their quality.

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a. Contributorship statement: BKN, DPM, and LB designed the planned systematic review and meta-analysis. BKN drafted the manuscript. AB contributed additional text and edits. DPM and LB reviewed the manuscript and oversaw the work. SKK and GHV provided additional input. All authors approved the final version of the manuscript.

b. Competing interests: The authors have no competing interests to declare.

c. Funding: The authors received no sources of financial or other support for the protocol or the planned review.

d. Data sharing statement: Data sharing not applicable as no datasets were generated and/or analysed for this protocol.

Figure 1. Number of results on PubMed for the search query (eye-tracking[Title/Abstract]) AND (depression[Title/Abstract]).

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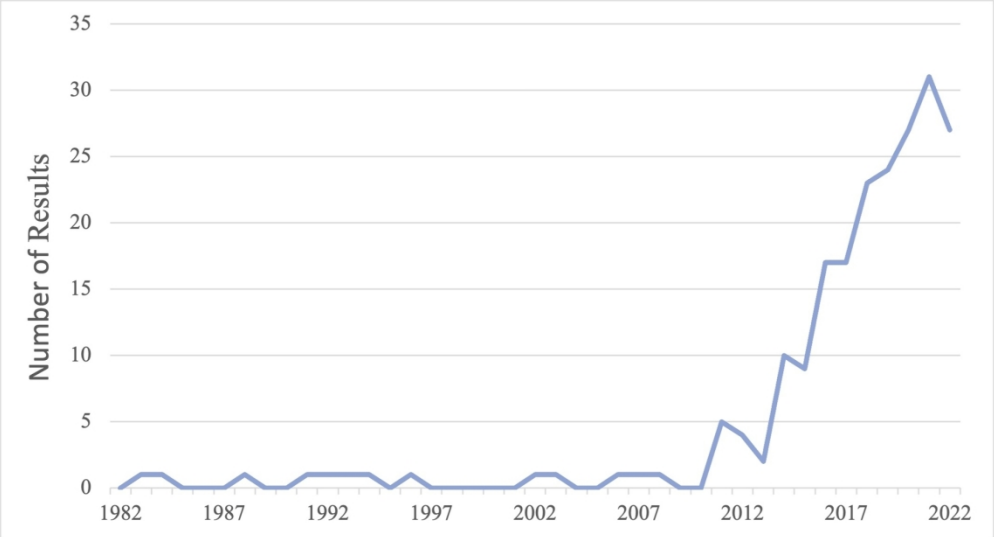

Number of results on PubMed for the search query (eye-tracking[Title/Abstract]) AND (depression[Title/Abstract]).

163x88mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			i
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	i
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	i
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	NA
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	1
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9

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Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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