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**From depression to where are my keys:
unlocking the behavioral disorders of old
age**

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Understanding how memories are stored and retrieved is one of the glittering scientific prizes of the 21st Century. In mammals, the hippocampus appears to be required for encoding memory, but how and where in the brain long-term storage occurs is still a mystery. Nevertheless, storage is presumed to reside in neural circuits mediated by selective reinforcement and inhibition of synaptic strength. Strangely, because of cloning and sequencing our molecular understanding of learning and memory far exceeds our cellular insights. However, knowledge of the mechanisms of decreased memory function in old age is still in its infancy.

In the special section on translational research in this issue, the reports all deal with disorders of memory in old age. In a pair of papers, Murphy and colleagues probe the most benign of these afflictions, normal age-related cognitive decline, using behavioral, molecular and electrophysiological studies in mice. About 40% of people over the age of 65 suffer from some sort of age related cognitive impairment, independent of overt pathology such as Alzheimer disease. Thus, this form of cognitive impairment is a topic of considerable theoretical and practical importance. While normal age-related cognitive decline has been studied in humans, the power of the mouse as a model organism has yet to be applied to this problem. Most importantly, mice offer the possibility of genetic studies through the use of both engineered animals and genetic mapping using the diverse phenotypes of inbred strains accumulated over many decades of basic research.

In their first paper Murphy et al. used the workhorse inbred mouse strain C57BL/6 to examine the spatial learning abilities of both young and old mice (1). In this case, young means 4-6 months old and aged means 22-24 months, very different from what counts as young and old in humans. However, since mice usually do not live much beyond 2.5 y the authors' choice of age is suitable. Two different tests of spatial learning were employed, the Morris water maze and the delay win-shift version of the Olton radial arm maze. Interestingly the extent of age related impairment differed between the two tasks. Careful controls established that the patterns of memory deficits were not due to a non-specific sensory or motor impairment. The contrasting results from two tasks may be due to inherent performance differences in dry land and wet maze tests in rodents. Nevertheless, the differing results may eventually also lead to clues about the mechanisms of normal age-related cognitive decline.

There is increasing evidence that a number of age-related changes in neuronal function may be due to dysregulation of activity dependent neuronal free calcium. The most direct data comes from imaging experiments showing an increase in free calcium in neurons from aged rats. In their second paper, Murphy et al. explored the role of calcium in normal age-related cognitive decline using electrophysiology (2). Calcium homeostasis was evaluated in hippocampal nerve cells from young and aged mice using two separate techniques, slow afterhyperpolarization and voltage-dependent calcium channel mediated long-

term potentiation. In addition, the authors examined changes in the phosphorylation state of the predominant L-type calcium channel in the forebrain caused by the cAMP dependent protein kinase. Phosphorylation of this calcium channel strongly enhances its activity and the authors hypothesized that its phosphorylation may account for the major part of the age-related increase in activity-dependent neuronal calcium flux. Interestingly, both measures of calcium revealed an increase in activity dependent calcium influx in the aged mice compared to young. However, Western blots showed that the change in calcium physiology was not related to the phosphorylation status of the channel. This study is a fascinating first glimpse into the molecular physiology of age-related cognitive decline using mice, which may in the future provide novel therapeutic insights into this all too frequent condition.

While the inconveniences of age-related cognitive decline are usually accepted with a shrug of the shoulders (3), the same is not true for Alzheimer disease and its unpleasant cousin Lewy body dementia. These conditions cause considerable morbidity and mortality and the socioeconomic burden from these diseases can be expected to increase as the population ages in the industrialized nations. Sharp insights into the causation of Alzheimer disease have come from identifying the genes involved in rare monogenic forms of the disorder (4). However, the origins of the more common and complex forms of the disease due to the conspiracy of many genes and the environment have remained elusive apart from one exception. That exception is the $\epsilon 4$ allele of the apolipoprotein E

(APOE) gene, which was found to be a strong risk factor for developing the disease in the general population (5). This finding immediately brought the worlds of dementia and lipid metabolism into close proximity. However the role of the APOE ϵ 4 allele in other forms of dementia such as Lewy body dementia remains relatively unexplored.

In their manuscript, Borroni et al. investigate the relationship between APOE genotype and cholesterol levels in both Lewy body dementia and Alzheimer disease (6). The authors found that the ϵ 4 allele was more frequent not only in Alzheimer disease patients but also those with Lewy body dementia. However, the effects of cholesterol was different between the two groups, with hypercholesterolemia and the ϵ 4 allele together increasing the risk of Alzheimer disease but having no effect on Lewy body dementia. Suggesting that the findings may be specific, no differences were found in comorbid conditions such as hypertension, ischemic heart disease or diabetes between the Alzheimer disease, Lewy body dementia and control groups. The investigation confirms previous findings relating the APOE ϵ 4 allele and Lewy body dementia but also suggests that the APOE-cholesterol pathway has distinct effects on the two forms of cognitive impairment. Consequently, treatment of hypercholesterolemia might have differential benefits on the progression of these related but contrasting disorders. As genotyping technologies continue to improve in speed and power, we can expect many more such studies in the future illuminating the relationship between genes and environment in psychiatric disorders.

Although the dementias represent a major share of the psychiatric burden in the elderly population, other behavioral disorders also play their part. One of the most prominent of these is depression, whose malign influence is a frequent accompaniment of the dementias. Although we are beginning to have the inklings of a genetic understanding of age related cognitive impairment our molecular knowledge of depression is rudimentary. Wilkins and colleagues examined the role of vitamin D deficiency in both depressed mood and impaired cognitive performance in older adults (7). Vitamin D deficiency has a prevalence of between 25-50% in adults of greater than 60 y. Thus, the number of individuals suffering from this deficiency is potentially large. Since the main source of vitamin D is from the skin as a result of sunlight, nutritious diets may not be sufficient in preventing deficiency. There is evidence relating vitamin D deficiency and Alzheimer disease, while an association between vitamin D deficiency and mood disorders has been debated. A direct role of vitamin D in neural function has been suggested based on the presence of vitamin D receptors in the brain, decreased expression of these receptors in the hippocampus in Alzheimer disease and demonstration of neuroprotection by vitamin D in vitro.

After adjusting for age, race, gender and season of vitamin D determination, Wilkins et al. found that deficiency of the vitamin was associated with the presence of depressive symptoms. In addition, vitamin D deficiency was associated with decreased performance in two out of four measures of cognitive

performance. Like all correlative studies, this investigation does not demonstrate cause and effect relationships between vitamin D and cognitive performance or depressive symptoms. Nevertheless, the findings encourage further investigation into the potential role of vitamin D supplementation in the elderly population with disorders of cognition or mood.

In addition to the relation between cholesterol metabolism and Alzheimer disease, emerging data suggests that another metabolic disease, type 2 diabetes, may also result in impaired cognition. Like the relation between vitamin D and cognition and mood, evidence suggests that the relation between type 2 diabetes and impaired cognition may be due to a direct effect of insulin on the brain. The earlier stages of type 2 diabetes are characterized by insulin resistance and hyperinsulinemia. The increased levels of insulin may act on insulin receptors expressed throughout the brain, especially in the hippocampus, a critical cellular locus for memory. In animal models, injection of insulin inhibits neuronal firing. There is also a decreased activity of choline acetyltransferase the source of the neurotransmitter acetylcholine, which is thought to play an important role in enhancing learning and memory. In animal and human studies, increased insulin levels raises amyloid β protein, thought to be a key insult in the development of Alzheimer disease. One mechanism may be due to competitive inhibition of amyloid β protein degradation by the insulin degrading enzyme, which was the first protease demonstrated to degrade amyloid β protein and also the main enzyme responsible for insulin degradation in the body. However, there

is little direct epidemiological data examining the role of insulin levels in dementia. Most existing studies do not effectively disentangle the effect of insulin and the numerous accompaniments of diabetes.

Okereke et al. had previously examined cognitive function in older women without diabetes (8) and in this special issue extend their study to older men without diabetes (9). The investigation is a prospective cohort design using 367 men who provided blood samples in 1982. At that time the subjects had no lifetime history of diabetes and a mean age of 57 y. Insulin secretion was evaluated by quantitating plasma C-peptide in the stored blood samples. There was a broad distribution of C-peptide levels, with the median level in the top third of the study population being four times higher than the bottom third. Beginning in 2001, an average of 18 y after the blood collection, the authors administered tests of cognition by telephone. An effect of C-peptide was found for one of the tests of cognition, with men in the top third of C-peptide levels performing significantly worse than those in the bottom. The impact on performance was equivalent to an effect of 6 y in age. Combining the results from all the cognitive tests confirmed this trend, although the results were no longer statistically significant. While much additional work is necessary to confirm and extend these findings, this study is a warning on the possible future effects of the current diabetes epidemic on the prevalence of Alzheimer disease in the aging population.

Thus, the studies in this special translational issue range from basic studies in mice to epidemiological studies in humans. Equally striking are the diversity of methodologies employed, from rodent behavioral analysis to neurophysiology, from human molecular genetics to epidemiology and endocrinology. This multiplicity of techniques mirrors the disorders themselves, from depression to normal age-related cognitive decline, from Alzheimer disease to Lewy body dementia. Thus, the wide variety of approaches brought to bear on the behavioral disorders of old age stem from the broad and wide ranging nature of this most exciting and vibrant branch of biomedicine and augur well for its future.

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