MouseCircuits.org: An online repository to guide the circuit era of disordered affect

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Affective disorders rank amongst the most disruptive and prevalent psychiatric diseases, resulting in enormous societal and economic burden, and immeasurable personal costs. Novel therapies are urgently needed but have remained elusive. The era of circuit-mapping in rodent models of disordered affect, ushered in by recent technological advancements allowing for precise and specific neural control, has reenergized the hope for precision psychiatry. Here, we present a novel whole-brain cumulative network and critically access the progress made to-date on circuits mediating affective-like behaviors in rodents to seek unifying principles of this cumulative data. We identified 106 original manuscripts in which optogenetics or chemogenetics were used to dissect behaviors related to fear-like, depressive-like or anxiety-like behaviors in rodents. Focusing on the 60 manuscripts that investigated pathways rather than regions, we identified emergent themes. We found that while a few pathways have been validated across similar behaviors and multiple labs, the data is mostly disjointed, with evidence of bidirectional effects of several pathways. Additionally, there is a need for analysis informed by observation prior to perturbation. Given the complex nature of brain connectivity, we argue that the compartmentalized viewpoint that develops as a consequence of fragmented pathway-specific manipulations does not readily lend itself to an integrative picture. To address this, we launched an interactive online consortium, MouseCircuits.org, an open-source platform for consolidated circuit data. This tool aims to support the shared vision of informed circuit dissection that ultimately leads to prevention and treatment of human disorders.

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The ERA OF CIRCUIT MAPPING

Mood disorders account for most years lost to disability (1). There is an urgent need for new effective therapeutics, but translation of laboratory discoveries to treatments for human disorders has thus far proven difficult. Excitingly, we are on the brink of a historical turning point. Until recently – borrowing from groundbreaking advancement of other organ systems – mechanistic dissection of disordered affect has targeted singular neurotransmitter systems, brain regions, or genes. This approach enabled the understanding of the individual building blocks of brain function and continues to be supported by novel theories involving global mechanism of affect disruption, implicating for example the immune sys-

tem and the gut microbiome (2,3). However, the mysteries of the brain, a structure with idiosyncratic and interconnected architecture, are unlikely to be revealed solely on the basis of this type of sledgehammer approach.

Enter the era of circuit dissection. In the last decade, groundbreaking technological advances have allowed neuroscientists to take control of neural firing with impressive precision and specificity **(Figure 1)** (4–7). An in-depth description of these tools is outside the scope of this paper [see (4–8) for comprehensive descriptions]. Concisely, two techniques have fundamentally changed the landscape of neural circuit dissection: optogenetics, which controls neuronal firing with light, and chemogenetics, which alters neuronal firing with otherwise biologically inert compounds. Optogenetics uses genetically engineered transmembrane channels that open in response to specific wavelengths of light to allow selective passage of charged ions to either depolarize or hyperpolarize targeted neurons. Chemogenetics uses G-protein coupled receptors known as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to enhance or inhibit neuronal excitability in the presence of biologically inert compounds, such as clozapine N-oxide (CNO). Both tools can selectively activate or inactivate neurons of interest when combined with genetic labeling techniques. Optogenetic control provides high temporal precision on scales relevant to manipulations of individual action potentials. Chemogenetic control acts on slower timescales (minutes, hours, or days) but has the advantage of modulating endogenous activity by placing the neuron in either a depolarized state, for increased excitability, or hyperpolarized state, for decreased excitability.

Initial efforts used chemogenetic and optogenetic control of brain regions and confirmed findings from classical lesion studies (ex: (9)). Rapid progress followed, with increasingly refined targeting of neurons based on transcriptional-, projection- and/or activity-specificity **(Figure 1)**. However, despite substantial amassed data, knowledge of individual pathways exists largely in a realm that ignores the complexity of an interconnected whole-brain network. Therefore, at the moment, it is difficult to envision how these findings can be translated to improve the prevention and treatment of human mental health conditions. The goal of this paper is therefore threefold: (1) Summarize the cumulative knowledge of affective circuits obtained using chemogenetic and optogenetic manipulations in animal models; (2) Criti-

cally assess the current state of the era of circuit mapping, its promise and its perils; and (3) Introduce an online platform to help consolidate and integrate rapidly growing neurocircuit data moving forward: MouseCircuits.org.

Neural map criteria

Our goal was to develop a functional neural map of affective state circuitry data, enabled by chemogenetics and optogenetics. We searched PubMed (accessed on November 20th, 2019) for combinations of keywords referencing circuit dissection tools (e.g. "chemogenetics", "optogenetics", "DREADDs") and keywords referencing affect (e.g. "fear", "anxiety", "depression") or specific behavioral tests commonly used to asses affective-like responses in rodents (e.g. "social defeat stress", "elevated plus maze", "tail suspension"). Studies on mouse and rats only were included. These studies covered the investigation of circuits spanning 33 regions (**Table 1**). No date restrictions were used, but consistent with chemogenetic and optogenetic tools' recent development, all 102 identified manuscripts were from 2010 or later (**Table 2**). An additional three manuscripts were identified based on Twitter updates of BioRxiv preprints, for a total of 106 reviewed studies (**Table 2**, page 18).

DISSECTION OF RODENT CIRCUITS FOR DISORDERED AFFECT

Inclusion criteria for neural manipulations

A variety of tools can be used to manipulate neural activity including electric stimulation and transcranial magnetic stimulation. For the purpose of the creation of this neural network and guide, we restricted our search to studies in which optogenetics and/or chemogenetics were used to manipulate neuronal function, as these tools, when combined with genetic labeling, offer unprecedented specificity and control of microcircuits.

Inclusion criteria for rodent behaviors

The relevance and success of rodent models for studying human mental health diseases is currently fiercely debated (2,10–18). It is well-established that animal models cannot recapitulate the heterogeneous and complex symptomology of patients with major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), or any other disease of mood dysregulation. However, there is also general agreement that rodent models, when used appropriately, will continue to be a crucial intermediary step as we move treatments through the translational pipeline (17).

In the collection of data point for a whole-brain neural network we included rodent studies that share the broad conceptual framework of modeling core aspects of human affect. For feasibility, we did not search an exhaustive of all affective-like behaviors (e.g. "motivation" and "reward"

Table 1. Region names and abbreviations from the Allen Brain Atlas with the expectation of the inframimbic cortex (IL rather than ILA) and the addition of the amygdala (Amyg), dorsal hippocampus (dHPC), ventral hippocampus (vHPC), and medial prefrontal cortex (mPFC).

Abbreviation	Region
Amyg	Amygdala
ACC	Anterior cingulate cortex
Acx	Auditor cortex
BLA	Basolateral amygdala
BST	Bed nucleus of the stria terminalis
CeA	Central amygdala
DG	Dentate gyrus
DR	Dorsal raphe nucleus
EC	External capsule
H	Hypothalamus
HPF	Hippocampus formation
dHPC	Dorsal Hippocampus
vHPC	Ventral Hippocampus
AI	Insula
IL	Infralimbic cortex
ILT	Intralaminar thalamus
LA	Lateral amygdala
LC	Locus coeruleus
LDT	Laterodorsal tegmentum
LH	Lateral habenula
LS	Lateral septum
MDT	Mediodorsal nucleus of the thalamus
mPFC	Medial prefrontal cortex
ACB	Nucleus accumbens
NR	Nucleus reuniens
PAG	Periaqueductal gray
PL	Prelimbic cortex
PVT	Dorsal midline thalamus
PC	Piriform cortex
SC	Superior colliculus
T	Thalamus (including MFD)
VTA	Ventral tegmental area
VS	Ventral striatum

were not included) but targeted three types of behavioral responses in rodents: "fear-like" (innate or learned), "anxiety-like", and "depressive-like" (**Figure 2**). These behaviors and – the affective states they are associated with – are not necessarily separable in either humans or animal models. There is a high degree of overlapping symptomology in different diseases, as well as comorbidity among disorders (19–22). Nevertheless, understanding the precise pathways involved in specific symptoms can generate important ground truth about affective circuits and supports the establishment of precision psychiatry. Recent introduction of Research Domain Criteria (RDoC) is a notable effort to move the field away from classification into disorders that reflect constellations of symptoms, such as MDD and GAD, and toward dimensions of functioning (23–26). It is hypothesized that constructs such as "acute threat ('fear')" and "potential threat ('anxiety')" share genetic, environmental, developmental, and neurocircuit eti-
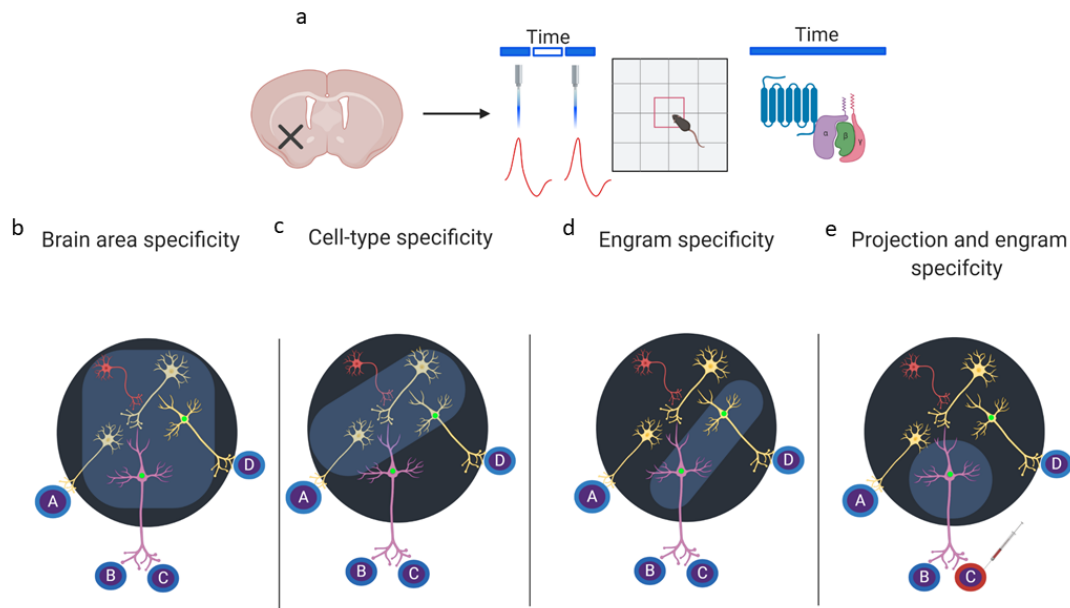
Fig. 1. Evolution of the era of circuit mapping: from regional mapping to increasingly refined circuit dissection. (a) The neural basis of behavior was initially determined by non-specific lesions followed by the era of circuit mapping with optogenetic and chemogenetic manipulations. Optogenetics and chemogenetics have several key differences, with timing being the most relevant to behavioral manipulations. Optogenetics can be regulated on a second timescale while chemogenetics relies on G-protein receptor dynamics. (b) Regional specificity of optogenetic and chemogenetic manipulations can be achieved with careful viral injections into a brain region of interest (light blue shading). (c) Combining optogenetics/chemogenetics with genetic targeting tools allows for cell-type specificity within regions of interest (light blue shading). (d) Growing use of activity-dependent targeting (green nuclei) further increased specificity of manipulations to temporally defined cell populations within a region. (e) Novel approaches using multiple systems such as Cre/loxp, inducible promoters, retrograde/intersectional/transsynaptic labeling allow for additional layers of specificity that combine cell-type, projection-type and/or temporally-defined targeting of neuronal populations.

ology across both diseases and species. Therefore, establishing a bird's eye view of the various pathways with proven functional relevance to "acute threat" and "potential threat" in animal models is of crucial importance to the overarching vision of the RDoC framework.

Figure 3 shows the richness of rodent affective circuit data amassed to date. An interactive, searchable and updatable version of this figure will soon be available on MouseCircuits.org. Several themes emerge in the context of visualizing the cumulative investigated connectome of rodent affective-like behaviors.

Landscape of studies dissecting rodent affective circuits
We identified a total of 106 studies investigating the role of brain regions or pathways in fear-like, anxiety-like and/or depressive-like behaviors using optogenetics or chemogenetics. Of these, 84% were mouse studies and 16% were rat studies. Optogenetics is more commonly used than chemogenetics, with region data investigated by optogenetics in 60% of studies, chemogenetics in 32% of studies, and both in 8% of studies. Pathway data was investigated by optogenetics in 70% of studies, chemogenetics in 20%, and both in 10% of studies. In both region and pathway investigations, the studies that utilized both methods (seven pathway focused and

five region focused) obtained congruent results. Bidirectional control of the region (4 studies) or pathway of interest (13 studies) was investigated in 16% of the studies. Interestingly, only 6 of these studies (one region focused and five pathway focused) used the same method for bidirectional control. The remaining used optogenetics for activation and chemogenetics for inhibition or vice versa (three region focused and two pathway focused).

Males rodents are overwhelmingly more commonly studied, with 81% of studies using only males (35/49 region focused and 51/60 pathway focused). In the remaining studies, none used only females, 17 (9 region focused and 8 pathway focused) studies used both males and females, and 7 studies did not report sex (5 region focused and 2 pathway focused).

A total of 49 studies targeted 15 different brain regions (**Table 3**). A minority of these regions have been looked at in the context of multiple types of affective behaviors. The three most commonly studied brain regions are the amygdala (Amyg, 17%), hippocampus (HPF, 20%) and medial prefrontal cortex (mPFC, 38%). HPF and mPFC have been implicated in both negative and positive affect and have each been tested in fear-like, anxiety-like and depressive-like behaviors. Amyg has mainly been tested in the context of fear

Stressors	Test	Output	Etological relevance
Open Space	Open field, Elevated plus maze	Time in center or open arm vs in corners/near walls or closed arms	Innate conflict: open space may expose animal to predator or danger but may also serve as a path to food or mate
Light	Light/Dark box	Time in the light vs time in the dark	Innate conflict: Light may expose an animal to a predator but may also serve as a path to food or mate
Predator odor	Predator odor exposure	Response type: avoidance, freezing, escape	Detection and response to predators are key for survival
Shock	Fear conditioning	Learned fear (freezing), flexible learning/updating (extinction), memory strength (retrieval)	Learned associations to aversive stimuli are critical for survival
Social defeat	Social defeat stress, Resident-intruder test	Social Interaction: social preference (resilient) vs avoidance (susceptible)	Social dynamics and conflict are critical for survival
Inescapable situation or threat	Forced swim test, restraint stress, tail suspension, learned helplessness, variable stress	Active vs passive coping (ex: swim vs float), anhedonia (ex: loss of sucrose preference)	Animals must adapt to changing environmental conditions and challenges

Fig. 2. The behavioral toolbox. Summary of common behavioral models for affective-like states in rodent models. Purple rows are associated with anxiety-like behavior, light-blue rows are associated with fear-like behavior, and dark-blue rows are associated with depressive-like behaviors.

where, consistent with early lesion studies, it is observed to primarily mediate negative affect. Despite a variety of efferent and afferent Amyg pathways being evaluated in anxiety- and depressive-like behaviors, no region-specific perturbation has evaluated its role in these behaviors. Of the 47 total region focused studies, 25% targeted molecularly identified subpopulations of neurons, with the majority targeting excitatory neurons with a Calcium calmodulin-dependent protein kinase II (CamKII) promoter.

A total of 60 studies targeting 65 unique pathways (including bidirectional control) were identified (3 pathway studies overlapped with targeting of particular brain regions, **Table 4**). Seventeen studies targeted more two pathways and three studies targeted three or more pathways. The majority (58%) targeted a specific cell type: 46% utilized CamKII to target excitatory neurons, 6% targeted somatostatin (SST)-expressing neurons, 3.4% targeted tyrosine hydroxylase (TH)-positive neurons, and 3.3% targeted parvalbumin (PV)-positive neurons. Dopamine (D2)-, vesicular glutamate (Vglut)-, serotonin (5HT)-, and corticotropin releasing factor (CRF)-expressing neurons were each targeted once (1.6% each). Of the 65 pathways, only eleven have been manipulated in more than one study. Ten of these pathways were investigated by different labs with three pathways showing incongruent results. Some inconsistencies are due to targeting different neuronal cell-types. Studies demonstrating increased negative affective-like behaviors with HPF to mPFC pathway (HPF→mPFC) stimulation, targeted excitatory neurons (27–29). On the other hand, studies demonstrating decreased negative affective-like behav-

iors with HPF→mPFC stimulation used a pan-neuronal promoter (30,31). Others are due to behavioral differences: HPF→Amyg is implicated in opposing affective valence, but negative affect is promoted in fear-related behavior (32,33) and positive affect is promoted in depression-related behaviors (34). Lastly, the ventral tegmental area to nucleus accumbens pathway (VTA→ACB) increases depressive-like behaviors with phasic stimulation (35,36), but decreases these behaviors with other stimulation patterns (37). Very few pathways display consistencies in both directions. For example, both the infralimbic and prelimbic connection (IL←→PL) (38,39) and the PL←→BLA (9, 62, 64) connection have been demonstrated to reliably increase fear-like behaviors. Implication of Amyg→HPF in increased depressive- and anxiety-like behaviors has been replicated across multiple studies, but the pathway was targeted exclusively by one research team, likely contributing to the reproducibility (40,41). In summary, most pathways have been investigated in single studies by unique teams with very few replicated across multiple studies and/or laboratories.

More than half the accumulated data (overall 62%, 34/60 pathway focused and 32/49 region focused) has been obtained with circuit perturbations during a single behavioral test. Very few studies have investigated a pathway across multiple affective-like domains (overall 12%, 7/59 pathway focused, 6/47 region focused). This generally entailed testing anxiety-like behavior using open field and fear-like behavior using fear conditioning, and mostly implicated the manipulated circuit in one and not the other behavior (42–44). Pathways investigated multiple times have primar-

ily only been dissected with one tool; for example, both VTA→ACB (35–37) and Amyg→bed nucleus of the stria terminalis (BST) (45–47) have only been studied with optogenetics.

Surprisingly, a minority of studies (40%) conducted some type of observation of the targeted circuit in an endogenous state prior to perturbation (21/60 pathway focused and 22/49 region focused). A loose definition of observation was applied, including checking that an IEG is expressed in the region or pathway of interest after behavior, using tracing to ensure a functional connection exists between two regions, and utilizing a "trapping" technology to indelibly mark neurons activated by a particular behavior (e.g. Tet/Tag (48) or TRAP (49) mice). After removal of studies using trapping techniques, only 22% report an observation of endogenous dynamics of a circuit prior to circuit manipulation.

CONNECTOMIC PRINCIPLES OF RODENT AFFECTIVE CIRCUITRY

Historical perspective

When visualized over time, a historical perspective emerges (**Supplementary video 1**). Initial studies targeted unitary regions. Studies tracing pathways to and from these identified nodes followed. Most recently, there was a return to regional analysis, motivated by cell-type specific circuit dissection. Initial studies focused heavily on the triad of brain regions strongly implicated in human mood disorders: Amyg, HPF, and mPFC (50–52). Over time, analysis expanded to regions further and further removed from this triad, some of which have less obvious ties to human conditions. For example, the Nucleus reuniens (NR) has not directly been investigated in human affective states. A PubMed search (accessed on December 30th, 2019) for 'N. reuniens', 'human', and 'affect' (or 'anxiety', 'fear', and 'depression') collectively only reveals one paper, which reviews the overall role of the thalamus and all its sub-regions in animal behaviors, both affective and cognitive (53). Therefore, although there are lines of evidence for the role of this nucleus in fear-like behavioral regulation in animal models (54), there is little evidence of its relevance to human mental health disorders.

Viewed as a whole, the cumulative connectome also conjures some obvious holes. The cerebellum for example, has recently become implicated in mood disorders in both humans (55–58) and rodents (59). The cerebellum sends and receives inputs from numerous cortical regions (60,61), yet neither regional nor pathway analysis has to-date probed cerebellar contribution to rodent affective-like behaviors.

Node centrality

The centrality of the Amyg, and its primary role of mediating

negative affect (red lines in **Figure 3**), is immediately apparent. The mPFC is another notable node, mediating both positive and negative affect depending on the specific pathway or subregion targeted. The bidirectional interaction between the mPFC and Amyg as a mediator of negative affect is well-replicated among multiple labs using multiple paradigms (illustrated by the thicker red line in **Figure 3**, which is proportional to the number of studies evaluating this pathway) (9,62–65).

When fear-, anxiety-, or depressive-like circuits are visualized separately (**Figure 4**), unique patterns emerge. The mPFC dominates the network for depressive-like behaviors, the amygdala dominates the fear circuit, and anxiety-like behaviors are mediated by a more distributed network.

It is important to consider that this node centrality emerged in a hypothesis-driven context. Thus, despite the cumulative evidence identifying Amyg as a "fear center" (and the preceding decades of non-circuit-based studies investigating this region's role in fear), none of the studies reviewed performed any type of brain-wide approach to first confirm the region's central role to the particular behavior studied. While this is intuitive given the stepwise progress expected of scientific inquiry, it is nevertheless an important observation that needs careful scrutiny. The danger of circuit era mapping is that, as each individual pathway is added to the rodent affective-like connectome, the resulting network structure could move further and further away from the "ground-truth" connectome associated with a particular behavior due to propagation of error (66).

Illuminating regional and subregional specificity

The multi-leveled specificity of circuit era tools (**Figure 1**) has led to increasingly refined understanding of regional and subregional contributions to behavioral outcomes. The first layer of specificity is imparted by viral injections, which offer improved anatomical localization over lesion and pharmacological studies (9,67). A secondary layer of specificity can then be added using cell-type specific gene-expression. As an example, serotonergic neurons are anatomically restricted to the raphe nuclei, tiny regions in the mid-hindbrain traditionally difficult to precisely target. To achieve high-degree of regional specificity, studies of raphe nuclei (dorsal raphe nucleus [DR] and/or medial raphe nucleus [MRN]) commonly restrict expression of opsins or DREADDs to serotonergic neurons using the tryptophan hydroxylase 2 (Tph2) promoter (68), the fifth Ewing variant (FEV) promoter (69), or the SIc6a4 gene (128). It should be noted however, that while such genetic labeling techniques impart high-degree of anatomical specificity, they can also potentially miss key aspects of functioning. Serotonergic neurons actually only make up 20% of all neurons in the median raphe region, with glutamatergic and GABAergic neurons predominating (71). Elucidation of a region's function should ideally include both regional specificity as well as an understanding of the interplay between various neuronal types. Of the four re-
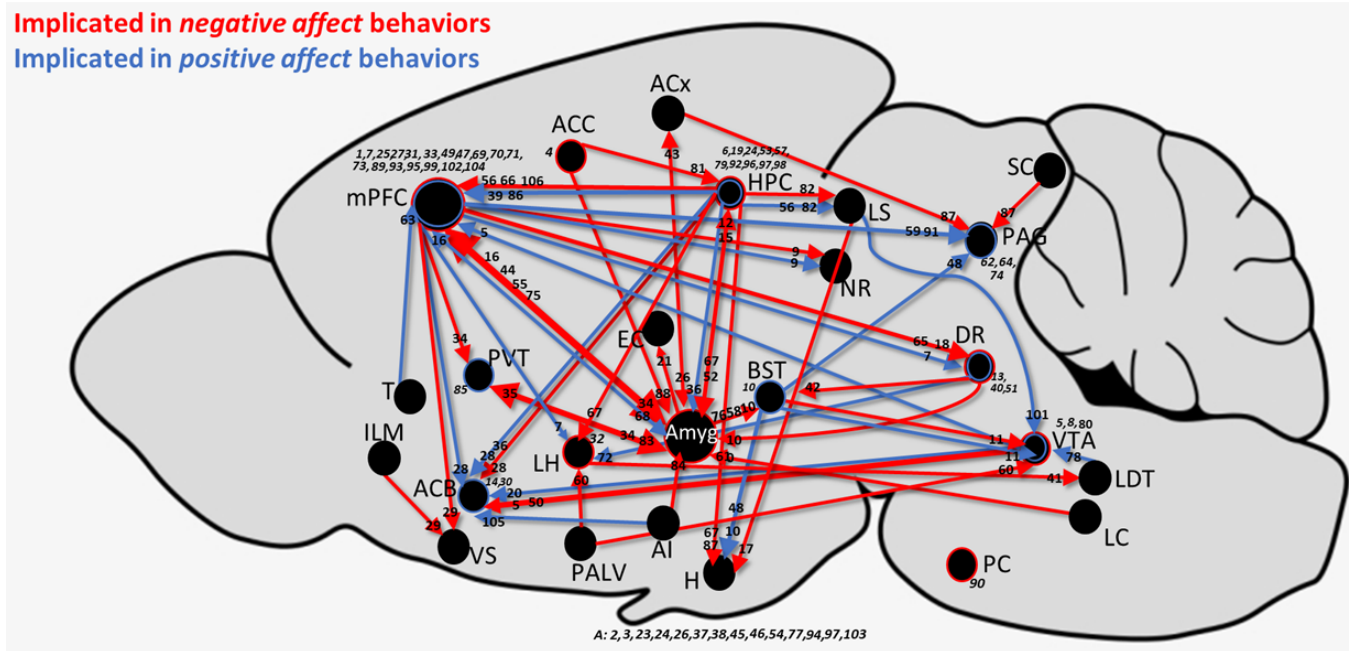
Fig. 3. Verified rodent brain functional connectivity for affective-like behaviors. Pathway and region manipulations from 106 identified studies in which optogenetics and/or chemogenetics was used to probe a brain region's or pathway's contribution to anxiety-, fear-, or depressive-like behaviors, presented in the backdrop of the whole rodent brain. Red indicates regions and pathways in which activation promotes negative affective-like behavior, while blue indicates regions and pathways in which activation promotes positive affective-like behavior. Size of arrow corresponds to number of studies that have targeted a particular pathway.

viewed studies of DR/MRN, one began addressing this issue by specifically targeting GABAergic neurons in the region (70).

Finally, intersectional approaches impart projection-specificity. This is achieved by injecting a retrograde virus carrying a recombinase, such as Cre, in an efferent region in combination with a second injection of a virus carying Cre-dependent opsins or DREADDs into the region of interest. This results in selective targeting of neurons based on their axonal projections.

Figure 5 shows the detailed subregional data generated using these approaches on two key brain areas involved in affective-like behaviors: the mPFC and the basolateral amygdala (BLA). The IL, a tiny subregion of the mPFC, is a great example of the technological advances ushered in with circuit era tools. Lesion and electrophysiological studies had previously provided contradicting data on the role of IL in fear extinction, with some studies implicating IL in fear extinction (72) and others reporting IL lesions not to impair extinction and IL firing not to be associated with extinction (72,73). Circuit manipulations, thus far, have unequivocally demonstrated that functional activation of the IL plays a crucial role in extinction learning (9,38,53,54,55,62,64,67,75). In contrast, the neighboring PL subregion of the mPFC has been implicated in fear memory formation (74-76).

Circuit era tools have also refined our understanding of different circuits within the BLA. This region contains various types of neurons that play distinctive roles in fear processing. Initially, this was appreciated using electrophysiological approaches that identified "fear neurons",

responding to fear learning, and "fear extinction" neurons, responding to extinction learning (77). Interestingly, these neurons also display different connectivity patterns, with fear neurons preferentially receiving inputs from the ventral hippocampus (vHPC) and extinction neurons from the mPFC (77), stressing the necessity of both structural and functional specificity in circuit manipulations. Following up on these experiments, optogenetic stimulation confirmed the vHPC→BLA pathway's involvement in fear memory formation (32,78), and chemogenetic inhibition confirmed the importance of the IL→BLA pathway in extinction learning (95). Distinct roles in fear learning have also been observed in various neuronal subtypes in the BLA. Activation of PV interneurons during a conditioned stimulus presentation promotes auditory fear learning whereas activation of SST interneurons inhibits learning (80).

The final frontier: activity-dependent targeting of circuits

The final frontier in specificity has taken advantage of immediate early genes (IEGs) to target neurons activated during particular behaviors, thereby adding temporal specificity. Memories and behavior are established by distributed networks of sparsely activated neurons, often called engrams (81). Neighboring neurons can have opposing functions or play different roles at various time points (82). Uniform targeting of neurons, even with pathway or cell-type specificity, might therefore not answer 'how the brain works', but rather how it 'can work' (83). Therefore, using IEG promotors to selectively express chemogenetic/optogenetic vectors in neurons normally activated during a particular behavior is essential for understanding how endogenous neural activity maps

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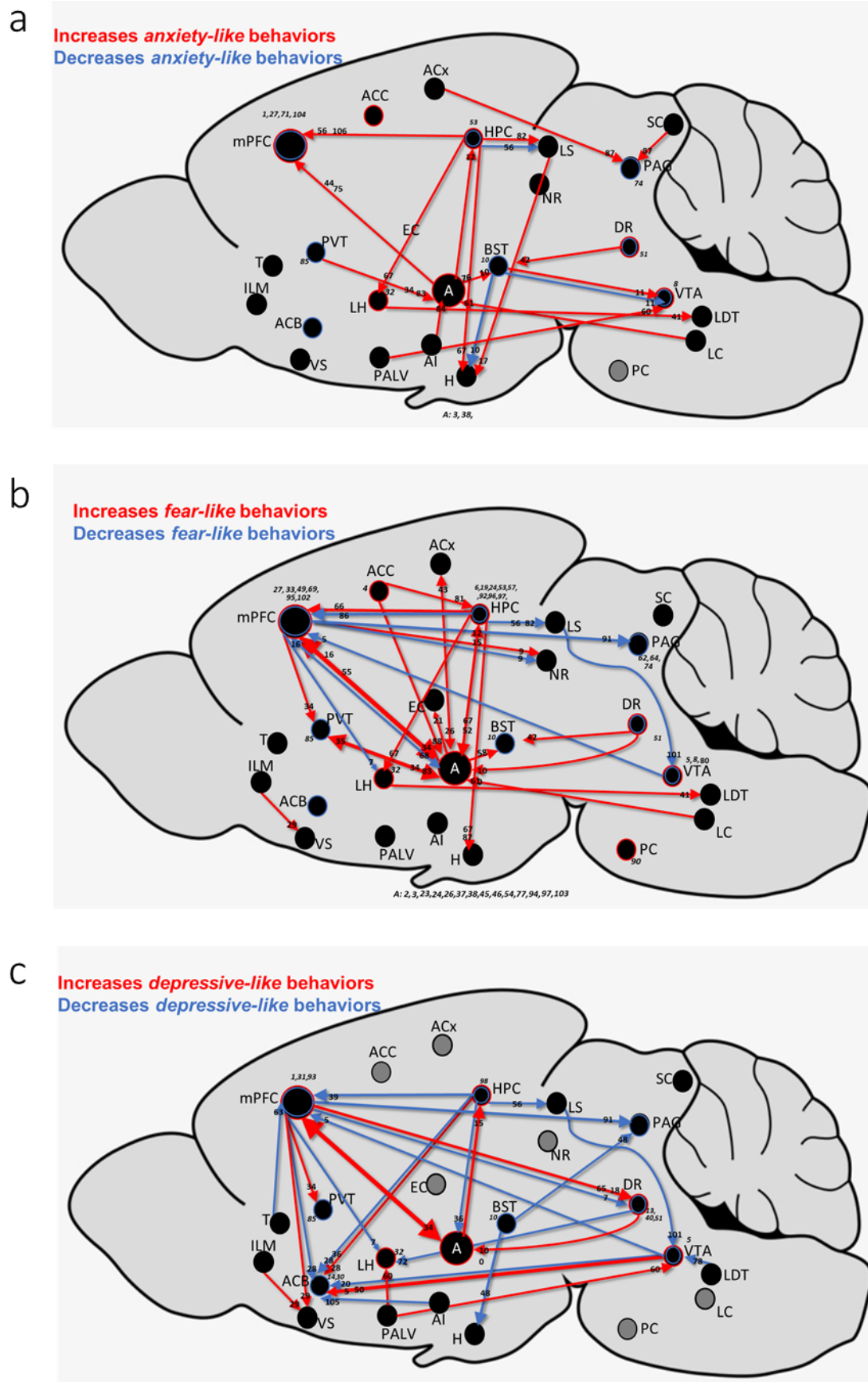
Fig. 4. Verified rodent brain functional connectivity in specific affective states: anxiety-, fear-, and depressive-like. Pathway and region manipulations sorted by the behavioral paradigm that was paired with the optogenetic or chemogenetic manipulation. (a) Anxiety-like behaviors presented in the backdrop of the whole rodent brain. (b) Fear-like behaviors presented in the backdrop of the whole rodent brain. (c) Depressive-like behaviors presented in the backdrop of the whole rodent brain. Red indicates regions and pathways in which activation promotes negative affective-like behavior, while blue indicates regions and pathways in which activation promotes positive affective-like behavior.
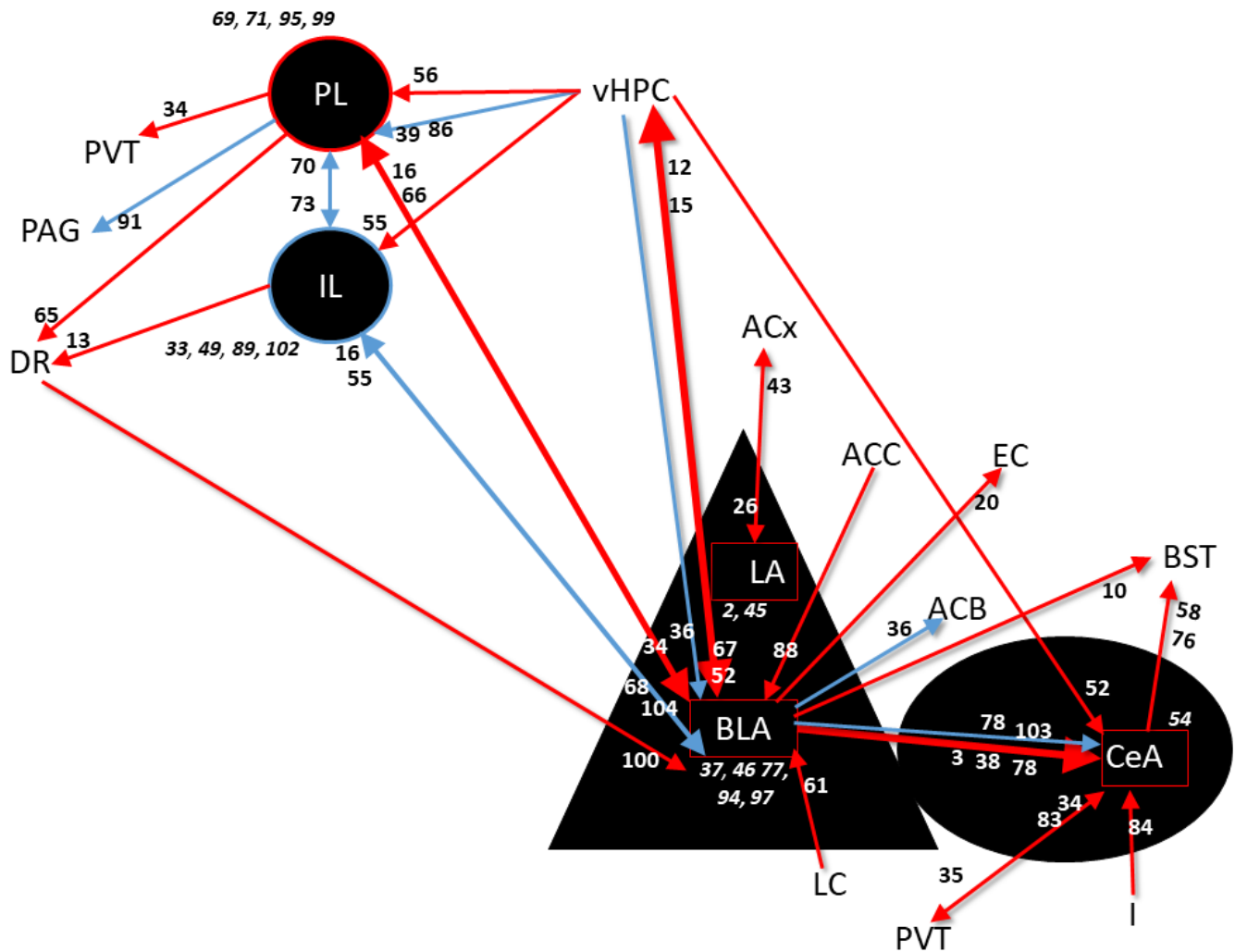
Fig. 5. Detailed dissection of subregional contributions to affective-like behaviors in two commonly studied regions. Zoom in on the medial prefrontal cortex, showing the opposing contributions of the prelimbic (PL) and infralimbic (IL) subregions to affective-like behaviors. Zoom in on the amygdala and its subregions: lateral amygdala (LA), basolateral amygdala (BLA), central amygdala(CeA). All studies represent optogenetic or chemogenetic studies coupled with rodent models of disordered affect.

onto the behavioral repertoire of both individual animals, as well as the variability within populations of animals. Is individual variability related to the neurons within a brain region? Or to how neurons are distributed within the whole-brain engram? Alternatively, individual variability could be related to different pathways predominating in different animals. These types of questions can only be answered by activity-dependent selective targeting of neurons. Six of the reviewed studies used a trapping method (cFos tTa, TetTag, TRAP mice) and the use of these technologies is likely to increase overtime, resulting in more refined understanding of neural circuit functions (33,34,84–87).

A prominent example of the role of engram-specificity in circuit dissection is the BLA. While the classical view of the BLA as a "fear" center largely remains uncontested (88,89), activity-dependent labeling has identified subsets of behaviorally activated neurons with distinct roles and functional connectivity (67,77,90,91). Distinct amygdala positive- and negative-valence neurons have been discovered (90). These neurons interact via mutual inhibition and ex-

hibit different functional connectivity. Furthermore, an overlap of positive-valence neurons with fear extinction neurons has been observed (91). Thus, manipulations of the BLA can result in divergent or even opposing behaviors depending on temporally-defined neuronal subpopulations targeted.

Because of the brain's organization into engrams, conclusions based on pathway or regional manipulations could therefore be either frankly erroneous or fall into the category of 'what the brain can do'. In a study utilizing activity-dependent tagging to label neurons activated during fear conditioning across 409 brain regions gives weight to this concept. A highly distributed pattern of activity and connectivity was observed, suggesting network redundancy within the brain (87). Single region activation of engram ensembles conferred fear memory recall (albeit not at the same level as multiple engram ensemble activation) demonstrating the ability of neurons within unitary regions to drive behavior despite not acting on their own endogenously (87).

Same pathway, different action

A visually apparent theme in **Figure 3** is that several pathways promote negative affect with some manipulations and positive affect with others, highlighting the complexity of the brain's architecture. Increasingly sophisticated targeting specificity have contributed to this pathway duality by improved targeting of small regions, cell-type specificity and, and projection-specificity. This increasing precision has both advantages and disadvantages.

An elegant example of "same pathway, different action" comes from combining projection and cell-type specificity in manipulations of BST→VTA. This pathway contains both glutamatergic and GABAergic projections. Importantly, photoactivation of BST→VTA glutamatergic projections results in aversive and anxiogenic behavior while photoactivation of BST→VTA GABAergic projections produce rewarding and anxiolytic phenotypes (92). However, such precise manipulations can also result in a distorted view, given that the endogenous interplay between BST→VTA GABAergic versus glutamatergic neurons remains poorly understood. Furthermore, this pathway has been implicated in human drug seeking behavior (93), but such studies do not provide data on cellular specificity. GABAergic and glutamatergic neuronal function is intricately interconnected in the brain and therefore, most likely, in the human case both types of neurons are involved. Interestingly, the organization of this pathway has also been found to contain key differences between mice and rats (94) and therefore precise manipulations may not translate between species.

Another cause of discordant results within a pathway comes from increasingly refined subregional localization. As mentioned previously, the mPFC→BLA pathway has been implicated in both fear memory learning and fear extinction learning, with the PL→BLA implicated in the former (9,62) and the IL→BLA responsible for the latter (62,95). Similarly, discrepancies in behavioral outcomes with manipulations of the HPF→Amyg pathway can be attributed to subregional targeting of both input neurons (dentate gyrus (DG) (34) versus the CA1 (32) subregions of the HPF) and output targets (basolateral versus central subregions of Amyg (78). Subregional specificity also plays a role in activation of the HPF→mPFC pathway in fear-related behaviors. HPF→IL promotes fear relapse (27), whereas HPF→PL attenuates fear renewal (31). Interestingly, HPF→mPFC activation leads to opposing results in terms of anxiety- versus depressive-like behaviors, potentially indicating affect-specific roles for subsets of neuronal populations in this pathway (28- 30).

Additional mechanisms by which the same pathway can display different actions include activity-dependent targeting of neurons for manipulation and the specific timing chosen for the stimulation. As mentioned before, the vHPC →BLA pathway has been implicated in fear memory learning (32, 78). However, the opposite contribution of this pathway was observed when vHPC→BLA neurons were targeted for opsin expression based on their engagement in a positive experience (34).Thus, even neurons of same molecular and projection identity can have opposing contributions to a behavior based on the memory trace they are recruited to. An example of timing effects on behavioral output comes from studies probing the role of the VTA→ACB pathway in social defeat stress. Phasic stimulation during stress and/or the social interaction testing induces susceptibility (35, 36), whereas stimulation after social defeat stress but before the social interaction test induces resilience (37).

Additional mediators of divergent pathway results likely exist. **Tables 3,4** and MouseCircuits.org provide a simplified way to compare studies for rapid insights into emergent properties of neural circuits. Such insights are vital to the eventual translation of identified rodent circuit function into clinical advances

GUIDING PRINCIPLES FOR MOVING THE ERA OF AFFECTIVE CIRCUITRY FORWARD

Methodological considerations

Outcomes of experiments are dependent on a number of methodical choices. For example, the choice of optogenetic versus chemogenetic perturbation can affect conclusions about the role of a circuit. For the most part, the 12 studies (7 pathway focused and 5 region focused) that utilized both optogenetics and chemogenetics came to similar conclusions with both tools. However, subtle differences have also been reported. Chemogenetic activation of vHPC→mPFC during the forced swim test leads to differences in immobility, swimming, and climbing while optogenetic photostimulation results in differences in climbing and swimming only (30). Less subtle differences have been identified in experiments not covered, including differences in specific behavioral outcomes when a circuit is targeted with optogenetics versus chemogenetics (87).

As popularity of activity-dependent labeling grows, it is also important to consider that not all IEGs are made equal. IEGs can have varying patterns of expression across different regions in response to stress (97,98). For example, Covington and colleagues found that optogenetic stimulation increases cFos expression in all conditions tested, but only increases Arc expression following stimulation longer than 30 minutes (97). Others have also found that optogenetic stimulation does not reliably increase Arc expression, potentially due to the complexity of Arc transcription (99,100). Therefore, experimental results following activity-dependent labeling will be partially dependent on IEG choice. Temporal-specific labeling also suffers from significant limitations in trapping window. Most methods have trapping windows of eight to 24 hours, a time-frame which is unlikely to be specific only to the neurons of interest.

It is also important to note that there are technical limitations in manipulations of increasing specificity. Viral spread and infection are tightly coupled to the amount of viral particles injected, which is difficult to precisely control. Viral affinity can differ among both viruses of different serotypes and neuronal types, thereby potentially leading to labeling of nonphysiological ratios of neurons. Labeling based on cell-type specific promoters is also not perfect. For example, CamKII, the choice promoter for selective targeting of excitatory neurons, also leads to expression of virally-packaged proteins in a percentage of inhibitory neurons (64,67).

Taken together, these methodological limitations imply a need for numerous controls to be added to each experimental design. Currently, this is not standard practice. Most commonly, controls involve the expression of a non-opsin/non-DREADD protein to control for injection, viral infection, and photo/drug delivery. An ideal experiment however would include: (1) both chemogenetic and optogenetic manipulation of the region or pathway of interest, (2) bidirectional control to test the pathway under both inhibitory and excitatory conditions, (3) delivery of the opsin/DREADD using viruses of multiple serotypes, (4) systematic dissection of the contribution of each cell-type within the region/pathway of interest as well as all neurons together, (5) "dose-response" analyses to assess the threshold number and location of neurons necessary for driving a behavior using varying amounts of viral particles, (6) "dose-response" analyses of photostimulation protocol and drug concentration, (7) time-course analyses for "trapping" and/or the delivery of photo/drug stimulation, and (8) investigation of the pathway across multiple behaviors testing behaviors spanning both equivalent and differing affective domains. This type of comprehensive experimental design is imperative for enhanced reproducibility but implausible for an individual lab. A resource such as MouseCircuits.org could therefore aid circuit dissection to move toward this goal as a collaborative open science enterprise by enabling comparisons across studies to effectively generate some of the above mentioned "controls".

Sample size considerations

The average number of animals used across all the studies reviewed ranges from 7-13 animals per behavior and manipulation group. In total, the aggregated functional connectome shown in **Figure 3** represents circuit manipulations in 742-1259 animals. In comparison, human studies investigating the role of regions or pathways in behavior or cognition are often based on hundreds to thousands of individuals (101–103). The impetus for the relatively low sample sizes in rodent circuit studies comes from a combination of feasibility of conducting technically demanding experiments with large sample sizes and the universal academic goal of reducing the number of animals used to the minimum. However, if findings from underpowered studies do not replicate, ultimately more resources and animals will need to be allocated to generate the ground truth functional connectome. MouseCircuits.org can help mitigate this risk by generating a centralized and iterative aggregate view of circuit function.

Sex as a biological variable

Despite the well-documented human preponderance of females afflicted by mood disorders (104,105), the majority of identified studies utilized males only, or did not report the sex of experimental animals. Importantly, out of the 17 studies that included both male and female animals, one study used males for inhibition and females for activation (106), another used females only for tracing studies (107), and a third used males for optogenetic and females for chemogenetic manipulation (108).

On January 25th, 2016, the National Institutes of Health (NIH) implemented a laudable policy requiring investigators to consider sex as a biological variable (SABV) in their grant submissions. SABV was first required for fiscal year 2016 research grant applications, taking effect in fiscal year 2017. Encouragingly, this policy has led to some progress in circuit dissection studies: only 5% (5 studies: 1 regional and 4 pathway) of studies prior to 2017 included females, but 11% (12 studies: 6 regional and 6 pathway) included females after 2017. This trend is likely to improve further and to greatly aid the transnational power of circuit data.

The need for informed analysis: observation before perturbation

The long-term goal of uncovering the mysteries of affective circuitry is improved understanding of human disorders. To move toward this goal, two guiding principles are necessary in future circuit manipulations: they should be based on identified human functional and structural disfunction, and they should aim to mimic endogenous neural function. The first principle requires a much closer alignment between human and animal research. There is a plethora of human literature on functional and structural connectivity in disordered affect (109–114). These human neural pathways should serve as a blueprint for rodent experimentation, yet most circuit studies to-date base their hypotheses on prior rodent work. As discussed previously, this could lead to propagation of error and movement away from translatability.

The second principle requires thorough examination of normal and abnormal circuit function, followed by careful consideration of experimental conditions that capture identified endogenous activity during perturbation. Is the examined pathway normally activated during the chosen behavior? If so, with what temporal dynamics? Is the signal in this pathway unique to the chosen behavior? Answering these questions involves significant experimental investment prior to chemogenetic/optogenetic manipulations using a combination of *in vivo* electrophysiological or optical recording techniques and *ex vivo* tracing and quantification of activity mark-

ers.

Currently, this type of approach is rarely used, with only a minority of reviewed studies reporting observation prior to perturbation of the target region or pathway. Yet poignant examples exist for such prudence moving forward. In particular, the importance of temporal dynamics has been demonstrated in multiple pathways. Stimulation at various time-points within the same behavioral paradigm results in different outcomes in vHPC→Amyg (78), BLA→mPFC (64), VTA→ACB(35,37), and vHPC→NAc (98). An additional example is the inhibition of PL during extinction, which in different studies has either accelerated extinction or had no effect, likely due to timing of manipulation with respect to tone presentation (38,67). Presumably, time-dependence is due to different circuits mediating varying aspects of a behavior. For instance, the PL→BLA pathway is critical for fear retrieval at 6 hours post fear conditioning (115), but at 1 and 28 days, fear retrieval has shifted to the anterior cingulate cortex (ACC)→LA (116).

Understanding the parts of the sum and the sum of the parts
In an era when both grants and papers are outside of the reach for researchers focused on replicating prior work, we predict the complexity of the single pathway connectome to grow disproportionally to confirmatory studies. This could be particularly troublesome given that the reductionism that has dominated both basic and translational psychiatric research has been increasingly coming into question, with recent evidence that psychiatric diseases might best be interpreted at the level of network emergent properties rather than individual symptoms or the behavioral level (96). There is therefore a crucial need for bidirectional understanding of how the individual components of a circuit contribute to brain-wide activity and how network states influence neuronal function.

The majority of reviewed studies targeted a specific neuronal subpopulation for manipulation of a region or pathway of interest, most commonly glutamatergic neurons expressing CaMKII. Because of the complex interplay between multiple cell-types involved in responding to a stimulus or generating a behavior, individual findings are currently hard to translate to human network function. Behaviors arise from coordinated activity in distributed networks across the entire brain (117). In fear learning for example, it was recently demonstrated that the memory is stored in connected engrams dispersed across the brain (87). While individual circuit findings cannot easily be interpreted in a brain-wide context, as data from individual cell types and pathways is added to a shared resource such as MouseCircuits.org, the interplay is likely to emerge over time.

Similarly, brain-wide connectivity influences the outcomes of manipulations of a specific pathway. Because of complex long-range connectivity, a change in the activity of one region or pathway ripples through the network, shifting activity of other circuits by compensatory or home-ostatic mechanisms (118). For example, compensatory pathways can support fear extinction even in the face of a compromised amygdala (119). Network degeneracy, the concept that a circuit generates more than one output and that a pattern of salient neural activity can be generated by more than one circuit (120), also plays a role. Evidence exists for network degeneracy in fear memory circuits. For example blocking dorsal hippocampus (dHPC) via local microinfusion of glutamatergic receptor antagonists disrupts fear memory recall, but the impairment can be overcome by optogenetic activation of a different region – the retrosplenial cortex (121).

The brain-wide effects of stimulation of a particular circuit are hard to predict and very few studies to-date have tackled this question. Using optogenetic stimulation and whole-brain light-sheet microscopy, brain-wide circuit interrogation in zebrafish has shed light on some of these complex interactions (133). Stimulation of one neuronal ensemble was found to increase activity of some brain regions and decrease activity of others. Additionally, inhibiting versus stimulating a particular circuit does not necessarily translate into opposite maps of brain-wide activity changes. Even the time-course of activity changes across the brain can vary for different regions (133). Another recent strategy to tackle this issue is "chemo-connectomics", which combines functional magnetic resonance imaging (fMRI) with chemogenetics. Using this approach, rapid Resting-State Network (RSN) connectivity changes have been observed following chemogenetic activation of locus coeruleus (LC) (123). These data are imperative in parsing out network effects of chosen circuit manipulations, but difficult to perform and out-of-the reach for most researchers. As data of individual pathways is added to MouseCircuits.org, informed decisions can be made during experimental design, by quickly scanning known upstream and downstream connectivity.

A SHARED OPEN-SOURCE TOOL FOR MOVING THE CIRCUIT ERA FORWARD

The movement toward open science has generated an abundance of recent resources for the neuroscience community, including the Allan Brain Mouse Connectivity Atlas (122), NeuroMorpho.Org (79, 124-126); GeneNetwork (129), MouseBytes (130), and MouseLight (131). These tools are changing the landscape and culture of neuroscience by maximizing data visibility and impact.

Within this landscape, we envision MouseCircuits.org to aid the translational goal of an integrative view of individual neurocircuit function and whole-brain network organization (132). NeuroMorpho.Org (125) serves as excellent precedent for this vision. As an online repository of neuronal reconstructions from labs around the world, it now hosts over 100,000 neurons from

dozens of species and virtually every brain region (79). The number of publications based on secondary analyses of these data currently exceeds the number of original publications for which the neurons were reconstructed (79). Importantly, these secondary analyses have used the raw data of neuronal morphology to generate emergent theories of connectivity in novel ways, e.g. by estimating diffusion tensor imaging (DTI) findings (126, 127). We foresee a repository of functionally dissected individual pathways to lead to emergent properties of other whole-brain imaging modalities, such as fMRI. Ultimately, this will connect rodent data, in which perturbation is possible, to human data, to which we are collectively aiming our clinical advances.

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Table 2. *Studies of perturbed affect reviewed.* Summary of studies reviewed and number assigned in Figure 3. Studies are presented in chronological order by publication date. See tables 3 and 4 for details. *Note: These numbers match Figure 3, not the above bibliography.*

Figure 3 Number	Reference
1	Covington et al., 2010
2	Johansen et al., 2010
3	Tye et al., 2011
4	Goshen et al., 2011
5	Chaudhury et al., 2012
Continued on next page	

Table 2 – continued from previous page

Figure 3 Number	Reference
6	Liu et al.,2012
7	Warden et al.,2012
8	Tye et al.,2013
9	Xu and Südhof 2013
10	Kim et al.,2013
11	Jennings et al.,2013
12	Felix-Ortiz et al.,2013
13	Challis et al.,2013
14	Lobo et al.,2013
15	Felix-Ortiz and Tye 2014
16	Senn et al.,2014
17	Anthony et al.,2014
18	Challis et al.,2014
19	Zhu et al.,2014
20	Friedman et al.,2014
21	Sparta et al.,2014
22	Ohmura et al.,2014
23	Wolff et al.,2014
24	Redondo et al.,2014
25	Soumier and Sibile,2014
26	Kwon et al.,2014
27	Yizhar et al.,2014
28	Bagot et al.,2015
29	Christoffel et al.,2015
30	Chase Francis et al.,2015
31	Perova et al.,2015
32	Sachs et al.,2015
33	Do-Monte et al., 2015a
34	Do-Monte et al.,2015b
35	Penzo et al.,2015
36	Ramirez et al.,2015
37	Gore et al.,2015
38	Namburi et al.,2015
39	Carreno et al.,2015
40	Teissier et al.,2015
41	Yang et al.,2016a
42	Marcinkiewcz et al.,2016
43	Yang et al.,2016b
44	Felix-Ortiz et al.,2016
45	Rashid et al.,2016
46	Kim et al.,2016a
47	Dejean et al., 2016
48	Johnson et al.,2016
49	Kim et al.,2016b
50	Wook Koo et al.,2016
51	Urban et al.,2016
52	Xu et al.,2016
53	Zou et al.,2016
54	Fadok et al.,2017
55	Klavir et al.,2017
56	Parfitt et al.,2017
57	Vetere et al.,2017
Continued on next page	

Table 2 – continued from previous page

Figure 3 Number	Reference
58	Asok et al.,2017
59	Franklin et al.,2017
60	Knowland et al.,2017
61	McCall et al.,2017
62	Arico et al.,2017
63	Miller et al.,2017
64	Assareh et al.,2017
65	Dolzani et al.,2018
66	Marek et al., 2018a
67	Jimenez et al.,2018
68	Bloodgood et al.,2018
69	DeNardo et al.,2018
70	Marek et al., 2018b
71	Diehl et al.,2018
72	Zhang et al.,2018
73	Mukherjee and Caroni 2018
74	Lowery-Gionta et al., 2018a
75	Lowery-Gionta et al.,2018b
76	Yamauchi et al.,2018
77	Tipps et al.,2018
78	Fernandez et al.,2018
79	Anacker et al., 2018
80	Salinas-Hernadez et al.,2018
81	Bian et al.,2019
82	Besnard et al.,2019
83	Chen and Bi 2019
84	Gehrlach et al.,2019
85	Kato et al.,2019
86	Vasquez et al.,2019
87	Wang et al.,2019
88	Ortiz et al.,2019
89	Berg et al.,2019
90	Bernard et al.,2019
91	Rozeske et al.,2018
92	Lacagnina et al.,2019
93	Moda-Sava et al., 2019
94	Zhang et al.,2019
95	Matos et al.,2019
96	Wilmot et al.,2019
97	Roy et al.,2019
98	Zhang et al.,2019b
99	Giannotti et al.,2019
100	Sengupta et al.,2019
101	Zhou et al.,2019
102	Gutzeit et al.,2019
103	Hartley et al.,2019
104	Salvi et al.,2019
105	Rogers-Carter et al.,2019
106	Padilla-Coreano et al.,2019

Table 4. **Region Focused.** Details from studies focused on dissecting the role of a region in a perturbed affective-like state. Blue rows/arrows represent activation, red rows/arrows represent inhibition, purple rows indicate both activation and inhibition.

Target region	Animal Model	Strain	Sex	n for behavior	Behavior	Method	Promotor	Impact on anxiety behaviors	Impact on fear behaviors	Impact on depressive behaviors	Reference	Lab	PMID	Pos-hoc confirm?	Observe?	Figure 3 #
mPFC	Mouse	C57	Male	6-10 mice	CSDS, SI, SPT	Opto	ChR2	—		↓	Covington et al., 2010	Eric J. Nestler	21123555	Yes	Yes	1
LA	Rat	Sprague-Dawley	Male	8 rats	FC	Opto	CaMKII and MCS		↑		Johansen et al., 2010	Joseph E. LeDoux	20615999	Yes	Yes	2
dCA1	Mouse	C57	Unknown	4-6 mice	FC, OFT	Opto	CaMKIIa	—	↓		Goshen et al., 2011	Karl Deisseroth	22019004	Yes		4
ACC	Mouse	C57	Unknown	4-6 mice	FC, OFT	Opto	CaMKIIa	—	↑		Goshen et al., 2011	Karl Deisseroth	22019004	Yes		4
VTA	Mouse	tyrosine hydroxylase (TH)-Cre or PRV-Cre	Male	7-19 mice	SSD, SI, SPT, OFT	Opto	TH and PRV	—		↑	Chaudhury et al., 2012	Ming-Hu Han	23235832	Yes		5
DG	Mouse	c-fos-tTA, TetTag, C57	Unknown	5-12 mice	FC	Opto	c-Fos		↑		Liu et al., 2012	Susumu Tonegawa	22441246	Yes	Yes	6
mPFC	Rat	Long-Evans	Male	8-16 rats	FST, OFT	Opto	CaMKIIα and hSyn	—		—	Warden et al., 2012	Karl Deisseroth	23160494	Yes		7
VTA	Mouse and Rat	TH-Cre IRES mice and BAC rats	Male	9-20 animals	Chronic mild stress, TST, SPT, OFT	Opto	TH and BAC			↑↓	Tye et al., 2013	Karl Deisseroth	23235822	Yes		8
BNST	Mouse	C57	Male	7-11 mice	EPM, OFT	Opto	hSyn and CaMKIIα	↑↓			Kim et al., 2013	Karl Deisseroth	23515158	Yes		10
DRN	Mouse	GAD2-Cre	Male	6-8 mice	CSDS, SI	Opto	GAD2			↓	Challis et al., 2013	Oliver Berton	23986235	Yes	Yes	18
vHPC	Mouse	TRE-HA-hM4Di x CaMKIIa-tTA	Unknown	12-17 mice	FC	Chemo	CaMKIIa		↓		Zhu et al., 2014	Bryan L Roth	24525710	Yes		19
MRN	Mouse	tTA::tetO-ChR2(C128S)	Male and female mice	7-9 mice	EPM	Opto	ChR2 knock-in mouse	↑			Ohmura et al., 2014	Mitsuhiro Yoshioka	24834486	Yes		22
BLA	Mouse	PV-cre and SOM-cre	Male	8-11 mice	FC	Opto	PV and SOM		PV+ = ↓↑ SOM+ = ↑↓		Wolff et al., 2014	Andreas Lüthi	24814341	Yes		23
DG and BLA	Mouse	C57	Male	16-48 mice	FC	Opto	TRE		↑		Redondo et al., 2014	Susumu Tonegawa	25162525	Yes	Yes	24
Frontal Cortex (prelimbic/precingulate)	Mouse	SST-IRES-Cre mice	Male and female	8-10 mice	EPM, NSF, cookie test, SPT, unpredictable chronic mild stress	Chemo	SST-IRES	Acute = ↑ Chronic = ↓			Soumier et al., 2014	Etienne Sibille	24690741	Yes		25
mPFC	Mouse	C57 and PV-Cre	Male	6-8 mice	SI, FC, OFT	Opto	CaMKIIα and PV	CaMKIIα = ↑ , PV = —	↓		Yizhar et al., 2011	Thomas J. Davidson	21796121	Yes		27

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Region	Species	Strain	Sex	N	Behavior	Technique	Target				Reference	PI	PMID			#
NAc	Mouse	D1-Cre + D2-Cre	Male	4-8 mice	CSDS, SSD	Opto, Chemo	D1 and D2			D1 medial spiny neurons: ↓ ↑ D2 medial spiny neurons: ↑	Chase Francis et al., 2015	Mary Kay Lobo	25173629	Yes	Yes	30
mPFC	Mouse	PV-Cre	Male	12 mice	LH	Chemo	PV			↑	Perova et al., 2015	Bo Li	25698754	Yes	Yes	31
LHb	Mouse	C57	Male	6-11 mice	CSDS	Chemo	hSyn			↓	Sachs et al., 2015	Marc G. Caron	25675490	Yes		32
IL	Rat	Sprague Dawley	Male	4-7 rats	FE	Opto	CaMKII		↓↑		Do-Monte et al., 2015a	Gregory J. Quirk	25716859	Yes		33
BLA	Mouse	C57	Male	5-10 mice	FC, olfactory & instrumental conditioning	Opto	EF1a		↑↓		Gore et al., 2015	Richard Axel	26140594	Yes	Yes	37
Raphe	Mouse	Pet1-cre, RC::PDq and RC::PDi	Male and Female	6-25 mice	OFT, FST, EPM	Chemo	DREADD mouse lines	↑		↓ –	Teissier et al., 2015	Mark S. Ansorge	26655908	Yes		40
LA	Mouse	C57	Male and Female	4-12 mice	FC	Opto, Chemo	ChR2, NpACY, and hM4Di		↓		Rashid et al., 2016	Sheena A. Josselyn	27463673	Yes	Yes	45
BLA	Mouse	C57, Cartpt-Cre mice, and Rspo2-Cre	Male	8-11 mice	FC	Opto	Cartpt and Rspo2		↓		Kim et al., 2016a	Susumu Tonegawa	27749826	Yes	Yes	46
dmPFC	Mouse	C57 mice, PV-IRES-Cre mice, and CamKIIalpha-Cre	Male	7 mice	FC	Opto	EF1a, PV-IRES, CamKIIa, and CAG		Ascending or descending phase of 4 Hz oscillation: ↓ or ↑		Dejean et al., 2016	Cyril Herry	27409809	Yes		47
IL and PL	Mouse	C57	Male	7-13 mice	FE	Opto	hSyn and CaMKIIα		IL: ↑↓ PL: –		Kim et al., 2016b	Jin Hee-Han	26354044	Yes	Yes	49
DRN	Mouse	Slc6a4-Cre	Male	8-17 mice	LD, FST, NSF	Chemo	Slc6a4	↑		↓	Urban et al., 2016	Bryan L Roth	26383016	Yes		51
DG	Mouse	PV-Cre	Male	19-27 mice	EPM, OFT, SI, TST, FE	Chemo	PV	↓	↓	–	Zou et al., 2016	Y Mao	26733123	Yes		53
CeA	Mouse	C57, Crf-ires-cre32, Som-ires-cre	Male	6-20 mice	Conditioned flight	Opto	CRF, Som		CRF: ↓ Som: ↑		Fadok et al., 2017	Andreas Lüthi	28117439	Yes		54
LSI, Re, LD, and CA1	Mouse	C57	Male	8 mice	FC	Chemo	EF1a		↓		Vetere et al., 2017	Paul W. Frankland	28426969	Yes		57
vlPAG	Rats	Sprague Dawley	Male	4-12 rats	FC	Chemo	hSyn		↓↓		Arico et al., 2017	Gavan P. McNally	28716712	Yes		62

Table 4.

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Region	Species	Strain	Sex	N	Behavior	Method	Promoter	Arrow1	Arrow2	Arrow3	Citation	PI	PMID			#
PAG	Rat	Sprague Dawley	Male	3-9 rats	FC and looming threat	Opto	hSyn		↑		Assareh et al., 2017	Gavan P. McNally	29083203	No		64
PL	Mouse	TRAP2 and Ai14	Unknown	3-20 mice	Discriminatory FC		TRAP2 and Ai14		↑↓		DeNardo et al., 2018	Liqun Luo	30692687	Yes	Yes	69
PL	Mice	C57	Male	~15 rats	Active avoidance	Opto	CaMKIIa	↓−			Diehl et al., 2018	Gregory J Quirk	29851381	Yes		71
vPAG	Mouse	Vgat-Cre	Male	6-16 mice	LD, OFT, FC	Chemo	Vgat	↑	↓		Lowery-Gionta et al., 2018a	Thomas Louis Kash	30076467	Yes		74
BLA	Mouse	CaMKII Cre and GAD Cre	Male and Female	5-10 mice	FC	Chemo	CaMKII and GAD		GABA: ↓↑ Pyramidal: −		Tipps et al., 2018	Kevin Wickman	30406197	Yes		77
vDG	Mouse	C57	Male	5-22 mice	SSD	Chemo	CamKII			↓↑	Anacker et al., 2018	René Hen	29950730	Yes		79
VTA	Mouse	C57 and Dat-Cre	Male	7-8 mice	FE	Opto	EF1a		↑↓		Salinas-Hernadez et al., 2018	Sevil Duvarci	30421719	Yes	Yes	80
IL	Mouse	Nex-Cre	Male	4-28 mice	OFT, NSF	Opto	Nex	↑			Berg et al., 2019	Olivia Andrea Masseck	30677060	Yes	Yes	89
Piriform	Mouse	cfos-tTA	Males for inhibition studies and females for activation studies	7-8 mice	Odor fear learning	Chemo	c-Fos		↓		Bernard et al., 2019	Alexander Fleischmann	30612908	Yes	yes	90
DG	Mouse	ArcCreERT2::Halo-eYFPflx and ArcCreERT2::ChR2-eYFPflx	Male and female		FC and FE	Opto	Mice lines for virus		Ext neurons: ↑ ↓ Training neurons: ↓↑		Lacagnina et al., 2019	Michael R. Drew	30936555	Yes	Yes	92
mPFC	Mouse	C57	Male	Read out: Spine formation	Chronic CORT stress	Opto	SARE			↑	Moda-Sava et al., 2019	C Liston	30975859	Yes		93
dCA1	Mouse	TetTag or cFos tTA	Male	4-17 mice	CSDS	Opto, Chemo	TetTag and cFos			↑↓	Zhang et al., 2019a	Susumu Tonegawa	doi: 10.1101/615096	Yes		94
dorsal mPFC region (PL + ACC)	Mouse	C57	Male	4-8 mice	FC	Chemo	cFos and hSyn		↓↑		Matos et al., 2019	Michel C. van den Oever	31127098	Yes	Yes	95
dCA1	Mouse	C57	Male and female	4-7 mice	Trace FC	Opto	CaMKIIa		↓		Wilmot et al., 2019	Brian J. Wiltgen	31191269	Yes		96
CA1, BLA, AM, and RE	Mouse	Fos-TRAP	Male	7-11 mice	FC	Opto, Chemo	cFos		↑↓		Roy et al., 2019	Susumu Tonegawa	doi: 10.1101/668483	Yes	Yes	97
CA1	Mouse	TetTag mice	Male	16-22 rats	CSDS	Opto	TetTag			↑↓	Zhang et al., 2019b		31405928	Yes	Yes	98

Table 4.

3

Region	Species	Strain	Sex	Sample	Behavior test	Method	Promoter					Reference	PI	DOI			#
IL	Mouse	TRAP	Male and female	3-6 mice	FC, bright field (innate fear), social buffering	Opto	Not mentioned		↓			Gutzeit et al., 2019	Zoe R Donaldson	doi: 10.1101/752386	Yes	Yes	102
Cortical regions	Mouse	CamKIIα-tTA:TetO-hM3Dq, CamKIIα-tTA:TetOhM4Di, and C57	Male	9-10 mice	OFT, EPM test, light–dark test, TST, and FST	Chemo	CamKIIa	↓−		−		Salvi et al., 2019	Vidita A. Vaidya	31736725	Yes		104
PL	Mouse	C57	Male and female	11-19 rats	Delayed FC	Chemo	cFos and hSyn		−↓			Giannotti et al., 2019	Jamie Peters	31341176	Yes	Yes	99

Table 5. Pathway-focused. Details from studies focused on dissecting the role of a pathway in a perturbed affective-like state Blue rows/arrows represent activation, red rows/arrows represent inhibition, purple rows indicate both activation and inhibition.

Target from	Target to	Animal Model	Strain	Sex	n for behavior	Behavior	Method	Promoter	Impact on anxiety behaviors	Impact on fear behaviors	Impact on depressive behaviors	Reference	Lab	PMID	Post-hoc confirm?	Obser-ve?	Figure 3 #
BLA	CeA	Mouse	C57	Male	7-8 mice	EPM	Opto	CaMKIIα	↓↑			Tye et al., 2011	Karl Deisseroth	21389985	Yes		3
VTA	NAc	Mouse	TH-Cre mice or PRV-Cre	Male	7-19 mice	SSD, SI, SPT, OFT	Opto	TH and PRV	—		↑↓	Chaudhury et al., 2012	Ming-Hu Han	23235832	Yes		5
VTA	mPFC	Mouse	TH-Cre or PRV-Cre	Male	7-19 mice	SSD, SI, SPT, OFT	Opto	TH and PRV			↑	Chaudhury et al., 2012	Ming-Hu Han	23235832	Yes		5
mPFC	DRN	Rat	Long-Evans	Male	8-16 rats	FST, OFT	Opto	CaMKIIα and hSyn	—		↑	Warden et al., 2012	Karl Deisseroth	23160494	Yes		7
mPFC	LhB	Rat	Long-Evans	Male	8-16 rats	FST, OFT	Opto	CaMKIIα and hSyn	—		↓	Warden et al., 2012	Karl Deisseroth	23160494	Yes		7
mPFC	N. reuniens	Mouse	C57	Male	8-10 mice	Contextual FC	Opto	WGA		Phasic: ↑ Tonic: ↓		Xu & Südhof 2013	Thomas C. Südhof	23493706	Yes		9
BLA	BNST	Mouse	C57	Male	7-11 mice	EPM, OFT	Opto	hSyn, CaMKIIα, and EF1α	↓↑			Kim et al., 2013	Karl Deisseroth	23515158	Yes		10
BNST	LH	Mouse	C57	Male	7-11 mice	EPM, OFT	Opto	hSyn, CaMKIIα, and EF1α	↓			Kim et al., 2013	Karl Deisseroth	23515158	Yes		10
BNST	VTA	Mouse	C57	Male	7-11 mice	EPM, OFT	Opto	hSyn, CaMKIIα, and EF1α	—			Kim et al., 2013	Karl Deisseroth	23515158	Yes		10
BNST	VTA	Mouse	Vglut2 and Vgat	Male	6 mice	EPM, OFT	Opto	CaMKIIa	Glutamatergic projections: ↑ GABAergic projections: ↓			Jennings et al., 2013	Garret D. Stuber	23515155	Yes		11
BLA	vHPC	Mouse	C57	Male	7-8 mice	EPM and OFT	Opto	CaMKIIα	↓↑			Felix-Ortiz et al., 2013	Kay M. Tye	23972595	Yes		12
VTA	NAc, mPFC, vHPC,	Mouse	D2-GFP	Male	4-5 mice	CSDS	Opto	hSyn and CaMKII			↓	Lobo et al., 2013	Eric J. Nestler	24259563	Yes		14

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Source	Target	Species	Strain	Sex	N	Test	Manip.	Promoter	Eff1	Eff2	Eff3	Citation	PI	PMID			#
BLA	vHPC	Mouse	C57	Male	7-8 mice	Resident-juvenile intruder home-cage test, three-chamber sociability test	Opto	CaMKII			↓↑	Felix-Ortiz & Tye 2014	Kay M. Tye	24403157	Yes		15
BLA	mPFC (IL or PL)	Mouse	C57	Male	5 mice	FC	Opto			BLA -> IL: ↑↓ / BLA -> PL: ↓↑		Senn et al., 2014	Andreas Lüthi	24462103	Yes		16
LS C	Hypothalamus (anterior)	Mouse	Crfr2a-eGFPCre	Unknown	9-17 mice	Restraint stress, LD, OFT	Opto	Crfr2a	↑↓			Anthony et al., 2014	David J. Anderson	24485458	Yes		17
vmPFC	DRN	Mouse	CaMKIIa-Cre	Male	6-8 mice	CSDS	Opto	CaMKIIa			↑↓	Challis et al., 2014	Olivier Berton	24596546	Yes		18
VTA	NAc	Mouse	TH-Cre	Male	7-12 mice	CSDS	Opto	TH			↓	Friedman et al., 2014	Ming-Hu Han	24744379	Yes	Yes	20
BLA	EC	Mouse	C57	Male	8-17 mice	FC	Opto	CaMKIIα			↓−	Sparta et al., 2014	Garret D. Stuber	24834031	Yes		21
ACx	LA	Mouse	129/C57 hybrid	Unknown	4-14 mice	FC	Opto	hSyn		↑		Kwon et al., 2014	Jin-Hee Han	25322798	Yes		26
vHPC	NAc	Mouse	C57	Male	6-21 mice	CSDS	Opto	CaMKIIa			↓	Bagot et al., 2015	Eric J. Nestler	25952660	Yes	Yes	28
ILT	vSTR medium spiny neurons (MSNs)	Mouse	C57	Male	11-18 mice	CSDS	Opto	Ef1a and CMV			↓	Christoffel et al., 2015	Scott J Russo	26030846	Yes		29
PL	PVT, CeA, BLA	Rat	Sprague-Dawley	Male	7-8 rats	FC	Opto	CaMKIIα		↓		Do-Monte et al., 2015b	Gregory J Quirk	25600268	Yes	Yes	34
CeL	PVT	Mouse	C57 and Som-Cre	Male and female	7-13 mice	FC	Chemo	GFP, CAV, TRE, Ef1a, and SOM		↓		Penzo et al., 2015	Bo Li	25600269	Yes	Yes	35
DG	BLA, Nac	Mouse	cFos tTA + TEtTag	Male	12-18 mice	OFT, EPM, TST, SPT	Opto	cFos tTA and TetTag			↓↑	Ramirez et al., 2015	Susumu Tonegawa	26085274	Yes		36
BLA	CeM, NAc	Mouse	C57	Male	6-9 mice	Nose poke, FC	Opto	EF1α and CAV2		↑↓		Namburi et al., 2015	Kay M. Tye	25925480	Yes	Yes	38
vHPC	mPFC	Rat	Sprague-Dawley	Male	8-9 rats	FST	Opto, Chemo	hSyn			↓	Carreno et al., 2015	D J Lodge	26619811	Yes		39

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Source	Target	Species	Strain	Sex	N	Behavior	Method	Promoter				Reference	PI	PMID			#
LHb	LDT	Mouse	VGAT-ChR2(H134R)-eYFP (VGAT), GAD67-GFP (GAD67), PV-Cre, PV-GFP, SOM-Cre	Male	5-15 mice	Open field, EPM, freezing to odor	Opto	VGAT, GAD67, PV, and SOM	↑		Excitatory LDT neurons: ↑, PV+ LDT neurons: ↑, SOM+ LDT interneurons: ↓, Hb-> LDT: ↑		Yang et al., 2016a	Mu-ming Poo	27595384	Yes	Yes	41
DRN	BNST	Mouse	C57	Male (optogenetic) and female (DREADD)	7-10 mice	FC, EPM, NSF, OFT	Opto, Chemo	ef1α and hsyn	↑	↑			Marcinkiewcz et al., 2016	Thomas L. Kash	27556938	Yes	Yes	42
LA	ACx	Mouse	C57	Male	3-9 mice	FC	Opto, Chemo	hSYN and CamKIIa		↓			Yang et al., 2016b	Hao Wang	26727549	Yes		43
BLA	mPFC	Mouse	C57	Male	9-12 Mice	EPM, OFT, resident-intruder SI test	Opto	CaMKIIα	↑↓				Felix-Ortiz et al., 2016	K.M. Tye	26204817	Yes		44
avBNST	PVH, vlPAG	Rat	Sprague Dawley	Male	3-7 rats	TST, FST	Opto	hSyn			↑↓		Johnson et al., 2016	Jason J. Radley	27535914	Yes		48
VTA	NAc	Mouse	C57	Male	5-11 mice	CSDS	Opto	hsyn			↑		Wook Koo et al., 2016	Eric J. Nestler	26858215	Yes		50
vHPC	BLA, CeA	Mouse	C57	Male	6-12 mice	FC	Opto	EF1α		vHPC→BLA: ↓—, vHPC→CEA: —↓			Xu et al., 2016	Andreas Lüthi	27773481	Yes		52
BLA	PL, IL	Mouse	C57	Male	5-20 mice	FE	Opto	hEF1α, EF1α, and CaMKIIα		↓			Klavir et al., 2017	Ofer Yizhar	28288126	Yes		55

Table 5.

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Region1	Region2	Species	Strain	Sex	N	Behavior	Technique	Promoter	Col A	Col B	Col C	Reference	PI	PMID			#
vHPC	PL and LS	Mouse	C57	Unknown	14-24 mice	OFT, EPM, NSF, Successive alley test	Chemo	CaMKIIα, CAV2, and hSyn	↓↑			Parfitt et al., 2017	Jun Chul Kim	28294135	Yes		56
CeL	BNST	Rat	Sprague Dawley	Male	8-13 rats	FC	Opto	CRF		↓		Asok et al., 2018	J B Rosen	28439099	Yes		58
mPFC	dPAG	Mouse	C57 and Vglut2 Cre	Male	10-12 mice	CSDS	Chemo	hSyn and Vglut2			↑, Glutamatergic only: ↓	Franklin et al., 2017	Cornelius T Gross	28067904	Yes	Yes	59
VP	LHb, VTA	Mouse	PV-Cre	Male (also used females for tracing studies only)	5-15 mice	CSDS, SI, SPT, TST	Opto, Chemo	PV			VP ↓, VTA ↓, LHb ↓, VP->VTA: ↓, VP->VTA: ↑, VP->LHb: ↑, VP -> LHb ↑	Knowland et al., 2017	Byung Kook Lim	28689640	Yes	Yes	60
LC	BLA	Mouse	C57	Male	4-10 mice	Pavlovian conditioned place aversion, OFT	Opto	EF1a	↑			McCall et al., 2017	Michael R Bruchas	28708061	Yes	Yes	61
MDT	mPFC	Mouse	GluN2B floxed	Male	10-17 mice	FST, TST, OFT	Chemo	CaMKII			↓	Miller et al., 2017	Benjamin J. Hall	28834750	Yes		63
PL	DRN	Rat	Sprague Dawley	Male and female	9-10 mice	Juvenile social exploration, uncontrollable stressors	Chemo	eSyn, hSyn, and NLS			↑	Dolzani et al., 2018	S. F. Maier	29516036	Yes		65
vHPC	IL	Rat	Wistar	Male	5-17 rats	FC	Chemo	CamKIIα, hSyn, CAV2, CMV, CAG, and EF1a		vHPC→ IL: ↑, vHPC→ IL ↓, vHPC ↓		Marek et al., 2018	Pankaj Sah	29403033	Yes	Yes	66
vCA1	LH, BLA	Mouse	C57 and DBA/2	Male	9-12 mice	OFT, FC	Opto	CaMKIIa, CAG, and Syn	↓↑	↓		Jimenez et al., 2018	Mazen A. Kheirbik	29397273	Yes	Yes	67
IL	BLA	Mouse	C57	Male	8-10 mice	FE	Chemo	hEF1α and hSyn		↓		Bloodgood et al., 2018	Thomas L. Kash	29507292	Yes	Yes	68

IL	PL	Mouse	C57	Male and female	7- 10 rats	FE	Opto	CAG and hSyn		↓		Marek et al., 2018b	Pankaj Sah	29686260	Yes		70
IL (PL)	PL (IL)	Mouse	PV-Cre	Male	5 mice	FE	Chemo	CAG and hSyn		At acquisition: PL = ↓,IL = –. At extinction: PL= ↓, IL = ↑		Mukherjee et al., 2018	Pico Caroni	30006525	Yes		73
BLA	mPFC	Mouse	C57 and DBA/2J	Male	19 mice	Chronic stress, EPM	Opto	CaMKII	↑			Lowery-Gionta et al., 2018b	Thomas Louis Kash	29959957	Yes		75
CeA	BNST	Rat	Sprague–Dawley	Male	6-7 rats	EPM	Opto	hSyn	↑			Yamauchi et al., 2018	Masabumi Minami	30240530	Yes	Yes	76
LDTg	VTA	Mouse	C57 and ChAT-IRES-Cre	Male	8-19 mice	CSDS, OFT, SPT	Chemo	hSyn			↓	Fernandez et al., 2018	Jacques Barik	30361503	No		78
ACC	vHPC	Mouse	C57	Male	11-13 mice	FC and FE	Opto, Chemo	hSyn and CaMKII		↓↑		Bian et al., 2019	Dong-Ya Zhu	31097621	Yes	Yes	81
DG/CA3	DLS	Mouse	SST-IRES-Cre	Male	6-7 mice	OFT, EPM, NSF, FC	Opto	EF1a	↓	↑↓		Besnard et al., 2019	Amar Sahay	30718902	Yes		82
PVT	CeL	Mouse	C57	Male	8-20 mice	EPM, OFT, FC, chronic stress	Opto	hSyn	–	↑, LTD: ↓		Chen & Bi 2019	Lin-lin Bi	30406427	Yes		83
Insula	CeA	Mouse	C57	Male	5-13 mice	EPM, elevated zero maze	Opto	Camk2a	↑↓			Gehrlach et al., 2019	Nadine Gogolla	31455886	Yes	Yes	84
PVT	mPFC	Mouse	CaMKIIα-promoter-loxP-STOP-loxP-tTA (Tg2) and TetO-TeTX (Tg3)	Male and female	5-9 mice	FST, TST, wheel running	Chemo	hSyn			↓	Kato et al., 2019	Tadafumi Kato	31712646	Yes		85
VH	PL	Mouse	C57	Male	7-11 mice	FC	Chemo	hSyn		↓–		Vasquez et al., 2019	I.A. Muzzio	30898692	Yes		86

Table 5.   5   Anderson et al. | MouseCircuits.org

Source	Target	Species	Line	Sex	N	Behavior	Technique	Promoter	Result A	Result B	Result C	Reference	PI	PMID			#
ACx, mSC	lPAG, dlPAG	Mouse	CaMKII-Cre	Male	5-8 mice	Auditory-related defensive behaviors (Escape behavior test, running test, wall rearing test), OFT	Opto, Chemo	Ef1α	↓↑			Wang et al., 2019	Zhi Zhang	31469831	Yes		87
ACC and vHPC	BLA	Mouse	C57	Male	4-8 mice	Contextual FC	Chemo	CaMKIIa		↓		Ortiz et al., 2019	Aaron M. Jasnow	31209172	Yes		88
dmPFC	vlPAG	Mouse	CaMKII-Cre	Male	5-7 mice	Contextual fear discrimination	Opto	EF1a, FLEX, and CAV2		↑↑↓↓		Rozeske et al., 2018	Cyril Herry	29398355	Yes	Yes	91
DRN	LHb	Rat	Sprague–Dawley	Male	8-16 rats	Chronic unpredictable stress, SPT, FST, splash test, NSF, OFT, EPM	Opto	hSyn			↓↑	Zhang et al., 2018	Jian-Guo Chen	29460052	Yes		94
DRN	BLA	Mouse	5-HTT-Cre	Male and female	8-11 mice	FC, FE	Opto	EF1a		↑		Sengupta et al., 2019	Andrew Holmes	31204082	Yes	Yes	100
LS	VTA	Mouse	GAD2-ires-Cre and C57	Male	5-16 mice	Looming test	Opto	CaMKIIa and Ef1a		VTA GAD2+: ↑ CaMKIIa SC-VTA: ↑ ↓		Zhou et al., 2019	Liping Wang	31202540	Yes	Yes	101
BLA	CeL	Mouse	SOM or CRF-ires-Cre::Ai14 and SOM-ires-Cre Flp mice	Male	9 - 26 mice	FC, FE	Opto, Chemo	SOM, CRF-ires, and SOM-ires		Before conditioning, before extinction, after extinction: ↓↓,−↓,↑		Hartley et al., 2019		31712775	Yes	Yes	103

Table 5.

IC	NaC	Rat	Sprague Dawley	Male	7-10 rats	Juvenile social exploration, uncontrollable stressors	Chemo	hSyn			↑↓	Rogers-Carter et al., 2019	John P Christianson	31591155	Yes	Yes	105
vHPC	mPFC	Mouse	129SvevTac	Male	6-10 mice	EPM	Opto	CaMKIIa	↑			Padilla-Coreano et al., 2019	Joshua A. Gordon	31521441	Yes		106

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