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Review

The endocannabinoid system: An emotional buffer in the modulation of memory function

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ABSTRACT

Extensive evidence indicates that endocannabinoids modulate cognitive processes in animal models and human subjects. However, the results of endocannabinoid system manipulations on cognition have been contradictory. As for anxiety behavior, a duality has indeed emerged with regard to cannabinoid effects on memory for emotional experiences. Here we summarize findings describing cannabinoid effects on memory acquisition, consolidation, retrieval and extinction. Additionally, we review findings showing how the endocannabinoid system modulates memory function differentially, depending on the level of stress and arousal associated with the experimental context. Based on the evidence reviewed here, we propose that the endocannabinoid system is an emotional buffer that moderates the effects of environmental context and stress on cognitive processes.

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1. Introduction

Emerging evidence indicates that cannabinoid drugs can induce distinct and often opposite effects on anxiety, cognition, and several other behaviors, depending on stress level and the aversiveness of the context (Campolongo et al., 2012; Haller et al., 2009; Szuster, Pontius, & Campos, 1988; Zanettini et al., 2011). Although cannabinoid signaling has been demonstrated to influence memory processing (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Marsicano et al., 2002), it is difficult to define its exact role because, regardless of the pharmacodynamic properties of the drug, both impairing and enhancing effects have been reported with cannabinoid drug administration. Although such discrepancies are not unusual in memory research, the factors contributing to these conflicting findings remain poorly understood.

In this review, we begin with a summary of the differing memory modulatory effects of endocannabinoids reported in the literature. We then discuss in detail the biphasic/opposite effects induced by cannabinoid drugs, including evidence that such effects may be strongly dependent on the aversiveness of environmental context and on the level of stress at the time of drug administration and/or training. Finally, with the ultimate aim of developing an explanation of the apparent discrepancies among studies of cannabinoid effects on memory function, we propose hypotheses to explain the observed dual/opposing effects of cannabinoids on emotional memory functions.

2. The endocannabinoid system

The discovery of the main psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), led to the identification of the endogenous endocannabinoid system (Gaoni & Mechoulam, 1964). The endocannabinoid system is a lipid signaling system in the brain that begins to exhibit functional activity early in brain development by way of modulating neurotransmitter release, pre- and post-natally (Campolongo, Trezza, Palmery, Trabace, & Cuomo, 2009; Campolongo, Trezza, Ratano, Palmery, & Cuomo, 2011; Fernandez-Ruiz, Berrendero, Hernandez, & Ramos, 2000; Fride, 2004; Harkany et al., 2007; Trezza et al., 2008, 2012). Although many molecular targets of the endocannabinoid system have been described, the primary targets of cannabinoid compounds are the type 1 and type 2 cannabinoid receptors (CB1 and CB2, respectively) (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Herkenham et al., 1990; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990).

The two major endogenous ligands for the CB1 and CB2 receptors are *N*-arachidonoyl ethanolamine (anandamide, AEA) (Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG) (Sugiura et al., 1995). AEA acts as a partial agonist of CB1 and CB2 receptors (Pertwee, 2010), whereas 2-AG is full agonist of these receptors (Stella, Schweitzer, & Piomelli, 1997). Unlike classical neurotransmitters,

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endocannabinoids are not stored in presynaptic vesicles, but rather are synthesized postsynaptically from lipid membrane precursor molecules in an activity-dependent manner (Kano, Ohno-Shosaku, Hashimotodani, Uchigashima, & Watanabe, 2009). Once released from the postsynaptic membrane into the synaptic cleft, they travel backward to bind cannabinoid receptors expressed on presynaptic terminals. Activation of CB1 receptors inhibits neurotransmitter release by modulating several ion channels and kinases (Kano et al., 2009; Turu & Hunyady, 2010). Following receptor activation, AEA and 2-AG are deactivated by a still poorly defined uptake process involving a transporter mechanism (Fu et al., 2011; Hillard, Edgemond, Jarrahian, & Campbell, 1997). Subsequently, they are metabolized mainly by their respective degradative enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Kano et al., 2009).

CB1 receptors represent the most abundant class of G-protein-coupled receptors in the central nervous system, and are also present in a variety of peripheral tissues. They couple with both G_i and G_o proteins, which inhibit adenylyl cyclase activity, activate potassium channels, and inhibit voltage-gated calcium channels (Howlett et al., 2002). CB1 receptors are expressed abundantly in major structures of the limbic system, including the hippocampus and basolateral complex of the amygdala (BLA), as well as in the prefrontal cortex (PFC), which is closely linked with limbic structures (McPartland, Glass, & Pertwee, 2007); low levels of CB1 mRNA have also been detected in the central nucleus of the amygdala (CeA) (Kamprath et al., 2010; Marsicano & Lutz, 1999; Matsuda, Bonner, & Lolait, 1993). Within these limbic regions, the CB1 receptor is expressed at very high levels in cholecystokinin-positive GABAergic interneurons (Azad et al., 2008; Marsicano & Lutz, 1999; Morozov, Torii, & Rakic, 2009) and at moderate levels in glutamatergic terminals (Kano et al., 2009; Kawamura et al., 2006; Monory et al., 2006). The CB1 receptor has also been detected on serotonergic, noradrenergic, and dopaminergic terminals (Haring, Marsicano, Lutz, & Monory, 2007; Hermann, Marsicano, & Lutz, 2002; Oropeza, Mackie, & Van Bockstaele, 2007).

The CB2 receptor is a $G_{i/o}$ protein-coupled receptor (Howlett et al., 2002). CB2 receptors are located mostly in the periphery on immunological tissues. They were confirmed only recently by immunohistochemical analyses to be expressed by neurons and glia in diverse rat brain areas, including the cerebellum and hippocampus (Onaivi et al., 2006; Van Sickle et al., 2005).

Studies examining the functions of endocannabinoid signaling in the limbic system have shown that CB1 receptors play a key role in modulating synaptic transmission (Katona et al., 2001; Tan et al., 2011) and neuronal firing (Pistis et al., 2004). Furthermore, growing evidence indicates that endocannabinoids play a key role in modulating emotional memory processes (Atsak, Roozendaal, & Campolongo, 2012; Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Ganon-Elazar & Akirav, 2009; Marsicano & Lafenetre, 2009; Marsicano et al., 2002; Tan et al., 2011; Wotjak, 2005). In the succeeding sections, we provide a review of findings from studies that examined cannabinoid effects on emotional memory function, focusing especially on the functional relationship between endocannabinoids and glucocorticoids in modulating cognitive processes. Subsequently, we discuss how stress and arousal state may modulate endocannabinoid effects on memory.

3. Modulation of memory for emotional experiences

Emotional learning is extremely important for the survival of an individual; indeed life events of positive and negative valence typically leave lasting and vivid memories due to arousal and stress hormone effects on memory consolidation (McGaugh, 2000). Emotionality describes a highly complex repertoire of behaviors triggered by various environmental stimuli. The regulation of emotional responses under different environmental conditions is essential for mental health and requires fine-tuned neurotransmitter release processes as well as functional neuronal circuits (Gold, 2004; McEwen, 2012; McGaugh, 2000). During emotionally arousing situations, stress hormones are released from the adrenal medulla (epinephrine) and cortex (corticosterone [CORT] in rats, cortisol in humans) into the bloodstream. These systemic stress hormones stimulate the vagus nerve in the periphery, thereby activating the nucleus of tractus solitarius (NTS) in the brainstem, which releases memory modulatory norepinephrine into limbic brain structures (McGaugh & Roozendaal, 2002).

Additionally, glucocorticoid hormones, which are highly lipophilic, readily enter the brain where they bind mineralocorticoid receptors (MRs) with high affinity and glucocorticoid receptors (GRs) with low affinity. Thus, under basal conditions, only MRs are occupied, but during and immediately after a stressful experience, both MRs and GRs are bound by glucocorticoids (Reul & de Kloet, 1985). Extensive evidence indicates that stress hormones, in concert with several other stress-activated systems, mediate the selective enhancement of consolidation of memory for emotionally significant experiences (de Kloet, Oitzl, & Joels, 1999; Joels & Baram, 2009; Oitzl & de Kloet, 1992; Roozendaal, 2000; Sandi & Rose, 1994). Conversely, glucocorticoids typically impair memory retrieval and working memory during emotionally arousing test situations (de Quervain, Aerni, Schelling, & Roozendaal, 2009; de Quervain, Roozendaal, & McGaugh, 1998; Roozendaal, 2000; Roozendaal, de Quervain, Schelling, & McGaugh, 2004).

The neural circuitry underlying emotionality is considerably complex, but broadly consists of subcortical limbic structures, such as the amygdala, hippocampus, ventral striatum, and thalamus, as well as cortical structures, including the anterior cingulate cortex and medial and orbital regions of the PFC (Price & Drevets, 2010). This corticolimbic circuit interacts with visceral autonomic centers in the hypothalamus and brain stem to regulate emotional expression and to modulate the activity of the hypothalamic–pituitary–adrenal (HPA) axis (Price & Drevets, 2010). In this assembly, the amygdala represents a key region for the association of environmental information with emotional significance. Although the acquisition of emotional salience by external stimuli has been studied most extensively in relation to fear and anxiety responses, the amygdala has also been shown to be important for the processing of positive emotions, such as in stimulus-reward learning (Aggleton, 1993; Baxter & Murray, 2002; Davis, Rainnie, & Cassell, 1994; Pape & Pare, 2010).

In particular, considerable evidence indicates not only that stressors increase neuronal activity in the BLA (Pelletier, Likhtik, Filali, & Pare, 2005), but also that emotional memory modulation requires activation of the BLA specifically. For example, lesions of the BLA, but not the CeA, block the memory enhancing effects of systemic GR activation on inhibitory avoidance retention (Roozendaal & McGaugh, 1996). Furthermore, posttraining infusion of norepinephrine or a β-adrenoceptor agonist into the BLA enhances memory of training on several learning tasks (Ferry & McGaugh, 1999; Hatfield, Spanis, & McGaugh, 1999; LaLumiere, Buen, & McGaugh, 2003; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008). In contrast, attenuation of noradrenergic signaling by infusion of a β-adrenoceptor antagonist (propranolol or atenolol) into the BLA, but not into the neighboring CeA, has been shown to block the memory enhancement induced by systemic or intra-BLA administration of a GR agonist (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal, Quirarte, & McGaugh, 2002). Considerable evidence developed in rodent studies indicates that glucocorticoid-induced enhancement of memory consolidation depends upon an interaction with noradrenergic activation within the BLA (Roozendaal, McEwen, & Chattarji, 2009). Importantly, a

recent clinical study corroborated this model by showing that the amygdala is also an important locus of glucocorticoid–norepinephrine interactions in the enhancement of memory for emotionally salient information in humans (van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010). Indeed, a convergence of five decades of research now points to the amygdala, especially the BLA, as a critical structure in the acquisition and retention of lasting memories of emotional experiences (McGaugh, 2000; Roozendaal et al., 2009).

4. Cannabinoid modulation of memory for emotional experiences

Recent evidence suggests that endocannabinoid signaling may be a key system in the regulation of synaptic efficacy within and between amygdaloid subnuclei (Ramikie & Patel, 2012). Notably, glucocorticoids regulate the endocannabinoid response, which in turn, modulates glucocorticoid secretion through both local and distal regulation of HPA axis activity (Hill & McEwen, 2010; Hill, Patel, et al., 2010; Steiner & Wotjak, 2008). Indeed, endocannabinoid activity is necessary for some central effects of glucocorticoids (Barna, Zelena, Arszovszki, & Ledent, 2004; Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Weidenfeld, Feldman, & Mechoulam, 1994).

It has been demonstrated that an increase in glucocorticoid levels leads to a concomitant increase in endocannabinoid levels in the hypothalamus (Di, Malcher-Lopes, Halmos, & Tasker, 2003). Endocannabinoids then act retrogradely to inhibit glutamate release in the paraventricular nucleus and suppress HPA axis activity (Di, Malcher-Lopes, Marcheselli, Bazan, & Tasker, 2005; Di et al., 2003). Conversely, endocannabinoid content in limbic brain regions, which can augment or terminate stress responses, can itself be modulated by stress or exogenous glucocorticoid administration (Hill & McEwen, 2010). Additionally, Morrish and colleagues found that the endocannabinoid system mediates stress responses and emotional homeostasis by targeting noradrenergic circuits (Morrish, Hill, Riebe, & Gorzalka, 2009).

The supposition that the endocannabinoid system may mediate a noradregeneric-modulatory role is supported by anatomic and physiological evidence. Autoradiography and immunohistochemistry experiments have demonstrated moderate CB1 receptor expression in the principal noradrenergic nuclei, namely the locus coeruleus (LC) and the NTS, and reverse transcription polymerase chain reaction experiments have confirmed local CB1 transcription in these regions (Derbenev, Stuart, & Smith, 2004; Herkenham et al., 1991; Jelsing, Larsen, & Vrang, 2008; Mailleux & Vanderhaeghen, 1992; Matsuda et al., 1993). Systemic administration of the synthetic cannabinoid receptor agonist WIN55,212-2 (WIN) increases noradrenergic release in the PFC (Oropeza, Page, & Van Bockstaele, 2005), and intravenous injection of WIN or Δ^9-THC, increases the firing rate of LC noradrenergic neurons in a manner that is dose dependent and can be blocked by the cannabinoid receptor antagonist rimonabant (Muntoni et al., 2006). These findings suggest a role for the cannabinoid system in at least basic brain activities regulated by norepinephrine, such as arousal and wakefulness (Berridge, Schmeichel, & Espana, 2012).

More recent evidence suggests that the cannabinoid system may also play a key role in higher level noradrenergic functions, such as regulation of emotional states and memory processes (Akirav, 2011; Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Kano et al., 2009; Marsicano & Lafenetre, 2009; Wotjak, 2005). However, the literature regarding cannabinoid effects on cognition remains contradictory. Human cannabis users have been reported to show impairments in aspects of executive functioning such as planning, working memory, and mental flexibility (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006). Cannabis abusers also show short-term memory deficits (Ranganathan & D'Souza, 2006; Riedel & Davies, 2005). However, Fisk and Montgomery (2008) found no evidence of cannabis-related deficits in executive component processes or associative learning. Moreover, the acute effects of cannabis need to be distinguished from the effects of chronic use. Acutely, cannabis has well-known psychoactive effects, can impair coordination, and may produce feelings of anxiety or paranoia. Meanwhile, chronic use of cannabis has been reported to induce mood disturbances, exacerbate psychiatric disorders in vulnerable people, impair cognition, and to increase the risk of cardiovascular and respiratory diseases (for a detailed review see Karila et al., 2013). Although new evidence continues to become available, it would be premature to draw any strong conclusions from clinical studies of cannabis users/abusers now due to the widely differing methodologies and participant selection strategies used, especially in terms of poly-drug abuse and pre-existing cognitive and emotional criteria (Ranganathan & D'Souza, 2006). Therefore, animal studies remain critical to elucidating the neural underpinnings of cannabinoid effects on cognition, particularly with respect to cannabinoid effects on memory for emotional experiences.

4.1. Cannabinoid effects on different memory phases

As will become clear, even basic research studies in this field are producing some controversial and difficult to resolve outcomes. In the following paragraphs, we summarize some basic research findings of cannabinoid effects on different phases of memory processes with the intent of disentangling which effects involve influences on particular stages of memory processing. Cannabinoid effects on memory acquisition, consolidation, retrieval, and extinction are summarized in Tables 1–4, respectively.

4.1.1. Cannabinoid effects on memory acquisition

There is general agreement about the observation that activation of the endocannabinoid system impairs memory acquisition (Table 1). Notably, systemic administration of a cannabinoid receptor agonist (i.e. Δ^9-THC or WIN) before training impairs acquisition of water maze, contextual fear, and object recognition tasks in rodents (Da & Takahashi, 2002; Lichtman, Dimen, & Martin, 1995; Pamplona & Takahashi, 2006). Similarly, indirect cannabinoid receptor agonism impairs memory acquisition in a recognition memory task (Campolongo et al., 2012) and in the inhibitory avoidance task Mazzola et al., 2009). However, as highlighted in Table 1, systemic administration of the cannabinoid receptor antagonist rimonabant has also been reported to impair acquisition in a spatial memory task (Robinson et al., 2008).

Local infusions of cannabinoid compounds within the same brain region have provided more consistent results, though comparing the results across brain areas remains difficult to explain. For example, pretraining activation of CB1 receptors in the hippocampus has consistently been shown to impair spatial learning (Abush & Akirav, 2010; Egashira, Mishima, Iwasaki, & Fujiwara, 2002; Lichtman et al., 1995; Wegener, Kuhnert, Thuns, Roese, & Koch, 2008), although pretraining blockade of CB1 receptor transmission in the BLA also impaired olfactory fear conditioning (Tan et al., 2011). Drawing conclusions from studies involving pretraining drug administration is extremely challenging given that such treatments necessarily affect diverse processes (McGaugh, 1966). Since cannabinoid compounds affect motivational and sensorimotor processes (Economidou et al., 2007; Solinas & Goldberg, 2005; Steiner, Bonner, Zimmer, Kitai, & Zimmer, 1999; Zimmer, Zimmer, Hohmann, Herkenham, & Bonner, 1999), it is difficult to discriminate between purely cognitive effects and confounding variables (e.g. alteration in pain sensitivity and/or locomotor activity and/or motivation) following pretraining cannabinoid administration.

Table 1
Cannabinoid effects on memory acquisistion in rodents.

Drug	Dose	Administration	Animals	Paradigm	Effect	References
CB1/CB2 receptor agonists						
WIN	2.5–5 mg/kg	i.p.	Wistar rats	CFC	Impairing	Pamplona and Takahashi (2006)
	1.2 mg/kg	i.p.	Sprague–Dawley rats	Object recognition	Impairing	Schneider, Schomig, and Leweke (2008)
	5 μg/side	Intra-CA1	Sprague–Dawley rats	MWM	Impairing	Abush and Akirav (2010)
Δ^9-THC	10 mg/kg	i.p.	FAAH −/−, +/+ mice	MWM	Impairing	Wise et al. (2012)
	20 μg/side	Intra-DH-VH-DMT	Wistar rats	Eight-arm radial maze	Impairing	Egashira et al. (2002)
CB1 antagonists (and inverse agonists)						
AM251	50–500 ng/side	Intra-BLA	Sprague–Dawley rats	Olfactory fear conditioning	Impairing	Tan et al. (2011)
Rimonabant	3 mg/kg	i.p	Sprague–Dawley rats	Radial arm maze	Enhancing	Lichtman (2000)
	3 mg/kg	i.p.	Lister Hooded rats	MWM	Impairing	Robinson et al. (2008)
AM281	2.5 mg/kg	i.p.	C57BL/6J mice	CFC	Enhancing	Lin et al. (2011)
	0.05 μg/rat	Intra-CA1	C57BL/6J mice	CFC	Enhancing	Lin et al. (2011)
Indirect agonists						
AM404 (AEA uptake inhibitor)	0.5–1 mg/kg	i.p.	Wistar rats	Spatial open field	Impairing	Campolongo et al. (2012)
	1 μg/rat	Intra-CA1	C57BL/6J mice	CFC	Impairing	Lin et al. (2011)
URB597 (FAAH inhibitor)	0.1–1.0 mg/kg	i.p.	Sprague–Dawley rats	IA	Impairing	Mazzola et al. (2009)
JZL195 (FAAH and MAGL inhibitor)	20 mg/kg	i.p.	FAAH −/− mice	MWM	Impairing	Wise et al. (2012)
	20 mg/kg	i.p.	FAAH +/+ mice	MWM	Impairing	Wise et al. (2012)
JZL184 (MAGL inhibitor)	20–40 mg/kg	i.p.	FAAH −/− mice	MWM	Impairing	Wise et al. (2012)
	40 mg/kg	i.p.	FAAH +/+ mice	MWM	Impairing	Wise et al. (2012)

AEA, anandamide; i.p., intraperitoneal; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; CFC, contextual fear conditioning; MWM, Morris water maze; IA, step-through inhibitory avoidance; BLA, basolateral complex of the amygdala; CeA, central amygdala; DH, dorsal hippocampus; VH, ventral hippocampus; DMT, dorsomedial thalamus nucleus.

Table 2
Cannabinoid effects on memory consolidation in rodents.

Drug	Dose	Administration	Animals	Paradigm	Effect	References
CB1/CB2 receptor agonists						
AEA	0.17 ng/side	Intra-CA1	Wistar rats	IA	Enhancing	De Oliveira Alvares et al. (2008)
HU-210	0.1 mg/kg	i.p.	Wistar rats	CFC	Impairing	Mackowiak et al. (2009)
WIN	1–3 mg/kg	i.p.	Long-Evans rats	MWM	Impairing	Yim et al. (2008)
	0.3 mg/kg	i.p.	Sprague–Dawley rats	HA-object recognition	Enhancing	Campolongo et al. (2013)
	50 ng/side	Intra-BLA	Sprague–Dawley rats	IA	Enhancing	Campolongo, Roozendaal, Trezza, Hauer, et al. (2009)
	0.1–0.25 μg/rat	Intra-CeA	Wistar rats	IA	Impairing	Zarrindast, Ghiasvand, Rezayof, and Ahmadi (2012)
	0.25–0.5 μg/rat	Intra-CA1	Wistar rats	IA	Impairing	Moshfegh, Babaei, Oryan, Soltani, and Zarrindast (2011)
	0.1–0.5 μg/rat	Intra-CA1	Wistar rats	IA	Impairing	Nasehi, Sahebgharani, Haeri-Rohani, and Zarrindast (2009)
	0.25–0.5 μg/rat	Intra-CA1	Wistar rats	IA	Impairing	Jamali-Raeufy et al. (2011)
	10 nmol/side	Intra-CA1	Wistar rats	Object recognition	Impairing	Clarke et al. (2008)
CB1 antagonists (and inverse agonists)						
AM251	0.28 ng/side	Intra-BLA	Sprague–Dawley rats	IA	Impairing	Campolongo, Roozendaal, Trezza, Hauer, et al. (2009)
	0.28 ng/side	Intra-BLA	Wistar rats	CFC	Impairing	Bucherelli, Baldi, Mariottini, Passani, and Blandina (2006)
	5.5 ng/side	Intra-CA1	Wistar rats	IA	Impairing	de Oliveira Alvares et al. (2005)
Rimonabant	1 mg/kg	i.p.	Sprague–Dawley rats	Eight-arm radial maze	Enhancing	Wolff and Leander (2003)
	1 mg/kg	i.p.	Swiss albino mice	Elevated T-maze	Enhancing	Takahashi, Pamplona, and Fernandes (2005)
CE	0.1 mg/kg	i.p.	Sprague–Dawley rats	Radial-arm maze	Enhancing	Wise et al. (2008)
Indirect agonist						
URB597 (FAAH inhibitor)	0.3–1 mg/kg	i.p.	Swiss albino mice	Object recognition	Impairing	Busquets-Garcia et al. (2011)
	1 mg/kg	i.p.	Swiss albino mice	Context recognition	Impairing	Busquets-Garcia et al. (2011)

AEA, anandamide; i.p., intraperitoneal; FAAH, fatty acid amide hydrolase; CFC, contextual fear conditioning; MWM, Morris water maze; IA, step-through inhibitory avoidance; HA, high arousal; BLA, basolateral complex of the amygdala; CeA, central amygdala.

Table 3
Cannabinoid effects on memory retrieval in rodents.

Drug	Dose	Administration	Animals	Paradigm	Effect	References
CB1/CB2 receptor agonists						
WIN	0.3 mg/kg	i.p.	Sprague–Dawley rats	HA-object recognition	Impairing	Campolongo et al. (2013)
	0.3 mg/kg	i.p.	Sprague–Dawley rats	LA-object recognition	Enhancing	Campolongo et al. (2013)
	10–30 ng/side	Intra-CA1	Sprague–Dawley rats	CFC	Impairing	Atsak, Hauer, et al. (2012)
	0.25–0.5 μg/rat	Intra-CA1	Wistar rats	IA	Impairing	Piri and Zarrindast (2011)
	5 μg/side	Intra-VSub	Sprague–Dawley rats	CFC	Impairing	Segev and Akirav (2011)
Δ^9-THC	5.6 mg/kg	i.p	Sprague–Dawley rats	Radial arm maze	Impairing	Wise, Thorpe, and Lichtman (2009)
	6 mg/kg	i.p.	Wistar rats	Eight-arm radial maze	Impairing	Mishima et al. (2001)
	10 mg/kg	i.p.	C57BL/6J mice	MWM	Impairing	Niyuhire, Varvel, et al. (2007)
	10 mg/kg	i.p.	Wistar rats	IA	Impairing	Mishima et al. (2001)

I.p., intraperitoneal; CFC, contextual fear conditioning; MWM, Morris water maze; IA, step-through inhibitory avoidance; VSub, ventral subiculum; HA, highly arousal; LA, low arousal.

Table 4
Cannabinoid effects on memory extinction in rodents.

Drug	Dose	Administration	Animals	Paradigm	Effect	References
CB1/CB2 receptor agonists						
WIN	0.25 mg/kg	i.p.	Wistar rats	CFC	Enhancing	Pamplona et al. (2006)
	5 μg/side	Intra-CA1	Sprague–Dawley rats	IA	Enhancing	Abush and Akirav (2010)
CB1 antagonists (and inverse agonists)						
Rimonabant	1.5–5 mg/kg	i.p	Sprague–Dawley rats	FPS	Impairing	Chhatwal et al. (2005)
	3 mg/kg	i.p.	C57BL/6J mice	Auditory fear conditioning	Impairing	Marsicano et al. (2002)
	3–10 mg/kg	i.p.	C57BL/6J mice	CFC	Impairing	Suzuki et al. (2004)
	3 mg/kg	i.p.	C57BL/6J mice	MWM	Impairing	Varvel et al. (2005)
	3 mg/kg	i.p.	C57BL/6J mice	IA	Impairing	Niyuhire, Varvel, Thorpe, et al. (2007)
Indirect agonists						
AM404 (AEA uptake inhibitor)	10 mg/kg	i.p	Sprague–Dawley rats	FPS	Enhancing	Chhatwal et al. (2005)
	1 μg/rat	i.c.v.	Wistar rats	CFC	Enhancing	Bitencourt, Pamplona, and Takahashi (2008)
OL-135 (FAAH inhibitor)	30 mg/kg	i.p.	C57BL/6J mice	MWM	Enhancing	Varvel et al. (2007)

I.p., intraperitoneal; i.c.v., intracerebroventricular; FAAH, fatty acid amide hydrolase; CFC, contextual fear conditioning; MWM, Morris water maze; IA, step-through inhibitory avoidance; FPS, fear-potentiaed startle.

Therefore, it remains to be resolved whether cannabinoids affect cognition *per se* during learning rather than other non-specific factors.

4.1.2. Cannabinoid effects on memory consolidation

Conflicting data have been reported regarding cannabinoid effects on memory consolidation (Table 2). Drugs can be administered after a learning event to isolate the consolidation phase of memory and exclude influences on acquisition or any sensory, motor, or motivational processes that may influence learning indirectly (McGaugh, 1966). Systemic posttraining administration of cannabinoid receptor agonists impairs memory consolidation (Mackowiak, Chocyk, Dudys, & Wedzony, 2009; Yim, Hong, Ejaredar, McKenna, & McDonald, 2008), while systemic posttraining injection of cannabinoid receptor antagonists improves it (Wise, Iredale, & Lichtman, 2008; Wolff & Leander, 2003). However, there are concerns related to non-specificity in experiments using systemic agonist manipulations. Drugs that inhibit endocannabinoid degradation can be employed to avoid such potentially confounding effects. For example, when Busquets-Garcia and colleagues tested the effects of systemic posttraining administration of the FAAH inhibitor URB597, which increases AEA levels only in those brain regions where it is released endogenously, they observed impaired memory consolidation in an object recognition task (Busquets-Garcia et al., 2011).

Conflicting data have been reported concerning the effects on memory consolidation of infusing cannabinoid drugs locally into discrete brain regions. Posttraining intra-hippocampal administration of the synthetic cannabinoid receptor agonist WIN (0.25–10 μg/rat) has been reported to impair memory consolidation of several behavioral tasks (i.e. step-through inhibitory avoidance, Morris water maze) (Jamali-Raeufy, Nasehi, & Zarrindast, 2011; Yim et al., 2008; Zarrindast, Navaeian, & Nasehi, 2011). However, other authors reported enhancing effects of AEA in the hippocampus (0.17 ng/side) (De Oliveira Alvares, Genro, Diehl, & Quillfeldt, 2008) and of WIN in the BLA (50 ng/side) (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009). Moreover, cannabinoid receptor antagonists have been found to yield memory impairing effects similar to those induced by cannabinoid receptor agonists described above (Jamali-Raeufy et al., 2011; Yim et al., 2008; Zarrindast et al., 2011). In particular, it has been shown that intra-hippocampal (de Oliveira Alvares et al., 2005) administration of the CB1 receptor antagonist AM251 impairs memory consolidation in an aversive hippocampus-dependent task (de Oliveira Alvares et al., 2005). Differences in handling procedures, experimental conditions, behavioral tasks, doses, and the drug administered may account for the diversity of findings reported (Table 2). Indeed WIN is less selective than the endogenous ligand AEA (Howlett et al., 2002) and, when administered at high doses in discrete brain regions, could induce broader effects, complicating interpretation. However, there are other intriguing possibilities that should be

explored. In particular, given the robust effects of glucocorticoids, norepinephrine, and other neurotransmitters including acetylcholine and dopamine in limbic structures on memory consolidation (McGaugh, 2000), it could be that factors related to arousal, stress, and emotional state at the time of training may influence cannabinoid effects on memory. This issue is discussed further in Section 5.

4.1.3. Cannabinoid effects on memory retrieval

Although the literature related to cannabinoid effects on retrieval is fairly limited, no controversy exists with regards to cannabinoid effects on memory retrieval (Table 3). Detrimental effects of cannabinoid receptor agonism on memory retrieval have been documented when administered either systemically (Mishima et al., 2001; Niyuhire, Varvel, Martin, & Lichtman, 2007) or in discrete brain areas (Atsak, Hauer, et al., 2012; Piri & Zarrindast, 2011; Segev & Akirav, 2011). In particular, it has been demonstrated that systemic administration of Δ^9-THC impairs memory retrieval in a Morris water maze task (Niyuhire, Varvel, et al., 2007) and a step-through inhibitory avoidance task (Mishima et al., 2001). In line with these findings, cannabinoid agonists infused directly into the hippocampus impair aversive memory retrieval (Atsak, Hauer, et al., 2012; Piri & Zarrindast, 2011; Segev & Akirav, 2011). Interestingly, intra-BLA infusions of the same drugs did not affect memory retrieval (Segev & Akirav, 2011). Taken together, the preclinical evidence reported above, although still sparse, suggests that cannabinoids induce impairing effects on memory retrieval, at least under the experimental conditions investigated thus far (Table 3).

4.1.4. Cannabinoid effects on memory extinction

There is a strong consensus in the memory extinction literature that the endocannabinoid system is a key modulator in the facilitation of memory extinction (Table 4). Inhibition of endocannabinoid transmission robustly inhibits extinction of fear conditioning (Marsicano et al., 2002; Pamplona, Prediger, Pandolfo, & Takahashi, 2006; Suzuki et al., 2004). Conversely, stimulation of endocannabinoid signaling accelerates fear extinction (Barad, Gean, & Lutz, 2006; Chhatwal, Davis, Maguschak, & Ressler, 2005; Pamplona et al., 2006; Suzuki et al., 2004). Similarly, in a Morris water maze task, Varvel, Anum, Niyuhire, Wise, and Lichtman (2005), Varvel, Wise, Niyuhire, Cravatt, and Lichtman (2007) found that the inverse CB1 receptor agonist rimonabant or genetic CB1 receptor disruption impaired extinction, whereas Δ^9-THC did not affect extinction (Varvel, Anum, Niyuhire, Wise, & Lichtman, 2005; Varvel, Wise, Niyuhire, Cravatt, & Lichtman, 2007). Interestingly, Niyuhire, Varvel, Thorpe, et al. (2007) reported that rimonabant administration disrupted extinction significantly in two different aversively motivated behavioral tasks (e.g., conditioned freezing and inhibitory avoidance) but failed to affect extinction in an appetitively motivated operant conditioning task (Niyuhire, Varvel, Thorpe, et al., 2007). Thus, the evidence obtained to date suggests that activation of the cannabinoid system facilitates aversive memory extinction.

5. Role of emotional arousal in influencing cannabinoid effects on memory

Discrepant findings have been reported concerning the role of the endocannabinoid system in the modulation of cognitive processes, especially with regard to memory acquisition and consolidation. Such reports are very reminiscent of the dual effects on emotionality reported by cannabis users. That is, although cannabis consumption is commonly associated with euphoria and contentment (Velez & Ungemack, 1989), some people report experiencing anxiety, dysphoria, and a depressive mood with cannabis consumption (Reilly, Didcott, Swift, & Hall, 1998). Clinical studies have indicated that the context of cannabinoid consumption—that is, the nature of both one's physical state and social setting—has a direct influence on emotionality (Del Porto & Masur, 1984; Zinberg, 1984). Biphasic effects of cannabinoid consumption on anxiety-related behavior have also been reported in preclinical studies (for a detailed review see Micale, Di Marzo, Sulcova, Wotjak, & Drago, 2013). The indirect cannabinoid receptor agonists URB597 and AM404, which increase AEA levels in the synaptic cleft, have been reported to exert both anxiolytic- and antidepressant-like effects in rodents (Bortolato et al., 2006; Gobbi et al., 2005; Kathuria et al., 2003). Haller et al. (2009) showed that URB597 does not reduce anxiety when a behavioral task (i.e. elevated plus maze) is performed under mildly aversive conditions (e.g., in a familiar room or under low light) (Haller et al., 2009). Sciolino, Zhou, and Hohmann (2011) found that an increase in 2-AG levels, induced by administration of the MAGL inhibitor JZL184, induced an anxiolytic-like effect in the same behavioral task under highly aversive conditions (i.e. bright light), but had no detectable effect on anxiety under low-stress conditions (Sciolino et al., 2011). Likewise, Campos, Ferreira, Guimaraes, and Lemos (2010) reported that the cannabinoid uptake inhibitor AM404 was anxiolytic in the elevated plus maze test in rats previously exposed to a 2-h restraint stress, but anxiogenic in rats that were not previously stressed (Campos et al., 2010). Thus, it may be that stress conditions during the test, as well as housing and handling procedures prior to the test, influence cannabinoid effects on emotionality. A similar scenario is now emerging with regards to cannabinoid effects on memory. In the following sections, we describe evidence demonstrating how cannabinoid effects on memory may depend on the level of stress associated with an experimental context (i.e. footshock intensity in the inhibitory avoidance task), previous stress experiences completely unrelated to the task, and/or a combination of these two factors.

5.1. Context-induced stress shapes cannabinoid modulation of memory

The cannabinoid system may have a particularly important role in the control of neuronal responses to environmental challenges. This notion is consistent with the observation that CB1 receptors are expressed abundantly in limbic structures (Herkenham et al., 1991; Tsou, Brown, Sanudo-Pena, Mackie, & Walker, 1998). It is possible to speculate that the endocannabinoid system may shape how environmental stimuli affect emotional responses, rather than producing an overall aspecific effect on memory. This putative context-dependence may help to explain apparently conflicting data obtained with different training and drug administration paradigms.

To investigate the importance of emotionality in cannabinoid effects on memory function, we compared the effects of cannabinoid receptor activation on novel object recognition in high arousal (HA) vs. low-arousal (LA) conditions. Briefly, in the HA condition, the rats were not handled and the task was performed under bright light in an empty arena. In the LA condition, the rats were habituated to the experimenter through daily handling (1 min per day for 1 week) and the task was performed under dim red light in an arena in which the ground was covered with familiar bedding. Animals were administered with the endocannabinoid transport inhibitor AM404 30 min before commencing the novel object recognition task. The behavioral paradigm consisted of six consecutive 5-min sessions, separated by 3-min intervals, wherein one familiar object was replaced with a new object in the last session, which served as the test trial. We found that exogenous enhancement of endocannabinoid signaling impaired novel object recognition in rats tested in the HA condition, but had no effect in rats tested in the LA condition (Campolongo et al., 2012). This study demonstrated for the first time that acute effects of cannabinoid agonism

on memory function are influenced by the stress state of the subject. Because this experiment employed a pretraining drug administration, we cannot exclude the possibility that the memory performance effect observed could have been due, even in part, to confounding variables associated with a pretraining manipulation.

In a subsequent study, we employed a previously validated, modified version of the object recognition task that enabled us to administer the drug immediately after training to isolate the effect of the drug on memory consolidation. We followed a previously described procedure to induce two different levels of arousal during the object recognition task (Okuda, Roozendaal, & McGaugh, 2004). One group of rats received extensive prior habituation to the training apparatus (in the absence of any objects), while a second group was not exposed to the experimental apparatus until training. Animals were injected with the cannabinoid receptor agonist WIN immediately after a single 3-min training trial and then tested for memory retention 1 h or 24 h later. As shown in Fig. 1A and B, WIN, administered immediately after object recognition training, impaired short-term (1-h) retention performance in rats not habituated to the experimental context. The same dose of WIN enhanced short-term memory in rats that had been habituated to the experimental context (Campolongo et al., 2013). Meanwhile, WIN enhanced long-term (24-h) retention in non-habituated rats, but had no effect on long-term memory in habituated rats (Fig. 1C and D). This experience-dependent cannabinoid effect on memory is highly comparable to the glucocorticoid effects described by Okuda et al. (2004), Roozendaal, Hui, et al. (2006) and Roozendaal, Okuda, Van der Zee, and McGaugh (2006). That is, glucocorticoid compounds administered after object recognition training enhanced memory consolidation in non-habituated rats (a relatively higher stress condition) but not in habituated rats (a relatively lower stress condition (Okuda et al., 2004; Roozendaal, Okuda, et al., 2006). Moreover, posttraining exposure to an out-of-context stressor (i.e. elevated platform) after object recognition training has been reported to enhance long-term memory only in rats not previously habituated to the experimental apparatus (Maroun & Akirav, 2008).

Given the close relationship between the cannabinoid system and HPA axis activity (Armario, 2010; Atsak, Hauer, et al., 2012; Barna et al., 2004; Hill, Karatsoreos, Hillard, & McEwen, 2010; Hill & McEwen, 2010), we proceeded to explore the possibility that the conditionally divergent effects of systemic WIN on object recognition memory could be related to differential effects of WIN on training-induced glucocorticoid levels. We found that WIN elevated plasma CORT levels in non-habituated rats, but decreased

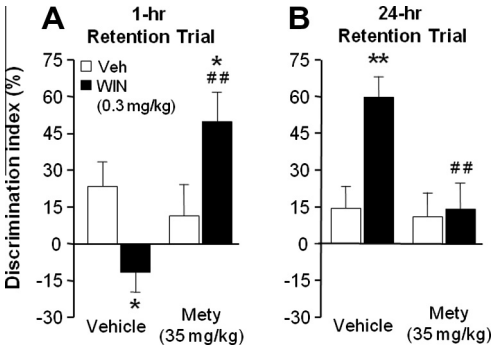

Fig. 2. Effects of the CB receptor agonist WIN on short- and long-term retention of object recognition in rats trained under HA conditions and pretreated with the CORT synthesis inhibitor metyrapone (Mety). Metyrapone (35 mg/kg, i.p.) administered to non-habituated rats 40 min before training reverted the impairing effect of posttraining WIN (0.3 mg/kg, i.p.) on 1-h retention performance (A) and the enhancing effect of WIN (0.3 mg/kg, i.p.) on 24-h retention performance (B) in such a way that their performances became similar to that seen in habituated animals (compare to Fig. 1). Data are expressed as means ± SEM. $^{*}p < 0.05$; $^{**}p < 0.01$ vs. the corresponding vehicle group; $^{\#\#}P < .01$ vs. WIN alone group. Adapted from Campolongo et al. (2013).

CORT levels in habituated rats. Most importantly, as shown in Fig. 2, we demonstrated that adrenocortical suppression with the CORT-synthesis inhibitor metyrapone altered the effects of posttraining WIN administration on non-habituated rats' short- and long-term recognition memory in such a way that their cognitive performance became similar to that seen in habituated animals (Campolongo et al., 2013). Thus, our findings suggest that differential effects of cannabinoid receptor agonism on memory may be related to the ability of cannabinoids to interact with the HPA axis, depending on the stress state of the animal in relation to the aversiveness of the environmental conditions. A WIN-induced increase in CORT levels likely affected short-term memory performance (1-h test) in the HA condition by influencing retrieval. In the long-term memory experiment (24-h test), however, increased CORT levels could only have influenced consolidation. Since habituation attenuates training-induced surges in noradrenergic activity, glucocorticoids might not modulate recognition memory in habituated rats due to their relatively low levels of norepinephrine (Roozendaal, Okuda, et al., 2006). Together, these aforementioned findings provide strong support for the view that cannabinoid-mediated regulation of glucocorticoid secretion may play an important role in determining the pattern of cannabinoid effects on memory.

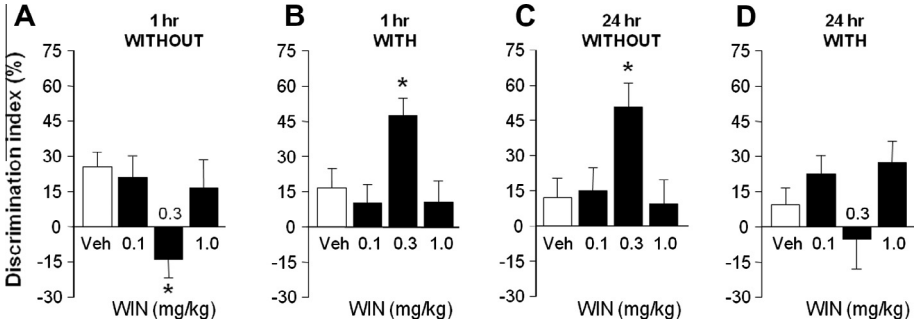

Fig. 1. Effects of the CB receptor agonist WIN on short- and long-term retention of object recognition training are influenced by the level of training-associated emotional arousal. Rats were either habituated for 7 days (WITH) or not habituated (WITHOUT) to the training context. On day 8, they were given a 3-min training trial during which they could freely explore two identical objects, training was followed by a systemic administration of WIN (0.1, 0.3 or 1 mg/kg, i.p.). Retention was tested 1 h or 24 h later. Data represent discrimination index (%) at the retention trial, expressed as mean ± SEM. The discrimination index was calculated as the difference in the time spent exploring the novel and the familiar object, expressed as a ratio of the total time spent exploring both objects. Posttraining WIN impaired 1-h object recognition performance of non-habituated rats (A) but enhanced performance of habituated rats (B). In contrast, posttraining administration of WIN, at a dose that impaired 1-h retention, enhanced 24-h object recognition performance of non-habituated rats (C) but not of habituated rats (D). $^{*}p < .05$ vs. vehicle. Adapted from Campolongo et al. (2013).

Although the administration of direct cannabinoid receptor agonists mimics cannabis consumption, the use of indirect agonists or antagonists can provide more focal specificity and may be particularly useful for elucidating the physiological role of the endogenous "on-demand" endocannabinoid system. Indeed, de Oliveira Alvares et al. (2010) reported that the hippocampal endocannabinoid system is recruited to enhance memory consolidation of contextual fear conditioning only under HA conditions. Specifically, they found that blockade of cannabinoid receptors induced by immediate posttraining infusion of the cannabinoid receptor antagonist AM251 into the dorsal hippocampus impaired 24-h memory retention of conditioning with a 0.7-mA footshock, but did not affect memory when a less aversive 0.3 mA footshock was used (de Oliveira Alvares et al., 2010). Hence, the hippocampal endocannabinoid system may modulate memory consolidation only when there is some threshold level of aversiveness involved. Intriguingly however, Jacob, Marsch, Marsicano, Lutz, and Wotjak (2012) reported that CB1 knockout mice required a higher intensity footshock than wild-type mice to exhibit enhanced fear conditioning memory and generalized contextual fear (Jacob et al., 2012). However, with mice lacking CB1 receptors, it is not possible to discriminate which memory phase has been affected. Furthermore when a receptor is genetically deleted, other compensatory mechanisms may occur (Fraser & Wahlestedt, 1997; Giros, Jaber, Jones, Wightman, & Caron, 1996).

Interestingly, clinical research has shown that the nature of the social setting in which a drug is taken has a direct influence on the probability of particular drug effects occurring (Porto & Masur, 1984; Zinberg, 1984). Researchers have also found that past experiences dictate the content and structure of future drug-taking experiences (Smith, 1978) and that cannabinoid drugs modulate memory for emotionally arousing experiences preferentially, without modulating memory for mundane experiences (Ballard, Bedi, & de Wit, 2012).

Together, the preclinical and clinical findings reviewed above indicate that some degree of training-associated arousal or stress is required for glucocorticoids to affect memory consolidation and that endocannabinoids may act as a buffer system in this regard. This interaction between stress hormones and the cannabinoid system provides support for the notion that differential sensitivity to cannabinoids may be related to the level of activation of stress pathways (Carvalho & Van Bockstaele, 2012; Oropeza et al., 2005; Page et al., 2007; Patel & Hillard, 2003). Taken together, these findings provide evidence in support of the view that the endocannabinoid system may play a key role in mediating the effects of arousal and stress on memory.

5.2. Out-of-context stress shapes cannabinoid modulation of memory

Intra-cerebroventricular administration of a CB1 receptor antagonist has been demonstrated to activate the HPA axis (Manzanares, Corchero, & Fuentes, 1999), thus indicating a central site of action despite the presence of CB1 receptors in the pituitary and adrenal glands (Cota et al., 2007; Ziegler et al., 2010). Conversely, both stress and glucocorticoids alter endocannabinoid levels in healthy volunteers subjected to stressful conditions (Feuerecker et al., 2012), in patients with stress-related disorders (Hauer et al., 2012, 2013; Neumeister et al., 2013), and in limbic regions of CORT-injected rats (Hill & McEwen, 2010). This glucocorticoid–cannabinoid interaction may serve to maintain homeostatic balance. Collectively, these and other data (Hill & Tasker, 2012)—together with the broad expression of cannabinoid receptors in cortico-limbic and hypothalamic circuitry where they seem to dampen HPA axis activation (Gonzalez et al., 2004; Hill, Miller, Carrier, Gorzalka, & Hillard, 2009; Manzanares et al., 1999; Newsom et al., 2012; Patel, Roelke, Rademacher, Cullinan, & Hillard, 2004; Steiner et al., 2008)—suggest that the endocannabinoid system could play a critical role in mediating response to stress as well as the effects of stress on memory processes.

Few studies have investigated the effects of out-of-context and non-pharmacologically induced stress and its interaction with the endocannabinoid system in modulating cognitive functions. Ganon-Elazar and Akirav (2009) have shown that infusion of the cannabinoid receptor agonist WIN into the BLA inhibits the increase in plasma CORT in rats exposed to an elevated platform stress for 30 min. Pretraining intra-BLA infusion of WIN did not induce any effect by itself, but prevented the enhancing effects of elevated platform stress on inhibitory avoidance memory and prevented the impairment of extinction induced by pre-extinction stress exposure (Ganon-Elazar & Akirav, 2009). Likewise, in a food-reward-reduction straight-alley maze task, intra-BLA WIN (5 μg/side) infusions had no effect on memory consolidation alone, but blocked the memory enhancing effects of stress exposure (i.e. elevated platform for 30 min) (Ramot & Akirav, 2012). These findings appear, at least superficially, to be at odds with our observation that intra-BLA infusions of WIN (50 ng/side) immediately after inhibitory avoidance training enhanced memory consolidation (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009). These differential outcomes could be due to the different doses used or differences in the nature of the behavioral tasks employed. The inhibitory avoidance task is an aversive, fear-motivated task, whereas the alley-maze task has a strong reward component and the reduction of a reward has been associated with a state of frustration (Spence, 1956). Interestingly, de Oliveira Alvares et al. (2010) showed that intra-hippocampal infusions of the cannabinoid receptor antagonist AM251 reverted the stress-induced facilitatory effect on memory consolidation. In this experiment, rats were trained in a contextual fear conditioning paradigm (0.3-mA footshock intensity) and tested 24 h later. AM251 had no effect *per se* on memory consolidation, but yielded a reversion to the memory enhancing effects of a preconditioning stressor (two 0.1-mA footshocks in a different context) (de Oliveira Alvares et al., 2010). Although it is possible that preconditioning stress might have influenced task acquisition, this finding provides further evidence that stress hormones interact with endocannabinoids in enhancing memory consolidation of aversive experiences. In light of the findings of these still limited and sometimes seemingly contradictory studies, it is becoming increasingly evident how the endocannabinoid system, by modulating stress responses (and *vice versa*), could affect memory functions differently depending on the aversiveness of the experimental conditions.

6. The endocannabinoid system as an emotional buffer: a possible explanation for variable cannabinoid effects on memory

It is difficult to pinpoint the exact role exerted by cannabinoid compounds on memory function given that they can induce biphasic behavioral effects that may arise from different factors and may alter sensorimotor and motivational processes (Economidou et al., 2007; Solinas & Goldberg, 2005; Steiner et al., 1999; Zimmer et al., 1999). However, growing evidence suggests that apparently conflicting findings with cannabinoid manipulations across studies may be due, perhaps in large part, to variations in the stressfulness of experimental conditions. This evidence has led us to hypothesize that the interaction of cannabinoids with stress hormones is of crucial importance in determining their modulatory effects on memory processes.

Stress effects on both consolidation and retrieval of emotionally arousing experiences require concurrent glucocorticoid and noradrenergic activity (McGaugh & Roozendaal, 2002; Roozendaal, 2002).

Stress hormone effects on memory typically follow an inverted-U shaped (rather than linear) dose–response relationship, in which modulatory effects are seen most prominently with doses in the mid-range of the inverted-U curve (Mendl, 1999; Yerkes & Dodson, 1908). Although this stress-memory relationship seems not to apply to all cases with respect to several factors (i.e. stress duration, intensity, and timing in relation to memory phase) (Sandi & Pinelo-Nava, 2007), it is plausible that, depending on stress hormone levels, the subsequent interplay between endocannabinoids and glucocorticoids and/or norepinephrine could produce opposing effects of cannabinoids on memory performance.

Cannabinoid administration can both activate and inhibit the HPA axis (Cota et al., 2007; Ganon-Elazar & Akirav, 2009); and systemically administered CORT can produce rapid elevation of endocannabinoid levels in the amygdala (Hill, Karatsoreos, et al., 2010). Noradrenergic signaling within the BLA plays an important role in the modulation of memory for emotionally arousing experiences, a process highly dependent on the integrity of the BLA (McGaugh, 2000; Quirarte et al., 1997; Roozendaal, 2002; Roozendaal et al., 2004, Roozendaal, Hui, et al., 2006). The BLA appears to orchestrate the use of various memory systems during periods of emotional arousal, rather than serving as a substrate of long-term memory storage (Packard & Wingard, 2004). There are multiple ways in which the BLA may modulate memory processes. First, aversive tasks can augment autonomic and humoral stress responses and activate the amygdala (Roozendaal, 2002; Roozendaal, Koolhaas, & Bohus, 1992). These augmented stress responses may in turn interact differentially with cannabinoids and affect cognitive functions in other brain regions such as the hippocampus and PFC. Second, the BLA can modulate cognitive functions through direct or indirect neural connections to other limbic structures. The BLA has efferents projecting to the medial PFC, nucleus accumbens, and hippocampus (Krettek & Price, 1978; Pape & Pare, 2010). Most of the amygdalo-hippocampal projections reach the ventral hippocampus, which appears to have limited involvement in learning and memory (Moser, Moser, & Andersen, 1993). Thus, the BLA may influence dorsal hippocampal memory processes indirectly via projections through the nucleus accumbens and entorhinal cortex. Therefore, cannabinoids could influence memory processes by modulating BLA activity and, thus, BLA efferents to other brain regions.

Within the BLA, CB1 receptors are expressed abundantly by GABAergic interneurons (Katona et al., 2001) and activation of CB1 receptors has consistently been shown to suppress GABA release (Katona et al., 1999, 2001; Ohno-Shosaku, Maejima, & Kano, 2001) via rapid inhibition of calcium entry into the terminals (Hoffman & Lupica, 2000; Wilson & Nicoll, 2001). Moreover, the amygdalar GABAergic system modulates memory storage (McGaugh, 2000) and inhibition of GABAergic activity within the BLA enhances memory consolidation by increasing the release of norepinephrine (Hatfield et al., 1999). We demonstrated recently that endocannabinoids in the BLA enhance memory consolidation for an emotionally salient event by interacting with glucocorticoids (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009). Indeed, we found that intra-BLA administration of the CB1 receptor antagonist AM251 blocked the ability of systemically administered CORT to facilitate memory consolidation of inhibitory avoidance training (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009). These findings showed, for the first time *in vivo*, that glucocorticoids recruit endocannabinoid signaling in the BLA while modulating aversive memory consolidation (Hill & McEwen, 2009; Hill, Patel, et al., 2010). Moreover, de Oliveira Alvares and co-workers demonstrated that intra-hippocampal AM251 infusion impaired memory in rats that had received a synthetic glucocorticoid (dexamethasone) injection immediately after, but not 30 min before training. Their study demonstrated that, in the context of modulation of aversive memory consolidation, hippocampal endocannabinoid transmission is activated in a time-dependent manner and interacts with glucocorticoids (de Oliveira Alvares et al., 2010).

An interaction between glucocorticoids and endocannabinoids in modulating memory retrieval has also been examined recently. Infusion of the cannabinoid receptor antagonist AM251 into the dorsal hippocampus blocked the retrieval impairing effects of systemic CORT, which were dependent upon elevation of hippocampal 2-AG levels (Atsak, Hauer, et al., 2012). Moreover, the β-adrenoceptor antagonist propranolol blocked the impairing effect of WIN on memory retrieval and, conversely, infusion of the CB1 receptor antagonist AM251 into hippocampus together with an impairing dose of norepinephrine failed to abolish the impairing effect of norepinephrine on memory retrieval (Atsak, Hauer, et al., 2012). Collectively, these findings indicate that endocannabinoids interact with glucocorticoids and may modulate memory functions differentially depending on the activation state of the noradrenergic system.

In view of this evidence, we have proposed a model in which CORT binds to membrane bound receptors in the BLA that activate a G-protein signaling cascade to stimulate the synthesis of endocannabinoids. Once in the synaptic cleft, endocannabinoids may inhibit GABA release from presynaptic terminals, which in turn may lead to disinhibition of norepinephrine release and increased noradrenergic activation of postsynaptic β-adrenoceptors, enhancing the consolidation of emotionally aversive memories (Fig. 3) (Atsak, Roozendaal, et al., 2012; Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Hill & McEwen, 2009).

There are several characteristics of the endocannabinoid system that should be considered and might be involved in the dual cannabinoid effects on memory. First, endocannabinoids are synthesized and released on-demand and, as a result, they are released only in those brain regions where and when there is active endocannabinoid signaling. Brain endocannabinoid responses, and the relative activation of the endocannabinoid system in discrete brain areas, may vary depending on the nature and intensity of environmental stimuli. Interestingly, pharmacological manipulations with indirect cannabinoid receptor agonists or antagonists increase and block, respectively, the endocannabinoid response only in those brain areas where signaling was concurrently active. Conversely, direct agonists bind all cannabinoid receptors in the brain and the periphery, regardless of their involvement in a particular process.

Second, CB1 receptors are widely expressed in brain regions that play key roles in responding to stressful stimuli. It is possible that CB1 receptors produce opposite behavioral effects, depending on their anatomical location. Since CB1 receptors are expressed presynaptically, they can suppress the release of neurotransmitters such as GABA and glutamate (Azad et al., 2008; Kano et al., 2009; Marsicano & Lutz, 1999; Monory et al., 2006), which often act in opposition to each other in the control of neurophysiological processes related to memory and emotional responses (Chevaleyre, Takahashi, & Castillo, 2006; Metna-Laurent et al., 2012; Millan, 2003; Myhrer, 2003). Furthermore, the densities of the molecular endocannabinoid system components differ between synapse types in general (i.e. glutamatergic vs. GABAergic) and among the great variety of individual synapses expressing cannabinoid receptors (Katona & Freund, 2012). For instance, the highest density of CB1 receptors is found on cholecystokinin-positive GABAergic synapses in the hippocampus (Katona et al., 1999, 2000), and much lower levels of CB1 receptors are found on glutamatergic synapses (Katona et al., 2006; Kawamura et al., 2006). Hence, cannabinoid influences on behavior may differ qualitatively depending on the synapses activated and neuronal circuits recruited in a particular situation. CB1 receptors might shape the environmental impact on memory functions by balancing inhibitory and excitatory neuronal activity. The functional interaction of the endocannabinoid system with these inhibitory or excitatory neurotransmitters

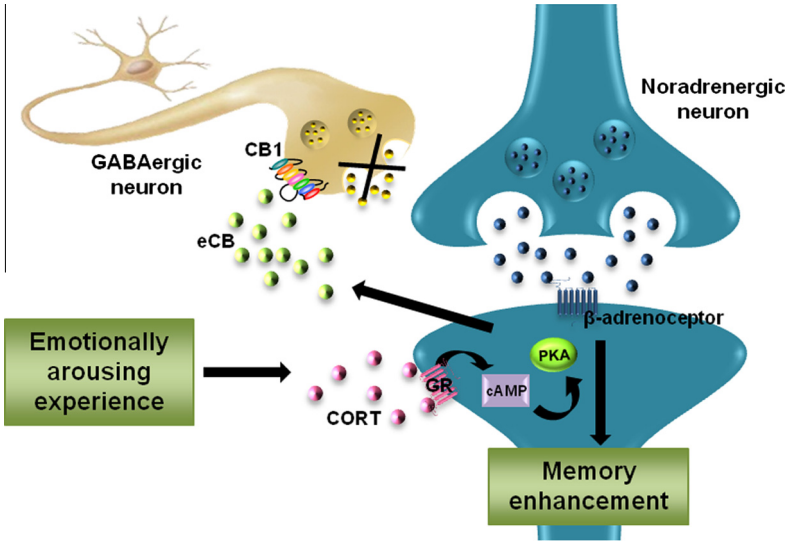

Fig. 3. Model of endocannabinoid role in the modulation of memory consolidation within the BLA. Stress hormones (i.e. CORT and epinephrine) are released into the bloodstream during training. CORT binds metabotropic GRs within the BLA, activating the G_s–cAMP/PKA pathway to induce endocannabinoid (eCB) synthesis. Endocannabinoids are released into the synaptic cleft where they bind CB1 receptors on GABAergic terminals, thereby inhibiting GABA release. Suppression of GABAergic transmission results in the disinhibition of noradrenergic neurons and increases noradrenergic activation of postsynaptic β-adrenoreceptors, enhancing the consolidation of emotionally aversive memories. Adapted from Hill and McEwen (2009).

may consequently be particularly relevant for the dual effects of cannabinoids in learning and memory processes. A small change in the environment might recruit new neurons in a different circuit, changing the location and the neurochemical nature of the cannabinoid-modulated synapses that were activated. This unique characteristic makes the endocannabinoid system well suited to serve as a buffer system to balance emotional reactivity and ensure an appropriate stress response.

Furthermore, the capacity of endocannabinoids to activate receptors other than CB1 should be considered. CB2 receptors were also proposed to be relevant for emotional responses (Onaivi et al., 2006). Moreover, endocannabinoids also activate the peroxisome proliferator-activated nuclear receptor (O'Sullivan, 2007), which modulates both aversive memory consolidation (Campolongo, Roozendaal, Trezza, Cuomo, et al., 2009) and acquisition (Mazzola et al., 2009), and the transient receptor potential vanilloid type 1 (Starowicz, Nigam, & Di Marzo, 2007) which has been shown to mediate opposing effects on emotional responses with respect to CB1 (Maione et al., 2006).

7. Conclusions

The findings reviewed here shed light on the divergent effects of cannabinoids on memory processes reported in the literature, indicating that environmental events characterized by different levels of stress can shape responses to the cognitive effects of cannabinoids. Given its modulatory role, we propose that the endocannabinoid system may moderate environmental impacts on emotional memory and attenuate excessive behavioral responses to stress. As a key modulator of environmental and stress influences on memory, the endocannabinoid system should be explored as a possible therapeutic target for neuropsychiatric illness involving memory dysfunction, such as post-traumatic stress disorder.

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References

Abush, H., & Akirav, I. (2010). Cannabinoids modulate hippocampal memory and plasticity. *Hippocampus, 20*(10), 1126–1138.
Aggleton, J. P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends in Neurosciences, 16*(8), 328–333.
Akirav, I. (2011). The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus. *Frontiers in Behavioral Neuroscience, 5*, 34.
Armario, A. (2010). Activation of the hypothalamic–pituitary–adrenal axis by addictive drugs: Different pathways, common outcome. *Trends in Pharmacological Sciences, 31*(7), 318–325.
Atsak, P., Hauer, D., Campolongo, P., Schelling, G., McGaugh, J. L., & Roozendaal, B. (2012). Glucocorticoids interact with the hippocampal endocannabinoid system in impairing retrieval of contextual fear memory. *Proceedings of the National Academy of Sciences of the United States of America, 109*(9), 3504–3509.
Atsak, P., Roozendaal, B., & Campolongo, P. (2012). Role of the endocannabinoid system in regulating glucocorticoid effects on memory for emotional experiences. *Neuroscience, 204*, 104–116.
Azad, S. C., Kurz, J., Marsicano, G., Lutz, B., Zieglgansberger, W., & Rammes, G. (2008). Activation of CB1 specifically located on GABAergic interneurons inhibits LTD in the lateral amygdala. *Learning & Memory, 15*(3), 143–152.
Ballard, M. E., Bedi, G., & de Wit, H. (2012). Effects of delta-9-tetrahydrocannabinol on evaluation of emotional images. *Journal of Psychopharmacology, 26*(10), 1289–1298.
Barad, M., Gean, P. W., & Lutz, B. (2006). The role of the amygdala in the extinction of conditioned fear. *Biological Psychiatry, 60*(4), 322–328.
Barna, I., Zelena, D., Arszovszki, A. C., & Ledent, C. (2004). The role of endogenous cannabinoids in the hypothalamo–pituitary–adrenal axis regulation: In vivo and in vitro studies in CB1 receptor knockout mice. *Life Sciences, 75*(24), 2959–2970.
Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews Neuroscience, 3*(7), 563–573.
Berridge, C. W., Schmeichel, B. E., & Espana, R. A. (2012). Noradrenergic modulation of wakefulness/arousal. *Sleep Medicine Reviews, 16*(2), 187–197.
Bitencourt, R. M., Pamplona, F. A., & Takahashi, R. N. (2008). Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. *European Neuropsychopharmacology, 18*(12), 849–859.
Bortolato, M., Campolongo, P., Mangieri, R. A., Scattoni, M. L., Frau, R., Trezza, V., et al. (2006). Anxiolytic-like properties of the anandamide transport inhibitor AM404. *Neuropsychopharmacology, 31*(12), 2652–2659.
Bucherelli, C., Baldi, E., Mariottini, C., Passani, M. B., & Blandina, P. (2006). Aversive memory reactivation engages in the amygdala only some neurotransmitters involved in consolidation. *Learning & Memory, 13*(4), 426–430.
Busquets-Garcia, A., Puighermanal, E., Pastor, A., de la Torre, R., Maldonado, R., & Ozaita, A. (2011). Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. *Biological Psychiatry, 70*(5), 479–486.
Campolongo, P., Morena, M., Scaccianoce, S., Trezza, V., Chiarotti, F., Schelling, G., et al. (2013). Novelty-induced emotional arousal modulates cannabinoid effects on recognition memory and adrenocortical activity. *Neuropsychopharmacology, 38*, 1276–1286.

Campolongo, P., Ratano, P., Manduca, A., Scattoni, M. L., Palmery, M., Trezza, V., et al. (2012). The endocannabinoid transport inhibitor AM404 differentially modulates recognition memory in rats depending on environmental aversiveness. *Frontiers in Behavioral Neuroscience, 6*, 11.

Campolongo, P., Roozendaal, B., Trezza, V., Cuomo, V., Astarita, G., Fu, J., et al. (2009). Fat-induced satiety factor oleoylethanolamide enhances memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America, 106*(19), 8027–8031.

Campolongo, P., Roozendaal, B., Trezza, V., Hauer, D., Schelling, G., McGaugh, J. L., et al. (2009). Endocannabinoids in the rat basolateral amygdala enhance memory consolidation and enable glucocorticoid modulation of memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*(12), 4888–4893.

Campolongo, P., Trezza, V., Palmery, M., Trabace, L., & Cuomo, V. (2009). Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations. *International Review of Neurobiology, 85*, 117–133.

Campolongo, P., Trezza, V., Ratano, P., Palmery, M., & Cuomo, V. (2011). Developmental consequences of perinatal cannabis exposure: Behavioral and neuroendocrine effects in adult rodents. *Psychopharmacology (Berlin), 214*(1), 5–15.

Campos, A. C., Ferreira, F. R., Guimaraes, F. S., & Lemos, J. I. (2010). Facilitation of endocannabinoid effects in the ventral hippocampus modulates anxiety-like behaviors depending on previous stress experience. *Neuroscience, 167*(2), 238–246.

Carvalho, A. F., & Van Bockstaele, E. J. (2012). Cannabinoid modulation of noradrenergic circuits: Implications for psychiatric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 38*(1), 59–67.

Chevaleyre, V., Takahashi, K. A., & Castillo, P. E. (2006). Endocannabinoid-mediated synaptic plasticity in the CNS. *Annual Review of Neuroscience, 29*, 37–76.

Chhatwal, J. P., Davis, M., Maguschak, K. A., & Ressler, K. J. (2005). Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. *Neuropsychopharmacology, 30*(3), 516–524.

Clarke, J. R., Rossato, J. I., Monteiro, S., Bevilaqua, L. R., Izquierdo, I., & Cammarota, M. (2008). Posttraining activation of CB1 cannabinoid receptors in the CA1 region of the dorsal hippocampus impairs object recognition long-term memory. *Neurobiology of Learning and Memory, 90*(2), 374–381.

Cota, D., Steiner, M. A., Marsicano, G., Cervino, C., Herman, J. P., Grubler, Y., et al. (2007). Requirement of cannabinoid receptor type 1 for the basal modulation of hypothalamic–pituitary–adrenal axis function. *Endocrinology, 148*(4), 1574–1581.

Da, S., & Takahashi, R. N. (2002). SR 141716A prevents delta 9-tetrahydrocannabinol-induced spatial learning deficit in a Morris-type water maze in mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 26*(2), 321–325.

Davis, M., Rainnie, D., & Cassell, M. (1994). Neurotransmission in the rat amygdala related to fear and anxiety. *Trends in Neurosciences, 17*(5), 208–214.

de Kloet, E. R., Oitzl, M. S., & Joels, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neurosciences, 22*(10), 422–426.

de Oliveira Alvares, L., de Oliveira, L. F., Camboim, C., Diehl, F., Genro, B. P., Lanziotti, V. B., et al. (2005). Amnestic effect of intrahippocampal AM251, a CB1-selective blocker, in the inhibitory avoidance, but not in the open field habituation task, in rats. *Neurobiology of Learning and Memory, 83*(2), 119–124.

de Oliveira Alvares, L., Engelke, D. S., Diehl, F., Scheffer-Teixeira, R., Haubrich, J., & de Freitas Cassini, L. (2010). Stress response recruits the hippocampal endocannabinoid system for the modulation of fear memory. *Learning & Memory, 17*(4), 202–209.

De Oliveira Alvares, L., Genro, B. P., Diehl, F., & Quillfeldt, J. A. (2008). Differential role of the hippocampal endocannabinoid system in the memory consolidation and retrieval mechanisms. *Neurobiology of Learning and Memory, 90*(1), 1–9.

de Quervain, D. J., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology, 30*(3), 358–370.

de Quervain, D. J., Roozendaal, B., & McGaugh, J. L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature, 394*(6695), 787–790.

Del Porto, J. A., & Masur, J. (1984). The effects of alcohol, THC and diazepam in two different social settings: A study with human volunteers. *Research Communications in Psychology, Psychiatry and Behavior, 9*, 201–212.

Derbenev, A. V., Stuart, T. C., & Smith, B. N. (2004). Cannabinoids suppress synaptic input to neurones of the rat dorsal motor nucleus of the vagus nerve. *Journal of Physiology, 559*(Pt 3), 923–938.

Devane, W. A., Dysarz, F. A., 3rd, Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology, 34*(5), 605–613.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., et al. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science, 258*(5090), 1946–1949.

Di, S., Malcher-Lopes, R., Halmos, K. C., & Tasker, J. G. (2003). Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: A fast feedback mechanism. *Journal of Neuroscience, 23*(12), 4850–4857.

Di, S., Malcher-Lopes, R., Marcheselli, V. L., Bazan, N. G., & Tasker, J. G. (2005). Rapid glucocorticoid-mediated endocannabinoid release and opposing regulation of glutamate and gamma-aminobutyric acid inputs to hypothalamic magnocellular neurons. *Endocrinology, 146*(10), 4292–4301.

Economidou, D., Mattioli, L., Ubaldi, M., Lourdusamy, A., Soverchia, L., Hardiman, G., et al. (2007). Role of cannabinoidergic mechanisms in ethanol self-administration and ethanol seeking in rat adult offspring following perinatal exposure to Delta9-tetrahydrocannabinol. *Toxicology and Applied Pharmacology, 223*(1), 73–85.

Egashira, N., Mishima, K., Iwasaki, K., & Fujiwara, M. (2002). Intracerebral microinjections of delta 9-tetrahydrocannabinol: Search for the impairment of spatial memory in the eight-arm radial maze in rats. *Brain Research, 952*(2), 239–245.

Fernandez-Ruiz, J., Berrendero, F., Hernandez, M. L., & Ramos, J. A. (2000). The endogenous cannabinoid system and brain development. *Trends in Neurosciences, 23*(1), 14–20.

Ferry, B., & McGaugh, J. L. (1999). Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task. *Neurobiology of Learning and Memory, 72*(1), 8–12.

Feuerecker, M., Hauer, D., Toth, R., Demetz, F., Holzl, J., Thiel, M., et al. (2012). Effects of exercise stress on the endocannabinoid system in humans under field conditions. *European Journal of Applied Physiology, 112*(7), 2777–2781.

Fisk, J. E., & Montgomery, C. (2008). Real-world memory and executive processes in cannabis users and non-users. *Journal of Psychopharmacology, 22*(7), 727–736.

Fraser, G. L., & Wahlestedt, C. (1997). Understanding gene function: Antisense knockdown versus homologous recombination knockout techniques. In L. R. Caplan, D. J. Reis, B. K. Siesjo, & B. Weir (Eds.), *Welch KMA primer on carebrovascular diseases* (pp. 129–133). San Diego, CA: Academic Press.

Fride, E. (2004). The endocannabinoid-CB(1) receptor system in pre- and postnatal life. *European Journal of Pharmacology, 500*(1–3), 289–297.

Fu, J., Bottegoni, G., Sasso, O., Bertorelli, R., Rocchia, W., Masetti, M., et al. (2011). A catalytically silent FAAH-1 variant drives anandamide transport in neurons. *Nature Neuroscience, 15*(1), 64–69.

Ganon-Elazar, E., & Akirav, I. (2009). Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance. *Journal of Neuroscience, 29*(36), 11078–11088.

Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society, 86*, 1646–1647.

Giros, B., Jaber, M., Jones, S. R., Wightman, R. M., & Caron, M. G. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature, 379*(6566), 606–612.

Gobbi, G., Bambico, F. R., Mangieri, R., Bortolato, M., Campolongo, P., Solinas, M., et al. (2005). Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences of the United States of America, 102*(51), 18620–18625.

Gold, P. E. (2004). Coordination of multiple memory systems. *Neurobiology of Learning and Memory, 82*(3), 230–242.

Gonzalez, S., Fernandez-Ruiz, J., Di Marzo, V., Hernandez, M., Arevalo, C., Nicanor, C., et al. (2004). Behavioral and molecular changes elicited by acute administration of SR141716 to Delta9-tetrahydrocannabinol-tolerant rats: An experimental model of cannabinoid abstinence. *Drug and Alcohol Dependence, 74*(2), 159–170.

Haller, J., Barna, I., Barsvari, B., Gyimesi Pelczer, K., Yasar, S., Panlilio, L. V., et al. (2009). Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. *Psychopharmacology (Berlin), 204*(4), 607–616.

Haring, M., Marsicano, G., Lutz, B., & Monory, K. (2007). Identification of the cannabinoid receptor type 1 in serotonergic cells of raphe nuclei in mice. *Neuroscience, 146*(3), 1212–1219.

Harkany, T., Guzman, M., Galve-Roperh, I., Berghuis, P., Devi, L. A., & Mackie, K. (2007). The emerging functions of endocannabinoid signaling during CNS development. *Trends in Pharmacological Sciences, 28*(2), 83–92.

Hatfield, T., Spanis, C., & McGaugh, J. L. (1999). Response of amygdalar norepinephrine to footshock and GABAergic drugs using in vivo microdialysis and HPLC. *Brain Research, 835*(2), 340–345.

Hauer, D., Schelling, G., Gola, H., Campolongo, P., Morath, J., Roozendaal, B., et al. (2013). Plasma concentrations of endocannabinoids and related primary fatty acid amides in patients with post-traumatic stress disorder. *PLoS One, 8*(5), e62741.

Hauer, D., Weis, F., Campolongo, P., Schopp, M., Beiras-Fernandez, A., Strewe, C., et al. (2012). Glucocorticoid-endocannabinoid interaction in cardiac surgical patients: Relationship to early cognitive dysfunction and late depression. *Reviews in the Neurosciences, 23*(5–6), 681–690.

Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1991). Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *Journal of Neuroscience, 11*(2), 563–583.

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., et al. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America, 87*(5), 1932–1936.

Hermann, H., Marsicano, G., & Lutz, B. (2002). Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. *Neuroscience, 109*(3), 451–460.

Hill, M. N., Karatsoreos, I. N., Hillard, C. J., & McEwen, B. S. (2010). Rapid elevations in limbic endocannabinoid content by glucocorticoid hormones in vivo. *Psychoneuroendocrinology, 35*(9), 1333–1338.

Hill, M. N., & McEwen, B. S. (2009). Endocannabinoids: The silent partner of glucocorticoids in the synapse. *Proceedings of the National Academy of Sciences of the United States of America, 106*(12), 4579–4580.

Hill, M. N., & McEwen, B. S. (2010). Involvement of the endocannabinoid system in the neurobehavioural effects of stress and glucocorticoids. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34*(5), 791–797.
Hill, M. N., Miller, G. E., Carrier, E. J., Gorzalka, B. B., & Hillard, C. J. (2009). Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. *Psychoneuroendocrinology, 34*(8), 1257–1262.
Hill, M. N., Patel, S., Campolongo, P., Tasker, J. G., Wotjak, C. T., & Bains, J. S. (2010). Functional interactions between stress and the endocannabinoid system: From synaptic signaling to behavioral output. *Journal of Neuroscience, 30*(45), 14980–14986.
Hill, M. N., & Tasker, J. G. (2012). Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic–pituitary–adrenal axis. *Neuroscience, 204*, 5–16.
Hillard, C. J., Edgemond, W. S., Jarrahian, A., & Campbell, W. B. (1997). Accumulation of N-arachidonoylethanolamine (anandamide) into cerebellar granule cells occurs via facilitated diffusion. *Journal of Neurochemistry, 69*(2), 631–638.
Hoffman, A. F., & Lupica, C. R. (2000). Mechanisms of cannabinoid inhibition of GABA(A) synaptic transmission in the hippocampus. *Journal of Neuroscience, 20*(7), 2470–2479.
Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., et al. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacological Reviews, 54*(2), 161–202.
Jacob, W., Marsch, R., Marsicano, G., Lutz, B., & Wotjak, C. T. (2012). Cannabinoid CB1 receptor deficiency increases contextual fear memory under highly aversive conditions and long-term potentiation in vivo. *Neurobiology of Learning and Memory, 98*(1), 47–55.
Jamali-Raeufy, N., Nasehi, M., & Zarrindast, M. R. (2011). Influence of N-methyl D-aspartate receptor mechanism on WIN55,212-2-induced amnesia in rat dorsal hippocampus. *Behavioural Pharmacology, 22*(7), 645–654.
Jelsing, J., Larsen, P. J., & Vrang, N. (2008). Identification of cannabinoid type 1 receptor expressing cocaine amphetamine-regulated transcript neurons in the rat hypothalamus and brainstem using in situ hybridization and immunohistochemistry. *Neuroscience, 154*(2), 641–652.
Joels, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience, 10*(6), 459–466.
Kamprath, K., Romo-Parra, H., Haring, M., Gaburro, S., Doengi, M., Lutz, B., et al. (2010). Short-term adaptation of conditioned fear responses through endocannabinoid signaling in the central amygdala. *Neuropsychopharmacology, 36*(3), 652–663.
Kano, M., Ohno-Shosaku, T., Hashimotodani, Y., Uchigashima, M., & Watanabe, M. (2009). Endocannabinoid-mediated control of synaptic transmission. *Physiological Reviews, 89*(1), 309–380.
Karila, L., Roux, P., Rolland, B., Benyamina, A., Reynaud, M., Aubin, H. J., et al. (2013). Acute and long-term effects of cannabis use: A review. *Current Pharmaceutical Design*.
Kathuria, S., Gaetani, S., Fegley, D., Valino, F., Duranti, A., Tontini, A., et al. (2003). Modulation of anxiety through blockade of anandamide hydrolysis. *Nature Medicine, 9*(1), 76–81.
Katona, I., & Freund, T. F. (2012). Multiple functions of endocannabinoid signaling in the brain. *Annual Review of Neuroscience, 35*, 529–558.
Katona, I., Rancz, E. A., Acsady, L., Ledent, C., Mackie, K., Hajos, N., et al. (2001). Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. *Journal of Neuroscience, 21*(23), 9506–9518.
Katona, I., Sperlagh, B., Magloczky, Z., Santha, E., Kofalvi, A., Czirjak, S., et al. (2000). GABAergic interneurons are the targets of cannabinoid actions in the human hippocampus. *Neuroscience, 100*(4), 797–804.
Katona, I., Sperlagh, B., Sik, A., Kafalvi, A., Vizi, E. S., Mackie, K., et al. (1999). Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *Journal of Neuroscience, 19*(11), 4544–4558.
Katona, I., Urban, G. M., Wallace, M., Ledent, C., Jung, K. M., Piomelli, D., et al. (2006). Molecular composition of the endocannabinoid system at glutamatergic synapses. *Journal of Neuroscience, 26*(21), 5628–5637.
Kawamura, Y., Fukaya, M., Maejima, T., Yoshida, T., Miura, E., Watanabe, M., et al. (2006). The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. *Journal of Neuroscience, 26*(11), 2991–3001.
Krettek, J. E., & Price, J. L. (1978). Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. *Journal of Comparative Neurology, 178*(2), 225–254.
LaLumiere, R. T., Buen, T. V., & McGaugh, J. L. (2003). Post-training intra-basolateral amygdala infusions of norepinephrine enhance consolidation of memory for contextual fear conditioning. *Journal of Neuroscience, 23*(17), 6754–6758.
Lichtman, A. H. (2000). SR 141716A enhances spatial memory as assessed in a radial-arm maze task in rats. *European Journal of Pharmacology, 404*(1–2), 175–179.
Lichtman, A. H., Dimen, K. R., & Martin, B. R. (1995). Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats. *Psychopharmacology (Berlin), 119*(3), 282–290.
Lin, Q. S., Yang, Q., Liu, D. D., Sun, Z., Dang, H., Liang, J., et al. (2011). Hippocampal endocannabinoids play an important role in induction of long-term potentiation and regulation of contextual fear memory formation. *Brain Research Bulletin, 86*(3–4), 139–145.
Mackowiak, M., Chocyk, A., Dudys, D., & Wedzony, K. (2009). Activation of CB1 cannabinoid receptors impairs memory consolidation and hippocampal polysialylated neural cell adhesion molecule expression in contextual fear conditioning. *Neuroscience, 158*(4), 1708–1716.
Mailleux, P., & Vanderhaeghen, J. J. (1992). Distribution of neuronal cannabinoid receptor in the adult rat brain: A comparative receptor binding radioautography and in situ hybridization histochemistry. *Neuroscience, 48*(3), 655–668.
Maione, S., Bisogno, T., de Novellis, V., Palazzo, E., Cristino, L., Valenti, M., et al. (2006). Elevation of endocannabinoid levels in the ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors. *Journal of Pharmacology and Experimental Therapeutics, 316*(3), 969–982.
Manzanares, J., Corchero, J., & Fuentes, J. A. (1999). Opioid and cannabinoid receptor-mediated regulation of the increase in adrenocorticotropin hormone and corticosterone plasma concentrations induced by central administration of delta(9)-tetrahydrocannabinol in rats. *Brain Research, 839*(1), 173–179.
Maroun, M., & Akirav, I. (2008). Arousal and stress effects on consolidation and reconsolidation of recognition memory. *Neuropsychopharmacology, 33*(2), 394–405.
Marsicano, G., & Lafenetre, P. (2009). Roles of the endocannabinoid system in learning and memory. *Current Topics in Behavioral Neurosciences, 1*, 201–230.
Marsicano, G., & Lutz, B. (1999). Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. *European Journal of Neuroscience, 11*(12), 4213–4225.
Marsicano, G., Wotjak, C. T., Azad, S. C., Bisogno, T., Rammes, G., Cascio, M. G., et al. (2002). The endogenous cannabinoid system controls extinction of aversive memories. *Nature, 418*(6897), 530–534.
Matsuda, L. A., Bonner, T. I., & Lolait, S. J. (1993). Localization of cannabinoid receptor mRNA in rat brain. *Journal of Comparative Neurology, 327*(4), 535–550.
Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature, 346*(6284), 561–564.
Mazzola, C., Medalie, J., Scherma, M., Panlilio, L. V., Solinas, M., Tanda, G., et al. (2009). Fatty acid amide hydrolase (FAAH) inhibition enhances memory acquisition through activation of PPAR-alpha nuclear receptors. *Learning & Memory, 16*(5), 332–337.
McEwen, B. S. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences of the United States of America, 109*(Suppl. 2), 17180–17185.
McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science, 153*, 1351–1358.
McGaugh, J. L. (2000). Memory – A century of consolidation. *Science, 287*(5451), 248–251.
McGaugh, J. L., & Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Current Opinion in Neurobiology, 12*(2), 205–210.
McPartland, J. M., Glass, M., & Pertwee, R. G. (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: Interspecies differences. *British Journal of Pharmacology, 152*(5), 583–593.
Mendl, M. (1999). Performing under pressure: Stress and cognitive function. *Applied Animal Behaviour Science, 65*, 221–244.
Metna-Laurent, M., Soria-Gómez, E., Verrier, D., Conforzi, M., Jego, P., Lafenetre, P., et al. (2012). Bimodal control of fear-coping strategies by CB1 cannabinoid receptors. *The Journal of Neuroscience, 32*(21), 7109–7118.
Micale, V., Di Marzo, V., Sulcova, A., Wotjak, C. T., & Drago, F. (2013). Endocannabinoid system and mood disorders: Priming a target for new therapies. *Pharmacology & Therapeutics, 138*(1), 18–37.
Millan, M. J. (2003). The neurobiology and control of anxious states. *Progress in Neurobiology, 70*(2), 83–244.
Mishima, K., Egashira, N., Hirosawa, N., Fujii, M., Matsumoto, Y., Iwasaki, K., et al. (2001). Characteristics of learning and memory impairment induced by Δ^9-tetrahydrocannabinol in rats. *The Japanese Journal of Pharmacology, 87*, 297–308.
Monory, K., Massa, F., Egertova, M., Eder, M., Blaudzun, H., Westenbroek, R., et al. (2006). The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron, 51*(4), 455–466.
Morozov, Y. M., Torii, M., & Rakic, P. (2009). Origin, early commitment, migratory routes, and destination of cannabinoid type 1 receptor-containing interneurons. *Cerebral Cortex, 19*(Suppl. 1), i78–i89.
Morrish, A. C., Hill, M. N., Riebe, C. J., & Gorzalka, B. B. (2009). Protracted cannabinoid administration elicits antidepressant behavioral responses in rats: Role of gender and noradrenergic transmission. *Physiology & Behavior, 98*(1–2), 118–124.
Moser, E., Moser, M. B., & Andersen, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *Journal of Neuroscience, 13*(9), 3916–3925.
Moshfegh, A., Babaei, P., Oryan, S., Soltani, B., & Zarrindast, M. R. (2011). Involvement of dorsal hippocampal alpha1-adrenergic receptors in the effect of WIN55,212-2 on memory retrieval in inhibitory avoidance task. *Neuroscience Letters, 489*(2), 69–73.
Muntoni, A. L., Pillolla, G., Melis, M., Perra, S., Gessa, G. L., & Pistis, M. (2006). Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. *European Journal of Neuroscience, 23*(9), 2385–2394.
Myhrer, T. (2003). Neurotransmitter systems involved in learning and memory in the rat: A meta-analysis based on studies of four behavioral tasks. *Brain Research. Brain Research Reviews, 41*(2–3), 268–287.
Nasehi, M., Sahebgharani, M., Haeri-Rohani, A., & Zarrindast, M. R. (2009). Effects of cannabinoids infused into the dorsal hippocampus upon memory formation in

3-days apomorphine-treated rats. *Neurobiology of Learning and Memory, 92*(3), 391–399.
Neumeister, A., Normandin, M. D., Pietrzak, R. H., Piomelli, D., Zheng, M. Q., Gujarro-Anton, A., et al. (2013). Elevated brain cannabinoid CB receptor availability in post-traumatic stress disorder: A positron emission tomography study. *Molecular Psychiatry*.
Newsom, R. J., Osterlund, C., Masini, C. V., Day, H. E., Spencer, R. L., & Campeau, S. (2012). Cannabinoid receptor type 1 antagonism significantly modulates basal and loud noise induced neural and hypothalamic–pituitary–adrenal axis responses in male Sprague–Dawley rats. *Neuroscience, 204*, 64–73.
Niyuhire, F., Varvel, S. A., Martin, B. R., & Lichtman, A. H. (2007). Exposure to marijuana smoke impairs memory retrieval in mice. *Journal of Pharmacology and Experimental Therapeutics, 322*(3), 1067–1075.
Niyuhire, F., Varvel, S. A., Thorpe, A. J., Stokes, R. J., Wiley, J. L., & Lichtman, A. H. (2007). The disruptive effects of the CB1 receptor antagonist rimonabant on extinction learning in mice are task-specific. *Psychopharmacology (Berlin), 191*(2), 223–231.
Ohno-Shosaku, T., Maejima, T., & Kano, M. (2001). Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron, 29*(3), 729–738.
Oitzl, M. S., & de Kloet, E. R. (1992). Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behavioral Neuroscience, 106*(1), 62–71.
Okuda, S., Roozendaal, B., & McGaugh, J. L. (2004). Glucocorticoid effects on object recognition memory require training-associated emotional arousal. *Proceedings of the National Academy of Sciences of the United States of America, 101*(3), 853–858.
Onaivi, E. S., Ishiguro, H., Gong, J. P., Patel, S., Perchuk, A., Meozzi, P. A., et al. (2006). Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Annals of the New York Academy of Sciences, 1074*, 514–536.
Oropeza, V. C., Mackie, K., & Van Bockstaele, E. J. (2007). Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex. *Brain Research, 1127*(1), 36–44.
Oropeza, V. C., Page, M. E., & Van Bockstaele, E. J. (2005). Systemic administration of WIN 55,212-2 increases norepinephrine release in the rat frontal cortex. *Brain Research, 1046*(1–2), 45–54.
O'Sullivan, S. E. (2007). Cannabinoids go nuclear: Evidence for activation of peroxisome proliferator-activated receptors. *British Journal of Pharmacology, 152*(5), 576–582.
Packard, M. G., & Wingard, J. C. (2004). Amygdala and "emotional" modulation of the relative use of multiple memory systems. *Neurobiology of Learning and Memory, 82*(3), 243–252.
Page, M. E., Oropeza, V. C., Sparks, S. E., Qian, Y., Menko, A. S., & Van Bockstaele, E. J. (2007). Repeated cannabinoid administration increases indices of noradrenergic activity in rats. *Pharmacology, Biochemistry and Behavior, 86*(1), 162–168.
Pamplona, F. A., Prediger, R. D., Pandolfo, P., & Takahashi, R. N. (2006). The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. *Psychopharmacology (Berlin), 188*(4), 641–649.
Pamplona, F. A., & Takahashi, R. N. (2006). WIN 55212–2 impairs contextual fear conditioning through the activation of CB1 cannabinoid receptors. *Neuroscience Letters, 397*(1–2), 88–92.
Pape, H. C., & Pare, D. (2010). Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiological Reviews, 90*(2), 419–463.
Patel, S., & Hillard, C. J. (2003). Cannabinoid-induced Fos expression within A10 dopaminergic neurons. *Brain Research, 963*(1–2), 15–25.
Patel, S., Roelke, C. T., Rademacher, D. J., Cullinan, W. E., & Hillard, C. J. (2004). Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic–pituitary–adrenal axis. *Endocrinology, 145*(12), 5431–5438.
Pelletier, J. G., Likhtik, E., Filali, M., & Pare, D. (2005). Lasting increases in basolateral amygdala activity after emotional arousal: Implications for facilitated consolidation of emotional memories. *Learning & Memory, 12*(2), 96–102.
Pertwee, R. G. (2010). Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Current Medicinal Chemistry, 17*(14), 1360–1381.
Piri, M., & Zarrindast, M. R. (2011). Modulation of WIN55,212-2 state-dependent memory by alpha2-adrenergic receptors of the dorsal hippocampus. *Archives of Iranian Medicine, 14*(6), 389–395.
Pistis, M., Perra, S., Pillolla, G., Melis, M., Gessa, G. L., & Muntoni, A. L. (2004). Cannabinoids modulate neuronal firing in the rat basolateral amygdala: Evidence for CB1- and non-CB1-mediated actions. *Neuropharmacology, 46*(1), 115–125.
Porto, J. A. D., & Masur, J. (1984). The effects of alcohol, THC and diazepam in two different social settings. A study with human volunteers. *Research Communications in Psychology, Psychiatry and Behavior, 9*, 201–212.
Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology, 35*(1), 192–216.
Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 94*(25), 14048–14053.
Ramikie, T. S., & Patel, S. (2012). Endocannabinoid signaling in the amygdala: Anatomy, synaptic signaling, behavior, and adaptations to stress. *Neuroscience, 204*, 38–52.
Ramot, A., & Akirav, I. (2012). Cannabinoid receptors activation and glucocorticoid receptors deactivation in the amygdala prevent the stress-induced enhancement of a negative learning experience. *Neurobiology of Learning and Memory, 97*(4), 393–401.
Ranganathan, M., & D'Souza, D. C. (2006). The acute effects of cannabinoids on memory in humans: A review. *Psychopharmacology (Berlin), 188*(4), 425–444.
Reilly, D., Didcott, P., Swift, W., & Hall, W. (1998). Long-term cannabis use: Characteristics of users in an Australian rural area. *Addiction, 93*(6), 837–846.
Reul, J. M., & de Kloet, E. R. (1985). Two receptor systems for corticosterone in rat brain: Microdistribution and differential occupation. *Endocrinology, 117*(6), 2505–2511.
Riedel, G., & Davies, SN. (2005). Cannabinoid function in learning, memory and plasticity. *Handbook of Experimental Pharmacology, 168*, 445–477.
Robinson, L., McKillop-Smith, S., Ross, N. L., Pertwee, R. G., Hampson, R. E., Platt, B., et al. (2008). Hippocampal endocannabinoids inhibit spatial learning and limit spatial memory in rats. *Psychopharmacology (Berlin), 198*(4), 551–563.
Roozendaal, B. (2000). 1999 Curt P. Richter award. Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology, 25*(3), 213–238.
Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning and Memory, 78*(3), 578–595.
Roozendaal, B., Castello, N. A., Vedana, G., Barsegyan, A., & McGaugh, J. L. (2008). Noradrenergic activation of the basolateral amygdala modulates consolidation of object recognition memory. *Neurobiology of Learning and Memory, 90*(3), 576–579.
Roozendaal, B., de Quervain, D. J., Schelling, G., & McGaugh, J. L. (2004). A systemically administered beta-adrenoceptor antagonist blocks corticosterone-induced impairment of contextual memory retrieval in rats. *Neurobiology of Learning and Memory, 81*(2), 150–154.
Roozendaal, B., Hui, G. K., Hui, I. R., Berlau, D. J., McGaugh, J. L., & Weinberger, N. M. (2006). Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. *Neurobiology of Learning and Memory, 86*(3), 249–255.
Roozendaal, B., Koolhaas, J. M., & Bohus, B. (1992). Central amygdaloid involvement in neuroendocrine correlates of conditioned stress responses. *Journal of Neuroendocrinology, 4*(4), 483–489.
Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience, 10*(6), 423–433.
Roozendaal, B., & McGaugh, J. L. (1996). Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiology of Learning and Memory, 65*(1), 1–8.
Roozendaal, B., Okuda, S., Van der Zee, E. A., & McGaugh, J. L. (2006). Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 103*(17), 6741–6746.
Roozendaal, B., Quirarte, G. L., & McGaugh, J. L. (2002). Glucocorticoids interact with the basolateral amygdala beta-adrenoceptor–cAMP/cAMP/PKA system in influencing memory consolidation. *European Journal of Neuroscience, 15*(3), 553–560.
Sandi, C., & Pinelo-Nava, M. T. (2007). Stress and memory: Behavioral effects and neurobiological mechanisms. *Neural Plasticity, 2007*, 78970.
Sandi, C., & Rose, S. P. (1994). Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive avoidance learning paradigm. *Brain Research, 647*(1), 106–112.
Schneider, M., Schomig, E., & Leweke, F. M. (2008). Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. *Addiction Biology, 13*(3–4), 345–357.
Sciolino, N. R., Zhou, W., & Hohmann, A. G. (2011). Enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-arachidonoylglycerol hydrolyzing enzyme monoacylglycerol lipase, produces anxiolytic effects under conditions of high environmental aversiveness in rats. *Pharmacological Research, 64*(3), 226–234.
Segev, A., & Akirav, I. (2011). Differential effects of cannabinoid receptor agonist on social discrimination and contextual fear in amygdala and hippocampus. *Learning & Memory, 18*(4), 254–259.
Smith, H. W. (1978). Effects of set on subjects interpretation of placebo marihuana effects. *Social Science and Medicine, 12*(2A), 107–109.
Solinas, M., & Goldberg, S. R. (2005). Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems. *Neuropsychopharmacology, 30*(11), 2035–2045.
Spence, K. W. (1956). *Behavior theory and conditioning*. New Haven: Yale University Press.
Starowicz, K., Nigam, S., & Di Marzo, V. (2007). Biochemistry and pharmacology of endovanilloids. *Pharmacology & Therapeutics, 114*(1), 13–33.
Steiner, H., Bonner, T. I., Zimmer, A. M., Kitai, S. T., & Zimmer, A. (1999). Altered gene expression in striatal projection neurons in CB1 cannabinoid receptor knockout mice. *Proceedings of the National Academy of Sciences of the United States of America, 96*(10), 5786–5790.
Steiner, M. A., Marsicano, G., Nestler, E. J., Holsboer, F., Lutz, B., & Wotjak, C. T. (2008). Antidepressant-like behavioral effects of impaired cannabinoid receptor type 1 signaling coincide with exaggerated corticosterone secretion in mice. *Psychoneuroendocrinology, 33*(1), 54–67.
Steiner, M. A., & Wotjak, C. T. (2008). Role of the endocannabinoid system in regulation of the hypothalamic–pituitary–adrenocortical axis. *Progress in Brain Research, 170*, 397–432.

Stella, N., Schweitzer, P., & Piomelli, D. (1997). A second endogenous cannabinoid that modulates long-term potentiation. *Nature, 388*(6644), 773–778.
Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., et al. (1995). 2-Arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. *Biochemical and Biophysical Research Communications, 215*(1), 89–97.
Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. J., & Kida, S. (2004). Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *Journal of Neuroscience, 24*(20), 4787–4795.
Szuster, R. R., Pontius, E. B., & Campos, P. E. (1988). Marijuana sensitivity and panic anxiety. *Journal of Clinical Psychiatry, 49*(11), 427–429.
Takahashi, R. N., Pamplona, F. A., & Fernandes, M. S. (2005). The cannabinoid antagonist SR141716A facilitates memory acquisition and consolidation in the mouse elevated T-maze. *Neuroscience Letters, 380*(3), 270–275.
Tan, H., Lauzon, N. M., Bishop, S. F., Chi, N., Bechard, M., & Laviolette, S. R. (2011). Cannabinoid transmission in the basolateral amygdala modulates fear memory formation via functional inputs to the prelimbic cortex. *Journal of Neuroscience, 31*(14), 5300–5312.
Trezza, V., Campolongo, P., Cassano, T., Macheda, T., Dipasquale, P., Carratu, M. R., et al. (2008). Effects of perinatal exposure to delta-9-tetrahydrocannabinol on the emotional reactivity of the offspring: A longitudinal behavioral study in Wistar rats. *Psychopharmacology (Berlin), 198*(4), 529–537.
Trezza, V., Campolongo, P., Manduca, A., Morena, M., Palmery, M., Vanderschuren, L. J., et al. (2012). Altering endocannabinoid neurotransmission at critical developmental ages: Impact on rodent emotionality and cognitive performance. *Frontiers in Behavioral Neuroscience, 6*, 2.
Tsou, K., Brown, S., Sanudo-Pena, M. C., Mackie, K., & Walker, J. M. (1998). Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience, 83*(2), 393–411.
Turu, G., & Hunyady, L. (2010). Signal transduction of the CB1 cannabinoid receptor. *Journal of Molecular Endocrinology, 44*(2), 75–85.
Van Sickle, M. D., Duncan, M., Kingsley, P. J., Mouihate, A., Urbani, P., Mackie, K., et al. (2005). Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science, 310*(5746), 329–332.
van Stegeren, A. H., Roozendaal, B., Kindt, M., Wolf, O. T., & Joels, M. (2010). Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiology of Learning and Memory, 93*(1), 56–65.
Varvel, S. A., Anum, E., Niyuhire, F., Wise, L. E., & Lichtman, A. H. (2005). Delta(9)-THC-induced cognitive deficits in mice are reversed by the GABA(A) antagonist bicuculline. *Psychopharmacology (Berlin), 178*(2–3), 317–327.
Varvel, S. A., Wise, L. E., Niyuhire, F., Cravatt, B. F., & Lichtman, A. H. (2007). Inhibition of fatty-acid amide hydrolase accelerates acquisition and extinction rates in a spatial memory task. *Neuropsychopharmacology, 32*(5), 1032–1041.
Velez, C. N., & Ungemack, J. A. (1989). Drug use among Puerto Rican youth: An exploration of generational status differences. *Social Science and Medicine, 29*(6), 779–789.
Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: An examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society, 12*(3), 405–415.
Wegener, N., Kuhnert, S., Thuns, A., Roese, R., & Koch, M. (2008). Effects of acute systemic and intra-cerebral stimulation of cannabinoid receptors on sensorimotor gating, locomotion and spatial memory in rats. *Psychopharmacology (Berlin), 198*(3), 375–385.
Weidenfeld, J., Feldman, S., & Mechoulam, R. (1994). Effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo–pituitary–adrenal axis in the rat. *Neuroendocrinology, 59*(2), 110–112.
Wilson, R. I., & Nicoll, R. A. (2001). Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature, 410*(6828), 588–592.
Wise, L. E., Iredale, P. A., & Lichtman, A. H. (2008). The cannabinoid CB(1) receptor antagonist CE prolongs spatial memory duration in a rat delayed radial arm maze memory task. *European Journal of Pharmacology, 590*(1–3), 246–249.
Wise, L. E., Long, K. A., Abdullah, R. A., Long, J. Z., Cravatt, B. F., & Lichtman, A. H. (2012). Dual fatty acid amide hydrolase and monoacylglycerol lipase blockade produces THC-like Morris water maze deficits in mice. *ACS Chemical Neuroscience, 3*(5), 369–378.
Wise, L. E., Thorpe, A. J., & Lichtman, A. H. (2009). Hippocampal CB(1) receptors mediate the memory impairing effects of Delta(9)-tetrahydrocannabinol. *Neuropsychopharmacology, 34*(9), 2072–2080.
Wolff, M. C., & Leander, J. D. (2003). SR141716A, a cannabinoid CB1 receptor antagonist, improves memory in a delayed radial maze task. *European Journal of Pharmacology, 477*(3), 213–217.
Wotjak, C. T. (2005). Role of endogenous cannabinoids in cognition and emotionality. *Mini Reviews in Medicinal Chemistry, 5*(7), 659–670.
Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology, 18*, 459–482.
Yim, T. T., Hong, N. S., Ejaredar, M., McKenna, J. E., & McDonald, R. J. (2008). Post-training CB1 cannabinoid receptor agonist activation disrupts long-term consolidation of spatial memories in the hippocampus. *Neuroscience, 151*(4), 929–936.
Zanettini, C., Panlilio, L. V., Alicki, M., Goldberg, S. R., Haller, J., & Yasar, S. (2011). Effects of endocannabinoid system modulation on cognitive and emotional behavior. *Frontiers in Behavioral Neuroscience, 5*, 57.
Zarrindast, M. R., Ghiasvand, M., Rezayof, A., & Ahmadi, S. (2012). The amnesic effect of intra-central amygdala administration of a cannabinoid CB1 receptor agonist, WIN55,212-2, is mediated by a beta-1 noradrenergic system in rat. *Neuroscience, 212*, 77–85.
Zarrindast, M. R., Navaeian, M., & Nasehi, M. (2011). Influence of three-day morphine-treatment upon impairment of memory consolidation induced by cannabinoid infused into the dorsal hippocampus in rats. *Neuroscience Research, 69*(1), 51–59.
Ziegler, C. G., Mohn, C., Lamounier-Zepter, V., Rettori, V., Bornstein, S. R., Krug, A. W., et al. (2010). Expression and function of endocannabinoid receptors in the human adrenal cortex. *Hormone and Metabolic Research, 42*(2), 88–92.
Zimmer, A., Zimmer, A. M., Hohmann, A. G., Herkenham, M., & Bonner, T. I. (1999). Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. *Proceedings of the National Academy of Sciences of the United States of America, 96*(10), 5780–5785.
Zinberg, N. E. (1984). *Drugs, set and setting: The basis for controlled intoxicant use*. New Haven, CT: Yale University Press.