Neurobiology of Learning and Memory 175 (2020) 107319

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Using internal memory representations in associative learning to study hallucination-like phenomenon

Ming Teng Koh*, Michela Gallagher

Department of Psychological and Brain Sciences, Johns Hopkins University, USA

ARTICLE INFO

Keywords:
Cognition
Dopamine
Hallucination
Mediated learning
Psychosis
Schizophrenia

ABSTRACT

Studies of Pavlovian conditioning have enriched our understanding of how relations among events can adaptively guide behavior through the formation and use of internal mental representations. In this review, we illustrate how internal representations flexibly integrate new updated information in reinforcer revaluation to influence relationships to impact actions and outcomes. We highlight representation-mediated learning to show the similarities in properties and functions between internally generated and directly activated representations, and how normal perception of internal representations could contribute to hallucinations. Converging evidence emerges from recent behavioral and neural activation studies using animal models of schizophrenia as well as clinical studies in patients to support increased tendencies in these populations to evoke internal representations from prior associative experience that approximate hallucination-like percepts. The heightened propensity is dependent on dopaminergic activation which is known to be sensitive to hippocampal overexcitability, a condition that has been observed in patients with psychosis. This presents a network that overlaps with cognitive neural circuits and offers a fresh approach for the development of therapeutic interventions targeting psychosis.

1. Introduction

Studies of Pavlovian conditioning have contributed to understanding fundamentals of associative learning in paradigms that have wide applicability across species and behavioral systems. Delay conditioning, in which a neutral stimulus (CS) that reliably precedes an unconditioned stimulus (US) acquires the power to elicit a learned response, exhibits many similar properties in laboratory animals and humans, and contributed to a 'model systems' approach for studies of neural circuitry and mechanisms of neural plasticity in a productive era of research in decades past (e.g., Christian & Thompson, 2003; Fanselow & Wassum, 2016; Greco & Liberzon, 2015; Hawkins & Byrne, 2015; McLaughlin & Powell, 1999). Using many variations of Pavlovian protocols, information processing accounts of associative learning further advanced a rich understanding of how relations among events endow biological systems with adaptive behavior (Pearce & Hall, 1980; Rescorla & Wagner, 1972; Wagner, 1981). Here, too, the use of laboratory animals alongside studies in human subjects were productive settings for the study of learning processes in neurobehavioral systems.

In the context of information processing, memory representations of previously experienced events have been found to play important roles in associative learning in animals and people. For example, studies of reinforcer revaluation (described below) using comparable procedures in rodents, non-human primates, and humans revealed corresponding neurobehavioral systems. This review and commentary will further open the way for translational neuroscience in which such research has potential for rational discovery of therapeutics across preclinical to clinical drug development.

2. Internal representations in reinforcer revaluation

The establishment of associations through Pavlovian conditioning creates internal memory representations of the CS, the US, and their relationships that contain rich, detailed information that can be dynamically used to modulate learning. The importance of internal representations and its plasticity in response to adaptive change based on subsequent experience for guiding actions has been demonstrated extensively over the last several decades using reinforcer revaluation paradigms in a range of species including humans. In a common variant of a reinforcer revaluation (more specifically devaluation) task, a subject receives CS-food association, the food is subsequently devalued through satiation or pairings with an illness-inducing agent in a separate occasion in the absence of the CS, which consequently results in a decrease in the likelihood of the CS to elicit CRs. The performance of

* Corresponding author at: Department of Psychological and Brain Sciences, Dunning Hall 120, Johns Hopkins University, 3400, North Charles Street, Baltimore, MD 21218, USA.
E-mail address: mtkoh@jhu.edu (M.T. Koh).

https://doi.org/10.1016/j.nlm.2020.107319
Received 24 August 2020; Received in revised form 24 September 2020; Accepted 27 September 2020
Available online 30 September 2020

the CRs is therefore inferred to be mediated by the CS that, through its prior associative experience with the actual US, activates not only a memory representation of the US but one with a current updated value, serving as a simple yet compelling example of how internal representations have the capacity to integrate new information to guide actions adaptively.

The construct of reinforcer representation has been investigated using both Pavlovian and instrumental devaluation procedures in rats (Balleine & Dickinson, 1992), mice (Crombag, Johnson, Zimmer, Zimmer, & Holland, 2009), monkeys (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Málková, Gaffan, & Murray, 1997; West, DesJardin, Gale, & Málková, 2011), and humans (Corlett et al., 2004; Gottfried et al., 2003; Valentin et al., 2007), which attests to the excellent translation from animal to human of the concept and procedures used to study it. Additionally, converging evidence from those cross-species studies points to a neurobehavioral system that involves the interaction between the basolateral amygdala and the orbitofrontal cortex in the formation and the use of reinforcer representations (see reviews by Holland & Gallagher, 2004; Pickens & Holland, 2004). The use of reinforcer devaluation has also expanded more recently to the assessment of neurobehavioral dysfunction associated with psychiatric disorders on the integration of reinforcer representations to action-outcome associations (e.g., Barch & Dowd, 2010; Griffiths, Morris, & Balleine, 2014; Morris, Quail, Griffiths, Green, & Balleine, 2015; Morris, Cyrzon, Green, Le Pelley, & Balleine, 2018). For the rest of the article, we will further illustrate the role internal memory representations in associative learning through representation-mediated learning, and consider how irregularities in the activation of internal representations may drive hallucination-like phenomena in pathological and non-pathological populations.

3. Representation-mediated learning

Though not as extensively studied as reinforcer devaluation, representation-mediated learning has also traveled an investigatory route through studies in laboratory animals and recently in humans. These investigations found that associatively activated internal representations possess many of the features of directly activated representations of those events, and can also serve the same functions as directly activated representations in mediating and modulating learning about other cues. In a series of seminal studies starting in the early 1980s, Peter Holland established that internal representations activated from prior experiences could enter into current associations to form new learning in animals (see review by Holland and Wheeler (2008). This was demonstrated using activation of internal representations of food to form a conditioned food aversion. In one such study (Holland, 1981), rats first received repeated pairings of a tone CS with a novel flavored food to endow the tone with the ability to activate an internal representation of the food. The presentation of the tone alone was then paired with an illness-inducing agent. Finally, a food consumption test was given in the absence of the tone to assess mediated learning of a food aversion. Rats subjected to these training procedures consumed less of the food than rats in the control groups, suggesting that the tone, through its prior associative experience with the food, activated an internal representation of the food that entered into an association with the illness-inducing agent to induce a conditioned aversion to the food. Unlike reinforcer devaluation, representation-mediated learning is sensitive to the amount of training such that learning is found only under limited CS-US pairings (e.g., tone-food), and extended training reduces the ability of the US to support new learning (e.g., an aversion), possibly due to changes in the sensory features and associability of the US representations activated by the CS (Holland, 1998; Holland, 2005).

The cognitive representation of the food from mediated learning under optimal training procedures is activated with sufficient strength and specificity at a perceptual level to serve as a potent CS to support new learning to that food. Indeed, evoked representations share sensory qualities and activate corresponding perceptual processing as directly activated representations (e.g., Delamater, LoLordo, & Berridge, 1986; Holland, 1990; Kerfoot, Agarwal, Lee, & Holland, 2007). For instance, in Kerfoot et al. (2007), rats received repeated pairings of tone and intraoral delivery of sucrose solution. The hedonic value of sucrose was then either maintained or reduced through a pairing with an illness-inducing agent in the absence of the tone. Responding to the tone was tested days later with intraoral water infusion to assess orofacial activity for liking and disgust reactions that reflects taste palatability. Compared to those in the control group that received tone and sucrose unpaired, the rats that had the experience of tone and sucrose paired together with the palatability of the sucrose maintained showed more appetitive taste-reactivity responses to water, indicating that the rats responded in a manner consistent with drinking sucrose. Hence, the tone has seemingly evoked, through its prior associative experience, an internal representation with sufficient sensory authenticity of a real sucrose solution in the test session that the rats behaved as though they were drinking sucrose while in fact they were drinking water. Most remarkably, the rats that received tone-sucrose pairing with subsequent sucrose devaluation displayed fewer appetitive and more aversive taste-reactivity responses akin to the tasting of unpalatable flavors. In this case, the tone was able to evoke an internal representation of the sucrose solution that had been devalued at a different occasion during the absence of the tone, demonstrating the potency and dynamic nature of evoked memory representations that incorporate updated content through mediated learning in guiding behavior. In addition to mediating acquisition and extinction learning (Holland & Forbes, 1982), associatively activated internal representations can also modulate learning by facilitating or interfering with association formation; potentiation (Holland, 1983; 2006) and overshadowing (Holland, 1983) for example have both been shown with associatively activated internal representations indicating that they can functionally mimic directly activated representations.

4. Hallucination-like phenomenon

These intriguing findings with mediated learning have potential relevance for the phenomenon of hallucination with implications for normal and dysfunctional biological processing relevant for psychiatry. Commonly observed in psychiatric illnesses including schizophrenia, hallucinations occur when a stimulus is perceived in the absence of external input of the stimulus, not unlike the evocation of internal representations under normal circumstances. Under that view, hallucinations in fact can be observed in nonclinical healthy populations presumably arising from functioning in non-pathological brain circuits (Larøi et al., 2012). Increasingly, the role of internal representations elicited by prior associative experiences in accounting for hallucinatory perception has received more attention from a cognitive perspective in both animal and human research (e.g., Adams, Stephan, Brown, Frith, & Friston, 2013; Dwyer, 2018; Feeney, Groman, Taylor, & Corlett, 2017; McDannald & Schoenbaum, 2009).

Using well-established animal models of schizophrenia, we and others have begun to investigate whether animals that are known to exhibit symptoms consistent with psychosis-like behavior display a greater tendency to use a representation of a prior experience to form mediated associations in learning (Busquets-Garcia et al., 2017; Kim & Koh, 2016; McDannald et al., 2011). In our studies (Koh, Ahrens, & Gallagher, 2018), we used mice that were exposed subchronically to ketamine during adolescence and tested them ketamine-free in young adulthood; such exposures are known to be highly effective in reproducing positive symptoms of schizophrenia (Frohlich & Van Horn, 2014; Krystal et al., 1994). Using a representation taste aversion paradigm, the mice were exposed to an odor–taste compound to endow the odor with the ability to activate a representation of the associated taste. The odor alone was subsequently paired with gastrointestinal illness in the absence of the taste. A subsequent test with the taste was

given in the absence of the odor to assess the presence of a conditioned taste aversion which would signify that an internal representation of the taste activated by the odor during conditioning had entered into an association with illness. Compared to control mice, the mice with a history of ketamine exposure during adolescence showed a more pronounced taste aversion, suggesting (1) a heightened tendency to activate an internal representation from a prior associative experience (i.e., odor activates taste representation during conditioning), and/or (2) a stronger propensity to associate an internal representation with another stimulus or event (i.e., taste representation associates with illness). Recent work using mice with dominant negative expression of Disrupted-In-Schizophrenia-1 (DISC-1), a mutation that increased the risk for neuropsychiatric conditions, shed some light on these possibilities using a simple Pavlovian approach (Fry et al., 2019). The mice were first given conditioning of an auditory stimulus such as a tone paired with the delivery of sucrose solution for consumption. After extensive training, the mice were tested with water in the presence of the tone. Compared to control mice, the DISC-1 transgenic mice showed enhanced licking of water with increased palatability profile suggestive of consumption of a sucrose-like solution. Hence, the prior associative experience between tone and sucrose appeared to have endowed the tone with the ability to trigger a sucrose representation while drinking water, which provided strong support for a heightened tendency to activate internal representations of associative experiences in DISC-1 transgenic mice.

5. Neural activation of internal memory representation

Additional evidence on the nature of representations comes from studies using imaging of neural activity to capture activation in neural systems. We and others have assessed the predisposition of animals used to model schizophrenia for cues previously paired with a taste to induce a taste percept at the neural level in the absence of the taste itself, using the expression of an immediate early gene, c-fos, as a marker to detect neural activation in taste-responsive brain regions such as the insular cortex. Prior research importantly has shown the cued activation of the taste area in the insular cortex to resemble natural neural representation of taste stimuli (Saddoris, Holland, & Gallagher, 2009), and stimulation of the taste cortex in the absence of an actual taste can initiate taste percepts to guide behavior (Peng et al., 2015). In our experiment using a ketamine mouse model of schizophrenia, mice received odor–taste compound exposures, and then odor exposure alone (with water to drink) aimed at activating a taste representation (Wu, Haberman, Gallagher, & Koh, 2020). We found that the previously taste-associated odor induced a stronger neural activation in the insular taste cortex in mice exposed to ketamine during adolescence than control mice. Using DISC-1 transgenic mice, Fry et al. (2019) similarly found those mice to display a greater c-fos expression in the insular cortex in response to an auditory cue previously paired with a taste. Taken together with the behavioral studies, the neural activation data further strengthened the assertion that animals used to model symptoms of schizophrenia, which do not exhibit any general alteration in simple associative conditioning (Johnson et al., 2013; Koh, Ahrens, & Gallagher, 2018, Fig. 2A), have increased tendency to induce internal representations akin to hallucination-like percepts, but these data do not discount the additional possibility of an increased propensity to associate an internal representation with other stimuli or events.

6. Conditioned hallucinations in humans

The role of prior associative experience in mediating hallucinations has also been demonstrated in the laboratory setting with humans, both with and without diagnosed psychiatric illnesses. When a tone and a visual stimulus were repeatedly paired together, people reported hearing the tone subsequently in response to the visual stimulus alone (i.e., in the absence of tone); patients diagnosed with hallucinations reported hearing the tone more frequently and with higher confidence in their conditioned hallucinations than control subjects without pre-existing hallucinations (Powers, Mathys, & Corlett, 2017). The probability and confidence of the conditioned hallucinations were also strongly correlated with the severity of diagnosed hallucinations of the subjects. Furthermore, the conditioned hallucinations in those subjects involved evoked sensory representations as evidenced by increased neural activation in tone-responsive brain regions during the conditioned hallucinations.

Through such sensory conditioning, the susceptibility to hallucinate has been studied in different populations including normal individuals in the absence of any detectable illnesses, by examining the tendency to evoke internal stimulus representations based on prior experience established by associative learning (Ellson, 1941; Kot & Serper, 2002; Powers, Mathys, & Corlett, 2017). Prior knowledge is therefore critical in this top-down account of the source of hallucinations as it is used to compare to incoming sensation; if the prior expectation is strong and precise, it will dominate perception with internal representations based on the prior knowledge (Corlett et al., 2019; Teufel et al., 2015). It is worth noting again that by this account, hallucinations are maladaptive extremes along a continuum of normal functioning as opposed to mediation by some distinct pathological processes or circuitry that is extraneous to existing neurobehavioral systems (Powers, Kelley, & Corlett, 2017). Indeed, auditory hallucinations appear to elicit similar brain activation in a network of cortical and subcortical regions in both psychotic and normal individuals (e.g., Diederen et al., 2012).

7. Circuits and networks in neurocognitive function

Not unlike other manifestations of psychosis, the increased tendency to evoke internal representations in animal models of schizophrenia appears to be driven, at least in part, by dopamine hyperfunction. Adult mice exposed to ketamine sub-chronically during adolescence display hyper-responsiveness to the dopamine-releasing agent, amphetamine. The same mice when treated with the antipsychotic risperidone showed both reduced hyper-responsiveness to amphetamine and an attenuated tendency for representation-mediated learning, suggesting that conditioned hallucinations as conceptualized here may be due, at least in part, to dopamine hyperfunction (Koh, Ahrens, & Gallagher, 2018). Further substantiating those findings, treatment with haloperidol, which exhibits high affinity dopamine D_2 receptor antagonism, also effectively reduced the tendency to evoke internal representations in DISC-1 transgenic mice (Fry et al., 2019). A role for dopaminergic function demonstrated in those studies is consistent with the view that internal representations elicited in the context of mediated learning approximates hallucinations in patients insofar that hallucinations have also shown some sensitivity to antipsychotics that target dopamine function, and that hallucinations might arise from a dysregulation of the dopamine system causing misattribution of salience to internal representations of percepts and memories (Kapur, 2003).

Dopamine function, at the same time, is under the regulation of the hippocampus. Notably, increased metabolic activity in the hippocampus itself has been reported in individuals with schizophrenia (e.g., Allen et al., 2018; McHugo et al., 2019; Medoff, Holcomb, Lahti, & Tamminga, 2001; Sanderson et al., 2012; Schobel et al., 2013; Tregellas et al., 2014; Zierhut et al., 2013). The increased level of metabolic activity in the hippocampus of these individuals was predictive of the disease progression from a prodromal condition to the onset of psychosis, and further positively correlated with the severity of clinical symptoms of psychosis (Schobel et al., 2009). Increased hippocampal activity has also been recapitulated in well-established neurodevelopmental animal models of schizophrenia, including those using chronic ketamine exposure during adolescence (Schobel et al., 2013) and methylazoxymethanol (MAM) during gestation (Gill, Lodge, Cook, Aras, & Grace, 2011; Lodge & Grace, 2007). As noted in this recent research,

pathologically increased hippocampal activation can contribute to dopamine hyperfunction that triggers or exacerbates psychosis; targeting hippocampal overactivity could thus present a route to treat psychosis by reducing dopamine hyperfunction with additional normalization of other forebrain circuitries. With respect to dopaminergic regulation, intracranial administration of a $GABA_A$ α5 receptor agonist into the hippocampus has been shown to reduce excess dopamine activity in the ventral tegmental area (VTA) and psychosis-like symptoms in the MAM animal model of schizophrenia (Gill et al., 2011). Also, overexpression of $GABA_A$ α5 receptors with viral-mediated gene transfer in the hippocampus of MAM-exposed rats both modulated tonic currents and firing rates in the hippocampus, normalized aberrant dopamine neuron population activity in the VTA, and attenuated cognitive symptoms associated with schizophrenia (Donegan, Boley, Yamaguchi, Toney, & Lodge, 2019). Indeed, our treatment studies in the ketamine model using the antiepileptic medication levetiracetam aimed at reducing hippocampal overactivity similarly reduced hippocampal-dependent cognitive impairment as well as dopamine-dependent amphetamine-induced hyperlocomotor activity (Koh, Shao, et al., 2018).

These findings suggest that normalizing hippocampal overactivity might be beneficial for reducing the tendency to evoke hallucination-like percepts as instantiated in representation-mediated learning that is sensitive to dopamine signaling. Interestingly, the hippocampus itself also plays an important role in mediated learning with lesion or inactivation of the hippocampus producing impairment (Iordanova, Good, & Honey, 2011; Wheeler, Chang, & Holland, 2013), and deletion of cannabinoid type 1 receptors in hippocampal GABAergic neurons also disrupts mediated learning (Busquets-Garcia et al., 2018). Recent work additionally shows that the interaction between the hippocampus and the orbitofrontal cortex is important for inferring future outcomes using internal representations under sensory preconditioning, a learning paradigm that shares some procedural similarity with representation-mediated learning (Wang, Schoenbaum, & Kahnt, 2020). In addition to its role in dopaminergic regulation, consideration of the hippocampus as a component of a network contributing to neurocognitive dysfunction in schizophrenia may afford the opportunity to gain efficacy for cognitive deficits that are not remediated by antipsychotics that target dopaminergic function (Koh, Ahrens, & Gallagher, 2018; Scott and Tamminga, 2018; Segev, Yanagi, Scott, Southcott, Lister, Tan, Li, Birnbaum, Kourrich, & Tamminga, 2018; Smucny, Stevens, & Tregellas, 2015). Further extensions in forebrain cortical circuitry are under study within the affected network in psychiatric illness (e.g., Donegan et al., 2019; Nelson, Kraguljac, Maximo, Briend, Armstrong, Ver Hoef, Johnson, & Lahti, 2020). This approach is tied to the Research Domain Criteria (RDoC) initiative with greater emphasis on cognitive processes (Ford et al., 2014; Morris & Cuthbert, 2012).

8. Summary

In this brief review, we illustrated how internal representations through their flexibility are normally used to adaptively guide behavior in reinforcer devaluation. We then highlighted representation-mediated learning to further show the similarities in properties and functions between internally generated and directly activated representations, and how normal perception of internal representations could be a contributing basis for hallucinations. We discussed examples of how this has been investigated in animals and humans neurobehaviorally, and how conceptualization of hallucinations in these terms would allow for a rational development of drug therapies that may go beyond the current limitations of antipsychotics. This current research continues to leverage systems neurobiology in laboratory animals and clinical studies both grounded in a common formal theoretical framework, illustrating that core functions of circuits and more extended networks are retained in ways amenable to study across species.

CRediT authorship contribution statement

Ming Teng Koh: Conceptualization, Writing - original draft, Writing - review & editing. **Michela Gallagher:** Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition.

Acknowledgements

We thank Professor Peter C. Holland for his suggestions on an earlier version of this manuscript. This work was supported by the National Institutes of Health P50MH094268.

References

Adams, R. A., Stephan, K. E., Brown, H. R., Frith, C. D., & Friston, K. J. (2013). The computational anatomy of psychosis. *Frontiers in Psychiatry, 4*, 47.
Allen, P., Azis, M., Modinos, G., Bossong, M. G., Bonoldi, I., Samson, C., ... McGuire, P. (2018). Increased resting hippocampal perfusion in people at ultra high risk for psychosis: Replication in a second cohort. *Schizophrenia Bulletin, 44*, 1323–1331.
Balleine, B., & Dickinson, A. (1992). Signalling and incentive processes in instrumental reinforcer devaluation. *The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology, 45*, 285–301.
Barch, D. M., & Dowd, E. C. (2010). Goal representations and motivational drive in schizophrenia: The role of prefrontal-striatal interactions. *Schizophrenia Bulletin, 36*, 919–934.
Baxter, M. G., Parker, A., Lindner, C. C., Izquierdo, A. D., & Murray, E. A. (2000). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *The Journal of Neuroscience, 20*, 4311–4319.
Busquets-Garcia, A., da Cruz, J. F. O., Terral, G., Zottola, A. C. P., Soria-Gómez, E., Contini, A., ... Marsicano, G. (2018). Hippocampal CB_1 Receptors Control Incidental Associations. *Neuron, 99*, 1247–1259.
Busquets-Garcia, A., Soria-Gómez, E., Redon, B., Mackenbach, Y., Vallée, M., Chaouloff, F., ... Marsicano, G. (2017). Pregnenolone blocks cannabinoid-induced acute psychotic-like states in mice. *Molecular Psychiatry, 22*, 1594–1603.
Christian, K. M., & Thompson, R. F. (2003). Neural substrates of eyeblink conditioning: Acquisition and retention. *Learning & Memory, 10*, 427–455.
Corlett, P. C., Aitken, M. R. F., Dickinson, A., Shanks, D. R., Honey, G. D., Honey, A. E., ... Fletcher, P. C. (2004). Prediction error during retrospective revaluation of causal associations in humans: fMRI evidence in favor of an associative model of learning. *Neuron, 44*, 877–888.
Corlett, P. R., Horga, G., Fletcher, P. C., Alderson-Day, B., Schmack, K., & Powers, A. R. (2019). Hallucinations and strong priors. *Trends in Cognitive Sciences, 23*, 114–127.
Crombag, H. S., Johnson, A. W., Zimmer, A. M., Zimmer, A., & Holland, P. C. (2009). Deficits in sensory- specific devaluation task performance following genetic deletions of cannabinoid (CB1) receptor. *Learning & Memory, 17*, 18–22.
Delamater, A. R., LoLordo, V. M., & Berridge, K. C. (1986). Control of fluid palatability by exteroceptive Pavlovian signals. *Journal of Experimental Psychology Animal Behavior Processes, 12*, 143–152.
Diederen, K. M. J., Daalman, K., de Weijer, A. D., Neggers, S. F. W., van Gastel, W., Blom, J. D., ... Sommer, I. E. C. (2012). Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. *Schizophrenia Bulletin, 38*, 1074–1082.
Donegan, J. J., Boley, A. M., Yamaguchi, J., Toney, G. M., & Lodge, D. J. (2019). Modulation of extrasynaptic GABAA alpha 5 receptors in the ventral hippocampus normalizes physiological and behavioral deficits in a circuit specific manner. *Nature Communications, 10*, 1–12.
Dwyer, D. M. (2018). Associations and hallucinations in mice and men. *Learning & Behavior, 46*, 223–224.
Ellson, D. G. (1941). Hallucinations produced by sensory conditioning. *Journal of Experimental Psychology, 28*, 1–20.
Fanselow, M. S., & Wassum, K. M. (2016). The origins and organization of vertebrate Pavlovian conditioning. *Cold Spring Harbor Perspectives in Biology, 8*, Article a021717.
Feeney, E. J., Groman, S. M., Taylor, J. R., & Corlett, P. R. (2017). Explaining delusions: Reducing uncertainty through basic and computational neuroscience. *Schizophrenia Bulletin, 43*, 263–272.
Ford, J. M., Morris, S. E., Hoffman, R. E., Sommer, I., Waters, F., McCarthy-Jones, S., ... Cuthbert, B. N. (2014). Studying hallucinations within the NIMH RDoC framework. *Schizophrenia Bulletin, 40*, S295–S304.
Frohlich, J., & Van Horn, J. D. (2014). Reviewing the ketamine model for schizophrenia. *Journal of Psychopharmacology, 28*, 287–302.
Fry, B. R., Russell, N., Gifford, R., Robles, C. F., Manning, C. E., Sawa, A., ... Johnson, A. W. (2019). Assessing reality testing in mice through dopamine-dependent associatively evoked processing of absent gustatory stimuli. *Schizophrenia Bulletin, 46*, 54–67.
Gill, K. M., Lodge, D. J., Cook, J. M., Aras, S., & Grace, A. A. (2011). A novel α5GABA(A) R-positive allosteric modulator reverses hyperactivation of the dopamine system in the MAM model of schizophrenia. *Neuropsychopharmacology, 36*, 1903–1911.
Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science, 301*, 1104–1107.
Greco, J. A., & Liberzon, I. (2015). Neuroimaging of fear-associated learning. *Neuropsychopharmacology, 41*, 320–334.

Griffiths, K. R., Morris, R. W., & Balleine, B. W. (2014). Translational studies of goal-directed action as a framework for classifying deficits across psychiatric disorders. *Frontiers in System Neuroscience, 8*, 101.
Hawkins, R. D., & Byrne, J. H. (2015). Associative learning in invertebrates. *Cold Spring Harbor Perspectives in Biology, 7*, Article a021709.
Holland, P. C. (1981). Acquisition of representation-mediated conditioned food aversions. *Learning & Motivation, 12*, 1–18.
Holland, P. C. (1983). Representation mediated overshadowing and potentiation of conditioned aversions. *Journal of Experimental Psychology: Animal Behavior Processes, 9*, 1–13.
Holland, P. C. (1990). Event representation in Pavlovian conditioning: Image and action. *Cognition, 37*, 105–131.
Holland, P. C. (1998). Amount of training affects associatively-activated event representation. *Neuropharmacology, 37*, 461–469.
Holland, P. C. (2005). Amount of training effects in representation-mediated food aversion learning: No evidence of a role for associability changes. *Learning & Behavior, 33*, 464–478.
Holland, P. C. (2006). Limitations on representation-mediated potentiation of flavour or odour aversions. *Quarterly Journal of Experimental Psychology, 59*, 233–250.
Holland, P. C., & Forbes, D. T. (1982). Representation mediated extinction of flavor aversions. *Learning and Motivation, 13*, 454–471.
Holland, P. C., & Gallagher, M. (2004). Amygdala-frontal interactions and reward expectancy. *Current Opinion of Neurobiology, 14*, 148–155.
Holland, P. C., & Wheeler, D. S. (2008). Representation-mediated food aversions. In S. Reilly, & T. R. Schachtman (Eds.). *Conditioned taste aversion: Behavioral and neural processes* (pp. 196–225). New York, NY: Oxford University Press.
Iordanova, M. D., Good, M., & Honey, R. C. (2011). Retrieval-mediated learning involving episodes requires synaptic plasticity in the hippocampus. *The Journal of Neuroscience, 31*, 7156–7162.
Johnson, A. W., Jaaro-Peled, H., Shahani, N., Sedlak, T. W., Zoubovsky, S., Burruss, D., ... Gallagher, M. (2013). Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 12462–12467.
Kapur, S. (2003). Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *The American Journal of Psychiatry, 160*, 13–23.
Kerfoot, E. C., Agarwal, I., Lee, H. J., & Holland, P. C. (2007). Control of appetitive and aversive taste- reactivity responses by an auditory conditioned stimulus in a devaluation task: A FOS and behavioral analysis. *Learning & Memory, 14*, 581–589.
Kim, H. J., & Koh, H. Y. (2016). Impaired reality testing in mice lacking phospholipase Cβ1: Observed by persistent representation-mediated taste aversion. *PLoS ONE, 11*, Article e0146376.
Koh, M. T., Ahrens, P. S., & Gallagher, M. (2018). A greater tendency for representation mediated learning in a ketamine mouse model of schizophrenia. *Behavioral Neuroscience, 132*, 106–113.
Koh, M. T., Shao, Y., Rosenzweig-Lipson, S., & Gallagher, M. (2018). Treatment with levetiracetam improves cognition in a ketamine rat model of schizophrenia. *Schizophrenia Research, 193*, 119–125.
Kot, T., & Serper, M. (2002). Increased susceptibility to auditory conditioning in hallucinating schizophrenic patients: A preliminary investigation. *The Journal of Nervous and Mental Disease, 190*, 282–288.
Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., ... Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry, 51*, 199–214.
Larøi, F., Sommer, I. E., Blom, J. D., Fernyhough, C., Ffytche, D. H., Hugdahl, K., ... Waters, F. (2012). The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: State-of-the-art overview and future directions. *Schizophrenia Bulletin, 38*, 724–733.
Lodge, D. J., & Grace, A. A. (2007). Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *The Journal of Neuroscience, 27*, 11424–11430.
Málková, L., Gaffan, D., & Murray, E. A. (1997). Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *The Journal of Neuroscience, 17*, 6011–6020.
McDannald, M., & Schoenbaum, G. (2009). Toward a model of impaired reality testing in rats. *Schizophrenia Bulletin, 35*, 664–667.
McDannald, M. A., Whitt, J. P., Calhoon, G. G., Piantadosi, P. T., Karlsson, R. M., O'Donnell, P., & Schoenbaum, G. (2011). Impaired reality testing in an animal model of schizophrenia. *Biological Psychiatry, 70*, 1122–1126.
McHugo, M., Talati, P., Armstrong, K., Vandekar, S. N., Blackford, J. U., Woodward, N. D., & Heckers, S. (2019). Hyperactivity and reduced activation of anterior hippocampus in early psychosis. *American Journal of Psychiatry, 176*, 1030–1038.
McLaughlin, J., & Powell, D. A. (1999). Pavlovian heart rate and jaw movement conditioning in rabbit: Effects of medial prefrontal lesions. *Neurobiology of Learning and Memory, 71*, 150–166.
Medoff, D. R., Holcomb, H. H., Lahti, A. C., & Tamminga, C. A. (2001). Probing the human hippocampus using rCBF: Contrasts in schizophrenia. *Hippocampus, 11*, 543–550.
Morris, R. W., Cyrzon, C., Green, M. J., Le Pelley, M. E., & Balleine, B. W. (2018). Impairments in action- outcome learning in schizophrenia. *Translational Psychiatry, 8*, 54.
Morris, R. W., Quail, S., Griffiths, K. R., Green, M. J., & Balleine, B. W. (2015). Corticostriatal control of goal- directed action is impaired in schizophrenia. *Biological Psychiatry, 77*, 187–195.
Morris, S. E., & Cuthbert, B. N. (2012). Research domain criteria: Cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience, 14*, 29–37.
Nelson, E. A., Kraguljac, N. V., Maximo, J. O., Briend, F., Armstrong, W., Ver Hoef, L. W., Johnson, V., & Lahti, A. C. (2020). Hippocampal dysconnectivity and altered glutamatergic modulation of the default mode network: a combined resting-state connectivity and magnetic resonance spectroscopy study in schizophrenia. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, [Online ahead of print].
Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review, 87*, 532–552.
Peng, Y., Gillis-Smith, S., Jin, H., Tränkner, D., Ryba, N. J., & Zuker, C. S. (2015). Sweet and bitter taste in the brain of awake behaving animals. *Nature, 527*, 512–515.
Pickens, C. L., & Holland, P. C. (2004). Conditioning and cognition. *Neuroscience and Biobehavioral Reviews, 28*, 651–661.
Powers, A. R., Kelley, M. S., & Corlett, P. R. (2017). Varieties of voice-hearing: Psychics and the psychosis continuum. *Schizophrenia Bulletin, 43*, 84–98.
Powers, A. R., Mathys, C., & Corlett, P. R. (2017). Pavlovian conditioning–induced hallucinations result from overweighting of perceptual priors. *Science, 357*, 596–600.
Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black, & W. F. Prokasy (Eds.). *Classical conditioning II* (pp. 64–99). New York: Appleton–Century–Crofts.
Saddoris, M. P., Holland, P. C., & Gallagher, M. (2009). Associatively learned representations of taste outcomes activate taste-encoding neural ensembles in gustatory cortex. *The Journal of Neuroscience, 29*, 15386–15396.
Sanderson, T. M., Cotel, M. C., O'Neill, M. J., Tricklebank, M. D., Collingridge, G. L., & Sher, E. (2012). Alterations in hippocampal excitability, synaptic transmission and synaptic plasticity in a neurodevelopmental model of schizophrenia. *Neuropharmacology, 62*, 1349–1358.
Schobel, S. A., Chaudhury, N. H., Khan, U. A., Paniagua, B., Styner, M. A., Asllani, I., ... Small, S. A. (2013). Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron, 78*, 81–93.
Schobel, S. A., Lewandowski, N. M., Corcoran, C. M., Moore, H., Brown, T., Malaspina, D., & Small, S. A. (2009). Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Archives of General Psychiatry, 66*, 938–946.
Segev, A., Yanagi, M., Scott, D., Southcott, S.A., Lister, J. M., Tan, C., Li, W., Birnbaum, S. G., Kourrich, S., & Tamminga, C.A. (2018). Reduced GluN1 in mouse dentate gyrus is associated with CA3 hyperactivity and psychosis-like behaviors. Molecular Psychiatry, [Online ahead of print].
Scott, D., & Tamminga, C. A. (2018). Effects of genetic and environmental risk for schizophrenia on hippocampal activity and psychosis-like behavior in mice. *Behavioral Brain Research, 339*, 114–123.
Smucny, J., Stevens, K. E., & Tregellas, J. R. (2015). The antiepileptic drug levetiracetam improves auditory gating in DBA/2 mice. *NPJ Schizophrenia, 1*, 15002.
Teufel, C., Subramaniam, N., Dobler, V., Perez, J., Finnemann, J., Mehta, P. R., ... Fletcher, P. C. (2015). Shift toward prior knowledge confers a perceptual advantage in early psychosis and psychosis-prone healthy individuals. *Proceedings of the National Academy of Sciences of the United States of America, 112*, 13401–13406.
Tregellas, J. R., Smucny, J., Harris, J. G., Olincy, A., Maharajh, K., Kronberg, E., ... Freedman, R. (2014). Intrinsic hippocampal activity as a biomarker for cognition and symptoms in schizophrenia. *The American Journal of Psychiatry, 171*, 549–556.
Valentin, V. V., Dickinson, A., & O'Doherty, J. P. (2007). Determining the neural substrates of goal-directed learning in the human brain. *The Journal of Neuroscience, 27*, 4019–4026.
Wagner, A. R. (1981). SOP: A model of automatic memory processing in animal behavior. In N. E. Spear, & R. R. Miller (Eds.). *Information processing in animals: Memory mechanisms* (pp. 95–128). Hillsdale, NJ: Erlbaum.
Wang, F., Schoenbaum, G., & Kahnt, T. (2020). Interactions between human orbitofrontal cortex and hippocampus support model-based inference. *PLoS Biology, 18*, Article e3000578.
West, E. A., DesJardin, J. T., Gale, K., & Málková, L. (2011). Transient inactivation of orbitofrontal cortex blocks reinforcer devaluation in macaques. *The Journal of Neuroscience, 31*, 15128–15135.
Wheeler, D. S., Chang, S. E., & Holland, P. C. (2013). Odor-mediated taste learning requires dorsal hippocampus, but not basolateral amygdala activity. *Neurobiology of Learning and Memory, 101*, 1–7.
Wu, J. L., Haberman, R. P., Gallagher, M., & Koh, M. T. (2020). Probing for conditioned hallucinations through neural activation in a ketamine mouse model of schizophrenia. *Neuroscience Bulletin, 36*, 937–941.
Zierhut, K. C., Graßmann, R., Kaufmann, J., Steiner, J., Bogerts, B., & Schiltz, K. (2013). Hippocampal CA1 deformity is related to symptom severity and antipsychotic dosage in schizophrenia. *Brain, 136*, 804–814.