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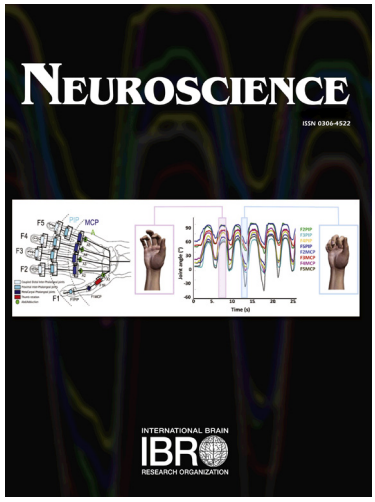

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Magdalena Miranda, Pedro Bekinschtein

PII: S0306-4522(17)30398-6
DOI: http://dx.doi.org/10.1016/j.neuroscience.2017.06.002
Reference: NSC 17814

To appear in: *Neuroscience*

Received Date: 27 March 2017
Revised Date: 26 May 2017
Accepted Date: 1 June 2017

Please cite this article as: M. Miranda, P. Bekinschtein, Plasticity mechanisms of memory consolidation and reconsolidation in the perirhinal cortex, *Neuroscience* (2017), doi: http://dx.doi.org/10.1016/j.neuroscience.2017.06.002

Plasticity mechanisms of memory consolidation and reconsolidation in the perirhinal cortex

Magdalena Miranda and Pedro Bekinschtein

Laboratory of Memory Research and Molecular Cognition. Institute for Cognitive and Translational Neuroscience. Universidad Favaloro, Instituto de Neurología Cognitiva y CONICET, Buenos Aires, Argentina.

*Correspondence to pbekinschtein@fmed.uba.ar

Abstract

In this review we explore the role of the perirhinal cortex (Prh) in memory, focusing on the cellular and molecular mechanisms that have been described to happen in this structure. The Prh is part of the medial temporal lobe, but the evidences show that is has a different function than that of the hippocampus. In particular, the Prh is known to be important for object recognition memory, although it could have a role in other types of memory. However, despite the fact that object recognition tasks are widely used, information regarding the molecular and cellular mechanisms underlying this type of memory in Prh is lacking. We discuss a series of studies of memory and plasticity in this region and how they might relate. In addition, we propose that Prh could play a role as a "pattern separator" for object memories, similar to the function of the dentate gyrus of the hippocampus in the spatial domain.

The perirhinal cortex

The rat perirhinal cortex (PRh) is an association cortex that occupies a central position in the limbic system, receiving feedforward information from diverse sensory modalities of the neocortex and from the amygdala, and feedback from the hippocampal formation[1, 2]. This anatomical location makes the PRh an ideal region for the association of the individual features that represent a stimulus as a whole. Although its role in memory has been studied in the past decades, the molecular and plasticity mechanisms involved in its function are not very well established yet.

Regarding the function of this structure, there is a substantial amount of work indicating that the PRh is important for familiarity discrimination. PRh lesions impair visual discrimination as well as object recognition (OR) memory, both in rats and monkeys ([3-14] but see[15]). A similar impairment has also been reported for human subjects with perirhinal damage [16]. Confirmation

of the involvement of this region in familiarity discrimination has come from studies where temporary inactivation [17] and local perirhinal infusions of glutamatergic antagonist [17, 18] similarly disrupted recognition memory. Additionally, several immediate early gene studies have shown that the PRh is activated after an OR task [19-21] and functional magnetic resonance imaging (fMRI) in humans has also implicated PRh in recognition memory [22-24]. Additionally, the PRh is known to be involved in associative memory within and across sensory modalities, and also in appetitive and aversive conditioning [25-29].

One interesting observation supporting the role of this structure in object recognition memory is that PRh neurons in non human primates and rats exhibit decreases in firing rates as novel objects become familiar ([30-34] but see [35, 36]). This change is specific of a particular stimulus, develops with a single trial and is so strong that can also be seen through inmunohistochemical studies [19, 36]. There is evidence to suggest that this response could be the basis of long-term memory storage, and may be sufficient to solve recognition memory tasks that rely on familiarity discrimination of individual items. Such as one-trial recognition memory, this response change can last for more than 24h [37] and occurs after a single exposure to the stimulus [31, 33]. Furthermore, several interventions that disrupt recognition memory such as infusion of scopolamine, lorazepam, verapamil or pCREB inhibitors, also disrupt perirhinal Fos activation pattern (novel>familiar) ([38-40] but see Miller and Desimone [41]).

In addition to their role in processing the history of a stimulus, PRh neurons could also process information about the identity of the objects. PRh neurons show selectivity for particular visual images and objects [42-44]. There is compelling evidence that the PRh is critically involved not only in the familiarity aspect of OR memory but also on the perceptual functions involved in the representation of the complex conjunctions of features that define a stimulus ([29, 45-47] but see [48]). The question of how PRh might code for novelty and familiarity while also coding for the identity of an object is subject of debate [49-51]. On this subject, Xiang and Brown [52] showed that perirhinal neurons that responded to a familiarity discrimination-based serial recognition task constituted a separate population from the ones that responded to a conditional visual discrimination task. This issue will be discussed further in the section *"The role of perirhinal cortex in feature identification and discrimination"*.

The well-defined and widely accepted anatomical locus for familiarity detection makes the perirhinal cortex ideal for studying the neural substrates of memory, since one can selectively target specific types of receptors and plastic processes within the perirhinal cortex and see the

behavioral consequence of that manipulation directly by assessing recognition memory. These manipulations allow for a more detailed study of the processes underlying recognition memory than it would be currently possible in humans. It must be taken into account that declarative memory in humans involves multiple cognitive functions, such as familiarity and recollection, that possibly demand dissociable neural substrates (for review see [53, 54]). The majority of the tests normally used to evaluate declarative memory in rodents rely on recognition memory that is measured using the animal´s spontaneous preference for novelty [5]. These tasks are generally soluble on the basis of familiarity judgments and do not normally involve recollective processes [11]. Since previous findings indicate that the hippocampus (HP) is not involved in OR memory when task parameters are controlled so as to avoid the influence of spatial information, in this review we will concentrate on investigations that use mainly non-spatial OR memory tasks on which the bulk of the research was done. We will focus on the molecular mechanisms involved in perirhinal storage of information, leaving behind studies where it is difficult to discern what implications are specific for familiarity discrimination and which are related to the spatio-temporal processing of information, which is secondary to the discrimination.

Role of the Prh in mnemonic processing

Much of what is known about the PRh comes from ablation studies and studies on human subjects with permanent lesions. While PRh lesions were essential to elucidate the anatomical locus of recognition memory, transient pharmacological manipulations can provide additional information to discern at which stages of the memory the PRh is particularly necessary. Moreover, the discrete one-trial nature of the spontaneous object recognition paradigm (SOR) allows for this specific analysis. Using these methods it is possible to evaluate which neurotransmitters mediate this involvement and the molecular mechanisms that participate at different stages of memory processing. For example, Winters and Bussey [55] analyzed the effect of transient lidocaine-induced PRh inactivation during sample presentation (encoding), during the retention delay (consolidation), and previous to the choice phase (retrieval) at 180min/20min/30s delay. They found that PRh is necessary at all three memory stages, indicating that PRh is involved in the formation, storage and retrieval of the memory trace. Since the effect is delay-independent, they concluded that this is not just an effect on memory formation but also on perceptual encoding and object identification functions. Similarly, stopping almost all excitatory synaptic transmission by

infusion of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (AMPA and kainate receptor antagonist) , impaired all stages of OR memory[17]. Similar results were observed using infusions of the benzodiazepine lorazepam [39].

Several compounds that affect distinct neurotransmitter systems have an effect on acquisition of OR memory. This effect is usually dependent on the delay between the sample and choice phases. For example, perirhinal infusions of Voltage Dependent L- Type Calcium Channel (VDLCC) Blockers as verapamil [40], antagonists of kainate [18], N-methyl D-aspartate (NMDA) [17, 56] and metabotropic glutamate receptors (Barker, 2006b), nicotinic cholinergic receptor antagonists [38, 57-59] and dopamine receptor antagonist [60] produced impairments only after long delays, while performance after short delays was unaltered. Because these drugs are active during acquisition, is not possible to differentiate between a role in the transmission of information or in storage (consolidation). The delay-dependence indicates that these receptors are probably not necessary for encoding or perceptual functions, but are likely required for induction of synaptic plasticity process necessary for memory storage.

Consolidation

After a learning event, memory traces are fragile and susceptible to disruption. To establish a long-lasting memory, these traces need to go through a period of consolidation in which they stabilize over time [61]. At the cellular level, a large body of work postulates that learning triggers fast post-translational modifications that underlie short-term memory (STM), and this is accompanied by translational and gene transcription programs that lead to the synthesis of plasticity-related proteins that allow for consolidation of changes at a specific subset of synapses (for review, see [61, 62]). It is widely believed that these changes in synaptic strength are the substrate for long-term memory storage in the brain [62]. If the PRh is the location where object memories are stored, the object trace that is supposedly encoded within this region needs to go through a period of consolidation after the experience in which the trace may experience a period of active maintenance and during which cellular and molecular processes necessary for memory stabilization and storage should be triggered. Therefore, interfering with these processes during a time window in a location-specific manner should impair the object memory. According to this, many pharmacological studies pointed to a role of PRh in the consolidation of object recognition memories [55, 63, 64].

Deficits in familiarity discriminations are found when drugs that effectively silence PRh (lidocaine, CNQX) are infused during the first 40 min of the 24h-delay interval after acquisition [55]. This delay-dependent post-sample infusion pattern of deficits indicates that PRh is necessary for the consolidation of OR memory, and not just for the encoding since it is still required for memory after removal of the learning stimulus. What remains to be answered is whether this deficit is related to a failure to actively maintain the activity-dependent processing of the trace, or is due to a disruption of the intracellular signaling caused by the silencing of the neurons. In this regard, blockade of protein synthesis by post-sample anisomycin infusion in the PRh impairs long-term but not short-term recognition memory [63], showing that protein synthesis is necessary for long-term recognition memory in rats, as has been shown for many other systems and types of memories [65]. This result points to a scenario where PRh is not just a processing stage but a site where plasticity changes crucial for OR memory storage occur. Furthermore, blockade of NMDARs immediately, but not 40 min, after the sample phase disrupted OR memory. This effect was only seen for long delays, but not for 5 or 20min delays [17, 56, 66]. Since NMDAR antagonists do not disrupt normal fast excitatory transmission and only have an effect upon the induction of synaptic plasticity processes [67, 68], this strongly suggests that recognition memory impairments are not merely due to the fact that PRh is in the route to access the storage site. More likely, this deficit arises from a storage impairment of information in the PRh, because it is present even when the PRh is still capable of transmitting information to other regions. However, it is not completely possible to discard that there could be more general effects of the antagonists on excitability and intracellular signaling pathways, not only specific effects on plasticity mechanisms. Nevertheless, other more specific pharmacological manipulations like the infusion of kainate receptor antagonists do not seem to have an effect on memory consolidation [18, 56], so it seems unlikely that unspecific effects of the drugs could explain these results.

In addition to the classic neurotransmitters, the PRh is also able to signal through neurotrophins that act through binding of TrkB receptors[69]. Neurotrophins, particularly BDNF, modulate activity dependent changes in synaptic strength in the HP: threshold levels of BDNF are necessary to induce LTP and, on the contrary, exogenous BDNF can prevent the induction of LTD [70-72]. Accordingly, patterns of stimulation that lead to LTP elicit a large increase in BDNF secretion, while patterns that lead to LTD are followed by a reduction in BDNF secretion in PRh [73]. Moreover, infusion of an oligonucleotide (ODN) antisense of BDNF immediately (but not 6h) after the sample phase impaired only long-term (24h) familiarity discrimination, establishing that BDNF expression

is necessary for OR memory consolidation [64]. Also, icv administration of a broad-spectrum tyrosine kinase antagonist impaired 24h-delay recognition memory (Callaghan and Kelly, 2013). Callaghan et al. [74], used a hippocampus-dependent version of the OR task [75] and found an increase in the phosphorylation of PI3K and a lack of ERK activation in the perirhinal cortex, and conversely phosphorylation of ERK without a change in PI3K in the HP. In addition, exercise-induced improvement in OR memory is correlated with increased BDNF levels in the PRh [76].
The current most accepted model of memory storage posits that the memory trace is codified by maintained changes in the synaptic efficacy of the connections of the network involved [77]. Evidence indicates that the maintenance of LTP and LTD relies on the induction of a genetic program that leads to protein synthesis [78, 79], and depends on the activation of protein kinases, transcription factors and immediate early genes (IEGs) [78, 80, 81]. Although the intracellular processes involved in LTP and LTD have been mainly studied in the HP[82], several of the synaptic plasticity mechanisms that operate in the HP seem to also play a part in PRh. Since such plasticity processes are hypothesized to be involved in the storage of information, interfering with them within the PRh should impair OR memory if at least part of the memory trace is stored in this structure. Accordingly, some of the elements necessary for the persistence of LTP or LTD in the PRh are also necessary for long-term OR memory. For example,post-sample infusions of drugs that interfere with CamKII or CamKK [83, 84] and also MAPK/ERK [85]impaired long-,but not short-term recognition memory, suggesting a role of these kinases in the consolidation of recognition memory. Supporting this view, CamKII activity can promote either LTP or LTD, depending on its phosporylation state [86], and a recent publication showed that levels of activation of ERK in two knockout mice that had either lower (Ras ERK1 KO) or higher (ERK1 KO) ERK activity than control animals corresponded to respectively low and high levels of synaptic plasticity in perirhinal slices [85].
In addition, CamKs and MAPKs can in turn phosphorylate c-AMP responsive element-binding protein (CREB)[87]. Then pCREB dimerizes and can act as a transcription factor, binding to cAMP response elements present in the promoter region of IEGs as c-fos and zif268 [88, 89]. Adenoviral transduction of the PRh with a dominant negative inhibitor that prevents CREB from binding to the DNA (A-CREB) impaired recognition memory at 24h but not 15min, and disrupted LTP [20]. Fos, the protein product of c-fos, has been implicated in synaptic weakening mechanisms such as LTD [90, 91] and CREB can induce the expression of c-fos [89]. Perirhinal infusion of an ODN antisense of Fos before or immediately after the sample phase (but not before the retrieval phase) impaired

recognition memory evaluated at 24h, pointing to a role of Fos in the consolidation of OR memory [92]. One method to investigate learning-related changes in synaptic transmission is the paired viewing procedure [93, 94]. In this task, while novel visual stimuli are presented to one eye, familiar stimuli are presented to the other eye under the same conditions. Using this task, Warburton, Glover, Massey, Wan, Johnson, Bienemann, Deuschle, Kew, Aggleton, Bashir, Uney and Brown [20] found that A-CREB disrupted the normal reduction of perirhinal Fos and pCREB activation to familiar vs novel stimuli. As with NMDAR, since interfering with these intracellular signaling proteins associated with synaptic plasticity does not affect normal transmission of information and only learning-related plastic changes are compromised, this results point to a role of PRh in information storage.

Regulation of gene expression during memory consolidation has been also linked to epigenetic mechanisms [95]. DNA methylation and histone acetylation are established regulators of protein transcription [96, 97]. Using an hippocampal dependent version of the OR task, the object in place task, Mitchnick, Creighton, O'Hara, Kalisch and Winters [98] found that inhibition of DNA methyl transferases (DNMTs) impairs long- but not short-term in both PRh and HP, but there is a dissociation in the epigenetic mechanisms involved in both regions, with de novo DNMT3a upregulated and involved in hippocampal effects and DNMT1 for perirhinal effects. Comparably, in the hippocampus inhibition of CREB-binding protein (CBP) and p300 acetyltransferases impaired long- but not short-term memory, while in the PRh CBP and PCAF inhibition disrupted long term memory [99]. Remarkably, there seems to be different epigenetic mechanisms operating in brain regions that process different kinds of information.

In summary, the dependence of familiarity discrimination on plastic processes in the PRh supports the idea that the information critical to solve these tasks is stored in the PRh, and, although there may be other areas of storage, such areas cannot compensate for the lack of function within the PRh.

Reconsolidation

Consolidation was originally thought to be a unidirectional process in which the memory, once consolidated, was resistant to disruption. But this view was challenged by studies that reported that presentation of a ‘reminder’ cue could make memories again labile and susceptible to disruption (for review [100, 101]). Since this new stabilization process shared the requirement of

many specific plasticity proteins with consolidation (ie. CREB, MAPK requirements) [102-107], it was thought to recapitulate consolidation and thereafter named reconsolidation. However, many reports found differences in the cellular mechanisms and brain regions involved in both processes[108-112]; for review [113], suggesting that the memory trace goes through different functional states. Nonetheless, to date only few studies have identified mechanisms that are specifically required for reconsolidation ([108, 114]; but see [115]). These studies showed that, in the case of contextual fear conditioning, although both consolidation and reconsolidation require NMDA activity in the hippocampus, consolidation is associated with the NMDAR-ERK1-BDNF pathway while reconsolidation is linked to the NMDAR-IKKa-Zif268 [114].Using the paired viewing task, Tinsley, Narduzzo, Brown and Warburton [84] showed that processing of familiar pictures increased the inmunoreactivity for a CamKK reaction product in the PRh compared with the processing of novel pictures, and suggested that, since the direction of that change is opposite to the ones of CREB, c-fos and CamKII, they suggested that CaMKK could be a mechanism related to reconsolidation of the re-exposed familiar stimuli, but this still remains to be tested.

Reconsolidation has been shown to occur for OR memories [102, 115-120], but the cellular and molecular mechanisms in the PRh necessary for object memories to re-stabilize are only recently beginning to be addressed. Inhibition of protein synthesis by anisomycin infusion in the PRh immediately after a reactivation session where rats were exposed to both a familiar and a novel object impaired OR memory evaluated 24h after reactivation while exposure to familiar ones did not [118]. These results show that the PRh is essential for the reconsolidation of OR memory and agree with previous findings that indicate that a certain degree of novelty or mismatch is necessary for reconsolidation to occur [121-123]. However, weakly trained memories can also be strengthened by repeated training trials via a reconsolidation process [124-126] and, in fact, some studies have observed the reconsolidation process by exposure or the animals to the familiar objects only [115, 117]. This raises a question regarding the specific boundary conditions for reconsolidation of OR memories. Also, icv infusion of a MAPK/ERK inhibitor blocks consolidation and reconsolidation of long-term OR memories, but not short-term memory [102]. Additionally, zif268 mutant mice showed consolidation and reconsolidation deficits for both recent and remote memories, but no impairment at short delays [115]. However, these changes cannot be attributed to the PRh since they did not use localized infusions and also because they used an hippocampus-dependent version of the OR task. Nonetheless, these were amongst the first studies that identified molecular mechanisms involved in reconsolidation of OR memories. These results

indicate that similar transcriptional mechanisms are recruited for both consolidation and reconsolidation of OR memories, and that similar signaling cascades seem to be involved in both processes (i.e. MAPK). Since manipulating reconsolidation could be a therapeutic tool for treating people with anxiety disorders, like post traumatic stress disorder and phobias, there is an increasing interest in understanding the molecular mechanisms involved. Previous work suggests that reconsolidation gives an opportunity to integrate updated information into the memory trace. In order to do so, the newly acquired information must be compared with the stored memory traces. Update would occur through destabilization ofthe memory trace to allow the incorporation of new information followed by restabilization. Although retrieval seems like a logical mechanism for destabilization, anysomicin and NMDAR antagonists disrupted reconsolidation, even when retrieval was inhibited by infusion of the GABA receptor agonist muscimol or an AMPA receptor antagonist [60, 127].The authors conclude that retrieval is not necessary for memory destabilization. However, there are alternative explanations for this result, such as the fact that memory could be retrieved in the absence of behavioral expression. Further work needs to be carried out in order to fully understand these interesting observations.

Conversely, expression is not sufficient for the destabilization of a memory. In fact the strength and age of the memory as well as the presence of novel information will influence which memories go through a reconsolidation process [104, 122, 125, 128]. Stiver, Jacklin, Mitchnick, Vicic, Carlin, O'Hara and Winters [129] found that infusion of scopolamine in the PRh reversed the reconsolidation impairment caused by NMDAR antagonist MK-801 or anisomycin, and muscarinic antagonists mimicked the destabilizing effect of novel information presented during the reactivation session. They suggested that arousal associated with novel stimuli present during the reactivation session could lead to an increase in cholinergic activation in the PRh that would trigger intracellular mechanisms important for memory destabilization. Although several cellular mechanisms involved in destabilization of a memory have been proposed, such as activation of NMDA receptors and ubiquitin proteosome system-mediated synaptic degradation [124, 130, 131], these remain to be tested on object recognition memories and in particular, in the PRh.

Synaptic plasticity in the Prh

Presuming that the PRh is the actual storage site for object memories, and assuming that storage involves long-term synaptic changes, it should be possible to find these learning related-changes

at the synaptic level, for example, by evaluating mechanisms of synaptic plasticity in vitro. Long-term potentiation (LTP) and long-term depression (LTD) are forms of synaptic plasticity that involve AMPAR and NMDARs and can occur within the PRh [68, 132], so they can be potential candidates as the neural substrate of memory storage in this structure. Indeed, experience-dependent modifications underlying memory storage share many molecular mechanisms with activity-dependent synaptic plasticity processes as LTP and LTD [77, 133].

Computational network modeling has shown that, in order to have efficient familiarity discrimination with high storage capacity such as the one present in behavioral studies, models must include some element of synaptic weakening, such as LTD [51, 134]. Such synaptic weakening could provide a mechanism for the reduction in stimulus response when a stimulus becomes familiar [135]. In this respect, there is strong evidence that links recognition memory to LTD. There are several manipulations that impair familiarity discrimination selectively at long (not short) delays and also impair the induction of LTD. Simultaneous (but not separate) blockade of group I and group II metabotropic glutamate receptors (mGluRs) leads to an impairment in the acquisition of long but not short-term OR memory and are both necessary for LTD induction but not for LTP under certain circumstances [18, 67, 68, 136]. The same pattern of results is seen for VDLCC blockers: only long-term memory deficits, blockade of LTD but not LTP induction and disruption of the pattern of Fos response change seen normally for familiar stimuli [40]. Similarly, benzodiazepines that increase the inhibitory effects of GABA blocked LTD and recognition memory [39] while nitric oxide synthase inhibitors, that prevent activity-dependent and also muscarinic induced LTD but not LTP, produced a deficit in recognition memory at 24h-delay but not at 20 min [137]. Remarkably, selective interference with the expression of LTD produces a recognition memory impairment [138].

These results questioned the notion in the field that LTP was the fundamental experience-driven change in synaptic function, and LTD had a secondary role in which it only refined the circuitry but did not modify the behavioral output. This notion nourished on several studies that found strengthening of synapses by prior experience [139, 140]. However, LTP-like mechanisms could also be involved in familiarity discrimination learning. In fact, modeling indicates that increases in synaptic strength are also necessary for an efficient network in order to maintain the excitability [134, 135], and interfering with molecular mechanisms that block LTP can block familiarity discrimination [20]. Actually, one strength of synaptic plasticity as a substrate for encoding learning and memory is that synaptic strength can be controlled bidirectionally (decrease with LTD

and increase with LTP), allowing for a dynamic instead of a static modification of the synapses. Yet, AM251, an antagonist of endocannabinoid receptors that prevented LTP but not LTD in the PRh, had no effect on either short- or long-term visual recognition memory [137], lending support to the idea that LTP is less critical for recognition memory. In sum, the mechanisms that regulate both LTP and LTD are candidate processes for the effective storage of recognition memories in the PRh.

Electrophysiological recordings from slices of PRh where they interfered with neurotransmitters receptors and their downstream signaling cascades have been used to investigate the mechanisms involved in activity dependent synaptic plasticity in PRh. These studies may provide information about potential cellular and molecular changes underlying PRh-mediated familiarity discrimination.

There is evidence that 100 Hz high frequency stimulation (HFS) in layers II/III of the PRh in vitro [68, 132] and also theta-burst stimulation of field CA1 in vivo [141] produce NMDA receptor-dependent LTP. Perirhinal LTP is associated with an increase in BDNF secretion during the first 12 min of stimulation, and can be blocked by inhibition of the BDNF receptor and TrkB [73], and by an antagonist of the endocannabinoid receptors [137]. LTP can be disrupted also by inhibiting CREB [20] but apparently is independent of VDLCC channel activation [40] and mGluRs [67, 68]. Additionally, contiguous pre- and post-synaptic activity is necessary for PRh LTP, implying the operation of Hebbian mechanisms[132]. These associative properties could result from the voltage-sensitivity of the NMDAR.

Furthermore, 1Hz and 5Hz low frequency stimulation (LFS) can induce NMDA dependent mGluR independent LTD in perirhinal slices in vitro [68, 132] and this LTD can be made long lasting if 1 Hz stimulation is paired with depolarization [67, 138]. This induction is dependent on VDLCC [40] and nitric oxide (NO) [137], and is associated with a decrease in BDNF secretion [73]. Also, various mGluR agonists can induce LTD without LFS [142]. In fact, LTD in PRh requires both NMDAR and mGluR, while hippocampal LTD is either NMDA or mGluR-dependent. The contribution of these receptors to LTD is voltage-dependent: group II mGluR-dependent LTD can only be induced at resting membrane potentials when an interaction between group I and group II receptors is required. The selective requirement is probably due to the restricted calcium influx through NMDARs at resting membrane potentials [67, 136]. The interaction between mGluR could be required since Group II-mGluR can enhance group I-mGluR function, thereby contributing to LTD induction [143]. On the other hand, at depolarized potentials, coactivation of NMDAR and group I

mGluRs is sufficient to induce LTD, and there is no requirement for group II mGluRs [67]. NMDAR-dependent LTD requires internalization of AMPA receptors [138], while mGluR dependent LTD regulates AMPA receptors through another mechanism [143]. Despite the initial differences, both receptors generate at last an increase in the intracellular calcium concentration that will, in turn, activate the intracellular signaling cascades that will allow the proper induction of LTD [144, 145]. There has also been described a kainate receptor-dependent LTD, that is NMDAR-independent and is also regulated by group I mGluRs via PKC [146]. This LTD is linked to the $EPSC_{KA}$ and not of the $EPSC_{AMPA}$. Electrophysiological research indicates that there are different synaptic inputs to the PRh that can support long-term synaptic plasticity, which gives these projections functional significance as they could play a role in the storage and consolidation of PRh-dependent memories. Stimulation of the monosynaptic projections from CA1 to the PRh can induce LTP in the PRh of anaesthetized [141, 147] and freely moving rats [148]. This potentiation can be blocked by CNQX but not MK-801, suggesting that is AMPA/Kainate receptor mediated but NMDAR-independent [147].

Additionally, projections from the amygdala to the perirhinal cortex undergo LTP and LTD [149-151]. This LTP is dependent on β-adrenergic receptors (ADRs), VDLCC and PKA [150] for its induction, but independent of NMDAR. This is different for the LTP generated in perirhinal slices by stimulation of local cortical afferents in layers II/III of the PRh (intracortical LTP), which is NMDAR dependent and β-ADR, VDLCC and PKA independent. On the other hand, LTD at these projections appears to be NMDAR-dependent and -ADR, VDLCC and PKA independent. Specifically, NR2A containing receptors seem to be crucial, contrary to NR2B-related mechanisms described only for intracortical-LTD [151, 152]. Plasticity in this pathway could provide a mechanism for the emotional enhancement of recognition memory [153]. These differences in the distinct perirhinal afferent inputs might depend on the presence of differential complements of the receptors, but so far this aspect of the cellular biology of the perirhinal inputs has not been tested.

Although glutamate receptors are the ones most commonly associated with changes in synaptic strength, other neurotransmitters can also influence synaptic plasticity. Cholinergic neurons are mainly located in the basal forebrain and project to the cortex, where they act on ionotropic (nicotinic) and metabotropic (muscarinic) receptors on the pre and postsynapses. Application of the cholinergic receptor agonist carbachol in an in vitro PRh preparation induced LTD that was prevented by application of scopolamine and by the M1 muscarinic receptor antagonist

pirenzepine. This form of LTD is NMDAR-independent but relies on protein synthesis, NO and the release of calcium from intracellular stores [137, 154].

In summary, there are multiple forms of synaptic plasticity in the PRh that involve at least NMDARs, mGluRs and cholinergic receptors. However, plasticity in this structure has not yet been studied as thoroughly as in the HP, for example. So far, synaptic plasticity in the PRh seems to get more and more complex with each study.

Linking synaptic plasticity and memory

Antagonism of different types of receptors produces different temporal patterns of amnesia. OR memory is impaired at long, but not short delays, by perirhinal infusion of NMDAR, metabotropic and nicotinic antagonists, while antagonism of kainate and muscarinic receptors produce impairment at short but not long delays [17, 18, 56, 58, 139].This dissociable pattern indicates that there is probably more than one plastic mechanism involved in the acquisition of OR memory. At least two mechanisms seem to work independently and show different temporal properties. These different mechanisms could be attributed to the different kinds of LTP and LTD, and in fact the complexity of the different forms of LTD and LTP could be functionally significant and could influence distinct aspects of the PRh-dependent cognitive processes. In this regard, Barker et al. Barker, Warburton, Koder, Dolman, More, Aggleton, Bashir, Auberson, Jane and Brown [56] suggested that muscarinic and kainate receptor activation is necessary for the plastic process of fast changing perirhinal neuronal responses (novelty responses) that supposedly support short-term memory, while NMDA and nicotinic receptor activation is critical for plastic processes of slow-changing perirhinal neuronal responses (familiarity responses) that are proposed to support long term memory [33].Several studies have found differences between the cellular and molecular mechanisms involved in short- and long-term memory [155, 156]. So independently of whether the cellular substrate for short-term and long-term memory is different or not, the molecular mechanisms involved in both types of memories could differ.

Experiments using mi-RNAs have begun to help understanding the mechanisms that underlie this dissociation. Since mi-RNAs can be activated in response to neuronal activity, they could control the protein expression profile involved in memory formation. miR-132 is regulated by CREB by to the presence of CRE elements in its promoter region, and targets proteins involved in the modulation of actin turnover that regulate spine size and density [157, 158]. Injection of lentiviral

vectors expressing miR-132 disrupted short-term (20min) but not long-term (24h) memory. Conversely, miR-132 transduced perirhinal slices showed altered carbachol induced LTD (mAChR dependent) and altered HFS-induced LTP [159]. This results suggest that LTP and mAChR-dependent LTD are probable substrates of short-term OR memory.

Since NMDA receptors are associated with LTP and LTD, and are also necessary for long-term OR memory, it would be tempting to speculate that the behavioral effects of NMDAR antagonists are, in part, due to the blockade of LTP and LTD. However, this cannot be affirmed with certainty since, among other processes, information processing and transmission could be compromised as well [160-162]. Moreover, it is difficult to differentiate between the effects of LTP and LTD since NMDAR antagonists prevented both forms of synaptic plasticity in PRh. Although basic plasticity mechanisms differ between the HP and PRh, in both regions LTP and depotentiation were shown to depend on NMDAR containing N2A subunits, while LTD is dependent on receptors containing N2B subunit [163, 164]. This has prompted studies where they intended to use this dependency to investigate whether recognition memory relied on LTP or LTD-related mechanisms. Perirhinal infusions of NR2A and NR2B antagonists only produced impairment at a 24h delay when they were co-infused [18]. This suggests that LTP- and LTD-like processes are necessary for familiarity discriminationor, alternatively, only one is commonly involved, but when that one is disrupted the other can compensate for its absence. Nonetheless, differences in the effects of the antagonism in vitro and in vivo cannot be discarded because the afferent tone is distorted in perirhinal slices, and the stimulation patterns used to induce synaptic plasticity in vitro are not the same as the ones that occur in vivo.

Because effects of neurotransmitters on general excitability could be affecting the results, it would be interesting to target more specifically the plastic changes that are thought to underlie memory. One way of doing this is by preventing the expression mechanisms of synaptic plasticity. A common final step necessary for the expression LTD is the removal of AMPA receptors form the postsynapsis by endocytosis. For this internalization to occur, clathrin adaptor protein (AP2) must interact with GluA2 subunit of the AMPA receptor. Griffiths, Scott, Glover, Bienemann, Ghorbel, Uney, Brown, Warburton and Bashir [138] used a peptide to block this interaction and were able to prevent the activity-induced removal of AMPAR, leaving synaptic transmission of information via PRh unaffected. In animals infected with lentiviruses that express this peptide, LTD was blocked without producing an effect on LTP. Importantly, these animals showed recognition memory deficit both at long and short delays, providing strong evidence that LTD (and not LTP) is

necessary for recognition memory storage. This result implies that, although there may be two or more plasticity mechanism acting in synchrony with different temporality, they must all depend on the same molecular processes for their expression.

Regarding the cholinergic neurotransmitter system, systemic administration and also perirhinal infusions of the muscarinic antagonist scopolamine before the sample phase can disrupt recognition memory in humans, monkeys and rats [38, 165-169] while systemic administration of the acetylcholinesterase inhibitor physostigmine can facilitate performance in these tasks [167, 170]. The deficit induced by scopolamine is only seen for short, but not long retention intervals ([38, 58, 171]; but see [172]). Effects of post-acquisition scopolamine infusions are less clear, some have reported no effects [38], others reported an impairment [165], and there is even a report of post-training scopolamine facilitation [59]. An opposite effect is seen using the nicotinic antagonist MLA that caused a deficit at long but not short delays [58]. However, when both are administered together there is no additive effect, and short-term memory is not affected. Thus, a balance between the actions of both receptors seems to be necessary,suggesting that this could reflect their effects on the balance of excitation and inhibition in the perirhinal networkBrown, Barker, Aggleton and Warburton [173].

Selective permanent cholinergic denervation of the PRh by IgG-saporin immunotoxin infused in that region also impairs recognition memory in rats and monkeys [55]. Many reports suggest a role of acetylcholine (ACh) in enhancing afferent input while suppressing excitatory intrinsic activity, what should favor encoding and information processing [174-176]. For example, ACh can optimize the tuning of receptive fields of cortical pyramidal cells [177, 178]. This evidence suggests that the cholinergic system could contribute to familiarity discrimination facilitating the acquisition of new information through attentional or perceptual processes. However, Warburton et al.Warburton, Koder, Cho, Massey, Duguid, Barker, Aggleton, Bashir and Brown [38] found a compelling correlation between perirhinal scopolamine induced deficit in OR, the disruption of the reduction of perirhinal firing by familiarization, and a blockade of the induction of LTD but not LTP in brain slices (also see [154]). These results suggest that muscarinic receptors are necessary for the plastic changes induced by experience, so they would not just play a part in perceptual or encoding aspects of memory.

When new information is acquired, many changes occur in the brain, but only some of them are specific to the memory that is being stored and the rest could be noise related to sensory stimuli,

attentional states, etc. As we mentioned above, one method to investigate learning-related changes in synaptic transmission is the paired viewing procedure [93, 94]. Using this procedure, studies showed that LTP in vitro was not affected by the presentation of either novel or familiar stimuli, but LTD and depotentiation were occluded after previous in vivo presentation of familiar stimuli. When systemic administration of scopolamine is given previous to the presentation of the stimuli there is no occlusion effect ([152]; but see [41]). Since Ach has proven to be important for LTD-like processes and memory acquisition [38], this study directly links LTD and learning-related response changes in PRh.

An alternative hypothesis postulates that, rather than being encoded by firing rates, familiarity could be encoded by oscillatory or synchronized neuronal activity. Pre and post synaptic interactions might modulate the threshold to induce synaptic plasticity, so information storage could depend on input synchronization, such as what has been shown to happen in the HP [179]. In this regard, recordings from the human HP have shown that the power of brain oscillations in low-gamma frequency bands decreases as novel environments become familiar [180]. Moreover, behavioral exploration of novel and familiar visual images can be modulated differentially by stimulation of the PRh at specific frequencies: stimulation at low-gamma frequency band increases exploration of familiar images, and stimulation at low-beta frequency bands decreases exploration of novel images [181]. Thus, synchronous firing in the PRh could be another potential candidate substrate for OR memory storage.

The role of the Prh in feature identification and discrimination

The anatomical structure of the PRh is different from other neocortical areas, as it lacks the columnar organization and the inputs are not topographically organized so that features can be concentrated in modules [182].The PRh has a distributed rather than clustered connectivity by virtue of the extensive intrinsic connections of area 36 [183]. But it also differs from the distributed architecture of the hippocampus that allows for connections between every input that enters the circuit. In the PRh, neocortical axons form strong connections with interneurons whereas perirhinal longitudinal axons do not [184]. Sites distant to a neocortical stimulation spot will evoke pure excitatory responses while sites near the stimulation will activate interneurons that will limit the excitatory response, favoring LTD. On the other hand, simultaneous activation of two distant neocortical sites will shift the balance toward excitation and promote the induction of

LTP [185]. These longitudinal connections will allow association of spatially distributed inputs from different sensory modalities that arrive to the PRh at different rostrocaudal levels. Computational models suggest that this pattern of connectivity will limit the specificity of the stored representations because, not only the cells receiving paired inputs will be recruited, but also the other rostrocaudally distant cells. In addition, the PRh would depend on its targets, such as the entorhinal cortex, to increase the specificity of the stored representations [186].

A network can weaken synapses that were previously excited by the first presentation of a stimulus, so it can spot what is not shared across stimuli (novelty detector), or it can enhance the strength of a synapse when a feature is re-encountered, making the network responsive for common features across stimuli (feature detector)[32]. Hence, the refinement of the neuronal ensamble may be essential for novelty detection and this might be particularly important in the face of ambiguous information.

According to their nature and complexity, particular stimuli or objects might be processed by different regions in the brain[187]. As discussed earlier, perirhinal lesions usually disrupt performance on the OR task without an effect on spatial memory, and conversely hippocampal lesions only disrupted performance on spatial memory tasks such as delayed non-matching to place and Morris water maze tasks [11, 94, 188-190]. Similarly, functional imaging studies have associated hippocampal cortex with recollective aspects of recognition memory, and PRh with familiarity discrimination in humans [16, 23, 24]. These studies argue for a dissociation of function between PRh and HP in episodic memories, such that each structure may play a different cognitive function related to their representational capabilities.

There is convincing evidence to indicate that PRh is involved in discrimination of complex stimuli with overlapping components and in configural object recognition where there is feature ambiguity [14, 28, 29, 46, 47, 191-193]. Moreover, the hierarchical representational hypothesis posits that object representations are stored throughout the ventral visual object-processing stream in a hierarchically organized manner with PRh at the top of this hierarchy [187, 194, 195]. Thus, the PRh, rather than storing simple features of the objects, stores conjunctive representations of the encountered items that define unique objects and can later be used to disambiguate particular objects during memory retrieval.

Successful completion of object recognition tasks requires the ability to discriminate between the identities of two objects. How the brain separates similar input patterns into non-overlapping representations is a fundamental question for the neuroscience of perception and memory.

Computational models have postulated the existence of a process of transformation of similar input representations into less correlated information named 'pattern separation'[196]. The ability to separate the components of memories into distinct non-overlapping memory representations is thought to rely on this process to disambiguate similar events, thereby increasing the likelihood of accurate encoding and subsequent retrieval. In this sense, PRh could be thought as a structure that acts as a 'pattern separator' disambiguating overlapping information into less confusable representations. Pattern separation has normally been mapped to the dentate gyrus (DG) of the HP, and in particular, to adult neurogenesis [197, 198]. This process is absent in the PRh, so, the cellular mechanisms for disambiguation ought to differ between these two brain structures [199]. In contrast to associative memory networks, sparse encoding generally does not report any advantage for familiarity discrimination networks so it may not be of importance for encoding in the PRh. As explained by Bogacz and BrownBogacz and Brown [37], sparse coding increases the capacity of associative networks because it reduces the neuronal activity noise increasing the accuracy of the response. But in familiarity networks, although sparse coding increases the individual accuracy, it also decreases the number of activated novelty neurons. Since the decision is based on the activity of a group of neurons, the influence of sparse coding is practically inexistent.

Whereas there must be differences at the cellular level, there is still a question of whether the same molecular mechanisms and proteins are involved in both structures. Considering that all the brain is plastic, it is possible that the same plasticity rules govern all brain regions. However, as has been mentioned above, there are many differences in the plasticity mechanisms present in the PRh and the HP, so the answer may not be so straightforward.

Concluding remarks

In summary, we have reviewed a vast amount of evidences regarding the function and plasticity mechanisms of memory in the PRh. There are many results that point at LTD as a main plasticity mechanism for OR memory in this structure, a balance between potentiation and depression might be required for consolidation and storage of unique representations of object memories. Although reconsolidation of OR memory has been described in PRh, there is virtually no information regarding the molecular mechanisms involved. This is a particularly interesting path to follow in memory research. We also propose a function of this region in the consolidation and

storage of non-confusable object memories through a process of pattern separation, previously described for the dentate gyrus. However, we must develop appropriate behavioral tasks to evaluate this cognitive function in the object, rather than the spatial domain. Future work will definitely shed light on the mechanisms governing memory and perception in the PRh.

Figure Legends

Figure 1. LTD pathways in the Prh involved in short and long term OR memory. A. Mechanisms involved in short term OR memory in the Prh. Activation of cholinergic and glutamatergic afferents leads to the release of the respective neurotransmitters. Both kainate receptor (KAR) and muscarinic acetylcholine receptos (mAChR) activation are required for familiarity discrimination at short but not long delays. Although there is no information regarding the role of KARs in perirhinal plasticity, since AMPAR endocytosis was shown to also be important for short-term memory, kainate receptors could mediate their effect by favouring AMPAR endocytosis. Muscarinic acetylcholine receptors (mAChR), in turn, could mediate their effects through the activation of CamKs and MAPK/ERK, and the subsequent phosphorylation of CREB. CREB in turn is able to regulate the expression of miRNAs (ie. miR-132) that can control the expression of proteins important for memory formation and LTP/LTD by post-transcriptional gene silencing. **B. Mechanisms involved in long term OR memory in the Prh.** Both nicotinic acetylcholine receptors (nAChRs) and glutamatergic receptors (NMDAR and AMPAR) have been associated with both long term memory retention and LTD. Activation of VDLCC, mGlu and NMDA receptors are all required for long term memory and synaptic plasticity like LTD. NMDAR and nAChRs can initiate cytoplasmatic calcium signals, while also activating by depolarization VDLCC that can increase the signal. This signal can lead to the activation of CamKs and other kinases like MAPK/ERK, that can also be activated by neurotrophins like BDNF. These kinases can give rise to the activation of transcription factors (i.e. phosphorylation of CREB), stimulating the transcription and, in the case of CREB, inducing the production of Fos protein. In fact, CREB was shown to be necessary for LTP and long-term recognition memory. CamK activation can lead to AMPAR phosphorylation and endocytosis. Since AMPAR endocytosis was shown to be necessary for both long-term object recognition memory and LTD, these could be one of the processes mediating the synaptic plasticity in the PRH that is substrate for object recognition memory.

Acknowledgments

This work was funded by the National Agency for Promotion of Science and Technology grant (PICT 2012-1119) to PB, the IBRO Return Home Fellowship to PB and the ISN Return Home Award to PB.

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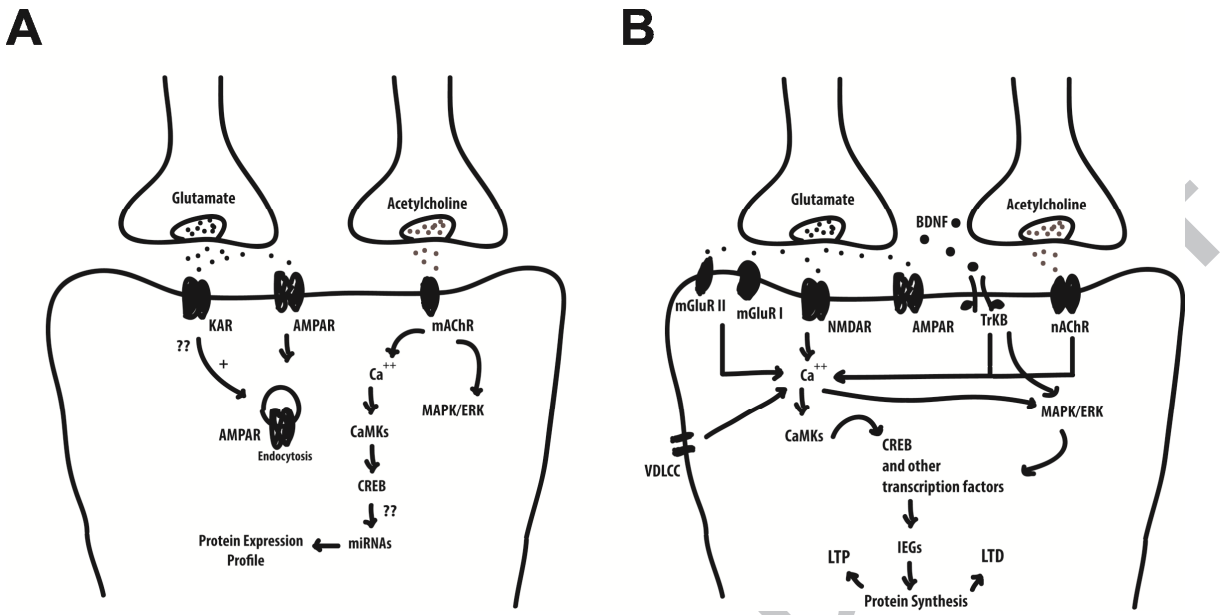

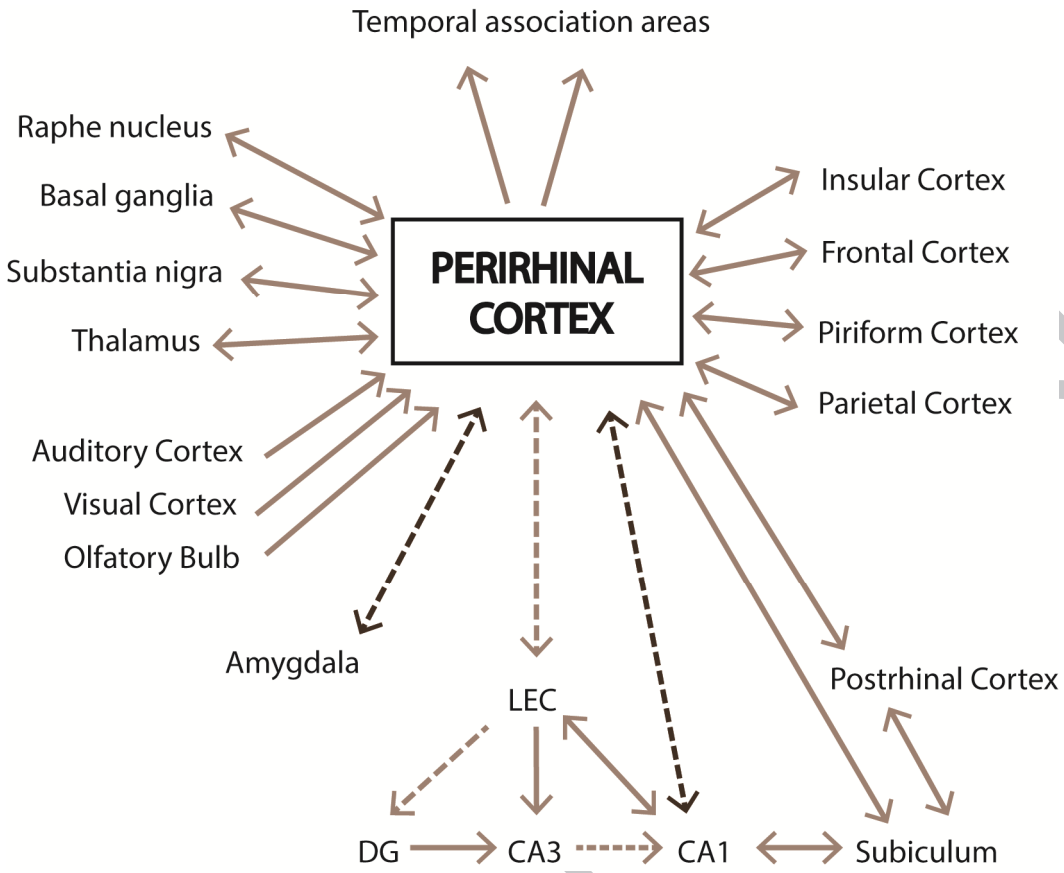

Highlights for reviewers

1. The perirhinal cortex is an essential part of the object recognition memory circuit
2. Object recognition memory consolidation and reconsolidation occur within the perirhinal cortex
3. LTD in the perirhinal cortex has been linked to object recognition memory
4. Some of the mechanisms of plasticity within this structure are required for recognition memory consolidation
5. The perirhinal cortex could store complex representations of objects by means of these molecular processes