UNIVERSITÀ DEGLI STUDI DI VERONA

DIPARTIMENTO DI DIAGNOSTICA E SANITÀ PUBBLICA

SCUOLA DI DOTTORATO DI

Scienze della Vita e della Salute

DOTTORATO DI RICERCA IN

Neuroscienze, Scienze Psicologiche e Psichiatriche

CICLO XXXII / ANNO 2016

TITOLO DELLA TESI DI DOTTORATO

Reconsolidation of Appetitive Memory and Sleep:
Functional Connectomics and Plasticity

S.S.D BIO14/FARMACOLOGIA

Coordinatore: Prof. Gianluigi Zanusso

Tutor: Prof. Cristiano Chiamulera

Dottoranda: Dott.ssa Laura Padovani

Sommario

Introduzione: La dipendenza da cibo è un disturbo comportamentale caratterizzato da modelli maladattativi di consumo alimentare, in cui alimenti ricchi in zuccheri, sale e/o grassi possono indurre una dipendenza tale da essere paragonata ai disturbi relativi all'abuso di sostanze. Alla base di questo processo vi è l'associazione tra questi cibi altamente palatabili e la sensazione piacevole e rinforzante indotta dal loro consumo, che può essere codificata in una nuova memoria maladattativa sottostante il disturbo di dipendenza. Infatti, le nuove informazioni che riceviamo quotidianamente dall'esterno vengono processate dal nostro cervello tramite un primo stadio di codifica e un secondo stadio di consolidamento, durante il quale vengono stabilizzate in una nuova memoria e integrate nella rete cerebrale di conoscenze preesistenti. Tuttavia, dopo il suo consolidamento, una memoria può essere destabilizzata e riportata ad uno stato di labilità che ne permette la modifica e l'eventuale integrazione con nuove informazioni. Infine, un nuovo processo di stabilizzazione chiamato riconsolidamento è necessario affinché la traccia mnemonica aggiornata sia nuovamente stabilizzata.

Da recenti studi, è noto come il sonno sia rilevante sia per il consolidamento che per il riconsolidamento della memoria. Tuttavia, mentre è chiaro come il consolidamento che avviene durante il sonno permetta la stabilizzazione a lungo termine delle tracce mnemoniche, non è ancora stato del tutto chiarito il ruolo del sonno nel processo di riconsolidamento.

Scopo: Date queste premesse, e nota l'importanza dell'interazione tra amigdala basolaterale (BLA) e ippocampo nel riconsolidamento delle memorie appetitive, gli obiettivi della presente tesi erano: *i)* valutare come l'amigdala BLA e ippocampo interagiscono in termini di potenziali locali durante la riattivazione della memoria strumentale effettuata o durante la fase di attività o durante la fase di inattività del ciclo circadiano dei roditori; *ii)* valutare come il richiamo della memoria effettuato durante la fase attiva o quella inattiva possa influenzare il successivo processo di riconsolidamento, e *iii)* trovare, *in-vivo*, un marker di riattivazione della memoria appetitiva.

Metodi: Sono stati utilizzati 32 ratti maschi, ceppo Sprague Dawley, a cui sono stati impiantati due elettrodi profondi: uno in BLA e uno in ippocampo, per la registrazione dei potenziali locali. I ratti sono stati sottoposti ad un protocollo comportamentale in gabbia operante di auto-somministrazione di saccarosio,

composto da quattro stadi: addestramento (i), in cui i ratti imparavano l'associazione tra la pressione di una leva e l'emissione di un pellet di saccarosio; astinenza (ii), durante la quale i soggetti non venivano esposti al contesto di addestramento; riattivazione o non riattivazione (iii) della memoria strumentale in gabbia operante, svolta o durante la fase di attività, o durante la fase di inattività; test di ricaduta (iv).

I potenziali locali sono stati analizzati per lo stadio (iii) in modo da ottenere la potenza delle oscillazioni theta e gamma per i due elettrodi profondi; tali frequenze sono state scelte in quanto rilevanti per i processi mnemonici. Infatti, il richiamo della memoria è correlato alla sincronizzazione delle onde theta (4-12 Hz) tra BLA e altre aree cerebrali quali l'area CA1 dell'ippocampo, ed è inoltre correlato alle basse gamma (30-60 Hz) nell'ippocampo. Infine, l'accoppiamento tra le onde theta e gamma nell'ippocampo è un noto metodo di comunicazione tra sotto-aree ippocampali nel corso dei processi di memoria.

Risultati: I risultati hanno mostrato la presenza di una correlazione inversa tra la potenza delle basse gamma nell'area CA1 ippocampale e il tasso di risposta durante lo stadio di richiamo della memoria nella fase di attività, indipendentemente dal fatto che i soggetti stessero o meno premendo la leva. Le basse gamma potrebbero quindi rappresentare un marker di correlazione per il richiamo della memoria appetitiva. Inoltre, la potenza di basse e alte gamma ippocampali aumenta durante le epoche di pressione di leva quando il richiamo della memoria viene effettuato nella fase di inattività, suggerendo che le onde gamma potrebbero essere dei marker correlazionali specifici per la componente strumentale del richiamo della memoria effettuato durante la fase di inattività.

Conclusioni e limitazioni: Per concludere, i risultati hanno mostrato l'importanza delle frequenze basse gamma nel richiamo delle memorie appetitive, tuttavia non hanno mostrato alcuna differenza a livello delle onde theta, né a livello della BLA. Di conseguenza, si conclude che il protocollo utilizzato nella presente tesi non ha mostrato una sensibilità sufficientemente elevata nell'evidenziare i cambiamenti ipotizzati a livello dei potenziali locali. Lo svolgimento di ulteriori esperimenti che andranno a determinare misure di connettomica quali coerenza e accoppiamento, sia intra- che inter- area, aiuterà a determinare se e come le due aree comunicano tra di loro.

Abstract

Introduction: Food addiction is a behavioural disorder in which individuals develop maladaptive patterns of food consumption. Particularly, food containing processed sugars, salt, fat etc. can be addictive, and refined food consumption behaviours may meet the criteria for substance use disorders. For these characteristics, food addiction can also be considered a memory disorder.

Memories in the brain are processed as follows: new information is encoded and then long-term consolidated through a process allowing its integration into already existing knowledge networks. After a memory has been consolidated, it can be destabilized and brought back to a labile state, requiring a new re-stabilization process called reconsolidation.

Memory consolidation is known to require sleep. In fact, sleep allows new memory traces to long-term stabilize. Sleep also seems to influence memory reconsolidation; however, its involvement in this process is not yet clear.

Aim: Given these premises, the goals of the project were: to evaluate how basolateral amygdala (BLA) and hippocampus interact in terms of local field potentials (LFPs) when appetitive instrumental memory is retrieved either during active or inactive phase of rats circadian rhythm; to evaluate how retrieving the memory in the activity vs inactivity phase influences following memory reconsolidation; and to find an in vivo electrophysiological marker of appetitive memory retrieval. In fact, it has been shown that BLA and dorsal hippocampus interaction is crucial for appetitive memory reconsolidation.

Methods: Thirty-two male Sprague Dawley rats were implanted with in-depth electrodes for LFPs recordings in BLA and dorsal hippocampal CA1 and subject to a behavioural protocol apt to induce appetitive memory retrieval. The behavioural procedure consisted of four stages: training (i), in which animals learned lever pressing – sucrose reward association; abstinence (ii), during which subjects were not exposed to the training context; memory retrieval or no retrieval (iii): instrumental memory reactivation or no reactivation, performed either during active or inactive phase; and relapse test (iv), during which sucrose-seeking behaviour was analysed.

Theta and gamma oscillations powers were analysed during stage (iii). In fact, they are known to be involved in memory processes. Memory retrieval has been shown

to correlate with theta (4-12 Hz) synchronization between BLA and other brain areas (such as hippocampal CA1) and with low gamma (30-60 Hz) in hippocampus. Particularly, theta-gamma cross-frequency coupling has been shown to be used as a mean of communication between hippocampal sub-areas during memory processing.

Results: Results showed an inverse correlation between hippocampal CA1 low gamma power and reactivation rate of responding (either when rats were lever pressing or not) when reactivation was performed during the active phase. This suggests that low gamma may be a correlational marker of instrumental sucrose memory retrieval, independent of whether rats were lever-pressing or not. Moreover, hippocampal CA1 gamma bands increased when lever pressing during instrumental memory reactivation while in the inactive phase, suggesting that both low and high gamma bands may be correlational markers to actual instrumental responding retrieval during the inactive phase.

Conclusions and limitations: In conclusion, results showed that low gamma is relevant in sucrose appetitive memory retrieval. However, no difference was observed in the theta frequency band, nor at the level of BLA. Therefore, the current protocol did not have the sensitivity to detect predicted changes in LFPs. Further experiments would help investigating if and how the two areas interact, by determining connectomics measures such as coherence and coupling within and between areas.

TABLE OF CONTENTS

1. INTRODUCTION

The topics that will be covered in the present dissertation are visually presented in Figure 1. According to the diagram, the dissertation will at first describe food addiction; it will then span through memory processes involved in addiction, with a specific focus on memory retrieval and memory reconsolidation. Then, memory processes in both wakefulness and sleep will be covered; finally, electrophysiological correlates of memory retrieval and reconsolidation will be described for two brain areas both important for addiction and memory: basolateral amygdala (BLA) and hippocampus.

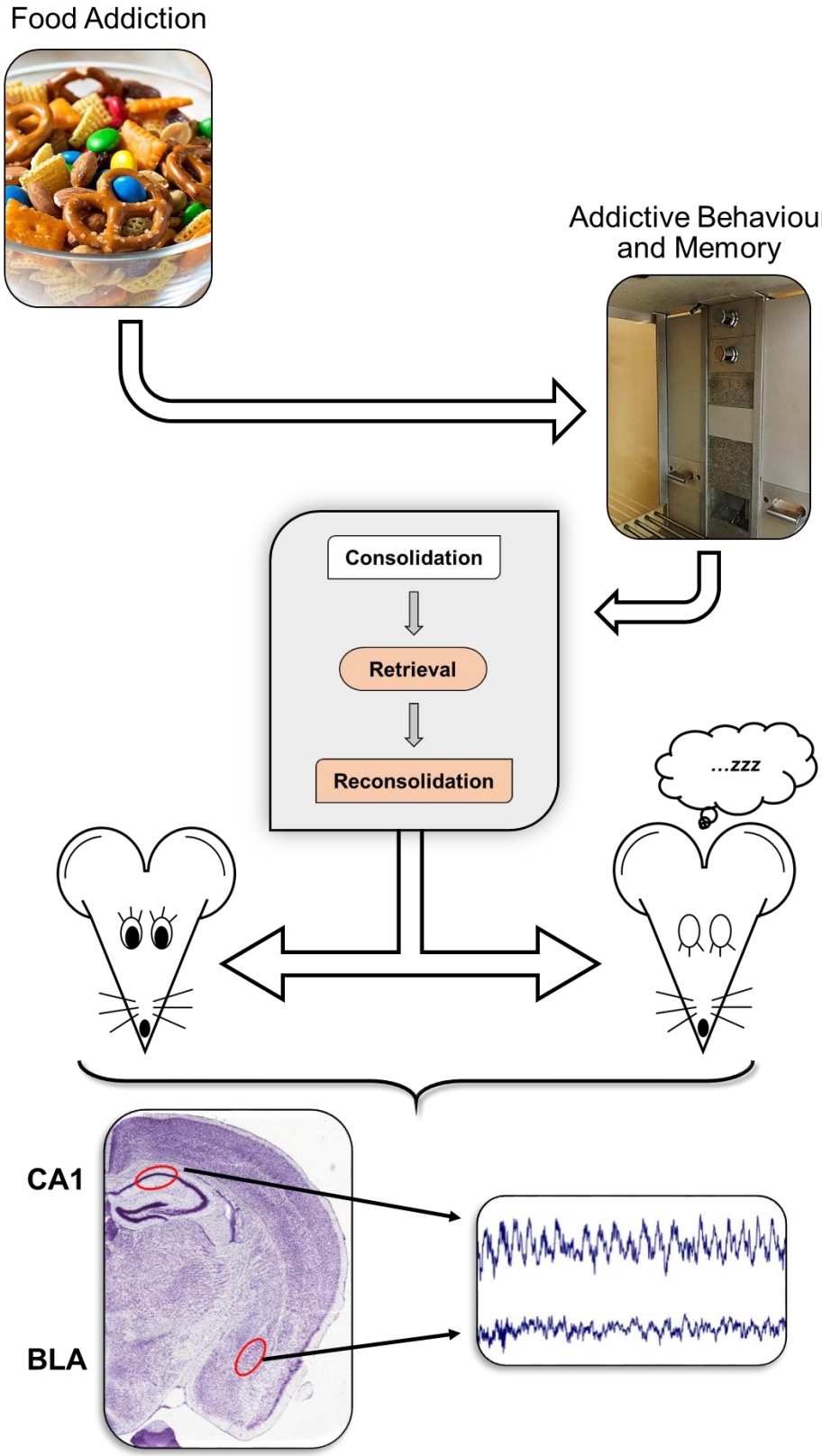


Figure 1. Visual list of topics debated in the introduction of the present dissertation. For a description, see main text. Abbreviations: CA1 = CA1 area of the hippocampus; BLA = basolateral amygdala.

1.1 Drug Addiction

Before starting the topic of food addiction, it is necessary to introduce what the word addiction means, starting from its origins, which go hand in hand with drug abuse. Therefore, the present paragraph will describe drug addiction.

The National Institute on Drug Abuse (NIDA) defines drug addiction as a "*complex illness*" with devastating consequences, which is characterised by drug craving and compulsive and persistent drug seeking (NIDA, 2018).

Today's concept and description of drug addiction is the result of a scientific research that started back in 1878 in the United States. At that time, Edward Levinstein published his work *Morbid Craving for Morphia* on morphine addiction where he identified two key characteristics of opiate addiction: substance seeking despite its deteriorating effects on user's life and withdrawal syndrome (Levinstein, 1878; Musto, 1996). Since then, other publications reported their definition of drug abuse, and they all reported the same key features; for example, in the early 1900s, Dr. Charles Towns reported three characteristics of drug addiction that are still accepted today: (i) compulsive need; (ii) need for greater drug intake: tolerance; and (iii) relapse after withdrawal. In accordance with Town's definition, Cameron described the following three features of narcotic addiction: (i) psychological dependence; (ii) tolerance; and (iii) physical dependence (Murray, 1967).

As of 1957, the *Treatment and Care of Drug Addicts* report of the World Health Organization (WHO) recognizes that the definition of drug addiction depends on the point of view of the observer; until then, drug addiction was considered only as affecting the individual's health. The Study Group added in this report a peculiarity of drug addiction: its impact on society. In fact, the report reads "*[…] the Study Group accepted the public health concept according to which an addict is a person who habitually and compulsively uses any narcotic drug so as directly to endanger his own or other's health, safety, or welfare*" (Study Group on the Treatment and Care of Drug Addicts, 1957).

Decades of basic research, case studies and clinical studies led us to today's definition of addiction, as thoroughly described in the 5th edition of the Diagnostics and Statistical Manual of Mental Disorders (DSM-5), in the "Substance-Related and Addictive Disorders" chapter, which does not depart from its first descriptions. In DMS-5, substance-related disorders are categorized into 10 classes, based on the substances (in alphabetical order: alcohol -i-; caffeine -ii-; cannabis -iii-;

hallucinogens -iv-; inhalants -v-; opioids -vi-; sedatives, hypnotics and anxiolytics -vii-, stimulants -viii-, tobacco -ix- and unknown -x-). Besides substance-related disorders, the DSM-5 describes gambling disorder but doesn't cover other behavioural addictions such as sex or shopping addiction (American Psychiatric Association, 2013). As for substance use disorders, the DSM-5 classifies them into 3 severity classes: mild, moderate and severe on the basis of the number of symptoms shown by a patient. Symptoms and their categorization are shown in Table 1.

Table 1. **Diagnostic criteria for substance use disorder**

On the basis of these criteria, the severity of the disorder is considered *mild* in presence of 2-3 symptoms, *moderate* in presence of 4-5 symptoms and *severe* in presence of more than 6 symptoms (American Psychiatric Association, 2013).

Grouping	**Individual criterion**
Impaired Control	1. Taking the drug over a longer period or in larger amounts than originally intended 2. Presence of a desire to regulate the use of the substance 3. Spending a lot of time obtaining, using or recovering from the effects of the substance 4. Craving: urge for the drug
Social Impairment	5. Failing to fulfil duties at work/school/home 6. Continuing drug use despite its negative effects on oneself social life 7. Giving up of social activities to continue using the substance
Risky Use	8. Using the substance in physically hazardous situations 9. Continuing using the substance despite knowing of having a problem caused (or intensified) by the substance
Pharmacological Criteria	10. Tolerance: increasing the dose to achieve the desired effect/reduced effect if consuming the usual dose 11. Withdrawal: syndrome caused by the reduction in blood and/or tissue concentration of the substance. Withdrawal syndrome induces the individual to make substance use to relieve the negative symptoms

1.1.1 The addiction cycle

Together with the NIDA definition of drug addiction as a "*complex illness*" (NIDA, 2018), O'Brien C. first in 1997 and Koob G.F. subsequently in a number of reviews, defined drug addiction as a chronic and relapsing disorder, characterized by a compulsion to seek and take the drug (O'Brien, 1997). Consistent with this widely accepted definition of addiction, the drug addiction process is seen as a recurring cycle composed of three stages (Koob and Volkow, 2016; Horseman and Meyer, 2019). For each of these stages, besides the specific effects of each drug of abuse and their active ingredients on the nervous system, there is a predominance of one specific brain circuit, which changes are suggested to be common to all sort of drugs and addictive behaviours (Goodman, 2008). The stages are the following:

1. *Binge/Intoxication*;
2. *Withdrawal/Negative affect*;
3. *Preoccupation/Anticipation* (craving).

The transition from drug abuse to drug addiction is characterized by a shift from an impulsive to a compulsive behaviour. Impulsivity can be defined as a decreased sensitivity to negative consequences, leading to a predisposition toward rapid and unplanned reactions to stimuli regardless of long-term consequences (Moeller et al., 2001). An impulsive subject is unable to resist impulses, presents unreflective decision-making and values short-term rewards as compared to long-term rewards (Robbins et al., 2012a). Moreover, impulsive behaviours are goal-directed behaviours. On the other hand, compulsivity is characterized by perseverative and repetitive actions (Robbins et al., 2012b) led by anxiety and stress. Finally, as opposed to impulsive behaviours, compulsive behaviours are not under the control of the goal as they are habit-based (Everitt and Robbins, 2005; Berlin and Hollander, 2014).

As previously said, moving from the early to the later stages of the addiction cycle the individual shifts from an impulsive to a compulsive behaviour. Thus, there is a shift from a goal-directed behaviour led by positive reinforcements to a habit-based behaviour led by negative reinforcements and automaticity (Koob and Volkow, 2010, 2016).

To summarize, substance use disorders are characterized by different symptoms. Yet, the dissertation aims to understand the neuroanatomical bases of the

underlying processes. Therefore, the following paragraphs will cover the three stages of addiction and their prevailing brain circuits and mechanisms. Particularly, five circuits are hypothesized to be engaged in the transition to addiction: mesolimbic dopamine system (1), ventral striatum (2), ventral striatum-dorsal striatum-thalamus (3), extended amygdala (4) and dorsolateral frontal cortex-inferior frontal cortex-hippocampus (5). The first three circuits are involved in stage 1, the fourth circuit in stage 2 and the fifth circuit in stage 3 (Koob and Volkow, 2010).

Binge/Intoxication Stage

The neurobiological mechanisms involved during the first stage depend on both the rewarding effects of the substance and the stimuli associated with drug consumption, also known as conditioned stimuli. The main pathway involved in the reward system is the *mesolimbic dopamine system* : the projection dopaminergic (DA-ergic) system connecting the ventral tegmental area (VTA) to the nucleus accumbens (NAc, part of the ventral striatum), prefrontal cortex (PFC) and other cortical regions and amygdala (Di Chiara and Imperato, 1988; Tanda et al., 1997; Watkins et al., 2000; Mameli-Engvall et al., 2006).

Rewarding stimuli act on the brain by increasing dopamine (DA) levels following phasic DA neurons firing in the VTA (Covey et al., 2014). Similarly, drugs of abuse cause DA levels to steeply increase and act on D1 receptors, emulating natural rewarding stimuli (Caine et al., 2007). However, differently from natural stimuli, drugs cause more prolonged and unregulated DA release, leading to synaptic plasticity in both the DA system and the DA-receptive neurons (Wolf, 2002).

Besides reward, other two important constructs to consider during the binge/intoxication stage are conditioned reinforcement and incentive salience. A reinforcement is said to be conditioned when previously neutral stimuli can strengthen behaviours through their association with the primary reinforcer and in turn become reinforcers (Robbins, 1976). The incentive salience theory was thoroughly described by Robinson and Beveridge in 1993 (Robinson and Berridge, 1993). Until then, Wise's anhedonia hypothesis, stating that the DA-ergic systems in the brain play a central role in the subjective experience of pleasure associated with positive rewards (Wise, 1982) was widely accepted. As opposed to this

hypothesis, Robinson and Berridge's incentive salience theory contrasts the psychological processes responsible for "liking" and "wanting" something (responsible for pleasure and incentive salience, respectively). With this regard the authors believe that incentive motivation involves three psychological processes acting jointly (Robinson and Berridge, 1993):

1. Pleasure: the "liking", which is insufficient to lead motivated behaviour (Berridge et al., 1989);
2. Associative learning: assignment of pleasure to a stimulus or an action, which predicts pleasure;
3. Incentive salience: the "wanting". Salience attribution to stimuli or actions cause the same stimuli or actions to be attractive.

The relevant circuit for salience attribution is the one of *ventral striatum*, particularly the NAc (Belin and Everitt, 2008; Belin et al., 2009; Wolf and Ferrario, 2010; Lüscher and Malenka, 2011). Dopamine D1 receptors in the NAc are activated following phasic DA release in the VTA, which in turn follows the presentation of new rewards or conditioned reinforcers. Consequently, NAc becomes more reactive to glutamate and two mechanisms seem to drive the drug-seeking behaviour: decreased glutamate levels in the NAc (1), and increased glutamate release from prefrontal cortical- and amygdalar- glutamatergic projections to the NAc (2) (Roberts et al., 1996; Weiss et al., 1996; Pierce and Kalivas, 1997; McFarland et al., 2003). The combination of low glutamate levels and its increased release from other areas to the NAc is hypothesized to be responsible for the drug-seeking behaviour (Kalivas, 2004).

As previously mentioned, a third system has been proposed to be involved in this first stage of the addiction cycle: the *ventral striatum-dorsal striatum-thalamus* circuit, involved in the transition from voluntary to habitual and compulsive drug seeking. The dorsal striatum is part of the basal ganglia and is composed of the caudate and putamen. It is thought to be an important area in the binge/intoxication stage because it receives projections from the ventral striatum and two PFC areas: the orbitofrontal cortex (OFC) responsible for reward processing and salience attribution and the cingulate gyrus, which disruption causes loss of inhibitory control and leads to impulsivity. These prefrontal areas are activated by drugs and conditioned stimuli (Koob and Bloom, 1988; Grant et al., 1996; Childress et al., 1999). Brain imaging studies on humans showed that drug-associated cues are able

to induce DA increases at the level of the dorsal striatum, with DA magnitude inversely correlating to addiction severity (Martinez et al., 2007). Studies suggest that DA increase observed in the dorsal striatum following conditioned stimuli is the result of the stimulation of DA neurons by means of glutamatergic afferents from PFC (which includes OFC) and amygdala. These effects on the dorsal striatum are thought to contribute to compulsive drug seeking (Volkow et al., 2006; Wong et al., 2006). Finally, thalamus regulates arousal and modulates attention, for this reason it is believed to have a role in the addictive. However, few studies investigate the involvement of thalamus in addiction and most of them were carried out on cocaine abusers. There seem to be abnormalities in DA transmission at the thalamic level in addict patients, which could contribute to impairments in attention and craving (Volkow et al., 1997; Tomasi et al., 2007; Koob and Volkow, 2010, 2016; Horseman and Meyer, 2019).

Withdrawal/Negative Affect Stage

The binge/intoxication stage is characterized by an excessive drug consumption, initiating neuroadaptations that lead to the withdrawal/negative affect stage through a process called *allostasis*. To understand allostasis, it is necessary to first explain the term homeostasis. Homeostasis has been defined as the necessary mechanism for survival, maintaining a narrow range of vital and physiological parameters (Sterling and Eyer, 1988; McEwen, 2000). Starting from this concept, allostasis has been described as the maintenance of stability outside physiological and homeostatic ranges and as "stability through change" (Sterling and Eyer, 1988). Thus, allostasis is characterized by a chronic deviation from homeostatic operating levels.

During acute withdrawal and chronic abstinence, addicts show peculiar physical and motivational signs such as physical pain, chronic irritability, dysphoria, emotional pain, sleep disturbance and loss of motivation for natural rewards. The allostatic state, which is characterized by both a decrease in reward function and an activation of the stress system, is hypothesized to be responsible for these negative emotional states (Koob and Le Moal, 2001; Koob and Volkow, 2016; Koob and Schulkin, 2018).

At the neurobiological level, negative emotional states were hypothesized to be mediated by both within-system and between-system neuroadaptations (Koob and Bloom, 1988). Within-system neuroadaptations are the first to be recruited during the second stage of addiction and involve the reward neurocircuitry. Changes that can be observed during withdrawal include: decreased firing of DA-ergic neurons in VTA with consequent decreased DA release in the NAc; decreased serotoninergic and Gamma-AminoButyric Acid-ergic (GABAergic) transmission in the NAc; and increased glutamatergic transmission in the NAc (Weiss et al., 1992; Diana et al., 1993; Parsons and Justice, 1993; Davidson et al., 1995; Dahchour et al., 1998).

On the other hand, in between-system neuroadaptations, neuronal circuits other than the ones involved in positive reinforcement are recruited or dysregulated by chronic activation of the reward system (Koob and Bloom, 1988). Particularly two stress-systems, conceptualized as anti-reward systems (Koob and Le Moal, 2008), are engaged and activated: the hypothalamic-pituitary-adrenal (HPA) axis through the adrenocorticotropic hormone (ACTH) release and the stress system mediated by extrahypothalamic release of corticotropin releasing factor (CRF) (Koob and Volkow, 2016).

The most important neural circuit affected by between-system neuroadaptations is what is termed the "extended amygdala". Extended amygdala is a macrostructure composed of the central medial amygdala, the bed nucleus of stria terminalis, the sublenticular substantia innominate and a zone of transition forming the NAc shell. The extended amygdala receives afferents from hippocampus, basolateral amygdala (BLA), limbic cortex, midbrain and lateral hypothalamus and sends efferent fibres to the medial VTA, brainstem and lateral hypothalamus (Heimer and Alheid, 1991; Heimer et al., 1991). During acute withdrawal it has been observed a response of elevated ACTH, corticosterone and amygdalar CRF. With protracted abstinence and withdrawal progression CRF, together with norepinephrine and dynorphin, is recruited in the extended amygdala producing aversive and stress-like states (Koob et al., 1994; Heinrichs et al., 1995; Gracy et al., 2001). Among the other structures affected by neuroadaptations there are the lateral habenula, which mediates and encodes aversive states controlling DA neurons firing in the VTA (Matsumoto and Hikosaka, 2007; Salas et al., 2009; Fowler et al., 2011); and the insula, which interfaces with the extended amygdala and has interoceptive functions, integrating

autonomic and visceral signals with emotion and motivation (Clark et al., 2008; Goudriaan et al., 2010; Verdejo-Garcia et al., 2014). To conclude, the endogenous anti-stress system (mediated by neuropeptide Y, nociception and endocannabinoids) influences vulnerability to the development of addiction, as it may be under-activated during withdrawal (Economidou et al., 2011; Sidhpura and Parsons, 2011; Reisiger et al., 2014).

In summary, the combination of within-system and between-system neuroadaptations, the former corresponding to decreased reward function, the latter corresponding to increased stress function, anti-reward system activation and/or anti-stress system under-activation, triggers the negative reinforcement contributing to addiction, compulsivity and chronic relapse (Koob and Volkow, 2016).

Preoccupation/Anticipation Stage

The third stage of the cycle has been investigated mainly in animal studies. In fact, the preoccupation/anticipation stage has been linked to craving, which is a difficult construct to evaluate in humans. Moreover, craving doesn't always correlate with relapse (Tiffany et al., 2000). As we might recall from the first stage of the addiction cycle, VTA DA cells project to the NAc contributing to incentive salience development. In turn PFC has been identified as necessary to maintain executive control over incentive salience. In fact, its excitatory glutamatergic projections to VTA DA neurons control DA release in PFC and basal ganglia areas connected with VTA.

Animal studies focusing on drug-induced reinstatement revealed the involvement of DA-regulated glutamatergic projection from prelimbic PFC to NAc. On the other hand, cue-induced reinstatement in rodents revealed the engagement of glutamatergic projections from prelimbic PFC, BLA and ventral subiculum to NAc, as well as DA modulation in BLA and dorsal striatum (Vorel et al., 2001; Everitt and Wolf, 2002; Vanderschuren et al., 2005). Humans imaging studies on cue-induced craving report similar results, with PFC activation and increased DA release in both ventral and dorsal striatum, amygdala and PFC (Lee et al., 2005; Risinger et al., 2005; Volkow et al., 2005; Volkow et al., 2006; Fotros et al., 2013; Jasinska et al., 2014; Kober et al., 2016; Milella et al., 2016).

Based on these observations, Koob and Volkow suggest that glutamatergic projections mediate craving responses (Koob and Volkow, 2016). Besides, glutamate-mediated PFC activation is accompanied by executive disfunctions, which are suggested to involve a disruption in GABAergic activity in PFC (George et al., 2012).
Craving seems to be associated also with insular disfunctions, as this area provides impulses conscious awareness. Insular reactivity has been observed to be so important as to suggest it as a biomarker for relapse prediction (Janes et al., 2010). Finally, a reduction of striatal D2 receptors was observed in addicted patients (Volkow et al., 2009), which seems to correlate with impulsivity and compulsivity (Martinez et al., 2007; Lee et al., 2009; Koob and Volkow, 2016).

Briefly, firing changes start to happen in the mesolimbic DA neurons after the first administration of a drug, which leads to long term potentiation in both VTA and NAc and finally involves the dorsal striatum. With prolonged drug-use, amygdala and medial PFC encounter long-term changes which, in combination with stress system activation and anti-stress system dysregulation, cause a drive for drug-seeking behaviour (Koob and Volkow, 2010).

To summarize, drug addiction is a chronic and relapsing behavioural disorder and it is thoroughly described in the DSM-5. However, the DSM-5 does not cover other behavioural disorders, such as sex, shopping or food addiction (American Psychiatric Association, 2013). Therefore, the following paragraph will define food addiction after a description of food intake physiology. Food addiction description will be based on the scientific literature published up to now.

1.2 Food addiction

1.2.1 Food intake physiology

Food consumption is necessary for survival and is physiologically regulated by five brain regions: amygdala, hippocampus, insula, OFC and striatum (Wang et al., 2009a), each controlling different aspects of feeding (learning food reward, allocating the right attention and salience to food rewards, integrating information from the outside world –for example food availability–, integrating information

about energy stores in the body and so on). Besides NAc, lateral hypothalamus (LH) and VTA have been identified as crucial in motivation for rewards in general, and for food as well (Castro et al., 2015). Particularly, LH has been shown to be so important as to earn the "feeding centre" epithet. In fact, studies showed that LH lesions cause aphagia (Anand and Brobeck, 1951) and, by contrast, LH activation through electrical stimulation causes increased food and water intake (Delgado and Anand, 1953). Moreover, LH roles have been extended as to include palatability, i.e. food affective processing (Teitelbaum and Epstein, 1962).

Physiologically, feeding homeostasis is regulated by four hormones, allowing for the interaction between the peripheral and central nervous system: ghrelin, synthesised in the stomach, raises food consumption (Wren et al., 2000); leptin informs the brain about fat reserves in the body (Maffei et al., 1995); insulin and peptide YY inform the brain about acute changes in energy levels (Blumenthal and Gold, 2010). At the level of the CNS, other important homeostatic peptides deserve to be briefly described, such as the anorexigenic alpha-Melanocyte-stimulating hormone (α-MSH), the orexigenic neuropeptide Y (NPY), the melanocortin antagonist agouti related peptide (AgRP), orexin, the melanin concentrating hormone (MCH) and endorphins (Moran and Ladenheim, 2016). Briefly, NPY and AgRP releasing neurons in the hypothalamus increase their activity with low levels of leptin, causing an increased release of these peptides. By contrast, high hypothalamic leptin levels inhibit NPY/AgRP containing neurons (Schwartz et al., 1996). The result of the high release of these two peptides is a potent feeding stimulation (Levine and Morley, 1984; Hahn et al., 1998). Besides NPY and AgRP, leptin-activated neurons in the hypothalamus express the prepropeptide proopiomelanocortin (POMC); POMC can be processed in opioid and melanocortin peptides, including α-MSH, which presence potently inhibits food intake (Thiele et al., 1998; Cowley et al., 2001). Furthermore, neurons in the perifornical region of the LH express orexin and MCH; both peptides are decreased in presence of high levels of leptin and, when present in high concentration, they increase food intake (Qu et al., 1996; Perez-Leighton et al., 2012). Finally, endorphins, together with DA-ergic mediation, play an important role in food-related reward signalling. The major site of action of both endorphins and the DA-ergic system is represented by the NAc. It has been shown that opiate agonists, such as morphine, increase eating through alterations in food palatability, enhancing the intake of preferred food and

hedonic responses to sweet solutions (Doyle et al., 1993; Gosnell and Krahn, 1993). As we know from the previous paragraphs, reward pathways are mediated by DA-ergic circuits, which regulate motivation for both food consumption itself and pleasure derived from eating. It has been reported that DA agonist injections within NAc increase eating (Sills and Vaccarino, 1991) and that DA extracellular levels in NAc is increased with feeding (Hernandez and Hoebel, 1988), with this increase being greater when highly palatable food is consumed (Martel and Fantino, 1996). The DA-ergic pathways are stimulated by ghrelin and inhibited by leptin and insulin (Dagher, 2009; Blumenthal and Gold, 2010).

The following paragraph will cover the topic of food addiction and will discuss the reward circuits that were previously described for drug addiction as well.

1.2.2 From food consumption to food addiction

An individual can be said to be a food addict when he/she develops maladaptive patterns of food consumption (Blumenthal and Gold, 2010). Particularly, based on the "refined food addiction" hypothesis, refined food (containing processed sugars, salt, fat etc.) can be addictive, and refined food consumption behaviours may meet the criteria for substance use disorders (Ifland et al., 2009). In fact, it is true that food is necessary for survival; however, palatable and highly appetitive foods such as those rich in refined sugar and fat are non-essential (Carter et al., 2016).

Food addiction has long been associated with obesity (Volkow and O'Brien, 2007; Davis et al., 2011; Gearhardt et al., 2011); support for the food addiction theory for obesity comes from similarities between obesity itself and drug addiction in terms of neurobiological and behavioural traits. However, food addiction and obesity are not and cannot be considered synonyms as not all obese patients meet the criteria for food addiction, while some non-obese individual does (Meule, 2011; Lee et al., 2014). Some authors suggest and believe that food addiction can be more likely associated with people suffering from binge-eating disorder, as their eating patterns resemble drug-use patterns typical of substance use disorders (Ziauddeen and Fletcher, 2013; Carter et al., 2016).

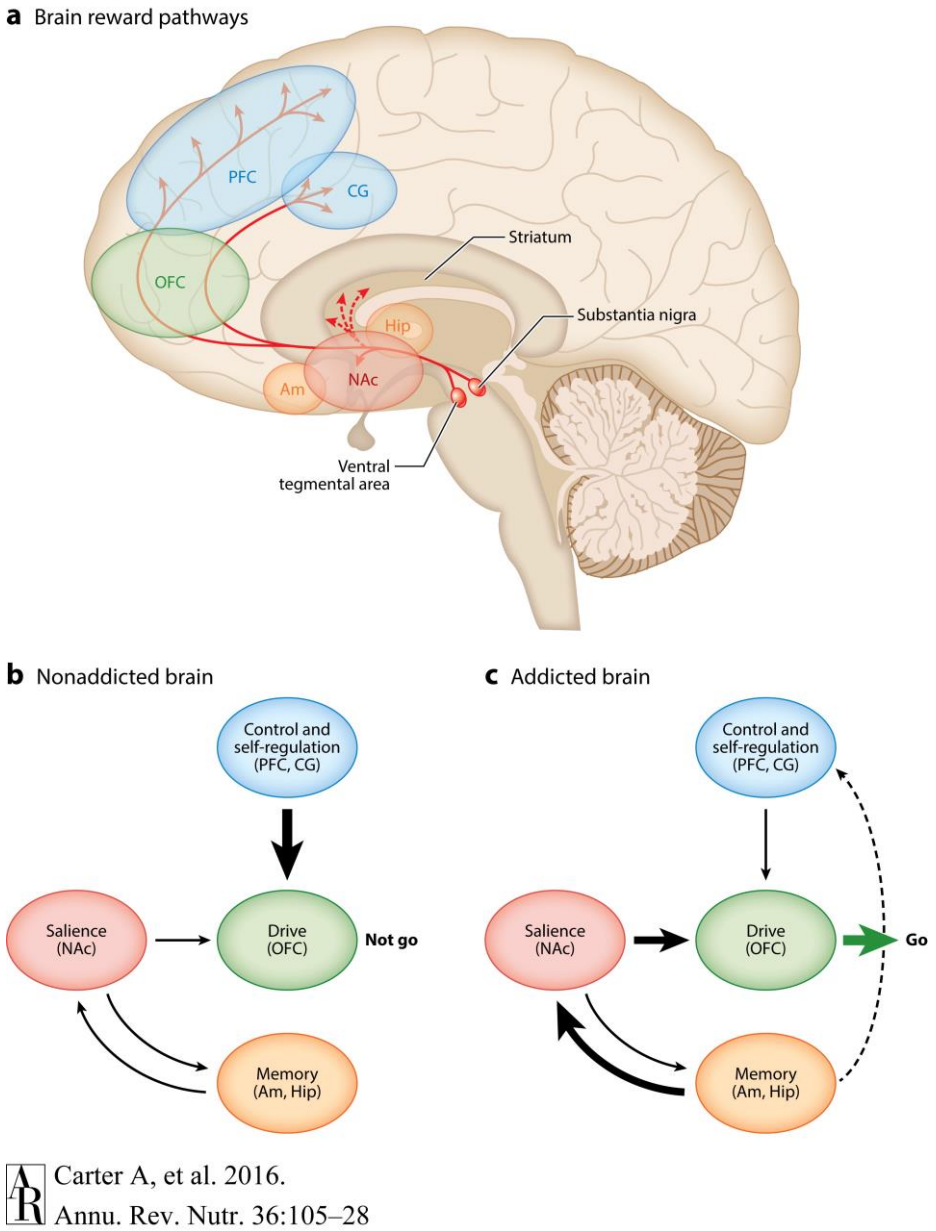
Similarities between obese individuals and people suffering from substance use disorders has been found at both neurocognitive/personality level and neurobiological level. At the neurocognitive level, they both show deficits in executive function, displaying impairments in decision making, impulsivity and delay discounting, the latter defined as the tendency to discount future rewards while focusing on prompt gratification (Bechara, 2005; Weller et al., 2008; Fitzpatrick et al., 2013). Other neurocognitive deficits comprehend reduced inhibitory control (Barry et al., 2009), raised attentional processing of food-related stimuli (Nijs and Franken, 2012; Hendrikse et al., 2015), increased cue-reactivity (Castellanos et al., 2009), motivationally mediated salience of food information (Carter et al., 2016), craving for food (Nijs et al., 2010).

At the neurobiological level, most of the information we have comes from animal studies, investigating neurochemical mechanisms in models of food overconsumption (Carter et al., 2016). First, as for addictive drugs, hyperpalatable foods act on the DA-ergic reward pathway, with VTA DA cells projecting to NAc and limbic and cortical regions (Stice et al., 2013; Nieh et al., 2015). The reward pathway and the specific mechanisms that were described for the drug addiction cycle (reward processing, salience attribution, loss of inhibitory control etc.) seem to be involved in food addiction and excessive food intake as well (Volkow et al., 2013b). The reward system seems to be activated by calorie-rich foods independently of taste (de Araujo et al., 2008). A decrease in D2 receptors is also observed, accompanied by a reduced DA signalling in the ventral striatum, which contributes to what is termed a reward-deficiency syndrome (reduction in sensitivity to natural rewards) (Blum et al., 2000; Koob and Le Moal, 2006; Geiger et al., 2009; Johnson and Kenny, 2010; Kenny et al., 2013). Moreover, D2 receptors reduction at the level of the striatum leads to a reduced metabolism in OFC and the anterior cingulate cortex (ACC), which disruption brings to loss of control (London et al., 2000). As for drug-reward exposure, after repeated food rewards exposure, the DA system is activated by conditioned stimuli that can induce craving (Berridge, 2009; Stice et al., 2013; Carter et al., 2016).

In human imaging studies similar results were observed, including: increased DA release when consuming hyper-palatable food; decreased striatal D2 receptors in obese patients; reduced activity in ACC and OFC, respectively responsible for inhibitory control and decision making; striatal DA increase associated to food-

associated cues, which plays an important role in craving and relapse; and dysregulation of the stress axis (Tang et al., 2012; Stice et al., 2013; Volkow et al., 2013b, a; Carter et al., 2016; Lemieux and al'Absi, 2016; Contreras-Rodriguez et al., 2017). Figure 2 shows for a summary of the addicted brain versus the non-addicted brain.

In summary, food addiction, as drug addiction, is a behavioural disorder. This section covered food addiction and its neurocognitive and neurobiological features, giving prominence to food and drug addiction similarities. Memory processes are strictly related to behavioural disorders, and can also be considered memory disorders; therefore, the following section will give an overview of memory, starting from its definition and spanning through memory consolidation, retrieval and reconsolidation processes.



Carter A, et al. 2016.
Annu. Rev. Nutr. 36:105–28

Figure 2. Brain circuits involved in drug and food addiction. (a) The nucleus accumbens (NAc) is important in salience attribution; orbitofrontal cortex (OFC) is involved in decision making and expecting rewards or punishments of an action. Amygdala and hippocampus (in the figure respectively, Am and Hip) are important for stimulus/reward memories formation. Prefrontal cortex (PFC) and anterior cingulate gyrus (CG) provide inhibitory control and emotional regulation. Addictive foods and drugs cause the release of dopamine from the ventral tegmental area to the NAc, a region regulating the activity in the frontal regions through the mesolimbic reward pathway (red arrows). (b) Reward pathway in the nonaddicted brain; (c) reward pathway in the addicted brain. In the addicted brain, compulsive behaviour is driven by hyperactivation of the memory/conditioning and

reward/saliency regions in the brain, together with a downregulation of the controlling regions PFC and CG (Baler and Volkow, 2006; Carter et al., 2016). *From (Carter et al., 2016). Reprinted with permissions from Annual Reviews.*

1.3 Addiction as a memory disorder

As anticipated in the previous section, memory processes are linked together with behavioural disorders. Therefore, to better understand how addiction can be considered a memory disorder, the following paragraphs will define and classify memory, and then will describe memory consolidation, retrieval and reconsolidation processes. Finally, the focus will be on sucrose instrumental memory reconsolidation, as the instrumental sucrose self-administration paradigm was used as a model for food addiction.

1.3.1 Memory classification

Memory is not a single entity; thus, its description cannot be limited to a single definition. First, a distinction is made between short-term, or working, memory and long-term memory (Atkinson and Shiffrin, 1968; Baddeley and Warrington, 1970; Milner, 1972). Working memory is used to store a limited amount of information during learning through a short time interval (usually seconds to hours) (Baddeley and Hitch, 1974; McGaugh, 2000). On the other hand, long-term memories are stored for hours to months, or even a lifetime; they allow to recall information from the past. Long-term memories don't occupy the current stream of thought, either because they exceed the working memory capacity or because attention is redirected to other memoranda (Jeneson and Squire, 2012).

One of the major contrasts between working memory and long-term memory is represented by their capacity. The former is highly limited in the amount of information it can simultaneously hold (Luck and Vogel, 1997; Cowan, 2001; Baddeley, 2003); the latter has a nearly boundless capacity (Eriksson et al., 2015). However, the two types of memory are not independent from each other. In fact, working memory capacity also depends on whether things to be remembered can be clustered in meaningful units: this clustering allows to use concepts stored in long-term memory to more efficiently store information in working memory and increase performance (Miller, 1956; Brady et al., 2009; Eriksson et al., 2015).

Moreover, a short-term memory can undergo what is termed "memory consolidation" and stabilize as a long-term memory, a time-dependent process requiring protein synthesis. The memory consolidation process will be discussed in the following section.

Long-term memory can be divided in two categories: declarative memory and nondeclarative memory, which in turn are composed of sub-categories, shown in Figure 3. Declarative memory makes it possible to consciously recall fact-based information; on the other hand, nondeclarative memory allows for nonconscious information storage and it is expressed through skills and abilities, which manifest through performance rather than on conscious recollection of information (Squire and Zola, 1996). Declarative memory can be divided in semantic memory, which is relative to facts and it involves learning of factual knowledge (Squire, 2004); and episodic memory, which is relative to events and it represents the set of information derived from personal experience and remembering a specific episode (Tulving, 2002).

Nondeclarative memory can be divided into procedural memory, priming, non-associative learning and conditioning (Squire and Dede, 2015). Procedural memory refers to motor and perceptual skills that can be measured through performance. Priming can be defined as an unconscious improved access to items (or associated items) that have been recently presented (Graf et al., 1984). Non-associative learning, also called trial-and-error learning, leads to habit formation and is characterized by automatized and repetitive behaviours (Dickinson, 1985). Finally, conditioning can be divided in classical or instrumental conditioning. Classical conditioning was independently discovered by two scientists: Edwin Burket Twitmyer in the United States and Ivan Petrovich Pavlov in Russia in the first 1900s. In its most basic form, an initially neutral stimulus, called conditioned stimulus (CS) predicts the occurrence of an unconditioned stimulus (US), a stimulus that can induce a measurable behavioural response (the unconditioned response) when presented alone. The CS may be a sound, an odour, or a light for example; the US may be a stimulus with positive or negative reinforcing properties, such as food or foot-shock, which elicit unconditioned responses such as salivation and freezing respectively for food and foot-shock. When the CS is repeatedly presented right before the US, it begins to elicit a response, called conditioned response, even

when presented alone. A conditioned response, unlike unconditioned responses, is not innate; rather, it is learned (Clark, 2004; Murphy and Lupfer, 2014).

Operant conditioning, or instrumental learning, has been described in 1938 by the American Burrhus Frederic Skinner. In operant conditioning, the subject does not passively learn associations between a CS and a US, rather he/she learns that his/her actions are followed by a consequence. Consequences can be categorized as follows: positive and negative reinforcements (procedures that induce an increase in the frequency of an action), and positive and negative punishments (procedures that induce a decrease in the frequency of an action). Positive reinforcements are also called "rewards"; an example of a reward is a food pellet which is given to a rat when a lever is pressed. The stimulus causing the increase of the rate of lever pressing is called a positive reinforcer. For negative reinforcements, the rate of responding is increased to prevent or terminate the presentation of a negative stimulus, which may be a foot-shock that can be interrupted by pressing a lever. On the other hand, a positive punishment follows a behaviour and decreases the probability of the same behaviour. For example, a rat may be foot shocked each time it presses a lever; this would induce a reduction in the lever pressing and the shock is said to be a positive punisher for lever pressing. Finally, in negative punishment, a behaviour causes the removal of a stimulus, which in turn causes the reduction of that same behaviour. An example of negative punishment is food removal: given a food-deprived rat, it may be given free access to food, with lever pressing provoking food removal. This consequence will induce the rat to decrease the rate of lever pressing (Miller, 2006; Murphy and Lupfer, 2014). In summary, in operant conditioning a subject learns an association between a behaviour (or non-behaviour) and a positive or negative consequence, which causes the subject to increase or decrease the rate of his/her behaviour as a function of the presentation or removal of a stimulus.

Among the different memory classifications, the focus of the present dissertation will be on positive reinforcement operant conditioning, by applying a sucrose self-administration paradigm.

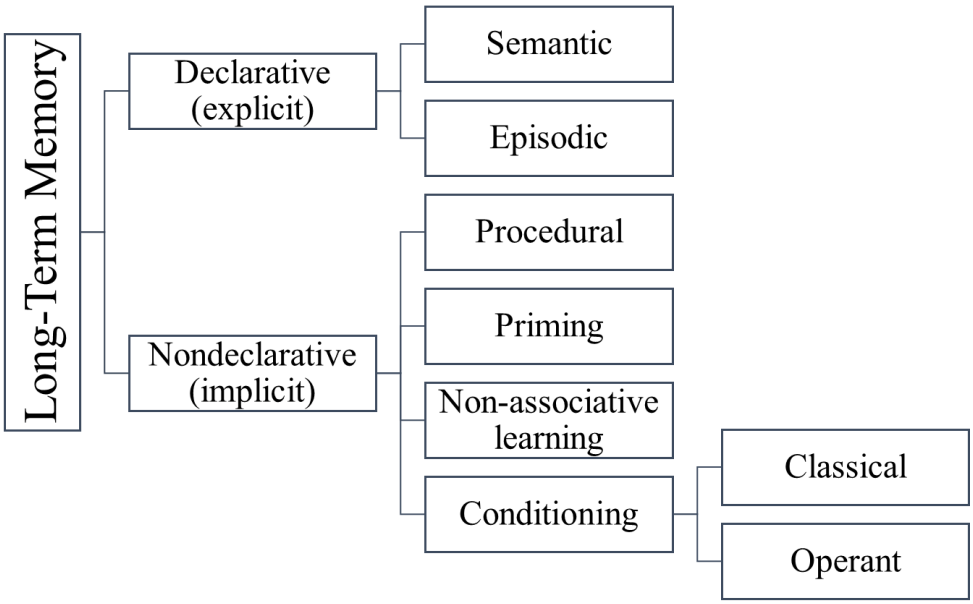


Figure 3. Long-term memory categories.

Long-term memory can be classified in declarative and nondeclarative memory. Declarative memory can be semantic and episodic; nondeclarative memory can be divided in procedural memory, priming, non-associative learning and conditioning, which can be classical (or Pavlovian) or operant (or instrumental).

1.3.2 Memory processing: from learning to consolidation

New information can evolve into a long-term memory following two stages: encoding (i), taking from milliseconds to seconds, which leads to acquisition and the formation of a short-term memory, susceptible to loss or change; and consolidation (ii), a set of processes needed to the long-term stabilization of new information (Stickgold and Walker, 2005). During encoding, receiving stimuli from the environment results in the development of a new memory trace; in its first stages, the memory trace is susceptible to decay, leading to forgetting (Rasch and Born, 2013). However, when a memory undergoes consolidation, the memory trace is stabilized (McGaugh, 2000) to be strengthened and integrated into already existing knowledge networks (Rasch and Born, 2013).

Memory consolidation theory was first proposed by Müller and Pilzecker in 1900 (Müller and Pilzecker, 1900) and it is described as the time-dependent process requiring protein synthesis by which a labile and temporary memory is transformed into a stable and long-lasting memory (Figure 4) (McGaugh, 2000; Squire et al.,

2015). The key observation that led to the consolidation theory is related to retrograde amnesia: recent memories are more susceptible to interferences than remote ones (Ribot, 1881). It has been observed that a memory could be disrupted or improved when interferences were presented soon after memory acquisition; this observation led to the distinction between the unstable and sensitive to interferences short-term memories and the stable and unsensitive to disruption long-term memories (Haubrich and Nader, 2018). Examples of disruptive interferences are electroconvulsive shock, protein synthesis inhibitors injection and newly learned competing information (Duncan, 1949; Flexner et al., 1965; Gordon and Spear, 1973). Conversely, examples of some treatments improving memory maintenance are strychnine, cholecystokinin receptors activation and amphetamines (McGaugh and Krivanek, 1970; Flood and Morley, 1989; Lee and Ma, 1995).

Present-day, the term consolidation is used to describe two types of events: synaptic consolidation and systems consolidation. Synaptic consolidation implicates the strengthening of memory representations at the level of the synapses; thus, it is the process by which synaptic plasticity induced by learning is stabilized at synaptic/cellular level and it implies changes in synaptic connections in localized neuronal circuits; this process happens within hours after learning and require gene transcription, new protein translation and synaptic growth (Bailey and Chen, 1983; Montarolo et al., 1986; Schacher et al., 1988; Bailey and Chen, 1989; Dudai, 2004; Born and Wilhelm, 2012; Asok et al., 2019). By contrast, system consolidation process is needed to allow memory consolidation; the term refers to the reorganization of the brain systems that support memory (Squire et al., 2015). During systems consolidation long-term memories, which initially depend on the hippocampus, find a more permanent storage in neocortical regions. These reorganizations at systems level include an increased complexity, distribution and connectivity among regions in the neocortex (Squire and Alvarez, 1995; Dudai and Morris, 2000; Squire et al., 2015). As opposed to synaptic consolidation, which seems to equally occur during sleep and wakefulness, system consolidation seems to take place exclusively during sleep, in order not to interfere with the normal processing of external stimuli (Diekelmann and Born, 2007; Born and Wilhelm, 2012).

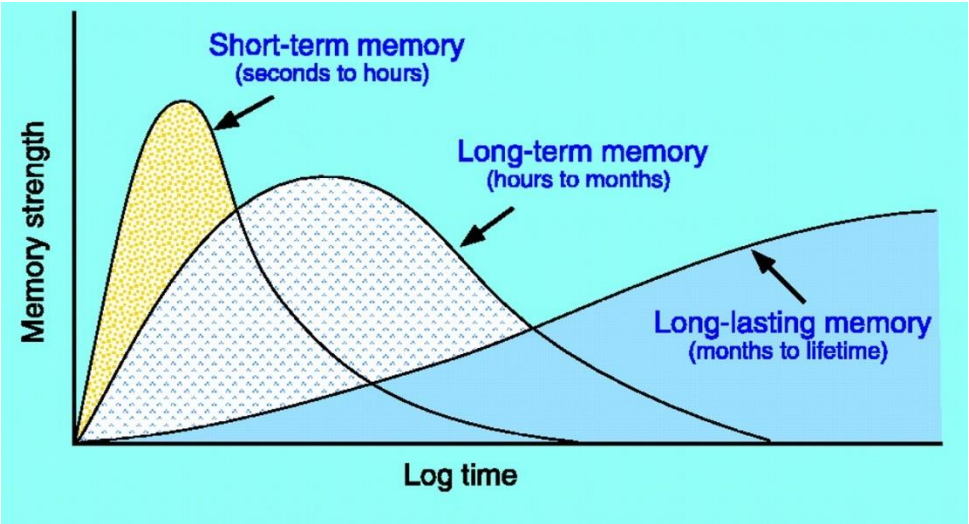


Figure 4. Memory consolidation phases. Memory consolidation is a time-dependent process. However, short-term and long-term memories are not strictly sequentially linked, as suggested in 1965 in the dual-trace hypothesis by Agranoff and colleagues (Agranoff et al., 1965). Rather, consolidation brings to the stabilization of a short-term memory into a long-term memory; however, different memory stages depend on different processes acting simultaneously. Later consolidation stages result in long-lasting memories formation, which involve the interaction and reorganization of the connections in different brain systems (McGaugh, 2000). *From (McGaugh, 2000). Reprinted with permissions from AAAS.*

1.3.3 Memory reconsolidation

Once a memory trace goes through the process of consolidation to become a long-term memory, it becomes stable. Long-term memories were once believed to be not only stable, but also static and immutable (Squire et al., 1984; Nader, 2003). Based on the first formulation of the consolidation theory, long-term memories retrieval was a simple and passive access to consolidated memories. This theory soon started to be confuted after the observation that fear memories (classical conditioning) could be impaired in rodents exposed to Electroconvulsive Shock (ECS) when ECS was presented 24 hours after fear conditioning (thus, consolidated) and soon after the fear memory was reactivated by means of CS presentation (Lewis et al., 1968; Misanin et al., 1968; Schneider and Sherman, 1968). A study published by Gordon in 1977 also shown that a consolidated memory can be disrupted when new information is acquired soon after memory reactivation (Gordon, 1977). Based on

these studies, a long-term memory is disrupted leading to amnesia only when the interference (ECS or acquisition of competing information) is applied soon after memory reactivation.

Thus, memory recall can destabilize a consolidated memory and bring it back to a labile state subject to degradation; the transformation of the destabilised memory trace to a re-stabilised form needs a phenomenon similar to a new learning, requiring protein synthesis, called reconsolidation (Figure 5) (Spear, 1973; Przybyslawski and Sara, 1997; Nader et al., 2000; Nader, 2003; Stickgold and Walker, 2005). However, if a memory is destabilised and not reconsolidated, it can degrade (Stickgold and Walker, 2005). Other studies confirmed or supported the reconsolidation theory (Terry and Holliday, 1972) across different species as well, such as the garden slug *Limax* (Sekiguchi et al., 1997) and both across aversive and appetitive paradigms (Bucherelli and Tassoni, 1992; Land et al., 2000; Sara, 2000).

When talking about reconsolidation, it is important to define the difference between the concepts of memory retrieval and memory reactivation. In literature the two terms are often used interchangeably, however they don't represent the same process. Memory retrieval can be defined as the process that allows to use previously acquired information; memory reactivation on the other hand is a necessary component of memory retrieval and can be defined as the process that allows to trigger the memory from a latent state to a "retrievable" state (Gisquet-Verrier and Riccio, 2012). Thus, if the memory is not reactivated, it cannot be retrieved. Memory reactivation is required in every case in which a knowledge needs to be modified: it is the case of retraining, during which supplementary information to the reactivated one is acquired; extinction, during which previously learned responses are not reinforced anymore; or, more in general, rule-shiftings which require a memory to be updated. Reactivation can occur if the subject is re-exposed to cues associated to a specific memory (Gisquet-Verrier and Riccio, 2012).

Reconsolidation studies continued also in more recent years. As previously mentioned, these studies propose and confirm that consolidated memory reactivation is a manipulation that destabilizes the memory itself. This destabilization returns the memory to a labile state requiring the protein synthesis-dependent stabilization process called reconsolidation. Reconsolidation has been

observed to be necessary both for memory maintenance (Tronson and Taylor, 2007; Hardt et al., 2010) and update (Morris et al., 2006; Lee, 2010).

Studying and observing the memory reconsolidation process behaviourally is a challenge. For this reason, memory reconsolidation occurrence has been demonstrated by different authors through its manipulation. For example, it has been demonstrated through its inhibition (Lee, 2009; Tedesco et al., 2014); more rarely, it has been demonstrated through its enhancement (Stern and Alberini, 2013). Based on the scientific literature, the reconsolidation process seems to be complete by 6-h after memory reactivation. After this time, as for consolidated memories, the memory trace becomes again resistant to interferences (Przybyslawski et al., 1999; Nader et al., 2000; Gruest et al., 2004; Stickgold and Walker, 2005).

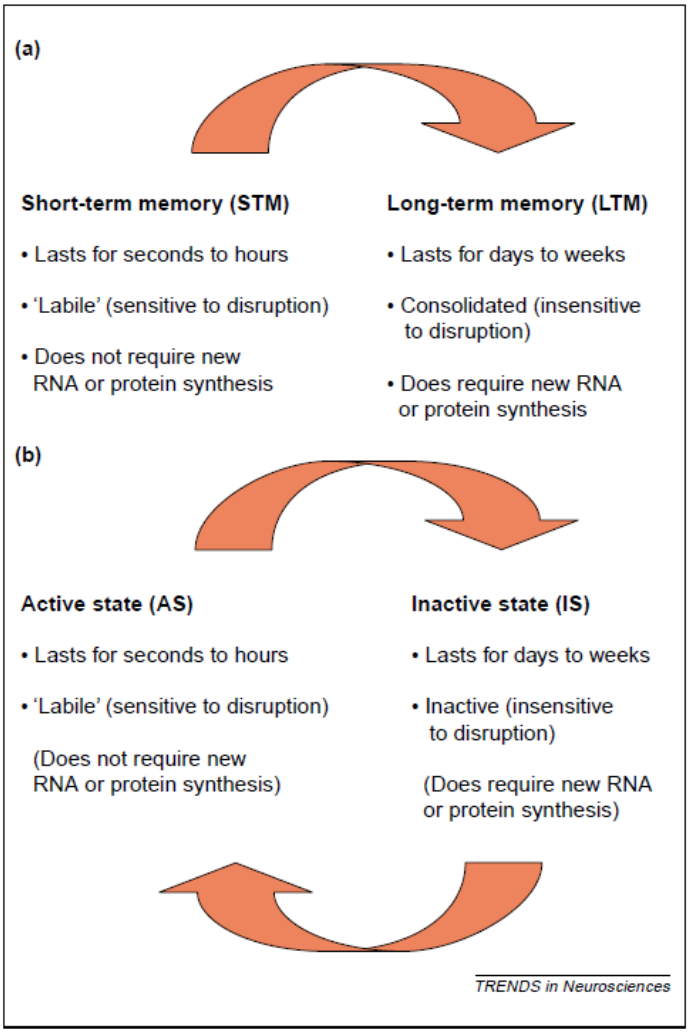


Figure 5. Traditional consolidation theory vs reconsolidation model.

The traditional consolidation theory (a) states that a labile short-term memory becomes consolidated into a stable long-term memory through the consolidation process, which requires protein synthesis. Long-term memories are posited to be permanent and unmodifiable. The reconsolidation model proposed by Lewis in 1979 (Lewis, 1979) (b) distinguishes between an active state (AS; analogous to short-term memory) and an inactive state (IS; analogous to long-term memory). New memories enter an AS and eventually enter an IS with time (top red arrow). If memories in IS are reactivated, they return to AS and they become susceptible again (bottom red arrow). *From (Nader, 2003). Reprinted with permissions from Elsevier*.

1.3.4 The boundary conditions of memory reconsolidation

In order to study appetitive memory reconsolidation, a behavioural protocol must be set up. Usually in rodents the behavioural protocol goes through the following steps: training (i), memory reactivation/manipulation (ii) and test for retention (iii). However, intrinsic characteristics of consolidated memories can influence the occurrence of memory reactivation, and specific parameters (called *boundary conditions*) in the behavioural protocol must be carefully chosen. In fact, not every retrieval session is able to destabilize and eventually reactivate a memory trace.

Important boundary conditions are represented by memory age and memory strength. In fact, while recent memories are in subcortical regions such as hippocampus, older memories are found in cortical areas and need stronger stimuli to be destabilized and disrupted (Frankland et al., 2006). On the other hand, memory strength can be defined by the length of the training stage. Wang and colleagues in 2009 showed that 10 tone-shock pairings in fear memory conditioning created a stronger memory trace with respect to a single pairing (Wang et al., 2009b). Two days after conditioning, fear memory reactivation was performed in a different context with respect to the training one. Following, anisomycin (ANI, an antibiotic inhibiting protein synthesis) injections in BLA could inhibit the weaker memory trace reconsolidation and could not disrupt the stronger memory reconsolidation, as the reactivation session wasn't able to destabilize the stronger memory trace (Wang et al., 2009b). Other boundary conditions have been reported to influence memory retrieval such as reactivation context (Hupbach et al., 2008), phase of reactivation (wake vs sleep) (Diekelmann et al., 2011) and CS specificity (Debiec et al., 2006).

Finally, one of the major constraints for memory reconsolidation is predictability (Pedreira et al., 2004): prediction error (defined as the mismatch between what is expected and what actually happens) is believed to function as a destabilizing factor for its ability to re-access previously consolidated memories (Fernandez et al., 2016).

1.3.5 Sucrose instrumental memory reconsolidation

Memory reconsolidation for sucrose has been studied using the typical drug addiction behavioural protocols. Among these, one widely used protocol follows drug addiction progression and consists of an initial bingeing stage for sucrose, a withdrawal stage in which incubation of reward craving happens and the final sucrose craving stage, which can be evaluated through a reinstatement test (Grimm et al., 2002; Avena et al., 2005; Grimm et al., 2005). Incubation for drug craving has first been proposed in 1986 by Gawin and Kleber and can be defined as time-dependent increase in cue-induced drug seeking during the first periods of withdrawal from the drug (Gawin and Kleber, 1986). Incubation for cocaine craving has been demonstrated by Grimm and colleagues in 2001 in rats, following a behavioural protocol of cocaine self-administration (Grimm et al., 2001). The phenomenon has been observed with different substances (Li et al., 2015), such as heroin (Shalev et al., 2001), methamphetamine (Shepard et al., 2004), alcohol (Bienkowski et al., 2004) and nicotine (Abdolahi et al., 2010). As for sucrose, Grimm and colleagues in 2002 applied the following behavioural protocol: 10-d training stage in which rats learned to associate lever presses for sucrose to acoustic and visual cues (tone and light respectively); 1-d or 15-d withdrawal; extinction session; memory reconsolidation test. In their study, authors showed that sucrose instrumental responding to tone and light (CS) exposure, was more resistant after 15-d withdrawal than after 1-d withdrawal demonstrating that, as it happens with drugs, incubation happens for sucrose craving as well (Grimm et al., 2002).

Hernandez and colleagues in 2002 and 2004 published two studies demonstrating that ANI injections were not able to disrupt memory reconsolidation (Hernandez et al., 2002; Hernandez and Kelley, 2004). Sucrose instrumental memory reconsolidation was first demonstrated by Wang and colleagues in 2005. Authors used an incentive learning protocol and tested rats for both consolidation and

reconsolidation following ANI or vehicle (VEH) injections in BLA. They showed that ANI inhibited both memory consolidation and reconsolidation and concluded that also sucrose memory reconsolidation depends on protein synthesis (Wang et al., 2005). Sucrose instrumental memory reconsolidation has also been demonstrated to depend on beta-adrenergic receptors, as their inhibition with systemic propranolol (Diergaarde et al., 2006; Milton et al., 2008) or MK-801 (Lee and Everitt, 2008a) injections immediately after retrieval inhibits memory reconsolidation. Particularly, the reactivation session performed by Lee and Everitt in 2008 consisted of a re-exposure to the training experimental session, except for the lack of sucrose US. In a subsequent study, the same authors reported the importance of the CS presentation: in fact, they observed that sucrose instrumental memory was successfully reactivated only when CS was presented contingently with active lever pressing (Lee and Everitt, 2008b). Their results showed the importance of salient memory-evoking stimuli presentation to target memory reconsolidation as a therapeutic tool for addictive behaviours.

In the previous paragraph the topic of boundary conditions was taken into consideration. It was reported that the features of a retrieval session are important to establish whether a memory will be effectively reactivated and undergo reconsolidation or if it will be extinguished. The balance between reconsolidation and extinction for sucrose instrumental memory was assessed in 2013 by Flavell and Lee, who showed that pure instrumental memory reconsolidation is not affected by MK-801 (a NMDA receptors antagonist) injections (Flavell and Lee, 2013). The first to show that MK-801 injections can inhibit pure sucrose instrumental memory reconsolidation were Exton-McGuinness and colleagues (Exton-McGuinness et al., 2014; Exton-McGuinness and Lee, 2015).

In summary, this section covered memory processes relevant for the self-administration operant conditioning paradigm. Following a drug addiction protocol, a subject (usually a mouse or rat) is trained to self-administer a substance/a sugar pellet following lever pressing. Operant conditioning training is a form of memory consolidation between the instrumental behaviour and the reinforcing sucrose pellet. After a period of forced abstinence (withdrawal), in which the subject cannot receive substance/sucrose, the consolidated memory can be retrieved through a reactivation session, which allows for memory reconsolidation occurrence.

Memory processes are influenced by sleep, and some of them exclusively happen when a subject is sleeping. Therefore, the following section will describe sleep and its involvement in memory consolidation and reconsolidation.

1.4 Memory and Sleep

1.4.1 Sleep

Sleep is a physiological and reversible state during which a subject shows loss of consciousness, relative inactivity and reduced responsiveness to external stimuli (Borbely and Achermann, 1999). Across sleep's functions, the followings have been proposed (Rasch and Born, 2013): energy-saving (Webb, 1988; Berger and Phillips, 1995), cell tissue repairing and energy resources restoration (Oswald, 1980), thermoregulation (Rechtschaffen and Bergmann, 1995), metabolic regulation (Knutson et al., 2007; Van Cauter et al., 2008), and adaptive immune functions (Lange et al., 2010). Sleep's features that these functions do not explain are the loss of consciousness and loss of responsiveness; these peculiarities induced researchers to state that sleep is mainly for the correct brain functioning (Kavanau, 1997; Hobson, 2005), including brain free radicals detoxication (Reimund, 1994; Inoue et al., 1995), glycogen replacement (Scharf et al., 2008), synaptic plasticity and memory formation (Tononi and Cirelli, 2006; Diekelmann and Born, 2010).
In mammals, two stages that cyclically alternate have been identified: slow-wave sleep (SWS) and rapid-eye-movement (REM) sleep, also called paradoxical sleep. The former is characterised by slow and high-amplitude electroencephalographic (EEG) oscillations; the latter is characterised fast and low-amplitude EEG oscillations. For having a wake-like oscillatory brain activity, REM sleep is also called paradoxical sleep (Rasch and Born, 2013).

1.4.2 Memory Consolidation and Sleep

Whereas the encoding of new information coming from external stimuli happens during wakefulness, the brain finds in its sleeping state the optimal conditions for memory consolidation processes that allow new memory traces to integrate in the long-term store (Rasch and Born, 2013). Two hypotheses have been proposed to explain mechanisms underlying memory consolidation during sleep: the synaptic homeostasis hypothesis and the active system consolidation

hypothesis, which explain processes probably acting together to optimize memory consolidation during sleep (Figure 6) (Diekelmann and Born, 2010).

In the synaptic homeostasis hypothesis (Crick and Mitchison, 1983; Tononi and Cirelli, 2006) wake encoding would serve to increase brain's synaptic strength, while sleep would be used to downscale this synaptic strength to a sustainable level in terms of tissue volume and energy demands, allowing future use of the same synapses for encoding (Vyazovskiy et al., 2008; Dash et al., 2009; Diekelmann and Born, 2010). Based on this hypothesis, SWS would be associated to downscaling (Tononi and Cirelli, 2006). However, synaptic downscaling would implicate that memories that were weakly encoded are forgotten, which is in contrast with behavioural evidence showing that weakly encoded memories benefit from sleep (Kuriyama et al., 2004; Drosopoulos et al., 2007). Thus, this hypothesis is not able to fully explain sleep dependence of memory consolidation.

On the other hand, to describe the active system consolidation hypothesis, it is first necessary to introduce the two-stage model of consolidation. Based on this model, the temporary store for short-term memories is the hippocampus, while the long-term store is represented by the neocortex. Briefly, events experienced during wakefulness are encoded in both hippocampus and neocortex. Subsequently, mainly during SWS, new memory traces that were encoded during wakefulness are repeatedly reactivated in the hippocampus and are redistributed to the neocortex, exploiting the SWS off-line period. As a result, neocortical synaptic connections are strengthened, giving rise to more persistent memory representations; transferred memories may completely lose their dependence from the hippocampus (Zola-Morgan and Squire, 1990; McClelland et al., 1995; Frankland and Bontempi, 2005; Born and Wilhelm, 2012). Slow waves enable hippocampal memories reactivation and guide the transferring. They are generated in the neocortical networks and their amplitude probably depends on neocortical network's usage during initial encoding: the more information is encoded during wake states, the higher the slow waves amplitude (Huber et al., 2004; Molle et al., 2004; Born and Wilhelm, 2012). Slow waves are relevant also in other brain regions that are involved in memory consolidation, such as the thalamus and the hippocampus. At the level of the thalamus there is the generation of the thalamo-cortical spindles; on the other hand, at the level of the hippocampus sharp-wave ripples, which allow reactivations of memory representations, are generated (Born and Wilhelm, 2012). Consistent with

this, slow oscillations, hippocampal ripple activity and spindle activity were shown to be increased during sleep after learning at the local field potentials level; moreover, increases were also shown to be linked to improved retention of new memories (Gais et al., 2002; Huber et al., 2004; Clemens et al., 2005; Eschenko et al., 2008; Girardeau et al., 2009; Molle and Born, 2009). The described process is used to consolidate new memories, but also to integrate new learnings and knowledge into pre-existing memory representations. Finally, the process is selective, in that memories that are more relevant for the subject will more probably and preferentially undergo consolidation (Born and Wilhelm, 2012).

Starting from this model, it is possible to introduce the second hypothesis: the active system consolidation hypothesis. It was first proposed for declarative memory (Marr, 1971; Buzsaki, 1989; McClelland et al., 1995; Frankland and Bontempi, 2005; Rasch and Born, 2007), however it might describe consolidation in other memory systems as well (Marshall and Born, 2007). Thus, memory transfer is enabled by the synchronous presence of slow waves, hippocampal sharp wave ripples and thalamo-cortical spindles, the latter reaching the neocortex during up-states of slow oscillations. When spindles reach the neocortex, they simulate Ca^{2+}influx starting the synaptic plasticity process (Sejnowski and Destexhe, 2000; Rosanova and Ulrich, 2005; Diekelmann and Born, 2010). Despite the ability of the active system consolidation hypothesis to explain memory consolidation and the integration of new information into the pre-existing long-term memories network, it does not explain how sleep can stabilize the involved synaptic connections in the long term, allowing to strengthen memory traces. The stabilization of synaptic connections, as previously stated, is called synaptic consolidation, and it seems to happen during REM sleep (Diekelmann and Born, 2010). In fact, studies suggest that REM sleep is associated with immediate early genes (IEG) activity upregulation related to plasticity (Ribeiro et al., 2002; Ulloor and Datta, 2005; Ribeiro et al., 2007). The upregulated IEG activity seems to be correlated with spindle activity during SWS that precedes REM sleep (Figure 6) (Ribeiro et al., 2007). Rapid eye movement sleep enhances cholinergic tone (von der Kammer et al., 1998; Teber et al., 2004), which allows the maintenance of long term potentiation (LTP) in the hippocampus-medial prefrontal cortex pathway, in turn involved in the transferring of memories in system consolidation (Takashima et al., 2006; Gais et al., 2007; Peyrache et al., 2009; Wierzynski et al., 2009). During REM

sleep brain activity is as high as in wake state; this activity could act in a non-specific way to locally amplify synaptic plasticity (Cantero et al., 2003; Axmacher et al., 2008; Montgomery et al., 2008; Diekelmann and Born, 2010).

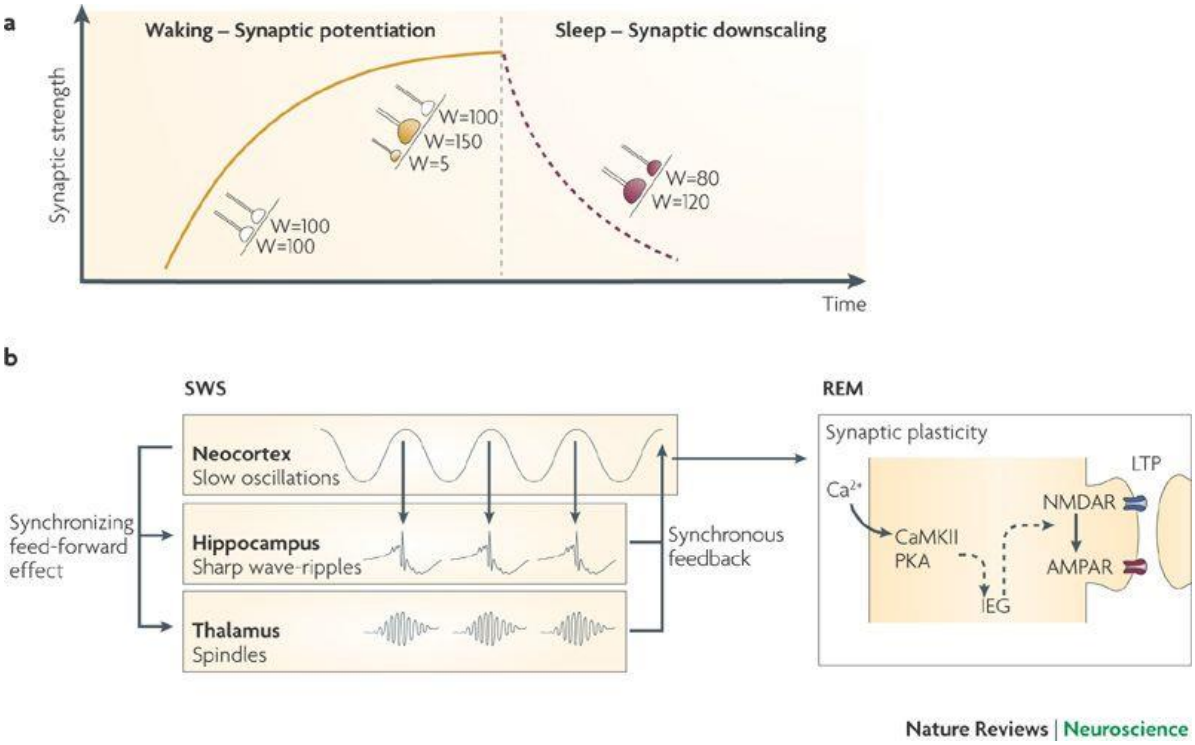


Figure 6. Memory consolidation hypotheses. The synaptic homeostasis hypothesis (a) proposes that encoding happens during wakefulness, during which synapses also become potentiated; SWS then downscales synaptic strength, so that weak connections are deleted, whereas relative strength of other connections is maintained. The active system consolidation model (b) proposes that encoding happens in both hippocampus and neocortex and that slow oscillations during slow wave sleep (SWS) drive the synchronous hippocampal memories reactivation, hippocampal sharp wave ripples and thalamo-cortical spindles. This synchronization allows reactivated memories transferring from hippocampus to neocortex. Arrival of information at the neocortical networks causes synaptic plasticity changes supported by rapid eye movement (REM) sleep. These changes include activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase A (PKA), which cause immediate early genes (IEG) expression (Diekelmann and Born, 2010). LTP, long-term potentiation; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; NMDAR, N-methyl-D-

aspartate receptor. *From (Diekelmann and Born, 2010). Reprinted with permissions from Springer Nature.*

1.4.3 Memory Reconsolidation and Sleep

Although a wealth of literature is available about sleep's role in memory consolidation, not much has been investigated and is known about sleep's role in memory reconsolidation. In a review of Stickgold and Walker of 2005, the authors hypothesize that both degradation and reconsolidation can/must occur during sleep (Stickgold and Walker, 2005). They argue that in most studies on reconsolidation performed on rodents, experiments are carried out during the light phase (rodent's inactivity phase) and they state that it is probable that subjects slept between the reactivation stage and following measurements of reconsolidation. Therefore, it is not easy to discriminate between time-dependent and sleep-dependent reconsolidation (Stickgold and Walker, 2005). Some studies on procedural memory reconsolidation in humans showed that sleep indeed has a role in memory reconsolidation. In fact, Walker and colleagues showed that the day after learning a motor sequence, subjects showed overnight sleep-dependent improvement in both speed and accuracy of the task (consolidation). They also showed that if a competing sequence is taught 10 minutes after the first one, sleep-dependent consolidation interference is observed (interference with consolidation); whereas if the time between learning the first sequence and the competing one was increased to 6-h or 24-h, no interference was observed (no interference with consolidation) (Walker et al., 2002; Walker et al., 2003). By contrast, if the consolidated memory was reactivated through 90-s rehearsal just before learning the interference sequence, subject's accuracy on the first task as tested the following day was shown to be reduced (Walker et al., 2003; Stickgold and Walker, 2005). In a more recent study, Klinzing and colleagues showed that a 40-m night sleep facilitates the re-stabilisation (thus, reconsolidation) of reactivated declarative memories (Klinzing et al., 2016). Finally, a rodent study applied REM sleep deprivation (RSD) to evaluate its effects on retrieval of methamphetamine reward memory; results showed that RSD impairs drug-related memory only when it occurs during memory reactivation (Shahveisi et al., 2019). Thus, sleep seems to play an important role in

memory reconsolidation, however there is limited evidence in support of this hypothesis.

In summary, sleep has been shown to be fundamental in memory consolidation, and it seems to be involved in memory reconsolidation as well. However, its connection to memory reconsolidation is not yet clear. Based on the topics displayed until now, the following section will illustrate the aim of the project presented in the present dissertation.

1.5 Aims of the thesis

The present dissertation focuses on two brain areas that are known to be involved and to interact in appetitive memory reconsolidation. In this regard, a paper from 2011 from Rita Fuchs' laboratory inspired the project: "Interaction between the basolateral amygdala and dorsal hippocampus is critical for cocaine memory reconsolidation and subsequent drug context-induced cocaine-seeking behaviour in rats" (Wells et al., 2011). In this work, Wells and colleagues focused their investigations on BLA and dorsal hippocampus (DH) as they were known to regulate cocaine-seeking behaviour (Meil and See, 1997; Fuchs et al., 2002; Kantak et al., 2002; Fuchs et al., 2005; Fuchs et al., 2007) and cocaine-related memory reconsolidation (Nader et al., 2000; Milekic et al., 2007; Mamiya et al., 2009; Ramirez et al., 2009; Li et al., 2010). However, it was not known whether the two areas interacted to control reconsolidation. To investigate this question, they applied a disconnection experiment. Briefly, they trained rats to self-administer cocaine and then exposed them to extinction sessions in a context different from the training one. Subsequently, they destabilised cocaine-related memories by re-exposing the rats to the training context and eventually unilaterally microinjected them with ANI into the BLA plus baclofen/muscimol (B/M) into the contralateral (full disconnection between the two areas) or ipsilateral DH, or vehicle into the contralateral or ipsilateral DH as a control. After 21 days and following another extinction training, rats were tested for cocaine-seeking behaviour. The authors showed that disconnection of the two areas following re-exposure to cocaine-paired context impaired context-induced cocaine-seeking behaviour with respect to subjects injected with vehicle or subjects injected ipsilaterally in the DH with B/M.

Authors concluded that BLA and DH interaction is necessary to regulate cocaine-related associative memories reconsolidation (Wells et al., 2011).

Therefore, the aim of the project described in the present dissertation was that of investigating functional connectomics measures (such as synchronization, coupling and coherence) between BLA and the CA1 area of the dorsal hippocampus during appetitive (sucrose) memory retrieval in both Dark (activity phase) and Light (inactivity phase) phases in rats. The first goal of the project was to evaluate differences in LFPs when memory retrieval is performed during Light or Dark phases, to improve our knowledge on the impact of performing an appetitive memory retrieval session during the inactivity vs activity phase in rodents on memory reactivation and following reconsolidation. The second goal of the project was to find an in vivo electrophysiological marker of appetitive memory reactivation. In fact, being able to identify a marker of appetitive memory reactivation would have a great translational value. Improving our knowledge on the electrophysiological mechanisms leading reactivation could provide us with information that could be exploited to face the problem of relapse to food addiction after withdrawal. For example, by applying new strategies to inhibit memory reconsolidation after its reactivation and avoid relapse to abuse.

In order to answer aim's questions, it is important to understand the underlying electrophysiological mechanisms. Therefore, brain rhythms in hippocampus and BLA and their involvement in memory processes will be described in the following paragraphs.

1.6 Brain rhythms

Brain rhythms, or network oscillations, are extracellular fluctuating waves (voltage deflections) of neuronal activity that can be revealed by local field potential (LFP) recordings (Colgin, 2016; Bocchio et al., 2017). These rhythms are the result of the synchronized activity of a large number of neurons: synchronized neuronal currents sum together and generate LFPs; non-synchronized neuronal currents do not sum together and cannot be detected as LFPs (Colgin, 2016). Thus, oscillatory waves are believed to be the cause of synchronous synaptic activity of a great

number of neurons (Buzsaki et al., 2012; Bocchio et al., 2017) and occur at different frequency bands. Synchronization between neurons is believed to be important for cognition and memory operations; in fact, individual neurons cannot execute complex cognitive operations when firing in isolation and must organize in functional networks with other neurons (Quiroga, 2013). Frequency bands can be divided in delta (0.5 – 4 Hz), theta (4 – 12 Hz), beta (12 – 30 Hz), and gamma (30 – 120 Hz), which amplitude and frequency depend on the behavioural state and brain area (Buzsaki, 2009). Power and synchrony of different brain rhythms have been shown to be controlled by neurotransmitters such as dopamine, noradrenaline, serotonin and acetylcholine (Kocsis et al., 2007; Benchenane et al., 2010; Sorman et al., 2011; Vandecasteele et al., 2014; Bocchio et al., 2017). As theta and gamma oscillations in BLA and hippocampus are known to be involved in memory processes, the following paragraphs will focus on these brain areas and oscillations.

1.6.1 Basolateral amygdala

The amygdala is a brain area located in the medial temporal lobe; it regulates emotional behaviour in both rodents and non-human and human primates (Phelps and LeDoux, 2005). Neuronal circuits belonging to BLA are very important for different memory functions, ranging from acquisition and consolidation to retrieval and extinction of emotional memories. Importantly, synchronous oscillations in theta and gamma frequency bands between BLA and other brain structures have been shown to be relevant for emotional (both fear and reward) memory consolidation and retrieval (Bocchio et al., 2017), and for storage and formation of associative memories (Fanselow and LeDoux, 1999; Blair et al., 2005). Basolateral amygdala is one of the two main amygdalar nuclei (the other one is represented by the central amygdala) and it regulates both negative emotions and reward-based memory processes (Tye and Janak, 2007; Tye et al., 2008; Gore et al., 2015; Namburi et al., 2015; Beyeler et al., 2016). In fact, in both fear and reward conditioning, researchers observed an increase in excitatory synaptic inputs to the lateral amygdalar nucleus, which allows the formation of associative memories (Tye et al., 2008). Some authors have shown that different BLA neurons encode either for associative fear or associative reward memories (Redondo et al., 2014; Namburi et al., 2015; Beyeler et al., 2016), with no topographical segregation

between neuronal populations encoding for aversive or reward memories (Shabel and Janak, 2009; Zhang et al., 2013; Gore et al., 2015; Namburi et al., 2015; Bocchio et al., 2017).

Phenomena related to memory processes that received attention are synaptic plasticity, engrams recruitment and network oscillations (Bocchio et al., 2017). With "engram" we mean a subset of neurons that act together; the term was first introduced by Richard Simon in the early 20th century, referring to is as the neural substrate for memory storage and recall (Schacter, 2001; Josselyn and Tonegawa, 2020). As mentioned before, network oscillations in BLA (theta and gamma oscillations for example) are important in regulating memory storage and retrieval; moreover, they synchronize BLA with other brain areas both during reward and fear memory retrieval. These long-range synchronizations, for example those between the BLA and the medial prefrontal cortex (mPFC), could play a main role in plasticity induction (Likhtik et al., 2014; Karalis et al., 2016). Oscillations in the BLA seem to originate from BLA neurons, which show intrinsic membrane oscillations at theta band (Pare et al., 1995; Pape and Driesang, 1998) and rhythmically fire with local gamma and theta oscillations (Stujenske et al., 2014; Karalis et al., 2016; Bocchio et al., 2017).

Theta

Differently from hippocampal theta, BLA theta do not occur during locomotion (Seidenbecher et al., 2003). Besides being generated locally by principal neurons, researchers suggested that BLA theta oscillations are likely generated by glutamatergic inputs from afferent areas such as the mPFC and the hippocampus (Bocchio et al., 2017).

It has been shown that oscillatory patterns in BLA are also important for emotional memories consolidation. For example, during REM sleep after fear memory conditioning, the strength of memory retrieval correlates with theta synchronization from the CA1 area of the hippocampus to the BLA and in turn from the BLA to the mPFC (Popa et al., 2010). Evidence showed that during contextual fear memory retrieval, lateral amygdala, dorsal hippocampus and mPFC synchronize at theta frequencies (Seidenbecher et al., 2003; Narayanan et al., 2007b; Lesting et al., 2011). Moreover, Cambiaghi and colleagues showed that the temporal association

cortex synchronizes with BLA at theta frequencies during fear memory retrieval (Cambiaghi et al., 2016).

Gamma

Gamma can be divided in low gamma (or low gamma, 30 – 70 Hz or 35 – 45 Hz) and high gamma (or high gamma, 70 – 120 Hz), which frequencies change depending on the study taken into consideration (Bauer et al., 2007; Popescu et al., 2009; Stujenske et al., 2014; Bocchio et al., 2017). High gamma band in the BLA can be long-range synchronized with mPFC theta oscillations via a phenomenon called theta-gamma cross-frequency coupling, which allows BLA gamma amplitude to be modulated by mPFC theta phase (Lisman and Jensen, 2013; Stujenske et al., 2014). Gamma oscillations in BLA probably originate from membrane fluctuations in principal neurons (Bocchio et al., 2017).

It has been shown that power and synchrony of low gamma increase in BLA and striatum during appetitive learning (Bauer et al., 2007; Popescu et al., 2009).

Like theta frequencies, gamma oscillations are important for memory retrieval as well. In fact, evidence showed that BLA high gamma power decreases when subjects recognize an auditory cue anticipating a foot-shock and decreases if the auditory cue is not paired with the punishment. Moreover, theta-high gamma cross-frequency phase-amplitude coupling between mPFC and BLA increases when subjects correctly discriminate stimuli leading to freezing. By contrast, neither low gamma power, nor phase amplitude cross-frequency coupling between low gamma and theta has been observed (Stujenske et al., 2014).

Finally, gamma synchrony between BLA, striatum and rhinal cortices seem to be important for appetitive memories retrieval (Bocchio et al., 2017).

1.6.2 Hippocampus

The hippocampus is an essential brain area for episodic memory and spatial memory (Squire et al., 2004). Pyramidal cells represent the principal excitatory neurons in the hippocampus; many of them are provided with receptive fields for different locations in space and for this reason are called “place cells” (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976). Pyramidal cells, particularly in the CA1 area, intrinsically generate LFPs. Dendrites of pyramidal cells in CA1 are in fact

parallelly aligned, characteristic that allows currents to flow in the same direction and sum together to produce LFPs. Moreover, hippocampal interneurons are very important to generate rhythm; in fact, they have divergent projections that allow them to synchronize activity across large numbers of neurons (Cobb et al., 1995). These characteristics make the hippocampus an excellent model for studying brain rhythms. The main hippocampal brain rhythms are theta (Vanderwolf, 1969) (4 – 12 Hz), sharp wave-ripples (110 – 250 Hz) and gamma (Buzsaki et al., 1983; Bragin et al., 1995) (25 – 100 Hz). Different rhythms are related to and perform different functions. For example, theta seems to allow encoding of new information (Colgin, 2013), while sharp wave-ripples seem to allow memory stabilization and consolidation (O'Neill et al., 2010; Colgin, 2016).

Theta

Theta oscillations in the hippocampus occur during active exploration and REM sleep (Vanderwolf, 1969; Colgin, 2013). Following, a simplified summary on how hippocampal theta rhythms are generated: the medial septum (MS) is believed to be the pacemaker for theta rhythm, as evidence showed that theta oscillations in the hippocampus are abolished by MS lesions (Green and Arduini, 1954). The theta pacemaker cells are GABAergic cells of the MS and target CA3, CA1 and dentate gyrus interneurons (Freund and Antal, 1988), which in turn disinhibit pyramidal cells and promote theta firing. However, it has been shown that theta may also generate not only from MS but also locally from circuit interactions in the hippocampus (Colgin, 2016).

The first electroencephalographic (EEG) studies showed that the extent to which theta was present in the hippocampus predicted animals learning rate and memory retention, leading to the theory that theta plays a central role in learning and memory (Landfield et al., 1972; Berry and Thompson, 1978). Recent studies on place fields called this theory into question (Wilson and McNaughton, 1993; Frank et al., 2004; Leutgeb et al., 2004; Yartsev and Ulanovsky, 2013; Brandon et al., 2014) demonstrating that theta is not essential for place fields formation nor for spatial memory representations at the level of the single cell (Colgin, 2016). However, memory does not involve isolated neurons; rather, it involves neuronal ensembles. Results from different authors suggested that theta function is to link in functional

ensembles different cells, so that they can support memory (Skaggs et al., 1996; Dragoi and Buzsaki, 2006; Foster and Wilson, 2007; Gupta et al., 2012; Feng et al., 2015; Wang et al., 2015; Wikenheiser and Redish, 2015; Colgin, 2016) and they can give integrated representations of complex experiences and concepts (Colgin, 2016). Theta is also present in the hippocampus during REM sleep, with a different profile than waking theta (meaning that it is present in different hippocampal regions) (Montgomery et al., 2008); REM sleep-associated theta is believed to have a role in memory consolidation, as spiking patterns of place cells that were activated during active state have been observed to reoccur during the following REM sleep (Louie and Wilson, 2001).

Gamma

Gamma frequencies can be divided in a lower end (low gamma, 25 – 55 Hz) and a higher end (60 – 100 Hz) (Schomburg et al., 2014). Low gamma oscillations couple activity in the CA1 area of the hippocampus to inputs from CA3. On the other hand, high gamma oscillations in CA1 and CA3 are entrained by inputs from the medial entorhinal cortex (MEC) (Colgin et al., 2009; Colgin, 2016). Thus, two independent gamma oscillations generators have been identified: one located in the MEC, the other one located in CA3, respectively producing fast and low gamma frequencies in CA1 (Colgin et al., 2009; Colgin and Moser, 2010; Colgin, 2016). Particularly, gamma oscillations seem to generate from inhibitory interneurons and reflect inhibitory events at the level of pyramidal cells in CA1 and CA3 and at the level of granule cells in the dentate gyrus (Soltesz and Deschenes, 1993; Bartos et al., 2007; Colgin and Moser, 2010; Pernia-Andrade and Jonas, 2014), with low gamma driven by CA3-activated interneurons and high gamma driven by MEC-activated interneurons (Lasztoczi and Klausberger, 2014; Schomburg et al., 2014). The primary force behind the generations of gamma oscillations in the hippocampus is rhythmic inhibitory postsynaptic potentials (IPSPs) in the pyramidal cells (Colgin and Moser, 2010). Gamma amplitude and phase in the hippocampus are modulated by theta phase; particularly, it has been suggested that gamma-generating interneurons are inhibited at a specific theta phase (Penttonen et al., 1998; Colgin et al., 2009; Wulff et al., 2009; Belluscio et al., 2012; Zheng et al., 2016), with slow

and high gamma oscillations occurring at different theta cycle phases (Colgin et al., 2009; Colgin and Moser, 2010).

Different functions have been proposed for gamma oscillations in the hippocampus: dynamic grouping, dynamic routing, memory encoding, memory retrieval, involvement in working memory and representation of spatial sequences (Colgin and Moser, 2010).

As for dynamic grouping, gamma oscillations have been proposed to explain the "binding problem": since during sensory processing complex stimuli are broken down by different cells coding for different aspects of the same stimuli, the binding problem asks how the brain puts the pieces back together, so to retrieve a complete perceptual experience (von der Malsburg, 1995; Colgin and Moser, 2010). Experimental evidence suggested that gamma oscillations provide the necessary temporal synchrony to allow binding (Gray et al., 1989).

Gamma oscillations are also believed to be involved in dynamic routing, and the "neuronal communication through neuronal coherence" hypothesis has been proposed (Fries, 2005). Based on this hypothesis, synchronization of gamma oscillations between different areas allow transmission of information between different levels of processing (Colgin and Moser, 2010). Two groups of neurons are said to be synchronized when their periods of high excitability coincide, leading to effective communications between the areas (Womelsdorf et al., 2007). Moreover, as previously mentioned, gamma oscillations tend to occur at specific theta phases, with slow and high gamma occurring at different theta phases in CA1 (Brankack et al., 1993; Kamondi et al., 1998; Hasselmo et al., 2002). Thus, different gamma frequencies seem to serve to route information to the CA1 from other brain areas and theta modulation of gamma amplitude may serve to facilitate this communication (Sirota et al., 2008; Tort et al., 2008).

Gamma oscillations also facilitate memory encoding, as demonstrated by studies involving intracranial recordings from humans. In these studies, subjects were asked to memorize a list of words; researchers observed that increased hippocampal gamma power during encoding of a single word was correlated with the probability that that word would be subsequently recalled (Sederberg et al., 2007a; Sederberg et al., 2007b). Moreover, gamma synchronization between hippocampus and rhinal cortices was found to be significantly higher during encoding of words that later were successfully remembered, compared with forgotten words (Fell et al., 2001).

Studies showed that high gamma, rather than low gamma, is mainly involved in sensory information encoding (Newman et al., 2013; Bieri et al., 2014; Zheng et al., 2016). Also, changes in high gamma may be linked to variations in the ongoing behaviour, for example to changes in running speed (Ahmed and Mehta, 2012; Zheng et al., 2015).

As for gamma involvement in working memory, studies have shown that gamma power in the hippocampus increases with increasing working memory load (van Vugt et al., 2010) and observed enhanced theta-gamma phase-amplitude cross-frequency coupling in the hippocampus during working memory maintenance (Axmacher et al., 2010). Given that working memory processes in the hippocampus also rely on other brain regions, such as the prefrontal cortex (Fuster, 2000; Ranganath, 2006; D'Esposito, 2007), gamma synchronization between the two areas may be involved in working memory tasks (Colgin and Moser, 2010).

As previously mentioned, gamma oscillations might be important for movement trajectories representations, with different classes of place cells firing at different gamma phases (some place cells fire phase locked to gamma trough, while others fire phase locked to gamma rising phase (O'Keefe and Recce, 1993; Skaggs et al., 1996; Mehta et al., 2002; Senior et al., 2008)). Particularly, high gamma-modulated cells fire on high gamma troughs; low gamma-modulated cells fire on low gamma ascending phase (Colgin et al., 2009).

Finally, and most importantly for the present thesis, gamma oscillations are thought to be important for memory retrieval. In support of this hypothesis, in a study from 2007 LFPs are recorded from rats performing a delayed spatial alternation task. At each trial, rats were required to retrieve information about a previously traversed trajectory and return where they received a reward. Results showed increased gamma coherence between CA1 and CA3 and increased gamma power in CA1 on the centre arm, which is believed to be the place were memory retrieval happens. Thus, authors suggested that gamma facilitate the transfer from CA3 to CA1 of retrieved memories (Montgomery and Buzsaki, 2007). Other studies agree with the observation that memory retrieval requires projections from CA3 to CA1 (Sutherland et al., 1983; Steffenach et al., 2002; Gilbert and Kesner, 2006; Nakashiba et al., 2008). Mainly low gamma is believed to promote memory retrieval; in fact, low gamma in CA1 is driven by CA3, which is believed to be the hippocampal area where memories are stored and retrieved from (Treves and Rolls,

1992; Brun et al., 2002; Nakazawa et al., 2002; Steffenach et al., 2002). In fact, low gamma amplitude in CA3 has been shown to be increased during retrieval of learned associations between contexts and items (Tort et al., 2009; Colgin and Moser, 2010). Moreover, theta phase – low gamma amplitude coupling in CA3 has been shown to be related to successful memory retrieval (Shirvalkar et al., 2010). low gamma coupling between lateral entorhinal cortex and CA1 during an odour-place association experiment performed in rats was found to develop as rats learned the task; this coupling was observed during odour-sampling, which is likely corresponding to the time when animals recall place association (Igarashi et al., 2014). However, authors observed this coupling in frequencies going from 20 Hz to 40 Hz, which may correspond to the beta band (related to odour sampling (Martin et al., 2007)) as well (Colgin, 2016). Supporting low gamma involvement in memory retrieval, these oscillations have also been found to allow activation of previously learned spatial sequences representations in place cell ensembles (Carr et al., 2012; Bieri et al., 2014; Pfeiffer and Foster, 2015; Zheng et al., 2016).

1.6.3 Electrophysiological correlates of emotional memory retrieval/ reconsolidation

Most of the scientific literature available on electrophysiological correlates of memory retrieval and reconsolidation comes from fear memory studies. In fact, little is known and studied about LFPs in hippocampus and amygdala during appetitive memory retrieval/reconsolidation. It has been shown that neuronal activity timing is crucial for effective communication across different brain areas in general (Buzsaki and Draguhn, 2004; Uhlhaas et al., 2009; Fell and Axmacher, 2011; Lesting et al., 2013) and this timing seems to be crucial for memory retrieval as well. For example, theta synchronization between lateral amygdala and the CA1 subfield of the hippocampus has been shown to be important for fear memory consolidation (Seidenbecher et al., 2003; Pape and Pare, 2010) and reconsolidation (Narayanan et al., 2007b), with the synchronization decreasing at remote memory stages (Narayanan et al., 2007a; Lesting et al., 2013). As previously stated, synchronization and coupling at the same or different frequencies between different brain areas are used as means of communications between neuronal ensembles.

Thus, similar measures can be used to understand whether areas are interacting and/or communicating with each other.

2. MATERIALS AND METHODS

2.1 Animals

Thirty-three male Sprague Dawley rats were individually housed in a temperature and humidity-controlled environment (19-23°C, 60 ± 20%) on a 12h light/dark cycle, with light on at 7:30 PM. Rats were food restricted to maintain their body weight in the range 300 ± 10 g (daily checked) and food (two to four pellets, 10-20 g/day) was made available hours after each experimental session. Water was available ad libitum, except during experimental sessions. Animals were trained or tested once daily during either the dark or light phase of the light/dark cycle (depending on the experimental group and on the experimental session). All procedures were carried out in accordance with the U.K. Animals (Scientific Procedures) Act 1986 and associated guidelines, and with EU Directive 2010/63/EU for animal experiments. All procedures were approved by the ethical committee (OPBA) of the University of Verona and by the Ministry of Health (authorization n. 50/2017-PR). All efforts were made to minimize animal suffering and to keep the lowest number of animals used.

2.2 Apparatus

Rats were trained and tested in operant chambers (Coulbourn Instruments, Lehigh Valley, Whitehall, PA, USA) 31 cm (width) x 25.5 cm (height) x 33 cm (depth) encased in sound-insulated cubicles 64 cm (width) x 44 cm (height) x 50 cm (depth) equipped with ventilation fans (Ugo Basile, Varese, Italy).

Each chamber was equipped with two levers, an active (right) and an inactive (left) lever, symmetrically oriented laterally to the food magazine, on the frontal panel. Levers were located 6 cm and food magazine 3 cm above the grid floor. A white light-emitting diode (LED) house light (HL) was located 27 cm above the grid floor on the front panel of the operant chambers and provided ambient illumination during the entire session duration of all the experimental and for the entire training sessions except for time-out (TO) periods. A red LED was located 23 cm above the grid floor and provided illumination during the entire session duration of all the experimental phases, allowing for video monitoring and recording. Operant chamber is shown in Figure 7. During training, right lever presses produced the delivery of a 45-mg sucrose food pellet (Bilaney Consultants Ltd, UK) with a fixed-

ratio 1 (FR1) schedule of reinforcement. During Retrieval, right lever presses did not correspond to pellet delivery. Left lever presses did not have consequences during the entire experimental protocol. Schedule parameters, data acquisition and pellet deliveries were controlled by MedPC software (version 1.15; Med Associates Inc., Georgia Regional Industrial Park, Fairfax, VT, USA). A small rear-view camera was placed in the middle of the top panel. The camera was used to video monitor the rats during the recording sessions and was controlled by means of a video grabber (Hamlet, Dublin, Ireland) connected to a computer. Finally, and infra-red (IR) emitting diode was placed over the white HL and allowed synchronization between behavioural data and brain waves recordings: every time the active lever was pressed, the IR diode emitted an IR signal which was detected by an IR detector placed on the recording logger.

Figure 7. Operant chamber used to carry out behavioural experiments. On the frontal panel is possible to note the right lever (a), the left lever (b), the food dispenser placed in between the two levers (c), the red house light (d), the white house light (e) right above the white one, the infrared emitting diode (f) and the video camera (g). All the Skinner boxes were placed inside a sound-isolated cubicle equipped with a fan providing ventilation and a background white noise.

2.3 Electrodes construction

In-depth electrodes consisted of an insulated tungsten wire (Advent Research Materials, Witney, UK) with bare diameter 50 μm and outer diameter 75 μm, welded to a pin (Harwin, Portsmouth, UK) and inserted into a cannula guide consisting of a 30 Gauge stainless steel tube (Pentaferte, Ferrara, Italy). Two golden screws (1 mm diameter; TSE Systems, Bad Homburg, Germany) were used respectively as Electrocorticogram (ECoG) and reference + ground. The screw used to record ECoG was an insulated copper wire (Advent Research Materials, Witney, UK) having bare diameter 100 μm and outer diameter 114 μm, in turn soldered to a pin. The screw used as reference and ground was welded to two insulated copper wires, each soldered to a pin. Finally, two muscular electrodes (one used to record the electromyogram -EMG-, the other one used as reference) consisted of insulated copper wires having bare diameter 100 μm and outer diameter 114 μm soldered to a pin. Electrodes are shown in Figure 8 together with their location on the skull.

2.4 Surgery

Rats were handled for at least 5 days, 5 minutes/day before performing the surgery to implant the electrodes. On day of the surgery, rats were anaesthetized with intra-muscular (i.m.) 0.05 mg/Kg medetomidine hydrochloride (Sedator, Dechra Pharmaceuticals PLC, Northwich, UK) and i.m. 10mg+10mg/Kg zolazepam + tiletamine (Zoletil 50/50, Virbac, Milano, Italy). Lungs secretions were reduced by subcutaneously (s.c.) injecting 0.05 mg/Kg atropine (Atropina solfato, Azienda Terapeutica Italiana A.T.I. s.r.l., Bologna, Italy). Carprofen was injected 5 mg/Kg s.c. as analgesic (Rimadyl, Pfizer, New York, NY, USA).

Rats were first checked for loss of reflexes, then fixed on the stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) by means of ear bars and kept warm during the whole procedure with a heating pad. Eyes were kept lubricated with drops of saline solution during the whole surgery. Hair on the skin above the skull were shaved and skin was disinfected with a 10% povidone-iodine solution (POVI-IODINE 100, Formevet, Milano, Italy). An incision was performed on the scalp and connective tissue was removed to expose the skull, which was cleared with 3% hydrogen peroxide. Coordinates for electrodes' insertion were taken and holes were performed on the skull by means of burrs (diameter of the tip: 0.5 mm; Fine Science

Tools, Heidelberg, Germany) for micro-drill (Dremel, Racine, WI, USA). Electrodes were inserted at the following coordinates with respect to Bregma: BLA electrodes were inserted at dorso-ventral (DV) -8.4 mm, rostro-caudal (RC) -2.8 mm and medio-lateral (ML) +4.8 mm; CA1 electrodes were inserted at DV -2.6 mm, RC -3.3 mm and ML +1.5 mm (Paxinos and Watson, 2007). The screw for ECoG recording was fastened on the skull at the level of the parietal cortex at the following coordinates with respect to bregma: RC -3.8 mm and ML -2.0 mm. The reference + ground golden screw was fastened to the skull over the right cerebellar hemisphere, as well as three support screws, two of which were fixed on the skull over the frontal cortex and one over the left cerebellar hemisphere. Muscular electrodes were inserted in the right shoulder's muscle by means of a suture needle. The insulating membrane was removed by means of a scalpel blade in the contact point between the wire and the muscle. Electrodes and their placement are shown in Figure 8. Pins of the electrodes were inserted into a socket to protect them and the skull was covered with dental cement (Paladur, Kulzer, Hanau, Germany), which allowed to fix the pins as well. After the surgery, rats were administered with 12.5 mg/Kg s.c. enrofloxacin (Baytril 50 mg/ml, Bayer, Leverkusen, Germany) as antibiotic. Baytril was administered for four days after surgery. Rats were daily checked and allowed to recover for at least 6 days before starting the experiments.

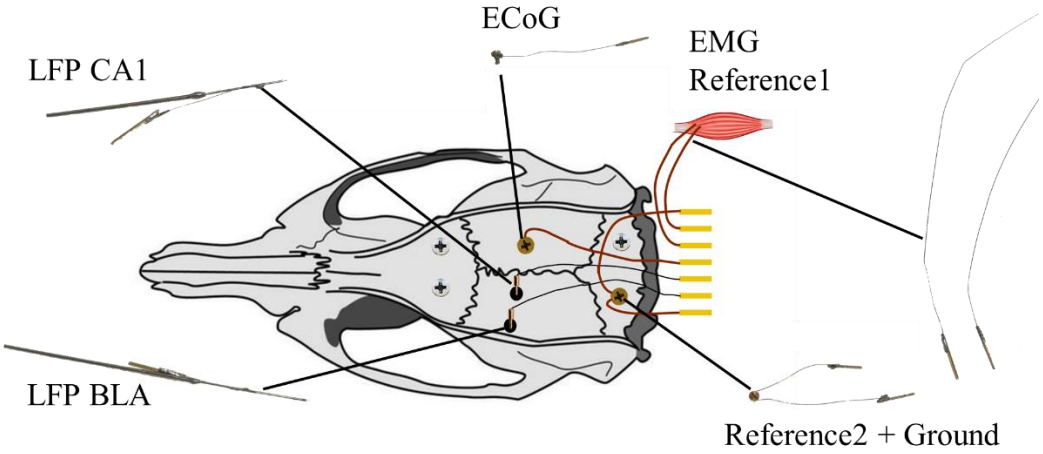


Figure 8. Electrodes and their location on the skull. In-depth electrodes were used to record LFPs and were inserted in the left CA1 area of the dorsal hippocampus (LFP CA1) and in left BLA (LFP BLA). A cortical electrode in the form of a golden screw was used to record sleep/wake waves from the right parietal cortex (ECoG). Another golden screw was implanted over the left cerebellum and served as reference and ground (Reference2 + Ground). Finally, two electrodes in the form of copper wires were inserted in the right shoulder's muscle (EMG; Reference1). The three grey screws represent support screws and were located two at the level of the prefrontal cortex, and one at the level of the cerebellum. Yellow rectangles on the right represent the pins that were inserted in Neurologger 2A (described in the next section) to record the animals.

Abbreviations: LFP, Local Field Potential; BLA, Basolateral Amygdala; ECoG, Electrocorticogram; EMG, Electromyogram.

2.5 Recording apparatus

Local field potentials were recorded by means of Neurologger 2A (Evolocus LCC, Tarrytown, NY, USA), shown in Figure 9. Neurologger 2A is a wireless recording device measuring 22 x 5 x 15 mm and weighting 2 g. It can record up to 4 channels at sampling rate up to 19.2 kHz and data is stored in a 1 Gb memory soldered to the Neurologger. Real-time infrared (IR) synchronization was possible by means of an IR receiver placed on the Neurologger, which received signals from an IR emitting diode connected to the Skinner box anytime the rats pressed the active lever. Neurologger was zinc-air batteries A312 powered. Recordings were carried out using the following sampling parameters: sampling rate 1600 Hz, oversampling 4x, recording of IR synchronization active. Recorded data were stored in the memory soldered to the Neurologger. A USB adapter was used to allow communication between the Neurologger and a computer, and the Downloader software (Evolocus LCC, Tarrytown, NY, USA) was used to download and convert data to a readable format.

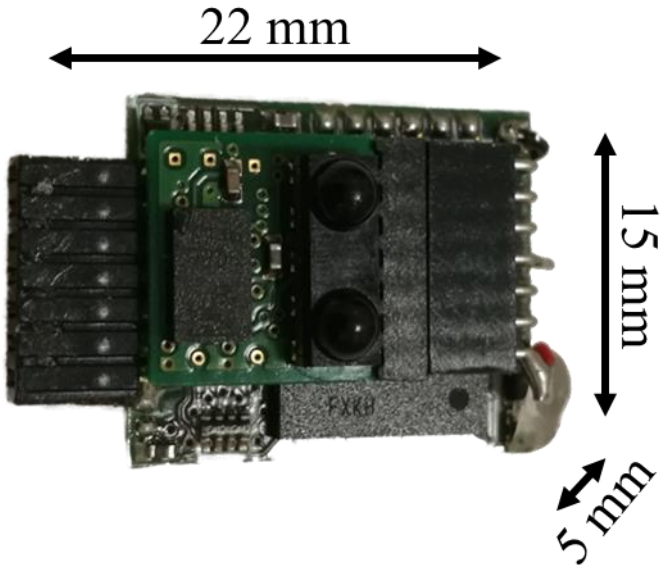


Figure 9. Neurologger 2A. The two black spheres represent the IR sensor that is used for external events synchronization (in my case active lever pressings). The black parallelepiped on the left is the socket that is placed on the pins on the rat's implant. The main feature of the logger is that it is wire-free thus, it allows to record LFPs in freely moving animals.

2.6 Behavioural procedure

2.6.1 General Procedure

The experimental protocols were designed according to the following phases (Figure 10): Stage I) Training to sucrose self-administration (S/A), Stage II) forced abstinence in home cage, Stage III) memory Retrieval (Ret) or No Retrieval (No Ret), and Stage IV) Relapse test. These stages are described in detail in the following sections. All the stages were performed during the Dark phase (light off), but the Retrieval/No-Retrieval stage, which was performed either during the Light or Dark phase of the light/dark cycle. Thus, rats were divided in 4 groups:

1. Retrieval Dark (Ret/Dark, n = 9): performed Ret during the dark phase;
2. No Retrieval Dark (No Ret/Dark, n = 7): performed No Ret during the dark phase;
3. Retrieval Light (Ret/Light, n = 8): performed Ret during the light phase;
4. No Retrieval Light (No Ret/Light, n = 8): performed No Ret during the light phase.

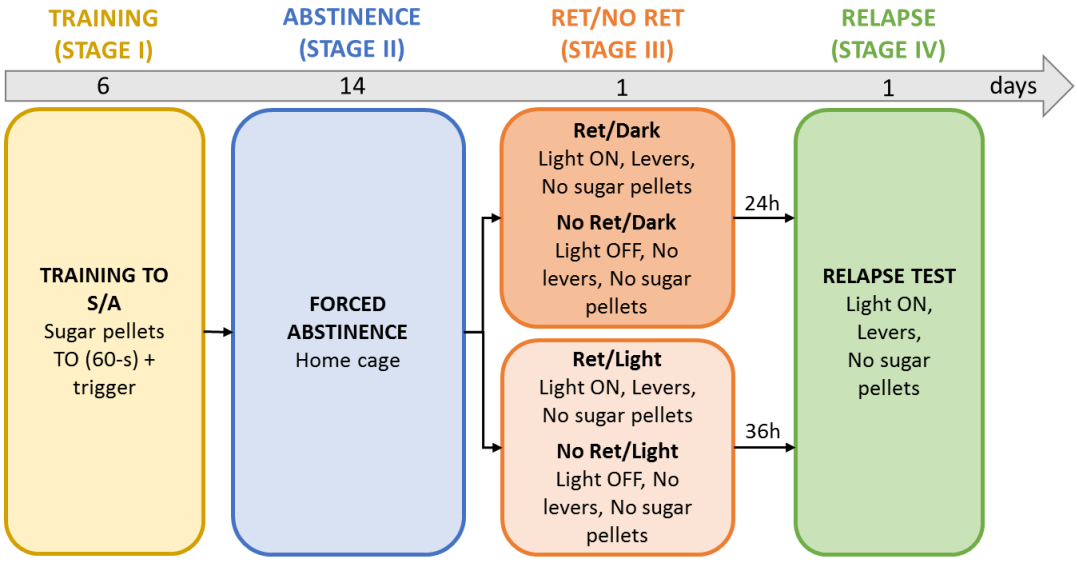


Figure 10. Behavioural protocol and its different stages. Stages are described in detail in the following paragraphs. Light refers to white HL. Abbreviations: TO, Time-Out.

2.6.2 Lever press shaping and training to sucrose self-administration

All rats were initially shaped to associate right lever presses with sucrose pellets as reinforcement. The schedule was a FR1 procedure, with the delivery of 45-mg sucrose food pellets, no delivery time-out (TO) during the procedures (white HL always ON) and sessions lasted up to 100 reinforcements or 120 min. Inactive lever presses (ILPs) had no consequences. Once the criterium of 100 reinforcements was reached, animals started training Stage I. During Stage I, rats were trained for 6 continuous days (1 session/day) to obtain sucrose reinforcements with the same FR1 schedule, plus a 60-s TO (HL OFF during TO), during which active lever presses (ALPs) had no consequence. Moreover, ALPs during TO caused TO itself to reset. Sessions lasted up to 12 reinforcements or 120-m. Local field potential recording was performed during the first and last days of training. Inactive lever presses had no consequence for all the experimental procedure. After Stage I ended, rats entered Stage II (forced abstinence) and remained in home cages for 14 days. During forced abstinence, rats were daily handled, weighted and fed to keep their body weight between 300 ± 10g.

2.6.3 Retrieval procedure and Relapse test

After Stage II, rats were divided in the four aforementioned groups and were subjected to Stage III. Ret and No Ret sessions were performed in the training context. During the Ret session both levers were presented, and rats were allowed to press the active lever up to 20 times, HL always ON. Inactive lever presses had no consequence. When 20 ALPs were reached, or after 60-m, the procedure was interrupted. During Ret, ALPs caused an IR diode to send an IR signal to the detector placed on the logger to allow synchronization between behavioural data and recordings. During the No Ret session no levers were presented, and HL was OFF. Procedure was interrupted after 216s (mean time animals in the Ret group spent in the operant chamber based on previous experiments from our laboratory). Ret and No Ret sessions were recorded using Neurologger 2A starting from 2 hours before the behavioural sessions. Rats belonging to the Ret/Dark and No Ret/Dark groups were moved in the experimental room at 9AM and the recording logger was fixed on their implant; rats belonging to Ret/Light and No Ret/Light groups were moved in the experimental room at 9 PM and the recording logger was fixed on

their implant. Two hours after fixing the recording logger, rats belonging to Ret/Dark and Ret/Light groups were subjected to Ret session; rats belonging to No Ret/Dark and No Ret/Light were subjected to No Ret session. Twenty-four hours after Stage III for Ret/Dark and No Ret/Dark groups and thirty-six hours after Stage IV for Ret/Light and No Ret/Light groups all subjects started Stage IV. During Stage IV they were exposed for 60-m to the training context in the presence of levers and HL ON for a non-reinforced Relapse test, to evaluate sucrose seeking behaviour in terms of ALPs. Thus, lever presses had no consequence.

2.7 Electrodes placement verification

After the behavioural procedure was over, animals were intraperitoneally administered with 350 mg/Kg/2 mL chloral hydrate to anesthetize them. Then, they were transcardially perfused first with a heparin (Sigma-Aldrich, Milan, Italy) solution 100 UI/L diluted in saline solution (0.9% NaCl), then in paraformaldehyde (PFA) 4% dissolved in a phosphate buffered solution (PBS). After perfusion, brains were extracted and post-fixed in PFA 4% in PBS for 24-h at 4 °C. The following day, brains were washed 3 times in PBS, each wash lasting for 30-m. Finally, brains were put in a sucrose 30% solution in PBS for 48-h, acting as cryoprotective. Forty μm free-floating sections containing electrodes placement sites were obtained by means of a Leica CM1950 cryostat (Leica Biosystems, Wetzlar, Germany). Free-floating slices were mounted on glass slides and let dry for at least 30 minutes before proceeding to Nissl staining. Once dry, slices were rehydrated with 3 washes, 5 minutes/wash, in PBS; then they were covered with a 1:5 ethanol and chloroform solution for 1 hour. Slices were then immersed in Cresyl Violet solution for 30-60 minutes and, after a fast wash in water, they were dehydrated with increasing ethanol concentrations (50%, 70%, 80%, 96% and 99%, 1-2 minutes/concentration) and two steps in xylene (10 minutes/step) and finally closed with the mounting medium Entellan (Merck Group, Darmstadt, Germany).

2.8 Behavioural data analysis

All statistical analyses were performed using the GraphPad software package (Prism, version 6; GraphPad, San Diego, California, USA).

Behavioural analysis was performed for behavioural stages I, III and IV. For behavioural stage I, the S/A training learning-curve was generated by computing the rate of responding for each training day and for each subject. Rate of responding was expressed in seconds as Inter Response Time (IRT), obtained with the following formula: IRT = (Time – Latency)/12, where Time is the time duration of the training session expressed in seconds; Latency is the time elapsed between the start of the training session and the first reinforcement expressed in seconds; finally, 12 is the number of reinforcements subjects receive during the training session. Going on with the training sessions, subjects become more and more efficient in the task; consequently, IRT becomes smaller and smaller until it reaches stability. Thus, in order to show an increasing graph (shown in the Results section), the inverse of IRT was computed. Data were inserted in Graphpad Prism v.6 software and two-way repeated measures (RM) ANOVA was computed for factors Session (six levels: from training session 1 to training session 6) and Group (four levels: Ret/Dark, No Ret/Dark, Ret/Light, No Ret/Light), followed by post-hoc Tukey's multiple comparisons test.

For behavioural stage III, Ret/Dark and Ret/Light rate of responding was computed as IRT = (Time - Latency)/20, where Time is the time duration of the Ret session expressed in seconds; Latency is the time elapsed between the start of the Ret session and the first ALP expressed in seconds; finally, 20 is the number of ALP subjects perform during Ret session. To evaluate differences between the two groups, Mann-Whitney test was computed. Since two subjects belonging to Ret/Light group did not reach the 20 ALPs criterion, they were excluded from the analysis from this stage on.

For behavioural stage IV, the number of ALPs was analysed to evaluate differences in sucrose-seeking behaviour during the whole 1-hour test between the four groups. Two-way ANOVA for factor Experimental Condition (two levels: Ret, No Ret) and for factor Phase (two levels: Dark, Light) was computed.

2.9 Local Field Potential Analysis

Local field potential data analysis was performed using Matlab software (MathWorks, Natick, MA, USA) and its EEGLAB (Delorme and Makeig, 2004) and Chronux (Mitra and Bokil, 2007; Bokil et al., 2010) toolboxes. All statistical

analyses were performed using the GraphPad software package (Prism, version 6; GraphPad, San Diego, California, USA). For Ret/Dark and Ret/Light recordings during Retrieval, epochs containing IR signals (indicating that the active lever was pressed) were extracted from 1-s before the IR signal to 1-s after the IR signal (2-s segments, Retrieval Active Lever Presses/Dark – Ret ALP/Dark – and Retrieval Active Lever Presses/Light – Ret ALP/Light – groups) using Matlab. Then, epochs were visually inspected with EEGLAB for artefact removal and only artefact-free epochs were considered. As a control to Ret ALP/Dark and Ret ALP/Light epochs, Ret No-ALP/Dark and Ret No-ALP/Light epochs were extracted respectively. Ret No-ALP/Dark and Ret No-ALP/Light epochs were randomly extracted as intra-recording artefact-free 2-s segments in the same number as the Ret ALP/Dark and Ret ALP/Light epochs. No Ret groups epochs were randomly extracted as twenty artefact-free 2-s segments. To analyse theta and gamma power, Matlab Chronux toolbox was used. Particularly, extracted epochs were band-pass filtered between 4 and 150 Hz. Then, multi-taper power spectra between 0.5 and 100 Hz were computed using the *mtspectrumc* function of the Chronux toolbox, using a time-bandwidth product of 3 and 5 tapers. Ret ALP/Dark and Ret ALP/Light epochs were averaged for each subject, as well as Ret No-ALP/Dark and Ret No-ALP/Light epochs. Theta (4-12 Hz) and gamma (30-100 Hz) relative powers were computed. Gamma band was analysed both as total-gamma (30-100 Hz) and as split in low-gamma (30-60 Hz) and high-gamma (60-100 Hz), since it has been suggested that low- and high-gamma frequencies may have different functions. For example, at the level of the hippocampus low-gamma has been suggested to be involved in memory retrieval (Shirvalkar et al., 2010), while high-gamma may be linked to memory encoding, spatial representation (Zheng et al., 2015) and/or working memory (Yamamoto et al., 2014). For each frequency band, the area under curve (AUC) was computed by means of the Matlab *trapz* function and normalized by dividing it by the total AUC (between 0.5 and 100 Hz).

Normalized data were then inserted into Graphpad Prism software for statistical analysis. For each electrode and each frequency band, two-way RM ANOVA was performed to compare Ret ALP/Dark and Ret ALP/Light respectively with Ret No-ALP/Dark and Ret No-ALP/Light groups for factors Lever Pressing (two levels: ALP and No-ALP) and for factor Phase (two levels: Dark, Light). To compare Ret No-ALP/Dark and Ret No-ALP/Light respectively with No Ret/Dark and No

Ret/Light groups, two-way ANOVA was performed for factors Experimental Condition (two levels: Ret and No Ret) and for factor Phase (two levels: Dark, Light). Moreover, to evaluate the correlation between the oscillations relative power and the rate of responding during the Retrieval session in Ret/Dark and Ret/Light groups, Pearson's correlation coefficient was computed between Ret ALP/Dark and IRT, Ret No-ALP/Dark and IRT, Ret ALP/Light and IRT and Ret No-ALP/Light and IRT for low and high gamma powers in CA1 electrode.

A summary of the performed statistical analyses is reported in Figure 11. Each analysis was carried out on both electrodes (CA1 and BLA) and on all frequency bands: theta, total gamma, low gamma and high gamma; except for linear regression which was carried out only on CA1 low and high gamma relative powers, since I observed significant differences only at the level of this electrode at the gamma frequency band.

Finally, sleep scoring was performed for Ret/Dark and Ret/Light groups during the Ret behavioural session. To perform this analysis, cortical electrode and muscular electrode recordings were split in 10-s epochs and visually inspected. A classification was assigned to each epoch based on cortical oscillations (wake or sleep): high frequency and low amplitude oscillations, associated with muscular activation are typical of wake epochs; very low frequency and high amplitude associated with muscular non-activation are typical of non-REM sleep epochs; finally, wake-like oscillations following non-REM sleep associated with muscular non-activation are typical of REM sleep epochs. After classifying each epoch as wake or sleep, the percentage of sleep epochs over the total number of epochs in the behavioural session was computed.

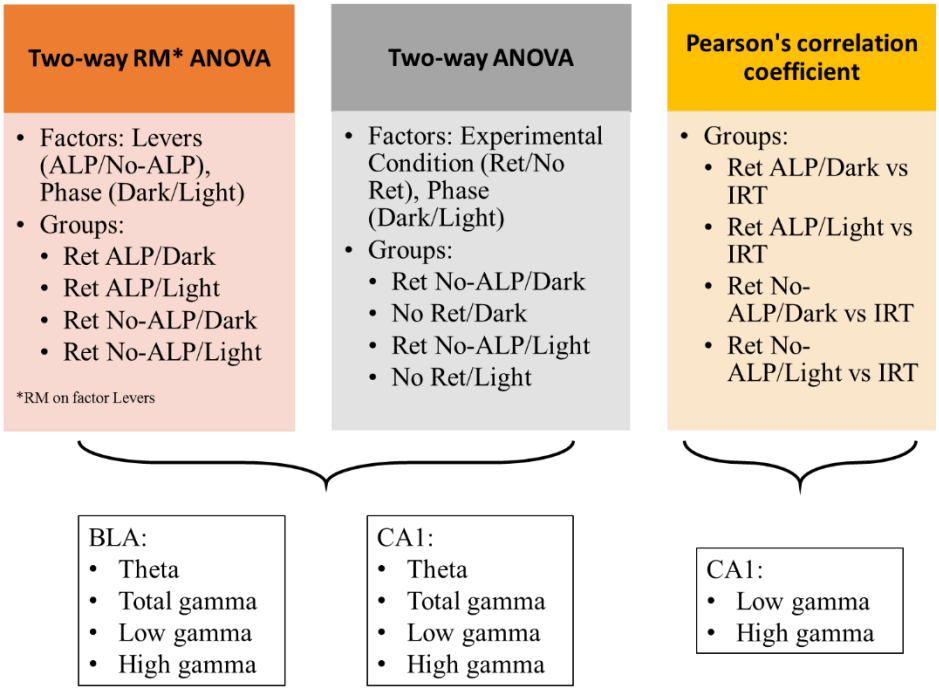


Figure 11. Schematic view of the statistical analyses. All statistics were carried out by means of Graphpad Prism v.6 software. Two-way RM ANOVA (repeated measures on factor Levers) and two-way ANOVA were performed for each in-depth electrode (BLA and CA1) and for each listed frequency band: theta (4-12 Hz), total gamma (30-100 Hz), low gamma (30-60 Hz) and high gamma (60-100 Hz). Pearson's correlation coefficient was computed for CA1 electrode and for low and high gamma. To compare the groups, relative powers were extracted for each frequency band. All the different groups are previously described in the text. Abbreviations: Ret, Retrieval; No Ret, No Retrieval; ALP, Active Lever Presses; No-ALP, No Active Lever Presses; RR, Rate of Responding.

3. RESULTS

3.1 Behavioural results

Behavioural results can be divided based on the behavioural stage that is taken into consideration.

3.1.1 Stage I: Training

To evaluate behaviour in terms of performance at the training stage, the inverse of IReT (1/IReT) was computed for each group and for each training session, as reported in Figure 12. To analyse improved performance, two-way RM ANOVA was computed for factors Session (six levels: from training session 1 to training session 6) and Group (four levels: Ret/Dark, No Ret/Dark, Ret/Light, No Ret/Light) and showed a significant matching between subjects [$F(28,140) = 1.831$; $p = .0119$], a significant main effect of factor Session [$F(5,140) = 24.485$ $p < .0001$], but not of factor Group [$F(3,28) = .1123$; $p = .9522$] or their interaction [$F(15,140) = .4817$; $p = .9466$]. As expected, no significant main effect was observed for factor Group; thus, post-hoc Tukey's multiple comparisons test between training sessions was carried out pooling groups data. Table 2 shows mean 1/IReT ± Standard Error of the Mean (S.E.M.) for each training session from 1 to 6 from pooled data.
Table 3 shows results of post-hoc Tukey's multiple comparisons test. In summary, training session 1 showed a significant difference vs training session 3 to 6; training session 2 showed a significant difference vs. training sessions 4 to 6; finally, training session 3 was significantly different from training session 5 and 6.

Table 2. Mean ± S.E.M. of 1/IReT (s^{-1}) for each training session for pooled data from the four groups (N = 32).

Training session	Mean 1/IReT ± S.E.M. s^{-1}
1	0.003749 ± 0.000220 s^{-1}
2	0.004114 ± 0.000216 s^{-1}
3	0.005085 ± 0.000313 s^{-1}
4	0.006383 ± 0.000343 s^{-1}
5	0.007416 ± 0.000424 s^{-1}
6	0.007497 ± 0.000433 s^{-1}

Table 3. Training sessions IReTs were compared by applying two-way RM ANOVA, followed by Tukey's post-hoc multiple comparisons test. The table shows results for Tukey's multiple comparisons test. Results are obtained from pooled data from the four groups (N = 32).

NS = not significant; * p < .05; **** p < .0001

Training session	1	2	3	4	5	6
1		NS	*	****	****	****
2			NS	****	****	****
3				NS	****	****
4					NS	NS
5						NS
6						

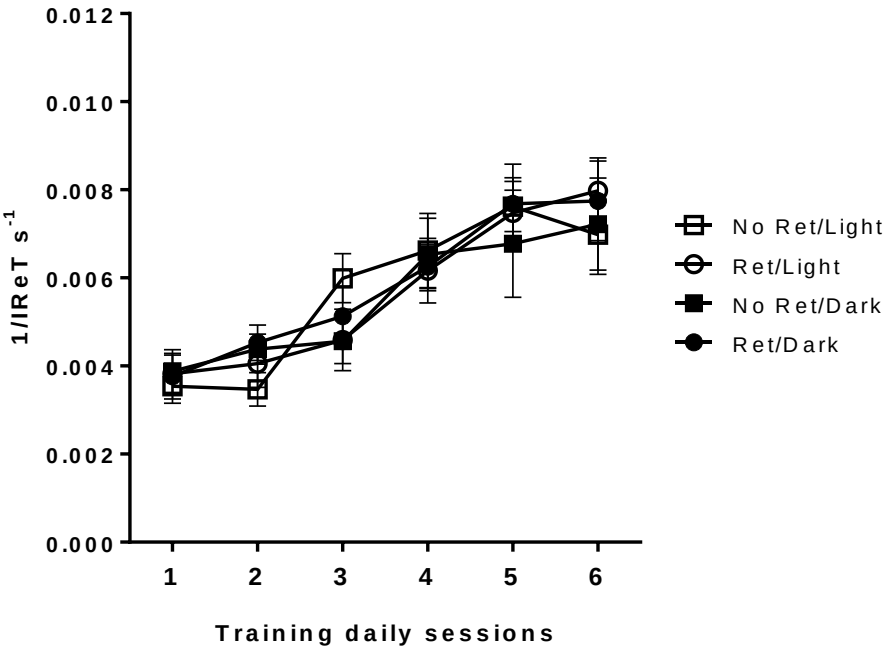


Figure 12. Training stage. The graph shows the training sessions on the x-axis and 1/IReT on the y-axis. Lines represent 1/IReT from session 1 to session 6 for No Ret/Light (open squares, n = 8), Ret/Light (open circles, n = 8), No Ret/Dark (solid squares, n = 7), Ret/Dark (solid circles, n = 9) groups. The inverse of IReT is reported instead of IReT in order to show an increasing learning curve. In fact, IReT decreases from session 1 to session 6 meaning that the subjects are more efficient in performing the task. Significant differences between training sessions are reported in

Table **3**. Data are presented as mean ± S.E.M. IReT = Inter Reinforcement Time.

3.1.2 Stage III: Retrieval

At stage III, IRT was analysed for Ret/Dark and Ret/Light groups, to evaluate whether performing Retrieval during the Dark or Light phases had an influence on rate of responding (Figure 13). Being IRT values non-normally distributed, Mann-Whitney test was applied to statistically compare the two groups. Mann-Whitney test showed a significant difference ($p = .0312$) for Ret/Dark group with respect to Ret/Light group, with the former having lower IRT with respect to the latter. Two subjects belonging to the Ret/Light group were excluded from the analyses from this stage on, as they did not reach the 20 ALPs criterion for stage III.

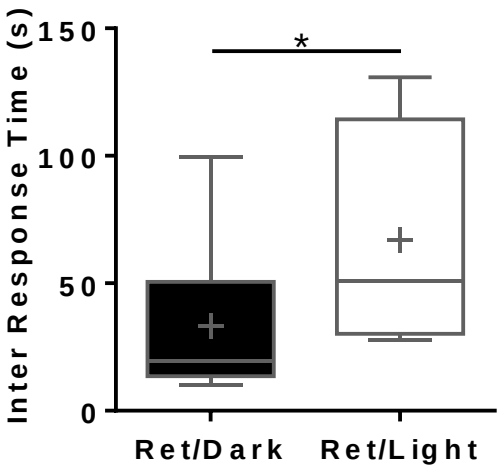


Figure 13. IRT during Retrieval for Ret/Dark (n = 9) and Ret/Light (n = 6) groups. Data are shown as box (25^{th} to 75^{th} percentile) and whiskers (minimum to maximum). Horizontal lines represent median values with + symbol indicating the mean. Two animals from the Ret/Light group did not reach the 20 ALP criterion and were excluded from the analysis. Mann-Whitney test, * $p < .05$.

To evaluate whether the higher IRT shown for Ret/Light group with respect to the Ret/Dark group was due to a difference in the percentage of sleep that rats showed performing the Retrieval session (Figure 14), sleep scoring was performed during the behavioural session and expressed as percentage over the total time duration of the behavioural session. Being sleep percentages non-normally distributed, Mann-

Whitney test was applied to statistically compare the two groups. No significant difference was observed between the groups (p = .1678). Two subjects belonging to the Ret/Dark group was excluded from sleep analysis because of lack of LFP recording.

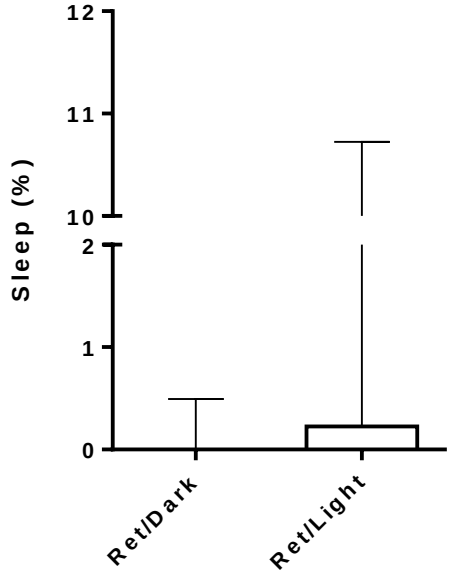


Figure 14. Percentage of sleep during Retrieval for Ret/Dark (n = 7) and Ret/Light (n = 6) groups. Data are shown as median + interquartile range. Mann-Whitney test. No statistical difference has been observed between the groups.

3.1.3 Stage IV: Relapse Test

At stage IV, the number of ALPs was analysed for the four groups to evaluate sucrose-seeking behaviour during the whole 1-hour test (Figure 15). Two-way ANOVA for factor Experimental Condition (two levels: Ret, No Ret) and for factor Phase (two levels: Dark, Light) showed no significant main effect for factors Experimental Condition [F(1,26) = .1038, p = .7499], Phase [F(1,26) = .4326, p = .5165], or their interaction [F(1,26) = .002, p = .964].

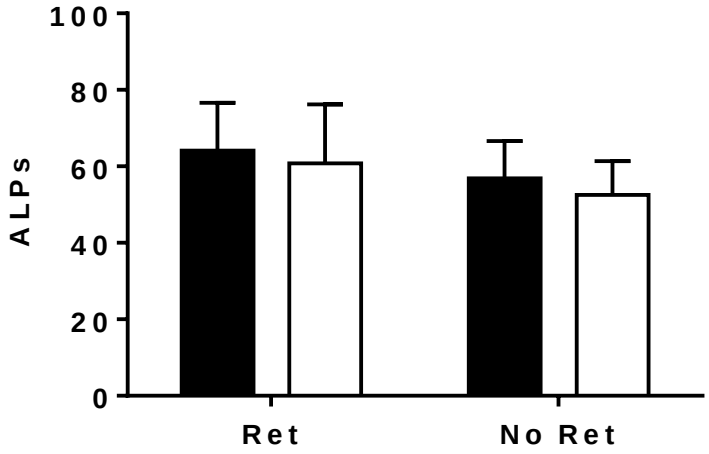


Figure 15. Number of active lever presses (ALPs) at Relapse test are expressed as mean + S.E.M for the four groups. Solid columns represent Dark groups (n = 9 and 7 respectively for Ret/Dark and No Ret/Dark groups), open columns represent Light groups (n = 6 and 8 respectively for Ret/Light and No Ret/Light groups). Two-way ANOVA showed no significant difference between the groups.

3.2 Local Field Potential results

3.2.1 Gamma frequency and rate or responding correlation

As mentioned in section 2.8 Behavioural data analysis Pearson's correlation coefficients were computed for Ret ALP/Dark, Ret No-ALP/Dark, Ret ALP/Light and Ret No-ALP/Light relative powers vs their respective IRT during Ret session. Pearson's correlation coefficients were computed for low gamma and high gamma from CA1 electrode.

The analysis showed a significant correlation between Ret ALP/Dark low gamma and Ret IRT (R = 0.6745; p = 0.0235) (Figure 16, panel A) and between Ret No-ALP/Dark low gamma and IRT (R = 0.5706; p = 0.0496) (Figure 16, panel B). On the other hand, no significant correlation was found between Ret ALP/Dark high gamma and IRT (R = 0.0005, p = 0.09613) (Figure 17, panel A) and between Ret No-ALP/Dark high gamma and IRT (R = 0.0615; p = 0.5917) (Figure 17, panel B). Finally, no significant correlation was observed between Ret ALP/Light low gamma and IRT (R = 0.0092; p = 0.8563) (Figure 16**Errore. L'origine riferimento non è stata trovata.**, panel C), Ret No-ALP/Light low gamma and IRT (R = 0.0002; p = 0.9772) (Figure 16, panel D), Ret ALP/Light high gamma and IRT (R

< 0.0001; p = 0.9899) (Figure 17 , panel C) or Ret No-ALP/Light high gamma and IRT (R = 0.2407; p = 0.3232) (Figure 17, panel D).

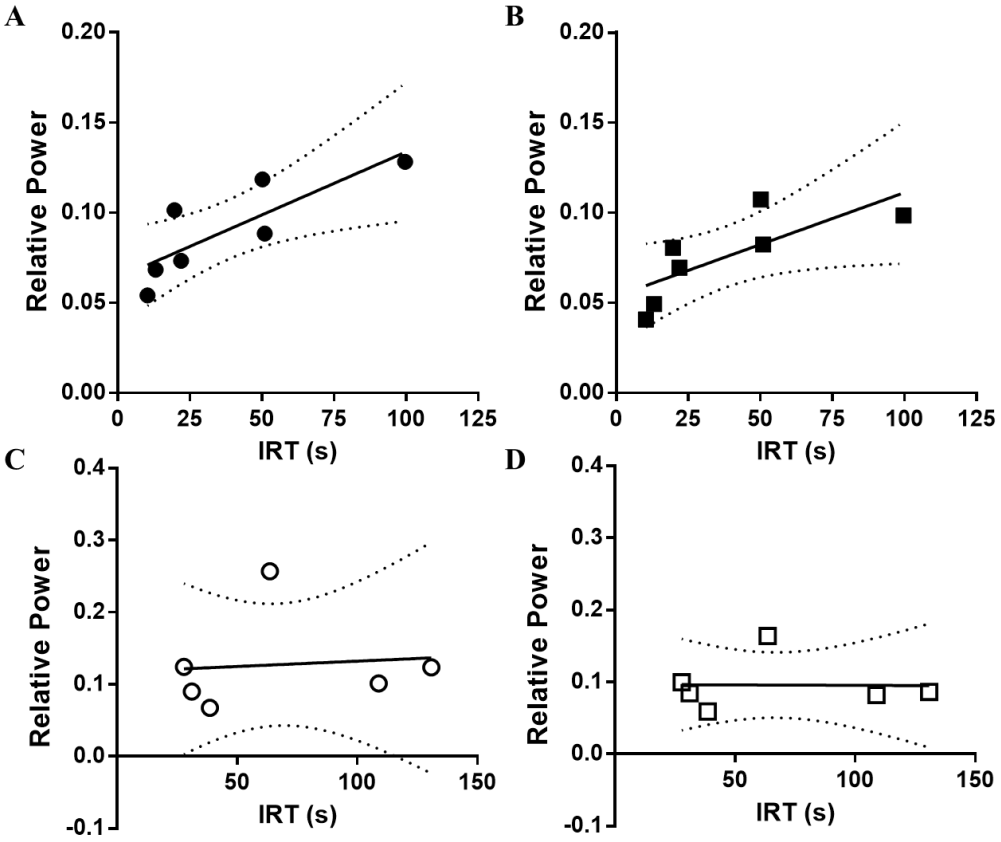


Figure 16. Correlation plots between Inter-Response Time (IRT; seconds) and low-gamma relative power for Ret ALP (A; closed circles) or Ret No-ALP (B; closed squares) epochs during the Dark phase Retrieval session and low-gamma relative power for Ret ALP (C; open circles) or Ret No-ALP (D; open squares) epochs during the Light phase Retrieval session. Closed and open circles and squares represent data of single subjects (N = 7, Dark; N = 6, Light). Solid lines represent the linear regression line, dotted lines represent 95% confidence intervals. Pearson's correlation coefficient showed a significant correlation for both sub-plots in panels A (R = 0.6745, p = 0.0235) and B (R = 0.5706, p = 0.0496). Conversely, no significant correlation was found for data shown in panels C and D.

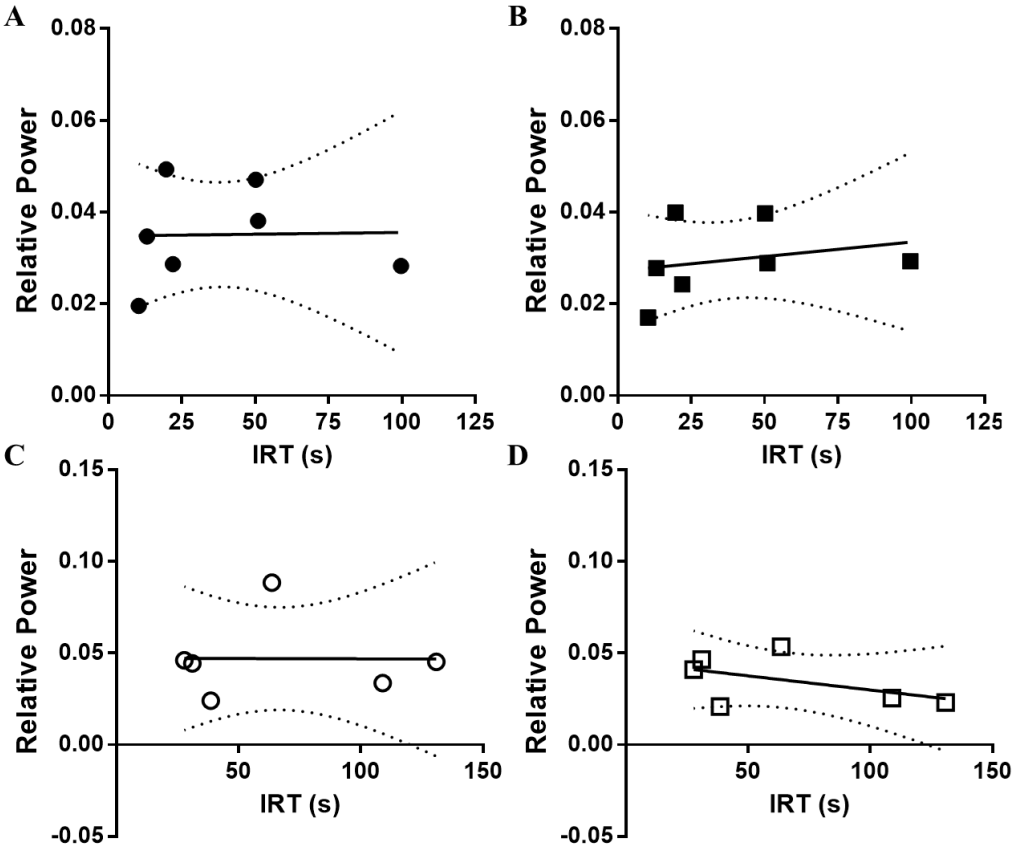


Figure 17. Correlation plots between Inter-Response Time (IRT; seconds) and high-gamma relative power for Ret ALP (A; closed circles) or Ret No-ALP (B; closed squares) epochs during the Dark phase Retrieval session and low-gamma relative power for Ret ALP (C; open circles) or Ret No-ALP (D; open squares) epochs during the Light phase Retrieval session. Closed and open circles and squares represent data of single subjects (N = 7, Dark; N = 6, Light). Solid lines represent the linear regression line, dotted lines represent 95% confidence intervals.

3.2.2 Comparison between instrumental memory retrieval in Dark and Light phases

As mentioned in section 2.8, two-way RM ANOVA was used to compare four groups with factors Lever Pressing (two levels: ALP, No-ALP) and Phase (two levels: Dark, Light). A summary of two-way RM ANOVA statistics is reported in Table 4. Thus, groups subjects of this analysis were Ret ALP/Dark, Ret No-ALP/Dark, Ret ALP/Light and Ret No-ALP/Light.

In BLA, two-way RM ANOVA on theta relative power (Figure 18, panel A) showed no significant matching between subjects [$F(11,11) = 2.146$; $p = .1105$] and

no main effects of factors Lever Pressing [F(1,11) = 1.056; p = .3262] and Phase [F(1,11) = .6834; p = .426] or their interaction [F(1,11) = .9059; p = .3616]. Two-way RM ANOVA on total gamma relative power (Figure 18, panel B) showed a significant matching between subjects [F(11,11) = 4.184; p = .0128], a main effect of factor Lever Pressing [F(1,11) = 5.233; p = .043] but not of Phase [F(1,11) = .0842; p = .777] or their interaction [F(1,11) = 2.135; p = .1719]; post-hoc Sidak's multiple comparisons test showed no significant differences between groups. Two-way RM ANOVA on low gamma relative power (Figure 18, panel C) showed no significant matching between subjects [F(11,11) = .789; p = .6494], a main effect of factor Lever Pressing [F(1,11) = 4.981; p = .0474] but not of Phase [F(1,11) = 2.896; p = .1169] or their interaction [F(1,11) = 1.615; p = .23]; post-hoc Sidak's multiple comparisons test showed no significant differences between groups. Two-way RM ANOVA on high gamma relative power (Figure 18, panel D) showed a significant matching between subjects [F(11,11) = 14.5; p < .0001], a main effect of factor Lever Pressing [F(1,11) = 4.583; p = .0555] but not of Phase [F(1,11) = .6194; p = .4479] or their interaction [F(1,11) = 2.42; p = .148].

In CA1, two-way RM ANOVA on theta relative power (Figure 19, panel A) showed a significant matching between subjects [F(11,11) = 8.909; p = .0005] and no main effects of factors Lever Pressing [F(1,11) = 2.193; p = .1667] and Phase [F(1,11) = 3.658; p = .0822] or their interaction [F(1,11) = .4559; p = .5135]. Two-way RM ANOVA on total gamma relative power (Figure 19, panel B) showed a significant matching between subjects [F(11,11) = 10.55; p = .0002], a main effect of factor Lever Pressing [F(1,11) = 13.3; p = .0038] but not of Phase [F(1,11) = 1.705; p = .2182] or their interaction [F(1,11) = 1.721; p = .2163]; post-hoc Sidak's multiple comparisons test showed a significant difference between Ret ALP/Light and Ret No-ALP/Light groups (0.175 ± 0.036 vs. 0.131 ± 0.019; p < 0.05) but not between Ret ALP/Dark and Ret No-ALP/Dark groups (0.126 ± 0.013 vs. 0.105 ± 0.012; NS). Two-way RM ANOVA on low gamma relative power (Figure 19, panel C) showed a significant matching between subjects [F(11,11) = 11.86; p = .0001], a main effect of factor Lever Pressing [F(1,11) = 13.34; p = .0038] but not of Phase [F(1,11) = 1.708; p = .2179] or their interaction [F(1,11) = 1.711; p = .2176]; post-hoc Sidak's multiple comparisons test showed a significant difference between Ret ALP/Light and Ret No-ALP/Light groups (0.127 ± 0.027 vs. 0.096 ± 0.015; p < 0.05) but not between Ret ALP/Dark and Ret No-ALP/Dark groups (0.090 ± 0.010 vs. 0.075 ±

0.009; NS). Two-way RM ANOVA on high gamma relative power (Figure 19, panel D) showed a significant matching between subjects [F(11,11) = 7.399; p = .0012], a main effect of factor Lever Pressing [F(1,11) = 10.24; p = .0084] but not of Phase [F(1,11) = 1.352; p = .2695] or their interaction [F(1,11) = 1.375; p = .2657]; post-hoc Sidak's multiple comparisons test showed a significant difference between Ret ALP/Light and Ret No-ALP/Light groups (0.047 ± 0.009 vs. 0.035 ± 0.006, $p < 0.05$) but not between Ret ALP/Dark and Ret No-ALP/Dark groups (0.035 ± 0.004 vs. 0.030 ± 0.003; NS).

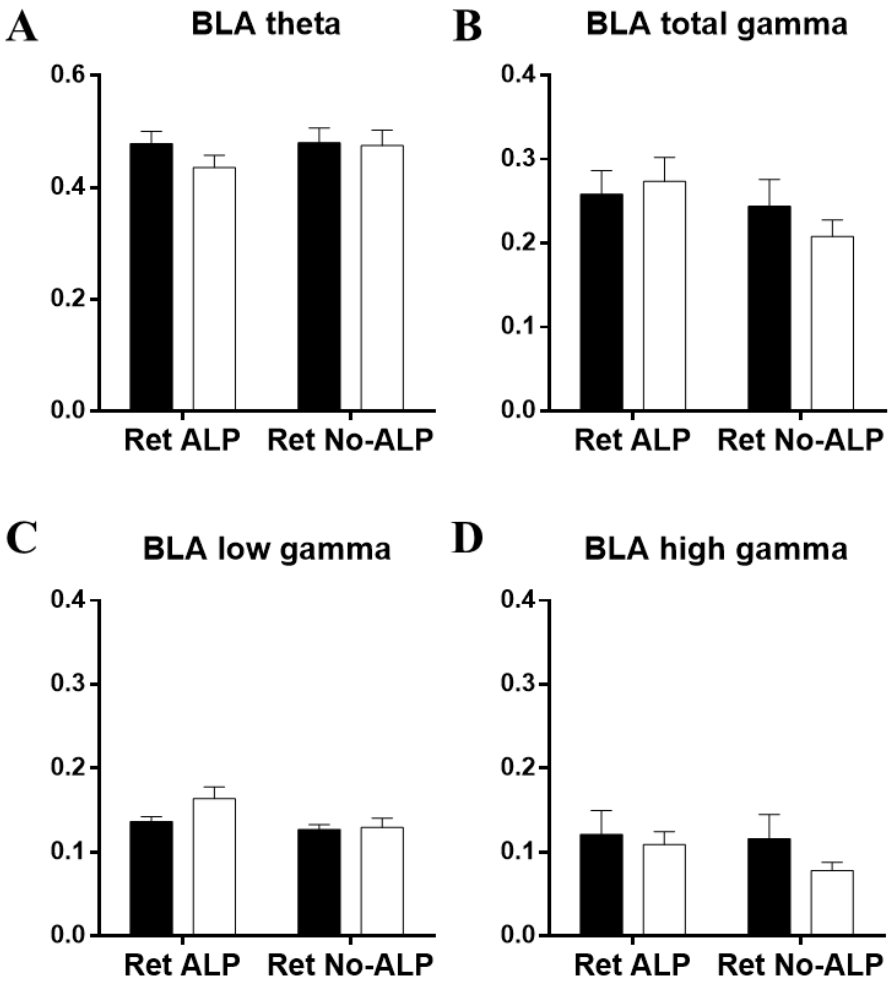


Figure 18. Bar plots show BLA relative powers for theta, total gamma, low gamma and high gamma oscillations. Relative powers are reported on the y-axis for Retrieval Active Lever Presses (Ret ALP) and Retrieval No-Active Lever Presses (Ret No-ALP) epochs during Dark (solid columns, N = 7) and Light (open columns, N = 6) phases. Data are shown as mean + S.E.M. Two-way RM ANOVA showed no significant difference between the groups.

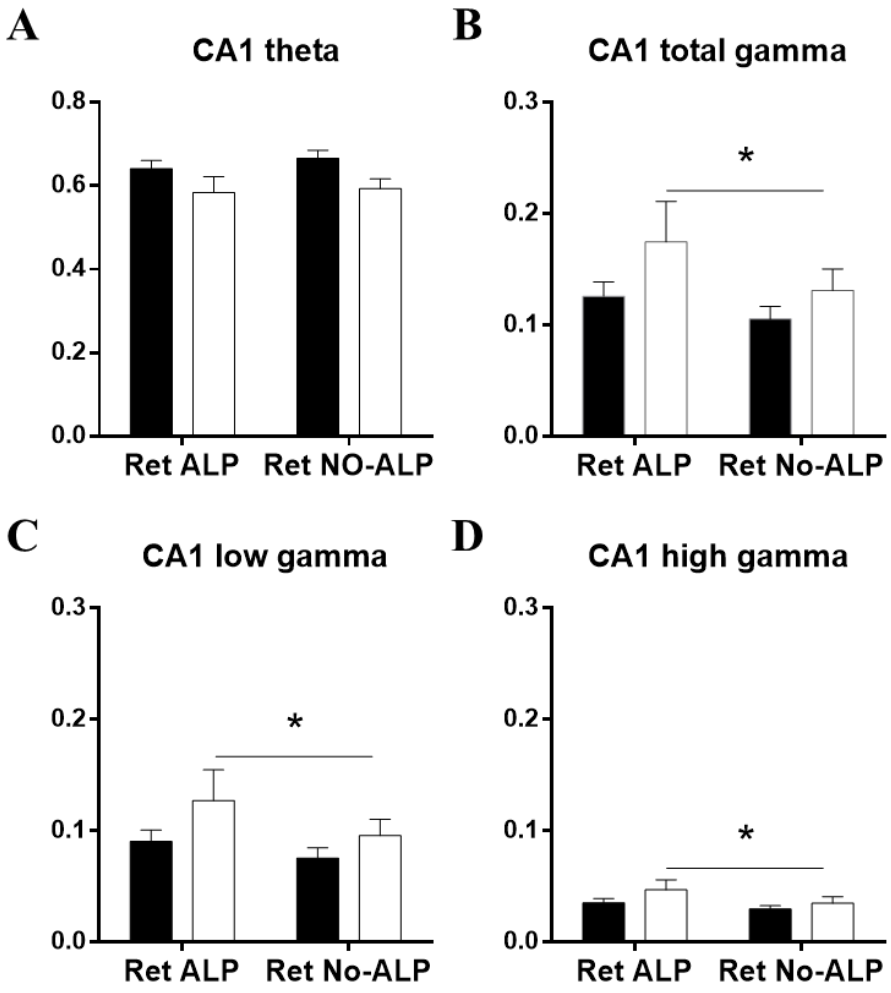


Figure 19 Bar plots show CA1 relative powers for theta, total gamma, low gamma and high gamma oscillations. Relative powers are reported on the y-axis for Retrieval Active Lever Presses (Ret ALP) and Retrieval No-Active Lever Presses (Ret No-ALP) epochs during Dark (solid columns, N = 7) and Light (open columns, N = 6) phases. Data are shown as mean + S.E.M. * = $p < 0.05$, two-way RM ANOVA followed by Sidak's post-hoc multiple comparisons test.

Table 4. Summary of two-way RM ANOVA statistics.

Area	Frequency band	ANOVA table	F (DFn, DFd)	P value	P value summary
CA1	Theta	Interaction	F (1, 11) = 0,4559	P = 0,5135	
		Lever Pressing	F (1, 11) = 2,193	P = 0,1667	
		Phase	F (1, 11) = 3,658	P = 0,0822	
		Subjects (matching)	F (11, 11) = 8,909	P = 0,0005	***
	Total Gamma	Interaction	F (1, 11) = 1,721	P = 0,2163	
		Lever Pressing	F (1, 11) = 13,30	P = 0,0038	**
		Phase	F (1, 11) = 1,705	P = 0,2182	
		Subjects (matching)	F (11, 11) = 10,55	P = 0,0002	***
	Low Gamma	Interaction	F (1, 11) = 1,711	P = 0,2176	
		Lever Pressing	F (1, 11) = 13,34	P = 0,0038	**
		Phase	F (1, 11) = 1,708	P = 0,2179	
		Subjects (matching)	F (11, 11) = 11,86	P = 0,0001	***
	High Gamma	Interaction	F (1, 11) = 1,375	P = 0,2657	
		Lever Pressing	F (1, 11) = 10,24	P = 0,0084	**
		Phase	F (1, 11) = 1,352	P = 0,2695	
		Subjects (matching)	F (11, 11) = 7,399	P = 0,0012	**
BLA	Theta	Interaction	F (1, 11) = 0,9059	P = 0,3616	
		Lever Pressing	F (1, 11) = 1,056	P = 0,3262	
		Phase	F (1, 11) = 0,6834	P = 0,4260	
		Subjects (matching)	F (11, 11) = 2,146	P = 0,1105	
	Total Gamma	Interaction	F (1, 11) = 2,135	P = 0,1719	
		Lever Pressing	F (1, 11) = 5,233	P = 0,0430	*
		Phase	F (1, 11) = 0,08424	P = 0,7770	
		Subjects (matching)	F (11, 11) = 4,184	P = 0,0128	*
	Low Gamma	Interaction	F (1, 11) = 1,615	P = 0,2300	
		Lever Pressing	F (1, 11) = 4,981	P = 0,0474	*
		Phase	F (1, 11) = 2,896	P = 0,1169	
		Subjects (matching)	F (11, 11) = 0,7890	P = 0,6494	
	High Gamma	Interaction	F (1, 11) = 2,420	P = 0,1480	
		Lever Pressing	F (1, 11) = 4,583	P = 0,0555	
		Phase	F (1, 11) = 0,6194	P = 0,4479	
		Subjects (matching)	F (11, 11) = 14,50	P < 0,0001	****

3.2.3 Comparison between instrumental memory retrieval and no retrieval in Dark and Light phases

As mentioned in section 2.8, two-way ANOVA was used to compare four groups with factors Experimental Condition (two levels: Ret, No Ret) and Phase (two levels: Dark, Light). Thus, groups subjects of this analysis were Ret No-ALP/Dark, No Ret/Dark, Ret No-ALP/Light and No Ret/Light.

In BLA, two-way ANOVA on theta relative power (Figure 20, panel A) showed no main effect of factors Experimental Condition [$F(1,25) = .1302$; $p = .7212$] and Phase [$F(1,25) = .0496$; $p = .8256$], nor their interaction [$F(1,25) = .0015$; $p = .9692$]. Two-way ANOVA on total gamma relative power (Figure 20, panel B) showed no main effect of factors Experimental Condition [$F(1,25) = .004$; $p = .9502$] and Phase [$F(1,25) = .7106$; $p = .4072$], nor their interaction [$F(1,25) = .5146$; $p = .4798$]. Two-way ANOVA on low gamma relative power (Figure 20, panel C) showed no main effect of factors Experimental Condition [$F(1,25) = 1.875$; $p = .183$] and Phase [$F(1,25) = .6267$; $p = .436$], nor their interaction [$F(1,25) = .2849$; $p = .5982$]. Two-way ANOVA on high gamma relative power (Figure 20, panel D) showed no main effect of factors Experimental Condition [$F(1,25) = .7253$; $p = .4025$] and Phase [$F(1,25) = 2.592$; $p = .12$], nor their interaction [$F(1,25) = .4964$; $p = .4876$].

In CA1, two-way ANOVA on theta relative power (Figure 21, panel A) showed a main effect of factor Phase [$F(1,25) = 9.563$; $p = .0048$], but not of factor Experimental Condition [$F(1,25) = .5655$; $p = .4591$] or their interaction [$F(1,25) = .0006$; $p = .9396$]; post-hoc Tukey's multiple comparisons test showed no significant differences between groups. Two-way ANOVA on total gamma relative power (Figure 21, panel B) showed a main effect of factor Phase [$F(1,25) = 8.993$; $p = .0061$], but not of factor Experimental Condition [$F(1,25) = .0162$; $p = .8999$] or their interaction [$F(1,25) = 1.148$; $p = .2943$]; post-hoc Tukey's multiple comparisons test showed a significant difference between No Ret/Dark and No Ret/Light groups (0.093 ± 0.011 vs. 0.147 ± 0.012; $p < 0.05$). Two-way ANOVA on low gamma relative power (Figure 21, panel C) showed a main effect of factor Phase [$F(1,25) = 9.922$; $p = .0042$], but not of factor Experimental Condition [$F(1,25) = .0064$; $p = .9365$] or their interaction [$F(1,25) = 1.253$; $p = .2735$]; post-hoc Tukey's multiple comparisons test showed a significant difference between No Ret/Dark and No Ret/Light groups (0.065 ± 0.008 vs. 0.108 ± 0.009; $p < 0.05$).

Two-way ANOVA on high gamma relative power (Figure 21, panel D) showed no main effect of factors Experimental Condition [F(1,25) = .0385; p = .846] and Phase [F(1,25) = 3.77; p = .0635], nor their interaction [F(1,25) = .4984; p = .4867].

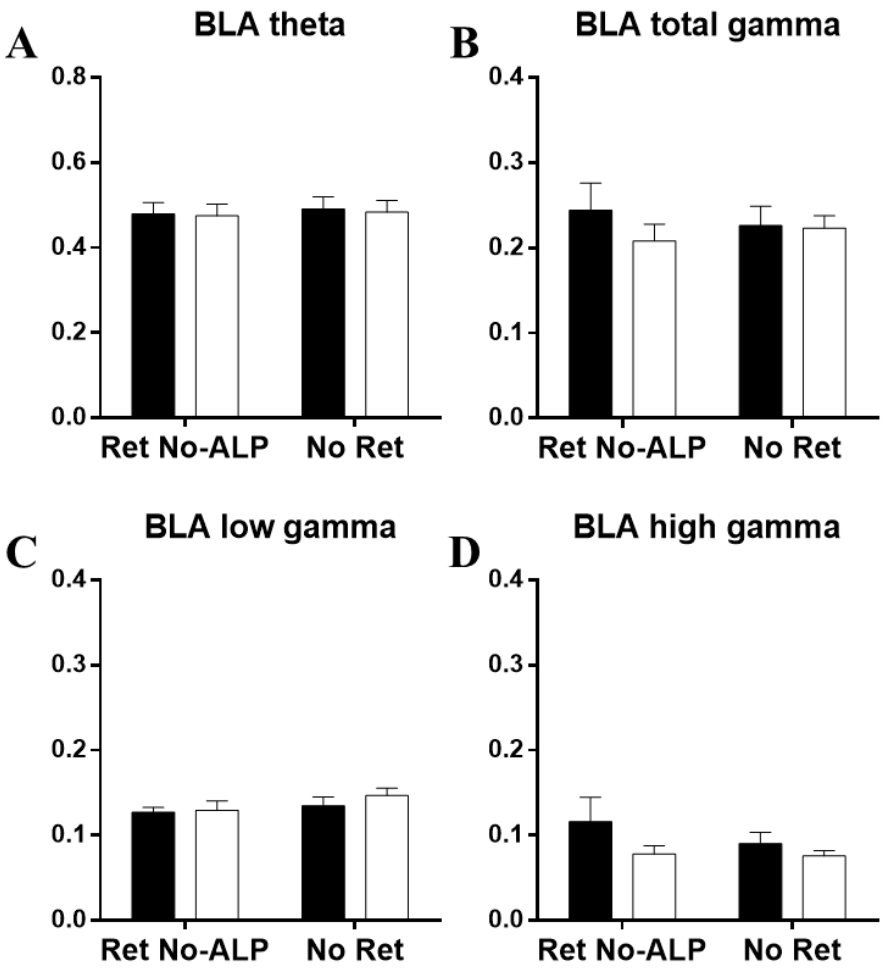


Figure 20. Bar plots show BLA relative powers for theta, total gamma, low gamma and high gamma oscillations. Relative powers are reported on the y-axis for Retrieval No-Active Lever Presses (Ret No-ALP) and No Retrieval (No Ret) epochs during Dark (solid columns, N = 7 and N = 7, respectively) and Light (open columns, N = 6 and N = 8, respectively) phases. Data are shown as mean + S.E.M. Two-way RM ANOVA showed no significant difference between the groups.

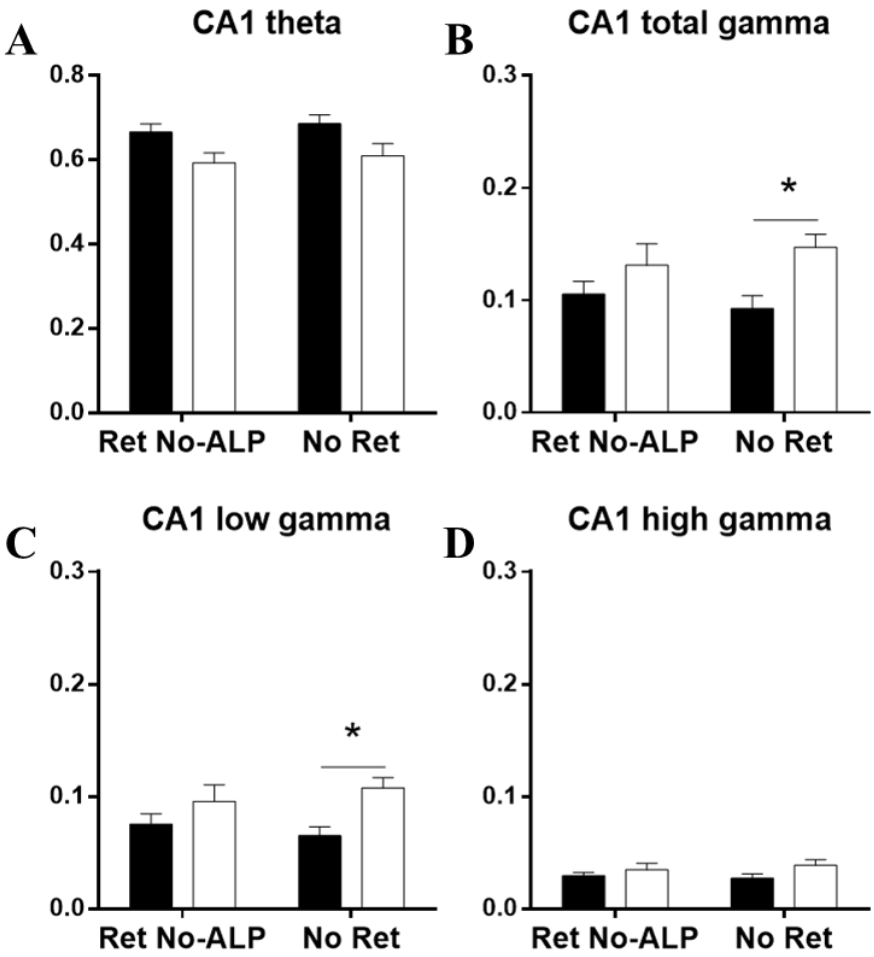


Figure 21. Bar plots show CA1 relative powers for theta, total gamma, low gamma and high gamma oscillations. Relative powers are reported on the y-axis for Retrieval No-Active Lever Presses (Ret No-ALP) and No Retrieval (No Ret) epochs during Dark (solid columns, N = 7 and N = 7, respectively) and Light (open columns, N = 6 and N = 8, respectively) phases. Data are shown as mean + S.E.M. * = $p < 0.05$, two-way ANOVA followed by Tukey's post-hoc multiple comparisons test.

Table 5. Summary of two-way ANOVA statistics.

Area	Frequency band	ANOVA table	F (DFn, DFd)	P value	P value summary
CA1	Theta	Interaction	F (1, 25) = 0,005860	P = 0,9396	
		Experimental Condition	F (1, 25) = 0,5655	P = 0,4591	
		Phase	F (1, 25) = 9,563	P = 0,0048	**
	Total Gamma	Interaction	F (1, 25) = 1,148	P = 0,2943	
		Experimental Condition	F (1, 25) = 0,01615	P = 0,8999	
		Phase	F (1, 25) = 8,993	P = 0,0061	**
	Low Gamma	Interaction	F (1, 25) = 1,253	P = 0,2735	
		Experimental Condition	F (1, 25) = 0,006476	P = 0,9365	
		Phase	F (1, 25) = 9,922	P = 0,0042	**
	High Gamma	Interaction	F (1, 25) = 0,4984	P = 0,4867	
		Experimental Condition	F (1, 25) = 0,03851	P = 0,8460	
		Phase	F (1, 25) = 3,770	P = 0,0635	
BLA	Theta	Interaction	F (1, 25) = 0,001520	P = 0,9692	
		Experimental Condition	F (1, 25) = 0,1302	P = 0,7212	
		Phase	F (1, 25) = 0,04958	P = 0,8256	
	Total Gamma	Interaction	F (1, 25) = 0,5146	P = 0,4798	
		Experimental Condition	F (1, 25) = 0,003973	P = 0,9502	
		Phase	F (1, 25) = 0,7106	P = 0,4072	
	Low Gamma	Interaction	F (1, 25) = 0,2849	P = 0,5982	
		Experimental Condition	F (1, 25) = 1,875	P = 0,1830	
		Phase	F (1, 25) = 0,6267	P = 0,4360	
	High Gamma	Interaction	F (1, 25) = 0,4964	P = 0,4876	
		Experimental Condition	F (1, 25) = 0,7253	P = 0,4025	
		Phase	F (1, 25) = 2,592	P = 0,1200	

4. DISCUSSION

In summary, rats belonging to different groups display a similar learning curve during the Training stage, confirming that there is no a priori difference between the subjects. At the Retrieval stage, subjects reactivating the memory during the Dark (i.e. active) phase show a higher rate of responding with respect to subjects reactivating the memory during the Light (i.e. inactive) phase. Moreover, no difference is observed among the groups at the Relapse test in terms of active lever presses.

From the electrophysiological point of view, hippocampal CA1 low gamma power values are inversely correlated to reactivation rate of responding when measured either when rats were actually lever pressing or not during the Dark, but not in the Light phase. This correlation was not observed in the high gamma frequency band. Furthermore, results show that hippocampal CA1 gamma bands power increased when lever pressing during instrumental sucrose memory reactivation while in the Light. This finding suggests that gamma bands (both low and high) may be specific correlational markers to actual instrumental responding reactivation during the inactive phase only when rats were pressing the levers. In fact, the same difference was not observed when rats were lever pressing during instrumental sucrose memory reactivation while in the Dark. In addition, hippocampal CA1 low gamma power increased in subjects not reactivating appetitive instrumental memory in the Light versus the Dark phase. Finally, no difference is observed in the theta frequency band in hippocampal CA1, suggesting that theta power is not a discriminating factor of memory retrieval neither during the Dark nor Light phase. At the level of the basolateral amygdala, no difference is observed neither in theta nor gamma frequency bands, suggesting that this area, in our conditions, is not relevant for memory retrieval.

Sucrose appetitive memory reconsolidation has been investigated in rodents following typical drug-addiction behavioural protocols, consisting of a training stage, an abstinence period, a memory reactivation stage and a final test to evaluate memory reconsolidation occurrence. In the present project, behavioural data at the training stage showed that subjects belonging to different groups displayed a similar learning curve (measured as inter reinforcement time), with no significant differences between the groups. Statistical analysis comparing inter reinforcement

time between the training sessions showed a lack of significant differences between the last three training sessions, suggesting self-administration stability achievement. At the Retrieval stage, subjects reactivating the memory during the Dark phase showed a lower inter response time with respect to subjects reactivating the memory during the Light phase (i.e. rats reactivating the instrumental memory during their active phase were faster in reaching the criterion to stop the Retrieval session with respect to rats reactivating the instrumental memory during their inactivity phase). Sleep scoring performed during Retrieval session excludes that subjects in the Ret/Light group slept during the behavioural procedure. Finally, at Relapse stage, no difference in terms of sucrose-seeking behaviour (measured as active lever presses) was observed between subjects performing Retrieval and subjects performing No Retrieval sessions in either Dark or Light phases. Based on the scientific literature, reconsolidation occurrence from the behavioural point of view has been observed only through its inhibition. For example, in 2014 Tedesco and colleagues, following a similar protocol to the one applied in the present project, showed that administering the NMDA receptor antagonist MK-801 after nicotine-related instrumental memory retrieval can reduce following nicotine-seeking behaviour measured as active lever presses over the 60 minutes behavioural session at Relapse test (Tedesco et al., 2014). In the present project, no protein synthesis inhibitor was administered to inhibit appetitive memory reconsolidation.

From the electrophysiological point of view, theta and gamma powers have been analysed in dorsal hippocampus and in basolateral amygdala, as the two areas (and their interaction) have been shown to be crucial for appetitive memory reconsolidation, as shown by Wells and colleagues in 2011 (Wells et al., 2011). Furthermore, theta and gamma oscillations in the two brain areas have been shown to be relevant for memory processing.

Particularly, results showed that hippocampal low gamma power correlates with reactivation rate of responding during the Dark, but not the Light phase, when measured either when rats were lever pressing or not: the higher the rate of responding, the lower the low gamma power. The same correlation was not observed in the high gamma frequency band. When comparing theta and gamma powers among groups performing reactivation in either Dark or Light phases, results showed that hippocampal CA1 gamma bands (both low and high) power

increased during instrumental sucrose memory reactivation in subjects performing the Retrieval session during the Light phase when they were lever pressing compared to when they were not lever pressing. This result suggests that gamma bands may be specific for instrumental responding reactivation during the Light phase. In fact, the same difference was not observed when the Retrieval session was performed during the Dark phase. However, further experiments should be done to show whether instrumental memory retrieval occurs during sleep. As reported in section 1.5.2, gamma oscillations can be divided in low and high gamma, based on the oscillation's frequencies. High gamma is mainly involved in sensory information encoding (Newman et al., 2013; Bieri et al., 2014; Zheng et al., 2016) and was also shown to be linked to changes in running speed (Ahmed and Mehta, 2012; Zheng et al., 2015). Based on the last evidence, increased high gamma power observed in rats lever pressing during the Retrieval session in their inactivity phase, might be correlated to lever-pressing related movement. However, the same difference was not observed for the group performing Retrieval in its activity phase, ruling out this option.

The same increase was observed for low gamma frequency; low gamma in CA1 is driven by CA3, which is believed to be the hippocampal area where memories are stored and retrieved from (Treves and Rolls, 1992; Brun et al., 2002; Nakazawa et al., 2002; Steffenach et al., 2002). Particularly, theta phase – low gamma amplitude coupling in CA3 has been shown to be related to successful memory retrieval (Shirvalkar et al., 2010). Thus, as previously stated, the observed difference in low gamma frequency in CA1 may suggest that low gamma band power may be specific for instrumental responding reactivation during the Light phase. However, further experiments and analyses are needed to confirm this statement. For example, the same experiments could be replicated by recording local field potentials in both CA1 and CA3 to evaluate coherence and synchrony between the two areas during memory retrieval. Particularly, analysis of theta-gamma phase-amplitude cross-frequency coupling in CA3 may provide a better insight in the memory reactivation process.

Finally, local field potential analysis in hippocampal CA1 showed total and low gamma power increase in subjects not reactivating appetitive instrumental memory in the Light versus the Dark phase. Groups performing the No Retrieval session

were not expected to show differences in terms of oscillations powers, as they represented the "negative control" groups. However, it cannot be ignored that the No Retrieval session was performed during two different phases of their circadian rhythm, which may bring along physiological oscillatory differences. In fact, gamma amplitude is modulated by the slower delta and theta frequencies; in the hippocampus, delta is prominent during sleep, while theta is predominant during active wake and REM sleep (Headley and Pare, 2017). Therefore, differences in neuronal oscillations due to different activity states might directly influence gamma frequencies power. This observation leads to the conclusion that, when comparing lever pressing versus non-lever pressing related gamma power in groups performing Retrieval in both active and inactive phases, not only we are observing differences related to memory reactivation, but also to circadian physiological differences. Therefore, it is difficult to discern the two components using this technique. As a control, further analysis may be carried out by analysing baseline recordings from when subjects were in their home cage during the two hours preceding the Retrieval/No Retrieval behavioural sessions.

4.1 Limitations

The stated goals of the project were first to evaluate differences in local field potentials when memory retrieval is performed during Light or Dark phases, in order to improve our knowledge on the impact of performing an appetitive memory Retrieval session during the inactivity vs activity phase in rodents on memory reactivation and following reconsolidation. And, secondly, to find an in vivo electrophysiological marker of appetitive memory reactivation.

The obtained results left the project with some unanswered questions and observations that are difficult to explain. Moreover, they were not able to give answers to its original goals.

On this regard, one of the limitations of the project is related to the difference between what is termed reactivation and what is termed retrieval: the former represents the operational methodology applied to reactivate the memory (which doesn't ensure that the memory will eventually be retrieved); the latter is the memory retrieval (molecular) process itself. As previously mentioned, it is possible to evaluate whether a memory has been retrieved or not by testing for

reconsolidation, either by means of molecular markers (for example, the immediate early gene zif268 and the phosphorylation of the ribosomal protein rpS6 (Piva et al., 2019)), or by means of reconsolidation inhibition (Tedesco et al., 2014).

While memory retrieval and reconsolidation occurrence has already been shown for the protocol adopted in the present dissertation with Retrieval session during the Dark phase (Tedesco et al., 2014; Piva et al., 2019), they have never been shown by applying the same protocol with Retrieval session during the Light phase. Therefore, further experiments should be performed to evaluate retrieval and reconsolidation occurrence in the group reactivating the memory during the inactivity phase before drawing conclusion from the obtained results.

Moreover, further analyses and experiments are needed. Indeed, local field potentials analyses shown in the present dissertation were limited to theta and gamma power analysis evaluating the two areas (hippocampal dorsal CA1 and basolateral amygdala) independently from each other. However, the project aimed at understanding if (and how) the two areas interact during appetitive memory reactivation and reconsolidation. Therefore, a re-analysis of electrophysiological data should be performed to evaluate connectomics measures such as coherence and coupling within and between areas. For example, synchrony of distant areas can be measured by power correlation or phase coherence analyses; Granger causality test can be useful to assess whether a time series predicts another one (Bocchio et al., 2017). Performing a similar analysis between hippocampus and basolateral amygdala could allow to understand whether the two areas communicate with each other and, more importantly, to assess directionality of rhythmic activity between regions.

4.2 Conclusion

Behavioural data presented in the current dissertation are in line with the literature. In fact, with the described protocol, reconsolidation occurrence as tested through the reinstatement test can only be observed through reconsolidation inhibition following memory reactivation (Tedesco et al., 2014).

What deserves to be highlighted is the Retrieval stage, as results showed that the instrumental memory Retrieval session lasts longer if performed during the inactive period of the circadian cycle. The reason of this is unknow, as up to date no similar

experiments are reported in the literature. However, rodents lower their locomotor activity during their inactive phase (Borbély and Neuhaus, 1978). Therefore, it could be speculated that the physiological decrease in their locomotion caused the subjects to respond slower during Retrieval; this may have had an impact on memory reactivation itself.

From the electrophysiological point of view and considering the scientific literature mentioned above on the relationship between CA1 and CA3 (Nakazawa et al., 2002; Steffenach et al., 2002), the inverse correlation between reactivation rate of responding and CA1 low gamma power suggests that with decreasing CA1 low gamma power there could be an increased output processing for memory reactivation. However, it cannot be excluded the opposite: maybe the increasing rate of responding acts as a sort of negative feedback by affecting CA3-dependent low gamma power in CA1. The lack of the same correlation for subjects performing Retrieval during the inactive phase may suggest that this result can only be seen within a limited time-window, and that the rate of responding for Light group was outside these limits.

In CA1, increase in both low and high gamma powers suggest a specific relationship between gamma oscillations and actual instrumental memory reactivation. This specificity emerges only when subjects are performing Retrieval in their inactive phase. It could be speculated that during the light phase of the dark/light cycle the instrumental memory is more labile and susceptible to reactivation. Therefore, low gamma increase would support the instrumental reactivation hypothesis; on the other hand, increase in high gamma might be related to 'novelty'. In fact, as stated above, it has been shown that high gamma is involved in information encoding and, even if the Retrieval context is the same as the Training one, subjects in the Light group were exposed to a novel temporal context (i.e. Retrieval stage when the light was on).

In conclusion, although results taken together show that hippocampal gamma power is differently modulated during instrumental memory reactivation either in the dark of light phases, speculations need to be cautiously made. In fact, when reading these data, physiological oscillatory differences must be taken into consideration, as

demonstrated by the higher hippocampal low gamma power in subjects not reactivating the instrumental memory during the active vs. inactive phases.

5. REFERENCES

Abdolahi A, Acosta G, Breslin FJ, Hemby SE, Lynch WJ (2010) Incubation of nicotine seeking is associated with enhanced protein kinase A-regulated signaling of dopamine- and cAMP-regulated phosphoprotein of 32 kDa in the insular cortex. Eur J Neurosci 31:733-741.

Agranoff BW, Davis RE, Brink JJ (1965) Memory fixation in the goldfish. Proc Natl Acad Sci U S A 54:788-793.

Ahmed OJ, Mehta MR (2012) Running speed alters the frequency of hippocampal gamma oscillations. J Neurosci 32:7373-7383.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition: American Psychiatric Publishing.

Anand BK, Brobeck JR (1951) Hypothalamic control of food intake in rats and cats. Yale J Biol Med 24:123-140.

Asok A, Leroy F, Rayman JB, Kandel ER (2019) Molecular Mechanisms of the Memory Trace. Trends Neurosci 42:14-22.

Atkinson RC, Shiffrin RM (1968) Human Memory: A Proposed System and its Control Processes. In: Psychology of Learning and Motivation, pp 89-195: Academic Press.

Avena NM, Long KA, Hoebel BG (2005) Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol Behav 84:359-362.

Axmacher N, Helmstaedter C, Elger CE, Fell J (2008) Enhancement of neocortical-medial temporal EEG correlations during non-REM sleep. Neural Plast 2008:563028.

Axmacher N, Henseler MM, Jensen O, Weinreich I, Elger CE, Fell J (2010) Cross-frequency coupling supports multi-item working memory in the human hippocampus. Proc Natl Acad Sci U S A 107:3228-3233.

Baddeley A (2003) Working memory: looking back and looking forward. Nat Rev Neurosci 4:829-839.

Baddeley AD, Warrington EK (1970) Amnesia and the distinction between long- and short-term memory. In: Exploring Working Memory, pp 176-189: Journal of Verbal Learning and Verbal Behavior.

Baddeley AD, Hitch G (1974) Working Memory. In: Psychology of Learning and Motivation (Bower GH, ed), pp 47-89: Academic Press.

Bailey CH, Chen M (1983) Morphological basis of long-term habituation and sensitization in Aplysia. Science 220:91-93.

Bailey CH, Chen M (1989) Structural plasticity at identified synapses during long-term memory in Aplysia. J Neurobiol 20:356-372.

Baler RD, Volkow ND (2006) Drug addiction: the neurobiology of disrupted self-control. Trends Mol Med 12:559-566.

Barry D, Clarke M, Petry NM (2009) Obesity and its relationship to addictions: is overeating a form of addictive behavior? Am J Addict 18:439-451.

Bartos M, Vida I, Jonas P (2007) Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 8:45-56.

Bauer EP, Paz R, Pare D (2007) Gamma oscillations coordinate amygdalo-rhinal interactions during learning. J Neurosci 27:9369-9379.

Bechara A (2005) Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neurosci 8:1458-1463.

Belin D, Everitt BJ (2008) Cocaine Seeking Habits Depend upon Dopamine-Dependent Serial Connectivity Linking the Ventral with the Dorsal Striatum. Neuron 57:432-441.

Belin D, Jonkman S, Dickinson A, Robbins TW, Everitt BJ (2009) Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. Behav Brain Res 199:89-102.

Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsaki G (2012) Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. J Neurosci 32:423-435.

Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, Battaglia FP, Wiener SI (2010) Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. Neuron 66:921-936.

Berger RJ, Phillips NH (1995) Energy conservation and sleep. Behav Brain Res 69:65-73.

Berlin GS, Hollander E (2014) Compulsivity, impulsivity, and the DSM-5 process. CNS Spectr 19:62-68.

Berridge KC (2009) 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav 97:537-550.

Berridge KC, Venier IL, Robinson TE (1989) Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. Behav Neurosci 103:36-45.

Berry SD, Thompson RF (1978) Prediction of learning rate from the hippocampal electroencephalogram. Science 200:1298-1300.

Beyeler A, Namburi P, Glober GF, Simonnet C, Calhoon GG, Conyers GF, Luck R, Wildes CP, Tye KM (2016) Divergent Routing of Positive and Negative Information from the Amygdala during Memory Retrieval. Neuron 90:348-361.

Bienkowski P, Rogowski A, Korkosz A, Mierzejewski P, Radwanska K, Kaczmarek L, Bogucka-Bonikowska A, Kostowski W (2004) Time-dependent changes in alcohol-seeking behaviour during abstinence. Eur Neuropsychopharmacol 14:355-360.

Bieri KW, Bobbitt KN, Colgin LL (2014) Slow and fast gamma rhythms coordinate different spatial coding modes in hippocampal place cells. Neuron 82:670-681.

Blair HT, Huynh VK, Vaz VT, Van J, Patel RR, Hiteshi AK, Lee JE, Tarpley JW (2005) Unilateral storage of fear memories by the amygdala. J Neurosci 25:4198-4205.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE (2000) Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. Journal of psychoactive drugs 32 Suppl:i-iv, 1-112.

Blumenthal DM, Gold MS (2010) Neurobiology of food addiction. Curr Opin Clin Nutr Metab Care 13:359-365.

Bocchio M, Nabavi S, Capogna M (2017) Synaptic Plasticity, Engrams, and Network Oscillations in Amygdala Circuits for Storage and Retrieval of Emotional Memories. Neuron 94:731-743.

Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitrab P (2010) Chronux: A Platform for Analyzing Neural Signals. Journal of Neuroscience Methods 192:146-151.

Borbely AA, Achermann P (1999) Sleep homeostasis and models of sleep regulation. J Biol Rhythms 14:557-568.

Borbély AA, Neuhaus HU (1978) Daily Pattern of Sleep, Motor Activity and Feeding in the Rat: Effects of Regular and Gradually Extended Photoperiods Journal of Comparative Physiology A 124:1-14.

Born J, Wilhelm I (2012) System consolidation of memory during sleep. Psychol Res 76:192-203.

Brady TF, Konkle T, Alvarez GA (2009) Compression in visual working memory: using statistical regularities to form more efficient memory representations. J Exp Psychol Gen 138:487-502.

Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G (1995) Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. J Neurosci 15:47-60.

Brandon MP, Koenig J, Leutgeb JK, Leutgeb S (2014) New and distinct hippocampal place codes are generated in a new environment during septal inactivation. Neuron 82:789-796.

Brankack J, Stewart M, Fox SE (1993) Current source density analysis of the hippocampal theta rhythm: associated sustained potentials and candidate synaptic generators. Brain Res 615:310-327.

Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI (2002) Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. Science 296:2243-2246.

Bucherelli C, Tassoni G (1992) Engram activation reinstates the susceptibility of consolidated memory traces to retrograde amnesia by functional blockade of parabrachial nuclei. Behav Brain Res 51:61-65.

Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551-570.

Buzsaki G (2009) Rhythms of the Brain.

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926-1929.

Buzsaki G, Leung LW, Vanderwolf CH (1983) Cellular bases of hippocampal EEG in the behaving rat. Brain Res 287:139-171.

Buzsaki G, Anastassiou CA, Koch C (2012) The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. Nat Rev Neurosci 13:407-420.

Caine SB, Thomsen M, Gabriel KI, Berkowitz JS, Gold LH, Koob GF, Tonegawa S, Zhang J, Xu M (2007) Lack of self-administration of cocaine in dopamine D1 receptor knock-out mice. J Neurosci 27:13140-13150.

Cambiaghi M, Grosso A, Likhtik E, Mazziotti R, Concina G, Renna A, Sacco T, Gordon JA, Sacchetti B (2016) Higher-Order Sensory Cortex Drives Basolateral Amygdala Activity during the Recall of Remote, but Not Recently Learned Fearful Memories. J Neurosci 36:1647-1659.

Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B (2003) Sleep-dependent theta oscillations in the human hippocampus and neocortex. J Neurosci 23:10897-10903.

Carr MF, Karlsson MP, Frank LM (2012) Transient slow gamma synchrony underlies hippocampal memory replay. Neuron 75:700-713.

Carter A, Hendrikse J, Lee N, Yücel M, Verdejo-Garcia A, Andrews ZB, Hall W (2016) The Neurobiology of "Food Addiction" and Its Implications for Obesity Treatment and Policy. Annu Rev Nutr 36:105-128.

Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, Cowan RL (2009) Obese adults have visual attention bias for food cue images: evidence for altered reward system function. Int J Obes (Lond) 33:1063-1073.

Castro DC, Cole SL, Berridge KC (2015) Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. Front Syst Neurosci 9:90.

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. The American journal of psychiatry 156:11-18.

Clark L, Bechara A, Damasio H, Aitken MRF, Sahakian BJ, Robbins TW (2008) Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain 131:1311-1322.

Clark RE (2004) The classical origins of Pavlov's conditioning. Integr Physiol Behav Sci 39:279-294.

Clemens Z, Fabo D, Halasz P (2005) Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 132:529-535.

Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 378:75-78.

Colgin LL (2013) Mechanisms and functions of theta rhythms. Annu Rev Neurosci 36:295-312.

Colgin LL (2016) Rhythms of the hippocampal network. Nat Rev Neurosci 17:239-249.

Colgin LL, Moser EI (2010) Gamma oscillations in the hippocampus. Physiology (Bethesda) 25:319-329.

Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI (2009) Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462:353-357.

Contreras-Rodriguez O, Martin-Perez C, Vilar-Lopez R, Verdejo-Garcia A (2017) Ventral and Dorsal Striatum Networks in Obesity: Link to Food Craving and Weight Gain. Biol Psychiatry 81:789-796.

Covey DP, Roitman MF, Garris PA (2014) Illicit dopamine transients: reconciling actions of abused drugs. Trends Neurosci 37:200-210.

Cowan N (2001) The magical number 4 in short-term memory: a reconsideration of mental storage capacity. Behav Brain Sci 24:87-114; discussion 114-185.

Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, Cone RD, Low MJ (2001) Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 411:480-484.

Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111-114.

D'Esposito M (2007) From cognitive to neural models of working memory. Philos Trans R Soc Lond B Biol Sci 362:761-772.

Dagher A (2009) The neurobiology of appetite: hunger as addiction. Int J Obes (Lond) 33 Suppl 2:S30-33.

Dahchour A, De Witte P, Bolo N, Nedelec JF, Muzet M, Durbin P, Macher JP (1998) Central effects of acamprosate: part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. Psychiatry Res 82:107-114.

Dash MB, Douglas CL, Vyazovskiy VV, Cirelli C, Tononi G (2009) Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. J Neurosci 29:620-629.

Davidson M, Shanley B, Wilce P (1995) Increased NMDA-induced excitability during ethanol withdrawal: a behavioural and histological study. Brain Res 674:91-96.

Davis C, Curtis C, Levitan RD, Carter JC, Kaplan AS, Kennedy JL (2011) Evidence that 'food addiction' is a valid phenotype of obesity. Appetite 57:711-717.

de Araujo IE, Oliveira-Maia AJ, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MA, Simon SA (2008) Food reward in the absence of taste receptor signaling. Neuron 57:930-941.

Debiec J, Doyere V, Nader K, Ledoux JE (2006) Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. Proc Natl Acad Sci U S A 103:3428-3433.

Delgado JM, Anand BK (1953) Increase of food intake induced by electrical stimulation of the lateral hypothalamus. Am J Physiol 172:162-168.

Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9-21.

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274-5278.

Diana M, Pistis M, Carboni S, Gessa GL, Rossetti ZL (1993) Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: electrophysiological and biochemical evidence. Proc Natl Acad Sci U S A 90:7966-7969.

Dickinson A (1985) Actions and habits: the development of behavioural autonomy. Phil Trans R Soc Land B Biol Sci 308:67-78.

Diekelmann S, Born J (2007) One memory, two ways to consolidate? Nat Neurosci 10:1085-1086.

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114-126.

Diekelmann S, Buchel C, Born J, Rasch B (2011) Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nat Neurosci 14:381-386.

Diergaarde L, Schoffelmeer AN, De Vries TJ (2006) Beta-adrenoceptor mediated inhibition of long-term reward-related memory reconsolidation. Behav Brain Res 170:333-336.

Doyle TG, Berridge KC, Gosnell BA (1993) Morphine enhances hedonic taste palatability in rats. Pharmacol Biochem Behav 46:745-749.

Dragoi G, Buzsaki G (2006) Temporal encoding of place sequences by hippocampal cell assemblies. Neuron 50:145-157.

Drosopoulos S, Windau E, Wagner U, Born J (2007) Sleep enforces the temporal order in memory. PLoS One 2:e376.

Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 55:51-86.

Dudai Y, Morris RGM (2000) To consolidate or not to consolidate: what are the questions? In: Brain, Perception, Memory: Advances in Cognitive Neuroscience (Bolhuis JJ, ed): Oxford University Press.

Duncan CP (1949) The retroactive effect of electroshock on learning. J Comp Physiol Psychol 42:32-44.

Economidou D, Cippitelli A, Stopponi S, Braconi S, Clementi S, Ubaldi M, Martin-Fardon R, Weiss F, Massi M, Ciccocioppo R (2011) Activation of brain NOP receptors attenuates acute and protracted alcohol withdrawal symptoms in the rat. Alcohol Clin Exp Res 35:747-755.

Eriksson J, Vogel EK, Lansner A, Bergstrom F, Nyberg L (2015) Neurocognitive Architecture of Working Memory. Neuron 88:33-46.

Eschenko O, Ramadan W, Molle M, Born J, Sara SJ (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15:222-228.

Everitt BJ, Wolf ME (2002) Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 22:3312-3320.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481-1489.

Exton-McGuinness MT, Lee JL (2015) Reduction in Responding for Sucrose and Cocaine Reinforcement by Disruption of Memory Reconsolidation. eNeuro 2.

Exton-McGuinness MT, Patton RC, Sacco LB, Lee JL (2014) Reconsolidation of a well-learned instrumental memory. Learn Mem 21:468-477.

Fanselow MS, LeDoux JE (1999) Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 23:229-232.

Fell J, Axmacher N (2011) The role of phase synchronization in memory processes. Nat Rev Neurosci 12:105-118.

Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernandez G (2001) Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. Nat Neurosci 4:1259-1264.

Feng T, Silva D, Foster DJ (2015) Dissociation between the experience-dependent development of hippocampal theta sequences and single-trial phase precession. J Neurosci 35:4890-4902.

Fernandez RS, Boccia MM, Pedreira ME (2016) The fate of memory: Reconsolidation and the case of Prediction Error. Neurosci Biobehav Rev 68:423-441.

Fitzpatrick S, Gilbert S, Serpell L (2013) Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? Neuropsychol Rev 23:138-156.

Flavell CR, Lee JL (2013) Reconsolidation and extinction of an appetitive pavlovian memory. Neurobiol Learn Mem 104:25-31.

Flexner LB, Flexner JB, Stellar E (1965) Memory and cerebral protein synthesis in mice as affected by graded amounts of puromycin. Exp Neurol 13:264-272.

Flood JF, Morley JE (1989) Cholecystokinin receptors mediate enhanced memory retention produced by feeding and gastrointestinal peptides. Peptides 10:809-813.

Foster DJ, Wilson MA (2007) Hippocampal theta sequences. Hippocampus 17:1093-1099.

Fotros A, Casey KF, Larcher K, Verhaeghe JA, Cox SM, Gravel P, Reader AJ, Dagher A, Benkelfat C, Leyton M (2013) Cocaine cue-induced dopamine release in amygdala and hippocampus: a high-resolution PET [(1)(8)F]fallypride study in cocaine dependent participants. Neuropsychopharmacology 38:1780-1788.

Fowler CD, Lu Q, Johnson PM, Marks MJ, Kenny PJ (2011) Habenular α5 nicotinic receptor subunit signalling controls nicotine intake. Nature 471:597-601.

Frank LM, Stanley GB, Brown EN (2004) Hippocampal plasticity across multiple days of exposure to novel environments. J Neurosci 24:7681-7689.

Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119-130.

Frankland PW, Ding HK, Takahashi E, Suzuki A, Kida S, Silva AJ (2006) Stability of recent and remote contextual fear memory. Learn Mem 13:451-457.

Freund TF, Antal M (1988) GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. Nature 336:170-173.

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9:474-480.

Fuchs RA, Weber SM, Rice HJ, Neisewander JL (2002) Effects of excitotoxic lesions of the basolateral amygdala on cocaine-seeking behavior and cocaine conditioned place preference in rats. Brain Res 929:15-25.

Fuchs RA, Eaddy JL, Su ZI, Bell GH (2007) Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. Eur J Neurosci 26:487-498.

Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH, See RE (2005) The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 30:296-309.

Fuster JM (2000) Cortical dynamics of memory. Int J Psychophysiol 35:155-164.

Gais S, Molle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830-6834.

Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, Rauchs G, Schabus M, Sterpenich V, Vandewalle G, Maquet P, Peigneux P (2007) Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A 104:18778-18783.

Gawin F, Kleber H (1986) Pharmacologic treatments of cocaine abuse. Psychiatr Clin North Am 9:573-583.

Gearhardt AN, Grilo CM, DiLeone RJ, Brownell KD, Potenza MN (2011) Can food be addictive? Public health and policy implications. Addiction 106:1208-1212.

Geiger BM, Haburcak M, Avena NM, Moyer MC, Hoebel BG, Pothos EN (2009) Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience 159:1193-1199.

George O, Sanders C, Freiling J, Grigoryan E, Vu S, Allen CD, Crawford E, Mandyam CD, Koob GF (2012) Recruitment of medial prefrontal cortex neurons during alcohol withdrawal predicts cognitive impairment and excessive alcohol drinking. Proc Natl Acad Sci U S A 109:18156-18161.

Gilbert PE, Kesner RP (2006) The role of the dorsal CA3 hippocampal subregion in spatial working memory and pattern separation. Behav Brain Res 169:142-149.

Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12:1222-1223.

Gisquet-Verrier P, Riccio DC (2012) Memory reactivation effects independent of reconsolidation. Learn Mem 19:401-409.

Goodman A (2008) Neurobiology of addiction. An integrative review. Biochem Pharmacol 75:266-322.

Gordon WC (1977) Similarities of recently acquired and reactivated memories in interference. American Journal of Psychology 90:231-242.

Gordon WC, Spear NE (1973) Effect of reactivation of a previously acquired memory on the interaction between memories in the rat. J Exp Psychol 99:349-355.

Gore F, Schwartz EC, Brangers BC, Aladi S, Stujenske JM, Likhtik E, Russo MJ, Gordon JA, Salzman CD, Axel R (2015) Neural Representations of Unconditioned Stimuli in Basolateral Amygdala Mediate Innate and Learned Responses. Cell 162:134-145.

Gosnell BA, Krahn DD (1993) The effects of continuous morphine infusion on diet selection and body weight. Physiol Behav 54:853-859.

Goudriaan AE, De Ruiter MB, Van Den Brink W, Oosterlaan J, Veltman DJ (2010) Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addiction Biology 15:491-503.

Gracy KN, Dankiewicz LA, Koob GF (2001) Opiate Withdrawal-Induced Fos Immunoreactivity in the Rat Extended Amygdala Parallels the Development of Conditioned Place Aversion. Neuropsychopharmacology 24:152-160.

Graf P, Squire LR, Mandler G (1984) The information that amnesic patients do not forget. J Exp Psychol Learn Mem Cogn 10:164-178.

Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A (1996) Activation of memory circuits during cue-elicited cocaine craving. Proceedings of the National Academy of Sciences of the United States of America 93:12040-12045.

Gray CM, Konig P, Engel AK, Singer W (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338:334-337.

Green JD, Arduini AA (1954) Hippocampal electrical activity in arousal. J Neurophysiol 17:533-557.

Grimm JW, Shaham Y, Hope BT (2002) Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behav Pharmacol 13:379-388.

Grimm JW, Fyall AM, Osincup DP (2005) Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. Physiol Behav 84:73-79.

Grimm JW, Hope BT, Wise RA, Shaham Y (2001) Neuroadaptation. Incubation of cocaine craving after withdrawal. Nature 412:141-142.

Gruest N, Richer P, Hars B (2004) Memory consolidation and reconsolidation in the rat pup require protein synthesis. J Neurosci 24:10488-10492.

Gupta AS, van der Meer MA, Touretzky DS, Redish AD (2012) Segmentation of spatial experience by hippocampal theta sequences. Nat Neurosci 15:1032-1039.

Hahn TM, Breininger JF, Baskin DG, Schwartz MW (1998) Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. Nat Neurosci 1:271-272.

Hardt O, Einarsson EO, Nader K (2010) A bridge over troubled water: reconsolidation as a link between cognitive and neuroscientific memory research traditions. Annu Rev Psychol 61:141-167.

Hasselmo ME, Bodelon C, Wyble BP (2002) A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput 14:793-817.

Haubrich J, Nader K (2018) Memory Reconsolidation. Curr Top Behav Neurosci 37:151-176.

Headley DB, Pare D (2017) Common oscillatory mechanisms across multiple memory systems. NPJ Sci Learn 2.

Heimer L, Alheid GF (1991) Piecing together the puzzle of basal forebrain anatomy. Adv Exp Med Biol 295:1-42.

Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C (1991) Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41:89-125.

Heinrichs SC, Menzaghi F, Schulteis G, Koob GF, Stinus L (1995) Suppression of corticotropin-releasing factor in the amygdala attenuates aversive consequences of morphine withdrawal. Behav Pharmacol 6:74-80.

Hendrikse JJ, Cachia RL, Kothe EJ, McPhie S, Skouteris H, Hayden MJ (2015) Attentional biases for food cues in overweight and individuals with obesity: a systematic review of the literature. Obes Rev 16:424-432.

Hernandez L, Hoebel BG (1988) Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. Physiol Behav 44:599-606.

Hernandez PJ, Kelley AE (2004) Long-term memory for instrumental responses does not undergo protein synthesis-dependent reconsolidation upon retrieval. Learn Mem 11:748-754.

Hernandez PJ, Sadeghian K, Kelley AE (2002) Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. Nat Neurosci 5:1327-1331.

Hobson JA (2005) Sleep is of the brain, by the brain and for the brain. Nature 437:1254-1256.

Horseman C, Meyer A (2019) Neurobiology of Addiction. Clin Obstet Gynecol 62:118-127.

Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430:78-81.

Hupbach A, Hardt O, Gomez R, Nadel L (2008) The dynamics of memory: context-dependent updating. Learn Mem 15:574-579.

Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, Jacobs WS, Kadish W, Manso G (2009) Refined food addiction: a classic substance use disorder. Med Hypotheses 72:518-526.

Igarashi KM, Lu L, Colgin LL, Moser MB, Moser EI (2014) Coordination of entorhinal-hippocampal ensemble activity during associative learning. Nature 510:143-147.

Inoue S, Honda K, Komoda Y (1995) Sleep as neuronal detoxification and restitution. Behav Brain Res 69:91-96.

Janes AC, Pizzagalli DA, Richardt S, de BFB, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ (2010) Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. Biol Psychiatry 67:722-729.

Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y (2014) Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci Biobehav Rev 38:1-16.

Jeneson A, Squire LR (2012) Working memory, long-term memory, and medial temporal lobe function. Learn Mem 19:15-25.

Johnson PM, Kenny PJ (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 13:635-641.

Josselyn SA, Tonegawa S (2020) Memory engrams: Recalling the past and imagining the future. Science 367.

Kalivas PW (2004) Glutamate systems in cocaine addiction. Current Opinion in Pharmacology 4:23-29.

Kamondi A, Acsady L, Wang XJ, Buzsaki G (1998) Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. Hippocampus 8:244-261.

Kantak KM, Black Y, Valencia E, Green-Jordan K, Eichenbaum HB (2002) Dissociable effects of lidocaine inactivation of the rostral and caudal basolateral amygdala on the maintenance and reinstatement of cocaine-seeking behavior in rats. J Neurosci 22:1126-1136.

Karalis N, Dejean C, Chaudun F, Khoder S, Rozeske RR, Wurtz H, Bagur S, Benchenane K, Sirota A, Courtin J, Herry C (2016) 4-Hz oscillations synchronize prefrontal-amygdala circuits during fear behavior. Nat Neurosci 19:605-612.

Kavanau JL (1997) Memory, sleep and the evolution of mechanisms of synaptic efficacy maintenance. Neuroscience 79:7-44.

Kenny PJ, Voren G, Johnson PM (2013) Dopamine D2 receptors and striatopallidal transmission in addiction and obesity. Current opinion in neurobiology 23:535-538.

Klinzing JG, Rasch B, Born J, Diekelmann S (2016) Sleep's role in the reconsolidation of declarative memories. Neurobiol Learn Mem 136:166-173.

Knutson KL, Spiegel K, Penev P, Van Cauter E (2007) The metabolic consequences of sleep deprivation. Sleep Med Rev 11:163-178.

Kober H, Lacadie CM, Wexler BE, Malison RT, Sinha R, Potenza MN (2016) Brain Activity During Cocaine Craving and Gambling Urges: An fMRI Study. Neuropsychopharmacology 41:628-637.

Kocsis B, Li S, Hajos M (2007) Behavior-dependent modulation of hippocampal EEG activity by the selective norepinephrine reuptake inhibitor reboxetine in rats. Hippocampus 17:627-633.

Koob GF, Bloom FE (1988) Cellular and molecular mechanisms of drug dependence. Science 242:715-723.

Koob GF, Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24:97-129.

Koob GF, Le Moal M (2006) Neurobiology of Addiction: Academic Press.

Koob GF, Le Moal M (2008) Addiction and the brain antireward system. Annu Rev Psychol 59:29-53.

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacology 35:217-238.

Koob GF, Volkow ND (2016) Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3:760-773.

Koob GF, Schulkin J (2018) Addiction and stress: An allostatic view. Neurosci Biobehav Rev.

Koob GF, Heinrichs SC, Menzaghi F, Pich EM, Britton KT (1994) Corticotropin releasing factor, stress and behavior. Seminars in Neuroscience 6:221-229.

Kuriyama K, Stickgold R, Walker MP (2004) Sleep-dependent learning and motor-skill complexity. Learn Mem 11:705-713.

Land C, Bunsey M, Riccio DC (2000) Anomalous properties of hippocampal lesion-induced retrograde amnesia. Psychobiology 28:476-485.

Landfield PW, McGaugh JL, Tusa RJ (1972) Theta rhythm: a temporal correlate of memory storage processes in the rat. Science 175:87-89.

Lange T, Dimitrov S, Born J (2010) Effects of sleep and circadian rhythm on the human immune system. Ann N Y Acad Sci 1193:48-59.

Lasztoczi B, Klausberger T (2014) Layer-specific GABAergic control of distinct gamma oscillations in the CA1 hippocampus. Neuron 81:1126-1139.

Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009) Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J Neurosci 29:14734-14740.

Lee EH, Ma YL (1995) Amphetamine enhances memory retention and facilitates norepinephrine release from the hippocampus in rats. Brain Res Bull 37:411-416.

Lee JL (2009) Reconsolidation: maintaining memory relevance. Trends Neurosci 32:413-420.

Lee JL (2010) Memory reconsolidation mediates the updating of hippocampal memory content. Front Behav Neurosci 4:168.

Lee JL, Everitt BJ (2008a) Appetitive memory reconsolidation depends upon NMDA receptor-mediated neurotransmission. Neurobiol Learn Mem 90:147-154.

Lee JL, Everitt BJ (2008b) Reactivation-dependent amnesia for appetitive memories is determined by the contingency of stimulus presentation. Learn Mem 15:390-393.

Lee JL, Di Ciano P, Thomas KL, Everitt BJ (2005) Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. Neuron 47:795-801.

Lee NM, Hall WD, Lucke J, Forlini C, Carter A (2014) Food addiction and its impact on weight-based stigma and the treatment of obese individuals in the U.S. and Australia. Nutrients 6:5312-5326.

Lemieux A, al'Absi M (2016) Stress psychobiology in the context of addiction medicine: from drugs of abuse to behavioral addictions. Prog Brain Res 223:43-62.

Lesting J, Narayanan RT, Kluge C, Sangha S, Seidenbecher T, Pape HC (2011) Patterns of coupled theta activity in amygdala-hippocampal-prefrontal cortical circuits during fear extinction. PLoS One 6:e21714.

Lesting J, Daldrup T, Narayanan V, Himpe C, Seidenbecher T, Pape HC (2013) Directional theta coherence in prefrontal cortical to amygdalo-hippocampal pathways signals fear extinction. PLoS One 8:e77707.

Leutgeb S, Leutgeb JK, Treves A, Moser MB, Moser EI (2004) Distinct ensemble codes in hippocampal areas CA3 and CA1. Science 305:1295-1298.

Levine AS, Morley JE (1984) Neuropeptide Y: a potent inducer of consummatory behavior in rats. Peptides 5:1025-1029.

Levinstein E (1878) Morbid Craving for Morphia (Die Morphiumsucht). 15 Waterloo Place, London: Smith, Elder, & CO.

Lewis DJ (1979) Psychobiology of active and inactive memory. Psychol Bull 86:1054-1083.

Lewis DJ, Misanin JR, Miller RR (1968) Recovery of memory following amnesia. Nature 220:704-705.

Li FQ, Xue YX, Wang JS, Fang Q, Li YQ, Zhu WL, He YY, Liu JF, Xue LF, Shaham Y, Lu L (2010) Basolateral amygdala cdk5 activity mediates consolidation and reconsolidation of memories for cocaine cues. J Neurosci 30:10351-10359.

Li X, Caprioli D, Marchant NJ (2015) Recent updates on incubation of drug craving: a mini-review. Addict Biol 20:872-876.

Likhtik E, Stujenske JM, Topiwala MA, Harris AZ, Gordon JA (2014) Prefrontal entrainment of amygdala activity signals safety in learned fear and innate anxiety. Nat Neurosci 17:106-113.

Lisman JE, Jensen O (2013) The theta-gamma neural code. Neuron 77:1002-1016.

London ED, Ernst M, Grant S, Bonson K, Weinstein A (2000) Orbitofrontal cortex and human drug abuse: functional imaging. Cerebral cortex (New York, NY : 1991) 10:334-342.

Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29:145-156.

Luck SJ, Vogel EK (1997) The capacity of visual working memory for features and conjunctions. Nature 390:279-281.

Lüscher C, Malenka RC (2011) Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 69:650-663.

Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S, et al. (1995) Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1:1155-1161.

Mameli-Engvall M, Evrard A, Pons S, Maskos U, Svensson TH, Changeux JP, Faure P (2006) Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. Neuron 50:911-921.

Mamiya N, Fukushima H, Suzuki A, Matsuyama Z, Homma S, Frankland PW, Kida S (2009) Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. J Neurosci 29:402-413.

Marr D (1971) Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 262:23-81.

Marshall L, Born J (2007) The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci 11:442-450.

Martel P, Fantino M (1996) Mesolimbic dopaminergic system activity as a function of food reward: a microdialysis study. Pharmacol Biochem Behav 53:221-226.

Martin C, Beshel J, Kay LM (2007) An olfacto-hippocampal network is dynamically involved in odor-discrimination learning. J Neurophysiol 98:2196-2205.

Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang DR, Broft A, Huang Y, Cooper TB, Fischman MW, Kleber HD, Laruelle M (2007) Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. Am J Psychiatry 164:622-629.

Matsumoto M, Hikosaka O (2007) Lateral habenula as a source of negative reward signals in dopamine neurons. Nature 447:1111-1115.

McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 102:419-457.

McEwen BS (2000) The neurobiology of stress: from serendipity to clinical relevance. Brain Res 886:172-189.

McFarland K, Lapish CC, Kalivas PW (2003) Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. The Journal of neuroscience : the official journal of the Society for Neuroscience 23:3531-3537.

McGaugh JL (2000) Memory--a century of consolidation. Science 287:248-251.

McGaugh JL, Krivanek JA (1970) Strychnine effects on discrimination learning in mice: effects of dose and time of administration. Physiol Behav 5:1437-1442.

Mehta MR, Lee AK, Wilson MA (2002) Role of experience and oscillations in transforming a rate code into a temporal code. Nature 417:741-746.

Meil WM, See RE (1997) Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. Behav Brain Res 87:139-148.

Meule A (2011) How Prevalent is "Food Addiction"? Front Psychiatry 2:61.

Milekic MH, Pollonini G, Alberini CM (2007) Temporal requirement of C/EBPbeta in the amygdala following reactivation but not acquisition of inhibitory avoidance. Learn Mem 14:504-511.

Milella MS, Fotros A, Gravel P, Casey KF, Larcher K, Verhaeghe JA, Cox SM, Reader AJ, Dagher A, Benkelfat C, Leyton M (2016) Cocaine cue-induced dopamine release in the human prefrontal cortex. J Psychiatry Neurosci 41:322-330.

Miller GA (1956) The magical number seven plus or minus two: some limits on our capacity for processing information. Psychol Rev 63:81-97.

Miller LK (2006) Principles of everyday behavior analysis, 4th Edition. Belmont (CA, USA): Thomson/Wadsworth.

Milner B (1972) Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 19:421-446.

Milton AL, Lee JL, Everitt BJ (2008) Reconsolidation of appetitive memories for both natural and drug reinforcement is dependent on {beta}-adrenergic receptors. Learn Mem 15:88-92.

Misanin JR, Miller RR, Lewis DJ (1968) Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160:554-555.

Mitra P, Bokil H (2007) Observed Brain Dynamics: Oxford University Press.

Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC (2001) Psychiatric aspects of impulsivity. Am J Psychiatry 158:1783-1793.

Molle M, Born J (2009) Hippocampus whispering in deep sleep to prefrontal cortex--for good memories? Neuron 61:496-498.

Molle M, Marshall L, Gais S, Born J (2004) Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. Proc Natl Acad Sci U S A 101:13963-13968.

Montarolo PG, Goelet P, Castellucci VF, Morgan J, Kandel ER, Schacher S (1986) A critical period for macromolecular synthesis in long-term heterosynaptic facilitation in Aplysia. Science 234:1249-1254.

Montgomery SM, Buzsaki G (2007) Gamma oscillations dynamically couple hippocampal CA3 and CA1 regions during memory task performance. Proc Natl Acad Sci U S A 104:14495-14500.

Montgomery SM, Sirota A, Buzsaki G (2008) Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. J Neurosci 28:6731-6741.

Moran TH, Ladenheim EE (2016) Physiologic and Neural Controls of Eating. Gastroenterol Clin North Am 45:581-599.

Morris RG, Inglis J, Ainge JA, Olverman HJ, Tulloch J, Dudai Y, Kelly PA (2006) Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. Neuron 50:479-489.

Müller GE, Pilzecker A (1900) Experimentelle beiträge zur lehre vom gedächtniss [Experimental contributions to the science of memory]. Leipzig: J. A. Barth

Murphy ES, Lupfer GJ (2014) Basic Principles of Operant Conditioning. In: The Wiley Blackwell Handbook of Operant and Classical Conditioning (McSweeney FK, Murphy ES, eds), pp 167-194: Wiley-Blackwell.

Murray JB (1967) Drug addiction. J Gen Psychol 77:41-68.

Musto DF (1996) Drug Abuse Research in Historical Perspective. In: Pathways of Addiction: Opportunities in Drug Abuse Research, pp 284-294. Washington, D.C.: National Academy Press.

Nader K (2003) Memory traces unbound. Trends Neurosci 26:65-72.

Nader K, Schafe GE, Le Doux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406:722-726.

Nakashiba T, Young JZ, McHugh TJ, Buhl DL, Tonegawa S (2008) Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. Science 319:1260-1264.

Nakazawa K, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA, Tonegawa S (2002) Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 297:211-218.

Namburi P, Beyeler A, Yorozu S, Calhoon GG, Halbert SA, Wichmann R, Holden SS, Mertens KL, Anahtar M, Felix-Ortiz AC, Wickersham IR, Gray JM, Tye KM (2015) A circuit mechanism for differentiating positive and negative associations. Nature 520:675-678.

Narayanan RT, Seidenbecher T, Sangha S, Stork O, Pape HC (2007a) Theta resynchronization during reconsolidation of remote contextual fear memory. Neuroreport 18:1107-1111.

Narayanan RT, Seidenbecher T, Kluge C, Bergado J, Stork O, Pape HC (2007b) Dissociated theta phase synchronization in amygdalo- hippocampal circuits during various stages of fear memory. Eur J Neurosci 25:1823-1831.

Newman EL, Gillet SN, Climer JR, Hasselmo ME (2013) Cholinergic blockade reduces theta-gamma phase amplitude coupling and speed modulation of theta frequency consistent with behavioral effects on encoding. J Neurosci 33:19635-19646.

NIDA (2018) Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). National Intitute on Drug Abuse website.

Nieh EH, Matthews GA, Allsop SA, Presbrey KN, Leppla CA, Wichmann R, Neve R, Wildes CP, Tye KM (2015) Decoding neural circuits that control compulsive sucrose seeking. Cell 160:528-541.

Nijs IM, Franken IH (2012) Attentional Processing of Food Cues in Overweight and Obese Individuals. Curr Obes Rep 1:106-113.

Nijs IM, Franken IH, Muris P (2010) Food-related Stroop interference in obese and normal-weight individuals: behavioral and electrophysiological indices. Eat Behav 11:258-265.

O'Brien CP (1997) A range of research-based pharmacotherapies for addiction. Science 278:66-70.

O'Keefe J (1976) Place units in the hippocampus of the freely moving rat. Exp Neurol 51:78-109.

O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171-175.

O'Keefe J, Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3:317-330.

O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J (2010) Play it again: reactivation of waking experience and memory. Trends Neurosci 33:220-229.

Oswald I (1980) Sleep as restorative process: human clues. Prog Brain Res 53:279-288.

Pape HC, Driesang RB (1998) Ionic mechanisms of intrinsic oscillations in neurons of the basolateral amygdaloid complex. J Neurophysiol 79:217-226.

Pape HC, Pare D (2010) Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev 90:419-463.

Pare D, Pape HC, Dong J (1995) Bursting and oscillating neurons of the cat basolateral amygdaloid complex in vivo: electrophysiological properties and morphological features. J Neurophysiol 74:1179-1191.

Parsons LH, Justice JB, Jr. (1993) Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. Brain Res 606:195-199.

Paxinos G, Watson C (2007) The Rat Brain in Stereotaxic Coordinates. In: 123Library, 6 Edition: Academic Press.

Pedreira ME, Perez-Cuesta LM, Maldonado H (2004) Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. Learn Mem 11:579-585.

Penttonen M, Kamondi A, Acsady L, Buzsaki G (1998) Gamma frequency oscillation in the hippocampus of the rat: intracellular analysis in vivo. Eur J Neurosci 10:718-728.

Perez-Leighton CE, Boland K, Teske JA, Billington C, Kotz CM (2012) Behavioral responses to orexin, orexin receptor gene expression, and spontaneous

physical activity contribute to individual sensitivity to obesity. Am J Physiol Endocrinol Metab 303:E865-874.

Pernia-Andrade AJ, Jonas P (2014) Theta-gamma-modulated synaptic currents in hippocampal granule cells in vivo define a mechanism for network oscillations. Neuron 81:140-152.

Peyrache A, Khamassi M, Benchenane K, Wiener SI, Battaglia FP (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat Neurosci 12:919-926.

Pfeiffer BE, Foster DJ (2015) PLACE CELLS. Autoassociative dynamics in the generation of sequences of hippocampal place cells. Science 349:180-183.

Phelps EA, LeDoux JE (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48:175-187.

Pierce RC, Kalivas PW (1997) A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. Brain Research Reviews 25:192-216.

Piva A, Gerace E, Di Chio M, Padovani L, Paolone G, Pellegrini-Giampietro DE, Chiamulera C (2019) Reconsolidation of sucrose instrumental memory in rats: The role of retrieval context. Brain Res 1714:193-201.

Popa D, Duvarci S, Popescu AT, Lena C, Pare D (2010) Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc Natl Acad Sci U S A 107:6516-6519.

Popescu AT, Popa D, Pare D (2009) Coherent gamma oscillations couple the amygdala and striatum during learning. Nat Neurosci 12:801-807.

Przybyslawski J, Sara SJ (1997) Reconsolidation of memory after its reactivation. Behav Brain Res 84:241-246.

Przybyslawski J, Roullet P, Sara SJ (1999) Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. J Neurosci 19:6623-6628.

Qu D, Ludwig DS, Gammeltoft S, Piper M, Pelleymounter MA, Cullen MJ, Mathes WF, Przypek R, Kanarek R, Maratos-Flier E (1996) A role for melanin-concentrating hormone in the central regulation of feeding behaviour. Nature 380:243-247.

Quiroga RQ (2013) Gnostic cells in the 21st century. Acta Neurobiol Exp (Wars) 73:463-471.

Ramirez DR, Bell GH, Lasseter HC, Xie X, Traina SA, Fuchs RA (2009) Dorsal hippocampal regulation of memory reconsolidation processes that facilitate drug context-induced cocaine-seeking behavior in rats. Eur J Neurosci 30:901-912.

Ranganath C (2006) Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. Neuroscience 139:277-289.

Rasch B, Born J (2007) Maintaining memories by reactivation. Current opinion in neurobiology 17:698-703.

Rasch B, Born J (2013) About sleep's role in memory. Physiol Rev 93:681-766.

Rechtschaffen A, Bergmann BM (1995) Sleep deprivation in the rat by the disk-over-water method. Behav Brain Res 69:55-63.

Redondo RL, Kim J, Arons AL, Ramirez S, Liu X, Tonegawa S (2014) Bidirectional switch of the valence associated with a hippocampal contextual memory engram. Nature 513:426-430.

Reimund E (1994) The free radical flux theory of sleep. Med Hypotheses 43:231-233.

Reisiger AR, Kaufling J, Manzoni O, Cador M, Georges F, Caille S (2014) Nicotine self-administration induces CB1-dependent LTP in the bed nucleus of the stria terminalis. J Neurosci 34:4285-4292.

Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci 22:10914-10923.

Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, Lin SC, Wada K, Lemos NA, Nicolelis MA (2007) Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci 1:43-55.

Ribot T (1881) Les Maladies de la Memoire [Diseases of memory]. New York: Appleton-Century-Crofts.

Risinger RC, Salmeron BJ, Ross TJ, Amen SL, Sanfilipo M, Hoffmann RG, Bloom AS, Garavan H, Stein EA (2005) Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. Neuroimage 26:1097-1108.

Robbins T, Curran H, de Wit H (2012a) Special issue on impulsivity and compulsivity. Psychopharmacology (Berl) 219:251-252.

Robbins TW (1976) Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature 264:57-59.

Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD (2012b) Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn Sci 16:81-91.

Roberts AJ, Cole M, Koob GF (1996) Intra-amygdala Muscimol Decreases Operant Ethanol Self-administration in Dependent Rats. Alcoholism: Clinical and Experimental Research 20:1289-1298.

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247-291.

Rosanova M, Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25:9398-9405.

Salas R, Sturm R, Boulter J, De Biasi M (2009) Nicotinic Receptors in the Habenulo-Interpeduncular System Are Necessary for Nicotine Withdrawal in Mice. The Journal of Neuroscience 29:3014.

Sara SJ (2000) Retrieval and reconsolidation: toward a neurobiology of remembering. Learn Mem 7:73-84.

Schacher S, Castellucci VF, Kandel ER (1988) cAMP evokes long-term facilitation in Aplysia sensory neurons that requires new protein synthesis. Science 240:1667-1669.

Schacter DL (2001) Forgotten ideas, neglected pioneers: Richard Semon and the story of memory. Philadelphia: Psychology Press.

Scharf MT, Naidoo N, Zimmerman JE, Pack AI (2008) The energy hypothesis of sleep revisited. Prog Neurobiol 86:264-280.

Schneider AM, Sherman W (1968) Amnesia: a function of the temporal relation of footshock to electroconvulsive shock. Science 159:219-221.

Schomburg EW, Fernandez-Ruiz A, Mizuseki K, Berenyi A, Anastassiou CA, Koch C, Buzsaki G (2014) Theta phase segregation of input-specific gamma patterns in entorhinal-hippocampal networks. Neuron 84:470-485.

Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG (1996) Identification of targets of leptin action in rat hypothalamus. J Clin Invest 98:1101-1106.

Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, Litt B, Brandt A, Kahana MJ (2007a) Gamma oscillations distinguish true from false memories. Psychol Sci 18:927-932.

Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, McCarthy DC, Brandt A, Tully MS, Kahana MJ (2007b) Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cerebral cortex (New York, NY : 1991) 17:1190-1196.

Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 301:846-850.

Sejnowski TJ, Destexhe A (2000) Why do we sleep? Brain Res 886:208-223.

Sekiguchi T, Yamada A, Suzuki H (1997) Reactivation-dependent changes in memory states in the terrestrial slug Limax flavus. Learn Mem 4:356-364.

Senior TJ, Huxter JR, Allen K, O'Neill J, Csicsvari J (2008) Gamma oscillatory firing reveals distinct populations of pyramidal cells in the CA1 region of the hippocampus. J Neurosci 28:2274-2286.

Shabel SJ, Janak PH (2009) Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. Proc Natl Acad Sci U S A 106:15031-15036.

Shahveisi K, Khazaie H, Farnia V, Khodamoradi M (2019) REM sleep deprivation impairs retrieval, but not reconsolidation, of methamphetamine reward memory in male rats. Pharmacol Biochem Behav 185:172759.

Shalev U, Morales M, Hope B, Yap J, Shaham Y (2001) Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. Psychopharmacology (Berl) 156:98-107.

Shepard JD, Bossert JM, Liu SY, Shaham Y (2004) The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. Biol Psychiatry 55:1082-1089.

Shirvalkar PR, Rapp PR, Shapiro ML (2010) Bidirectional changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes. Proc Natl Acad Sci U S A 107:7054-7059.

Sidhpura N, Parsons LH (2011) Endocannabinoid-mediated synaptic plasticity and addiction-related behavior. Neuropharmacology 61:1070-1087.

Sills TL, Vaccarino FJ (1991) Facilitation and inhibition of feeding by a single dose of amphetamine: relationship to baseline intake and accumbens cholecystokinin. Psychopharmacology (Berl) 105:329-334.

Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsaki G (2008) Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. Neuron 60:683-697.

Skaggs WE, McNaughton BL, Wilson MA, Barnes CA (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus 6:149-172.

Soltesz I, Deschenes M (1993) Low- and high-frequency membrane potential oscillations during theta activity in CA1 and CA3 pyramidal neurons of the rat hippocampus under ketamine-xylazine anesthesia. J Neurophysiol 70:97-116.

Sorman E, Wang D, Hajos M, Kocsis B (2011) Control of hippocampal theta rhythm by serotonin: role of 5-HT2c receptors. Neuropharmacology 61:489-494.

Spear NE (1973) Retrieval of memory in animals. Psychological Review 80:163-194.

Squire LR (2004) Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem 82:171-177.

Squire LR, Alvarez P (1995) Retrograde amnesia and memory consolidation: a neurobiological perspective. Current opinion in neurobiology 5:169-177.

Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A 93:13515-13522.

Squire LR, Dede AJ (2015) Conscious and unconscious memory systems. Cold Spring Harb Perspect Biol 7:a021667.

Squire LR, Cohen NJ, Nadel L (1984) The medial temporal region and memory consolidation: a new hypothesis. In: Memory Consolidation: Psychobiology of Cognition (Weingartner HW, Parker ES, eds), pp 185-210. Hillsdale, NJ: Lawrence Erlbaum Associates.

Squire LR, Stark CE, Clark RE (2004) The medial temporal lobe. Annu Rev Neurosci 27:279-306.

Squire LR, Genzel L, Wixted JT, Morris RG (2015) Memory consolidation. Cold Spring Harb Perspect Biol 7:a021766.

Steffenach HA, Sloviter RS, Moser EI, Moser MB (2002) Impaired retention of spatial memory after transection of longitudinally oriented axons of hippocampal CA3 pyramidal cells. Proc Natl Acad Sci U S A 99:3194-3198.

Sterling P, Eyer J (1988) Allostasis: A new paradigm to exaplain arousal pathology. In: Handbook of life stress, cognition and health, pp 629-649. Oxford, England: John WIley & Sons.

Stern SA, Alberini CM (2013) Mechanisms of memory enhancement. Wiley Interdiscip Rev Syst Biol Med 5:37-53.

Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE (2013) The contribution of brain reward circuits to the obesity epidemic. Neurosci Biobehav Rev 37:2047-2058.

Stickgold R, Walker MP (2005) Memory consolidation and reconsolidation: what is the role of sleep? Trends Neurosci 28:408-415.

Study Group on the Treatment and Care of Drug Addicts (1957) Treatment and Care of Drug Addicts, Report of a Study Group. In: World Health Organization Technical Report Series. Palais de Nations, Geneva: World Health Organization.

Stujenske JM, Likhtik E, Topiwala MA, Gordon JA (2014) Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala. Neuron 83:919-933.

Sutherland RJ, Whishaw IQ, Kolb B (1983) A behavioural analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. Behav Brain Res 7:133-153.

Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernandez G (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 103:756-761.

Tanda G, Pontieri FE, Di Chiara G (1997) Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science 276:2048-2050.

Tang DW, Fellows LK, Small DM, Dagher A (2012) Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. Physiol Behav 106:317-324.

Teber I, Kohling R, Speckmann EJ, Barnekow A, Kremerskothen J (2004) Muscarinic acetylcholine receptor stimulation induces expression of the activity-regulated cytoskeleton-associated gene (ARC). Brain Res Mol Brain Res 121:131-136.

Tedesco V, Mutti A, Auber A, Chiamulera C (2014) Nicotine-seeking reinstatement is reduced by inhibition of instrumental memory reconsolidation. Behav Pharmacol 25:725-731.

Teitelbaum P, Epstein AN (1962) The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. Psychol Rev 69:74-90.

Terry L, Holliday JH (1972) Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace: A replication. Psychonomic Science 29:137-138.

Thiele TE, van Dijk G, Yagaloff KA, Fisher SL, Schwartz M, Burn P, Seeley RJ (1998) Central infusion of melanocortin agonist MTII in rats: assessment of c-Fos expression and taste aversion. Am J Physiol 274:R248-254.

Tiffany ST, Carter BL, Singleton EG (2000) Challenges in the manipulation, assessment and interpretation of craving relevant variables. Addiction 95 Suppl 2:S177-187.

Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, Volkow ND (2007) Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. Psychiatry Res 155:189-201.

Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49-62.

Tort AB, Komorowski RW, Manns JR, Kopell NJ, Eichenbaum H (2009) Theta-gamma coupling increases during the learning of item-context associations. Proc Natl Acad Sci U S A 106:20942-20947.

Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ (2008) Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. Proc Natl Acad Sci U S A 105:20517-20522.

Treves A, Rolls ET (1992) Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 2:189-199.

Tronson NC, Taylor JR (2007) Molecular mechanisms of memory reconsolidation. Nat Rev Neurosci 8:262-275.

Tulving E (2002) Episodic memory: from mind to brain. Annu Rev Psychol 53:1-25.

Tye KM, Janak PH (2007) Amygdala neurons differentially encode motivation and reinforcement. J Neurosci 27:3937-3945.

Tye KM, Stuber GD, de Ridder B, Bonci A, Janak PH (2008) Rapid strengthening of thalamo-amygdala synapses mediates cue-reward learning. Nature 453:1253-1257.

Uhlhaas PJ, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolic D, Singer W (2009) Neural synchrony in cortical networks: history, concept and current status. Front Integr Neurosci 3:17.

Ulloor J, Datta S (2005) Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. J Neurochem 95:418-428.

Van Cauter E, Spiegel K, Tasali E, Leproult R (2008) Metabolic consequences of sleep and sleep loss. Sleep Med 9 Suppl 1:S23-28.

van Vugt MK, Schulze-Bonhage A, Litt B, Brandt A, Kahana MJ (2010) Hippocampal gamma oscillations increase with memory load. J Neurosci 30:2694-2699.

Vandecasteele M, Varga V, Berenyi A, Papp E, Bartho P, Venance L, Freund TF, Buzsaki G (2014) Optogenetic activation of septal cholinergic neurons suppresses sharp wave ripples and enhances theta oscillations in the hippocampus. Proc Natl Acad Sci U S A 111:13535-13540.

Vanderschuren LJ, Di Ciano P, Everitt BJ (2005) Involvement of the dorsal striatum in cue-controlled cocaine seeking. J Neurosci 25:8665-8670.

Vanderwolf CH (1969) Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr Clin Neurophysiol 26:407-418.

Verdejo-Garcia A, Contreras-Rodríguez O, Fonseca F, Cuenca A, Soriano-Mas C, Rodriguez J, Pardo-Lozano R, Blanco-Hinojo L, de Sola Llopis S, Farré M, Torrens M, Pujol J, de la Torre R (2014) Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects. Addiction Biology 19:272-281.

Volkow ND, O'Brien CP (2007) Issues for DSM-V: should obesity be included as a brain disorder? Am J Psychiatry 164:708-710.

Volkow ND, Wang GJ, Tomasi D, Baler RD (2013a) The addictive dimensionality of obesity. Biol Psychiatry 73:811-818.

Volkow ND, Wang GJ, Tomasi D, Baler RD (2013b) Obesity and addiction: neurobiological overlaps. Obes Rev 14:2-18.

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009) Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56 Suppl 1:3-8.

Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, Ding YS, Hitzemann R, Swanson JM, Kalivas P (2005) Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. J Neurosci 25:3932-3939.

Volkow ND, Wang G-J, Telang F, Fowler JS, Logan J, Childress A-R, Jayne M, Ma Y, Wong C (2006) Cocaine Cues and Dopamine in Dorsal Striatum: Mechanism of Craving in Cocaine Addiction. The Journal of Neuroscience 26:6583.

Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386:827-830.

von der Kammer H, Mayhaus M, Albrecht C, Enderich J, Wegner M, Nitsch RM (1998) Muscarinic acetylcholine receptors activate expression of the EGR gene family of transcription factors. J Biol Chem 273:14538-14544.

von der Malsburg C (1995) Binding in models of perception and brain function. Current opinion in neurobiology 5:520-526.

Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL (2001) Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 292:1175-1178.

Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11:200-208.

Walker MP, Brakefield T, Hobson JA, Stickgold R (2003) Dissociable stages of human memory consolidation and reconsolidation. Nature 425:616-620.

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205-211.

Wang GJ, Volkow ND, Thanos PK, Fowler JS (2009a) Imaging of brain dopamine pathways: implications for understanding obesity. J Addict Med 3:8-18.

Wang SH, de Oliveira Alvares L, Nader K (2009b) Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. Nat Neurosci 12:905-912.

Wang SH, Ostlund SB, Nader K, Balleine BW (2005) Consolidation and reconsolidation of incentive learning in the amygdala. J Neurosci 25:830-835.

Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E (2015) Theta sequences are essential for internally generated hippocampal firing fields. Nat Neurosci 18:282-288.

Watkins SS, Stinus L, Koob GF, Markou A (2000) Reward and somatic changes during precipitated nicotine withdrawal in rats: centrally and peripherally mediated effects. J Pharmacol Exp Ther 292:1053-1064.

Webb WB (1988) An objective behavioral model of sleep. Sleep 11:488-496.

Weiss F, Markou A, Lorang MT, Koob GF (1992) Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Res 593:314-318.

Weiss F, Parsons LH, Schulteis G, Hyytiä P, Lorang MT, Bloom FE, Koob GF (1996) Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. The Journal of neuroscience : the official journal of the Society for Neuroscience 16:3474-3485.

Weller RE, Cook EW, 3rd, Avsar KB, Cox JE (2008) Obese women show greater delay discounting than healthy-weight women. Appetite 51:563-569.

Wells AM, Lasseter HC, Xie X, Cowhey KE, Reittinger AM, Fuchs RA (2011) Interaction between the basolateral amygdala and dorsal hippocampus is critical for cocaine memory reconsolidation and subsequent drug context-induced cocaine-seeking behavior in rats. Learn Mem 18:693-702.

Wierzynski CM, Lubenov EV, Gu M, Siapas AG (2009) State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. Neuron 61:587-596.

Wikenheiser AM, Redish AD (2015) Hippocampal theta sequences reflect current goals. Nat Neurosci 18:289-294.

Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. Science 261:1055-1058.

Wise RA (1982) Neuroleptics and operant behavior: The anhedonia hypothesis. Behavioral and Brain Sciences 5:39-53.

Wolf ME (2002) Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. Mol Interv 2:146-157.

Wolf ME, Ferrario CR (2010) AMPA receptor plasticity in the nucleus accumbens after repeated exposure to cocaine. Neuroscience and biobehavioral reviews 35:185-211.

Womelsdorf T, Schoffelen JM, Oostenveld R, Singer W, Desimone R, Engel AK, Fries P (2007) Modulation of neuronal interactions through neuronal synchronization. Science 316:1609-1612.

Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A, Brašić JR, Kimes AS, Maris MA, Kumar A, Contoreggi C, Links J, Ernst M, Rousset O, Zukin S, Grace AA, Rohde C, Jasinski DR, Gjedde A, London ED (2006) Increased Occupancy of Dopamine Receptors in Human Striatum during Cue-Elicited Cocaine Craving. Neuropsychopharmacology 31:2716-2727.

Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S, Kennedy AR, Roberts GH, Morgan DG, Ghatei MA, Bloom SR (2000) The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. Endocrinology 141:4325-4328.

Wulff P, Ponomarenko AA, Bartos M, Korotkova TM, Fuchs EC, Bahner F, Both M, Tort AB, Kopell NJ, Wisden W, Monyer H (2009) Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. Proc Natl Acad Sci U S A 106:3561-3566.

Yamamoto J, Suh J, Takeuchi D, Tonegawa S (2014) Successful execution of working memory linked to synchronized high-frequency gamma oscillations. Cell 157:845-857.

Yartsev MM, Ulanovsky N (2013) Representation of three-dimensional space in the hippocampus of flying bats. Science 340:367-372.

Zhang W, Schneider DM, Belova MA, Morrison SE, Paton JJ, Salzman CD (2013) Functional circuits and anatomical distribution of response properties in the primate amygdala. J Neurosci 33:722-733.

Zheng C, Bieri KW, Trettel SG, Colgin LL (2015) The relationship between gamma frequency and running speed differs for slow and fast gamma rhythms in freely behaving rats. Hippocampus 25:924-938.

Zheng C, Bieri KW, Hsiao YT, Colgin LL (2016) Spatial Sequence Coding Differs during Slow and Fast Gamma Rhythms in the Hippocampus. Neuron 89:398-408.

Ziauddeen H, Fletcher PC (2013) Is food addiction a valid and useful concept? Obes Rev 14:19-28.

Zola-Morgan S, Squire LR (1990) The neuropsychology of memory. Parallel findings in humans and nonhuman primates. Ann N Y Acad Sci 608:434-450; discussion 450-436.