



REVIEW

# mGlu<sub>5</sub>: A double-edged sword for aversive learning related therapeutics

Shawn Zheng Kai Tan <sup>1, 2,\*</sup> and Jee Hyun Kim <sup>3</sup><sup>1</sup>School of Biomedical Science, Li Ka Shing Faculty of Medicine, The University of Hong Kong <sup>2</sup>European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Cambridgeshire, United Kingdom <sup>3</sup>IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, VIC, Australia 

\*shawntan@ebi.ac.uk

## Abstract

Aversive memories underlie many types of anxiety disorders. One area of research to more effectively treat anxiety disorders has therefore been identifying pharmacological targets to affect memory processes. Among these targets, the metabotropic glutamate 5 receptor (mGlu<sub>5</sub>) has received attention due to the availability of drugs to utilize its role in learning and memory. In this review, we highlight preclinical studies examining the role of mGlu<sub>5</sub> at various stages of aversive learning and its inhibition via extinction in order to gain a better understanding of its therapeutic potential. We suggest that mGlu<sub>5</sub> has distinct roles at different stages of memory that not only makes it a tricky target, but a double-edged sword as a therapeutic. However, the selective involvement of mGlu<sub>5</sub> in different memory stages allows for certain precision that could be harnessed clinically. We therefore suggest potential applications, limitations, and pitfalls when considering use of mGlu<sub>5</sub> modulators as therapeutics. In addition, we recommend future studies to address important gaps in this literature, such as sex and age factors in light of anxiety disorders being more prevalent in those demographics.

**Key words:** mGlu<sub>5</sub>; Learning and Memory; Aversive Learning; Fear Conditioning; Neuropharmacology

## 1. Introduction

Learning and memory are crucial for survival. In particular, aversive learning allows prevention and avoidance of detrimental outcomes (e.g., injury, predator etc.) [1]. When expressed pervasively, however, the memory of an aversive event can lead to symptoms such as heightened fear, avoidance, etc. that can interfere with necessary activities, resulting in anxiety disorders. Anxiety disorders are highly prevalent and are among the biggest causes of health burden worldwide [2]. Yet, current therapeutics often face issues with efficacy and relapse [3–6]. This has led researchers to seek novel pharmacotherapies to affect aversive memory to treat anxiety disorders [7–9].

### 1.1. Aversive learning and memory

Aversive memory is widely studied in the laboratory through Pavlovian conditioning paradigm, in which an initially neutral conditioned stimulus (CS) is paired with an intrinsically aversive

unconditioned stimulus (US). The CS is typically a discrete cue such as a tone or a light. Additionally, the context in which the US takes place can serve as a type of CS that can be associated with the US. After such pairings, presentation of the CS by itself can elicit a range of behaviors related to the US, such as defensive action associated with fear (e.g., immobility) [10]. Notably, Pavlovian conditioning is the process whereby the occurrence of either the CS or the US is not necessarily dependent on the behavior of the animal [11].

In contrast, instrumental conditioning refers to the learning of an action–outcome relationship that requires the animal to perform a specific behavior for the US to occur [12]. In aversive instrumental learning, an animal may move away from its current location to escape discomfort or pain [13]. Although rarely treated as such, the Morris water maze is an example of aversive instrumental learning [14]. It involves an animal swimming to find a submerged platform using distal and/or proximal spatial cues to escape the water. Alternatively, it could involve an animal avoiding a context or even some flavors. For example, in passive or in-

hibitory avoidance tasks, an animal is conditioned to avoid certain areas of a maze after being exposed to an aversive stimulus there (e.g. footshock, cat urine, etc.) [15, 16]. Similarly in conditioned taste aversion tasks, animals are conditioned to avoid and/or show disgust to a flavor (usually done through injection of LiCl to cause toxicosis in the lab [17]. Importantly, Pavlovian conditioning can be incorporated into instrumental conditioning as powerful mediators of behavior [18]. Specifically, an instrumental response can be followed by both the CS and the US. Subsequently, CS can initiate the instrumental response by itself [11, 19, 20]. Behaviors arising from Pavlovian and/or instrumental conditioning are referred to as conditioned responses (CRs).

Aversive memories can amplify the excessive worry/stress in anxiety disorders [21]. Consistent with this idea, one treatment approach that has received significant attention in the last two decades is exposure therapy, which often forms a part of cognitive behavior therapy [7, 8, 22–27]. It typically involves repeatedly exposing a patient to the stimulus that elicits fear in the absence of any danger. Exposure therapy is based on the process of extinction, which is the decrease in CR following presentations of the CS without the US. In instrumental learning, the CR can also be extinguished when the US no longer follows the CR. Furthermore, repeated presentations of the CS alone without explicit extinction training of the action–outcome contingency can also significantly reduce instrumental CR [19, 28] demonstrating the potency of the CS in influencing action–outcome behaviors.

Extinction is readily observed across species, and due to its high clinical relevance, extinction is the most commonly utilized paradigm to study how the expression of an aversive memory can be reduced [21, 22, 29–31]. The decrease in CR is due to the animal learning that the CR or the CS no longer predicts the US. The dominant theory is that extinction involves acquisition of CS–no US and/or CR–no US memory that inhibits the original aversive memory [21, 29], although there is also evidence for erasure of aversive memory due to extinction [4, 32–34].

Another commonly studied memory process in the context of anxiety disorders is reconsolidation, for which a previous consolidated memory destabilizes and becomes labile through its reactivation/recall [35, 36] Once recalled, the previously consolidated memory requires reconsolidation in order to stabilize again, failing which, the memory would not be retained [37, 38]. This reconsolidation window therefore allows consolidated memories to be reinforced or altered, making it an attractive target for therapeutics aiming to alter memories. A focus of contemporary research has been to target receptors involved in acquisition, extinction, or reconsolidation of aversive memories with the aim to either reduce initial threat learning or facilitate extinction to ultimately promote adaptive behaviors in people with anxiety disorders.

## 1.2 Glutamate and metabotropic glutamate 5 receptors

The widely accepted putative neural mechanism for learning and memory is synaptic plasticity, which refers to when the strength of synaptic transmission is either upregulated or downregulated [39, 40]. Hebb [41, pp. xix, 335–xix, 335] was the first to describe a process in which synaptic changes are observed when either a cell excites another cell repeatedly or is consistently involved in its excitability. This process causes synaptic changes so that the first cell's efficiency in activating the second cell is increased. At present, the most studied form of synaptic plasticity is long-term potentiation (LTP) that is found in the hippocampus, prefrontal cortex, and the amygdala [42, 43], neural structures critical for aversive learning and memory [44–48]. LTP is a long term enhancement in synaptic excitability resulting from coincident activity of pre- and post-synaptic elements [49] and is a putative mechanism for learning and memory [50].

Glutamate plays an important role in LTP [51]. L-glutamate

is the major excitatory neurotransmitter in the central nervous system. It acts on ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). iGluRs are ligand gated channels, namely N-methyl-D-aspartate (NMDA) receptors,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors [52]. Typically, excitatory transmission happens when glutamate is released into the synapse and acts on AMPA receptors, causing an influx of depolarizing ions. This depolarization can then activate NMDA receptors, which function as coincidence detectors that are critical for LTP as well as learning [53]. For example, antagonism of NMDA receptors, can block LTP in the hippocampus in vivo [54]. Correspondingly, animals administered with the NMDA antagonists ( $\pm$ )-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid or MK-801 show impaired acquisition of spatial learning [55, 56].

Modulating NMDA receptors directly can however be tricky as NMDA antagonist and agonists are highly associated with cell toxicity [57, 58], while the efficacy of safer partial agonists like d-cycloserine has not been supported [59]. Overall, this creates a need for other targets affecting learning and memory. mGluRs presents a way to modulate NMDA transmission in a more controlled manner – a fine tuning mechanism of sorts. The metabotropic glutamate 5 receptor (mGlu<sub>5</sub>), in particular, has received significant attention as a potential therapeutic target. Compared to other mGluRs, mGlu<sub>5</sub> is highly expressed in the amygdala [60, 61], a central structure for fear learning and memory. Furthermore, compared to other mGluRs, mGlu<sub>5</sub> is densely expressed in the cortical brain regions in the first 3 weeks of development [60, 62, 63], which highlights its potential involvement in emotional learning and memory involved in anxiety disorders which typically starts in childhood/adolescence [64]. mGlu<sub>5</sub> is a seven transmembrane G protein-coupled receptor belonging to Group I mGluRs predominantly expressed postsynaptically (typically extrasynaptic). When activated by the neurotransmitter glutamate, they cause a cascade of chemical changes which leads to an influx of  $Ca^{2+}$  via the inositol 1,4,5-triphosphate and diacyl-glycerol pathway, which cause further downstream effects [65, 66]. Importantly, mGlu<sub>5</sub> is co-localized and interacts with N-methyl-D-aspartate (NMDA) receptors [67]. For example, low concentrations of NMDA are able to reverse desensitization of signaling caused by phosphorylation of specific serine/threonine molecules in mGlu<sub>5</sub>, whilst high NMDA concentrations can inhibit mGlu<sub>5</sub> [68]. Further, mGlu<sub>5</sub> positive allosteric modulators (PAM) are also able to potentiate the activation of NMDA receptor activation and reverse inhibition by the NMDA antagonist D-APV [69].

Such relationship between NMDA receptors and mGlu<sub>5</sub> is believed to affect long-term potentiation (LTP). For example, Lu *et al.* [70] was the first to show that mGlu<sub>5</sub> knockout (KO) mutant mice had reduced LTP in CA1 and DG region of the dorsal hippocampus. Early phase LTP seems to be dependent on NMDA receptors and not on mGlu<sub>5</sub> [71]. This is further evidenced by Gerstein *et al.* [118], who showed that late- but not early-phase LTP is impaired in hippocampal slices of mice lacking Homer1c (a scaffolding protein associated with mGlu<sub>5</sub>). We do note that the purpose of the review is not to compare and contrast NMDA vs mGlu<sub>5</sub> but to understand the role of mGlu<sub>5</sub> in regard to behavior. In addition, mGlu<sub>5</sub> on its own has been shown to be necessary for LTP [72]. Notably, mGlu<sub>5</sub> signaling has also been shown to be crucial for NMDA-independent long-term depression (LTD) and depotentiation [73], which are also synaptic plasticity mechanisms involved in extinction more than conditioning [74–77]. Therefore, mGlu<sub>5</sub> may particularly be suited to modulating extinction processes that occur in exposure therapy.

In addition, mGlu<sub>5</sub> are densely expressed in structures important for learning and memory such as the hippocampus, amygdala, striatum and nucleus accumbens [78, 79]. Considering that reduction of memory expression following extinction involves the formation of a new inhibitory memory, mGlu<sub>5</sub> manipulation to

reduce or enhance emotional memory is in fact a “double-edged sword”. That is, attempts to enhance extinction may enhance conditioning processes, whereas disrupting conditioning may also disrupt extinction processes. A clear understanding of the role of mGlu<sub>5</sub> signaling in conditioning and extinction is necessary to exploit mGlu<sub>5</sub> as a therapeutic target. In this mini-review, we describe and assess the role of mGlu<sub>5</sub> in the various stages of acquisition and extinction of aversive memories based on extensive rodent literature, in order to gain a better understanding of how to target memory processes using mGlu<sub>5</sub> modulators as potential therapy for anxiety disorders.

## 2. Metabotropic glutamate 5 receptor in acquisition and maintenance of aversive memories

### 2.1 Acquisition

The role of mGlu<sub>5</sub> in learning and memory has been demonstrated firstly using the Morris water maze [70]. While this task is not typically studied in the context of aversive learning, it requires the animal's motivation to escape an aversive situation using spatial memory. Systemic injections of mGlu<sub>5</sub> PAMs CDPPB (10 mg/kg) or ADX47273 (10 mg/kg) once before each day of Morris water maze trials enhanced the acquisition of learning in mice, as indicated by fewer number of days to reach criterion [80]. Although all mice were trained to criterion, drug-free probe trial showed that mice previously injected with CDPPB or ADX47273 spent more time in the target quadrant compared to the vehicle group [80], which highlights that the effects of mGlu<sub>5</sub> PAMs on acquisition of learning is long-lasting and may indicate stronger memory overall (Table 1).

While such study using PAMs suggests that mGlu<sub>5</sub> signaling is sufficient to acquire aversion-motivated spatial memory, whether mGlu<sub>5</sub> signaling is necessary for acquisition of spatial memory is less clear. Ballard *et al.* [81] showed that intraperitoneal (i.p.) injection of mGlu<sub>5</sub> negative allosteric modulator (NAM) MPEP (3, 10 and 30 mg/kg) in rats once before each day of Morris water maze trials had no effects on acquisition (Table 2). Car *et al.* [82] also showed in rats that MPEP (1 mg/kg) administered intravenously once before each day of Morris water maze trials had no effects compared to vehicle injections on acquisition. This discrepancy between the effects of PAMs vs. NAMs may be related to limitations with pharmacological approaches, including how allosteric modulators allow continued orthosteric binding of glutamate. On the other hand, mGlu<sub>5</sub> KO mice implicate the function of mGlu<sub>5</sub> at a global and chronic level. Indeed, mGlu<sub>5</sub> KO mice are significantly impaired in acquisition of Morris water maze task compared to wildtype mice [70, 83]. A limitation in interpreting such finding is that germline KO mice may experience developmental differences/compensation compared to their wildtype littermates. In addition, while these studies highlight the hippocampus as the likely locus of mGlu<sub>5</sub> effects, deletion of mGlu<sub>5</sub> is not anatomically specific in germline KO mice. Tan *et al.* [84] addressed some of these limitations by knocking down mGlu<sub>5</sub> selectively in the dorsal hippocampus (dHPC) during adulthood using mGlu<sub>5</sub> floxed mice. Significant acquisition deficits in the Morris water maze were observed in that study, providing causal evidence for hippocampus mGlu<sub>5</sub> involvement in the acquisition of aversion-motivated spatial learning.

Consistent with findings using Morris water maze, systemic injection of the mGlu<sub>5</sub> NAM MPEP (0.3–30 mg/kg) before fear conditioning has been shown to dose-dependently block acquisition of conditioned fear-potentiated startle to a light CS in rats [85]. Similarly, systemic injection of MTEP (3–30 mg/kg), a mGlu<sub>5</sub> NAM with ten-fold greater selectivity than MPEP, prior to fear conditioning also dose-dependently blocked acquisition of conditioned fear to both context and tone CS in mice [86]. MTEP also

impaired acquisition in a passive avoidance task and conditioned fear potentiated startle [87]. Although Lu *et al.* [70] showed no difference in post-shock freezing between mGlu<sub>5</sub> KO and wild-type mice following a single tone-footshock pairing, with multiple tone-footshock pairings, Xu *et al.* [88] showed impaired post-shock freezing in mGlu<sub>5</sub> KO mice to both tone and context. In terms of studies examining positive modulation of mGlu<sub>5</sub>, the mGlu<sub>5</sub> PAM CDPPB had no effects when administered pre-training for a single-trial step-down inhibitory avoidance learning task and conditioned taste aversion [89]. Taken together, while these findings generally highlight that mGlu<sub>5</sub> is important for the acquisition of aversive learning, more work is needed to understand the nuances of their effects in different tasks, and the difference between positive and negative modulation.

### 2.2 Consolidation and retrieval

While mGlu<sub>5</sub> plays a major role in acquisition of aversive learning, it does not appear to be necessary for the consolidation of aversive memory. Administration of the mGlu<sub>5</sub> agonist CHPG or NAM MPEP immediately following fear conditioning did not produce any effects [90]. Similarly, MTEP given post-conditioning did not affect conditioned fear to context nor tone CS at test [86]. The lack of involvement of mGlu<sub>5</sub> in consolidation of contextual fear memory is surprising given the critical role of mGlu<sub>5</sub> in hippocampal LTD [91], which has been shown to be important for consolidation of spatial memory [92]. More work, especially using the selective NAM MTEP following Morris water maze training, would be helpful to delineate whether mGlu<sub>5</sub> is involved in consolidation of spatial memory.

Retrieval of Morris water maze memory does not appear to require mGlu<sub>5</sub>. Following Morris water maze training, Lu *et al.* [70] showed that mGlu<sub>5</sub> KO mice were impaired in probe trial suggesting a possible impairment in retrieval of memory. However, Xu *et al.* [88] showed no effect of genotype during the probe trial. It is likely that the impairment seen in Lu *et al.* [70] is due to the pre-existing differences in acquisition. Specifically, mGlu<sub>5</sub> KO mice had significantly higher latency to platform at last acquisition trial in Lu *et al.* [70], whereas there were no genotype differences by the end of acquisition in Xu *et al.* [88]. Similarly, Tan *et al.* [84] noted no effect of dHPC specific mGlu<sub>5</sub> knockdown during probe trial of Morris water maze. One study did report that 30 mg/kg of MPEP, but not 3 nor 10 mg/kg, given prior to probe trial had a small but statistically significant reduction in proportional distance travelled in platform quadrant [81]. In that study, however, the platform location was cued and visible.

In retrieval of conditioned fear memory, mGlu<sub>5</sub> KO mice were impaired in freezing to the conditioned context but not to the tone [70, 88]. However, Xu *et al.* [88] suggested that this was an effect on acquisition rather than expression of once-memorized fear response, suggesting no effect on retrieval of memory. It is indeed difficult to assess retrieval effects using mGlu<sub>5</sub> KO mice following impairments in acquisition – genotype effects could be due to carry-over from differences at acquisition. Interestingly, 30 mg/kg MPEP, but not 0.3 or 3.0 mg/kg, administered 60 min before retrieval test reduced expression of conditioned fear measured by potentiated startle [85]. At this dose, the authors noted that MPEP may be having a broadly anxiolytic effect rather than affecting memory retrieval. It remains equivocal whether mGlu<sub>5</sub> is involved in retrieval of aversive memories.

## 3. Metabotropic glutamate 5 receptor in aversive memory extinction and reconsolidation

Adaptive learning and behavioral flexibility are highly important in response to an ever-changing environment. Importantly, it has

**Table 1.** Studies using positive allosteric modulators (PAM) or agonists of mGlu<sub>5</sub> cited in this paper

	Reference	Task	Drug	Route	Time Injected	Outcome
Acquisition	Ayala <i>et al.</i> 2009	MWM	CDPPB	Systemic (I.P.)	Pre-acquisition	Enhanced Acquisition
	Ayala <i>et al.</i> 2009	MWM	ADX47273	Systemic (I.P.)	Pre-acquisition	Enhanced Acquisition
	Fowler <i>et al.</i> 2011	Inhibitory Avoidance	CDPPB	Systemic (S.C.)	Pre-acquisition	No effect
	Fowler <i>et al.</i> 2011	Conditioned Taste Aversion	CDPPB	Systemic (S.C.)	Pre-acquisition	No effect
	Sethna <i>et al.</i> 2014	Contextual Fear Conditioning	CDPPB	Systemic (I.P.)	Pre-acquisition	Enhanced Consolidation (no effect on Acquisition, Increase freezing during test)
Consolidation & Retrieval	Maciejak <i>et al.</i> 2003	Contextual Fear Conditioning	CHPG	Hippocampus microinfusion	Post-acquisition	No effect
	Sethna <i>et al.</i> 2014	Contextual Fear Conditioning	CDPPB	Systemic (I.P.)	24h Post-acquisition/24h pre-test	No effect
Extinction & Reconsolidation	Xu <i>et al.</i> 2013	Context and Tone Fear Conditioning	ADX47273	Systemic (I.P.)	Pre-extinction	No effect
	Sethna <i>et al.</i> 2014	Contextual Fear Conditioning	CDPPB	Systemic (I.P.)	Pre-extinction	Enhanced extinction acquisition
	Ganella <i>et al.</i> 2016	Tone Fear Conditioning	CDPPB	Systemic (S.C.)	Pre-extinction	Enhanced consolidation of extinction at P17 but not P24 or adult
	Xu <i>et al.</i> 2013	Contextual Fear Conditioning	ADX47273	Systemic (I.P.)	Multi Session Pre-extinction	No effect
	Xu <i>et al.</i> 2013	Contextual Fear Conditioning	ADX47273	Systemic (I.P.)	Multi Session Post-extinction	No effect
	Xu <i>et al.</i> 2013	Tone Fear Conditioning	ADX47273	Systemic (I.P.)	retrieval–reconsolidation window (30–45min after single tone retrieval)	No difference in extinction day, lowered freezing day after; no effect on spontaneous recovery; lowered freezing in renewal

implications on treatment of pervasively expressed memory disorders – the ability to respond differently to cues with established associations is crucial to the success of treatment. This can be modelled through extinction and reconsolidation.

### 3.1 Extinction

Similar to conditioning, extinction is largely a new memory that involves acquisition, consolidation, and retrieval [9], which strongly suggests that the role of mGlu<sub>5</sub> signaling in acquisition of conditioning may also apply for acquisition of extinction. Indeed, Sethna & Wang [93] showed that pre-extinction systemic injection of mGlu<sub>5</sub> PAM CDPPB facilitated acquisition of extinction, and further significantly reduced freezing at test the next day. This suggests either an effect on acquisition of extinction alone, or an effect on both acquisition and consolidation of extinction that resulted in reduced freezing. In contrast, an i.p. injection of mGlu<sub>5</sub> NAM MPEP before extinction did not affect extinction acquisition but significantly increased freezing at test the next day [94]. This effect was replicated when MPEP was injected into the infralimbic cortex (IL), a part of the prefrontal cortex that is critical for consolidation of extinction [47, 94, 95]. Those results suggest MPEP effects on extinction consolidation rather than acquisition.

mGlu<sub>5</sub> KO mice also showed impairments in between-session extinction to context and cue [88], suggesting mGlu<sub>5</sub>'s role in extinction consolidation. In contrast, mGlu<sub>5</sub> PAM ADX47273 system-

ically injected prior to either context or tone extinction session had no effects during extinction or test, though the lack of ADX47273 effects may be due to insufficient dosing, or due to a floor effect with the vehicle group freezing very low at test [95]. Interestingly, the role of mGlu<sub>5</sub> on extinction consolidation may be age-dependent. CDPPB or MTEP injection before extinction facilitated or impaired consolidation of extinction, respectively, in postnatal day 17 (P17) juvenile rats without affecting P24 or adult rats [96]. The authors proposed that their findings were due to rodent mGlu<sub>5</sub> having an unusual neurodevelopmental profile compared to other mGluRs, with a high expression at birth that steadily decreases from 3<sup>rd</sup> week into adulthood [78].

### 3.2 Reconsolidation

A relatively modern approach to “remove” aversive memories has been to target reconsolidation [97–101]. This works on the basis that memories become labile following reactivation – referred to as a reconsolidation window [37]. Therefore, the short reconsolidation period following reactivation may be vulnerable to therapeutics to disrupt aversive memory. For example, Monfils *et al.* [99] showed that extinction 10 min or 1 hr following fear memory reactivation (by a single CS presentation) significantly reduced spontaneous recovery of fear compared to extinction that was not followed by memory reactivation.

Xu *et al.* [95] aimed to test whether mGlu<sub>5</sub> signaling plays a

**Table 2.** Studies using negative allosteric modulators (NAM) of mGlu<sub>5</sub> cited in this paper

	Reference	Task	Drug	Route	Time Injected	Outcome
Acquisition	Schulz <i>et al.</i> 2001	Fear Conditioning	MPEP	Systemic (I.P.)	Pre-acquisition	Impaired acquisition
	Ballard <i>et al.</i> 2005	MWM	MPEP	Systemic (I.P.)	Pre-acquisition	No difference in Acquisition nor probe
	Gravius <i>et al.</i> 2005	Passive Avoidance Response	MTEP	Systemic (I.P.)	Pre-acquisition	Impaired acquisition
	Gravius <i>et al.</i> 2005	Conditioned Fear Potentiated Startle	MTEP	Systemic (I.P.)	Pre-acquisition	Impaired acquisition
	Car <i>et al.</i> 2007	MWM	MPEP	Systemic (I.V.)	Pre-acquisition	No difference in Acquisition, nor probe
	Handford <i>et al.</i> 2014	Fear Conditioning	MTEP	Systemic (I.P.)	Pre-acquisition	Impaired acquisition
Consolidation & Retrieval	Handford <i>et al.</i> 2014	Fear Conditioning	MTEP	Systemic (I.P.)	Post-acquisition	No effect
	Maciejak <i>et al.</i> 2003	Contextual Fear Conditioning	MPEP	Hippocampus microinfusion	Post-acquisition	No effect
	Gravius <i>et al.</i> 2005	Passive Avoidance Response	MTEP	Systemic (I.P.)	Post-acquisition	No effect
Extinction & Reconsolidation	Fontanez-Nuin <i>et al.</i> 2011	Tone Fear Conditioning	MPEP	Systemic (I.P.)	Pre-extinction	Normal extinction, impaired recall 24h later
	Fontanez-Nuin <i>et al.</i> 2011	Tone Fear Conditioning	MPEP	IL microinfusion	Pre-extinction	Normal extinction, impaired recall 24h later
	Ganella <i>et al.</i> 2016	Tone Fear Conditioning	MPEP	Systemic (S.C.)	Pre-extinction	Impaired consolidation of extinction at P17 but not P24 or adult

role in reconsolidation. Mice first received three tone-footshock pairings. The next day, mice received a single but prolonged tone CS trial, to which they showed high levels of freezing indicating memory reactivation. Within 45 minutes of this reactivation trial, mice were given either the mGlu<sub>5</sub> PAM ADX47273 or vehicle, and then received CS extinction. ADX47273 showed no effects during extinction. At test the next day, however, ADX47273 group showed reduced freezing compared to vehicle group. The authors suggested that increased mGlu<sub>5</sub> signaling during the reconsolidation window disrupted the original memory. However, it appears that mGlu<sub>5</sub> PAM simply facilitated CS extinction because a critical control group (i.e., extinction without reactivation) was missing. It may well be the case that PAM facilitated CS extinction even without any reactivation. Hence this finding may not be indicative of affecting any reconsolidation process. Future studies can utilize mGlu<sub>5</sub> PAM or NAM following reactivation without any extinction, to really determine whether mGlu<sub>5</sub> is involved in reconsolidation. Specifically, if mGlu<sub>5</sub> signaling is necessary and/or sufficient for reconsolidation, then NAM will disrupt CS memory and/or PAM will enhance CS memory when given following reactivation.

Overall, mGlu<sub>5</sub> appears to have distinct roles in acquisition and inhibition of aversive memories. While there still are inconsistencies between studies, the overall conclusion, taking into considerations limitations of each study, is that mGlu<sub>5</sub> is both sufficient and necessary for acquisition but not consolidation of aversive memories. While mGlu<sub>5</sub> does not seem to play a role in retrieval of aversive memories, studies examining this are limited, and more work would be necessary to rule out mGlu<sub>5</sub>'s role in aversive memory retrieval. Importantly, mGlu<sub>5</sub> appears to play a role in acquisition and consolidation of extinction memory, which has major implications in the modulation of mGlu<sub>5</sub> as a pharmacotherapeutic target – a topic we will cover in the next section.

#### 4. Metabotropic glutamate 5 receptor as a potential pharmacotherapy

Learning and memory clearly involve mGlu<sub>5</sub> signaling, highlighting its powerful potential as a target for anxiety disorder therapeutics. Yet its distinct roles at different stages of memory make it not only a tricky target, but a double-edged sword as a therapeutic. For acquisition of aversive learning, mGlu<sub>5</sub> signaling is likely necessary and sufficient (Table 1, 2). Consolidation of conditioned fear or Morris water maze learning appears mGlu<sub>5</sub> independent. Retrieval also is unlikely to involve mGlu<sub>5</sub> signaling, with studies attributing any effects to anxiolysis or pre-existing differences in acquisition. Therapeutically, mGlu<sub>5</sub> not being involved in consolidation of fear memory allows for certain precision – there is then reduced concern of increasing consolidation of a previous stressful or traumatic event. This, however, also means that mGlu<sub>5</sub> antagonist are probably not the most useful therapeutics for lowering the impact of recent traumatic memories.

Extinction is mGlu<sub>5</sub>-dependent, with more evidence for its sufficiency/necessity during consolidation than acquisition (Table 1, 2). Together with the fact that mGlu<sub>5</sub> is unlikely to affect retrieval of memory, increasing mGlu<sub>5</sub> signaling using PAMs may be an exciting psychological adjunct to strengthen exposure therapy. Whether taken during or post-therapy, it would not unnecessarily increase the recall of aversive memory, which is a perceived risk by clinicians during exposure therapies [102]. However, strong conclusions cannot be drawn without assessing mGlu<sub>5</sub>'s role in extinction recall. Exposure therapy typically require repeat sessions, and it would be important to first understand how mGlu<sub>5</sub> agents may affect extinction recall in subsequent sessions. It would also be a risk in case of new trauma, with the effects of mGlu<sub>5</sub> agonism showing to enhance aversive memory acquisition.

The use of mGlu<sub>5</sub> PAM during retrieval-reconsolidation window to disrupt the memory process is also an interesting avenue to explore, however, the study on mGlu<sub>5</sub> modulation during reconsolidation is too limited. Furthermore, techniques that manipu-

late memories during the retrieval–reconsolidation window work within a narrow window of time [103] and if not handled properly, could lead to exacerbation of the problem (multiple consolidations would serve to reinforce rather than extinguish the original memory [119]). These issues will only increase with the addition of pharmacotherapeutics like mGlu<sub>5</sub> modulators. Overall, better understanding of mGlu<sub>5</sub> modulators on reconsolidation is needed to ascertain the efficacy of such an intervention.

In summary, mGlu<sub>5</sub> is both sufficient and necessary for acquisition but not consolidation of aversive memories. This indicates that giving an antagonist to disrupt the initial aversive memory would be impractical because consolidation does not require mGlu<sub>5</sub> signaling. mGlu<sub>5</sub> does not seem to play a role in retrieval. mGlu<sub>5</sub> appears to play a role in acquisition and consolidation of extinction memory. Therefore, the potentially most efficacious way of applying mGlu<sub>5</sub> modulator to alter traumatic memory processes would be to use an agonist before or after acute or chronic exposure therapy.

We do also note that while learnt fear is a well-established model to study processes underlying the treatment of anxiety disorders [9], it by no means fully capture all aspects of anxiety disorders [104]. While beyond the scope of this review, it would be important to consider other mGlu<sub>5</sub> studies that assess state or trait anxiety (e.g., elevated plus maze) following stress that may provide additional information relevant towards anxiety disorders [105–107].

## 5. Conclusions

Future efforts with development of mGlu<sub>5</sub> modulators as a therapeutic of aversive learning/memory-based disorders should aim to accurately ascertain effects of mGlu<sub>5</sub> PAMs and NAMs on different stages of aversive learning. In particular, the relationship between mGlu<sub>5</sub> signaling and extinction retrieval needs more attention. Further complicating the matters, mGlu<sub>5</sub> signaling in extinction retrieval has been thoroughly assessed with preclinical studies modelling substance use disorders, with NAMs (rather than PAMs) being promoted because they reduce reinstatement of drug-seeking in rodents [108]. It would be important to determine whether mGlu<sub>5</sub>'s role in extinction recall is dissociated between aversive vs appetitive memories, given the co-morbidity of anxiety and substance use disorders [109]. Further work examining sex difference should also be considered. Sex-specific mGlu<sub>5</sub> expression is unknown [110], with studies examining mGlu<sub>5</sub> expression in the brain only using female rats [61–63], or not specific on sex [60]. These studies showed highest mGlu<sub>5</sub> expression in the first 3 weeks of postnatal life. Consistent with this observation, highest efficacy in mGlu<sub>5</sub> positive or negative allosteric modulation on extinction was observed in P17 male rats relative to older male rats [96], suggesting that the developmental profile of mGlu<sub>5</sub> expression in males may be similar to females. Nevertheless, the possibility of differential rate of decline in mGlu<sub>5</sub> expression across maturation in males versus females remains.

Lastly, it is striking that every mGlu<sub>5</sub> behavioral study described in this review has used males, despite the higher prevalence of anxiety disorders in females over males [111, 112]. In addition, all but one study used adult rodents, when 75% of all anxiety disorders are diagnosed by adolescence [64]. There is clear evidence of age-specific sex differences in aversive learning and memory [113–117]. Given mGlu<sub>5</sub>'s consistent role in extinction, we hope future research to highlight potential age- and sex-specific mechanisms of how mGlu<sub>5</sub> signaling impacts extinction learning and recall, which are cognitive processes critical for treatment of anxiety disorders.

## Declarations

### Funding

None.

### Conflict of Interest Declaration

SZKT is a reviewing editor for Neuroanatomy and behaviour and sits on the committee for Episteme Health.

## Editorial Notes

### History

- Received: 2020-11-08
- Revisions Requested: 2020-12-08
- Revised: 2021-01-15
- Accepted: 2021-01-16
- Published: 2021-01-18

### Editorial Checks

- Plagiarism: Plagiarism detection software found no evidence of plagiarism.
- References: Zotero did not identify any references in the [Re-tractionWatch](#) database.

### Peer Review

The review process for this paper was conducted double-blind because one of the authors is a member of the committee of management of the publisher, Episteme Health Inc. During review, neither the authors nor the reviewers were aware of each other's identities.

For the benefit of readers, reviewers are asked to write a public summary of their review to highlight the key strengths and weaknesses of the paper. Signing of reviews is optional.

### Reviewer 1 (Anonymous)

The authors discuss a role for mGlu<sub>5</sub> in learning and memory processes. The review outlines much of this work, stating that mGlu<sub>5</sub> modulators should be used as a therapeutic tool to reduced maladaptive responding from aversive learning. However, there are portions of the review that are unclear and topics that should be introduced prior to their discussion.

### Reviewer 2 (Anonymous)

This review on the “double-edged sword” of targeting the mGlu<sub>5</sub> receptor for anxiety disorders is interesting and well written. However, I feel that this review could be improved further if the researchers touched on more naturalistic models of anxiety. I think it is important that the authors put their work into a larger context outside of fear conditioning, particularly if the focus is on the clinical potential of mGlu<sub>5</sub>.

## References

1. Roy M. Weighting Pain Avoidance and Reward Seeking: A Neuroeconomics Approach to Pain. *Journal of Neuroscience*. 2010;30(12). doi: [10.1523/jneurosci.0262-10.2010](https://doi.org/10.1523/jneurosci.0262-10.2010).

2. World Health Organization. World health report 2001: Mental health: New understanding, new hope. Geneva: World Health Organization; 2001.
3. Baum M. Spontaneous recovery from the effects of flooding (exposure) in animals. *Behaviour Research and Therapy*. 1988;26(2). doi: [10.1016/0005-7967\(88\)90118-0](https://doi.org/10.1016/0005-7967(88)90118-0).
4. Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological Psychiatry*. 2002;52(10). doi: [10.1016/s0006-3223\(02\)01546-9](https://doi.org/10.1016/s0006-3223(02)01546-9).
5. Farach FJ, Pruitt LD, Jun JJ, Jerud AB, Zoellner LA, Roy-Byrne PP. Pharmacological treatment of anxiety disorders: Current treatments and future directions. *Journal of Anxiety Disorders*. 2012;26(8). doi: [10.1016/j.janxdis.2012.07.009](https://doi.org/10.1016/j.janxdis.2012.07.009).
6. Klucken T, Kruse O, Schweckendiek J, Kuepper Y, Mueller EM, Hennig J, et al. No evidence for blocking the return of fear by disrupting reconsolidation prior to extinction learning. *Cortex*. 2016;79. doi: [10.1016/j.cortex.2016.03.015](https://doi.org/10.1016/j.cortex.2016.03.015).
7. Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacology & Therapeutics*. 2015;149. doi: [10.1016/j.pharmthera.2014.12.004](https://doi.org/10.1016/j.pharmthera.2014.12.004).
8. Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, et al. Cognitive Enhancers as Adjuncts to Psychotherapy. *Archives of General Psychiatry*. 2004;61(11). doi: [10.1001/archpsyc.61.11.1136](https://doi.org/10.1001/archpsyc.61.11.1136).
9. Ganella DE, Kim JH. Developmental rodent models of fear and anxiety: from neurobiology to pharmacology. *British Journal of Pharmacology*. 2014;171(20). doi: [10.1111/bph.12643](https://doi.org/10.1111/bph.12643).
10. Blanchard RJ, Blanchard DC. Crouching as an index of fear. *Journal of Comparative and Physiological Psychology*. 1969;67(3). doi: [10.1037/h0026779](https://doi.org/10.1037/h0026779).
11. Rescorla RA, Solomon RL. Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning. *Psychological Review*. 1967;74(3). doi: [10.1037/h0024475](https://doi.org/10.1037/h0024475).
12. Thorndike E. Some experiments on animal intelligence. *Science*. 1898;7(181). doi: [10.1126/science.7.181.818](https://doi.org/10.1126/science.7.181.818).
13. LeDoux JE, Moscarello J, Sears R, Campese V. The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm. *Molecular Psychiatry*. 2016;22(1). doi: [10.1038/mp.2016.166](https://doi.org/10.1038/mp.2016.166).
14. Harrison FE, Hosseini AH, McDonald MP. Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks. *Behavioural Brain Research*. 2009;198(1). doi: [10.1016/j.bbr.2008.10.015](https://doi.org/10.1016/j.bbr.2008.10.015).
15. Tan S, Poon CH, Chan YS, Lim LW. [PREPRINT] Deep brain stimulation of the prelimbic cortex disrupts consolidation of fear memories. *bioRxiv*. 2019;doi: [10.1101/537514](https://doi.org/10.1101/537514).
16. Ögren SO, Stiedl O, Stolerman IP, Price LH. Passive avoidance. In: Stolerman IP, Price LH, editors. *Encyclopedia of Psychopharmacology*. Berlin, Heidelberg: Springer; 2015. p. 1220–1228. doi: [10.1007/978-3-642-36172-2\\_160](https://doi.org/10.1007/978-3-642-36172-2_160).
17. Schier LA, Hyde KM, Spector AC, Glendinning II. Conditioned taste aversion versus avoidance: A re-examination of the separate processes hypothesis. *PLOS ONE*. 2019;14(6). doi: [10.1371/journal.pone.0217458](https://doi.org/10.1371/journal.pone.0217458).
18. Baker AG, Steinwald H, Bouton ME. Contextual conditioning and reinstatement of extinguished instrumental responding. *The Quarterly Journal of Experimental Psychology Section B*. 1991;43(2).
19. Campese V, McCue M, Lázaro-Muñoz G, LeDoux JE, Cain CK. Development of an aversive Pavlovian-to-instrumental transfer task in rat. *Frontiers in Behavioral Neuroscience*. 2013;7. doi: [10.3389/fnbeh.2013.00176](https://doi.org/10.3389/fnbeh.2013.00176).
20. Tsutsui-Kimura I, Boučekiyoua Y, Mimura M, Tanaka KF. A New Paradigm for Evaluating Avoidance/Escape Motivation. *International Journal of Neuropsychopharmacology*. 2017;20(7). doi: [10.1093/ijnp/pyx031](https://doi.org/10.1093/ijnp/pyx031).
21. Maren S, Phan KL, Liberzon I. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*. 2013;14(6). doi: [10.1038/nrn3492](https://doi.org/10.1038/nrn3492).
22. Forcadell E, Torrents-Rodas D, Vervliet B, Leiva D, Tortella-Feliu M, Fullana MA. Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study. *International Journal of Psychophysiology*. 2017;121. doi: [10.1016/j.ijpsycho.2017.09.001](https://doi.org/10.1016/j.ijpsycho.2017.09.001).
23. Hauner KK, Mineka S, Voss JL, Paller KA. Exposure therapy triggers lasting reorganization of neural fear processing. *Proceedings of the National Academy of Sciences*. 2012;109(23). doi: [10.1073/pnas.1205242109](https://doi.org/10.1073/pnas.1205242109).
24. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognitive Therapy and Research*. 2012;36(5). doi: [10.1007/s10608-012-9476-1](https://doi.org/10.1007/s10608-012-9476-1).
25. Reinecke A, Waldenmaier L, Cooper MJ, Harmer CJ. Changes in Automatic Threat Processing Precede and Predict Clinical Changes with Exposure-Based Cognitive-Behavior Therapy for Panic Disorder. *Biological Psychiatry*. 2013;73(11). doi: [10.1016/j.biopsych.2013.02.005](https://doi.org/10.1016/j.biopsych.2013.02.005).
26. Wozney L, Baxter P, Newton AS. Usability evaluation with mental health professionals and young people to develop an Internet-based cognitive-behaviour therapy program for adolescents with anxiety disorders. *BMC Pediatrics*. 2015;15(1). doi: [10.1186/s12887-015-0534-1](https://doi.org/10.1186/s12887-015-0534-1).
27. Kim JH, Ganella DE. A Review of Preclinical Studies to Understand Fear During Adolescence. *Australian Psychologist*. 2015;50(1). doi: [10.1111/ap.12066](https://doi.org/10.1111/ap.12066).
28. Bouton ME. Extinction of instrumental (operant) learning: interference, varieties of context, and mechanisms of contextual control. *Psychopharmacology*. 2018;236(1). doi: [10.1007/s00213-018-5076-4](https://doi.org/10.1007/s00213-018-5076-4).
29. Milad MR, Quirk GJ. Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology*. 2012;63(1). doi: [10.1146/annurev.psych.121208.131631](https://doi.org/10.1146/annurev.psych.121208.131631).
30. Meyer HC, Odriozola P, Cohodes EM, Mandell JD, Li A, Yang R, et al. Ventral hippocampus interacts with prelimbic cortex during inhibition of threat response via learned safety in both mice and humans. *Proceedings of the National Academy of Sciences*. 2019;116(52). doi: [10.1073/pnas.1910481116](https://doi.org/10.1073/pnas.1910481116).
31. Zbukvic IC, Kim JH. Divergent prefrontal dopaminergic mechanisms mediate drug- and fear-associated cue extinction during adolescence versus adulthood. *European Neuropsychopharmacology*. 2018;28(1). doi: [10.1016/j.euroneuro.2017.11.004](https://doi.org/10.1016/j.euroneuro.2017.11.004).
32. Barad M. Is extinction of fear erasure or inhibition? Why both, of course. *Learning & Memory*. 2006;13(2). doi: [10.1101/lm.211306](https://doi.org/10.1101/lm.211306).
33. Kim JH, Richardson R. New Findings on Extinction of Conditioned Fear Early in Development: Theoretical and Clinical Implications. *Biological Psychiatry*. 2010;67(4). doi: [10.1016/j.biopsych.2009.09.003](https://doi.org/10.1016/j.biopsych.2009.09.003).
34. Lin CH, Yeh SH, Lu HY, Gean PW. The Similarities and Diversities of Signal Pathways Leading to Consolidation of Conditioning and Consolidation of Extinction of Fear Memory. *The Journal of Neuroscience*. 2003;23(23). doi: [10.1523/jneurosci.23-23-08310.2003](https://doi.org/10.1523/jneurosci.23-23-08310.2003).
35. Misanin JR, Miller RR, Lewis DJ. Retrograde Amnesia Produced by Electroconvulsive Shock after Reactivation of a Consolidated Memory Trace. *Science*. 1968;160(3827). doi: [10.1126/science.160.3827.554](https://doi.org/10.1126/science.160.3827.554).
36. Riccio DC, Millin PM, Bogart AR. Reconsolidation: A brief history, a retrieval view, and some recent issues. *Learning & Memory*. 2006;13(5). doi: [10.1101/lm.290706](https://doi.org/10.1101/lm.290706).

37. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*. 2000;406(6797). doi: [10.1038/35021052](https://doi.org/10.1038/35021052).
38. Milton AL, Merlo E, Ratano P, Gregory BL, Dumbreck JK, Everitt BJ. Double Dissociation of the Requirement for GluN2B- and GluN2A-Containing NMDA Receptors in the Destabilization and Restabilization of a Reconsolidating Memory. *Journal of Neuroscience*. 2013;33(3). doi: [10.1523/jneurosci.3273-12.2013](https://doi.org/10.1523/jneurosci.3273-12.2013).
39. Kandel ER. The Molecular Biology of Memory Storage: A Dialogue Between Genes and Synapses. *Science*. 2001;294(5544). doi: [10.1126/science.1067020](https://doi.org/10.1126/science.1067020).
40. Martin SJ, Morris RGM. New life in an old idea: The synaptic plasticity and memory hypothesis revisited. *Hippocampus*. 2002;12(5). doi: [10.1002/hipo.10107](https://doi.org/10.1002/hipo.10107).
41. Hebb DO. The organization of behavior: A neuropsychological theory. New York: Jon Wiley & Sons; 1949.
42. Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993;361(6407). doi: [10.1038/361031a0](https://doi.org/10.1038/361031a0).
43. Laroche S, Jay TM, Thierry AM. Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. *Neuroscience Letters*. 1990;114(2). doi: [10.1016/0304-3940\(90\)90069-1](https://doi.org/10.1016/0304-3940(90)90069-1).
44. Bauer EP, Schafe GE, LeDoux JE. NMDA Receptors and L-Type Voltage-Gated Calcium Channels Contribute to Long-Term Potentiation and Different Components of Fear Memory Formation in the Lateral Amygdala. *The Journal of Neuroscience*. 2002;22(12). doi: [10.1523/jneurosci.22-12-05239.2002](https://doi.org/10.1523/jneurosci.22-12-05239.2002).
45. Frankland PW, Bontempi B. The organization of recent and remote memories. *Nature Reviews Neuroscience*. 2005;6(2). doi: [10.1038/nrn1607](https://doi.org/10.1038/nrn1607).
46. Park CHJ, Ganella DE, Perry CJ, Kim JH. Dissociated roles of dorsal and ventral hippocampus in recall and extinction of conditioned fear in male and female juvenile rats. *Experimental Neurology*. 2020;329. doi: [10.1016/j.expneurol.2020.113306](https://doi.org/10.1016/j.expneurol.2020.113306).
47. Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable Roles of Prelimbic and Infralimbic Cortices, Ventral Hippocampus, and Basolateral Amygdala in the Expression and Extinction of Conditioned Fear. *Neuropsychopharmacology*. 2010;36(2). doi: [10.1038/npp.2010.184](https://doi.org/10.1038/npp.2010.184).
48. Sotres-Bayon F, Sierra-Mercado D, Pardilla-Delgado E, Quirk GJ. Gating of Fear in Prelimbic Cortex by Hippocampal and Amygdala Inputs. *Neuron*. 2012;76(4). doi: [10.1016/j.neuron.2012.09.028](https://doi.org/10.1016/j.neuron.2012.09.028).
49. Cooke SF. Plasticity in the human central nervous system. *Brain*. 2006;129(7). doi: [10.1093/brain/awl082](https://doi.org/10.1093/brain/awl082).
50. Rianza Bermudo-Soriano C, Perez-Rodriguez MM, Vaquero-Lorenzo C, Baca-Garcia E. New perspectives in glutamate and anxiety. *Pharmacology Biochemistry and Behavior*. 2012;100(4). doi: [10.1016/j.pbb.2011.04.010](https://doi.org/10.1016/j.pbb.2011.04.010).
51. Izquierdo I. Role of NMDA receptors in memory. *Trends in Pharmacological Sciences*. 1991;12. doi: [10.1016/0165-6147\(91\)90527-y](https://doi.org/10.1016/0165-6147(91)90527-y).
52. Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, et al. Glutamate Receptor Ion Channels: Structure, Regulation, and Function. *Pharmacological Reviews*. 2010;62(3). doi: [10.1124/pr.109.002451](https://doi.org/10.1124/pr.109.002451).
53. Stawski P, Janovjak H, Trauner D. Pharmacology of ionotropic glutamate receptors: A structural perspective. *Bioorganic & Medicinal Chemistry*. 2010;18(22). doi: [10.1016/j.bmc.2010.09.012](https://doi.org/10.1016/j.bmc.2010.09.012).
54. Pananceau M, Gustafsson B. NMDA receptor dependence of the input specific NMDA receptor-independent LTP in the hippocampal CA1 region. *Brain Research*. 1997;752(1-2). doi: [10.1016/S0006-8993\(96\)01471-0](https://doi.org/10.1016/S0006-8993(96)01471-0).
55. Larkin AE, Fahey B, Gobbo O, Callaghan CK, Cahill E, O'Mara SM, et al. Blockade of NMDA receptors pre-training, but not post-training, impairs object displacement learning in the rat. *Brain Research*. 2008;1199. doi: [10.1016/j.brainres.2008.01.019](https://doi.org/10.1016/j.brainres.2008.01.019).
56. Sison M, Gerlai R. Associative learning performance is impaired in zebrafish (*Danio rerio*) by the NMDA-R antagonist MK-801. *Neurobiology of Learning and Memory*. 2011;96(2). doi: [10.1016/j.nlm.2011.04.016](https://doi.org/10.1016/j.nlm.2011.04.016).
57. Rothman SM, Olney JW. Excitotoxicity and the NMDA receptor. *Trends in Neurosciences*. 1987;10(7). doi: [10.1016/0166-2236\(87\)90177-9](https://doi.org/10.1016/0166-2236(87)90177-9).
58. Lipton SA. Failures and successes of NMDA receptor antagonists: Molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurological insults. *NeuroRX*. 2004;1(1). doi: [10.1602/neurorx.1.1.101](https://doi.org/10.1602/neurorx.1.1.101).
59. Ori R, Amos T, Bergman H, Soares-Weiser K, Ipson JC, Stein DJ. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database of Systematic Reviews*. 2015;doi: [10.1002/14651858.cd007803.pub2](https://doi.org/10.1002/14651858.cd007803.pub2).
60. Catania MV, Landwehrmeyer GB, Testa CM, Standaert DG, Penney JB, Young AB. Metabotropic glutamate receptors are differentially regulated during development. *Neuroscience*. 1994;61(3). doi: [10.1016/0306-4522\(94\)90428-6](https://doi.org/10.1016/0306-4522(94)90428-6).
61. Romano C, Sesma MA, McDonald CT, O'Malley K, van den Pol AN, Olney JW. Distribution of metabotropic glutamate receptor mGluR5 immunoreactivity in rat brain. *The Journal of Comparative Neurology*. 1995;355(3). doi: [10.1002/cne.903550310](https://doi.org/10.1002/cne.903550310).
62. Lum JS, Fernandez F, Matosin N, Andrews JL, Huang XF, Ooi L, et al. Neurodevelopmental Expression Profile of Dimeric and Monomeric Group 1 mGluRs: Relevance to Schizophrenia Pathogenesis and Treatment. *Scientific Reports*. 2016;6(1). doi: [10.1038/srep34391](https://doi.org/10.1038/srep34391).
63. Romano C, Van den Pol AN, O'Malley KL. Enhanced early developmental expression of the metabotropic glutamate receptor mGluR5 in rat brain: Protein, mRNA splice variants, and regional distribution. *The Journal of Comparative Neurology*. 1996;367(3). doi: [10.1002/\(sici\)1096-9861\(19960408\)367:3<403::aid-cne6>3.0.co;2-9](https://doi.org/10.1002/(sici)1096-9861(19960408)367:3<403::aid-cne6>3.0.co;2-9).
64. Kessler RC, Angermeyer M, Anthony JC, Graaf RD, Demyttenaere K, Gasquet I, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry*. 2007;6(3).
65. Abe T, Sugihara H, Nawa H, Shigemoto R, Mizuno N, Nakanishi S. Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca<sup>2+</sup> signal transduction. *Journal of Biological Chemistry*. 1992;267(19). doi: [10.1016/S0021-9258\(18\)42219-3](https://doi.org/10.1016/S0021-9258(18)42219-3).
66. Niswender CM, Conn PJ. Metabotropic Glutamate Receptors: Physiology, Pharmacology, and Disease. *Annual Review of Pharmacology and Toxicology*. 2010;50(1). doi: [10.1146/annurev.pharmtox.011008.145533](https://doi.org/10.1146/annurev.pharmtox.011008.145533).
67. Luccini E, Musante V, Neri E, Brambilla Bas M, Severi P, Raiteri M, et al. Functional interactions between presynaptic NMDA receptors and metabotropic glutamate receptors co-expressed on rat and human noradrenergic terminals. *British Journal of Pharmacology*. 2007;151(7). doi: [10.1038/sj.bjp.0707280](https://doi.org/10.1038/sj.bjp.0707280).
68. Alagarsamy S, Rouse ST, Junge C, Hubert GW, Gutman D, Smith Y, et al. NMDA-induced phosphorylation and regulation of mGluR5. *Pharmacology Biochemistry and Behavior*. 2002;73(2). doi: [10.1016/S0091-3057\(02\)00826-2](https://doi.org/10.1016/S0091-3057(02)00826-2).
69. Chen HH, Liao PF, Chan MH. mGluR5 positive modulators both potentiate activation and restore inhibition in NMDA re-



- ceptors by PKC dependent pathway. *Journal of Biomedical Science*. 2011;18(1). doi: [10.1186/1423-0127-18-19](https://doi.org/10.1186/1423-0127-18-19).
70. Lu YM, Jia Z, Janus C, Henderson JT, Gerlai R, Wojtowicz JM, et al. Mice Lacking Metabotropic Glutamate Receptor 5 Show Impaired Learning and Reduced CA1 Long-Term Potentiation (LTP) But Normal CA3 LTP. *The Journal of Neuroscience*. 1997;17(13). doi: [10.1523/jneurosci.17-13-05196.1997](https://doi.org/10.1523/jneurosci.17-13-05196.1997).
  71. Francesconi W, Cammalleri M, Sanna PP. The metabotropic glutamate receptor 5 is necessary for late-phase long-term potentiation in the hippocampal CA1 region. *Brain Research*. 2004;1022(1-2). doi: [10.1016/j.brainres.2004.06.060](https://doi.org/10.1016/j.brainres.2004.06.060).
  72. Naie K. Regulation by Metabotropic Glutamate Receptor 5 of LTP in the Dentate Gyrus of Freely Moving Rats: Relevance for Learning and Memory Formation. *Cerebral Cortex*. 2004;14(2). doi: [10.1093/cercor/bhg118](https://doi.org/10.1093/cercor/bhg118).
  73. O'Mara SM, Rowan MJ, Anwyl R. Metabotropic glutamate receptor-induced homosynaptic long-term depression and depotentiation in the dentate gyrus of the rat hippocampus in vitro. *Neuropharmacology*. 1995;34(8). doi: [10.1016/0028-3908\(95\)00062-b](https://doi.org/10.1016/0028-3908(95)00062-b).
  74. Hong I, Song B, Lee S, Kim J, Kim J, Choi S. Extinction of cued fear memory involves a distinct form of depotentiation at cortical input synapses onto the lateral amygdala. *European Journal of Neuroscience*. 2009;30(11). doi: [10.1111/j.1460-9568.2009.07004.x](https://doi.org/10.1111/j.1460-9568.2009.07004.x).
  75. Kim J, Lee S, Park K, Hong I, Song B, Son G, et al. Amygdala depotentiation and fear extinction. *Proceedings of the National Academy of Sciences*. 2007;104(52). doi: [10.1073/pnas.0710548105](https://doi.org/10.1073/pnas.0710548105).
  76. Lin CH, Lee CC, Gean PW. Involvement of a Calcineurin Cascade in Amygdala Depotentiation and Quenching of Fear Memory. *Molecular Pharmacology*. 2003;63(1). doi: [10.1124/mol.63.1.44](https://doi.org/10.1124/mol.63.1.44).
  77. Zhu G, Briz V, Seinfeld J, Liu Y, Bi X, Baudry M. Calpain-1 deletion impairs mGluR-dependent LTD and fear memory extinction. *Scientific Reports*. 2017;7(1). doi: [10.1038/srep42788](https://doi.org/10.1038/srep42788).
  78. Kim JH, Perry CJ, Ganella DE, Madsen HB. Postnatal development of neurotransmitter systems and their relevance to extinction of conditioned fear. *Neurobiology of Learning and Memory*. 2017;138. doi: [10.1016/j.nlm.2016.10.018](https://doi.org/10.1016/j.nlm.2016.10.018).
  79. Shigemoto R, Nomura S, Ohishi H, Sugihara H, Nakanishi S, Mizuno N. Immunohistochemical localization of a metabotropic glutamate receptor, mGluR5, in the rat brain. *Neuroscience Letters*. 1993;163(1). doi: [10.1016/0304-3940\(93\)90227-c](https://doi.org/10.1016/0304-3940(93)90227-c).
  80. Ayala JE, Chen Y, Banko JL, Sheffler DJ, Williams R, Telk AN, et al. mGluR5 Positive Allosteric Modulators Facilitate both Hippocampal LTP and LTD and Enhance Spatial Learning. *Neuropsychopharmacology*. 2009;34(9). doi: [10.1038/npp.2009.30](https://doi.org/10.1038/npp.2009.30).
  81. Ballard TM, Woolley ML, Prinssen E, Huwyler J, Porter R, Spooren W. The effect of the mGlu5 receptor antagonist MPEP in rodent tests of anxiety and cognition: a comparison. *Psychopharmacology*. 2005;179(1). doi: [10.1007/s00213-005-2211-9](https://doi.org/10.1007/s00213-005-2211-9).
  82. Car H, Stefaniuk R, Wiśniewska RJ. Effect of MPEP in Morris water maze in adult and old rats. *Pharmacological Reports*. 2007;59(1).
  83. Bird MK, Lohmann P, West B, Brown RM, Kirchhoff J, Raymond CR, et al. The mGlu5 receptor regulates extinction of cocaine-driven behaviours. *Drug and Alcohol Dependence*. 2014;137. doi: [10.1016/j.drugalcdep.2014.01.017](https://doi.org/10.1016/j.drugalcdep.2014.01.017).
  84. Tan SZK, Ganella DE, Dick ALW, Duncan JR, Ong-Palsson E, Bathgate RAD, et al. Spatial Learning Requires mGlu5 Signalling in the Dorsal Hippocampus. *Neurochemical Research*. 2015;40(6). doi: [10.1007/s11064-015-1595-0](https://doi.org/10.1007/s11064-015-1595-0).
  85. Schulz B, Fendt M, Gasparini F, Lingenhöhl K, Kuhn R, Koch M. The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats. *Neuropharmacology*. 2001;41(1). doi: [10.1016/S0028-3908\(01\)00036-3](https://doi.org/10.1016/S0028-3908(01)00036-3).
  86. Handford CE, Tan S, Lawrence AJ, Kim JH. The effect of the mGlu5 negative allosteric modulator MTEP and NMDA receptor partial agonist D-cycloserine on Pavlovian conditioned fear. *The International Journal of Neuropsychopharmacology*. 2014;17(09). doi: [10.1017/s1461145714000303](https://doi.org/10.1017/s1461145714000303).
  87. Gravius A, Pietraszek M, Sch??fer D, Schmidt WJ, Danysz W. Effects of mGlu1 and mGlu5 receptor antagonists on negatively reinforced learning. *Behavioural Pharmacology*. 2005;16(2). doi: [10.1097/00008877-200503000-00007](https://doi.org/10.1097/00008877-200503000-00007).
  88. Xu J, Zhu Y, Contractor A, Heinemann SF. mGluR5 Has a Critical Role in Inhibitory Learning. *Journal of Neuroscience*. 2009;29(12). doi: [10.1523/jneurosci.5716-08.2009](https://doi.org/10.1523/jneurosci.5716-08.2009).
  89. Fowler SW, Ramsey AK, Walker JM, Serfozo P, Olive MF, Schachtman TR, et al. Functional interaction of mGlu5 and NMDA receptors in aversive learning in rats. *Neurobiology of Learning and Memory*. 2011;95(1). doi: [10.1016/j.nlm.2010.11.009](https://doi.org/10.1016/j.nlm.2010.11.009).
  90. Maciejak P, Taracha E, Lehner M, Szyndler J, Bidziński A, Skórzewska A, et al. Hippocampal mGluR1 and consolidation of contextual fear conditioning. *Brain Research Bulletin*. 2003;62(1). doi: [10.1016/j.brainresbull.2003.08.003](https://doi.org/10.1016/j.brainresbull.2003.08.003).
  91. O'Riordan KJ, Hu NW, Rowan MJ. Physiological activation of mGlu5 receptors supports the ion channel function of NMDA receptors in hippocampal LTD induction in vivo. *Scientific Reports*. 2018;8(1). doi: [10.1038/s41598-018-22768-x](https://doi.org/10.1038/s41598-018-22768-x).
  92. Ge Y, Dong Z, Bagot RC, Howland JG, Phillips AG, Wong TP, et al. Hippocampal long-term depression is required for the consolidation of spatial memory. *Proceedings of the National Academy of Sciences*. 2010;107(38). doi: [10.1073/pnas.1008200107](https://doi.org/10.1073/pnas.1008200107).
  93. Sethna F, Wang H. Pharmacological enhancement of mGluR5 facilitates contextual fear memory extinction. *Learning & Memory*. 2014;21(12). doi: [10.1101/lm.035857.114](https://doi.org/10.1101/lm.035857.114).
  94. Fontanez-Nuin DE, Santini E, Quirk GJ, Porter JT. Memory for Fear Extinction Requires mGluR5-Mediated Activation of Infralimbic Neurons. *Cerebral Cortex*. 2010;21(3). doi: [10.1093/cercor/bhq147](https://doi.org/10.1093/cercor/bhq147).
  95. Xu J, Zhu Y, Kraniotis S, He Q, Marshall JJ, Nomura T, et al. Potentiating mGluR5 function with a positive allosteric modulator enhances adaptive learning. *Learning & Memory*. 2013;20(8). doi: [10.1101/lm.031666.113](https://doi.org/10.1101/lm.031666.113).
  96. Ganella DE, Thangaraju P, Lawrence AJ, Kim JH. Fear extinction in 17 day old rats is dependent on metabotropic glutamate receptor 5 signaling. *Behavioural Brain Research*. 2016;298. doi: [10.1016/j.bbr.2014.12.010](https://doi.org/10.1016/j.bbr.2014.12.010).
  97. Brunet A, Orr SP, Tremblay J, Robertson K, Nader K, Pitman RK. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research*. 2008;42(6). doi: [10.1016/j.jpsychires.2007.05.006](https://doi.org/10.1016/j.jpsychires.2007.05.006).
  98. Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience*. 2009;12(3). doi: [10.1038/nn.2271](https://doi.org/10.1038/nn.2271).
  99. Monfils MH, Cowansage KK, Klann E, LeDoux JE. Extinction-Reconsolidation Boundaries: Key to Persistent Attenuation of Fear Memories. *Science*. 2009;324(5929). doi: [10.1126/science.1167975](https://doi.org/10.1126/science.1167975).
  100. Schiller D, Monfils MH, Raio CM, Johnson DC, LeDoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*. 2009;463(7277). doi: [10.1038/nature08637](https://doi.org/10.1038/nature08637).
  101. Tan SZK, Sheng V, Chan YS, Lim LW. Eternal sunshine of the neuromodulated mind: Altering fear memories through

- neuromodulation. *Experimental Neurology*. 2019;314. doi: [10.1016/j.expneurol.2019.01.004](https://doi.org/10.1016/j.expneurol.2019.01.004).
102. Meyer JM, Farrell NR, Kemp JJ, Blakey SM, Deacon BJ. Why do clinicians exclude anxious clients from exposure therapy? *Behaviour Research and Therapy*. 2014;54. doi: [10.1016/j.brat.2014.01.004](https://doi.org/10.1016/j.brat.2014.01.004).
  103. Pedreira ME, Maldonado H. Protein Synthesis Sub-serves Reconsolidation or Extinction Depending on Re-minder Duration. *Neuron*. 2003;38(6). doi: [10.1016/s0896-6273\(03\)00352-0](https://doi.org/10.1016/s0896-6273(03)00352-0).
  104. LeDoux J. *Anxious*. London: Oneworld; 2015.
  105. Yap JJ, Covington HE, Gale MC, Datta R, Miczek KA. Behavioral sensitization due to social defeat stress in mice: antagonism at mGluR5 and NMDA receptors. *Psychopharmacology*. 2004;179(1). doi: [10.1007/s00213-004-2023-3](https://doi.org/10.1007/s00213-004-2023-3).
  106. Shin S, Kwon O, Kang JI, Kwon S, Oh S, Choi J, et al. mGluR5 in the nucleus accumbens is critical for promoting resilience to chronic stress. *Nature Neuroscience*. 2015;18(7). doi: [10.1038/nn.4028](https://doi.org/10.1038/nn.4028).
  107. Wagner KV, Hartmann J, Labermaier C, Häusl AS, Zhao G, Harbich D, et al. Homer1/mGluR5 Activity Moderates Vulnerability to Chronic Social Stress. *Neuropsychopharmacology*. 2014;40(5). doi: [10.1038/npp.2014.308](https://doi.org/10.1038/npp.2014.308).
  108. Olive MF. Cognitive effects of Group I metabotropic glutamate receptor ligands in the context of drug addiction. *European Journal of Pharmacology*. 2010;639(1-3). doi: [10.1016/j.ejphar.2010.01.029](https://doi.org/10.1016/j.ejphar.2010.01.029).
  109. Kessler RC, Ormel J, Petukhova M, McLaughlin KA, Green JG, Russo LJ, et al. Development of Lifetime Comorbidity in the World Health Organization World Mental Health Surveys. *Archives of General Psychiatry*. 2011;68(1). doi: [10.1001/archgenpsychiatry.2010.180](https://doi.org/10.1001/archgenpsychiatry.2010.180).
  110. Perry CJ, Campbell EJ, Drummond KD, Lum JS, Kim JH. Sex differences in the neurochemistry of frontal cortex: Impact of early life stress. *Journal of Neurochemistry*. 2020;doi: [10.1111/jnc.15208](https://doi.org/10.1111/jnc.15208).
  111. Kessler RC. Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States. *Archives of General Psychiatry*. 1994;51(1). doi: [10.1001/archpsyc.1994.03950010008002](https://doi.org/10.1001/archpsyc.1994.03950010008002).
  112. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research*. 2011;45(8). doi: [10.1016/j.jpsychires.2011.03.006](https://doi.org/10.1016/j.jpsychires.2011.03.006).
  113. Baran SE, Armstrong CE, Niren DC, Conrad CD. Prefrontal cortex lesions and sex differences in fear extinction and perseveration. *Learning & Memory*. 2010;17(5). doi: [10.1101/lm.1778010](https://doi.org/10.1101/lm.1778010).
  114. Gupta RR, Sen S, Diepenhorst LL, Rudick CN, Maren S. Estrogen modulates sexually dimorphic contextual fear conditioning and hippocampal long-term potentiation (LTP) in rats. *Brain Research*. 2001;888(2). doi: [10.1016/s0006-8993\(00\)03116-4](https://doi.org/10.1016/s0006-8993(00)03116-4).
  115. Park CHJ, Ganella DE, Kim JH. A dissociation between renewal and contextual fear conditioning in juvenile rats. *Developmental Psychobiology*. 2017;59(4). doi: [10.1002/dev.21516](https://doi.org/10.1002/dev.21516).
  116. Wiltgen BJ, Sanders MJ, Behne NS, Fanselow MS. Sex differences, context preexposure, and the immediate shock deficit in Pavlovian context conditioning with mice. *Behavioral Neuroscience*. 2001;115(1). doi: [10.1037/0735-7044.115.1.26](https://doi.org/10.1037/0735-7044.115.1.26).
  117. Perry CJ, Ganella DE, Nguyen LD, Du X, Drummond KD, Whittle S, et al. Assessment of conditioned fear extinction in male and female adolescent rats. *Psychoneuroendocrinology*. 2020;116. doi: [10.1016/j.psyneuen.2020.104670](https://doi.org/10.1016/j.psyneuen.2020.104670).
  118. Gerstein H, O'Riordan K, Osting S, Schwarz M, Burger C. Rescue of synaptic plasticity and spatial learning deficits in the hippocampus of Homer1 knockout mice by recombinant Adeno-associated viral gene delivery of Homer1c. *Neurobiology of Learning and Memory*. 2012;97(1). doi: [10.1016/j.nlm.2011.08.009](https://doi.org/10.1016/j.nlm.2011.08.009).
  119. Inda MC, Muravieva EV, Alberini CM. Memory Retrieval and the Passage of Time: From Reconsolidation and Strengthening to Extinction. *Journal of Neuroscience*. 2011;31(5). doi: [10.1523/jneurosci.4736-10.2011](https://doi.org/10.1523/jneurosci.4736-10.2011).

## Copyright and License

Copyright © 2021. Shawn Zheng Kai Tan, Jee Hyun Kim. Except where otherwise noted, the content of this article is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/). You are free to reuse or adapt this article for any purpose, provided appropriate acknowledgement is provided. For additional permissions, please contact the corresponding author.