THE EFFECTS OF AGEING AND EXERCISE ON RECOLLECTION AND FAMILIARITY BASED MEMORY PROCESSES

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ABSTRACT

In the UK's 2011 census there were high proportions of people between 20 and 49 years-old, with each 5-year band containing at least 4 million. Thus between 2022 and 2051 we can expect large numbers of people to enter their 60s, around 2 billion globally. As people live longer healthier lives, the natural decline in their cognitive abilities impacts on everyday activities and impairs quality of life. A major component of this is deterioration in memory. It is well established that as people age, although still able to recognize people as familiar, they are less likely to retrieve details such as their name or why they are familiar (the *butcher-on-the-bus* phenomenon). This has been taken as evidence that recognition memory comprises a number of interacting yet largely independent processes, and for the distinction between familiarity - recognizing people, places and objects - and retrieving contextual details such as a person's name - recollection. Research with both humans and animals suggests that this is due to a relative decline in functioning of the hippocampus, and that this structure is responsible for recollection, while familiarity based-processes are mediated in adjacent regions such as the rhinal cortex. Selective decline in the ability to retrieve contextual information is one of the more debilitating effects of age on memory, and so it is crucial to find ways of ameliorating this process. Although many studies indicate that even brief exercise interventions can enhance performance on a number of neuro-psychological tests of

cognitive function, the precise mechanisms underlying these effects are unclear. One intriguing possibility stems from evidence that physical activity produces synaptogenesis and neurogenesis in the hippocampus - which might ameliorate or reverse the age-related decline in hippocampal function thought to impair the recollection process. In this chapter we review the evidence for this hypothesis using data from both rodent and human studies.

In common with many other European countries the United Kingdom has an aging population. The percentage of people aged 65 or older has increased from 15% in 1985 to 17% in 2010, but is set to increase rapidly to a projected 25% of the population in 2035 (Office_for_National_Statistics, 2012). Over a similar period the number of centenarians has increased from 2500 in 1980 to 12,640 in 2010 (Office_for_National_Statistics, 2011). Cognitive decline is a normal part of ageing, but memory can be more sensitive to age than other aspects (Cullum et al., 2000).

A general decline in grey matter volume resulting from lower synaptic densities rather than cell death is the likely cause of cognitive decline (Hedden & Gabrieli, 2004). In particular a more rapid decline in hippocampal volume compared to associated areas is likely to result in noticeable effect on declarative or episodic memory compared to familiarity based memory.

A result frequently found is that older adults have greater impairments in recall or recollection than they do in familiarity or recognition judgements. This result has been found using multiple methods of measurement. For instance, using the subjective 'remember/know' method Parkin (1992) found that older adults made a similar number of correct recognitions of remembered items labelled as 'know' but fewer 'remember' judgements than younger adults. This reduction of remember judgements was correlated with reduced performance on tests that are thought to measure frontal or executive function.

One issue with using the remember/know methodology in older adults, however, is that some studies have reported an impairment in metacognition in older adults (Souchay, Isingrini, & Espagnet, 2000). It is difficult, therefore, to discriminate between loss of the ability to remember and the loss of the ability to subjectively discriminate between remembering and knowing.

Nevertheless, other methods for discriminating between recollection and recognition also show reduction in recollection and maintained familiarity in older adults. Performance in recall tasks are reduced relatively more in older adults than performance in recognition tasks (for a review see Yonelinas, 2002). Performance also declines on associative memory and source memory tasks (e.g. Naveh-Benjamin, 2000; Yonelinas, 2002).

Deficits in recall with age are usually presumed to be at the level of encoding, rather than at retrieval and are associated with reduced performance on tests of 'frontal' or executive function (Yonelinas, 2002). Recall memory in older adults can be improved by changes at the encoding stage. For example Park et al (1990) tested recall of picture pairs. Participants were instructed to remember pairs of images. Older adults were poor (compared to younger adults) at recalling unrelated pairings but better when the pictures showed interacting pairs or pairs with related meanings (see also Cheryl L Grady, 2000).

It is not clear, however, whether the loss of recall reflects an absolute impairment or a tendency to fail to engage appropriate encoding, or retrieval, strategies. It has been shown that even when a memory stimulus is not recognised on test, it can facilitate both repetition priming and matching based on meaning (Koutstaal, 2003).

There is a close relationship between context and explicit retrieval such as recall and recollection. For example, Mandler (1980) described the *butcher-on-the-bus* phenomenon to illustrate the independence of familiarity and recollection based memory processes. In the most widely used form the *butcher-on-the-bus* describes a scenario in which a person's face is recognized as being *familiar*, but the recognition is not accompanied by the *recollection* of contextual details such as the person's name or occupation. Although, some theoretical models might discuss these differences as an environmental context effect and the presence or absence of retrieval cues; the majority of models interpret the effect in terms of the

differing characteristics of recollection and familiarity based memory processes: namely that recollection encodes context but familiarity does not, or that the difference is one of memory strength and that context information is more easily retrieved for stronger memories such as people we know well as opposed to acquaintances.

In two experiments, Tunney, Mullett, Moross, and Gardner (2012) presented participants with pictures of faces and scenes as paired associates. At test, the faces were presented with either the previously associated scene or a different scene. In Experiment 1 participants made more remember responses to old face-scene pairs than to new face-scene pairings. Process estimates revealed that context increased the sensitivity of recollection-based memory and also the sensitivity of familiarity based memory (but see Gruppuso, Lindsay, & Masson, 2007, for a slightly different result). In Experiment 2 participants were first asked to make recognition judgements for the test faces and to report their subjective experience of remembering. They were then asked to identify the context that each test face was associated with from a choice of four (i.e. 4AFC). So if the hypothesis that recollection encodes context and familiarity does not is correct then, recognition responses for items reported as 'remembered' should be followed by more accurate context decisions items reported as 'knowing'. The data confirmed this pattern of results, but the accuracy of context judgements associated with 'knowing' was reliably above chance, albeit lower than remembered items. This pattern of results is more consistent with a single process explanation than a traditional dual-process account. Yovel and Paller (2004) report ERP data consistent with his latter interpretation. The magnitude and duration of ERPs attributed to recollection were greater than those attributed to familiarity, but the observation that their forms were not qualitatively distinct, suggests that they were produced by the same neural systems. Eldridge et al (2005) used *f*MRI to probe neural activation following remember and

know judgements. They observed the expected behavioural patterns in which participants could recall more contextual information for items reported as remembered than known. The *f*MRI analyses revealed that remember responses were accompanied by greater activation in the right medial temporal lobe, and in particular the subiculum subregion of the hippocampus. The CA1 and CA23DG regions also showed differential activity: CA1 activity was greater for remembered items compared to forgotten items, while the Ca23DG region showed deactivation for known items. Both remember and know responses were accompanied by increased activation in the left perirhinal cortex.

Age-related changes in the subjective experience of remembering and recollection of contextual details are paralleled by age-related changes in the underlying neural circuits. The entorhinal cortex and CA1 regions show little or no age-related decrease in volume. By contrast those areas associated with recollection by Eldridge et al (2005) such as the subiculum and dentate gyrus show age-related decreases in volume (see also Hedden & Gabrieli, 2004; Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002).

Although the precise relationship between recollection and familiarity-based memory as single or independent processes remains a matter of empirical investigation, it is clear that there are subtly different effects of aging on tests of memory. Indeed, a selective decline in the ability to retrieve contextual information is one of the more debilitating effects of age on memory, and raises the possibility that aging might also affect the sensitivity of older adults to context as a retrieval cue. Indeed a wide range of studies have found that memory for context appears to be particularly sensitive to aging (e.g., Spencer & Raz, 1995; Zacks, Hasher, & Li, 2000). Moreover, research with both animals and humans suggests that a decline in functioning of the hippocampus might mediate this age-related memory decline.

Although work on animals interprets the distinction between recollection and familiarity in a slightly different theoretical context (e.g. Tam, Bonardi, & Robinson, 2015), parallels with theorising on human memory still emerge. Exposure to a target item *directly* activates its memory trace, reflecting development of *familiarity* - meeting the butcher makes him familiar. In contrast, *recollection* occurs because the target becomes associated with its contextual details, and these associations result in *associative* activation of a memory trace: seeing the butcher recalls his name via the association between them.

However, direct memory trace activation is transient, but familiarity is not. Thus some argue that familiarity also results from associative activation, via *permanent* associations that form among the item's *constituent elements* during exposure. Recollection, in contrast, is solely the result of associative activation of contextual information by the target item. The environment where the target is encountered also becomes associated with its contextual information - so it is easier to recall the butcher's name in his shop than on the bus[1] - and will also associatively activate the target itself - another way associative activation contributes to the familiarity effect. In short, associative activation contributes to both familiarity and recollection, but the former can also benefit from direct activation of the item's memory trace. This is reminiscent of Tunney et al.'s (2012) findings that context judgements, which rely on associative memory, were related to both remembering and knowing, although more strongly with the former.

Most familiarity tests in animals employ the Spontaneous Object Recognition (SOR) task, exploiting rodents' predisposition to explore novel objects. Animals preexposed to item

[1] Context may also allow selective retrieval of associative information that was acquired in its presence: thus the association between the butcher's appearance and his name may be more readily retrieved in the context in which it was acquired (in the butcher's shop) than in others (such as on the bus).

A will subsequently explore A less than a novel B - evidence of A's familiarity. The task becomes harder as the test is delayed, because direct activation of A's memory trace dissipates; at longer delays only indirect activation of A's memory trace by the experimental environment makes A familiar.

SOR performance is typically unaffected by hippocampal damage (e.g. Barker & Warburton, 2011; Good, Barnes, Staal, McGregor, & Honey, 2007) unless the delay before test is extended (Clark, Zola, & Squire, 2000), or the lesions large (Broadbent, Squire, & Clark, 2004). Nonetheless, we have argued that familiarity relies on (i) *direct* activation of the memory trace by the target, and *associative* activation of the memory trace by (ii) constituent elements of the target, and (iii) the preexposure environment. Thus variants of the SOR task have been proposed as cleaner measures of these underlying processes. For example, in a Relative Recency (RR) task preexposure to A and *then* B results in a preference for the less recent A. As here processes (ii) and (iii) are equated, test performance must stem from differences in (i) - direct activation of the memory trace is stronger for the more recent item. Hippocampal damage impairs RR performance (e.g. Barker & Warburton, 2011; DeVito & Eichenbaum, 2010).

In contrast, in the Object-in-Context (OIC) task animals are exposed to four items: at test two items exchange position, and command more exploration at test. Here processes (i) and (ii) are equated, so performance must stem from differences in associative activation (iii): if local environmental features associate with each item during exposure, memory traces of stationary items will be more effectively activated. Hippocampal damage tends not to impair OIC performance (e.g. Barker & Warburton, 2011; DeVito & Eichenbaum, 2010; Good et al., 2007).

In summary, results from animals do not fully support the human findings. Evidence for hippocampal involvement is strongest for RR performance, which we argue relies on direct memory trace activation, and is thus more closely allied to familiarity. In contrast, OIC performance - a purer measure of associative memory (i.e. recollection) - is less reliably affected by hippocampal damage. But OIC tasks are not a perfect operational parallel of recollection tasks in humans, as in OIC the environment must activates the target item, whereas in human tasks the opposite is the case. Moreover, the majority of these lesion studies damaged the entire hippocampus, so if different parts of this structure play different roles, as was suggested above, important differences might be obscured. The handful of studies that selectively lesion different subfields suggest that CA1 might be especially critical for RR performance (Hoge & Kesner, 2007; Hunsaker, Rosenberg, & Kesner, 2008). But these findings do clearly demonstrate that the hippocampus plays a key role in performance on these memory tasks.

Studies of brain activation in humans have supported the findings of the behavioural work reviewed above. Older adults typically have different patterns of brain activation to younger adults, with brain activation in older adults being more related to familiarity-based memory than for younger adults. For example, in an early study on the topic, Daselaar et al (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006) indexed familiarity and recollection with confidence judgements, where low confidence correct judgements were considered to be based on familiarity and high confidence correct judgements were considered to be based on recall. Older adults showed more familiarity based judgements in a memory test than younger adults. Older adults also showed more brain activity on retrieval in the rhinal cortex than younger adults. Older adults also showed more functional connectivity between

prefrontal cortex and rhinal cortex whereas younger adults showed connectivity between the prefrontal cortex and the hippocampus (see also Cabeza et al., 2004).

Older adults show brain activity more consistent with familiarity based recognition and memory than with recall based memory. This would suggest that older adults would be worse at memory for associations. This does appear to be the case, however, when associations are made, it appears that older adults may use the same mechanisms as younger adults, up to a point. Miller et al (2008) asked older and younger adults to learn face-name pairs in an associative learning task. For those older adults who performed well overall, brain activation patterns in the hippocampus and associated regions was similar to younger adults. This suggests that older adults who maintain recall-based memory activate similar processes to young adults. For those older adults who did not, overall, perform well, activation in successful memory trials was associated with a different network of brain activations (including additional frontal activations).

The results above are consistent with older adults using different strategies for memory than younger adults for many tasks. The reasons for this shift in strategy are unclear. One cause may be deterioration in the brain areas that underlie recollection, i.e. the hippocampus. There is a growing consensus that the hippocampus suffers atrophy or deterioration in even healthy ageing (Pereira et al., 2014; Raz, 2000), although this is by no means a universal finding (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995; Sullivan & Pfefferbaum, 2014). One reason for the discrepant findings could be that hippocampus volume decline is not linear. Hippocampus volume has been shown to decline non-linearly, with a sharp decline starting somewhere between 60 and 80 but relative preservation until that point (Pfefferbaum et al., 2013). This is in contrast to a relatively steady decline of more frontal areas.

Age-related declines in memory formation have also been attributed to failures of encoding. There are well-documented declines in sensory processing (e.g. Owsley, 2011). Brain imaging results are consistent that where older adults are impaired in recall memory, this is due to a failure at encoding. In a classic study, Grady et al (1995) showed that older adults failed to activate the hippocampus at encoding (although younger adults did). There was also greater activity in the prefrontal cortex at retrieval for older adults. This, however, does not resolve the question of whether these changes are due to a change in the capacity of recall or a change in bias towards one or other strategy. That is, the ability to use recall memory might be maintained, but, because encoding is more difficult, might not generally be used. Similarly, the ability to use recall memory might be maintained but losses in other executive functions might mean that the necessary processes tend not to be evoked.

A related issue with literature investigating recall and familiarity in older adults is that mechanisms are frequently indexed via confidence ratings or criterion shifts. If older adults make confidence ratings in different ways or have a tendency to use different criteria for response compared to younger people, then this may be poor way to index differences in memory.

The importance of exercise for physical and cognitive function is well-known. Promoting physical activity is important across the lifespan, but in older adults there are significant implications for the maintenance of functional ability, independence and health-related quality of life. Physical activity is thought to be protective against cognitive decline, and can generate improvements in cognitive function. Indeed, protective effects of physical activity against cognitive impairment have been observed regardless of the way in which activity levels are measured (e.g. ActiGraph accelerometer, self-report, or doubly labelled water: Steinberg et al., 2014).

The link between exercise and cognitive function has been demonstrated in a range of populations including healthy middle-aged adults, healthy older adults and adults with mild cognitive impairments (a risk factor for the development of Alzheimer's disease). The precise nature of this link is still under investigation; although the beneficial effects of physical exercise on memory and executive function seem to be well-established (Colcombe & Kramer, 2003), and studies have investigated domain-specific effects of physical activity on cognition and detected improvements in a wide range of cognitive functions including executive function, memory, processing speed, and attention (Buchman, Boyle, Leurgans, Barnes, & Bennett, 2011; Lautenschlager et al., 2008; Scarmeas et al., 2011; C.-H. Wang et al., 2014; S. Wang, Luo, Barnes, Sano, & Yaffe, 2013).

Overall, this area of research is rapidly progressing, and exercise in older adults has been shown to improve task-related cognitive function, brain connectivity and regional brain volume (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). Our understanding of the biological mechanisms involved in the impact of exercise on cognitive function suggests that there are likely to be changes at the molecular, vascular, synaptic and neural levels (Lista & Sorrentino, 2010). These changes in brain health and cognitive function have been demonstrated in a wealth of human studies. For example, in middle-aged, cognitively healthy adults at risk for Alzheimer's Disease (AD), greater cardiorespiratory fitness was associated with increased grey matter volumes in several brain regions that are implicated in AD (including the hippocampus, amygdala, precuneus, supramarginal gyrus and rostral middle frontal gyrus) and those with greater fitness had better cognitive performance on tests of Verbal Learning and Memory, Speed and Flexibiity, and Visuo-Spatial Ability (Boots et al., 2014). Researchers have been adopting new techniques to investigate neural adaptability and efficiency during cognitive processing. Using Multiscale Entropy Analysis (MSE) of

electronencephalography (EEG), a recent study indicated that physically active older adults have better accuracy on both visuo-spatial attention and working memory conditions relative to their sedentary counterparts (C.-H. Wang et al., 2014). Finally, current research on brain microstructural integrity has found that in old, community dwelling adults being exercise active may help to preserve brain microstructural integrity in memory-related networks (Tian et al., 2014).

Some light on the mechanisms that might underlie these changes comes from work on animals. Although numerous changes in brain chemistry and cellular degeneration are likely to result from advancing age, Brain Derived Neurotrophic Factor (BDNF) occurs in relatively high concentrations in the hippocampus and cortex, and shows significant age-related changes in concentration (Erickson, Miller, & Roecklein, 2012; Voss et al., 2013). Lower concentrations of serum BDNF are found in older adults and Alzheimer's patients with more severe cognitive impairment (Laske et al., 2011), and BDNF is found in reduced concentrations in the hippocampi of older animals (Silhol, Bonnichon, Rage, & Tapia-Arancibia, 2005). Lower concentrations of BDNF in cerebrospinal fluid are predictive of memory performance and hippocampal volume (Li et al., 2009). Given the key relationship between lower BDNF hippocampal volume and memory performance it seems reasonable to believe that any intervention that increases BDNF might be beneficial, and indeed exercise (in the form of voluntary wheel-running) has consistently been shown to increase hippocampal BDNF levels in rats (e.g. Ploughman et al., 2005; Vaynman, Ying, & Gomez-Pinilla, 2004), and has also been shown to improve performance on tests of spatial learning and memory (e.g. Van Praag, Shubert, Zhao, & Gage, 2005; Vaynman et al., 2004). Likewise, regular aerobic exercise increases BDNF in humans, and can result in improved memory performance (Erickson et al., 2012). In rodents this type of exercise has also been related to

increased cell proliferation in the hippocampus, and selective increases in cerebral blood volume, which is related to reduction in age-linked decline in cell proliferation, and neurogenesis, in the dentate gyrus (e.g. Kronenberg et al., 2006; Pereira et al., 2014; Van Praag et al., 2005). While in older humans levels of aerobic fitness correlate with hippocampal volume (Erickson et al., 2012), and one intriguing study show that increased levels of BDNF associated with exercise improved rodent's performance in the Morris Water Maze (Vaynman et al., 2004), suggesting that the effect improved context-dependent learning.

Perhaps the most optimistic set of results are those that show that exercise has a prophylactic effect on age-related memory decline. In humans exercise is firmly associated with a decreased risk of mild cognitive impairment (Geda et al., 2010). In rodents, increased levels of Insulin-Like Growth Factor I (IGF-1) that result from treadmill exercise (although not voluntary wheel-running)[2] - reduce the effects of neurotoxins on the hippocampus (Ploughman et al., 2005).

Despite rapid advances in knowledge, at present, the precise causal mechanisms for each of the neurocognitive changes have not yet been fully determined. Furthermore, the best form of exercise to generate improvement remains unclear. Previous research has strongly advocated a link between aerobic fitness and cognitive function; one possible mechanism for this might be the increased energy expenditure resulting from moderately-vigorous physical activity, since community-based research with cognitive unimpaired elderly women has shown that those with the highest exercise frequency and who expended the most kilocalories were least likely to experience cognitive decline (Yaffe, Barnes, Nevitt, Lui,

[2] The effects of voluntary and forced wheel running on these measures often differs, and this may in part be attributed to the added stress associated with the latter procedure (Carruthers, Zampieri, & Damiano, 2014).

& Covinsky, 2001). Randomised trials have also shown that high-intensity, progressive resistance training can improve global cognitive function, and executive functioning over 18 months (Singh et al., 2014). Benefits of combination training (e.g. combining aerobic and resistance exercise) have also been indicated (Snowden et al., 2011).

Nevertheless, it is still unclear which approaches to exercise are most important for targeting particular cognitive functions. Research studies often include interventions that are based on aerobic exercise and/or resistance training at various intensities. Exercise in older age is a complex issue, since poor physical function and chronic disease can preclude the participation of many older adults in structured or higher-intensity exercise training programmes. Whilst increased aerobic fitness and resistance training have been associated with the prevention or delay of cognitive decline, this is not always feasible in some settings since the majority of older adults are sedentary and many have difficulty with engagement in, and maintenance of exercise programmes. For healthcare practitioners, promotion of age-appropriate, easily accessible, and socially engaging physical activities is therefore paramount.

As such, there is an emerging body of research that focuses on the relationship between non-exercise, lifestyle physical activities (eg. 'mind-body' approaches; or encouraging active lifestyles) and whether they have similarly beneficial effects on neurocognitive outcomes. For example, moderate-intensity low-impact forms of physical activity, which are based on cognitive enrichment 'mind-body' strategies (such as Tai Chi), have shown potential for improvement in measures of executive function, language, learning, and/or memory (Blake & Hawley, 2012; S. M. Miller & Taylor-Piliae, 2014). Studies of objectively measured habitual physical activity behaviour have shown that a greater amount, duration and frequency of daily walking activity may be associated with larger hippocampal volume in older women (Varma, Chuang, Harris, Tan, & Carlson).

Whilst it is generally agreed that physical exercise maintains or improves cognitive function, further work is required to fully understand both the causal mechanisms for observed cognitive changes, and the type, dose and intensity of exercise that is required to generate clinically significant changes in cognition.

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