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Infralimbic cortex functioning across motivated behaviors: Can the differences be reconciled?

Kelle E. Nett^{a, *}, Ryan T. LaLumiere^{a,b,c}

^a Interdisciplinary Neuroscience Program, University of Iowa, Iowa City, IA 52242, United States

^b Department of Psychological and Brain Sciences, University of Iowa, Iowa City, IA 52242, United States

^c Iowa Neuroscience Institute, University of Iowa, Iowa City, IA 52242, United States

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ABSTRACT

The rodent infralimbic cortex (IL) is implicated in higher order executive functions such as reward seeking and flexible decision making. However, the precise nature of its role in these processes is unclear. Early evidence indicated that the IL promotes the extinction and ongoing inhibition of fear conditioning and cocaine seeking. However, evidence spanning other behavioral domains, such as natural reward seeking and habit-based learning, suggests a more nuanced understanding of IL function. As techniques have advanced and more studies have examined IL function, identifying a unifying explanation for its behavioral function has become increasingly difficult. Here, we discuss evidence of IL function across motivated behaviors, including associative learning, drug seeking, natural reward seeking, and goal-directed versus habit-based behaviors, and emphasize how context-specific encoding and heterogeneous IL neuronal populations may underlie seemingly conflicting findings in the literature. Together, the evidence suggests that a major IL function is to facilitate the encoding and updating of contingencies between cues and behaviors to guide subsequent behaviors.

1. Introduction

The rodent infralimbic cortex (IL), a ventral subregion of the medial prefrontal cortex (mPFC) that is homologous to part of the ventromedial prefrontal cortex (vmPFC) in humans, regulates multiple behaviors, such as fear conditioning, drug seeking, reward processing, and habit learning (Gourley and Taylor, 2016; Muller Ewald and LaLumiere, 2017; Peters et al., 2009; Quirk et al., 2006; Smith and Graybiel, 2016). Early fear conditioning studies found that the IL inhibits fear conditioning following extinction learning and facilitates the encoding of fear extinction learning (Quirk et al., 2006). Similar observations were soon made for the extinction and ongoing inhibition of cocaine seeking (Peters et al., 2008a). This led to the hypothesis that the IL acts as a "brake" on certain behaviors, an idea consistent with the human vmPFC inhibiting improper responding and negative emotional responses (Hiser and Koenigs, 2018). However, our laboratory as well as others have found that, under some circumstances, the IL plays precisely the opposite role in drug seeking - i.e., promoting, rather than inhibiting, such behavior (Bossert et al., 2011, 2012; Gutman et al., 2016; Rogers et al., 2008). Moreover, evidence from studies investigating natural reward seeking and habit-based behavior suggests IL function is considerably more nuanced than that of a "brake" (Caballero et al., 2019; Gourley and Taylor, 2016; Smith and Graybiel, 2016). These conflicting findings raise fundamental questions about how we define IL function in rodent behavior.

It is unclear, yet of critical importance, whether the IL has a common function across behaviors and learning. The IL maintains anatomical connections with limbic regions, such as the nucleus accumbens (NA) shell and the amygdala, placing the IL in a position to regulate a variety of learning and behavioral processes. However, the IL is often not distinguished from other mPFC regions, particularly its dorsal counterpart, the prelimbic cortex (PL). This is a significant problem for elucidating IL and mPFC function, as prior studies indicate contrasting roles for the IL and the PL in a variety of behavioral paradigms (Gourley and Taylor, 2016; Peters et al., 2009). Moreover, recent work identifies heterogeneous populations of neuronal ensembles in the IL that appear to encode distinct, and sometimes opposing, behaviors that may, in part, be responsible for the seemingly disparate findings (Bossert et al., 2011; Peters et al., 2013; Pfarr et al., 2015; Warren et al., 2019, 2016). These distinct neuronal populations may be involved in contingency learning

E-mail address: kelle-nett@uiowa.edu (K.E. Nett).

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Review article

^{*} Corresponding author at: G60 Psychological and Brain Sciences Building, University of Iowa, Department of Psychological and Brian Sciences, Iowa City, IA 52242, United States.

and allow the IL to guide appropriate behaviors. Contingency learning is often viewed as the unifying principle underlying both associative and instrumental learning, as the organism must learn the relationships among various stimuli in the environment and between the organism's behavior and consequences (Schwartz et al., 2002). Indeed, the IL may be particularly important in updating such knowledge and guiding future behavior, especially when this involves behaviors based on competing contingencies. Here, we will provide a comprehensive review of the IL across a variety of behaviors to consolidate findings and identify common threads to place IL function in a more coherent framework.

2. Anatomy of the rodent mPFC and IL

In considering the function of the IL, it is important to place this brain region in an anatomical context within the mPFC and its homologous regions in primates. The human vmPFC regulates a variety of higher order processes, including long-term memory consolidation, goal-directed behaviors, and the retention of fear extinction (de Wit et al., 2009, 2012; Delgado et al., 2008; Hartley et al., 2011; Milad et al., 2013, 2005; Nieuwenhuis and Takashima, 2011; Plassmann et al., 2007). The vmPFC also mediates behavioral inhibition, the dysfunction of which is linked to drug addiction (Courtney et al., 2013; Ersche et al., 2011; Fowler et al., 2007; Goldstein and Volkow, 2011; Sjoerds et al., 2013; Volkow et al., 2003). However, functional imaging studies of the human mPFC often do not distinguish between subregions (Amaro and Barker, 2006), which is of particular concern when making cross-species comparisons, as the rodent mPFC has multiple subregions with distinct and sometimes opposing functions (Gourley and Taylor, 2016; Peters et al., 2009, 2013). Moreover, human mPFC functions are often mapped onto regions of the rodent mPFC without considering homology between the human and rodent brain. Box 1 provides clarification as to what comprises the human vmPFC and where homologies may exist in the rodent mPFC.

Despite evidence supporting homology between primate anterior cingulate cortex (ACC)/mPFC and rodent mPFC, years of contradicting, overlapping, and changing nomenclature have resulted in confusing and sometimes inconsistent references to mPFC. The same anatomical terminology is often used to describe different regions between species. For example, the human ACC could encompass multiple regions of the rodent mPFC, whereas the rodent ACC is often a unique region among the cingulate cortices, PL, and IL (Laubach et al., 2018). Moreover, individual researchers and laboratories define mPFC anatomy differently, guided by preference and tradition rather than clear, agreed-upon

Box 1

Historical context of rodent mPFC and IL.

anatomical demarcations. Even within the same rodent atlas, one region may be identified in different ways (Laubach et al., 2018). As a result, mPFC studies in rodents, non-human primates, and humans are often difficult to reconcile within a single species, let alone across species.

For the above reasons, the present review will focus only on rodent studies that independently target the IL, the rodent homologue of Brodmann's Area 25 in primates, rather than include studies targeting the whole mPFC. One notable exception to this is the "vmPFC", as many rodent studies target the IL yet refer to it as vmPFC. However, other descriptions of rodent vmPFC may encompass IL, medial orbital cortex (which is immediately rostral to the IL), and sometimes, portions of ventral PL. It is critical to note that other regions of rodent vmPFC may not function similarly to IL. For example, our own findings suggest that identical manipulations of the medial orbital cortex and IL produce different behavioral effects with regard to cocaine seeking (Cosme et al., 2018). These regional differences may underlie certain discrepancies in the literature, though this has not been as well studied as other regional contrasts, such as IL and PL. Therefore, this review will use "IL" when the IL/vmPFC boundaries are strictly confined to the IL. Occasionally, studies targeting vmPFC that are less precise will be included, though the review will note in those cases the other regions included.

Of note, many studies emphasize a dichotomy between PL and IL function, demonstrating functional dissociations between the regions. This provides an opportunity to identify distinct and/or unique roles for the IL across different behavioral paradigms. In this way, a clearer understanding can be formed concerning how the IL (and consequently the PL) does and does not function. Recognizing ways in which the IL differs from neighboring structures, specifically the PL, will help to identify nuances of IL function. Thus, where applicable, this review will highlight several places where key observations regarding the IL differ from observations regarding the PL.

3. Associative learning: footshock-based and appetitive

Rodent fear conditioning studies using tone-shock pairings were some of the first to identify a unique role for the IL in regulating behavior. Work had previously suggested that the plasticity necessary for tone fear conditioning could occur entirely within the amygdala (LeDoux, 2000). However, emerging evidence began to point to the mPFC, and more specifically the IL, in regulating the extinction of conditioned fear (Morgan et al., 1993; Quirk et al., 2000). Based on these early studies, a large volume of work has now examined in greater detail how the IL influences and controls tone fear extinction (Quirk et al.,

Evidence largely supports homology between the human vmPFC (specifically Brodmann's area 25) and the rodent IL, yet this is often misunderstood due to the origin of the term "prefrontal cortex". Much of the history of what constitutes the prefrontal cortex (PFC) can be traced back to the late 1800s and early 1900s, especially to the work of Brodmann (Brodmann, 1909). He used the presence of a granular cortical layer, which does not exist in the rodent frontal cortex, to classify the Regio frontalis, otherwise known as Brodman's areas 8, 9, 10, 11, 44, 45, 46, 47. Brodmann himself only referred to Area 11 as PFC, yet over time it became common to refer to all of Brodmann's Regio frontalis as PFC (Preuss, 1995). A variety of "higher-level" functions, such as executive function, decision making, and cognitive control, were ascribed to and viewed as defining features of the PFC (Euston et al., 2012; Hiser and Koenigs, 2018; Schneider and Koenigs, 2017). However, primate research found that another portion of the frontal lobe, specifically the anterior portions of Brodmann's Regio cingularis (i.e., anterior cingulate cortex, ACC), shared some functional similarities with classic PFC. This led primate researchers to refer to the ACC as a PFC subregion, specifically denoting it as mPFC and referring to the classic PFC as dorsolateral PFC. However, in contrast to the dorsolateral PFC, the primate ACC/mPFC is agranular and has cytoarchitectonically homologous regions in rodents (Preuss, 1995). Moreover, the primate ACC and rodent mPFC receive similar patterns of mediodorsal thalamic and dopaminergic innervation and have similar outputs to ventral regions of the striatum (Heilbronner et al., 2016; Ongur and Price, 2000). These cytoarchitectural and anatomical similarities support homology between the primate ACC/mPFC and the rodent mPFC. Thus, although no evidence exists of a granular PFC in the rodent brain, it is not inaccurate to refer to anterior portions of the rodent cingulate cortex as mPFC (Preuss, 1995). Fig. 1 provides diagrams of the human, monkey, and rodent brains with the separate regions of the frontal cortex color-coded based on homology.

2006; Quirk and Mueller, 2008). Fig. 2 illustrates basic fear conditioning procedures and how extinction is evaluated in these procedures.

3.1. Acquisition and consolidation of tone fear extinction learning

Early lesion work identified the IL as a region involved in tone fear extinction memories (Quirk et al., 2000) and a number of pharmacological manipulation studies supported and expanded upon the idea that the IL is important for the acquisition and consolidation of tone fear extinction memories. Acquisition of fear extinction learning is inferred from a decrease in freezing levels upon repeated conditioned stimulus (CS) presentations in the absence of an unconditioned stimulus (US). However, acquisition can be difficult to dissociate from consolidation of tone-shock extinction learning when manipulations are given *prior to* the learning event, as consolidation likely occurs within a session in tandem with acquisition. Nonetheless, the critical information that is acquired and consolidated during tone fear extinction is the change in contingencies between the CS and US.

IL activity is not required for initial tone fear conditioning (Zelikowsky et al., 2013), suggesting that the initial contingency learning does not rely upon IL activity. However, evidence suggests the IL plays a role in the acquisition and consolidation of tone-shock extinction. Impairing IL/vmPFC function during extinction training impairs acquisition and consolidation of tone-shock extinction learning, and impairing IL/vmPFC function immediately following extinction training impairs the consolidation of the tone-shock extinction learning (Burgos-Robles et al., 2007; Do-Monte et al., 2010; Fontanez-Nuin et al., 2011; Mueller et al., 2010, 2008; Rosas-Vidal et al., 2014; Santini et al., 2004, 2012; Sierra-Mercado et al., 2006, 2011). Similarly, enhancing IL, but not PL, activity during tone-shock extinction training facilitates extinction acquisition and consolidation (Do-Monte et al., 2015; Thompson et al., 2010) and enhancing IL activity immediately following tone-shock extinction training facilitates consolidation (Do-Monte et al., 2010, 2013; Thompson et al., 2010). Additionally, evidence supports that the IL is important for extinction learning when the CS and US are separated by a trace interval, as chemogenetic IL inhibition impairs the extinction

of trace fear conditioning (Mukherjee and Caroni, 2018), and pharmacological IL inhibition via $GABA_A$ agonism impairs the extinction of trace eyeblink conditioning (Oswald et al., 2015). Taken together, a large body of evidence supports that IL activity is important for the extinction of learned associations with footshock stimuli.

In some instances, manipulating IL activity via electrical stimulation and GABAA agonism during tone-shock extinction training has no effect on the acquisition of such learning but enhances and impairs, respectively, the retention of extinction memory, as expressed during the retrieval test (Do-Monte et al., 2015; Kim et al., 2010), suggesting that the IL is important for the consolidation of such memories. Indeed, optogenetic IL stimulation during CS presentation in extinction training facilitates learning and improves retrieval (Do-Monte et al., 2015). However, optogenetic inhibition given in the same manner impairs retrieval but has no effect on acquisition of the extinction learning (Do-Monte et al., 2015). This may mean that IL signaling is capable of inhibiting freezing during extinction learning but primarily inhibits freezing after extinction contingencies are acquired and/or consolidated (i.e., during a retrieval test). Thus, the IL is likely involved in learning the change in contingency that occurs during extinction training (i.e., CS no longer predicts the US/tone no longer predicts the footshock) to inhibit freezing on subsequent recall days.

Fear conditioning studies with extracellular recordings have provided insight into potential mechanisms involved in IL-based encoding of extinction learning. Tone fear conditioning in rodents reduces intrinsic IL excitability, whereas extinction training increases IL excitability (Koppensteiner et al., 2019; Santini et al., 2008). Supporting the importance of such neurophysiological changes, pharmacological IL manipulations during tone shock fear extinction that prevent extinction-induced enhancement of intrinsic excitability impair extinction memory retrieval 24 h later (Santini et al., 2012). Altered IL excitability may be reflective of AMPA receptor insertion into IL synapses, as fear extinction increases AMPA/NMDA ratio in the IL (Sepulveda-Orengo et al., 2013). Moreover, during extinction learning, neurons in the IL, but not the PL, fire in response to the CS that is no longer paired with the US (Chang et al., 2010; Milad and Quirk, 2002).



Fig. 1. Homology of the frontal cortex in humans, monkeys, and rats-adapted from Preuss et al. 1995. Lateral view (top), sagittal view (middle) and corresponding Brodmann's areas/cingulate cortex subregions (bottom) of the human (A), monkey (B), and rat (C) brain. Brodmann's area 25 in the human and primate brain corresponds to the rat infralimbic cortex (IL), Brodmann's area 32 in the human and primate brains corresponds to the rat prelimbic cortex (PL), and Brodmann's area 24 in humans and monkeys corresponds to dorsal and ventral anterior cingulate cortex (ACd/ACv) in rats. Colors correspond to demarcations of larger frontal regions initially defined by Brodmann and expanded upon in Preuss et al. 1995.







1 CS t

CS

t

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Day 2: Extinction training

Fig. 2. Tone fear conditioning procedures. A. Left, On the first day of training, rats are placed in a chamber and given repeated presentations of a CS (tone) that co-terminates with a US (footshock). Right, with multiple CS-US pairings, rats will learn to freeze in response to the CSs. B. Left, On the next day of training, rats are placed in the same chamber and given repeated CS presentations in the absence of the US. Right, with repeated unpaired CS presentations, rats will decrease their freezing in response to the CS. C. Left, On the third day, to test extinction learning recall, rats are again placed in the chamber and presented with the CS alone. Right, The degree of freezing during this test is interpreted as the strength of extinction recall, with low freezing suggesting good extinction recall and high freezing suggesting poor extinction recall.

This CS-evoked response in the IL decreases as the new extinction contingencies are acquired (Chang et al., 2010). Taken together, these observations suggest that extinction training alters IL activity to inhibit conditioned freezing in response to the previously shock-paired CS. Thus, the IL likely plays a role in encoding this new contingency (i.e., that the CS no longer signals a US) to guide appropriate behaviors (e.g., inhibiting the freezing response to the CS).

3.2. Expression of tone fear extinction memories

Despite evidence that the IL plays a critical role in the normal acquisition of tone fear extinction, whether the IL serves as a storage location for these extinction memories remains unclear. Several studies suggest a role for the IL as a potential site of long-term plasticity for extinction memories. For example, extinction recall tests increase levels of immediate early gene transcripts in the IL (Khalaf and Graff, 2019), suggesting IL activity during this time. Additionally, increased IL neuronal activity and bursting in response to the CS predict better extinction recall (Burgos-Robles et al., 2007; Milad and Quirk, 2002). However, CS-evoked firing rates in the IL are higher in rats that fail to acquire the extinction contingency (Chang et al., 2010), suggesting that precisely how the IL facilitates the encoding of CS-associated contingencies is not as simple as an increase or decrease in firing. Nonetheless, electrical and optogenetic IL stimulation given during CS presentation in an extinction recall test improves extinction recall (Do-Monte et al., 2015; Kim et al., 2016; Milad et al., 2004; Vidal-Gonzalez et al., 2006), and optogenetic inhibition given in the same manner impairs extinction recall (Kim et al., 2016). Thus, these data suggest that, following extinction training, the IL is at least part of a circuitry that promotes the ongoing inhibition of conditioned fear.

However, not all evidence supports the IL as a storage location for these extinction memories. Early work indicates that IL-lesioned animals acquire additional extinction training faster than control animals (Lebron et al., 2004), suggesting that some aspect of the extinction memory is stored outside the IL. Indeed, pharmacological IL inhibition via NMDA receptor antagonism, GABA_A agonism, and sodium-channel blockade during an extinction recall test 24 h after extinction training does not impair extinction memory retrieval (Burgos-Robles et al., 2007; Sierra-Mercado et al., 2006, 2011). Similarly, optogenetic IL inhibition during CS presentation in retrieval has no effect on fear expression (Do-Monte et al., 2015), though this differs from a similar study in which optogenetic IL inhibition during CS presentation *and* the inter-stimulus interval impaired fear extinction retrieval (Kim et al., 2016). Overall, mixed evidence on whether the IL mediates the *expression* of tone-fear extinction may reflect how subtle parameter and methodological differences influence findings for IL involvement in such behavior.

Taken together, these findings raise difficult-to-address questions regarding IL function in the extinction of tone fear conditioning. Manipulations that impair extinction acquisition would be expected to alter plasticity within the IL, rendering it unclear why, in some studies, altering IL activity (and likely IL plasticity, as well), during recall tests does not affect extinction recall. One possibility is that such IL plasticity is only transiently necessary during the acquisition session and shortly thereafter, whereas the critical plasticity for storage purposes occurs outside this window, potentially downstream of IL cell bodies – e.g., at IL synapses in other brain regions (Do-Monte et al., 2015; Kim et al., 2016). However, conflicting findings on whether IL activity is necessary for tone-fear extinction expression make it difficult to speculate further.

3.3. Contextual fear conditioning and extinction

In contextual fear conditioning paradigms, repeated pairings of a shock either with or without an associated CS (e.g., signaled or unsignaled, respectively) occur in a particular context such that reexposure to the shock-paired context alone, and not a novel context, is sufficient to reinstate freezing behavior. Evidence supports a critical role for the IL in context extinction. IL lesions impair the acquisition and expression of context extinction (Zelikowsky et al., 2013). Similarly, post-training inhibition of protein synthesis or sodium-channel blockade in the IL impairs the consolidation of context extinction (Awad et al., 2015), and pharmacological IL inactivation via GABA_A agonism impairs long-term retention of context fear extinction (Laurent and Westbrook, 2009). These studies support a critical role for IL activity in encoding the change in contingency between context and shock that occurs during extinction training.

Similar to tone fear conditioning, evidence also suggests that the IL maintains the ongoing inhibition of contextual fear. Contextual fear memory retrieval suppresses IL levels of a neuronal marker of activity (Zelikowsky et al., 2013), and pharmacological IL inactivation via GABA_A agonism prior to a retrieval test increases freezing (Laurent and Westbrook, 2009). These studies suggest that IL activity is important for the suppression of contextual fear. Indeed, the expression of contextual fear conditioning is associated with reduced IL activity (Kugelman et al., 2016; Soler-Cedeno et al., 2016), supporting the possibility that IL activity is important for inhibiting contextual fear. Overall, it appears that the IL is involved in the encoding and expression of context extinction, further supporting a broader role for the IL in inhibiting/promoting specific behaviors when environmental contingencies change.

An intriguing finding from the contextual fear conditioning literature is that the IL is involved in preventing the generalization of fear (i.e., increased freezing to a novel, un-conditioned context), either through promoting conditioned fear in the proper context or inhibiting conditioned fear in the improper context. Fear generalization itself is associated with a reduction in IL activity (Pollack et al., 2018), and IL lesions and pharmacological IL inhibition via GABAA agonism during or immediately after contextual fear conditioning increase fear generalization (Bayer and Bertoglio, 2020; Zelikowsky et al., 2013). This function of the IL to prevent context fear generalization also appears to extend to tone fear generalization, as chemogenetic IL stimulation during a retrieval test reverses fear generalization previously induced by ethanol (Scarlata et al., 2019). Taken together, these studies suggest that the IL is important for constraining fear behaviors to the appropriate context, potentially through inhibiting conditioned fear in improper contexts. More broadly, such findings raise the possibility that a more general function of the IL relates to its ability to narrowly focus an organism's behavior based on the "strictest" interpretation of the environmental relationships among stimuli. This could reflect the most recent contingency learned (e.g., extinction over original fear conditioning) or a more constrained circumstance for expressing the original learning (i.e., not generalizing to novel contexts). However, more work is needed to examine this possibility.

3.4. Appetitive pavlovian conditioning

Associative learning with rewarding stimuli (e.g., food pellets) versus aversive stimuli (e.g., footshocks) likely involves overlapping yet distinct neural circuits. In appetitive conditioning, a CS co-terminates with the delivery of a food reward, such that the conditioned response is approach behavior toward the food magazine at the onset of the CS. Indeed, evidence suggests some similarities in IL functioning between aversive and appetitive Pavlovian conditioning.

Consistent with evidence that the IL contributes to the inhibition of conditioned fear, studies indicate that the IL maintains the ongoing inhibition of appetitive conditioning after extinction has been acquired. IL lesions and IL optogenetic stimulation increase and decrease, respectively, cued renewal, contextual renewal, and spontaneous recovery of appetitive pavlovian conditioning (Rhodes and Killcross, 2007, 2004; Villaruel et al., 2018). Surprisingly, in contrast to the extinction of tone fear conditioning literature, evidence suggests that the IL does *not* promote the extinction of appetitive pavlovian conditioning, as IL, but not PL, inactivation via GABA_{A+B} agonism *facilitates* the extinction of appetitive pavlovian conditioning (Lay et al., 2019; Mendoza et al., 2015). Overall, these studies provide conflicting evidence concerning the role of the IL in the extinction and ongoing inhibition of appetitive pavlovian conditioning.

It is possible that appetitive versus aversive conditioning differentially engage the IL. Nonetheless, the IL appears to be sensitive to cue exposure prior to any conditioned association, either appetitive or aversive, as pharmacological IL inhibition via GABA_A agonism during cue pre-exposure impairs latent inhibition (Lingawi et al., 2018). This would suggest that the IL is sensitive to cues regardless of appetitive or aversive associations that the cues may later acquire. Indeed, pharmacological IL activation via GABA_A antagonism facilitates fear extinction learning only if the rat had previously been exposed to that CS through appetitive conditioning and extinction (Lingawi et al., 2018), suggesting that extinction memory, and the role of the IL, is CS, but not US, dependent. Nevertheless, considerably more work, especially involving studies that attempt to mirror approaches used in fear conditioning, is needed to determine the role of the IL in appetitive Pavlovian conditioning and whether its function is substantially different from that during fear conditioning.

3.5. Mediating opposing behavioral strategies: body mobilization versus inaction

Some theories of IL function in rodent behavior suggest that the IL promotes behavioral strategies that mobilize the body (Halladay and Blair, 2017). This is consistent with the tone fear conditioning literature described above, as the IL promotes the extinction of conditioned fear (i. e., decreases freezing). The idea that the IL promotes mobilizing behaviors is also supported by research examining the transition between two competing Pavlovian fear responses: conditioned motor inhibition (i.e., freezing in response to the CS) and conditioned motor excitation (i. e., increased locomotion in response to the CS). Importantly, the CS elicits opposing behavioral responses depending on the temporal context, or the length of time since the last CS-US pairing. Pharmacological IL inhibition via GABAA agonism attenuates conditioned motor excitation and pharmacological IL activation via GABAA antagonism potentiates conditioned motor excitation (Halladay and Blair, 2017), consistent with the idea that the IL promotes body mobilization. This idea is further supported by the role of the IL during

the social buffering of fear, a phenomenon in which social interaction decreases fear responses. Specific populations of IL neurons respond to social interactions, and optogenetic activation of these populations decreases freezing in response to fearful stimuli and contexts (Gutzeit et al., 2020), supporting the idea that IL activity facilitates the encoding of relevant cue information to promote action.

However, other studies suggest that the IL is also capable of promoting inaction. This is observed in specific circumstances such as platform-mediated avoidance, where rodents learn that a CS predicts a footshock, much like traditional fear conditioning. In this paradigm, and in contrast to standard tone-shock fear conditioning, rodents learn to avoid the footshock by moving onto a platform in response to CS presentation (Fig. 3). During the extinction of this behavior, the rat no longer needs escape to the platform to avoid a shock and thus spends less time moving in response to the CS. IL c-fos levels following an extinction retrieval test correlate with the successful extinction of platformmediated avoidance (Bravo-Rivera et al., 2015), and pharmacological IL inactivation via GABAA agonism prior to extinction training in this task impairs the extinction of platform-mediated avoidance (Bravo-Rivera et al., 2014). These data corroborate a role for the IL in the extinction and inhibition of cue-response associations in general without necessarily promoting action versus inaction. The extinction of tone-shock conditioning increases mobility and the extinction of platform-mediated avoidance decreases mobility, yet the IL promotes extinction learning in each case.

The ability to mediate opposing behavioral strategies suggests that the IL is not directly controlling the behavioral output *per se*, but rather promotes advantageous behaviors based upon the nature of the stimulus relationships in the environment. For example, pharmacological IL inhibition via GABA_{A+B} agonism decreases performance accuracy in an active avoidance task (i.e., pressing a lever to avoid shock) and an inhibitory avoidance task (i.e., withholding a lever press to avoid a shock) (Capuzzo and Floresco, 2020), revealing how the IL promotes or



C.



Fig. 3. Platform-mediated avoidance procedures. A. Left, rats are placed in a chamber and given repeated presentations of a CS (tone) that co-terminates with a US (footshock). Over time, the rat learns to escape to a raised platform in the chamber upon CS presentation to avoid the shock given at its cessation. Right, with multiple CS-US pairings, rats will spend more time on the platform during CS presentation to avoid the US. B. Left. On the next day of training, rats are placed in the same chamber and given repeated CS presentations in the absence of the US. Right, with repeated CS-alone presentations, rats will decrease their time spent on the platform in response to the CS. C. Left, On the third day, to test extinction learning recall, rats are again placed in the chamber and presented with the CS alone. Right, the amount of time the rat spends on the platform is interpreted as the strength of extinction learning recall, where less time on the platform suggests good extinction recall and more time on the platform suggests poor extinction recall.

inhibits the same behavior depending on the learned relationships. Additionally, during a discriminative stimulus (DS) task in which one cue signals reward (i.e., X+, food pellet delivery) and another cue signals fear (i.e., Y+, footshock delivery), but simultaneous compound cue presentation signals safety (i.e., XY-, no consequence), IL inactivation via GABA_{A+B} agonism increases freezing to the compound cue (Sangha et al., 2014). This inappropriate freezing to a learned safety cue suggests that IL activity is necessary for guiding appropriate behavior based on previously learned knowledge about the relationships between cues and specific outcomes related to the cues.

Overall, these data suggest that the IL mediates the extinction of learned associations, thus promoting adaptive responding based on current contingencies, rather than directing a specific behavioral outcome. Indeed, post-extinction IL inactivation via sodium channel blockade impairs the extinction consolidation of conditioned odor aversion (Awad et al., 2015), further supporting a role for the IL in extinction learning, irrespective of the behaviors involved. However, how the IL promotes newly acquired contingencies to oppose behaviors is still largely unknown.

3.6. Considering heterogeneous ensembles and afferent/efferent signaling

Increasing evidence suggests that only a small fraction of neurons within a region are involved in the encoding of a specific behavior. For example, work using in situ hybridization of immediate early genes indicates extinction and recall of contextual fear conditioning activates 5-7 % of IL neurons (Khalaf and Graff, 2019). Behavioral control by such a small population of neurons may partially explain why previous studies using global IL manipulation do not always support a role for the IL in extinction memory storage and recall. Whole-structure manipulations may miss or cancel out the effects of small and/or competing ensemble activity, particularly as evidence suggests that populations of neurons within a single region are dedicated to different functions (Liu et al., 2012). Indeed, freezing versus fleeing in response to a fear-conditioned auditory CS alters distinct IL ensembles (Halladay and Blair, 2015). Despite a growing body of evidence supporting the involvement of small, discrete ensembles in behavioral control, it is less clear how these populations convey functional specificity when dispersed throughout a singular region, though one possibility is that such ensembles have distinct or, at least, disproportionate efferent projections.

Early work proposed that the IL gates downstream structures to regulate behavioral responses in response to fear stimuli (Milad et al., 2004). One such downstream structure is the basolateral amygdala (BLA), a region that is essential for the expression of tone fear conditioning (Fanselow and LeDoux, 1999). Pharmacological IL inhibition via GABA_A agonism prevents extinction-induced synaptic changes in the BLA (Amano et al., 2010), and the inhibition of conditioned fear during extinction retrieval activates neurons in the lateral portion of the BLA, specifically neurons that receive inputs from the IL (Knapska et al., 2012). In fact, projection-specific targeting of IL-BLA and IL-NAcore projections has provided evidence that the IL differentially affects behavior depending on its output target. Tone-fear extinction increases the excitability of IL-BLA neurons, but not IL-NAcore neurons (Bloodgood et al., 2018). Moreover, chemogenetic IL-BLA inhibition during fear extinction training impairs extinction memory formation (Bloodgood et al., 2018), and vmPFC-BLA stimulation (vmPFC: IL and dorsal peduncular cortex) facilitates extinction memory formation (Bukalo et al., 2015). These data suggest that the IL regulates the extinction of conditioned fear through a subpopulation of neurons that project to the BLA.

Other shock-associated behaviors may utilize similar IL neuronal subpopulations to regulate the general extinction of conditioned behaviors, as the extinction of active avoidance increases c-fos levels in IL- BLA projections (Martinez-Rivera et al., 2019). However, the retrieval of active avoidance extinction memories does not alter c-fos levels in this pathway (Martinez-Rivera et al., 2019), suggesting that extinction memory storage for this paradigm may be in an alternate pathway. One such pathway may be IL inputs to the paraventricular nucleus of the thalamus, as tone fear extinction retrieval requires IL projections to this region (Tao et al., 2020). The retrieval of fear memories may also involve IL projections to the NAshell, as NAshell inhibition causes the expression of fear behaviors, but pharmacological IL activation via GABA_A antagonism suppresses this effect (Richard and Berridge, 2013). Additionally, reciprocal connections between the IL and PL raise the possibility that these regions influence each other, as IL-to-PL, and not PL-to-IL, projections likely mediate trace fear extinction (Mukherjee and Caroni, 2018). Downstream targets likely help define functionally distinct neuronal ensembles in the IL with regards to the acquisition, consolidation, and expression of tone fear conditioning. However, beyond these findings, relatively minimal work has examined IL projections to non-amygdala regions in tone fear conditioning.

It is also important to consider afferent projections to the IL, as the distribution of specific inputs to the IL may determine which neuronal ensembles are activated by a specific learning event or behavior. Recent evidence indicates that the mPFC encodes response-outcome information in a laminar-specific manner (Spellman et al., 2021), suggesting that afferent signaling may define heterogeneous subpopulations within the IL. Such inputs may arise from the locus coeruleus and the ventral tegmental area, as blocking noradrenergic and dopaminergic receptors, respectively, in the IL immediately prior to tone fear extinction training impairs extinction learning (Mueller et al., 2010, 2008). However, to our knowledge, no work has yet examined the role of such inputs to the IL in fear extinction.

The extinction of learned behaviors is highly context-dependent (Bouton et al., 2006), raising the possibility that hippocampal inputs to the IL signal context-appropriate responses in tone fear conditioning or extinction (Corcoran and Quirk, 2007). Indeed, dorsal hippocampal brain-derived neurotrophic factor (BDNF) infusions reduce tone fear conditioning in the absence of any extinction training, but not when BDNF is also blocked in the IL (Peters et al., 2010). However, anatomical evidence indicates that the ventral hippocampus, and not the dorsal hippocampus, projects to the IL (Hoover and Vertes, 2007; Ishikawa and Nakamura, 2006; van Groen and Wyss, 1990), suggesting a potential role for this region in extinction. Indeed, ventral hippocampus BDNF infusions potentiate IL neuron firing (Rosas-Vidal et al., 2014), indicating that the ventral hippocampus influences extinction learning through modulation of IL activity. In support of this idea, the extinction of active avoidance increases BDNF in ventral hippocampus-IL projections, and blocking ventral hippocampus BDNF impairs active avoidance extinction recall (Rosas-Vidal et al., 2018). Overall, these data point to the importance of considering afferent signaling from the hippocampus, specifically the ventral hippocampus, to the IL in tone shock extinction learning.

Distinct IL efferents and afferents create an opportunity for creating function-specific ensembles, yet the internal state of a neuron influences whether it will be recruited for specific ensembles. Evidence suggests that fluctuations in the levels of certain neuronal proteins (e.g., CREB) prime a neuron for preferential recruitment when activated by a particular input (Park et al., 2020). Thus, intracellular molecular signaling may strengthen connections that are already present. Prior work indicates that IL activation via BDNF, even in the absence of extinction training, reduces fear expression (Peters et al., 2010; Rosas-Vidal et al., 2014). This suggests that IL neurons are connected in such a way that allows for inhibiting conditioned fear prior to tone-fear extinction encoding, and the cellular environment (i.e., levels of CREB) at the time of learning selects for neurons to execute this function. Thus, future studies will benefit from circuit-based approaches that consider how a neuron's baseline state during fear conditioning influences how ensembles are recruited within the IL.

Overall, the literature supports a role for the IL in the extinction and ongoing inhibition of conditioned fear. As evidenced by classical fear conditioning and platform-mediated avoidance, the IL promotes the correct behavioral response to the CS rather than promoting a particular behavior. Whether the IL is a storage site for these memories remains unclear, though work using pathway-specific and/or activity-dependent manipulations may help elucidate the mechanisms of fear extinction memory storage. However, evidence is mixed as to whether the IL plays a similar role for appetitive conditioning and more work must be done to clarify this issue. Finally, evidence from fear generalization studies suggests that the IL plays an important role in constraining associative learning to the appropriate context.

4. Drug seeking

4.1. The extinction of drug seeking

The distinct role of the IL in the extinction and inhibition of conditioned fear led to exploration of its role in the inhibition of other types of behaviors, particularly drug seeking. In contrast to the footshock-based, Pavlovian fear conditioning procedures, drug seeking (and more generally, reward seeking) involves instrumental motivated behaviors, making it initially unclear whether findings from the fear conditioning literature would transfer to drug seeking paradigms. Although drug seeking involves similar periods of acquisition, consolidation, and retrieval as in fear conditioning, the nomenclature used in traditional learning and memory work does not translate well to drug seeking and similar work. For example, "acquisition" and "consolidation" have precise meanings withing learning paradigms that do not easily map onto self-administration work, even if drug-seeking studies refer to the "acquisition of lever pressing". Such work typically involves many trials, including multiple sessions, in contrast to the more discrete training that is typical with fear conditioning. As such, the learning processes are often intermixed and difficult to disentangle in a way that directly compares with fear conditioning. Moreover, whereas "reinstatement" of drug-seeking behavior can be thought of as a type of retrieval, the procedures used to induce reinstatement (e.g., a drug-priming injection or restoration of cues that serve as a secondary reinforcer) are notably different from those used in common learning and memory work. Therefore, to avoid providing a false sense of equivalent processes, this review attempts to use the nomenclature traditionally used within each field, while pointing out direct comparisons when appropriate.

Early work found that inhibition of the NAshell via GABAA and $GABA_{A+B}$ agonism, a downstream projection target of the IL, increases feeding behavior (Hanlon et al., 2004; Stratford and Kelley, 1997), and enhances cue-driven cocaine seeking (Di Ciano et al., 2008), pointing to the NAshell as a possible region for the inhibition of drug-seeking behaviors. This raised the question of whether the IL influences the inhibition of drug-seeking behaviors through its projections to the NAshell, much as it influences the inhibition of freezing behaviors through projections to the amygdala (Bergstrom, 2016; Berretta et al., 2005; Likhtik et al., 2005; Milad et al., 2004; Peters et al., 2009). Despite an early study showing no effect of pharmacological IL inactivation via GABAA+B agonism on cocaine-primed reinstatement (McFarland and Kalivas, 2001), more evidence began to emerge linking the IL to the inhibition of drug seeking. Indeed, pharmacological IL inhibition via GABAA+B agonism, as well as NAshell inhibition, induces cocaine seeking following extinction training (Peters et al., 2008a), suggesting that both regions promote the ongoing inhibition of drug seeking. In this case, extinction sessions following sufficient extinction training can be considered a type of "extinction retrieval", and these findings suggest that IL activity is necessary for such retrieval. Since then, considerable work has investigated IL function regarding drug-seeking behavior in general, leading to a plethora of findings, including conflicting evidence. Below, we discuss evidence regarding IL function within different behavioral stages and procedures associated with drug seeking.

Several lines of evidence suggest that the IL mediates the learning associated with the extinction of drug seeking. Much of this work has used self-administration paradigms in which rodents engage in an instrumental behavior, such as a lever press, to receive a drug infusion. Fig. 4A illustrates procedures for the self-administration, extinction, and reinstatement procedures that have frequently been used to investigate drug seeking. Evidence using such procedures to examine cocaine seeking indicates that pharmacologically inhibiting IL activity via GABA_{A+B} agonism immediately following extinction sessions impairs the consolidation of extinction learning (LaLumiere et al., 2010), providing evidence that the IL may be a critical site of plasticity for the extinction of an instrumental behavior. Additionally, the same study reported that activating and blocking noradrenergic receptors in the IL enhances and impairs such consolidation, respectively. This finding is consistent with the importance of noradrenergic signaling in the IL during the consolidation of tone fear extinction (Mueller et al., 2008), providing further parallels between IL function in the extinction of fear conditioning and drug seeking.

Work has since expanded upon the precise role of the IL in the acquisition and consolidation of drug extinction memories. Pharmacologically enhancing IL activity immediately prior to extinction training sessions facilitates the extinction of heroin seeking (Chen et al., 2016) and ethanol seeking (Gass et al., 2014). Additionally, pharmacologically blocking IL activity via $GABA_{A+B}$ agonism immediately prior to extinction training sessions impairs the extinction of ethanol seeking (Khoo

et al., 2019), and optogenetic vmPFC (IL and dorsal peduncular cortex) inhibition impairs the extinction of cocaine conditioned place preference (Van den Oever et al., 2013). These studies provide evidence that the IL regulates the acquisition and/or consolidation for the extinction of drug seeking for several drugs of abuse in addition to cocaine. Although this suggests consistency across drugs of abuse, Struik et al. (2019b) found that 6 s of optogenetic vmPFC (IL and dorsal peduncular cortex) inhibition and excitation given during or following cue presentation does not alter the cued extinction of nicotine seeking (i.e., extinction in which the lever press still produces the drug-associated cues but not the drug itself). Whether this is the result of differences between nicotine and other drugs of abuse (Struik et al., 2019a), or a procedural difference is unclear. Nonetheless, there appears to be general agreement for a role for the IL in the acquisition of extinction learning for drug-seeking behavior.

During extinction learning for drug seeking, a lever press has a new contingency (i.e., a lever press is now unreinforced), and evidence supports that IL activity is necessary for encoding this change in contingency. Work from our own laboratory found that briefly inhibiting IL activity, and not PL activity, using optogenetics immediately following an unreinforced lever press during extinction training impairs extinction learning for cocaine seeking (Gutman et al., 2017). Notably, this work used 20 s of illumination compared to 6 s used by Struik et al. (2019b), suggesting that the period necessary for extinction encoding lasts longer than 6 s, and that sufficient information regarding the new



Fig. 4. Commonly used drug self-administration procedures. **A.** Extinction-Reinstatement procedures. *Left*, rats self-administer a drug reward. The active lever (green) produces a drug infusion paired with a light and tone cue, and the inactive lever (black) has no consequence. *Middle*, if All consequences of an active lever press are removed, and rats will extinguish their lever pressing, as the active lever no longer produces a reward. *Right*, drug seeking can be reinstated, as indicated by increased active lever pressing (green) compared to an extinction baseline (striped) using procedures depicted in the inset. For cued reinstatement, previously drug-paired light and tone cues can again be paired with a lever press. For stress-induced and drug-primed reinstatement, rats receive a footshock or small priming injection of the drug, respectively, prior to a normal extinction session. In contextual renewal the rat extinguishes lever pressing in a distinct context (Context B) and is then reexposed to the drug-associated context (Context A) in the reinstatement session. All types of reinstatement increase active lever presses and are inferred to induce drug seeking. *B.* Withdrawal-Incubation procedures. *Left*, Rats undergo self-administration as described in A. *Middle*, rats undergo a cued seeking test, where a lever press results in the light and tone cue, but no drug infusions. Then, rats go through homecage withdrawal without access to the drug for a period of time that is unique to each drug of abuse. *Right*, After homecage withdrawal, rats undergo the same cued seeking test where they now press more than in the first cued test. This increase in drug seeking is referred to as incubation of craving.

contingencies is still available after 6 s in the IL for successful extinction to occur. Importantly, pseudo-random optogenetic IL inhibition throughout the extinction training had no effect (Gutman et al., 2017), supporting the idea that critical information regarding the reward-prediction error is processed in the IL during the 20 s period after an unreinforced lever press. During this post-lever press period, the IL is likely involved in the process for encoding extinction contingencies through its projections to the NAshell, as evidence indicates that higher post-lever press neural activity in IL-NAshell neurons correlates with reduced cocaine seeking (Cameron et al., 2019). Taken together, these data provide strong support for a critical role for the IL in the acquisition/consolidation of new extinction contingencies during a period immediately following the unreinforced instrumental behavior.

4.2. Ongoing inhibition of drug seeking

Following extinction training, IL activity is also involved in the expression of the extinction learning - i.e., the ongoing inhibition of drug-seeking behavior. Indeed, some studies show that inhibiting IL activity potentiates drug seeking. Pharmacological IL inhibition via GABA_{A+B} agonism following extinction training increases the spontaneous recovery of extinguished cocaine seeking following a period of abstinence (Peters et al., 2008b) and induces cocaine seeking under extinction conditions, an effect reversed by concurrent PL inhibition (Peters et al., 2008a). Additionally, pharmacological vmPFC (IL and ventral PL) inhibition via GABA_{A+B} agonism during conditioned place preference procedures increases heroin seeking (Ovari and Leri, 2008), pharmacologically impairing IL activity through protein kinase inhibition disrupts the expression of the extinction of morphine conditioned place preference and conditioned place aversion (He et al., 2011), optogenetic IL inhibition during cued reinstatement increases cocaine seeking (Gutman et al., 2017), and ablation of drug cue-responsive IL neurons potentiates cue-induced ethanol and cocaine seeking (Pfarr et al., 2015; Warren et al., 2019). These studies support that the IL is involved in the ongoing inhibition of drug seeking after extinction training.

Additionally, enhancing IL activity decreases drug seeking. Pharmacological IL activation via AMPA receptor potentiation decreases cueinduced cocaine seeking (LaLumiere et al., 2012) and cue-induced heroin seeking (Chen et al., 2016; Van den Oever et al., 2008). Similarly, IL activation using chemogenetic and optogenetic approaches reduces cued and cocaine-primed reinstatement of cocaine seeking (Augur et al., 2016; Muller Ewald et al., 2019). Overall, these studies highlight how the IL promotes the ongoing inhibition of drug seeking behavior following extinction training.

4.3. Is extinction necessary for the IL to inhibit drug seeking?

Interestingly, the same manipulations of the IL in both studies noted above had no effect in the absence of prior extinction training (Augur et al., 2016; Muller Ewald et al., 2019). This suggests that extinction training recruits the IL to inhibit drug seeking, though not all work agrees with this idea. Evidence indicates that the IL, via projections to the NAshell, inhibits cocaine seeking in the absence of prior extinction training (Cameron et al., 2019; Ma et al., 2014). Synaptic alterations in IL-NAshell and PL-NAcore projections exist following a 45-day forced withdrawal period after cocaine self-administration (Ma et al., 2014). Optogenetic reversal of IL-NAshell synaptic changes potentiates cue-induced cocaine seeking at the 45-day test, whereas optogenetic reversal of PL-NAcore synaptic changes inhibits cocaine seeking in this test. These results are consistent with roles for the IL-NAshell and PL-NAcore pathways inhibiting and promoting drug seeking, respectively (Peters et al., 2009). However, they also suggest that the IL-NAshell pathway actively opposes cue-induced cocaine seeking in an incubation-of-craving paradigm even in the absence of extinction training (see Fig. 4B for schematic explaining incubation-of-craving

procedures). Further evidence indicates that optogenetic stimulation of IL-NAshell neurons given one day and 15 days after the self-administration period inhibits cocaine seeking (Cameron et al., 2019). These findings suggest that the IL, and its projections to the NAshell, are capable of inhibiting drug seeking even in the absence of extinction training, in contrast to the work by Augur et al. (2016) and Muller Ewald et al. (2019). The reasons for these discrepancies are unclear, though the precise nature of the manipulations may play a role.

4.4. Promoting drug seeking

Not all evidence supports that the IL inhibits drug seeking. In fact, some evidence suggests the IL *promotes* drug seeking. Pharmacological vmPFC (dorsal IL and ventral PL) activation via GABA_{A+B} antagonists on the first day of withdrawal increases cocaine seeking, and pharmacological inhibition via GABA_{A+B} agonism after 30 days of homecage withdrawal decreases cocaine seeking (Koya et al., 2009). Similarly, pharmacological IL, but not PL, inhibition via GABA_{A+B} agonism after 21 days of homecage withdrawal decreases discriminative stimulus (DS)-controlled cocaine seeking (i.e., when discrete stimuli signal the presence or absence of the reward)(Madangopal et al., 2021), further supporting that the IL promotes drug seeking, particularly following a homecage- abstinence period (i.e., no extinction training).

However, evidence suggests that the IL can promote drug seeking following extinction training as well. Pharmacological IL inhibition via GABA_{A+B} agonism and vmPFC (dorsal IL and ventral PL) inhibition via GABA_A agonism following extinction training decreases cue-induced methamphetamine seeking (Rocha and Kalivas, 2010) and nicotine seeking (Lubbers et al., 2014). Other studies have found that pharmacological IL inactivation via GABA_{A+B} agonism following extinction training reduces cue-induced, heroin-primed, and contextual reinstatement of heroin seeking (Bossert et al., 2011; Rogers et al., 2008). These findings demonstrate that, under some circumstances, the IL promotes drug seeking, though it is unclear precisely under which conditions the IL promotes or inhibits drug seeking.

4.5. Contextual influences

The critical nature of context in extinction learning may explain how the IL is able to bidirectionally regulate the same behavior under different circumstances. Extinction is a context-specific behavior (Bouton, 2019), and as a result, a reversion to the original context following extinction training produces a renewal of the original behavior. Thus, the IL is likely necessary for encoding context-specific information along with extinction contingencies to inhibit drug seeking in that context. Indeed, re-exposure to drug-associated contexts activates IL neurons, suggesting that some aspect of IL function is sensitive to the context in which drug use is occurring (Hamlin et al., 2009, 2008; Hamlin et al., 2007; Marchant et al., 2010; Marinelli et al., 2007; Wedzony et al., 2003).

It is possible that conflicting evidence for IL function in contextual reinstatement/renewal paradigms reflects the context specificity of extinction training. This is observed in work from Bossert et al. (2011), where pharmacological IL inhibition via GABAA+B agonism during the contextual renewal decreases heroin seeking. In a contextual renewal paradigm, re-exposure to the original self-administration context would presumably activate neuronal ensembles associated with drug seeking contingencies, whereas re-exposure to the extinction context would activate neuronal ensembles associated with extinction contingencies. In this case, if the IL contains neuronal ensembles that encode both drug seeking and extinction contingencies, then the effects of IL inactivation depend upon the context, and the associated ensemble, in which the manipulation occurs. Consequently, in contextual renewal paradigms, IL inactivation via GABA_{A+B} agonism during re-exposure to the original context would be expected to reduce drug seeking, as has been observed (Bossert et al., 2011).

The evidence presented so far raises the possibility that the IL promotes or inhibits drug-seeking behavior depending on the contingencies associated with a specific context. Indeed, work using discriminative stimuli (DS) to evaluate drug seeking suggests that the IL plays a major role in controlling behavior determined by the relationship between environmental cues and the presence/absence of the drug reward. In such procedures, a DS signals the availability (DS+) or absence (DS-) of a reward. Evidence indicates that an ethanol DS + preferentially activates the IL compared to the DS- (Dayas et al., 2007), suggesting that the IL is particularly sensitive to the DS that signals the presence of a reward.

Other evidence suggests the IL may also be involved in encoding cues associated with the absence of a reward. Laque et al. (2019) found that during self-administration, a DS- for cocaine and alcohol activates 6% and 5.6 % of IL neurons, respectively, and that ablation of cocaine DSneurons increases cued, cocaine-primed, and stress-induced reinstatement following extinction training (Laque et al., 2019). Additionally, our own work indicates that pharmacological IL inhibition via GABA_{A+B} agonism during a cocaine DS task disrupts task accuracy by increasing DS- responding (Gutman et al., 2016). However, a separate study reported no effect of pharmacological IL inhibition via GABA_{A+B} agonism on DS-controlled cocaine self-administration (Madangopal et al., 2021). Nevertheless, a majority of the evidence suggests that the IL may be especially important for suppressing maladaptive responses (i.e., lever press for a DS-) even as it also plays a role in promoting the adaptive response (i.e., lever press for a DS+).

4.6. Heterogeneous IL ensembles and projections

Consistent with what has been suggested for the extinction of fear conditioning, distinct populations of IL neurons likely regulate different aspects of drug seeking. Indeed, evidence suggests that separate populations of neurons in the mPFC and NA mediate self-administration for different drugs of abuse (Chang et al., 1998), and distinct IL ensembles promote cocaine versus standard chow seeking (Kane et al., 2021). Additionally, electrophysiological recordings of vmPFC (IL and medial orbital cortex) activity support the existence of distinct ensembles that encode lever presses versus lever-press omissions (Halladay et al., 2019). These populations make up relatively few of the overall number of IL neurons. Studies have found that cocaine-associated cues, ethanol-associated cues, and heroin-associated contexts activate as little as 11 % (Warren et al., 2019), 7% (Bossert et al., 2011) and 1-3 % (Pfarr et al., 2015) of IL neurons, respectively. Ablation of cue-responsive IL ensembles following extinction training potentiates cue-induced ethanol and cocaine seeking (Pfarr et al., 2015; Warren et al., 2019), and ablation of the context-responsive ensembles attenuates contextual renewal of heroin seeking (Bossert et al., 2011). Thus, these findings suggest that unique IL ensembles associated with drug-associated cues and/or contexts may mediate drug seeking versus its inhibition.

Altering the activity of specific ensembles, therefore, may be particularly revelatory for understanding IL function. Findings indicate that ablation of IL neurons activated by ethanol-associated cues, and not non-specifically activated ensembles of similar size, increases cueinduced ethanol seeking (Pfarr et al., 2015). The difference between activity-dependent ensemble manipulations and whole-region manipulations observed by Pfarr et al. (2015) may hint at a larger reason as to why evidence of IL function is not always consistent. For example, the vmPFC (IL and medial orbital cortex) promotes the punishment-induced suppression of ethanol seeking through its projections to the NAshell, but not through projections to the BLA (Halladay et al., 2019). Less precise (e.g., whole-region) manipulations, may not detect an effect on punishment-induced ethanol seeking. Alternatively, if either BLA-projecting or NAshell-projecting populations were activated disproportionately at the time of the manipulation, whole-region manipulations could have provided a misleading conclusion.

Additionally, which ensembles control a behavior can change following training. *Prior to* extinction training, IL-NAcore projections promote cocaine seeking, but *after* extinction training IL-NAshell projections inhibit cocaine seeking (Warren et al., 2019). Together, these findings support the idea of heterogeneous populations within the IL and point to the critical importance of targeting such populations using pathway-specific and/or activity-dependent manipulations. Moreover, they speak to the critical nature of the behavioral circumstances during the time of the manipulation and prior history of the animal for interpreting drug-seeking results with IL manipulations.

Thus, evidence from studies utilizing projection-specific and/or activity-dependent manipulations have challenged the idea that the IL exclusively inhibits drug seeking. Although some discrepancies in the literature may reflect either paradigm differences or the drug of abuse, a growing body of research suggests that the IL can promote and inhibit drug seeking depending upon the inputs/outputs involved. Which pathway is mediating behavior appears to reflect the presence or absence of extinction training and the duration of time with or without the drug of abuse. Nonetheless, in contrast to other regions such as the PL, the IL appears to have an important role in the extinction and inhibition of drug seeking.

5. Natural reward seeking

5.1. The extinction and inhibition of natural reward seeking

The role for the IL in drug seeking led to more pointed research addressing whether the IL regulates natural reward seeking. Yet, the evidence on this question has been even less clear than what has been found for drug seeking. Several studies suggest the IL promotes the extinction and ongoing inhibition of natural reward seeking. For example, pharmacological IL inhibition via GABAA+B agonism and NMDA receptor antagonism, and activation via NMDA receptor agonism during the extinction of sucrose seeking impairs and enhances, respectively, extinction learning (Moorman and Aston-Jones, 2015; Peters and De Vries, 2013). However, contrary to findings from Moorman and Aston-Jones (2015) using the same manipulation, pharmacological vmPFC (IL and ventral PL) inhibition via GABAA+B agonism during the extinction of sucrose seeking improves extinction learning (Caballero et al., 2019). Moreover, some studies fail to observe an effect of IL manipulations, as pharmacological IL inhibition via GABA_{A+B} agonism during the first or third extinction session has no effect on food seeking (Warren et al., 2016). Similarly, optogenetic IL inhibition immediately following an unrewarded lever press during extinction training does not affect food seeking (Gutman et al., 2017), which is in contrast to the increased cocaine seeking found with the same manipulation.

The evidence presented above suggests that the extinction of natural reward seeking may be regulated in a way that is distinct from the extinction of drug seeking, particularly as drugs of abuse pharmacologically and artificially alter neuronal plasticity. Indeed, evidence supports distinct IL ensembles for food seeking versus cocaine seeking, and selective ablation of cocaine seeking ensembles decreases cocaine, but not food, seeking (Kane et al., 2021), and potentiation of AMPA receptor transmission decreases cue-induced heroin, but not sucrose, seeking (Van den Oever et al., 2008). Nonetheless, more work is needed to better understand how the extinction of natural reward seeking versus the extinction of drug seeking may be differentially encoded.

5.2. Heterogeneous IL ensembles mediate adaptive behavioral responses

As with drug seeking, studies using DS-based procedures provide evidence that the IL guides appropriate responding for a natural reward. During early extinction training, IL activity increases in response to the DS+ (Francois et al., 2014), potentially reflecting the encoding of new extinction contingencies associated with the DS + . Indeed, pharmacological IL, but not PL, inactivation via GABA_{A+B} agonism decreases DS + responding during sucrose seeking (Moorman and Aston-Jones, 2015). However, evidence also supports IL involvement in the

encoding of contingencies associated with the DS-, as pharmacological IL inactivation via $GABA_{A+B}$ agonism during a DS task for standard chow and for sucrose reward increases DS- responding (Gutman et al., 2016; Ishikawa et al., 2008). Further evidence suggests that the IL is sensitive to both the DS + and DS-, as pharmacological IL inhibition via $GABA_{A+B}$ agonism decreases accuracy in a sucrose go/no-go task (i.e., DS + means a lever press leads to a sucrose reward and DS- means *withholding* a lever press leads to a sucrose) (Capuzzo and Floresco, 2020). This broader effect on both DS + and DS- responding suggests that the IL is involved in encoding relevant DS-contingency information, regardless of the specific outcome, to properly guide behavior.

The IL likely mediates the encoding of opposing DS contingencies via separate neuronal ensembles. Indeed, distinct populations of IL neurons respond to the DS + and DS- for sucrose, and the degree of neuronal activity in these populations corresponds with correct responses (i.e., higher IL activity is associated with responding to the DS + and withholding a response to the DS-) (Moorman and Aston-Jones, 2015). In further support of distinct IL ensembles encoding DS+/DS- contingencies, ablation of IL ensembles activated by a DS+ decreases DS + responding, and ablation of IL ensembles activated by the DS- *increases* DS- responding (Suto et al., 2016). The evidence from DS task studies points to how separate IL neuronal ensembles can mediate different, and even opposing, behaviors, likely through the encoding of relevant contingencies.

Activity-dependent targeting of neuronal ensembles reveals evidence that suggests that moderate effects of IL control over food seeking may be obscured by non-specific manipulations of heterogeneous ensembles in the IL. Selective ablation of food-seeking IL ensembles and extinction IL ensembles decreases and increases food seeking, respectively (Warren et al., 2016), but whole-region, pharmacological IL inhibition via GABA_{A+B} agonism does not significantly alter behavior. As suggested in the drug-seeking section, distinct IL ensembles likely control opposing behaviors for natural reward seeking, potentially through distinct inputs and outputs.

In general, more work is needed to determine how the IL and its projections influence natural reward seeking, particularly regarding the similarities and differences between the pathways involved in natural reward versus drug seeking. Nonetheless, the IL appears to be capable of both promoting and inhibiting natural reward seeking through discrete ensembles, which aligns with evidence presented thus far, and further emphasizes the importance of pathway-specific and activity-dependent targeting in future studies.

6. Habitual versus goal-directed responding

6.1. Habitual responding

Instrumental behaviors, such as those used for self-administration, are initially acquired through action-outcome learning, where actions are shaped by their consequences. With extended training/overtraining goal-directed behaviors shift to habitual responding, where a stimulus elicits a particular behavioral response regardless of the outcome (Dickinson, 1985). Thus, habitual behavior is considered extinction-resistant (Dickinson, 1985). Habitual behaviors are often advantageous, as they decrease the cognitive demand necessary to produce behaviors, whereas goal-directed behaviors require constant feedback about the relationship between the behavior and the outcome (Coutureau and Killcross, 2003; Dickinson, 1985), which is advantageous when contingencies change within the environment. The inability to shift back to goal-directed behavior exists in many psychiatric disorders (Antonini et al., 2001; Gillan et al., 2011; Joel, 2001; Marsh et al., 2004; Saint-Cyr et al., 1995), including drug addiction, where drug use progresses from goal-directed to habitual, compulsive behavior (Everitt et al., 2008, 2001; Kalivas, 2008). However, this section will focus on the shift to habitual responding for natural rewards, commonly studied using procedures depicted in Fig. 5. Nevertheless, conclusions from habitual



Fig. 5. Goal devaluation. *A* Rats are trained in separate sessions to associate two separate levers with two separate rewards. This can also be done in a T-maze where right and left turns result in separate rewards. *B*. One of the rewards is then paired with a noxious drug, such as Lithium Chloride (LiCl), to produce conditioned taste aversion, or given *ad libitum* to produce specific satiety to that reward. *C*. The rat is then given the opportunity to choose between the two rewards, and its behavior informs whether it is engaging in goal-directed or habitual behavior. If the rat engages in goal-directed behavior it will respond more to the goal that has not been devalued and ignore the devalued goal. However, if the rat responds to both rewards equally, the behavior is thought to be habitual. A transition to habitual behavior often occurs with extended training in part A.

responding for natural rewards may broadly speak to drug-related habitual behaviors.

In the previous sections, we provided evidence that the IL promotes extinction learning. However, considerable evidence suggests that the IL promotes extinction-resistant, habit-based behaviors as well. IL lesions, optogenetic inhibition, and pharmacological inhibition via $GABA_{A+B}$ agonism decrease habitual responding and restore goal-directed responding (Barker et al., 2017; Coutureau and Killcross, 2003; Haddon and Killcross, 2011; Killcross and Coutureau, 2003; Shipman et al., 2018; Smith et al., 2012). Additionally, optogenetic IL inhibition during overtraining prevents habit formation (Smith et al., 2012). Taken together, these studies suggest the IL promotes the transition to, and ongoing maintenance of, habitual behaviors.

6.2. Flexible decision-making

Other evidence suggests that the IL facilitates flexible behaviors and inhibits inappropriate responding, two outcome-sensitive behaviors seemingly at odds with extinction-resistant, habit-based responding. IL and vmPFC (IL and ventral PL) lesions increase perseverative responding (or continued incorrect responding) in an appetitive operant task (Passetti et al., 2002), and impair reversal learning in T-maze (Li and Shao, 1998). This suggests that IL activity promotes proper responding when contingencies change, potentially by inhibiting inappropriate or maladaptive behaviors. Consistent with this idea, pharmacological IL inhibition via $GABA_{A+B}$ agonism biases responding toward the disadvantageous option in a rat gambling task (Zeeb et al., 2015), pharmacological vmPFC (IL and ventral PL) inhibition via GABAA agonism disrupts inhibitory control in an operant stop-signal task (Bari et al., 2011) and chemogenetic IL inhibition impairs set-shifting between learned rules (Mukherjee and Caroni, 2018). Similarly, disrupting IL function increases premature responding in the 5-choice serial reaction time task (Chudasama et al., 2003; Feja and Koch, 2014; Murphy et al., 2005, 2012). Taken together, these studies provide evidence that the IL inhibits improper responding, in line with findings from the drug seeking literature.

6.3. Extended training alters IL function

Overall, it appears that early in behavior the IL is necessary for learning action-outcome contingencies and inhibiting inappropriate responding, but with extended training, the IL becomes insensitive to contingency changes and promotes continued habitual responding. This raises the provocative idea that, rather than the IL serving as a critical mediator of the learning, the learning itself may alter how the IL functions and controls future behavior. Electrophysiological IL recordings provide evidence for how IL function may change to promote habitual responding. Work indicates that, during goal-directed behaviors, IL neural activity is sensitive to contingencies between actions and outcomes, as response outcome bidirectionally modulates IL pyramidal neuron firing rate (i.e., firing increases when the action is rewarded and decreases when the action is not rewarded)(Barker et al., 2017). Indeed, recent evidence highlights how both responses and outcomes significantly modulate IL activity at similar timepoints after trial completion (Spellman et al., 2021). Therefore, IL activity appears to be sensitive to action-outcome contingencies early in training.

Overtraining, however, appears to change the role of the IL. During habitual responding, response outcome no longer modulates IL firing rate (Barker et al., 2017). This suggests that IL neuronal activity becomes insensitive to response outcome, in concert with the behavioral insensitivity to response outcome during habitual behaviors. Instead of encoding response-outcome contingencies, after extended training IL neuronal activity increases in a "task-bracketing" manner (Smith and Graybiel, 2013), in which IL activity peaks at the beginning and end of each trial, though precisely how this promotes habitual responding is unclear. A clear transition in IL function occurs with extended training, as the IL is involved in encoding action-outcome contingencies in early goal-directed behaviors but is insensitive to changing contingencies in extensively trained habitual behaviors

It is unknown how the IL transitions from promoting goal-directed to habitual responding, though one possibility is that dopaminergic signaling plays a role. Dopamine infusions into the IL restore goaldirected responding following extended training (Hitchcott et al., 2007), and IL D1 receptor blockade and D2 receptor activation restore goal-directed behaviors (Barker et al., 2013). The IL contains more D1 than D2 receptors, and IL GABAergic neurons express a larger proportion D1 receptors compared to pyramidal neurons (Santana and Artigas, 2017), suggesting that dopamine signaling in the IL, specifically via inhibitory neurons, gates excitatory neuronal activity in the IL and its outputs to downstream regions. Thus, overtraining may alter IL dopamine receptor expression in a way that promotes habitual responding.

6.4. IL circuitry/pathway specific targeting

Like drug seeking, evidence suggests inhibitory control over natural reward seeking involves IL-NAshell projections, as pharmacological

vmPFC-NAshell (vmPFC: IL and ventral PL) disconnection via GABAA agonism increases premature responding in a 5-choice serial reaction time task (Feja and Koch, 2015). However, pharmacological vmPFC-NAcore (vmPFC: IL and ventral PL) disconnection via GABAA agonism increases response omission rates and latency of reward collection (Feja and Koch, 2015). These findings provide evidence that distinct IL projections regulate different aspects of behavior. More specifically, IL-NAshell signaling appears to maintain inhibitory control, much like its role in the inhibition of cocaine seeking, whereas IL-NAcore projections are more important for motivation and attention. Additionally, chemogenetic inhibition of IL projections to the mediodorsal thalamus increases premature responding in a 5-choice serial reaction time task (directly opposing effects of PL-to-mediodorsal thalamus inhibition), whereas inhibition of IL projections to the dorsal striatum has no effect (de Kloet et al., 2021). Taken together, these findings highlight how pathway-specific targeting can lead to distinct pictures of IL function, as the transition of IL function from promoting goal-directed to habitual responding may reflect differentially engaged ensembles

Prior to overtraining, the IL appears to promote proper behavioral responding based upon the currently established contingencies between instrumental behaviors and consequences. However, an interesting distinction in IL function occurs with overtraining. The IL promotes extinction-resistant, or habitual, responding, which is at odds with evidence that the IL promotes the extinction of conditioned fear, drug seeking, and natural reward seeking. The process of overtraining appears to shift IL function away from goal-directed/outcome-sensitive responding to habitual/extinction-resistant responding. It is unclear precisely how the IL transitions from promoting goal-directed responding to promoting habitual responding, however the capability of the IL to promote opposing functions depending upon the specific circumstances supports functionally distinct ensembles and pathways.

7. Discussion

7.1. The IL facilitates learning contingencies among environmental stimuli and between stimuli and responses

Evidence across a range of paradigms supports that the IL facilitates the encoding of the relationships among stimuli in the environment and/ or between instrumental behaviors and consequences, particularly when these contingencies change (apart from paradigms involving overtraining). Importantly, the IL guides behavior according to the newly acquired contingencies, regardless of the nature of the behavior involved. For example, the IL promotes the extinction of both tone fear conditioning and platform-mediated avoidance, even though the behaviors involve increasing and decreasing motor activity, respectively, depending upon the relationship among stimuli, behavior, and outcome.

The IL appears to similarly facilitate learning the changing contingencies between instrumental behaviors and their consequences during the extinction of drug seeking, despite differences between shock-based associative learning procedures and reward-based instrumental behaviors. Evidence suggests the IL promotes the extinction of drug seeking across various classes of drugs of abuse. Still, it is also clear that the IL can, under various circumstances, also promote drug-seeking behavior, indicating that a solely inhibitory function cannot be assigned to the IL for drug seeking. Whether the IL is necessary for encoding contingency changes for instrumental behaviors and consequences for natural reward seeking is mixed. Some evidence supports the idea that IL activity promotes the extinction of sucrose seeking, but this is not a consistent finding. However, no evidence to our knowledge supports that the IL promotes the extinction of standard chow seeking, suggesting that the palatability of reward may influence IL recruitment. Indeed, selfadministration of highly palatable food, but not standard chow, alters the dendritic spine plasticity of IL neurons (Dingess et al., 2017). Nevertheless, recording studies demonstrate that IL neuronal activity

tracks correct cue-response pairings during a DS task for sucrose seeking (i.e., IL activity increases with lever press/DS + and no lever press/DS pairings) (Moorman and Aston-Jones, 2015), suggesting that the IL may be involved in encoding behavioral contingencies in natural reward seeking for, at least, more palatable rewards.

Findings from the habit-based literature also support the idea that the IL is specifically important for encoding the relationship between instrumental behaviors and consequences, though in a manner that is not sensitive to changes in contingencies. The IL promotes habitual behaviors after overtraining, which requires a switch from responseoutcome to stimulus-response behaviors. Thus, overtraining may enhance contingency representations within the IL to drive habitual responding. Graybiel and colleagues (e.g., Smith et al., 2012) suggest that the IL promotes performance of the most recently trained contingency. If that is the case, it would provide further explanation for how the IL retains the capability to promote and inhibit drug-seeking behavior, as extinction training would consist of the most recently trained contingencies. Nevertheless, chronic exposure to drugs of abuse changes functioning and plasticity within the mPFC and other regions in ways that natural rewards do not (Lu et al., 2012; Radley et al., 2015), raising the possibility that drug self-administration and extinction procedures are not directly comparable to habitual behaviors for natural rewards.

From the review of studies across various behavioral paradigms, it is clear that the approaches used across such paradigms have not been identical, making it more difficult to identify core functions that cross behavioral boundaries. Indeed, there are at least several outstanding questions that should be addressed in future work that would be highly beneficial in resolving such critical issues. For example, current evidence does not support a role for the IL in the initial acquisition of tone fear conditioning or drug self-administration but, rather, supports a role in inhibiting the originally learned behavior after extinction training. However, if the IL is important for promoting the most recently trained behavior following a change in contingencies, then IL manipulations would be expected to alter retraining on such tasks following extinction training, an issue that has not, to our knowledge, been investigated. Moreover, IL studies using standard tone fear conditioning and drugseeking studies have not examined overtraining in these paradigms. Yet, to provide a better connection with the habit-based evidence, it is critical to investigate whether IL functioning with overtraining in different paradigms, such as tone fear conditioning and drug seeking, alters IL function as behaviors become extinction resistant. Such studies would bring considerably greater clarity to our understanding of IL function across motivated behaviors.

Future studies will also benefit from applying similar technical methods across paradigms. As an example, optogenetic manipulations that disrupt the extinction of conditioned fear are often given during CS presentation, whereas the same manipulation given during the extinction of drug seeking has been given post-lever press and continuing past the duration of the CS (Gutman et al., 2017; Struik et al., 2019b). An interesting finding from (Gutman et al., 2017) is that the post-lever press period is important for extinction learning, potentially through the recognition of the absence of a consequence. Theoretically, the absence of the shock during fear conditioning could be consolidated in a similar fashion. Fear conditioning and similar Pavlovian conditioning experiments should investigate the temporal nature of the role of the IL in the extinction learning for these paradigms to determine whether similar mechanisms exist.

7.2. Spatial and temporal context encoding

Context specificity of behaviors also influences IL engagement. Learning, especially extinction learning, is highly specific to the context in which it occurs. Thus, some conflicting findings concerning IL function within the literature may reflect differences in contextual encoding, rather than differences in IL function *per se*. One such example occurs in contextual renewal of heroin seeking used by Bossert et al. (2011). Here, extinction occurs in a distinct context, such that the IL likely facilitates the encoding of the instrumental new contingencies *but only in that context*. Thus, opposing effects of IL inhibition may reflect the specific spatial context in which the inhibition occurs (i.e., self-administration versus extinction contexts). However, contextual encoding is not exclusively linked to the *spatial* context. In fact, *temporal* context may also matter in terms of IL functioning. Work from Halladay and Blair (2017) indicates how temporal context can influence IL function, as distinct ensembles within the IL mediate freezing versus fleeing in response to the CS depending upon the timing of the last US encounter. In this way, the IL may drive opposing behaviors depending upon the spatial and temporal context in which the contingencies are learned.

7.3. IL pathways, region heterogeneity, and methodological considerations

Many conflicting results originate from studies in which wholeregion pharmacological manipulations have been performed, suggesting that such approaches are not especially useful for delineating the complex nuances of behaviors under IL control. Indeed, the most clarifying studies use approaches with increased temporal and/or spatial precision. Activity-dependent ablation provides improved spatial resolution by identifying distinct IL neuronal ensembles, and work using this method suggests a heterogeneous function of the IL while also indicating the importance of the type of learning (e.g., self-administration versus extinction learning) in creating the neuronal ensembles (Warren et al., 2019, 2016). Other work using pathway-specific manipulations has also been especially valuable in elucidating specific functions, such as spatial and temporal context encoding in IL-NAshell projections during drug seeking (Cameron et al., 2019). Together, these conclusions suggest that identifying a single, unifying theory of IL function in behavior may not be possible. It is more likely that a brain region has one core neural or computational function, rather than a core psychological function, that guides behavior depending upon a variety of behavioral circumstances.

In delineating the limits of the behavioral functions of the IL, the evidence described above also points to the critical need to use more precise approaches in measuring and altering IL function. Such approaches must include improved spatial and/or temporal precision, such as optogenetic manipulations or electrophysiological recordings, as separate neuronal ensembles mediating different behaviors or memories are active or develop at different times and in different manners. These approaches should also consider distinct IL afferent and efferent pathways. For example, evidence suggests that IL-NAshell projections regulate punishment-induced suppression of ethanol self-administration, whereas those to the BLA do not (Halladay et al., 2019). Such work also illustrates the use of comparisons and dissociations – such as between output pathways or between the PL and IL (e.g., (Gutman et al., 2017; Moorman and Aston-Jones, 2015) – to create a more refined understanding of the function of a brain region like the IL.

Comparisons across paradigms are increasingly important to understanding IL function, particularly as research narrows down the scope of IL function. For example, IL projections to the BLA are important for the extinction and inhibition of conditioned fear, yet it is unclear whether IL projections to the BLA are involved in the extinction and inhibition of other behaviors. A similar question exists for IL projections to the NAshell. Identifying how a pathway may be implicated in the inhibition of one behavior and not another will provide critical insight into the precise role for the IL across different motivated behaviors.

Another consideration is how afferent signaling may guide the influence of the IL on behavior. Indeed, relatively little work has focused on inputs to the IL, even though such inputs must be critical as context or reward contingencies evolve. In fact, recent evidence identifies laminarspecific encoding of response-outcome information in the mPFC (Spellman et al., 2021), which raises the possibility that inputs to the IL may be especially important for elucidating the heterogeneity of a region. For example, evidence supports that ventral hippocampus and thalamic inputs to the IL are involved in tone fear extinction and reward seeking, respectively (James and Dayas, 2013; Matzeu et al., 2014; Rosas-Vidal et al., 2014, 2018; Zhang et al., 2014). Such inputs may influence whether or how various ensembles within the IL are recruited to encode information and modulate behavior (Fig. 6).

Understanding how different inputs bias the IL to regulate behavior, potentially in different directions, might be particularly beneficial in considering the kind of neural function that occurs within the IL. BLA projections to the IL are active during fear extinction (Senn et al., 2014), but compete with the fear-promoting BLA-PL pathway (Hagihara et al., 2021). Whether such projections to the IL are important in other behavioral paradigms and oppose projections to the PL is unknown yet would provide further clarification of functioning for appetitive Pavlovian conditioning as well as instrumental-based procedures

Consequently, temporally precise manipulation of discrete populations of IL neurons combined with activity-dependent tagging and/or projection-specific targeting of IL inputs and outputs will aid our understanding of IL function. Daun02 ablation methods have been increasingly utilized in reward seeking studies, however, the use of such methods to elucidate competing ensembles during other behaviors, such as habit-based learning or fear conditioning, is limited. Studies addressing whether fear-promoting and fear-inhibiting ensembles exist within the IL much as ensembles that promote and inhibit drug seeking exist would further our understanding of IL functioning considerably.

7.4. Focused selection of behavior as a key IL function

Evidence described in Section 3 suggests that disrupting IL activity during initial fear conditioning results in fear generalization for novel contexts and tones. This raises the provocative hypothesis for IL function involving the *focused* selection of a specific behavior, akin to how the basal ganglia functions with regard to motor behavior. Studies have led to the idea that the basal ganglia regulates motor behavior through focused selection and inhibition of competing motor programs (Mink, 1996). That is, the basal ganglia selects and promotes a precise motor program while simultaneously inhibiting similar, competing motor programs. Likewise, the IL may function to constrain a behavior in a highly focused manner. In general, this would be reflected in the selection of the "correct" or adaptive behavior while simultaneously inhibiting many other "incorrect" or maladaptive behaviors. For fear generalization, this would explain the generalization of the fear



response to distinct or novel contexts or cues that occurs when IL function has been disrupted. In much of the work described herein, the maladaptive behavior would be the one associated with the original learning occurring prior to extinction training.

In order to appropriately inhibit the incorrect or maladaptive behavior, the IL would also need to have knowledge of the correct or adaptive behavior. This idea is supported by evidence described in this review indicating the existence of multiple competing ensembles that promote and inhibit the same behavior. However, focused selection of the correct/adaptive behavior would require strong inhibition of many similar or competing behaviors or memories, potentially explaining why, across so many studies, there appears to be a strong bias for the IL in its ability to inhibit behaviors, particularly following training that creates competing memories. Such bias may be a critical function for the IL, even without training to create competing memories, as evidenced by the fear generalization studies and some drug seeking work (e.g., Ma et al., 2014). Thus, a distinct possibility is that a major component of IL function is the focused selection of behaviors that involves inhibiting competing/inappropriate responses within the specific context or current set of learned contingencies, while simultaneously promoting the appropriate behavior for that particular context and/or learned contingencies. This idea would provide an explanation across many of the motivated behavior paradigms described herein.

7.5. Conclusion

The findings presented in this review support a diversity of IL functioning across associative and instrumental learning paradigms that may not easily be ascribed to a single behavioral or cognitive function. In general, evidence suggests that the IL plays a key role in learning and/or expressing contingencies among environmental stimuli and stimuli and behaviors in a context-specific manner, though there appears to be much to elucidate concerning precisely how this is accomplished. Although the IL is important for promoting various learned behaviors, sufficient evidence exists to suggest that the IL is biased toward inhibiting certain behaviors. In particular, it appears to be critical for mediating competing behaviors by inhibiting the maladaptive behavior or older memory while simultaneously promoting the adaptive or newest behavior, potentially in a focused-selection and inhibition manner as described above. However, to further clarify IL function, it is necessary to make cross-paradigm comparisons. These comparisons with similar theoretical and/or technical approaches will shed light on key

> Fig. 6. Schematic models for how distinct inputs and outputs may define heterogeneous neuronal ensembles in a single region. A. One brain region may promote and inhibit a behavior through separate efferent projection targets. B-D. Models for how afferents, efferent, and local microcircuits may interact to regulate divergent behaviors. B. Afferent projections may synapse directly onto distinct output ensembles to either promote or inhibit a behavior. C. Afferent projections may synapse onto local microcircuits involving both excitatory (ext.) and inhibitory (inh.) neurons to influence ensemble selection. The same region may activate one efferent projection while simultaneously sending signals to interneurons to inhibit the opposing efferent projection. D. Proper functioning likely involves a combination of direct projections onto distinct output ensembles as well as connections with local microcircuitry that may enhance or silence signaling of a separate ensemble.

similarities and differences between how the IL influences various forms of learning and behavior. Such comparison will be essential for further shaping our understanding of core IL functions, and how various circumstances can influence that function. In particular, results from studies that utilize circuit-based manipulations of distinct IL neuronal ensembles and carefully consider temporal and spatial precision will be particularly informative for creating a clearer view of IL function across motivated behaviors.

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