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INPLASY

Exercise effects on BDNF-mediated hippocampal neurogenesis in adult rodents: a systematic review

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Khalil, MH.

Corresponding author:
Mohamed Khalil

mhmhk2@cam.ac.uk

Author Affiliation:
University of Cambridge.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 August 2025 and was last updated on 24 August 2025.

INTRODUCTION

Review question / Objective Does exercise increase adult hippocampal neurogenesis in rodents through modulation of brain-derived neurotrophic factor (BDNF)?

Rationale Human neurogenesis studies are growing, and the efforts to design environmental affordances for physical activity that can increase BDNF are also growing in parallel. While numerous studies in rodents have reported that both aerobic (e.g., running wheels, treadmill running) and resistance-type exercise (e.g., ladder climbing) can modulate adult hippocampal neurogenesis, the evidence base is fragmented, with wide variability in study designs, exercise modalities, outcome measures, and markers used to assess neurogenesis. To facilitate human research, this systematic review aims to demonstrate if the exercise influence on adult hippocampal neurogenesis is modulated by hippocampal BDNF protein and/or mRNA.

Condition being studied Exercise-based enhancement of adult hippocampal neurogenesis through the modulation of BDNF.

METHODS

Search strategy This systematic review will search the following electronic databases: PubMed, MEDLINE, Web of Science, Scopus, and Embase.

Search string:

(exercise OR running OR training)
AND
("BDNF" OR "brain-derived neurotrophic factor")
AND
("neurogenesis" OR "neural stem cell*" OR "dentate gyrus" OR proliferation OR BrdU OR DCX OR Ki-67 OR PCNA OR NeuN OR MCM2)
AND
("rodent*" OR "rat*" OR "mice" OR "mouse")
AND
(adult)

This search is designed to capture studies evaluating the effects of exercise interventions on hippocampal BDNF expression and markers of neurogenesis in adult rodents.

Participant or population
Included
Adult rodents (rats or mice, any strain, sex, or health status).

Excluded
Studies using juvenile or adolescent animals, non-rodent species, or in vitro/ex vivo models will be excluded.

Intervention
Included
Any form of structured exercise, including aerobic (e.g., voluntary running wheel, treadmill running), resistance (e.g., ladder climbing, strength training), high-intensity interval training, and other exercise paradigms.

Excluded
Studies of environmental enrichment without a defined exercise component will be excluded.

Comparator This review includes both comparative and non-comparative studies.

Study designs to be included in vivo.

Eligibility criteria The screening process will be conducted in two phases:

1. Title and abstract screening to exclude clearly irrelevant studies.
2. Full-text screening of potentially eligible articles against the inclusion/exclusion criteria.

Eligibility criteria (exclusion)

Phase 1: Title/Abstract Screening
1. Not an animal study (e.g., human, in vitro, ex vivo).
2. Not a rodent study (non-rodent animal species).
3. Population not adult rodents (juvenile/developmental).
4. Not an exercise intervention (e.g., pharmacological, genetic, enrichment-only).
5. Not focused both BDNF and hippocampal neurogenesis.
6. Clearly not original research (e.g., review, editorial, abstract only).

Phase 2: Full-Text Screening
7. Full text not accessible (e.g., unavailable through institutional/library access).
8. Not an in vivo rodent exercise study (e.g., in vitro, ex vivo, non-rodent species, or non-exercise interventions).
9. No measurement of hippocampal BDNF expression (protein or mRNA) in full text.
10. No measurement of hippocampal neurogenesis markers (e.g., BrdU, DCX, Ki-67) in full text.

Information sources Original articles in English language through Electronic database.

Main outcome(s) Studies must report outcomes on both (i) Measures of hippocampal BDNF expression (e.g., protein, mRNA), and (ii) markers of hippocampal neurogenesis (e.g., BrdU, Ki-67, DCX, neural stem cell labeling).

Exclusion criteria: studies that do not measure hippocampal BDNF expression or hippocampal neurogenesis markers.

Additional outcome(s) Peripheral BDNF (serum/plasma), behavioral/cognitive outcomes.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the SYRCLE's Risk of Bias (RoB) tool. As the review is conducted by a single researcher transparently based on the available information provided in text by the authors.

Strategy of data synthesis A narrative synthesis of the included studies will be undertaken. This approach is appropriate given the expected variability in exercise modalities (e.g., voluntary running, treadmill, ladder climbing, swimming), outcome measures (hippocampal BDNF protein, mRNA; neurogenesis markers such as BrdU, DCX, Ki-67).

Subgroup analysis If sufficient studies are available, results will be stratified according to:

1. Type of exercise: aerobic (e.g., running wheel, treadmill, swimming) vs resistance (e.g., ladder climbing).
2. Mode of exercise: voluntary vs forced.
3. Rodent species: rats vs mice.
4. Sex: male vs female animals.
5. Model type: healthy vs disease/experimental models (e.g., Alzheimer's, depression, stroke).
6. Outcome measure: BDNF protein vs mRNA expression; proliferation markers (BrdU, Ki-67) vs immature neuron markers (DCX).

Sensitivity analysis Sensitivity analyses will be conducted to test the robustness of findings. Analyses will be repeated excluding studies judged at high risk of bias (based on SYRCLE's tool). Sensitivity analyses will be performed narratively by re-interpreting findings with and without the excluded studies.

Language restriction English language only.

Country(ies) involved United Kingdom.

Other relevant information No formal assessment of publication bias is planned, as a meta-analysis will not be conducted. Instead, potential publication bias will be addressed narratively by considering the balance of reported positive versus negative findings, the presence of selectively reported outcomes, and the diversity of exercise paradigms.

Keywords Neurogenesis; Hippocampus; Exercise; BDNF; Brain-derived neurotrophic factor BDNF; Physical activity; Training.

Contributions of each author

Author 1 - Mohamed Khalil.
Email: mhmhk2@cam.ac.uk