Review

ENTORHINAL CORTEX: ROLE IN EXTINCTION, AND THE INFLUENCES OF AGING

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ABSTRACT

The entorhinal cortex is the region of the brain where neurofibrillary tangles and amyloid plaques are first detectable in old age. This is seen both in people with and in people without cognitive impairment, and is prominent in Alzheimer´s disease. The entorhinal cortex plays a key role in memory formation, retrieval and extinction, as part of circuits that include the hippocampus, the amygdaloid nucleus, and several regions of the neocortex, in particular of the prefrontal cortex. Lesions or biochemical impairments of the entorhinal cortex hinder extinction and also other forms of learning. Microinfusion experiments have shown that glutamate NMDA receptors, calcium/calmodulin-dependent protein kinase II and protein synthesis in the entorhinal cortex are required for extinction. Aging also hinders extinction; it is possible that its effect may be in part mediated by the entorhinal cortex. The alterations of extinction caused by old age may be relevant to the genesis of depression.

KEYWORDS: learning – extinction learning – entorhinal cortex – aging.

INTRODUCTION

Extinction was discovered by Pavlov in the early 1900s (see Pavlov, 1927; Konorski, 1948). It consists of the inhibition of the retrieval of a previously acquired response. This inhibition is usually gradual. Since it is perceived as the inhibition of that response, it might be mistakenly taken for the expression of forgetting (Tsumoto, 1993). However, real forgetting involves the actual disappearance of memories (Eccles, 1963). Instead, contrarily to this, extinguished responses recover spontaneously with the passage of time (Rescorla, 2001); in addition, upon retraining, they recover very rapidly (Pavlov, 1927; Konorski, 1948; Izquierdo et al., 1965). This indicates that extinguished memories do not disappear but are just made less available for retrieval. Therefore, the current view is that extinction is just one more form of learning, in which the conditioned stimulus or constellation of stimuli (CS) is

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dissociated from the former unconditioned stimulus (US) and reassociated with a new US which consists precisely in the absence of the former US (Rescorla, 2001). In other words, a new CS-no US association is formed which supersedes the former CS-US association (Rescorla, 2001; Cammarota et al., 2003), and a new conditioned response (CR) develops: usually the omission of a formerly learned response.

Of course, other forms of learning that can not be readily qualified as CRs can also be extinguished, and this is in fact why it is widely used in the psychotherapy of learned fear. It was originally advocated for the treatment of phobias by Freud in the 1920's, but he gave it another name ("habituation"), which is a different form of learning (Pavlov, 1927; Vianna et al., 2000). Extinction has been also given other names when used for psychotherapeutic purposes (Rothbaum and Davis, 2003), such as exposure therapy (Beckett, 2002) or flooding (Difede et al., 2007; Sijbrandij et al., 2007). It is particularly useful for the treatment of posttraumatic stress disorder (see Cammarota et al., 2004; Davis et al., 2006; Quirk and Mueller, 2008). But it consists in all cases of what Pavlov (1927), Konorski (1948) and Rescorla (2001) called extinction (Davis et al., 2006).

Extinction is not habituation

There are similarities and differences between extinction and habituation. As defined by Pavlov (1927) and by hundreds of others after him (Konorski, 1948; Harlow et al., 1971; Vianna et al., 2000), habituation consists in the gradual reduction of the natural, unlearned response to an unassociated stimulus or constellation of stimuli; i.e, of the response to novelty. "As we sit by a highway we often quickly come to ignore the sounds of passing automobiles" (Harlow et al., 1971). The same can be said of exploration of a new environment (Vianna et al., 2000), of smelling the same odor for a long time, etc. The response to novelty or to a novel stimulus or set of stimuli is remarkably similar across species and stimuli, and involves arousal and movements of the eyes, ears, head or body towards the source of the stimuli; it is called the "orienting" (Sokolov et al., 2002) or "what is it?" reflex (Pavlov, 1927).

The hippocampal molecular correlates of the response to a novel stimulus have been studied only recently. It involves the activation of different protein kinases in the hippocampus (Izquierdo et al., 2000; Viola et al., 2000), and by the phosphorylation of the constitutive transcription factor CREB (cAMP response element binding protein) (Winograd and Viola, 2004; Moncada and Viola, 2006). This sequence of events underlies the effects of novelty on the formation of long-term memories, as part of a process of behavioral tagging (Moncada and Viola, 2007).

Like extinction, habituation results from the repetition of a stimulus; but of a novel stimulus rather than one that had been used to form a previous association (Pavlov, 1927; Vianna et al., 2000). However, unlike extinction (Rescorla, 2001; Cammarota et al., 2003), habituation is widely viewed as non-associative. Also unlike extinction, habituation must be differentiated from fatigue

Pavlov (1927) considered both habituation and extinction as forms of "internal inhibition", as opposed to the stimuli that cause distraction and eventually may induce dishabituation, which he and his followers considered as examples of "external inhibition". A major difference between both forms of "inhibition" is that whereas the "internal" type leads to diminished arousal levels, and even eventually to sleep, external inhibition causes an enhancement of arousal or alertness (Pavlov, 1927; Konorski, 1948). Dishabituation has been more recently viewed as another form of learning (Rankin and Carew, 1987), separate (Rankin and Carew, 1988) or linked to sensitization (Hawkins et al., 2006).

Extinction is not forgetting

Real forgetting involves the actual erasure of learned information. It may rely on the atrophy and eventual disappearance of synapses by disuse, as described by Eccles (1955). Indeed, we forget the face of people we saw just once or twice and then never again, unless they were highly arousing or emotionally important (Cahill, 2003; Izquierdo et al., 2006). Memories are believed to be formed and stored in synapses since Ramón y Cajal (1893) (see Eccles, 1963; Izquierdo et al., 2006).

In contrast, extinguished responses, knowledge or behavior are reinstated immediately after a presentation of the US even if unassociated with the cue (Vianna et al., 2001). Relearning after extinction is usually much quicker than the original learning (Izquierdo et al., 1965). In addition, it may occur even if the US is presented out of context; without pairing with the CS or even outside of the training apparatus (i.e., the so-called "reminder footshock", Schneider, 1974; Vianna et al., 2001).

Brain circuits in extinction

Several fMRI studies show an activation of prefrontal areas, notably the ventromedial prefrontal cortex (vmPFC), together with reduced blood flow in the basolateral amygdala (BLA) (Phelps et al., 2004; Akirav and Maroun, 2006, 2007) and/or the hippocampus (Milad et al., 2006; Kalisch et al., 2006), in the extinction of conditioned fear responses. Importantly, the data fit with the previous evidence for a crucial role for the vm PFC (Burgos-Robles et al., 2007; Milad et al., 2007; Quirk and Beer, 2006; Quirk and Mueller, 2008), and with important roles for the BLA (Myers and Davis, 2002, 2007) and the hippocampus in retrieval and in extinction (Vianna et al., 2001, 2004; Szapiro et al., 2003; Cammarota et al., 2005). Circuits linking the vmPFC with the amygdala (Phelps et al., 2004) and the hippocampus (Sotres-Bayon et al., 2007; Akirav and Maroun, 2007) in extinction have been proposed. A separate role for each of these two pathways in extinction has been envisaged by Corcoran and Quirk (2007). Circuits linking the vmPFC and as well as the dorsolateral PFC with the hippocampus have also been recently described for memory consolidation (Izquierdo et al. 2007); the vmPFC-hippocampus link has actually been viewed as obligatory both for consolidation and reconsolidation (Akirav and Maroun 2006).

In more than one respect, the physiology of extinction learning is similar to that of the non-inhibitory, or "regular" forms of learning; i.e., the acquisition and storage of the "original" tasks that are later to be extinguished (Vianna et al., 2001, 2004; Berman and Dudai, 2001). This of course agrees with the now widely accepted notion that extinction is just one more form of learning (Rescorla, 2001). Localized brain microinfusion studies have shown that, depending on the task, the hippocampus (Vianna et al., 2001; Szapiro et al., 2003) , the BLA (Myers and Davis, 2002, 2007), the vmPFC and (in conditioned taste aversion) the insular cortex (Berman and Dudai, 2001) are involved in, and are necessary for, extinction. The sequence of molecular events involved most of these regions includes glutamate N-methyl-D-aspartate (NMDA) receptors, protein kinase A and protein synthesis in all areas studied (Vianna et al., 2004), calcium and calmodulin-dependent protein kinase II (CaMKII) in some (Szapiro et al., 2003; Bevilaqua et al., 2006), and the extracellular signal regulated kinases (ERKs) in others (Vianna et al., 2004; Myers and Davis, 2007). Overall, these molecular requirements are analogous to those of memory consolidation of the original tasks (Izquierdo et al., 2006), which further stresses the point that extinction is indeed a form of learning.

In all cases, the molecular findings on extinction were determined by the use of receptor antagonists (AP5), inhibitors of CaMKII (KN62 or KN93 9,21], PKA inhibitors (Rp-cAMPs, KT5720 or others), ERK inhibitors, and protein synthesis inhibitors or inhibitors of gene expression (see Vianna et al., 2004 for references). In the case of NMDA receptors, the partial allosteric agonist D-cycloserine has also been studied (see below)

The entorhinal cortex: a role in learning and a role in extinction

Several early studies using localized brain lesion or stimulation techniques (Gauthier Destrade

1984; Oniani et al. 1989; Ueki et al., 1994; Freeman et al., 1997) and one recent pharmacological study (Bevilaqua et al. 2006) point to a crucial role of the entorhinal cortex (EC) in extinction, mostly of aversive tasks. Lesions of the entorhinal cortex inhibit not only various forms of extinction in rats but also some forms of habituation (Köhler and Sundberg, 1977, 1979).

Indeed, the best and most illustrative source of evidence in favor of a fundamental role of the entorhinal cortex in extinction, and indeed in all forms of learning, is human pathology: from the analysis of the famous amnestic patient H.M. (Corkin et al., 1997; Salat et al., 2006) to that of humans with mild cognitive impairment and/or with early Alzheimer's disease (Braak and Braak, 1990; see below). .

A few studies of lesions of the EC in animals have failed to produce any result on extinction (Sundberg and Köhler, 1977; Yee et al., 1997; Daum et al., 1992). But some of these negative studies have also failed to detect influences of EC lesions on acquisition and retention (Sundberg and Kohler, 1977) and simple discrimination (Daum et al., 1992), which disagrees with the vast majority of papers on the role of the EC in learning (see above, and Braak and Braak, 1990; Squire, 1992; Bevilaqua et al., 2006 for references). In several of the negative results with entorhinal lesions these were incomplete or encompassed other areas as well. Both the lesion and the stimulation techniques that were in vogue 20 or more years ago often gave artifactual results attributable to spread to neighboring physiologically unrelated areas (Izquierdo and Medina, 1998). In many cases those results have not been confirmed by the more selective and circumscribed imaging, histo- or neurochemical results of the last decade or so.

No doubt the entorhinal cortex must be a key component of any circuit that includes the vmPFC, the BLA and the hippocampus, particularly one that links the former to the latter two, as has been suggested for extinction (Corcoran and Quirk, 2007) (see above). First, a very large number of afferent and efferent connections between the vmPFC and the hippocampus and amygdala relay in the entorhinal cortex (Hyman et al. 1990]. Second, the entorhinal cortex is the afferent and efferent relay for BLA and hippocampal connections with other regions of the rest of the cerebral cortex, all of which are connected to the entorhinal cortex (van Hoesen, 1985). Van Hoesen (1985) has in fact stated that "it is clear that the entorhinal cortices receive potentially a significant portion of the sensory output generated by forebrain structures and this includes both interoceptive and exteroceptive information. In structural terms, it could be argued that the entorhinal cortex would be privy to or receive a digest of nearly all neural reactions… and many of the combinations or permutations that may result". Third, the entorhinal cortex probably plays an active learning role rather than a role as a mere relay in extinction, as microneuropharmacological studies suggest. Fourth, and perhaps very importantly, medial EC neurons display positional firing properties that are somewhat different from, but related to, that of hippocampal place cells (Quirk et al., 1992).

Molecular basis of the role of the entorhinal cortex in extinction

The molecular basis of inhibitory avoidance (Izquierdo et al., 2006) and other forms of learning (Riedel and Platt, 2004) has been studied in detail in recent years. In the case of extinction it was studied in the ventromedial prefrontal cortex (vmPFC), the basolateral amygdala (BLA), the CA1 region of the hippocampus, the insular cortex (for conditioned taste aversion) and in the entorhinal cortex.

The area of the brain in which the biological basis of extinction has been studied in most tasks is the vmPFC (see above). This area connects to the BLA and the hippocampus in order to regulate extinction, and this connection is through the entorhinal cortex (van Hoesen, 1985; Hyman et al., 1990).

The dorsal hippocampus has been studied in relation to extinction very extensively, but almost exclusively in one trial step-down inhibitory avoidance (Vianna et al., 2001, 2004; Szapiro et al., 2003; Cammarota et al., 2003, 2004). This is the task in which the molecular basis of consolidation is best known (Izquierdo et al., 2006).

Extinction of this form of learning is indeed susceptible to the deleterious effect of the glutamate NMDA (N-methyl-D-aspartate) receptor blocker, 2-amino-5-phosphono pentanoate (AP5), the CaMKII inhibitor, KN93, and the protein synthesis inhibitor, anisomycin, infused into the entorhinal cortex at the time of the first of a series of retrieval sessions (Bevilaqua et al., 2006). NMDA receptors, CaMKII and protein synthesis are crucial for the formation of a new memory and, of course, for consolidation of this task in the hippocampus (Izquierdo et al., 2006).

Therefore, both lesion and microinfusion experiments support a role for the entorhinal cortex in extinction; which was predictable from anatomical knowledge (van Hoesen, 1985).

Aging and extinction

It is widely agreed that aging is accompanied by a cognitive decline both in laboratory animals and in humans. Behavioral and molecular aspects of this decline have been studied extensively in the last two decades (see Barad, 2003). Recent studies have specifically demonstrated a decline of the capacity to extinguish in aged rats (Schneider-Rivas et al., 1995, 2007; Topic et al., 2005; Oliveira-Silva et al., 2007). Perhaps the first to study this systematically in laboratory animals was Schneider-Rivas and his group.

The decline of extinction seen in old rats correlates with changes in brain serotonin and 5-hydroxy-indole acetic acid in neocortex, hippocampus, thalamus and dorsal raphe nucleus compatible with predictions from the serotonin hypothesis of depression, as well as with other brain neurochemical correlates (Schneider-Rivas et al., 2007; see also Oliveira-Silva et al., 2007 and Pires et al., 2007).

Others have reported an abnormality of forced extinction in aged rats submitted to removal of the escape platform in a water maze (Schulz et al., 2004, 2007a,b; Topic et al., 2005; see also Bellebaum and Daum, 2004). In aged rats, this procedure quickly leads to immobility, which the authors have termed "despair" behavior by analogy with "learned helplessness" paradigms, and which they view as a model of depression (Schulz et al., 2007a,b). The immobility is accompanied by a number of symptoms of anxiety, and by a large number of neurotransmitter changes both in striatum and in hippocampus (Schulz et al., 2004, 2007b). The immobility triggered by forced extinction in aged rats can be reduced by chronic desimipramine, but is actually enhanced by chronic fluoxetine, however (Schulz et al., 2007a).

The incidence of depression does increase with advanced age in humans, and it does come often together with anxiety. Depression in old individuals with mild cognitive impairment corresponds to the well-known syndrome called pseudo-dementia.

Forced extinction might happen as a result of the losses suffered by the aged, which have been so often cited as triggers of depressive episodes. When the aging person loses friends or family, or is forced to retire, or finds to have lost sensory, mental or physical powers, (s)he automatically suffers the forced extinction of a rich and large variety of responses. The cues are there: objects, pictures, remembrances, smells, sounds pertaining to the elements lost; but the response is prevented from happening because the elements themselves are gone forever. This usually occurs with pain and often with despair; and may be viewed as a nonadaptive form of extinction.

The picture can be very distressing and thus lead the way to posttraumatic stress (Beckett, 2002; Davis et al., 2006). In the forced extinction experiments in the water maze the animals find themselves all of a sudden without the regular escape that they had learned to attain, which surely is traumatic and should cause despair.

The deficit of extinction in aging reported by most authors may have serious consequences, such as a proneness to perform dangerous behaviors and therefore be exposed to genuine fear situations (Izquierdo et al., 2004; Rauch et al., 2005; see Quirk and Mueller, 2008).

Aging and the entorhinal cortex

Perhaps the region of the brain which ages more rapidly is the entorhinal cortex. Normal aging has been known for many years to be accompanied by a reduction of neuron and synapse counts in many regions of the cerebral cortex, particularly the entorhinal cortex and then the hippocampus. The earliest occurrence of prototypical lesions in Alzheimer's disease is usually considered to be in the entorhinal cortex (Braak and Braak, 1990; Jellinger et al., 1991; see De Leon et al., 1989, 1993). However, in a sizable proportion of normal aged persons lesions typical of Alzheimer's disease, such as neurofibrillary tangles and neuritic plaques are also seen (Jellinger et al., 1991; Kesslak et al., 1991; Hyman et al., 1991; Arriagada et al., 1992; De Leon et al., 1996), together, of course, with computerized tomography or other imaging changes suggestive of a degree of brain atrophy (Gado et al., 1983; De Leon et al., 1989, 1996).

The question has been asked whether the mild cognitive impairment often seen in the aged correlates with a larger number of such lesions than that seen in the normal aged subjects, and/or with a peculiar concentration of them in the hippocampus and entorhinal cortex (De Leon et al., 1996; Reisberg et al., 2008). Recent findings indicate that the answer to both questions is positive (Bell-McGinty et al., 2005; Devanand et al., 2007). Years ago it was suggested that the early atrophy of the hippocampus and particularly the entorhinal cortex could be an early marker of Alzheimer's disease (De Leon et al., 1989, 1993). This correlates with the high incidence of lesions viewed as typical of Alzheimer's in the entorhinal cortex and in the hippocampus, in that order of importance in that disease (Braak and Braak, 1990; Jellinger et al., 1991). Recent observations are somewhat more cautious (De Leon et al., 2007; Devanand et al., 2007), and suggest that the combined used of imaging techniques plus that of cerebrospinal fluid biomarkers (De Leon et al., 2007) is more likely to yield an adequate monitoring of the preclinical diagnosis of Alzheimer's inasmuch as the occurrence of lesions and of imaging changes in the normal and the demented elderly overlaps perhaps more than was originally thought (De Leon et al., 1996, 2007).

However, many studies indicate that cortical losses in the hippocampus and entorhinal cortex of elderly patients do predict mild cognitive impairment (Smith et al., 2007). This prediction is more consistent than that of the eventual conversion of mild cognitive impairment into full-fledged Alzheimer symptomatology (Tapiola et al., 2008). The dissociation of hippocampal and entorhinal memory functions has been difficult and fraught with pitfalls inasmuch as there is such a close interconnection between the two (Hyman et al., 1990) and lesions of both structures cause very large and complete memory losses in animals (see Squire, 1992). There has been one purportedly successful attempt to dissociate the contribution of hippocampus and entorhinal cortex to different aspects of memory function in the elderly; namely, conscious recollection and familiarity-based judgments (Yonelinas et al., 2007).

CONCLUSIONS

The entorhinal cortex plays a key role in cognition. It contributes to, and processes, information that the rest of the cortex, particularly the prefrontal areas, sends to it in order to be relayed to the hippocampus and amygdala, as part of the acquisition, retrieval or extinction of many forms of learning. In addition, the entorhinal cortex also processes information generated by the hippocampus and sends it to the neocortex, and interconnects the hippocampus with its main regulatory nucleus complex, the amygdala. Thus the entorhinal cortex is crucially involved in all aspects of learning. Its role in extinction has been best studied in aversive tasks. The entorhinal cortex on one hand and extinction on the other suffer severe losses with aging. The changes are more marked in humans with mild cognitive impairment, and much worse in Alzheimer's disease, in which the entorhinal losses are diagnostic at early stages. The impairment of extinction seen in old age may be related to entorhinal cortex damage.

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