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MEMORY CONSOLIDATION – MECHANISMS AND OPPORTUNITIES FOR ENHANCEMENT

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Abstract

Memory consolidation is the process by which relevant information is selected and transferred from a short-term, fragile state, into a stable, longer term domain from which it can be recalled. Effective memory underpins our ability to carry out everyday activities. When memory consolidation fails, such as in Alzheimer's disease, the consequences can be devastating. Understanding the neurobiology of memory will help develop treatments for patients with memory loss. Here we describe the myriad processes involved in memory consolidation, including cholinergic and dopaminergic neurotransmission predominantly in hippocampal networks. We discuss established therapies as well as potential novel strategies for boosting cognition. Future approaches to enhancement of memory consolidation include not only pharmacological and neurosurgical treatments, but also lifestyle interventions – for example, modifications to sleep, exercise and diet.

Keywords

• Alzheimer's disease (AD) • Dementia • Sleep • Exercise • Diet • Calorie restriction • Hippocampus • Neurogeneration • Acetylcholine • Dopamine

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Introduction

Memory consolidation is the process by which information is transferred from the fragile, readily-disposable state of short-term memory, into a more robust, stable and interference-proof domain. This allows for memories to be stored and recalled over longer time scales, without being distorted by new incoming information. The importance of memory consolidation becomes readily apparent when we observe what happens in its absence. Patients with dementia, particularly Alzheimer's disease (AD) dementia, often lose their ability to consolidate memory with the devastating consequence of being locked to the past, unable to fully engage with the changing world around them. Here, we will review the mechanisms underlying memory consolidation, and methods by which these could be enhanced. We will include lifestyle approaches, pharmacological and non-pharmacological technical interventions that are emerging through our growing understanding of the neurobiology of cognition.

Who is affected by memory consolidation deficits?

Prominent memory impairment is a feature of AD. AD is a neurodegenerative disease affecting more than 35 million people worldwide costing in excess of $600 billion US per year. Prevalence of AD dramatically increases with age, affecting around 20% of those aged 85 years [1]. Neuropathological staging and sensitive neuroimaging techniques tell us that the hippocampus is affected in the very earliest stages of AD [2,3]. Given the role of the hippocampus in memory consolidation, it is therefore no surprise that AD is often characterised by decline in memory, although other cognitive domains are usually affected by the time a diagnosis is made [4]. In other dementias, including dementia with Lewy bodies, frontotemporal dementia and vascular dementia, memory is also often affected, but this is less consistently an early finding.

Although less critical socio-economically, other diseases in which memory consolidation is affected can be equally devastating to the individual. The hippocampus can be affected irreversibly in viral encephalitis and is a particular target for antibodies including voltage-gated potassium channel antibodies and other paraneoplastic antibodies producing amnesia as part of a syndrome of limbic encephalitis [5]. In addition, thiamine deficiency, recurrent seizures and hippocampal sclerosis can all also result in variable memory impairment. Many of these conditions can be treated, but often result in permanent memory consolidation impairment which would be potentially amenable to targeted therapy.

There is also evidence that memory consolidation is affected by normal ageing [6] and certain younger people (e.g. students, scientists, doctors, news reporters) might benefit from enhanced memory consolidation, raising the controversial possibility of cognitive enhancement in the neurologically healthy.

Mechanisms underlying memory consolidation

The unfortunate case of H.M. was particularly revealing in terms of the light it shed on the role of the hippocampus. After bilateral

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surgical removal of the hippocampi, H.M was unable to form new long-term declarative memories, holding onto information for just a few minutes; thus, this structure was revealed to be a potential gateway that allowed for short-term memories to join previously stored long-term information. This is the essence of the two-stage theory of memory [7,8]. This proposes that short-term memories are initially stored in the hippocampus, and later, during consolidation, transferred to the neocortex. During the acquisition of new memories, this information is encoded in specific ensembles of neurones within the hippocampus. It is worthy to note that while H.M. was unable to form new declarative memory, he was actually able to progressively learn new motor skills, demonstrating the now widely-acknowledged divergent systems for hippocampal-dependent declarative memory and separate procedural memory. We will focus in this review on hippocampal, declarative memory consolidation.

In order for consolidation of hippocampal-dependent memories to occur, the transfer of information from the hippocampus to the neocortex must take place. Sleep – specifically, slow wave sleep (SWS) – is thought to provide a unique physiological state that allows for this transfer, and mounting evidence points to the role of sleep in facilitating long-term memory consolidation. Enhancements in recall are such that sleep provides a clear improvement compared to an equal amount of time spent awake, something which has been found in both animals and humans [9-11]. Therefore the memory enhancement provided during sleep is not merely due to passage of time alone.

One of the hallmarks of SWS, and amongst the key events underlying memory consolidation, is the presence of hippocampal ripples. These are hippocampal field oscillations, reflecting bursts of high frequency (in animals 140 – 200 Hz; in humans, 80 – 140 Hz) population activity. Hippocampal ripples originate in the CA1 hippocampal subfield, and co-occur with a sharp-wave activity which is instigated by CA3 and propagates to CA1 via the Schaffer collaterals [12,13]. These hippocampal ripple events are often accompanied by a reactivation of recently-acquired information, reflected by reactivation of hippocampal neuronal patterns of activity that occurred during acquisition. When this activity coincides with thalamocortical spindle activity (field oscillation that can be measured by EEG, at a frequency of around 12 – 14 Hz), transfer of information from the hippocampus to the neocortex is facilitated.

Another key feature of SWS is the occurrence of slow oscillations resulting in '*down*' states, during which entire areas of the neocortex are silent, and '*up*' states, during which neocortical activity is as active as during wakefulness. Slow oscillations impose a temporal framework – *up* states are a window for hippocampal ripples and spindles to occur synchronously [14]. When the hippocampal ripple event (and its concurrently reactivated memory trace) coincides with the thalamocortical spindle, this convergence of the two oscillatory events allows for the memory trace reactivation to be fed into neocortical networks [15,16]. This occurs repeatedly during *up* states, such that the new memory trace is persistently activated, and gradually redistributed to the neocortex, where eventually, it will become part of pre-existing knowledge networks (see Figure 1).

Factors influencing memory consolidation and cognitive enhancing strategies

As with many neurological processes, a myriad of interacting neurotransmitter systems can be implicated. We will focus here on the critical involvement of acetylcholine (ACh) and dopamine, as these neurotransmitters are depleted in two of the commonest neurodegenerative diseases, AD and Parkinson's disease. Many other factors influence memory consolidation including sleep, exercise, diet, other neurotransmitters and neuronal growth factors including brain-derived neurotrophic

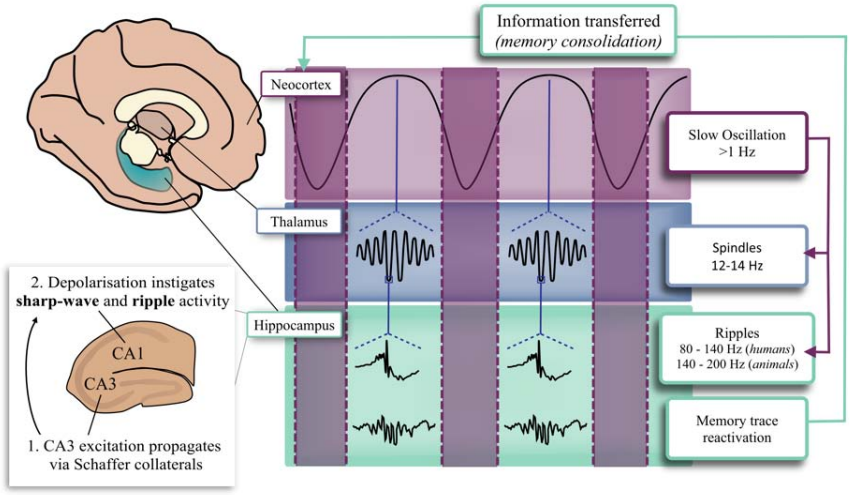

Figure 1. Mechanism of information transfer between neocortex and subcortical regions, underlying memory consolidation during slow wave sleep (SWS). Illustration of human brain through mid-sagittal section (with brainstem and cerebellum removed from view). Areas of interest are pointed out: neocortex, thalamus and hippocampus (*embedded within the temporal lobe, visible here in green*). Schematic diagram depicts the temporal relationship between the sleep events of interest – the neocortical slow oscillation imposes a timing relationship upon subcortical events in the thalamus and hippocampus. Spindle and ripple events cannot occur during *down* states of the slow oscillation (*indicated by in purple shaded areas contained by dashed lines*). Inhibition is lifted during neocortical *up* states, allowing subcortical events to occur. Spindles are phase-locked to a certain region of the slow oscillation activity – in turn, the hippocampal sharp-wave ripples are also locked to a certain phase of the spindle oscillation (*phase-locking shown by blue lines*). Ripples co-occur with reactivation of memory trace within the hippocampus, and temporal alignment of these events allows hippocampal information to travel to neocortical networks (*green line*) via thalamocortical pathways. Inset, bottom left, depicts cross-section through the hippocampus. Subfields involved in the generation of the sharp wave ripple (SWR) event are indicated. Excitatory input from CA3 via Schaffer collaterals results in strong depolarisation within CA1, evoking sharp-wave and consequent ripple activity.

factor (BDNF) and these will also be discussed along with their potential for modification.

Acetylcholine

ACh is an obvious starting point for a discussion on cognitive enhancement, as cholinesterase inhibitors – which act by increasing the levels of ACh – are the major licensed drugs for memory enhancement in AD [17]. The rationale for using these drugs was established along with the cholinergic hypothesis of memory dysfunction [18] on the basis of reduced cholinergic forebrain neurons in AD [19] and amnesia caused by antimuscarinic drugs [20]. However, cholinesterase inhibitors benefit fewer than 50% of those who take them, and patients often experience side effects. One of the limiting factors with the use of cholinesterase inhibitors is that they target all cholinergic receptors – both nicotinic and muscarinic. Different receptor subtypes have distinct, but overlapping functions, with nicotinic subtypes involved largely in attention and muscarinic subtypes underpinning memory [21]. Thus, cholinesterase inhibitors can boost both memory and attention and a wide range of other brain and body-wide functions in patients (which can often result in side-effects) rather than targeting specific memory deficits.

If we focus on the potential for targeted enhancement of memory consolidation in patients, the muscarinic subtypes are of particular importance [22]. Of subtypes M1-5, M1 is of specific interest, especially when we consider the fact that these receptors are expressed in brain areas implicated in the two-stage theory of memory , the hippocampus and neocortex [23]. M1-selective antagonists impair long-term, but not short-term memory [24,25]. In addition, a study looking at M1-selective knockout animals found no effect on early performance in spatial learning tasks; once the animal was tested after a *delay*, however, deficits became apparent in the M1-knockout but not the wild type animals, suggesting a critical role for the M1 receptor specifically in long-term consolidation, but not short-term memory [26]. Human work on M1 agonism and memory consolidation during sleep has shown effects on sleep, but no benefit to cognition [27,28]. However, newer more specific M1 agonists are now available, and much of the previous work looked at healthy young controls [27] (raising the strong possibility of ceiling effects), rather than looking at patients with AD, or even healthy elderly participants. Therefore, we think there is scope for further exploratory clinical evaluation of M1 agonists to enhance memory consolidation.

One further potential area of interest for memory enhancement is targeting of cholinergic nuclei by deep brain stimulation. Deep brain stimulation is used routinely in patients with Parkinson's disease [29] and less often in chronic pain and depression. There are small trials underway of deep brain stimulation of cholinergic networks in AD. Putative targets include the nucleus basalis of Meynert (brain stem cholinergic nucleus) [30] and fornix [31]. Further preliminary data in humans stimulating the entorhinal cortex has suggested memory can be enhanced [32] and mice with traumatic brain injury had improved memory after stimulation of the medial septal nucleus. Further work is needed to establish the optimum target for such stimulation and the precise risk vs. benefit ratio for patients.

So, while the modest benefit of cholinesterase inhibitors has tempered enthusiasm for cholinergic cognitive enhancement, it is still possible that targeted pharmacological or deep brain stimulation of cholinergic neurons or receptors may prove fruitful.

The role of dopamine and other monoamines in memory consolidation

How does the role of dopamine in memory consolidation differ from that of ACh? Animal work has suggested that dopamine is more involved in late memory consolidation (i.e. over hours) than early memory formation [33]. In addition, recent human data has suggested that dopamine might be important for long-term memory consolidation rather than early memory retention [34,35]. One study in patients with Parkinson's disease suggested that removal of exogenous dopamine impaired memory consolidation over one hour, but not over 20 minutes [35].

As well as being critical for longer term memory consolidation, dopamine may have a role in information *selection* prior to storage; potentiating memory traces for objects that are novel, rewarding or aversive and therefore, ensuring more biologically relevant information is stored e.g. [36]. Dopaminergic connections to the hippocampus come from the ventral tegmental area (VTA) and substantia nigra, interconnecting with brain regions processing the valence of incoming information. Regarding negative valence in particular, a dopamine receptor-dependent network has been suggested in rats, promoting the retention of information about aversive stimuli, presumably so danger can be avoided [37]. Therefore, dopamine appears to have a specific role in late memory consolidation and enhancing certain memories traces according to context.

Methylphenidate and modafinil act by increasing levels of dopamine and, to a lesser degree, noradrenaline, and can be prescribed for attention deficit hyperactivity disorder (ADHD) [38-40]. In addition, both are gaining recognition as cognitive enhancers [41,42]. Indeed, methylphenidate has been found to increase cognitive performance, including specifically memory consolidation, in healthy people without ADHD [43]. There is increased activity within the prefrontal cortex after taking methylphenidate [44] leaving open the possibility that prefrontal networks mediate part of the cognitive enhancement effect via a boost in alertness or processing capacity rather than a specific enhancement of memory circuits. Modafinil rescues memory consolidation in sleep deprived animals [45], and enhances memory consolidation in healthy humans [46]. However, mofadinil also acts via orexins [47] and the effects of the drug may be attributed in part by enhancement of wakefulness (and therefore attention) rather than directly exerting an effect on memory – hence its prescription in narcolepsy.

Amphetamine has been found to improve memory consolidation in rats [48,49]. It has also been found to improve memory encoding [50] and consolidation in humans [51] and has therapeutic potential to rectify memory deficits in patients with multiple sclerosis [52]. Its actions are certainly very interesting – it acts predominantly on dopaminergic

receptors, but at niche subtypes – those in the hippocampus (dopaminergic subtype 2 [D2] receptors) are not activated [53], with the main targets being the mesolimbic and mesocortical pathways [54,55]. It may seem, therefore, that its actions are not due to a direct effect on the memory system – rather, any improvement in performance may well be explained by increased motivation by recruitment of the reward/motivation networks, which may act to increase attention and salience, resulting in improved performance. However, intriguingly, amphetamine has also been shown to increase levels of ACh within the hippocampus [56] – an action thought to be mediated by its actions on the D1 receptor. Indeed, dopamine has been implicated in cholinergic release [57], and as we have explained, ACh is central in processing hippocampal-dependent memory – so dopamine may be acting not only via the reward pathways, but more directly by its effect on modulating hippocampal ACh, on the memory system. This may well be contributing to the memory-enhancing effects of the dopaminergic drugs discussed above.

It is also interesting to note that administration of both modafinil and amphetamine results in increased number of ripples during subsequent SWS [58]. This has been thus far attributed to 'rebound' of ripples following the increased wakefulness caused by these stimulant drugs. However, it may well be worth further investigating these effects to see if increase in ripples has any functional significance matching to the purported cognitive benefits of these drugs, particularly as increased ripple number is linked to increased consolidation.

Brain-derived neurotropic factor (BDNF)

Of particular interest is that increases in BDNF link many of the non-invasive interventions described later in this review - most notably, exercise and calorie restriction (see later sections). BDNF acts upon neurones in a variety of mechanisms, from providing neuroprotective and supportive roles during development and maintenance throughout the neuronal lifespan, to also playing a role in neurite outgrowth and targeting, and the regulation of channels. BDNF exerts its effects via a variety of signalling pathways, although its acute application can also produce synaptic responses. In short, its beneficial actions on cognition are convoluted and numerous – we focus here on those that relate directly to memory consolidation.

Interesting insights into the mechanisms behind memory consolidation have been revealed by studying BDNF. For example, specifically 12-hours post-training, there is a stage of memory consolidation which is BDNF-dependent; inhibition by blocking either BDNF, or its downstream signalling pathway, has no effect on memory recall at 2 days, but does produce an impairment in performance when tested 7 days post-training - implying that this BDNF-mediated mechanism is specifically involved in a longer-term facet of memory consolidation [59]. Intriguingly, the production of BDNF seems to be instigated by VTA dopaminergic system. Infusion of a dopamine antagonist into the CA1 subfield of the hippocampus at 12 hours following initial learning impairs 7 day-later recall, while leaving 2-day recall intact – seemingly impairing this same long-term consolidation mechanism. NMDA blockade in the VTA produced similar results. What is more, this impairment is ameliorated if the dopaminergic antagonist is accompanied by infusion of exogenous BDNF – this would suggest that BDNF production occurs downstream and in response to dopaminergic activation [60].

BDNF is of particular importance for AD, as levels have been found to be decreased in AD patients, and exogenously increasing BDNF levels has potent benefits for memory. Its exogenous infusion has been found to induce neurogenesis in rats [61], and in rodent models of AD prevents neuronal loss, reverses loss of synapses, and restores memory function. There are similar benefits in aged rats and primates, where age-related loss of neurones and memory function is not only prevented, but restored by infusion of BDNF post-onset of decline [62]. This does provide a potentially promising opportunity for therapy, a means by which to kindle the brain's potential for neurorestoration in order to ameliorate memory loss seen by neurodegeneration. Pioneering work currently underway in Bristol involves insertion of a permanent cerebral catheter and skull port into patients with Parkinson's disease, to deliver pulsed glial cell derived neurotrophic factor (Whone et al. unpublished, [63]). This potentially opens up the possibility of delivering neurotrophic factors through the blood brain barrier in other conditions such as AD, both for neurorestoration and cognitive enhancement.

Sleep, and its manipulation, as a cognitive enhancer

As discussed above, we know that significant memory consolidation occurs during sleep and therefore therapeutic modifications to sleep to enhance memory are the subject of investigation. In Drosophila, it is possible to induce sleep remotely by inducing genetically-controlled expression of temperature-gated cation channels at specific brain sites of interest, and controlling room temperature. This, in turn, has been shown to cause enhancements in memory [64]. Whilst such methodology of course cannot be directly recapitulated in humans, the parallel form of this is by inducing sleep through pharmacological means.

Certain hypnotics, for instance, have been found to enhance memory, which may be mediated through their sleep-inducing properties. Gaboxadol (otherwise known as 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol [THIP]) has been used as an effective treatment for sleep disorders [65], and has also been found to increase SWS [66]– making it a promising therapeutic target. However, given that its effects on memory are thus far mixed [65,67] and its effect on sleep EEG activity varies greatly between genders [68], further, more detailed investigation is certainly warranted.

Another strategy is to target SWS and slow oscillations in order to evoke some benefit to memory consolidation. Indeed, this does seem extremely promising – one way to do this has been by using transcranial magnetic stimulation (TMS) allowing for a more focussed intervention than can be afforded by pharmacological methods. This has been successful in increasing slow oscillations in rodents and humans [69] as well as eliciting corresponding enhancements in memory

consolidation [70]. Another intriguing method being explored is the induction of slow oscillations by using auditory cues. Here, the auditory stimulation is played during SWS, using low frequency range-auditory cues to augment the oscillatory activity of the < 1 Hz slow oscillations. This has, indeed, been found to increase the amount of slow-oscillations, but results were sometimes mixed [71]. More recently, however, a study in healthy humans [72] used online monitoring of slow oscillations in order to administer the auditory cue in phase with the ongoing slow wave activity. Playing such cues produced reliable increases in slow oscillations, and a corresponding increase in memory consolidation, above that which was found in unaltered sleep. This is a very appealing finding, given that it indicates very promising outcomes can be attained from such a non-invasive mechanism, without any pharmacological or neurosurgical intervention, and without the side-effects of TMS. These benefits were found in young healthy human subjects, but the merits are yet to be assessed in elderly or AD populations.

Exercise

There are a plethora of studies clearly illustrating that physical activity improves hippocampal function. Importantly, this improvement is not solely due to temporarily improved blood flow to the brain, but it has a robust neurophysiological basis, in the promotion of neurogenesis within the hippocampus (e.g., [73,74]). Neurogenesis is also accompanied by an increased neurite outgrowth, hence increased connectivity. Moreover, exercise also induces brain angiogenesis [75], thereby promoting a positive cycle for brain function. Hippocampal volume is also seen to increase in human subjects with physical activity – for instance, level of physical fitness has been linked with a higher hippocampal volume in children [76]. A multitude of studies demonstrate that this exercise-induced change also has its functional benefits, such as improved memory in animals [77] and healthy young human participants [78].

Ageing is accompanied by a decrease in neurogenesis in animals [79,80], and imaging in humans demonstrates that hippocampal volume is decreased with age [81]. Exercise, however, can ameliorate this – it improves spatial memory that normally deteriorates with age [77], and there is larger hippocampal volume in older adults with higher fitness [76]. This suggests that despite there being an age-related decline, there exists nevertheless a window of plasticity that can be harnessed through the beneficial effects of physical training.

Exercise is also a promising therapeutic aid. When looking at a mouse-models of AD (3xTg), aerobic exercise was found to decrease the symptoms and development of dementia [82] – moreover, while neurogenesis is normally impaired in this mouse model, it was actually restored to the extent of being comparable with wildtype control animals, after exercise [83]. This restoration of neurogenesis occurred once the AD-like symptoms were underway, revealing a potential for not only a delay of the symptoms, but actually a reversal. In a study of mild cognitive impairment (MCI) patients [84], those in the control condition found their declarative memory deteriorated after six months, as the course of the disease progressed. Strikingly, however, those in the exercise conditions had memory which was not only preserved after six months, but actually improved compared to baseline. There have also been exercise-instigated improvements reported in other studies involving adults who are at risk of AD [85]. Furthermore, one intriguing study suggests specific types of physical activity can differentially affect individual facets of memory; in MCI patients, verbal memory was improved by aerobic exercise, but spatial memory was improved by both aerobic and resistance training [84]. Animal work suggests a putative mechanism for these differential effects. In rats, aerobic exercise training increased insulin-like growth factor 2 (IGF-2), while resistance training exercised rats were found to have higher levels of BDNF [86]. Along with BDNF, IGF-2 may be an important factor in memory processes [87].

Therefore, the relationship between memory consolidation and physical activity is now well-established, and provides an enticing opportunity for memory enhancement through exercise, for both healthy and pathological populations.

Diet

Glucose

Glucose appears to be especially important for hippocampal-dependent memory [90,91], and for demanding tasks [92-94]. After awakening, blood glucose levels in the brain are relatively low [88], and improvements in working memory have been demonstrated upon glucose administration – regardless of whether blood glucose levels were depleted upon time of administration [89]. Moreover, this increase in blood glucose is dissociable from benefits in attention alone, as memory performance benefits both when glucose is administered before or after learning, and attention would only be a relevant factor at the point of learning rather than afterwards. Interestingly, the elderly population seem to derive more benefit in memory function from increasing glucose compared to healthy young participants [90]. The primary site of action or effects of glucose has been proposed to the hippocampus, where it may be involved in ACh synthesis, which in itself is a prominent player in memory, and target for therapeutics (as discussed in section '*Acetylcholine*'). It should be noted that although raised glucose in the short-term may boost cognition, persistently increased glucose, such as in poorly controlled diabetes mellitus, results in impaired cognitive function due to various mechanisms, including cerebrovascular disease.

Calorie Restriction

Calorie restriction (CR) is a dietary regime involving reducing calorie intake by around 10 – 30%. There are various methods by which this restriction can be achieved – by reducing daily food intake, by alternate day fasting, or by intermittent fasting [95]. Although it may seem somewhat counterintuitive at first glance, inhibiting intake in this way actually has profound, well-documented beneficial results. It is most well-known in the literature as having longevity-enhancing effects, something which has been demonstrated in a wide range of organisms [96,97], and it also acts to delay age-related diseases, and a combination of both these effects have been demonstrated in rodents [98] and rhesus monkeys [99]. CR has

been found to beneficially alter the expression of synaptic proteins that would normally be reduced by ageing [100] and ameliorates the effects of age-related cognitive decline in rodents by increasing levels of BDNF. Even aged rats that underwent late-onset CR had a degree of rescue of function [101]. CR protects against neurodegeneration, increases neurogenesis and memory performance, and decreases amyloid beta (Aβ) plaques in animal models of AD [102,103]. The mechanism for improvement through CR is thought to involve sirtuins (SIRT), which may, among other things, mediate neurogenesis. Intriguingly, SIRT are also involved in up-regulation of ketones, which have been found to have neuroprotective effects [104], and are of therapeutic interest, having been suggested to benefit in healthy people and AD patients [105,106].

How do we reconcile the conflicting findings that that both increased glucose and restricted dietary intake have beneficial effects on cognition and memory? One possibility is that the caloric intake restriction may not be reflecting the effects of decreased diet *per se*, but actually, the benefits of not excessively indulging. It may well be that benefit of CR on memory is not due to any inherent benefit of reducing calorie intake – any benefits in memory are, rather, seen as a contrast to the control group, which is allowed to eat freely and may be relatively overeating. However, the specific pathways and proteins associated with CR, and their isolated benefits, make this explanation less likely. It is now emerging that the benefits of CR, such as neuroprotection in AD, can be elicited by periods of hunger alone, in the absence of reducing overall calories [107]. This suggests that it is the period of hunger, and associated signalling pathways including SIRT, that are beneficial in the longer term, while briefly raised glucose levels give a shorter term boost to cognition.

Polyunsaturated fatty acids

Omega-3 fatty acids are emerging as a crucial factor for neuronal health and function. Observed at the mechanistic level, the importance of omega-3 fatty acids becomes readily apparent – they are central to the development and maintenance of neurones and synaptic function [108]. It follows that rats with low omega-3 intake had decreased neuronal plasticity [109], while animals given omega-3 within their diet have increased BDNF expression within the hippocampus and neocortex [110], which are key sites for memory consolidation.

An omega-3 fatty acid enriched diet also has therapeutic potential for AD – when given to the 3xTg mouse model of AD, the loss of neurones within the entorhinal cortex was reduced, and memory deficit development was delayed compared to controls [111]. Administration of omega-3 fatty acids in another mouse model (Tg2576) allowed for increased synaptic integrity, and again, manifested with a behavioural improvement – memory performance in the Morris water maze was increased.

Conclusion

There is a range of non-invasive, easy to implement factors, which have been robustly proven to enhance memory – increases in physical exercise, better-quality sleep, and dietary considerations. In addition, there are several very promising lines of pharmacological, neurosurgical and other interventional research that could benefit individual patients and reduce the huge socioeconomic burden of dementia. Therapeutic research not only has potential for patient benefit, but in turn informs our understanding of the complex networks underpinning normal memory consolidation.

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