Ageing, hippocampal synaptic activity and magnesium

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Abstract. Ageing is associated with a general decline in physiological functions. Amongst the different aspects of body deterioration, cognitive impairments, and particularly defects in learning and memory, represent one of the most frequent features in the elderly. However, a great variability exists among aged subjects. Clinical reports and experimental data in animal models of ageing have shown that age-associated memory deficits are broadly identical to those induced by damage to the hippocampus. It is therefore not surprising that many functional properties of hippocampal neuronal networks are particularly altered with ageing. Whereas passive membrane properties of neurons are conserved with age, neuronal excitability is altered, in keeping with weaker performances of aged subjects in memory tasks. Synaptic transmission within hippocampal networks also decreases in brain ageing. Deficits concern both glutamatergic and cholinergic pathways, which represent the main excitatory neurotransmitter systems responsible for neuronal communication in the hippocampus. In addition, long-term changes in synaptic transmission, possible cellular substrates for learning and memory, are also impaired in ageing in correlation with cognitive impairments. Neuronal properties and synaptic plasticity closely depend on ion exchanges between intra- and extracellular compartments. Changes in ion regulation during ageing may therefore participate in altering functional properties of neuronal networks. Calcium dysregulation has been extensively investigated in brain ageing but the role of magnesium has received less attention though ageing constitutes a risk factor for magnesium deficit. One of general properties of magnesium at presynaptic fibre terminals is to reduce transmitter release. At the postsynaptic level, it closely controls the activation of the N-methyl-D-aspartate receptor, a subtype of glutamate receptor, which is critical for the expression of long-term changes in synaptic transmission. In addition, magnesium is a cofactor of many enzymes localized either in neurons or in glial cells that control neuronal properties and synaptic plasticity such as protein-kinase C, calcium/calmodulin-dependent protein kinase II and serine racemase. It is therefore likely that a change in magnesium concentration would significantly impair synaptic functions in the aged hippocampus. Experiments addressing this question remain too scarce but recent data indicate that magnesium is involved in age-related deficits in transmitter release, neuronal excitability and in some forms of synaptic plasticity such as long-term depression of synaptic transmission. Further studies are still necessary to better delineate to what extent magnesium contributes to the impaired cellular mechanisms of cognitive functions in the elderly which will help to develop new strategies to minimize age-related memory declines.

Key words: ageing, hippocampus, magnesium, memory, synaptic plasticity, long-term potentiation, long-term depression
In the last fifty years, progress in the prevention and the treatment of illnesses, as well as the constant improvement of hygiene and nutrition conditions, have increased ageing of the world population and particularly in industrialized countries [1]. Unfortunately, this increase in life duration is generally associated with a progressive deterioration of body systems and functions. Not only reproduction and motor functions are concerned but also mental defects, including deficits in learning and memory (cognitive) or in motivation (emotional) frequently occur with advanced age [2]. One striking feature of ageing is that the degree of cognitive impairment can greatly vary across individuals, from a mild deficit, initially referred as age-associated memory impairment (AAMI) [3] to a severe dementia. A wealth of data has accumulated indicating that obvious alterations in the central nervous system (CNS) occur in dementia-associated memory declines. For instance, extracellular β-amyloid plaques and intracellular neurofibrillar tangles are salient brain features of Alzheimer’s disease [4, 5]. Regarding the milder deficits in AAMI as compared to dementia, it is likely that brain alterations are much more subtle [6], even cognitive capabilities are impaired enough to significantly disturb the quality of life of the elderly. A major constraint for the determination of cellular substrates of AAMI is the invasive nature of experiments, which led to the development of animal models of ageing [7-14]. Over the past decades, extensive behavioural experiments, mainly performed on rodents, investigated how the efficient learning and memory in young individuals is slowed down with age, whilst forgetfulness is accelerated [15-23]. In these studies too, the degree of memory decline shows significant variability from one animal to another as it does in the elderly human, allowing tight correlations between anatomical and functional changes in brain ageing and memory deficits. Such correlative studies have been of particular importance to significantly improve our understanding of the cellular basis of AAMI.

Experiments on brain ageing have largely been focussed on the hippocampus, a cytoarchitectonically well-defined structure of the limbic system. Several lines of evidence suggest that this structure is a privileged brain target for ageing processes: hippocampal integrity is critical for some forms of learning and memory [24-32] and deficits induced by damage to the hippocampus broadly resemble impairments associated with ageing [33-36]. Moreover, the functional plasticity of neuronal networks, which is proposed as a cellular mechanism critical for memory formation [37-40], was initially described and then fully characterized in the hippocampal formation [41-44].

Over the last forty years, hippocampal changes in brain ageing have extensively and differently been evaluated and, as expected, a substantial number of alterations detailed and correlated with memory impairments (for reviews see [45-50]). Which exact mechanisms govern these alterations now represents a major challenge for scientists aiming at reducing the occurrence or the magnitude of AAMI. Among other possibilities, the age-related dysfunction of hippocampal activity could be the consequence of changes in ion regulation [51] since cellular excitability, transmitter release and synaptic plasticity are closely dependent on ion flux across neuronal membranes. Regarding this issue, the role of divalent cations in brain ageing has been very differently addressed. Calcium homeostasis gathered the largest interest with the calcium dysregulation hypothesis of brain ageing in the mid-80s [52-55]. According to this hypothesis, multiple calcium-dependent processes change with ageing [56-59]. In contrast, the contribution of magnesium was much less addressed although magnesium is the most abundant divalent cation found in the body with a relative large concentration in the CNS [60]. Moreover, ageing is a risk factor for magnesium deficit that may be induced from two etiological mechanisms: deficiency or depletion (for a review see [61]). Although brain magnesium content is relatively stable in animal models of hypomagnesemia [60, 62], a significant decrease is found in age-associated neurodegenerative diseases [63]. In addition, magnesium deficit induces specific impairments of emotional memory [64] indicating that this cation may indeed play a significant role in the physiopathology of AAMI.

The goal of this review is to present the current knowledge on the age-related functional alterations of hippocampal networks that may account for AAMI. In addition, experimental results are presented and discussed to determine whether magnesium is concerned in these alterations, leading to the search for new relevant therapeutic strategies to minimize cognitive deficit in the elderly.

Age-related changes in neuronal properties

Whether functional properties of hippocampal networks are affected with age has been addressed in the different subregions of the hippocampus using electrophysiological recording techniques mostly performed in slice preparations, although some
studies have also investigated neuronal firing rates in vivo [65-67].

Basic membrane and cellular properties of hippocampal neurons including resting membrane potential, membrane time constant, input resistance and action potential height and width do not change with age [68-81]. In some studies however, the resting membrane potential of ageing neurons appears more hyperpolarized than that of young neurons [82, 83].

In contrast, ageing alters neuronal excitability: aged neurons display a lower ability to elicit action potentials [74, 75, 77, 81, 83], indicating that sodium channels involved in spike generation are impaired [84].

The calcium-dependent post-burst afterhyperpolarization (AHP) is another critical component of neuronal excitability, limiting the rate of repetitive discharges in response to a sustained depolarisation [85-88]. AHPs are reversibly depressed by the acquisition of hippocampus-dependent behavioural tasks such as trace eyelink conditioning or spatial water maze [89-91]. Increase in neuronal excitability has therefore been proposed as a possible cellular substrate of learning and memory [58]. AHPs are enhanced with age [56, 72, 76, 83, 92] (and see review in [48, 58]) although this result has not been fully confirmed [75, 77]. The age-related facilitation of AHPs results from a greater expression of L subtype calcium channels by aged neurons [93-95] with increased calcium conductances across the cell membrane [73, 75, 77, 82, 92, 93]. Age-related enhancement of AHPs and increase in the density of L-type calcium channels correlate with memory deficits [92, 96, 97] and pharmacological treatments, reducing AHPs in aged animals, prevent memory decline [98, 99]. In light of these data, a decrease in neuronal excitability may be a substantial cellular cause in the physiopathology of AAMI [92].

A role for magnesium in the age-related alteration of neuronal excitability has not yet been formally demonstrated although indirect evidence suggests that it may be involved in this deficit. Frequency potentiation (FP) represents an increase in synaptic transmission that develops during a train of electrical stimulations [100]. FP is dependent on cell firing and is negatively correlated to AHP magnitude [101]. Due to the enhanced AHP limiting the cell discharge, FP is reduced by age [102-105] but elevating magnesium to calcium ratio counteracts the deficit [104, 105]. This result strongly suggests that the facilitation of calcium conductances carrying the increase in AHP and consequently the decrease in neuronal excitability of aged neurons, is not only due to a greater density of calcium channels on cell membrane as initially proposed [93, 95, 97, 101]. Alternatively, a weaker competition between divalent cations due to magnesium deficit would also enhance single calcium channel activity. However, this hypothesis remains to be definitively confirmed; for example, by determining how the enhanced AHP magnitude in aged neurons behaves after altering magnesium to calcium ratio.

**Age-related changes in synaptic transmission**

Glutamate is the neurotransmitter involved in most of excitatory synapses in the CNS [106-108]. This is particularly salient in the hippocampus where synaptic activity of cortical afferent systems, including the perforant pathway and commissural fibres, as well as the neuronal communication within intra-hippocampal networks requires the release of glutamate [109-111].

Trying to determine whether mechanisms regulating extracellular concentration of glutamate are affected by age has led to divergent results in vitro (for a review see [112]) whereas experiments conducted in vivo report an increase in the basal release of glutamate [113]. Magnesium deficit may be involved in such an age-related increase in extracellular concentration of glutamate since magnesium is well known to reduce spontaneous transmitter release presynaptically [114-117]. Accordingly, experiments carried out at neuromuscular junctions indicate that spontaneous miniature end-plate potentials increase in amplitude during ageing due to an impaired regulation of transmitter release by magnesium [118].

Glutamate-dependent synaptic transmission is mediated by both ionotropic and metabotropic receptors [119, 120]. Fast glutamatergic synaptic responses mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate subtypes of ionotropic receptors as well as long-lasting potentials dependent on the activation of N-methyl-D-aspartate (NMDA) receptors are significantly depressed in the hippocampus during the course of ageing [65, 121-129]. Mechanisms of impaired glutamatergic neurotransmission, which correlate with memory deficits (for reviews see [46, 47]), are region-specific within the hippocampus and include a loss of functional synaptic contacts [65, 121, 129] and/or a weaker receptor density on postsynaptic cells [130-133].

Pharmacological properties of AMPA/kainate receptors of hippocampal pyramidal neurons are not sensitive to magnesium and raising the external
concentration of the cation does not affect evoked-AMPA receptor-mediated excitatory postsynaptic potentials neither in young nor in aged animals [104, 105, 128]. By contrast, magnesium tightly regulates NMDA receptor activation and elevating magnesium to calcium ratio depresses NMDA receptor-mediated responses [134-137]. Magnesium exerts a voltage-dependent block on NMDA receptor-associated channels and the strength of the blockade depends on the subunit composition of the receptor [138-140]. No change in NMDA receptor susceptibility to magnesium block occurs with ageing since the percent decrease in NMDA receptor activation is comparable in young and aged animals after increasing magnesium to calcium ratio [125, 128].

In addition to glutamate, activation of hippocampal NMDA receptors also requires the binding of a co-agonist, D-serine, at the glycine binding site [142-144]. The content of D-serine dramatically decreases in the hippocampus with age [145-147] and restoring D-serine levels in hippocampal tissues of aged animals reverses the functional impairment of NMDA receptors [144, 146, 147]. Moreover, a long-term treatment with D-cycloserine alleviates the age-related deficit in hippocampal memory tasks [148-150]. The decrease in D-serine availability in hippocampal tissues during ageing is related to alterations of the synthesizing enzyme serine racemase whereas D-amino acid oxidase, which metabolizes D-serine, is not affected [146]. Activity of serine racemase is potently stimulated by magnesium, which increases 5- to 10-fold the rate of racemization of L- to D-serine [151]. Impairment of magnesium-induced activation of serine racemase may therefore represent another mechanism by which a magnesium deficit contributes to the age-related NMDA receptor activation.

Although glutamate-mediated synaptic transmission is enhanced in a magnesium-free condition throughout the lifespan, the increase is significantly larger in young than in aged animals (figure 1A) [141]. If magnesium concentration is reduced in a medium supplemented with the NMDA receptor competitive antagonist D-2-amino-5-phosphonovalerate, the increase in synaptic responses is similar in both groups of animals (figure 1B). Thus, the weaker increase induced by low magnesium in hippocampal ageing does not reflect changes in the presynaptic release of glutamate but is the consequence of the weaker density of postsynaptic NMDA receptors in aged neurons [130, 131, 133]. Although the facilitation effect of low magnesium is reduced by age, it may represent a mechanism allowing magnesium deficit to counteract the age-related decrease in glutamatergic neurotransmission.

In contrast to ionotropic receptors, little is known about the impact of aging on metabotropic glutamate (mGlu) receptors. A recent study demonstrates only discrete region- and subtype-specific changes in the expression of mGlu receptors in the hippocampus with increasing age [152] while electrophysiological experiments indicate that activation of these receptors is not or is only poorly affected by age [79, 153].

Cholinergic afferents arising from the medial septum/diagonal band of Broca, represent the second major excitatory input to the hippocampal formation [154, 155]. Stimulation-induced release of acetylcholine induces a slow and long-lasting excitatory postsynaptic potential in neuronal networks of all hippocampal regions [75, 156-158], depending on the activation of muscarinic cholinergic receptors [159, 160]. The acetylcholine-mediated synaptic potential is depressed by age [69, 75, 157, 161, 162] due to a decrease in transmitter release from cholinergic terminals [163-166] and to an impaired responsiveness of postsynaptic muscarinic receptors [69, 75, 77, 162, 167]. However, no correlation has been found between the degree of memory deficit and changes in cholinergic synaptic activity [75, 158, 167] indicating that the involvement of acetylcholine in the age-related memory decline is not as critical as initially thought [168-170].

Besides its role in decreasing transmitter release including the release of acetylcholine [171, 172], magnesium regulates the activation of postsynaptic muscarinic receptors in a complex way: it reduces a nonselective cationic conductance activated by muscarinic agonists [173], it binds to the allosteric region of the receptor thus attenuating the inhibitory effects of some modulators [174] and finally it is required for the activation of G-proteins coupled to muscarinic receptors [175-177]. Considering this complex pattern of interactions, it is difficult to predict to what extent magnesium deficit contributes to the age-related alterations of cholinergic neurotransmission. However, indirect evidence argues for an age-dependent modulation of acetylcholine-dependent activity by magnesium: hypomagnesia reduces the effects of iontophoretically applied acetylcholine on neuronal responses [178] while the magnitude of reduced high-affinity binding at the muscarinic receptor in Alzheimer’s disease is closely regulated by magnesium [179].

Age-related changes in synaptic plasticity

The nature of the physiological basis of learning and memory still remains an open issue for
the neurobiologist. The current most popular hypothesis suggests that memory formation is related to changes in synaptic strength within neuronal networks. Initially proposed by Hebb [180], this postulate received the first convincing experimental support in the early-70s when long-term potentiation (LTP) of synaptic transmission was characterized in the dentate gyrus of the hippocampus [181, 182]. LTP consists of a long-lasting increase in the efficacy of synaptic transmission induced by a brief tetanic stimulation of presynaptic afferents [183-191], that persists for days or weeks in vivo [66, 192-195]. Since its discovery, LTP has been subjected to particularly intense scrutiny (more than 7000 papers deal with this form of synaptic plasticity), which reveals how mechanisms involved are multiple, closely interconnected and subjected to a large range of modulations [196-206]. This review will consider only mechanisms that are critical for the expression of LTP.

Figure 1. Effects of a free-magnesium medium on extracellularly recorded excitatory synaptic responses recorded in CA1 area of young and aged rat hippocampal slices after electrical stimulation of glutamatergic afferents. A) Time-course of the increase in the magnitude of the glutamate-mediated field excitatory postsynaptic potential (fEPSP) recorded in young and aged rats after perfusion with a free-magnesium medium. B) Time-course of the increase in the magnitude of the glutamate-mediated fEPSP recorded in young and aged rats after perfusion with a free-magnesium medium supplemented with the NMDA receptor antagonist 2-amino-5-phosphonovalerate acid (2-APV). Note that in a free-magnesium medium, the increase in the glutamatergic synaptic response is weaker in aged rats. On the contrary, no age-related differences were found in the presence of 2-APV. These results indicate that i) the increase in presynaptic release of glutamate by low magnesium is not altered by age and ii) the weaker increase of glutamate-mediated excitatory postsynaptic potential in aged animals reflects the weaker density of NMDA receptors expressed by postsynaptic neurons.
Glutamatergic NMDA receptors play a pivotal role in an early phase of LTP lasting 1 to 3 hours [186, 198, 203, 207-211], but other effectors such as voltage-gated calcium channels [212-219] or mGlu receptors [79, 220-225] may be involved, depending on the strength of the tetanic stimulation or on the hippocampal region where LTP is induced. At a longer lasting stage, LTP requires protein synthesis, which is promoted by activation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA) [226-229]. The tetanic-induced neuronal depolarization relieves NMDA receptors from their voltage-dependent magnesium block and also activates calcium channels, both mechanisms allowing a massive calcium entry into postsynaptic neurons [230-235]. Besides, mGlu receptor activation mediates calcium release from intracellular stores [236-239]. All these activated pathways therefore increase intracellular concentration of calcium that stimulates protein kinases (PKs) such as calcium/calmodulin-dependent protein kinase II (CaMKII) and PKC [240-244]. As a consequence, the phosphorylation of AMPA receptors present at neuronal membranes and the incorporation of new receptors in the postsynaptic apparatus are promoted, thus increasing the strength of synaptic transmission.

How LTP behaves during hippocampal ageing has been intensively investigated, mostly at CA3-CA1 synapses. Opposite conclusions were reached, at least concerning the first PKA-independent phase of LTP (for reviews see [46, 47, 245]). Whereas a first set of reports indicated that LTP is impaired by age in correlation with memory deficits, a second series did not found any significant changes. This apparent controversy is explained by differences in technical protocols used to induce LTP. In the case of “weak” conditioning stimulation, selectively activating NMDA receptors, LTP is impaired in aged animals due to the decreased density of receptors [246-249] or their weaker activation induced by D-serine deficit [144, 146, 147]. Using a stronger conditioning stimulation recruits, in addition to NMDA receptors, voltage-gated calcium channels [212, 213, 218, 219]. Because these channels are up-regulated in hippocampal tissues during ageing [93-95], they contribute much more to LTP than in adulthood [147, 250, 251]. This higher involvement of calcium channels is able to counteract the age-related impairment of NMDA receptor activation, thus preventing the deficit in LTP.

A role for mGlu receptors in changes of LTP during ageing remains a question largely neglected until now. Only one study shows that mGlu selective LTP, induced in hippocampal slices after blockade of NMDA receptors and voltage-gated calcium channels, is not affected by increasing age [79]. Finally, concerning PKA-dependent LTP, age-related defects in spatial memory are correlated with its alteration and both physiological and behavioural impairments are attenuated by pharmacological treatments enhancing the cAMP signaling pathway [252]. Magnesium may interfere with LTP induction and/or maintenance at different levels. Indeed, treatments that lower the depolarization-induced influx of calcium into postsynaptic elements such as raising the concentration of external magnesium, selectively antagonize LTP [230-234]. Interestingly, the complete removal of magnesium in the external medium also elicits a persistent suppression of LTP in hippocampal slices [235, 236]. This unexpected inhibitory effect of magnesium-free medium is not due to changes affecting NMDA receptor properties but rather to activation signaling cascades in postsynaptic neurons that still remain to be characterized [255].

Magnesium may also modulate calcium-activated protein kinases governing LTP. On the one hand, magnesium is able to control the subcellular localization of PKC, which closely determines the function of the protein [256]. Through this mechanism, magnesium acts as a potent neuroprotective agent against damage to glutamatergic synaptic transmission induced by cerebral anoxia [257]. On the other hand, the long-lasting potentiation of synaptic potentials induced by a magnesium-free treatment in cultured chick cerebral neurons is mediated by activation of PKC and CaMKII but not of PKA [258]. Finally, the dephosphorylation and deactivation of CaMKII in betaTC3-cells are stimulated by magnesium [259]. Taken together, these data raise the possibility that the early phases of LTP, which are closely dependent on PKC and CaMKII activation, may be sensitive to changes in magnesium environment whereas the PKA-mediated longer lasting stage may be much less influenced. This hypothesis has received its first experimental support since raising magnesium levels in hippocampal slices depresses LTP magnitude [230, 260].

The magnitude of short-lasting synaptic potentiation is decreased by magnesium in a similar way in hippocampal slices from both young and aged animals [260]. Although such experiments need to be replicated, they suggest that magnesium deficiency associated with ageing does not significantly interfere with the deficit of synaptic potentiation, at least when only NMDA receptors are concerned. However, the possibility that magnesium deficiency contributes to the higher expression of voltage-gated
calcium channels in LTP processes during ageing remains an open issue.

A role has been attributed to magnesium in the age-related alteration of another form of synaptic plasticity, namely long-term depression (LTD) of synaptic transmission. In striking contrast to LTP which requires a transient but massive calcium entry into postsynaptic cells, LTD is induced by a low frequency but prolonged conditioning stimulation producing a moderate and progressive increase in calcium concentration [261, 262]. This pattern of activation recruits protein phosphatases (PP) and particularly PP1 and PP2B (calcineurin) which promote the dephosphorylation or the internalization of AMPA receptors present at postsynaptic membranes, thus decreasing the strength of synaptic transmission [263-266]. Several forms of LTD coexist in the hippocampus, which involve activation of NMDA receptors, mGlu receptors or phospholipase C, depending on the sub-region considered or on the type of conditioning stimulation [263, 267-270].

As previously described for LTP, whether NMDA receptor-mediated LTD displays an increased [271, 272] or a decreased [273, 274] susceptibility with age remains controversial. Because the calcium/magnesium ratio determines the occurrence of LTD, a possible explanation may arise from differences in synaptic magnesium availability. A calcium/magnesium ratio close to 1 does not induce LTD in adulthood [261, 262, 275, 276] whereas a sustained

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**Figure 2.** Schematic representation of the mechanisms allowing magnesium to modulate functional properties of hippocampal networks. Age-related magnesium deficit may therefore impair hippocampal functioning through several mechanisms involving presynaptic terminals, postsynaptic neurons and astrocyte glial cells. AMPAr: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, DAAOx: D-amino acid oxidase, NMDAr: N-methyl-D-aspartate receptor, VGCC: voltage-gated calcium channels.

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depression is found in ageing [271, 277, 278]. This age-related facilitation of LTD processes is prevented by calcium channel antagonists [277], but also after raising magnesium levels [271] indicating that it is due to the up-regulation of voltage-gated calcium channels. On the other hand, a calcium/magnesium ratio exceeding 1.5 already induces a LTD strong enough to minimize a possible facilitation by voltage-gated calcium channels in young animals. Indeed in these conditions, LTD is not enhanced but decreased in aged animals due to the weaker activation of NMDA receptors [273, 274].

The status of the different divalent cations, and particularly of magnesium, at the synaptic cleft appears therefore essential to predict whether LTD processes will be favoured or not during ageing. This regulatory mechanism is of particular importance since LTD also determines the efficacy of learning and memory by limiting acquisition and favouring memory declines [279, 280]. Alternatively, competitive interactions between LTD and LTP in the hippocampus underlie the storage of emotional memories and stress-induced amnesia [281, 282]. Therefore, there is no doubt that an alteration in the balance between these forms of synaptic plasticity due to changes in magnesium status may significantly contribute to the memory defect of the elderly.

**Conclusion**

Reviewing forty years of research dedicated to brain ageing clearly indicates that most of the functional properties of neuronal networks within the CNS are affected by age. Considering the hippocampal formation, evidence is now provided that cellular mechanisms involved in memory formation, such as AHP or long-lasting synaptic plasticity, are significantly affected with advancing age in parallel to the impairment of cognitive performances. Although there remains a long way to go, experimental data progressively accumulate indicating that a magnesium deficit is a relevant factor for ageing-associated susceptibility to hippocampal decline, not only through a vicious circle involving magnesium, stress and hyperglucocorticism as previously suggested, [61, 283] but also by directly acting on cellular properties of hippocampal networks (figure 2).

**Acknowledgments**

The author is grateful to Drs A. Jouvenceau and J. Epelbaum for critical evaluation and generous assistance in correcting the manuscript.

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