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Memory and Genes – is there an Association?

In recent years, there has been an increasing interest in examining the role of genetic markers when it comes to cognitive functions. Researchers in behavioural genetics have made great efforts to make this area known to researchers in cognitive psychology. Plomin (1999; Plomin & Crabbe, 2000; Cardon, Faulkner, DeFries & Plomin, 1992) have been some of the most influential contributors in this respect. This new development has aroused great interest among cognitive psychologists, who now see genetics as an important tool to extend current knowledge about cognitive functions. The basic question in this kind of research is to determine whether, and, if so, to what extent genes can be associated with various cognitive functions. If such associations can be established, the question is to find out what the underlying mechanism is.

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In this paper, I will describe some studies that have focused on potential associations between some genes and human memory function. Nilsson et al. (1996) studied associations between six serum protein polymorphisms and two forms of memory, episodic and semantic memory. These polymorphisms were complement C3, haptoglobin, properdin factor B, orosomucoid, group-specific components, and transferring C. We predicted that complement C3 and the acute-phase reactant haptoglobin should be of special interest as immune response factors. As expected we found strong associations between these two markers and episodic memory suggesting that immune response factors may be of importance in preserving episodic memory. In the haptoglobin system, there was evidence of a primary phenotypic association involving heterozygotes. An association involving heterozygotes indicates that linkage disequilibrium with alleles at other loci influencing memory function is unlikely. The association with complement C3 alleles may be due to either linkage disequilibrium or functional involvement at the protein level. It is noteworthy that the genetic associations demonstrated in this study hold for episodic memory but not for semantic memory. These two memory systems differ in several ways. Episodic memory is responsible for remembering personal events that are defined in time and space. For example, in order to remember what was served for dinner last Saturday, one has to travel backwards in time to recall where one had dinner. The temporal and spatial cues emerging in doing this may then help in retrieving what was served for dinner. This travel backwards in time requires a conscious recollection of the dinner episode on Saturday. Such a conscious recollection of a certain study episode is not required for semantic memory, which is a memory system for general knowledge. For

example, in order to recall that the chemical formula for regular table salt is NaCl, it is not necessary to travel backwards in time to a certain episode in school when this piece of information was, most likely, first encountered. It is more likely that the response is generated by knowing implicitly that table salt is a chloride of sodium. At any rate, the finding of this dissociation between episodic and semantic memory is an important result for memory theory because it adds to other dissociations between episodic and semantic memory, thereby providing converging evidence for the differentiation between these two memory systems.

Another gene that we have studied in our own laboratory is ApolipoproteinE (APOE). This gene is located on chromosome 19. Its primary role is to influence the metabolism of lipids, primarily cholesterol. There are three alleles of this gene: ε2, ε3 and ε4. The most common form is ε3 occurring in about three-fourths of the population; ε2 and ε4 occur in about 10% and 15% of the population, respectively. The three alleles of APOE form six possible genotypes, 22, 23, 24, 33, 34, and 44. Allele ε4 is a risk factor for cardiovascular disease in middle age and for Alzheimer's disease in old age. The pathophysiological mechanism for the "bad" ε4 allele is not yet fully understood. One claim is that ε4 does not protect key neuronal structures from excessive phosphorylation, which leads to neuronal degeneration. Another claim is that APOE is involved in the continuous synthesis and repair of cellular membranes. Stone et al. (1998) demonstrated that the ε2 and ε3 isoforms of APOE serve an important role in this repair work, whereas the ε4 allele is less successful in this work. Persons with the ε2 and ε3 alleles receive necessary neuronal protection and are much less likely to develop cardiovascular disease and Alzheimer's disease.

In the Betula Study (Nilsson et al., 1997) we excluded persons with dementia and cardiovascular disease in order to examine whether the three APOE alleles have any direct influence on memory functions in healthy individuals in adulthood and old age. The results in several studies (Nilsson et al., 2001, 2002, in press) demonstrated that indeed the carriers of the ε4 allele show a lower episodic memory performance than carriers of the ε2 and ε3 alleles in old age (65-80 years). In Nilsson et al. (in press), we were able to demonstrate two additional, important findings. One finding was a dose effect showing that carriers of two ε4 alleles performed at the lowest level. Specifically, carriers of two ε4 alleles fail more profoundly in acquiring and recollecting episodic information than carriers of one ε4 allele, who in turn fail more than carriers of non-ε4 alleles. Although such a dose effect may support the notion that APOE has a direct effect on cognitive function, the dose effect per se does not necessarily differentiate this hypothesis from the alternative hypothesis of more preclinical dementia cases among the carriers of the ε4 allele despite the fact that care was taken to minimize the risk of including preclinical cases. However, the hypothesis of a differential potency of the APOE alleles in triggering (directly or indirectly) self-initiated cognitive processing needed for demanding memory tasks is certainly compatible with the dose effect demonstrated here. Another finding was that middle-age carriers of the ε4 allele showed a better performance than carriers of the ε2 and ε3 alleles in episodic memory tasks, and especially so in tasks requiring recall rather than recognition of information. The explanation of this unexpected result is not yet clear. The findings would seem to

suggest that a gene may have different functions at different stages in life. From an evolutionary perspective, it is difficult to imagine that one allele of a gene would have as its only function to lower cognitive function in old age. The present data may indicate that the ε4 allele indeed has some other, yet unknown, function, which is prominent earlier in life. A speculative hypothesis is that the ε4 allele may have a basic positive effect on the organism in early years and that this positive effect has a cost to the organism by means of exhaustiveness. When life expectancy was lower, this effect of the ε4 allele was not observed or noticed, but as life expectancy increases, it is increasingly devastating to the human mind and body. Obviously, more research is needed to explore this issue further.

A third approach in the Betula Study to examine this issue is about transmitter related genes. In the prefrontal cortex, the catechol O-methyltransferase (COMT) gene is essential in the metabolic degradation of dopamine, a neurotransmitter implicated in cognitive functions. In a 5-year longitudinal analysis, de Frias et al. (in press) examined the effect of a polymorphism in the COMT gene on individual differences and changes in memory in adults aged 35-85 years. De Frias et al. reported that carriers of the Met/Met genotype (with low enzyme activity) performed better on episodic memory, as compared to carriers of the Val allele (with higher enzyme activity). The COMT gene was not significantly related to semantic memory. Division of episodic memory into its recall and recognition components located the difference with respect to episodic recall; no gene-related differences were observed in recognition. The memory dissociation is parallel to that observed with carriers of the ε4 allele of APOE. The effect of COMT on memory was similar for middle-aged, young-old, and old-old adults and held across a 5-year period. Thus, the COMT gene is another candidate gene for memory functioning in adulthood and old age.

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