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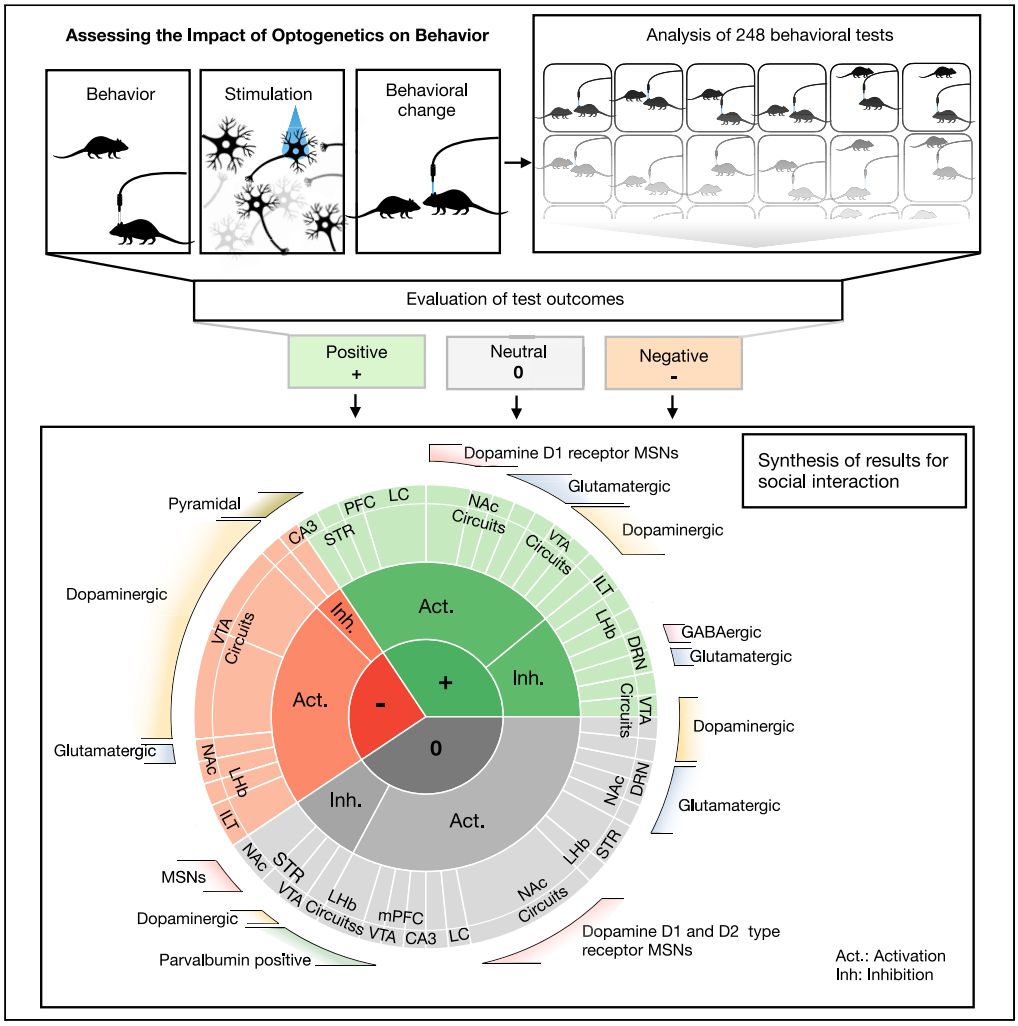

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Highlights

Social interaction is most intensively studied in optogenetic behavioral studies

24 different neuronal circuits and cell types were stimulated in stressed animals

Dopamine projections in the VTA and the NAc were studied most intensively

Optogenetic stimulation mitigated behavioral deficits in about a third of tests

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Optogenetic behavioral studies in depression research: A systematic review

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SUMMARY

Optogenetics has made substantial contributions to our understanding of the mechanistic underpinnings of depression. This systematic review employs quantitative analysis to investigate the impact of optogenetic stimulation in mice and rats on behavioral alterations in social interaction, sucrose consumption, and mobility. The review analyses optogenetic behavioral studies using standardized behavioral tests to detect behavioral changes induced via optogenetic stimulation in stressed or stress-naive mice and rats. Behavioral changes were evaluated as either positive, negative, or not effective. The analysis comprises the outcomes of 248 behavioral tests of 168 studies described in 37 articles, including negative and null results.

Test outcomes were compared for each behavior, depending on the animal cohort, applied type of stimulation and the stimulated neuronal circuit and cell type. The presented synthesis contributes toward a comprehensive picture of optogenetic behavioral research in the context of depression.

INTRODUCTION

Major depressive disorder (MDD) is a severe mental illness that strongly contributes to the global burden of disease.[1,2] According to the World Health Organization (WHO), approximately 280 million people worldwide suffer from depression, making it one of the leading causes of disability.[2] In 2018, the 12-month and lifetime prevalence of MDD in adults in the USA was reported to be 10.4% and 20.6%, respectively.[3] Moreover, MDD in adolescents and adults has increased over the past decades.[3,4] Furthermore, depression is a significant risk factor for suicide.[1,5] However, depression is often not diagnosed or treated sufficiently,[6] and established treatments like cognitive behavioral therapy and antidepressant drug therapy, are only moderately successful.[7,8] Other therapies, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) are still at the experimental stage, and their mechanisms of action are not yet fully understood.[9–14] The lack of effective treatment methods can be partially attributed to the heterogeneous clinical picture of depression. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), various combinations of symptoms can lead to the diagnosis of depression. Symptoms range from anxiety, anhedonia, depressive mood and lack of motivation to weight loss or gain, sleeping disorders, headaches, social withdrawal, and suicidal thoughts. This heterogeneous clinical picture is based on a complex network of biochemical processes at the neuronal level.[15,16] Basic research has provided insights into the complex neurological circuitry underlying the disease using neuroscientific methods, such as imaging techniques.[17]

The technique of optogenetics was developed in 2005 and continues to enlighten neuronal processes in both disease and health.[18–21] Optogenetics investigates the control of neuronal functions through the optical activation or inhibition of light-sensitive proteins (opsins), which are introduced into specific neurons by a virus.[22–24] Because of cell-type specificity and high temporal resolution, the induced neuronal processes can be related to distinct behavioral changes.[25,26] Therefore, optogenetic applications *in vivo* can provide unseen accessibility to the causal links between behavior and its neuronal underpinnings.[27] Over the last decades, optogenetics has contributed to the understanding of psychiatric disease mechanisms.[28–30] Combining optogenetic *in vivo* applications with established behavioral tests for depression has elucidated and confirmed disease-related brain circuits in living and behaving animals.[31,32] In future, findings from optogenetic behavioral studies might improve clinical treatment methods for depression, such as DBS and TMS, by identifying promising brain targets and effective protocols for stimulation.[33–36] Considering the rapidly growing pool of optogenetic studies on depression, identifying approaches, which are relevant for clinical applications is becoming progressively challenging. Difficulties arise from inconsistencies in preclinical studys and putative contradictory results. The heterogeneity of study designs complicates the interpretation of their outcomes with regard to their clinical potential.

Additionally, not reporting negative or null results, a problem well known from pharmacological studies, but widely neglected in basic research, leads to publication bias, making a realistic assessment of study outcomes and the formation of a coherent overall picture more difficult.[37,38]

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Table 1. Description of different behavioral tests for depression-related behaviors

Investigated Behavior	Behavioral Test	Description	Measurement Values
Social Interaction	The Social Interaction Test (SIT)	The social interaction test is an anxiety-based test in which an unfamiliar rodent in a small mesh box is placed in the investigated rodent's cage. The time that the rodent spends in an interaction zone around the intruder's cage serves as a measure for social interaction.	Social Interaction/Exploration: • Time (s) • Ratio (%) • Fold change
Sucrose Consumption	The Sucrose Preference Test (SPT)	The sucrose preference test is a reward-based test, in which subjects are allowed to choose between water and a sucrose solution. The number of licks on each solution is counted for a certain period of time and measures sucrose consumption.	Sucrose Preference (%)
Mobility	The Forced Swim Test (FST)	The forced swim test is a despair-based test in which the rodent is placed in an inescapable water tank. The time spent passive or active is recorded as a measure for mobility.	Immobility or Mobility: • Time (s) (min) (arbitrary units) • Change in kick frequency (Hz)
Mobility	The Tail Suspension Test (TST)	The tail suspension test is an alternative behavioral despair test, in which the rodent hangs from a horizontal bar suspended by its tail. The time spent passive or active is recorded as a measure for mobility.	Immobility or Mobility: • Time (s) (min) (arbitrary units) • Change in kick frequency (Hz)

Nevertheless, the large number of optogenetic studies on depression research is opening up new possibilities for quantitative analyses. The widespread use of standardized behavioral tests is allowing researchers to assess the effects of optogenetic stimulation in different brain targets. Moreover, comparisons of individual studies are possible through test-specific outcome measures and allow for evaluating optogenetic interventions on a quantitative level.

Rationale

In this systematic review, we have investigated the effect of optogenetic interventions on three behavioral conditions, that capture certain aspects of the symptomatology associated with human depression: social interaction, sucrose consumption, and mobility. We have reviewed optogenetic behavioral studies, which explore the effect of optogenetic stimulation in mice and rats, in standardized behavioral tests. We considered (i) the social interaction test to measure changes in social interaction, (ii) the sucrose preference test to measure changes in sucrose consumption, and (iii) the forced swim test, and (iv) the tail suspension test to measure changes in mobility (Table 1). For each study, we evaluated the outcome of the conducted tests via test-specific outcome measures. If there was a significant difference in the outcome measure between the test and the control group, we evaluated the test outcome either as "positive effect" or as "negative effect". If the outcome measure did not differ significantly between the groups, we evaluated the outcome as "no behavioral effect" (Figure 1).

For each reviewed behavioral test, we registered the essential study parameters (Table S1, Supplement). We quantitatively compared test outcomes for each behavior, depending on the animal cohort (stress or stress-naive), the applied type of stimulation (excitatory or inhibitory) and the stimulated brain target (area of light delivery). The final synthesis of the collected data provides an overview of optogenetic *in vivo* research in mice and rats, investigating the neuronal underpinnings of behavioral conditions of relevance to the clinical condition of depression (Table S1, Supplement). Based on our analysis, we visualized and discussed correlations between the optogenetic stimulation of specific neuronal projections and resulting changes in certain behaviors.

Research question

What is the quantitative effect of optogenetic stimulation in mice and rats, on behavioral conditions that mimic symptoms of human depression, depending on different stimulation types and targets?

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[39]

Search strategy. We conducted a literature search on PubMed and Web of Science. The search was restricted to journal articles written in English and published between 01.01.2009 and 03.01.2022. The following search string was used: "(optogenetics) and (depression or MDD or

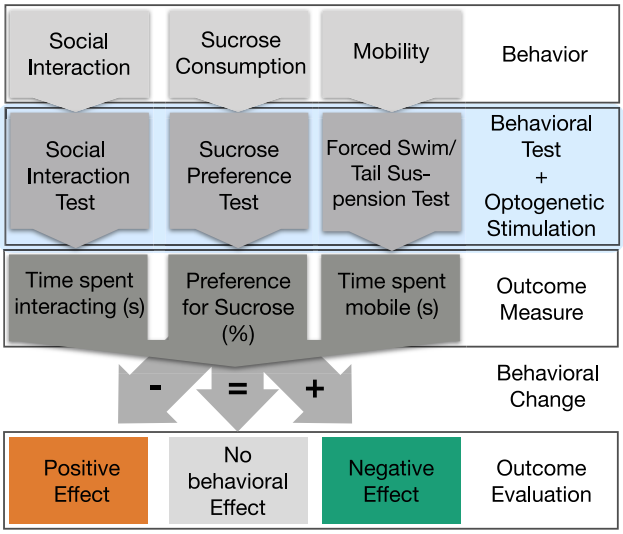

Figure 1. Schematic illustration depicting the procedure for assessing the impact of optogenetic stimulation on specific behaviors

Social interaction, sucrose consumption, and mobility are investigated in the social interaction test (SIT), the sucrose preference test (SPT), and the forced swim test (FST) or tail suspension test (TST), respectively. Behavioral changes are indicated through alterations in test-specific outcome measures and are evaluated as having a positive effect, a negative effect, or no behavioral effect.

major depressive disorder) and (rodents or mice or rats)." In addition, we searched reference lists of relevant review articles manually for any relevant records.

Eligibility criteria. Two independent reviewers (A.S. and D.A.) assessed the article eligibility in two screening phases. Discrepancies were resolved through discussion with a third reviewer (S.M.). We screened each selected article for relevant optogenetic behavioral studies matching the defined inclusion criteria.

In Screening Phase I, we screened titles and abstracts for *in vivo* optogenetic behavioral studies in mice and rats that investigated social interaction, sucrose consumption and mobility. In the context of optogenetic behavioral studies, we reference the conduct of behavioral assays in conjunction with optogenetic stimulation. One article may contain several relevant studies. We included only primary research articles.

In Screening Phase II we screened the main texts and supplementary materials of selected articles for relevant optogenetic behavioral studies, with regard to the type of behavioral test, the outcome measure, the animal type, and the stimulation protocol. We included only studies if they reported the results of at least one of the following standardized behavioral tests: (i) the social interaction test (SIT), (ii) the sucrose preference test (SPT), (iii) the forced swim test (FST), and (iv) the tail suspension test (TST).

Additionally, we included only studies in which the results of the behavioral tests were assessed by one of the following outcome measures: (i) time, change, or ratio of interaction during the SIT, (ii) preference for sucrose during the SPT or (iii) time or frequency of mobility or immobility during the FST or TST (Table 1). Furthermore, we included only studies using mice or rats (all species, all ages, male and female, stress-susceptible and stress-resilient, stress-naive and stressed). For stressed animals, the following stress paradigms were applied to induce depression-related behaviors: (i) chronic mild stress (CMS), (ii) chronic social defeat stress (CSDS), (iii) inescapable stress (IS) or (iv) chronic restraint stress (CRS) (Table 2).

Additionally, we included only studies with a control group comprising animals which were either injected with an optogenetic construct lacking the light controllable opsin or animals, which were injected with the light controllable opsin but were not stimulated with the wavelength required to activate the opsin. We excluded tests where the stimulation frequency of the control group was clearly different from that of the test group. We included studies in which optogenetic stimulation was applied in stress-naive animals as independent studies, allowing for comparison with optogenetic stimulation in stressed animals, if they had their own control group. Finally, we included studies with various types of stimulation protocols (wavelength, frequency, pulse duration, timing), studies in which the stimulation was applied before or during the behavioral test and studies in which the stimulation was applied during the application of a stress model.

Data extraction. Two reviewers (A.S. and D.A.) extracted the data independently using the PICOS approach. The collected parameters included general article information (first author, year of publication), detailed characteristics of the study protocol, information regarding the optogenetic stimulation and results of all the behavioral tests conducted. Additionally, we also collected the behavioral condition investigated (social interaction, mobility, sucrose consumption); the type, strain, and sex of the animals used; whether the animals were stress-naive, stressed, susceptible or resilient and which type of stress paradigm was applied for inducing behavioral deficits as well as the sample sizes of both the experimental and control groups. We registered the optical target (area of light delivery) and the viral target (area of virus

Table 2. Description of different animal models of depression

Stress Model	General Description
Social Defeat Stress (SDS)/Chronic Social Defeat Stress (CSDS)/Subthreshold Social Defeat Stress (SSDS)/Subthreshold Acute Defeat Stress (SADS)	The subject animals are repeatedly exposed to a novel aggressor over several days/weeks. In an initial 5–10 min period of exposure, animals are physically defeated by the aggressor, followed by sensory contact during the next 24 h. During this time, the animal is placed behind a plexiglass partition in the aggressor's home cage. Time periods may vary in different models.
Chronic Unpredictable Mild Stress (CUMS)/ Chronic Mild Stress (CMS)	Animals are exposed to one unpredictable mild stressor twice a day for 4–12 weeks. Stressors (among others) include a 45° angle cage tilt (1–16 h), food or water deprivation (12–16 h), white noise (1–16 h), strobe light illumination (1–16 h), crowded housing (1–3 h), separating cage-mates (1–16 h), and damp bedding (12–16 h). Time periods may vary in different paradigms.
Inescapable Stress (IS)	Animals are exposed to repeated, inescapable tailshocks of increasing intensity. 100 shocks, lasting 5 s each, are delivered with an inter-trial interval of 60 s. Shocks are delivered in a plexiglass box. Right after shock exposure, subjects are returned to the home cage.

injection) along with data regarding the stimulation protocol, such as the timing, duration, frequency, pulse duration, wavelength, as well as whether the simulation was excitatory or inhibitory. Additionally, we registered the optogenetic construct, consisting of a virus, promoter, opsin, and a fluorescent tag. Finally, we recorded the outcome measures for each performed behavioral test. Different types of tests were assigned to one study if the optogenetic construct, the optogenetic target (optical and viral) and the type of stimulation regarding the applied wavelength, frequency, and pulse duration were identical. Different tests conducted within one study sometimes differed in the cohort of animals used. Moreover, the timing and duration of the optogenetic stimulation sometimes differed in different types of tests, due to test-specific procedures and time frames.

Study evaluation. For each behavioral test, we examined how the outcome measure differed between the test and the control group. If there was a significant difference in the outcome measure between the groups, the effect of the stimulation was evaluated as "positive effect" (+) or "negative effect" (−). If the outcome measure did not differ significantly between the two groups, it was evaluated as "no behavioral effect" (0) (Table S1). Whether a difference was significant or not was retrieved from the respective articles. Measures for significance may differ in different articles.

The outcome of the stimulation was evaluated as positive if the following test criteria were met.

(i) SIT: If the time spent in the interaction zone was significantly increased in the test group compared with the control group, or if there was a significant increase in the interaction ratio between the groups.
(ii) FST/TST: If the time spent mobile/immobile was significantly increased/decreased in the test group compared with the control group, or if the kick frequency was significantly increased between the groups.
(iii) SPT: If sucrose consumption was significantly increased in the test group compared with the control group.

The outcome of the stimulation was evaluated as negative if the following test criteria were met.

(i) SIT: If the time spent in the interaction zone was significantly reduced in the test group compared with the control group, or if there was a significant decrease in the interaction ratio between the groups.
(ii) FST/TST: If the time spent mobile/immobile was significantly decreased/increased in the test group compared with the control group, or if the kick frequency was significantly decreased between the groups.
(iii) SPT: If the sucrose consumption was significantly reduced in the test group compared to the control group.

These evaluation criteria were applied to both stress-naive animals and animals in which behavioral deficits were induced through the application of stress paradigms.

RESULTS

Article selection

After the initial online search of PubMed and Web of Science, we identified 400 articles. We detected another 36 articles through the examination of relevant reviews. After the removal of duplicates, we screened the titles and abstracts of 354 articles for eligibility. After the first

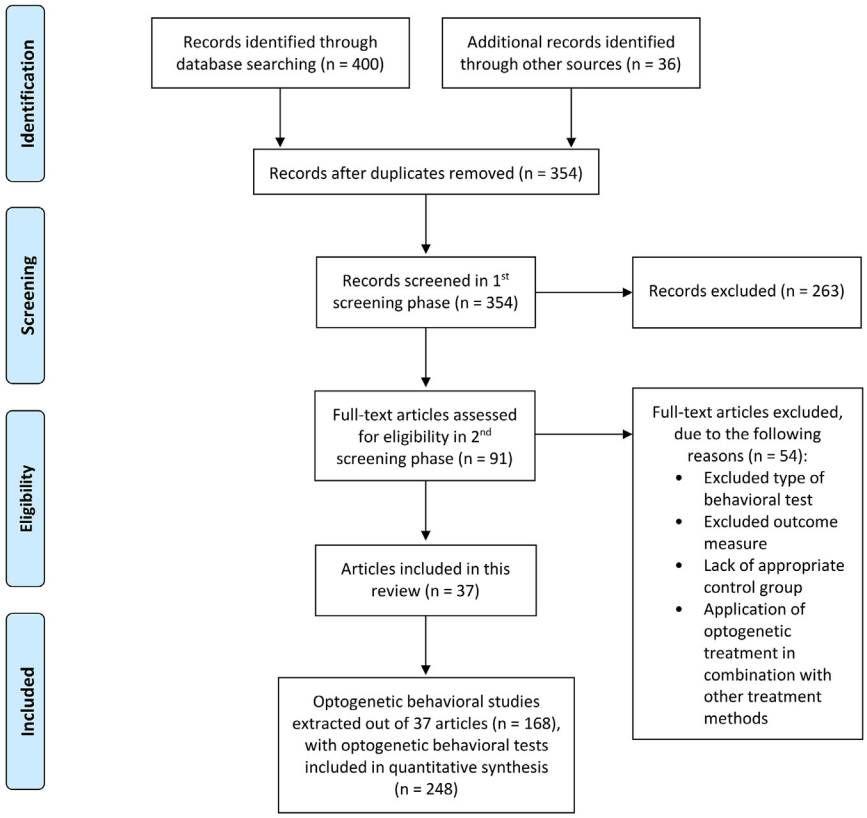

Figure 2. Prisma Flow Diagram

screening phase, we excluded 263 records. In a second screening phase, we screened the full texts and supplementary materials of the remaining 91 articles and excluded another 54 articles. In total, 37 articles were included in this review (Figure 2).

Out of the 37 articles, 168 studies were included in the analysis, with 248 behavioral tests evaluated within these 168 studies.

All included studies and behavioral tests are listed in Table S1, Supplement. The rows list the studies, while the columns present the study characteristics. Different studies extracted from one article are named with the first author and are numbered. For example, Chaudhury_1, Chaudhury_2, and Chaudhury_3 correspond to three different studies extracted from the article by Chaudhury et al. (2013).[40]

Behavioral conditions

One type of behavioral test was performed in 106 of the studies, two different types of tests were conducted in another 47 studies, and three or four different types of tests were conducted in the remaining 15 studies.

Figure 3A shows the number of behavioral tests performed for each type of behavioral condition: 112 tests for social interaction, 47 tests for sucrose consumption, and 89 tests for mobility. For each type of behavior, the number of behavioral tests with no behavioral effect was highest, followed by the number of tests with a positive effect and then with a negative effect (Figure 3A). The large number of tests without an effect can be explained by studies in stress-naive animals that were performed as additional controls as comparison to studies in stressed animals. Since they had an own control group, they were included as individual studies. A further classification into stressed and stress-naive animals is provided in the following section.

Cohorts of animals

In total, 137 studies used mice, while 31 studies used rats. Nearly all studies used exclusively males, while only seven studies used exclusively females[41] and 12 studies used both sexes.[42,43] A hundred and one studies used stress-naive animals (135 behavioral tests). Stress models were applied prior to optogenetic interventions in 67 studies (113 behavioral tests). Different models for inducing behavioral deficits were used: variations of social defeat paradigms (SDS, CSDS, SADS, and SSDS) in 63 studies; variations of a CMS and CUMS in three studies;[44–46] CRS in one study[47] and inescapable foot shocks in one study.[79] These studies also encompassed diverse animal housing and handling conditions.

Twenty-five studies performed an additional behavioral test after the stress model and prior to the optogenetic intervention in order to identify susceptible and resilient animals. Thirty studies only used animals susceptible to depression for behavioral testing, while four used

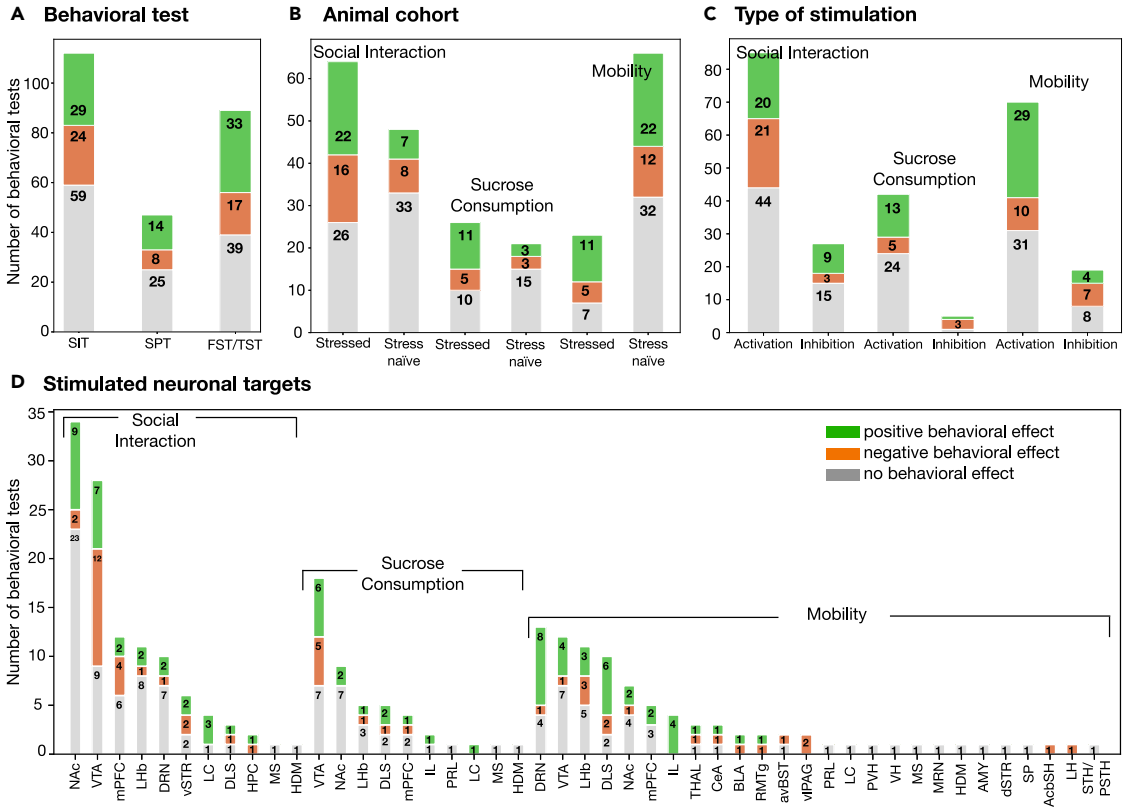

Figure 3. Outcomes of optogenetic behavioral tests

Quantities of performed behavioral tests with a positive, negative, or no behavioral effect (A) investigating social interaction, sucrose consumption, and mobility, (B) performed using stressed or stress-naive animals, (C) in which an activating or inhibitory stimulation protocol was applied, (D) for different stimulated brain targets.

resilient animals. Specific information, regarding the type, strain, sex of animals, as well as the applied stress paradigm are shown in Table S1, Supplement.

To investigate social interaction, 64 tests were performed on stressed animals and 48 tests on stress-naive animals (Figure 3B). For sucrose consumption, 26 tests used stressed animals and 21 stress-naive animals. For mobility, 66 tests used stress-naive animals and 23 tests stressed animals.

For stressed animals, the number of tests with a positive effect was greatest for sucrose consumption and mobility, while the number of tests with no behavioral effect was greatest for social interaction. For stress-naive animals, the number of tests with no behavioral effect was by far the largest for each investigated behavior (Figure 3B).

Optogenetic stimulation

In 129 of the studies (197 behavioral tests), optogenetic activation was applied via blue light stimulation (ca. 470 nm). Thirty-nine studies (51 behavioral tests) used optogenetic inhibition through yellow or green light stimulation (ca. 530–590 nm) (Figure 3C).

In three studies (3 behavioral tests) closed and open loop stimulation was applied using an activating stimulation protocol.[48]

In 64 studies, optogenetic activation was applied during behavioral testing, while in 47 studies it was applied prior to behavioral testing. In eight studies, it was applied before and during behavioral testing. In seven studies, the activation was applied during the execution of a stress model. Optogenetic inhibition was applied during behavioral testing in 29 studies, and prior to behavioral testing in two studies. In one study, it was applied before and during behavioral testing. In six studies, inhibition was applied during the execution of a stress paradigm, while in four studies the timing of the stimulation (activation or inhibition) was unclear. In studies, in which the stimulation was applied during the performance of a test, additional types of tests might have been performed afterwards without stimulation. For example, stimulation was often performed during the SIT, while the SPT was performed afterwards without stimulation.[40] The stimulation timing therefore varies for the different types of behavioral tests. Detailed study protocols regarding the stimulation timing duration and frequency can be found in Table S1, Supplement.

For each behavior, activating stimulation (social interaction: 85 tests; sucrose consumption: 42 tests; mobility: 70 tests) was used more often than inhibitory stimulation (social interaction: 27 tests; sucrose consumption: 5 tests; mobility 19 tests) (Figure 3C).

Brain targets

In total, optogenetic stimulation was performed in 28 different brain targets. The number of tests performed varied greatly for the different brain targets. Considering all types of behavioral tests collectively, we found that the most frequently stimulated targets were the ventral tegmental area (VTA) (58 tests), the nucleus accumbens (NAc) (50 tests) and the lateral habenula (LHb) (27 tests), followed by the dorsal raphe nucleus (DRN) (23 tests) and the medial prefrontal cortex (mPFC) (21 tests).

Looking at each type of behavioral test separately, we identified eleven different targets that were stimulated for social interaction, ten for sucrose consumption, and 26 for mobility (Figure 3D). For both social interaction and sucrose consumption, the VTA and NAc were the most investigated targets. For mobility the DRN, VTA, LHb, and DLS were mostly investigated. The number of different targets tested was highest for mobility, although a majority of targets was only investigated in one to three tests.

In several targets, the stimulation had no behavioral effect in the majority of tests (social interaction: NAc, DRN, LHb, mPFC; sucrose consumption: VTA, NAc, LHb; mobility: VTA, LHb, NAc, mPFC).

Risk of bias

Two independent reviewers (A.S. and D.A.) assessed the reporting of risk of bias for each article by using and adapting a CAMARADES study quality checklist. We searched for the reporting of maintenance of animals, randomization of animals, blinding of the experimenters, exclusion of animals, sample size calculations, compliance with animal welfare regulations, and possible conflicts of interest (Table S2, Supplement). All articles reported on the basic maintenance conditions of the animals, which included single or group housing, day-night rhythm, and access to food and water. We found nine articles reporting on the randomization of animals to treatment and control groups. Three articles reported on alternating testing between the test and control groups to avoid variation bias.[41,49,50] Fourteen articles reported on the blinding of experimenters to treatment conditions. In four articles, the exclusion of animals was reported due to a misplacement of fiber optics or viral mistargeting.[49,51–53] One article reported on the exclusion of animals due to a baseline sucrose consumption of less than 70%.[54] All but one article[55] reported on compliance with animal welfare regulations. Additionally, all but one article[56] provided sample sizes of control and experimental cohorts. Group sizes varied between three and 23 animals per group cohort (Table S1, Supplement). Twenty-five articles declared no conflict of interest, two articles declared competing interests, while nine articles provided no information on this.

Analysis of neuronal circuits and cell types

A major factor determining the positive or negative effect of optogenetic interventions is the targeted neuronal circuit or cell type. Within optogenetics, different parts of neurons, such as axon terminals or somas, as well as their projections, can be precisely stimulated. Moreover, employing various promoters enables the selective targeting of specific neuron populations (e.g., GABA, DA, serotonin). Thus, exclusive activation of certain neuron projections reaching from another brain area results in the stimulation of a distinct neuronal circuit.[57] Consequently, the stimulation of the same brain area in different experiments may elicit conflicting behavioral outcomes, attributable to the selective activation or inhibition of various microcircuits or cell types within the targeted brain area.[40,58–60]

To gain a deeper understanding of the impact of cell-specific optogenetic stimulation on behavioral changes, we examined outcomes from included optogenetic studies not only based on the targeted brain area but also considering the stimulated neuronal projections. Figure 4 provides a synthesis of results, considering the dependencies between the behavioral outcome, the type of stimulation as well as the specific stimulated circuits and cell types for social interaction, sucrose consumption, and mobility. Our focus centered on animals displaying behavioral deficits induced by diverse stress models to uncover the neuronal mechanisms correlated with these deficits.

Overall, our analysis shows the stimulation of eight different cell populations and neuronal subtypes (dopaminergic, glutamatergic, GABAergic, serotonergic, parvalbumin positive, orexin, pyramidal, medium spiny neurons) across 24 distinct neuronal areas or circuits. Regarding social interaction, a total of 20 different circuits were either activated or inhibited across 64 tests. Among these, stimulation in 17 neuronal circuits led to increased social interaction in 22 tests. In sucrose consumption analysis, 12 distinct circuits were stimulated across 26 tests, resulting in an increase in sucrose intake observed in 11 tests via the stimulation of eight different circuits. Mobility assessments involved the stimulation of 13 circuits across 23 tests, demonstrating an elevation in mobility in eleven tests, achieved through the stimulation of seven distinct circuits.

Among the stimulated cell types, dopamine neurons emerged as the most extensively studied in optogenetic behavioral studies. Optogenetic inhibition or activation of dopamine neurons projecting from the VTA consistently exhibited positive effects on all three behaviors. Similarly, the stimulation of pyramidal neurons connecting the hippocampus and dorsolateral striatum (DLS) showed positive behavioral outcomes across all investigated behaviors. In the context of social interaction and mobility, various glutamatergic projections between the NAc, hippocampus (HIP), amygdala (AMY), and medial prefrontal cortex (mPFC) were stimulated. The findings highlight that each of these circuits contributes to distinct behavioral outputs, underscoring their specific roles. Additionally, the stimulation of orexin projections in the VTA resulted in a reduction of behavioral deficits in social interaction and sucrose consumption. Selective stimulation of different parvalbumin (PV) projections within the ventral pallidum (VP) yielded diverse behavioral outcomes in terms of social interaction and mobility. Furthermore, the activation of orexin projections from the VTA to the perifornical lateral hypothalamus (peFLH) increased sucrose consumption and mobility. Contradictory effects are observed at this level of analysis for the stimulation of VTA projections, where both inhibition and activation resulted in an increase, decrease, and no effect on social interaction and sucrose consumption in different experiments. Similarly, contradictory effects were observed for glutamatergic projections in the NAc concerning social interaction. However, these inconsistencies can be attributed to

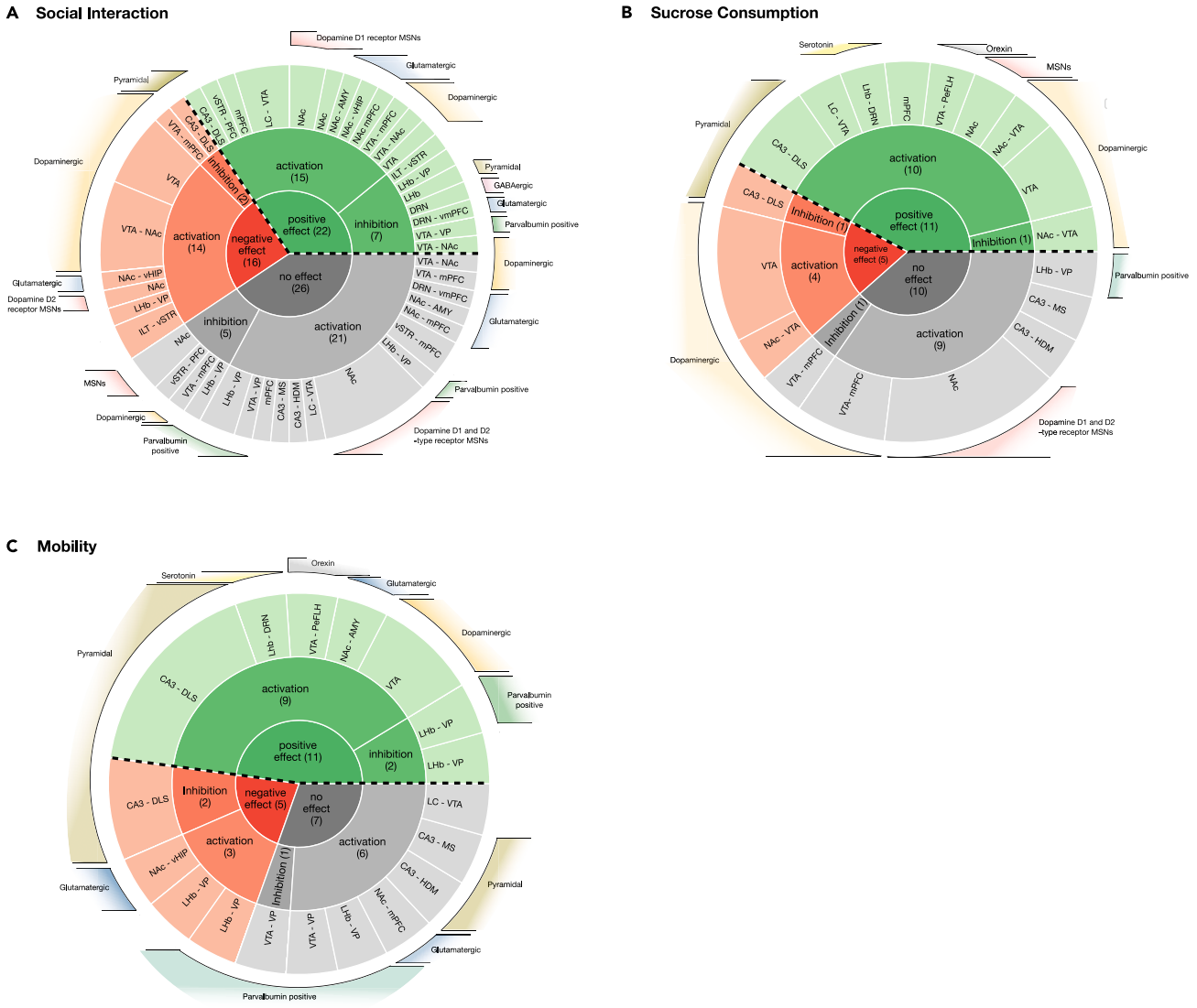

Figure 4. Effects of stimulated neuronal circuits on behavioral outcomes

Overview of all performed optogenetic behavioral tests exclusively in stressed cohorts for (A) social interaction, (B) sucrose consumption and (C) mobility, depending on the outcome (first circle), the applied type of stimulation (activation vs. inhibition) (second circle), stimulation target (third circle) and neuronal types (outer circle). The numbers in parantheses indicate the total number of conducted tests. Dashed lines (black) indicate portion of tests, in which optogenetic activation or inhibition caused a positive outcome.

variations in stimulation protocols and the utilization of different stress models, which can influence the response to optogenetic manipulation.

It is crucial to acknowledge that each circuit was examined in only one study, except for VTA dopamine projections. Therefore, in 20 of the 24 stimulated circuits no replications studies have been conducted.

Optogenetic findings relevant for the clinical treatment of depression

DBS or TMS are used for treating patients with treatment resistant depression.[61–63] These treatments allow the activation or inhibition of local brain areas depending on the target and the stimulation frequency. However, specific stimulation on a cellular level cannot be achieved.[64–67] Insights gained from optogenetic studies, which investigate behavioral deficits that partially resemble symptoms observed in individuals with depression, can contribute to the identification of optimal stimulation targets and protocols for DBS and TMS. Here, we point out studies, in which optogenetic stimulation had a positive behavioral effect in stressed animals, with special regard to the stimulation protocol and used stress model. We also address neuronal functions that appear to be related to successful optogenetic stimulation. Figure 5 gives an overview

of the different neuronal circuits and neuron populations in which optogenetic stimulation alleviates behavioral deficits in (A) social interaction, (B) sucrose consumption and (C) mobility.

VTA dopamine neurons. The VTA is part of the mesolimbic dopamine reward circuit and one of the most studied brain targets in stress models.[40,44,55,68] Impaired firing of VTA neurons resulting from stress, is associated with behavioral deficits that are relevant to the clinical presentation of depression.[68] In fact, multiple studies indicate hyperactivity of dopamine (DA) neurons in the VTA of stress-susceptible mice.[40,69] In several studies, optogenetic techniques were utilized in conjunction with behavioral tests such as the SIT, SPT, or FST to investigate the role of the VTA DA system in different behaviors. However, when similar stimulation protocols were employed in stressed animals, the results yielded partially contradictory findings.

Optogenetic chronic activation of VTA DA neurons increased social interaction, sucrose consumption and mobility in susceptible mice, that had previously undergone CSDS.[55] Optogenetic activation of VTA DA neurons during behavioral testing also increased sucrose consumption and mobility in mice, previously exposed to CMS.[44] In several other studies however, optogenetic activation of VTA DA local neurons during behavioral testing actually decreased social interaction and sucrose consumption.[40] Here the stimulation was applied in mice exposed to subthreshold social defeat stress (SSDS) and in resilient animals. These inconsistent results highlight that there must be further factors that determine how the stimulation of the VTA influences certain behaviors. These factors could be the stress paradigm and the timing and duration of the stimulation protocol.

NAc glutamatergic neurons. The NAc is a key part of the reward circuit which is known to play a critical role in the pathology of depression.[70] Therefore, DBS in the NAc has been tested in patients with treatment-resistant depression.[71] The NAc receives neuronal projections from various brain regions, such as the VTA, the prefrontal cortex, the amygdala and the hippocampus.[59,72]

Optogenetic activation applied in mice that had previously undergone CSDS, targeting either glutamatergic mPFC, AMY, or vHIP projections in the NAc increased social interaction.[59] In activating the vHIP-NAc circuit, a low-frequency stimulation protocol was applied, whereas in stimulating the AMY-NAc and mPFC-NAc circuits, acute stimulation was used. The application of these different stimulation protocols seems to be crucial for the respective circuits, as the application of a low-frequency protocol to the AMY-NAc and mPFC-NAc circuits has no effect on social interaction, whereas the application of an acute stimulation protocol to the vHIP-NAc circuit leads to a decrease in social interaction. Moreover, acute stimulation of the AMY-NAc circuit resulted in increased mobility, while acute activation of the mPFC-NAc or vHIP-NAc circuit had no effect or a negative effect on mobility.[59]

The authors of the referenced studies suppose that resilient mice exhibit a reduction in glutamate transmission at synapses connecting the vHIP and NAc, while experiencing an increase in synaptic glutamate levels between the mPFC and NAc.[59] Their results suggest that the enhanced glutamate release in mPFC-NAc or AMY-NAc connections observed in resilient mice can be triggered through the acute stimulation of these circuits in stressed mice. Moreover, reducing glutamate transmission at the synapses connecting the vHIP and NAc, which was observed in resilient animals, might be achieved through long-term depression, which in turn can be triggered by the low-frequency stimulation of vHIP-NAc projections in stressed animals.[59]

DLS—HIP circuit. The CA3 region of the hippocampus is involved in depression and coping with stress.[73] CA3 pyramidal neurons prominently project to the dorsolateral septum.[47] Activation of pyramidal neurons in the DLS projecting from the CA3 increased social interaction, sucrose consumption, and mobility.[47] The inhibition of identical projections decreased all three behaviors, suggesting that the stimulation bidirectionally regulates several behavioral conditions.[47]

VTA—pEFLH and VTA-LC circuit. The VTA receives orexinergic projections from the perifornical region of the lateral hypothalamic area (PeFLH).[46,74] The excitability of orexinergic axon terminals projecting to the VTA was reduced in stressed mice.[46,75] Increasing the orexin release through optogenetic activation of orexin terminals in the VTA significantly increased sucrose consumption and mobility in mice which previously underwent chronic unpredictable mild stress.[46]

The locus coeruleus is located in the brainstem and is the main source of the neuromodulator norepinephrine. It plays a role in the modulation of the sleep-wake cycle, arousal, attention, cognition and other functions, and was found to be involved in mechanisms promoting the resilience to stress.[76,77] The LC projects widely throughout the brain, with the VTA being a key downstream target. Activation of LC neurons projecting to the VTA increased social interaction and sucrose consumption but had no effect on mobility.[77] The stimulation was applied chronically over ten days in susceptible mice that had previously undergone CSDS.[77]

DRN—LHb circuit and DRN GABA neurons. The LHb is strongly connected to the DRN, which is together with the serotonergic system a critical neuronal hub for the development and regulation of social behavior.[40,78] Behavioral changes are mediated by increased serotonergic activity, which can be triggered by uncontrollable stress.[79] The DRN receives glutamatergic inputs from the LHb.[80] Optogenetic inhibition of LHb pyramidal neurons was applied in rats that were undergoing uncontrollable stress[79] and prevented the induction of social withdrawal.[79] This result supports the idea of a critical connection between LHb and DRN activity in the regulation of social behavior.[79]

DRN GABAergic neurons might also contribute to this regulation by controlling serotonergic neuronal firing.[81] DRN GABA neurons were optogenetically inhibited in mice that were experiencing CSDS.[81] When the stimulation was applied during sensory contact with an aggressor mouse, it increased social interaction. Interestingly, the same stimulation, applied after CSDS but during the performance of the SIT, had no

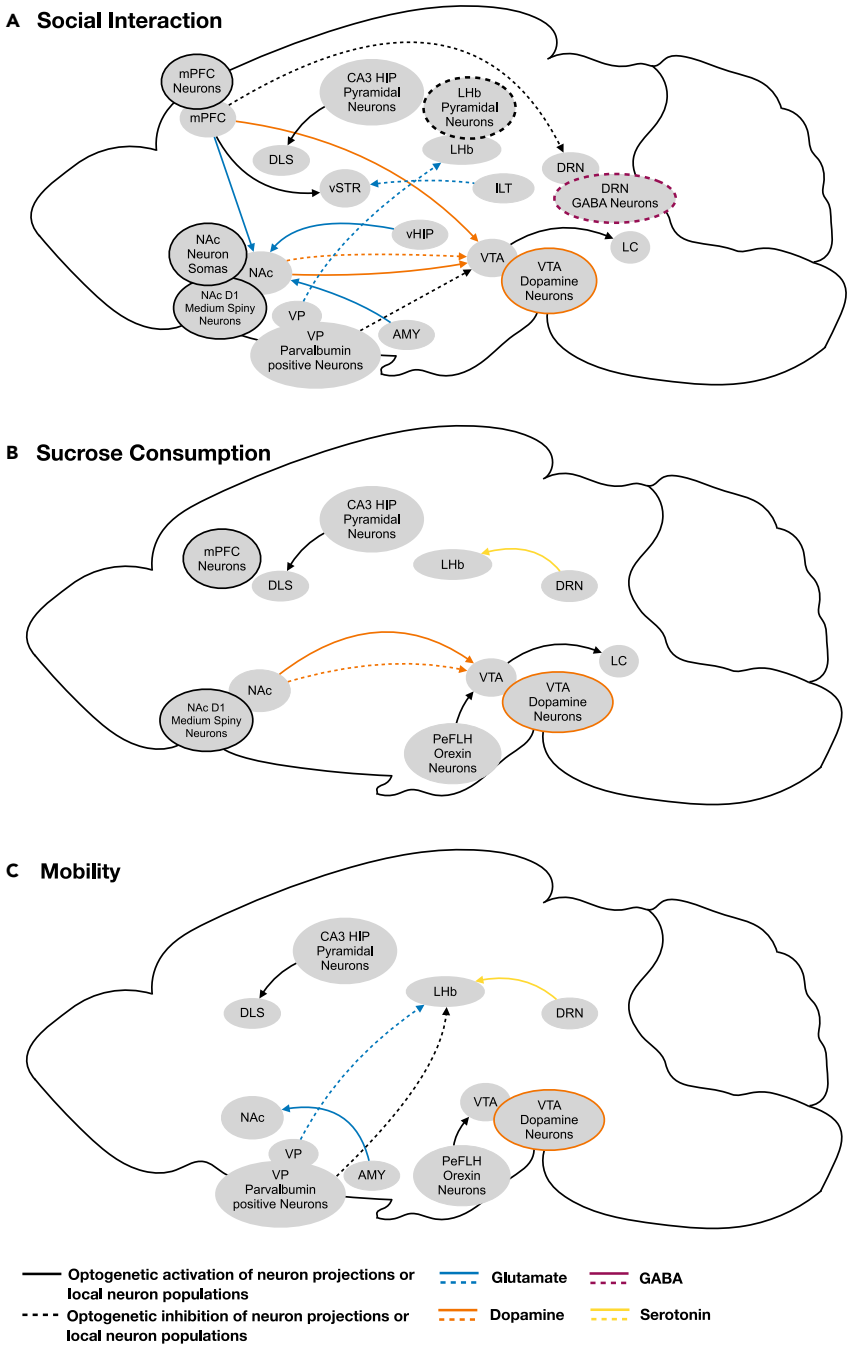

Figure 5. Optogenetic modulation of neuronal circuits in stressed animals

Schematic illustration of neuron projections and local neuron populations, in which optogenetic stimulation had a positive behavioral effect, in stressed animals for (A) social interaction, (B) sucrose preference and (C) mobility. Solid lines illustrate optogenetic activation. Dashed lines illustrate optogenetic inhibition. Encircled areas indicate the stimulation of local neuron populations. Arrows indicate the stimulation of neuron projections. Different colors indicate different populations of neurons, in case specific subtypes of projections or local neurons were stimulated within a circuit or a local area. Black lines indicate the stimulation of neuron projections or local neurons without further specification of neuronal subtypes. For example, regarding social interaction VTA-mPFC, mPFC-NAc, mPFC-vSTR, mPFC-DRN projections, and local neurons within the mPFC were stimulated as follows: Specifically dopamine neuron projections from the VTA to the mPFC were activated, specifically glutamate neuron projections from the mPFC to the NAc were activated, neuron projections from the mPFC to the vSTR were activated, neuron projections from the mPFC to the DRN were inhibited and local mPFC neurons were activated.

behavioral effect.[81] In a different study, DRN serotonergic projections in the LHb were activated prior to behavioral testing.[45] This activation increased sucrose consumption and mobility in mice that had previously undergone chronic mild unpredictable stress. This result suggests that serotonergic connections between the DRN and LHb regulate neuronal activity in the LHb.

DISCUSSION

Previous reviews have drawn conclusions that connect optogenetic interventions to the disease mechanisms of depression.[27,28,30,82–84] Most of these reviews provide qualitative analyses of a wide range of research results and discuss relevant brain targets involved in the mechanistic picture of depression. In addition, some articles discussed the accessibility of specific neuronal circuits for DBS.[34–36] While qualitative examinations of the impact of optogenetic studies for depression research have yet been performed,[85] the need for a statistical analysis is becoming increasingly apparent. To take a first step towards a meta-analysis, we quantitatively compared the outcomes of optogenetic behavioral tests. In order to provide a realistic picture of how successful interventions are in different brain targets, negative and null results were integrated into this analysis. A detailed description of the stimulated circuits and protocols applied in stressed animals, aims to support the identification of promising candidates for further therapeutic exploration, ultimately enhancing the potential for precise neural modulation in the clinical treatment of depression.

The analyzed optogenetic studies have very heterogeneous study designs with a great variety of additional study parameters regarding the detailed stimulation protocol (timing, duration, frequency), the particular cohort of animals used (type, strain, sex, housing, sample sizes), the type of applied stress (Table 2) and the distinct neuronal stimulation targets (type of neuron populations, specific neuronal circuits).

In the following section, we discuss advantages and limitations of the performed quantitative analysis and offer recommendations for further research in the field.

Behavioral tests and animal cohorts

The four chosen behavioral tests are widely used to assess behavioral conditions, which are considered as relevant in the clinical picture of depression. However, there are further behavioral tests that investigate similar behaviors, such as the three-chamber SIT among others. These tests were not included in this review due to a lack of comparability, which could have biased the results of the performed quantitative analysis.

Moreover, even though the included tests are standardized, they may be executed differently. In addition, the different sample sizes of the tests might contribute to bias. Additionally, possible bias must be considered, which could for example be caused by the lack of blinding of experimenters. Furthermore, both the stress paradigms and the standardized behavioral tests are too simple to model the complexity of psychiatric disorders.[86,87] Despite the high precision of optogenetic technology to identify mechanisms at the cellular level, the lack of accuracy in stress paradigms and behavioral tests leads to difficulties translating these findings.[88]

The studies were classified with regard to the cohort of animals used (stressed vs. stress-naive animals). In the case of stress-naive animals, a positive effect can be considered as enhancement, while a negative effect can be considered as an induction of behavioral deficits. Studies with a positive effect in stressed animals are of particular interest for clinical translations. However, the application of different stress paradigms may result in different behavioral outcomes.[86] For example, activating the VTA DA neurons in mice that were exposed to CSDS caused a positive effect,[40] while it caused a negative effect in mice exposed to CMS.[44] Additional variety in test outcomes might arise from the use of either mice or rats, as well as of the strain, sex, and age of the animals. Moreover, variable housing and handling conditions of tested animals might influence test results.[89] However, the variation in these additional parameters is too large for quantitatively comparing the test results. Moreover, the question remains to what extend elucidated neuronal mechanisms in mice or rats are transferable to the human brain.[84]

Optogenetic stimulation

In this review, we distinguished between excitatory and inhibitory optogenetic stimulation—two stimulation types that can be achieved by using different opsins.[23,90] While the exposure of cation conducting channelrhodopsins causes depolarization, which excites the cell,[91] the exposure of halorhodopsins,archaerhodopsins or anion conducting channelrhodopsins causes hyperpolarization and inhibits action potentials.[92,93] Both excitatory and inhibitory stimulation can also be achieved through DBS and TMS.[64,65] However, the stimulation protocols in the analyzed studies comprise further parameters, which also impact behavioral outcomes. The stimulation timing as well as its duration, also play decisive roles. Stimulation was applied either before or during the behavioral test. Moreover, stimulation during the induction of depressive behaviors is possible when applied during stress paradigms, such as SSDS, CSDS and others.

While stimulation during a stress paradigm seems to suppress the onset of behavioral deficits, stimulation during the behavioral test seems to inhibit specific behaviors.[81] The duration of the stimulation also differed among the studies, ranging from chronic stimulation over several days prior to the behavioral test, to a single stimulation immediately before or during the test. In addition, the frequency as well as the duration of single-time pulses differed in the different stimulation protocols. The optogenetic construct, which comprises the viral vector, the opsin and the promoter as well as its injection area, also plays a crucial role in induced behavioral changes. Furthermore, the opsin activation has several limitations. On the one hand, the duration and intensity of optogenetic illumination must be considered, as excessive illumination can lead to tissue heating, potentially influencing behavioral outcomes.[94] On the other hand, an insufficient penetration depth of the illumination as well as light scattering in brain tissue might limit the effective activation of opsins.[95] In addition, targeting opsins to specific cell types or regions within a neuron can be challenging.[96] Moreover, even correct targeting may result in off-target effects in neighboring cells, therefore stimulation effects on other brain areas cannot be ruled out.[97]

Recommendations for further research

In basic optogenetic research, it is crucial to design studies that align with the specific factor under investigation, considering the stimulation protocol. However, certain optogenetic behavioral studies hold substantial relevance for clinical research even at present. New insights obtained from optogenetic animal studies could contribute to the enhancement of stimulation protocols for DBS or TMS. Consequently, it is essential to purposefully design studies with a homogeneous protocol and the potential to be adapted into clinical research methodologies.

In the risk of bias analysis it becomes evident that the handling of animals is similar but not standardized across studies. To address this issue it would be beneficial to establish a uniform protocol for animal housing (e.g., single or group housing), maintaining a consistent day-night rhythm and standardized feeding practices. Implementing such a uniform procedure would enhance the reproducibility of future studies and facilitate more accurate comparisons and interpretations of results.

For clinical research, particularly studies performed in animals, in which behavioral deficits were induced via stress are relevant. The choice of the stress model can significantly impact study outcomes. Therefore, employing a specific stress model tailored to the investigation of a particular depression-related behavior would be advantageous. In the case of examining social interaction, sucrose consumption and mobility various variations of CSDS, which aim to mimic psychosocial stress experienced by humans, have demonstrated effectiveness in a majority of studies. However, for a better comparison of results it is essential to establish uniform procedures for this stress model. Additionally, it would be beneficial to incorporate assessments of resilience or susceptibility by default, as it would facilitate the interpretation of potential conflicting results.

Of special significance for clinical research are studies, wherein a single stimulation target and protocol successfully ameliorate all three behavioral conditions.[47,55] Hence, we advocate conducting different types of behavioral tests (SIT, SPT, TST, FST) in one study, to investigate whether the stimulated neuronal projections influence several behavioral deficits or solely one specific condition.

Regarding the stimulation protocol, factors such as wavelength, frequency, and pulse duration are specific to the expressed opsin and are adjusted accordingly. Therefore, standardization of these parameters is not possible. Moreover, timing and duration of stimulation pose difficulties for standardization as well. Different neuronal processes are triggered by low-frequency stimulation, applied for longer durations compared to acute high-frequency stimulation, or chronic stimulation.[59]

For the purpose of DBS protocols, that aim to effectively alleviate behavioral deficits over extended time scales, it would be advantageous to assess animals for adaptive behavioral changes over a longer time period. This approach allows for the assessment of both acute behavioral alterations during, or immediately after the stimulation, as well as the evaluation of potential long-term effects.

The VTA, dopamine system, and dopaminergic connections between the VTA and NAc have been extensively studied in multiple optogenetic investigations. The impact of optogenetic stimulation on social behavior, consumption and mobility in mice is evident. However, the use of different stress models and slight variations in stimulation protocols have resulted in seemingly conflicting findings. Therefore, it is advisable to conduct initial replication studies in susceptible mice to further validate the observed effects and ensure the reliability of the results. Moreover, there seem to be key areas for each behavior. Particularly, the NAc was successfully studied in relation to social interaction, as well as the VTA. The DRN seems to be significantly involved in the modification of mobility. Especially for these heavily studied brain targets, first replication studies with standardized stress models and defined stimulation protocols are necessary for verifying the preliminary evidence.

However, the collection of study outcomes also points to other brain areas that have been investigated in fewer studies so far, but which might also offer promising effects. These targets include the LC in the context of social behavior, and the DLS for all three behavioral conditions.

Conclusion

Over the last decade, optogenetics has investigated the brain areas that play a major role in the neuronal picture of depression. Our systematic evaluation of optogenetic behavioral studies shows how far the field has progressed in terms of controlling different behaviors of rodents that are relevant for depression research.

Recently, the application of optogenetics has partially recovered visual function in a patient suffering from Retinitis pigmentosa.[98] Furthermore, the translational potential of optogenetics and specific strategies for further application of optogenetic-based tools as therapeutic methods are discussed.[96,99–103] The insights gained from pre-clinical optogenetic studies can serve as a guide for advancing clinical practice. Integrating advanced imaging methods such as functional MRI (fMRI) and positron emission tomography (PET) allows clinicians to examine the neural activity patterns in patients, offering valuable insights into individual variations and disease-specific alterations.[17] Optogenetics can validate the results of imaging studies in humans and potentially contribute to the identification of causal relationships. Moreover, insights from preclinical optogenetic studies in rodents enable the identification of new imaging targets in clinical studies. This combination facilitates the identification of optimal parameters and targets for interventions like DBS or TMS.[36,104,105]

However, the diverse nature of optogenetic behavioral studies poses challenges to their translation into clinical settings. For a better adaption of optogenetic findings, future research should focus on standardized study designs to allow for meta-analyses. Additionally, conducting replication studies, particularly targeting the most promising brain regions is crucial for addressing and clarifying the current discrepancies among study results.

Limitations of the study

We limited the publication period from 01.01.2009 to 03.01.2022. However, it is important to acknowledge that this time frame may need to be continually extended to capture the rapid growth of the field and the multitude of optogenetic studies conducted each year. In addition,

restricting the literature search to two databases and to the English language might have limited our access to data from non-English journals and publications. Although we manually searched for relevant publications in review articles, there is a possibility that relevant optogenetic behavioral studies from non-English international sources could have been overlooked. Our quantitative analysis is constrained by its focus on the mere enumeration of conducted experiments and their outcomes. As a result, factors such as sample size and effect size were not taken into account. Despite the comparison of standardized tests, variations in animal handling methods and differences in test conditions were not systematically addressed. These limitations underscore the need for future research to employ more comprehensive methodologies that encompass a broader range of experimental variables and statistical analyses.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109776.

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AUTHOR CONTRIBUTIONS

Conceptualization: A.S. writing the paper: A.S. literature research: A.S. and D.A. analysis of the literature: A.S. and D.A. figures:A.S. tables: A.S. and D.A. editing the text: S.M. critical feedback to the text: H.W. supervision of the work process: S.M.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Other		
In this study, no experimental data were collected, thus there are no materials or additional resources to report		

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Anika Spreen (Anika.Spreen.1@hu-berlin.de).

Materials availability

This study did not generate new unique materials.

Data and code availability

- All data were collected from published articles and are registered in Tables S1 and S2.
- No original code was generated in this study.
- Any additional information required to reanalyze the data reported in this paper is available from the lead author.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This is not applicable to our study as it does not involve experimentation.

METHOD DETAILS

The methods detailing the search for relevant publications, the study selection based on eligibility criteria, data extraction procedures and the subsequent data evaluation are comprehensively outlined within the Methods section of the main text.

This delineation is an integral component of conducting a systematic review and accordingly, is integrated into the main text following the recommended structure for systematic reviews.

QUANTIFICATION AND STATISTICAL ANALYSIS

Not applicable to our study, since we performed a basic calculation to assess the outcomes of conducted behavioral tests under various test conditions. Statistical methods for analysis or quantification were not employed.

ADDITIONAL RESOURCES

The study has not generated or contributed to a new website/forum and is not part of a clinical trial.