Genetic Dissection of Learning and Memory in Mice

Yann S. Mineur,[1, 3] Wim E. Crusio[1] and Frans Sluyter[2]

[1]*Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School Worcester, MA 01604, USA;* [2]*SGDP Research Centre, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, UK,* [3] *Yale School of Medecine, Dept. of Psychiatry,New Haven, CT 06508, USA*

ABSTRACT

In this minireview, we discuss different strategies to dissect genetically the keystones of learning and memory. First, we broadly sketch the neurogenetic analysis of complex traits in mice. We then discuss two general strategies to find genes affecting learning and memory: candidate gene studies and whole genome searches. Next, we briefly review more recently developed techniques, such as microarrays and RNA interference. In addition, we focus on gene-environment interactions and endophenotypes. All sections are illustrated with examples from the learning and memory field, including a table summarizing the latest information about genes that have been shown to have effects on learning and memory.

INTRODUCTION

Learning and memory has always been one of the most captivating fields in the life sciences. As in most—if not all—complex traits, genes play an important role in the regulation of learning and memory. Already in the 1920s, Tryon (1929) showed that rats could be selectively bred for their performances in learning a complex maze to find food, thereby establishing a genetic component to learning and memory. Questions concerning the nature of these genes and the proteins they encoded remained a mystery until the early 1970s, when Benzer and Kandel's groups launched their respective studies on two invertebrate models. Whereas Benzer et al. (Tully, 1996) carried out genetic screens in Drosophila, Kandel and colleagues (Mayford & Kandel, 1999) used Aplysia, a marine snail, to identify the neuronal circuitry controlling learning and memory. Using different techniques, in time both studies converged, which resulted, among others, in the discovery of the cAMP response element binding protein (CREB) (Silva et al., 1998). In both species, this cAMP-responsive transcription factor plays an important role in the conversion of short-term to long-term memory. An obvious next step was to extend these findings to the more complex learning taking place in the mammalian brain.

Of all mammalian models, the mouse is presently the most popular one in the search for genes underlying complex traits like learning and memory. Three reasons for this development are

1. the rise of molecular biology,
2. the suitability of the mouse embryo to specific genetic manipulations, and
3. the large number of available mouse strains.

The combination of these factors has resulted in an increasing number of genetically modified strains. Knockouts, knockins, and transgenics now belong to the tool kit of most behavioral neuroscientists,

Reprint requests to: Y.S. Mineur, Yale School of Medecine, Department of Psychiatry, 34 Park Street, 3rd Floor Research, New Haven, CT 06598, USA; e-mail: yann.mineur@yale.edu

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and the application thereof has revolutionized the genetic dissection of learning and memory.

We start this minireview with a general outline of the neurogenetic analysis of complex traits in mice because the approach and methodology to dissect learning and memory are similar to those applied in the genetic dissection of other complex traits. Subsequently, we discuss two general strategies to identify genes affecting learning and memory: candidate gene studies and whole genome searches. Next, we discuss the more recently developed techniques, including microarrays and RNA interference and briefly pay attention to gene-environment interactions. Last, but certainly not least, we focus on endophenotypes. All sections are illustrated with examples from the learning and memory field.

FROM TRAIT TO GENE AND BACK: A GENERAL OUTLINE

Before boarding the latest flight to genetic wonderland, we should address two important issues. First, what is the exact phenotype that is to be dissected genetically? Like most complex traits, learning and memory can be measured in many ways. This approach is true not only for humans but also for animal species, including mice, for which multiple learning and memory pa radigms exist, varying from complex problem-solving tasks to simple learning tasks (for an enumeration see, for instance, Crusio, 1999). The choice of test is, therefore, crucial because the genetic analysis of one learning and memory task will lead to the identification of a different set of underlying genes than the dissection of another task. It is, for instance, very well possible that a gene explaining variation in Morris water-maze learning will not explain variation in radial-maze performance. On the other hand, there will also be genes that affect both types of learning. Clearly, the optimal strategy would be to refine the trait under study by using a combination of multiple measures of the trait that best capture a common underlying genetic factor. An example of such an approach is the ongoing search for the genes influencing the infamous *g* factor. This factor refers to the substantial overlap that exists between individual differences in diverse cognitive processes in humans, although its existence in mice is more controversial (Galsworthy et al., 2002; Locúrto et al., 2003). Importantly (see below), the *g* f actor appears to be substantially heritable (for more information about the *g* factor, see Galsworthy et al., 2002; Plomin, 1999, 2001; Plomin & Craig, 2001; Plomin & Spinath, 2002; Williams et al., 2002).

An important caveat in the study of learning and memory is that such processes cannot be measured directly but rather are inferred from performance variables. This approach can sometimes lead to interpretational difficulties. For instance, in the water-maze navigation task, motor coordination deficits (or differences) could increase the escape latency of the tested subjects, a measure that is often used as an index of memory performance. Likewise, stress and anxiety levels can also shape the results of learning tasks (an anxious animal would freeze for instance) but need not actually involve learning capabilities *per se*. In fact, a detailed analysis of mouse behavior in the Morris maze reveals that differences in spatial learning abilities explain only about 15% of the total behavioral variation observed (Wolfer et al., 1998). Another problem that can be encountered in tasks depending on visual abilities (such as the water navigation or radial maze tasks) is that blind animals can perform poorly because they are unable to orient themselves. Nevertheless, blind animals sometimes do not perform significantly worse than normal subjects (Lindner et al., 1997). In addition, the tests can be designed in such a way that they tax the visual system as little as possible, for instance by placing distinctive visual cues close to the maze (Crusio, 1999a). For instance, animals carrying a mutation causing retinal

degeneration (such as C3H mice) have a greatly reduced visual acuity and become blind eventually. By making a spatial radial maze task visually as easy as possible and testing animals at an age of about 3 months, when they are not yet completely blind (Nagy & Misanin, 1970), C3H animals can learn this task very well (Crusio et al., 1987; Schwegler et al., 1990). In short, the results of behavioral phenotyping have to be interpreted cautiously and, if necessary, adequate control tests should be performed to avoid potential artifacts in phenotypic analyses (Crawley, 2000).

The third issue to address is to establish whether the complex trait of interest—for example, learning and memory—is under the influence of genetic variation. To this end, two strategies are used in animal studies. The first is the comparison of inbred strains that are generated by repeatedly mating close relatives. Animals of the same inbred strain are like cloned individuals—they are almost genetically identical after a minimum of 20 generations of inbreeding (many inbred strains have been inbred for over 100 generations; Green, 1966; Staats, 1985). Within an inbred strain, nearly all trait variability will be caused by the environment, whereas differences among strains will be virtually genetic in origin (apart from maternal influences; see for example, van Abeelen, 1980). Thus, when in a controlled testing environment multiple strains are compared for a specific behavior, the extent to which among-strain differences exceed the pooled within-strain variability provides a test of the existence of genetic influence. A good illustration of the variation present in inbred strains is provided by radial-maze learning in mice. This is a task that mice will learn readily, as fast as or even faster than most rat strains (Whishaw & Tomie, 1996). As shown in Fig. 1, radial-maze performance varies enormously among strains and the between-strain variation is much larger than that within strains.

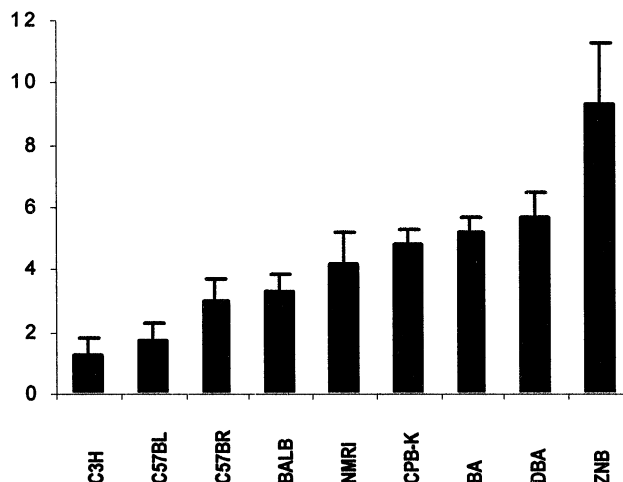

Fig. 1: Mean numbers of errors (repeat arm entrances) made by male mice from nine different inbred strains in the eight-arm radial maze on the fifth trial, one trial/day, six males per strain (data from Schwegler et al., 1990).

Another useful technique to show that a specific trait is genetically influenced is selective breeding or artificial selection. This technique is based on the observation that the offspring of animals with a desired quality are more likely to demonstrate that quality than will the progeny of random individuals. Mice can be bred for varying behaviors like learning performances or aggression. Usually, animals are selected for opposite directions of the desired behavior (bidirectional selection), such as the previously mentioned 'maze-bright' and 'maze-dull' rat lines (for recent information on these lines, but also on learning and memory in inbred strains, see Plomin, 1999, 2001; Plomin & Spinath, 2002). To our knowledge, such selected mouse lines do not exist.

If heritability has been demonstrated, then searching for the actual genes that explain the genetic variation becomes feasible. Finding the genes, however, is a difficult task for several reasons, one being the vast number of genes involved. Generally, two distinct approaches can be distinguished.

- *Candidate gene studies* can be used when previous experiments have identified a specific gene that codes for a protein involved in a pathway known to be relevant to the variation of the trait under study. This approach applies only to genes with known location and function and to pathways that we already partially understand.
- *Whole genome searches*. When no prior information exists about the genes affecting the trait, then whole genome searches are the standard way to go (Phillips et al., 2002). The searches are used to establish the most likely location in the genome of genes that influence the trait under study. Such genes can be those that were identified but not suspected as linked to the trait, or they may be new genes altogether. Until now and despite much effort, this strategy has resulted in the identification of only a very few genes affecting behavior (for an exceptional example, see Fehr et al., 2004; Shirley et al., 2004), but the development of new tools (for example, vastly expanded sets of recombinant inbred strains; Peirce et al., 2004) gives hope that such efforts will be more successful in the future.

Once a gene has been identified, several strategies are available to explore the exact biological pathway by which the gene influences variation in the neurophysiological or behavioral trait, including, among others, gene expression studies, transgenic approaches, and RNA interference. Also possible is the performance of *gene-by-environment* studies, in which the differential effects of environmental manipulation on different genotypes can be directly tested. Most important, the structural (for example, size of the hippocampal cell population) and functional aspects of the brain (for example, electrophysiological response to a stimulus) can be compared to uncover the actual biological pathways connecting genes and behavior.

Candidate gene studies

Two fundamentally different approaches are used to study candidate genes in mice. The first approach makes use of naturally occurring variants of the gene(s) under investigation and is similar in design to classic association studies in humans. In mice, however, the availability of specific strains[1] and genomic data[2] allows us to scale up mutation detection and screen through several genes for variation at the same time. Hence, instead of individually following up the loci identified as relevant to a particular trait, a systematic survey can identify multiple alleles of many genes and entire pathways associated with the trait of interest. Such an approach is currently in progress

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[1] see for example, www.jax.org
[2] see for example, www.ensembl.org/Mus_musculus and www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=mouse_chr.inf)

at the Institute of Psychiatry in London, where Leo Schalkwyk and coworkers are testing a large number of male mice from a heterogeneous stock in various learning and memory paradigms. This study focuses on more than 50 target genes from the serotonin, dopamine, and N-methyl D-aspartate (NMDA) receptor signaling pathways, which are known to be associated with learning and memory.

The second approach is aimed at actively manipulating the gene in question. Genes can, for instance, be inactivated (*knockout models*) or an extra copy or copies can be inserted (*transgenic animals*) to investigate the scope of the gene's effects and its way of operation. The development of targeted gene disruption has been one of the more important advances in mouse behavioral genetics. The aim is to inactivate a gene of interest selectively (namely, to disrupt a targeted gene) and to compare this so-called knockout mouse with a control or wildtype animal that has all its genes intact. The observed differences can then be attributed to the gene in question. Hence, by comparing the behavior and underlying neuronal processes of knockouts and wildtypes, one can deduce the function of the gene and determine its effects on complex traits. Many genes that affect learning and memory have been identified using the knockout technique (see Table 1).

Two facts are worth mentioning. First, as is sometimes believed, knocking out a gene does not necessarily lead to impairment in learning and memory. Sometimes an improvement in learning and memory can be observed as well. Second, sometimes the same mutation can be found to have opposite effects in different tests (for example, Dere et al., 2003), which once again emphasizes the importance of the definition of the trait.

A number of comments on knockout studies should be made. First, the possibility always exists that the knockout and the wildtype differ in more than one gene. This so called 'flanking gene' problem results from the technical procedure *per se* and can lead to false positives or to false negatives (Crusio, 2004; Wolfer et al., 2002). A second problem is the genetic background of the knockout, which is either randomized or, at best, homogeneous. In the latter case, the knockout is repeatedly crossed back to mice from the same inbred strain. After a number of back-crosses, usually 10 or more, in which the presence of the mutated allele is checked in every generation, the background is said to be homogeneous. A comparison between the knockout and the inbred strain will then yield information on the effect of the knocked out gene on a specific genetic background.

Also possible, however, is that an inactivated gene affects a trait on one background, whereas it has no effect or a different effect on another background. This phenomenon, in which (a) a gene(s) influence(s) the effect of another gene (namely, the background genes interact with the knockout gene) is called *epistasis* and has been found in animal models of mental retardation as well. A good example is provided by inactivation of the *Fmr1* gene. The lack of expression of the human homolog is associated with the development of the Fragile-X syndrome, leading to mental retardation. On a C57BL/6 background, knocking out the *Fmr1* gene leads to a smaller intra- and infrapyramidal mossy fiber projection (Mineur et al., 2002). The size of this projection is strongly correlated with spatial learning abilities in mice (Crusio et al., 1993; Schwegler & Crusio, 1995) and, indeed, Mineur and colleagues (2002) reported impairment in radial-maze learning in their mice. When the very same mutation was backcrossed onto an FVB background (Ivanco & Greenough, 2002), the mutants were found to have increased sizes of their intra- and infrapyramidal mossy fiber projections.

Perhaps the third comment is the most profound. Traditional knockouts are constitutive—they lack expression of the gene in every cell and tissue and from conception on. This phenomenon means that in practice one cannot study the effects of genes that on the one hand affect complex traits but that are also essential for normal development.

TABLE 1

Single-gene studies of learning and memory in mice

gene	Study Type	learning modification	Learning type	reference
5-HT1BR	KO	↓	Spatial (WN)	Buhot *et al.*, 2003
AC	Expression study	↓	Spatial (RAM)	Mons *et al.*, 2003
Adra2c	KO	↓	T-maze	Tanila *et al.*, 1999
α MUPA	Tr-overexpres.	↓	Spatial (WN)	Meiri *et al.*, 1994
α2c-AR	Tr-overexpres.	↓	Spatial (WN)	Sallinen *et al.*, 1999; Bjorklund *et al.*, 2000
APP	Tr-overexpres.	↓	Spatial (WN, T-maze)	(Chen *et al.*, 1998; Holcomb *et al.*, 1999; Chishti *et al.*, 2001; Corcoran *et al.*, 2002 ; Berger-Sweeney *et al.*, 1999
Ar	KO	↓	Spatial (Y-maze)	(Martin *et al.*, 2003)
AR- α(1β)	KO	↓	Passive avoidance	(Knauber and Muller, 2000)
Arc	QRT-PCR		ns	(Dickey *et al.*, 2003)
Atf4	Tta	↓	Maze	Chen *et al.*, 2003)
BCL-2	Tr-overexpres.	↓	Spatial WN)	Nakamura *et al.*, 1999)
Bdnf	Tr-overexpres., infusion	↓	Avoidance, Spatial WN	Linnarsson *et al.*, 1997; Croll *et al.*, 1999)
β2 nAChR	KO	↓	Passive avoidance	Picciotto *et al.*, 1995)
Bsg	KO	↓	Spatial Y-maze and WN)	Naruhashi *et al.*, 1997)
Calcineurin	Tta	↓	Spatial Hole board)	Mansuy *et al*, 1998)
C/EBP	Tta	↓	Maze	Chen *et al.*, 2003)
CaMKIIα2	KO	↓	Spatial WN), Fear cond., Object recog.	Silva *et al.*, 1992; Frankland *et al.*, 2001; Miller *et al.*, 2002; Dickey *et al.*, 2004)
Cbp	Cre-lox	↓	Fear cond.	Oike *et al.*, 1999

TABLE 1 (CONT'D)

gene	Study Type	learning modification	Learning type	reference
Cck2R	KO	↓	Spatial Y-maze	Dauge *et al.*, 2001
c-fos	Cre-lox, Anti-sense	↓	Spatial WN, Fear. cond.	Brennan *et al.*, 1992
	Expression study			Fleischmann *et al.*, 2003; Strekalova *et al.*, 2003
Cln8	Spontaneous mutation	↓	Fear cond.	Bolivar *et al.*, 2002
COX-2	Tr-overexpres.	↓	Spatial memory ; Avoidance	Andreasson *et al.*, 2001
CREB	KO, Cond. KO	↓	Taste aversion Spatial WN, Fear cond., Avoidance	Gass *et al.*, 1998; Impey *et al.*, 1998; Pittenger *et al.*, 2002; Balschun *et al.*, 2003
CuZn-SOD Sod2	Tr-overexpres.	↓	Spatial WN, Avoidance	Gahtan *et al.*, 1998
D1A	KO	↓	Spatial WN	El-Ghundi *et al.*, 1999
DARPP-32	KO	↓	Discriminated operant task	Heyser *et al.*, 2000
DAT	KO	↓	Social recog.	Spielewoy *et al.*, 2000; Rodriguiz *et al.*, 2004
Dcx	KO	↓	Fear cond.	Corbo *et al.*, 2002
EC-SOD	KO, Tr-overexpres.	↓	Spatial RAM	Levin *et al.*, 1998; Levin *et al.*, 2002
Egr-1	Expression study	↓	Object recog.	Jones *et al.*, 2001; Bozon *et al.*, 2003; Bozon *et al.*, 2003; Dickey *et al.*, 2003 Brennan *et al.*, 1992
En-2	KO	↓	Motor learning	Gerlai *et al.*, 1996
eNOS	KO	↑	Spatial WN	Frisch *et al.*, 2000
ERβ	KO	↓	Spatial WN	Rissman *et al.*, 2002
Fe65	KO	↓	Passive avoidance	Wang *et al.*, 2004
Fmr1	KO	↓	Spatial WN and RAM	D'Hooge *et al.*, 1997; Van Dam *et al.*, 2000; Mineur *et al.*, 2002
Fmr2	KO	↓	Fear Cond.	Gu *et al.*, 2002
Fmr2	KO	↓	Fear cond.	Gu *et al.*, 2002

TABLE 1 (CONT'D)

gene	Study Type	learning modification	Learning type	reference
Fxr2	KO	↓	Spatial WN	Bontekoe *et al.*, 2002
Fyn	KO	↓	Spatial WN	Grant *et al.*, 1992
Gabra5	KO, KI	↑	Avoidance; Fear cond.	Collinson *et al.*, 2002; Crestani *et al.*, 2002
Gabrb3	KO	↓	Avoidance	DeLorey *et al.*, 1998
Gal	Tr-overexpres.	↓	Spatial WN, Fear cond.	Wynick and Bacon, 2002; Wolff *et al.*, 2003
GAP-43	Tr-overexpres.	↑	Spatial RAM	Routtenberg *et al.*, 2000
Gdi1	KO	↓	Spatial WN, Episodic.	D'Adamo *et al.*, 2002
GIRK4	KO	↓	Spatial WN	Wickman *et al.*, 2000
GlcAT-P	KO	↓	Spatial WN	Yamamoto *et al.*, 2002
Glp1r	KO	↓	Spatial WN	During *et al.*, 2003
Glucocorticoid receptor	KO	↓	Spatial WN	Oitzl *et al.*, 1997
GluR1	QRT-PCR, KO		Y maze, Spatial WN and RAM	Jia *et al.*, 2001; Reisel *et al.*, 2002; Dickey *et al.*, 2003; Schmitt *et al.*, 2003; Dickey *et al.*, 2004
Hdc	KO	↑	Spatial WN;	Dere *et al.*, 2003
		↓	Obj. discrim.	
Homer-1a	QRT-PCR		ns	Dickey *et al.*, 2003
IAP	KO	↓	Avoidance	Chang *et al.*, 1999
IL-2	KO	↓	Spatial WN	Petitto *et al.*, 1999
IL-2/15Rβ	KO	↓	Spatial WN	Petitto *et al.*, 2002
Junb	Anti-sense	↓	Fear cond.	Strekalova *et al.*, 2003
klotho	KO	↓	Obj. rec., fear cond.	Nagai *et al.*, 2003
Lis1	KO	↓	Spatial WN	Paylor *et al.*, 1999
M1R	Anti-sense	↓	Avoidance	Ghelardini *et al.*, 1999
MAP2	KO	↓	Fear cond.	Khuchua *et al.*, 2003

TABLE 1 (CONT'D)

gene	Study Type	learning modification	Learning type	reference
mGLUR5	KO	↓	Spatial WN, fear cond.	Lu *et al.*, 1997
mGluR8	KO	↓	Spatial WN, fear cond.	Gerlai *et al.*, 2002
MOR-1	KO	↓	Spatial WN and RAM	Jamot *et al.*, 2003; Jang *et al.*, 2003
Mrg1	QRT-PCR	↓	Conditionning	D'Agata *et al.*, 2003
Ncam	Cre-Lox	↓	Spatial WN	Bukalo *et al.*, 2004
Ncx2	KO	↑	Spatial WN, Fear cond.	Jeon *et al.*, 2003
Nf1	KO	↓	Spatial WN	Costa *et al.*, 2001
Ngf	KO	↓	Spatial WN	Chen *et al.*, 1997
NMDAR1	Cond. KO CA3	↓	Spatial WN	Nakazawa *et al.*, 2002
nNOS	Expression study	↓	Olfactory;	Okere and Kaba, 2000
Npas2	KO	↓	Fear cond.	Garcia *et al.*, 2000
NR2A	KO	↓	Spatial WN	Sakimura *et al.*, 1995
NR2B	QRT-PCR			Dickey *et al.*, 2003
NT4	KO	↓	Fear cond.	Xie *et al.*, 2000
NTAN1	KO	↓	Discrimination; Spatial WN	Balogh *et al.*, 2001
Ntan1	KO	↓	Spatial WN and RAM	Kwon *et al.*, 2000
Nur77/TR3	QRT-PCR		ns	Dickey *et al.*, 2003
p25	Tr-overexpres.	↓	Fear cond.	Angelo *et al.*, 2003
PAC1	KO	↓	Fear cond.	Sauvage *et al.*, 2000
Pde1b	KO	↓	Spatial WN	Reed *et al.*, 2002
Psen1	Tr-overexpres.	↓	Spatial WN, Object recog., Y maze;	Vaucher *et al.*, 2002; Pak *et al.*, 2003 Holcomb *et al.*, 1999
PTPα	KO	↓	Spatial WN	Skelton *et al.*, 2003
PTPδ	KO	↓	Spatial WN	Uetani *et al.*, 2000

TABLE 1 (CONT'D)

gene	Study Type	learning modification	Learning type	reference
Rag-1	KO	↓	Spatial WN	Cushman *et al.*, 2003
Ras-GRF	KO	↓	Fear cond.	Finkbeiner and Dalva, 1998; Ghelardini *et al.*, 1999
RIIβ	KO	↓	Cond. taste avers.	Koh *et al.*, 2003
Rin1	KO	↑	Cond. taste avers.	Dhaka *et al.*, 2003
S100β	Tr-overexpres.	↓	T-maze, spatial WN and RAM, Social recog.	Gerlai *et al.*, 1994; Gerlai and Roder, 1996; Winocur *et al.*, 2001
Sca1	KO	↓	Spatial WN	Matilla *et al.*, 1998
Sdc3	KO	↓	Spatial WN	Kaksonen *et al.*, 2002
Sim2	Tr-overexpres.	↓	Spatial WN	Ema *et al.*, 1999
Sstr2	KO	↑	Spatial RAM	Dutar *et al.*, 2002
		↓	Bar press	
Tau	Tr-overexpress.	↓	Fear cond.	Tatebayashi *et al.*, 2002
Th	KO	↓	Fear cond., Avoidance	Kobayashi *et al.*, 2000
Tlx	KO	↓	Fear cond.	Roy *et al.*, 2002
Tmod2	KO	↓	Spatial WN	Cox *et al.*, 2003
TNF-α	Tr-overexpres.	↓	Passive avoidance, Spatial	Fiore *et al.*, 1996; Fiore *et al.*, 2000
TR α1	KO	↓	Fear cond.	Guadano-Ferraz *et al.*, 2003
trκB	Tr-overexpres.	↓	Spatial WN	Saarelainen *et al.*, 2000
Ube3a	KO	↓	Spatial WN	Miura *et al.*, 2002
WAVE-1	KO	↓	Spatial WN	Soderling *et al.*, 2003

Such knockouts simply die at or before birth. In addition, during development compensational processes sometimes work to obscure any effects of the induced mutation.

Joe Tsien (Tsien et al., 1996) at Princeton University was the one who developed a method that gets around these problems. He bumped into this problem when he knocked out various subunits of the NMDA receptor. This receptor is thought to increase the synaptic strength between two nerve cells, a process called *long-term potentiation* (LTP), which is fundamental for learning and memory. Therefore, he engineered NMDA knockout mice that lacked the subunit in a specific section of the hippocampus termed the CA1 region, which appears to be essential for memory. Hence, these so-called conditional, regionally restricted knockouts lack an essential 'memory' gene, but only in a specific part of the brain and nowhere else in the body. As expected, it appeared that these animals demonstrated not only decreased LTP but also poor spatial memory.

Genetic engineering can be used not only to knock out genes but also to insert extra copies of a gene. This method is called *transgenic integration*. One of the more convincing behavioral examples comes from the same laboratory that developed the conditional NMDA knockouts. Instead of inactivating a gene, the researchers inserted an extra copy of another 'memory' gene. The second gene codes for an NMDA subunit called NR2B, which is more strongly expressed in young people and stays open longer than "old people's" NR2A, a phenomenon that might explain the age-related differences in learning and memory. Indeed, transgenic mice that had an extra copy of the gene for this receptor learned better in certain tasks than did normal mice (Tang et al., 1999).

The development of such techniques has certainly deepened our knowledge about the effects of specific genes on complex traits. Nevertheless, besides more pragmatic problems (flanking gene effects, genetic background, and temporal and spatial limits), another, more theoretical pitfall exists. Fundamentally, two types of genes—polymorphic and monomorphic—coexist in nature. Polymorphic genes show natural variation in a population, whereas monomorphic genes do not. Hence, when studying the latter type, we will generally deal with the underlying mechanisms common to most or even to all members of a species. In contrast, when studying polymorphic genes, we are investigating the mechanisms underlying spontaneous individual differences. Analysis of this natural genetic variation, such as the above mentioned 'Schalkwyk approach', can thus enable us to identify genes that modify behavioral and neural function to a degree that is not grossly disadvantageous to the individual carrying such alleles. In short, whereas one type of question addresses, for example, how animals store information, the other type of question asks why in a given task certain individuals perform better than others. One should therefore realize that knockout or transgenic studies generally do not contribute to the explanation of naturally occurring inter-individual variation. In fact, in natural populations, most null mutations are not found to occur spontaneously.

Whole genome searches

Contrary to candidate gene studies, whole genome searches do not require *a priori* knowledge on the biology underlying the complex trait under investigation. Their major strength is that all relevant genes can be detected, including unknown genes (Kruglyak, 1999). In mice, whole genome searches usually start with a cross between strains or lines that differ markedly in the trait under investigation. As a result, the F_1 generation is heterozygous at all genes that differ in the parental strains. From this point on there are two ways to go. Either one can intercross the F_1 generation to obtain an F_2, or one can backcross the F_1 to one of the parental inbred strains. Both

types of crosses—and this is the important message—produce a generation that segregates genetically. In such segregating populations, some animals are homozygous for a particular marker allele from progenitor strain A, some for a particular marker allele from strain B, whereas others are heterozygous.

Markers are just landmarks in the genome; they need not be part of a functional gene. What we have to know, however, is their exact location on the genome (on which chromosome and where on that chromosome) and whether they are informative. The latter refers to the different allelic variants of the marker in question. In the above-mentioned example, for instance, only those markers that differ between progenitor A and B should be genotyped. Markers can be mutations in a single base pair (single nucleotide polymorphisms or SNPs) or a variable number of repeats of two or more base pairs (microsatellites).

When a particular marker is situated near a gene influencing the trait of interest, then the marker and the gene will more likely be transmitted together (co-segregate) to the next generation than if they are distant or on different chromosomes. Hence, the closer the marker and the gene are physically, the chance of linkage between the marker and the gene increases. By examining many individuals and by correlating the presence of certain marker alleles with the score of these animals for the trait of interest, one can identify chromosomal regions that contain one or more of the genes contributing to the phenotypic difference. These chromosomal regions are called *quantitative trait loci* (QTLs) because they are likely to result in dimensions (quantitative continua) rather than disorders (qualitative dichotomies; Plomin et al., 1994). Linkage analysis assigns a probability value (expressed as LOD scores) to all markers, and a LOD-score profile is obtained for each chromosome. Evidence for linkage is said to be present when the maximal LOD-score exceeds a predefined threshold, which depends on the size of the genome and the number of genotyped markers.

Success in detecting QTLs largely depends on the number and location of the markers genotyped, on the effect size of the QTL, and on the number of animals used. In an ideal experiment, the two progenitor strains should differ not only phenotypically to a large extent but also genetically. Genetically distinct progenitor strains make it more straightforward to choose and maximize the number of markers to be genotyped. As much as possible, markers should be chosen that are evenly dispersed throughout the entire genome. The more markers genotyped and the more they are equally scattered over the genome, the smaller the chromosomal region that can be shown to harbor the gene(s) of interest (namely, the narrower the QTL). This restriction is vital because it makes the next step (fine mapping, see below) less demanding.

The effect size is also of critical importance as genes are generally found more easily if they explain more of the variance in a trait. Gene finding is, therefore, relatively simple if only a single gene affects the trait. In such instances, a simple Mendelian segregation of a limited number of phenotypes is observed for all possible genotypes at a specific locus. Many rare diseases or disorders (but also Huntingtons Disease and the Fragile X Syndrome, which affect cognition) are caused by defects in a single gene only, and the genes in question were mapped through linkage analysis even before many of the currently used sophisticated molecular-genetic techniques became available. Unfortunately, most complex traits—learning and memory are no exception—are influenced by many genes. Consequently, most if not all these polygenes have only a small effect on the trait in question and are therefore difficult to detect through linkage analysis. Further complications are the possible interactions between genes (epistasis), gene-environment interactions, and environment-environment interactions. Suffice to say that the statistical power for the detection of

such QTLs remains a major concern to date. An obvious solution is the use of large numbers of animals and the application of large numbers of evenly dispersed markers. Other solutions to boost power are the use of selected individuals with very high or very low values for the trait or a refinement of the trait by using a combination of multiple measures that best capture a common underlying genetic factor.

Once a QTL with a significantly high LOD-score has been detected, the search for the actual gene(s) can start. This process, also called fine mapping, is essentially a repetition of the same procedure, but now with all markers concentrated in the area of interest on a single chromosome. If the region containing the putative gene is small, then the DNA in the entire region can be sequenced in full (positional cloning). Because genes have a specific structure, this procedure identifies all genes in the region. Comparing all base pairs in these genes in a number of different animals identifies the sites of allelic variation—also called polymorphisms—within these genes. Comparing the polymorphisms between, for instance, good and poor learning animals can then reveal which allelic variant is responsible for an increase or decrease in learning and memory.

Because of the ongoing sequencing of the entire mouse genome, a draft sequence of the genome covering 96% of the euchromatic, non-Y chromosome sequence is now available (Waterston et al., 2002). This feat will speed up gene hunting immensely because positional cloning and mutation analyses have become more and more redundant. Yet, the need to identify first the region of interest in a genomic search and then to narrow down that region by (repeated steps of) fine mapping remains. Only after the region is sufficiently small (for example < 100 genes) does the candidate gene approach become feasible. Repeated fine mapping is expensive and laborious, particularly when the low statistical power of each repeated search step is taken into account. Various strategies are available, constructing congenic strains being one of them. Such strains are produced by repeatedly backcrossing a strain with the mapped QTL (donor) to another strain (recipient) while checking each backcross for the presence of the QTL using flanking DNA markers. After a number of predefined backcrosses, one has developed a strain that except for the QTL area is genetically identical to the recipient strain. Phenotypic comparisons between congenic and recipient strains might then verify the existence of the QTL, its impact, and possible interactions with other QTLs. Once the existence of the QTL has been proved by means of congenic lines, the actual fine mapping can commence. Fine mapping is done by phenotyping substrains that are recombinant at various places in the QTL area.

Other strategies to fine map QTL are the use of recombinant inbred strains, the production of recombinant congenic strains, advanced intercross lines (AILs), or interval-specific congenic strains (ISCS). For a detailed review of these strategies, their pros and cons, the reader is referred to the specialized literature.

NEW TECHNOLOGIES: MICROARRAYS AND RNA INTERFERENCE

Another way to gain insight into the genetics of learning and memory is the application of DNA microarray technology, in particular commercially available high-density oligonucleotide arrays, such as those produced by Affymetrix.[1] This technique allows the simultaneous analysis of expression levels of thousands of genes (Schena, 2003) and is therefore, to a certain extent, a combination of a candidate gene approach and a whole genome search. High-density microarrays are also called DNA chips, and the latest mouse versions consist of more than 12,000 genes or expressed sequence tags

[1] www.affymetrix.com

(ESTs), which are represented by probes (cDNAs or oligonucleotides) immobilized on a solid substrate.

In general, the experimental sample (transcriptome) is prepared by extracting RNA from the tissue sample—for example, from the hippocampus of several inbred mouse strains known to differ in various learning and memory paradigms. The RNA is then reverse transcribed and labeled with fluorescent tags. The labeled target is then hybridized to the array, and the detected fluorescent signal correlates with the expression level of the genes of interest in the experimental sample. Hence, each sample has its own expression profile. This 'signature' can be used as a detailed molecular phenotype—which, for instance, can be correlated with more classic phenotypes, including behavioral scores—to nominate candidate genes for complex traits. For instance, Fernandes et al. (2004) correlated the baseline hippocampal gene-expression profiles of eight inbred strains with the aggression scores of these strains and identified two candidate genes for this complex trait. A similar expression-correlation approach but using learning and memory scores instead of aggression measures is likely to yield candidate genes that determine individual differences in learning and memory.

Other microarray procedures are also possible. Thus, two samples can be labeled with different fluorescent nucleotides, after which they are simultaneously co-hybridized to the same array. Genes expressed at equal levels in both samples contain a mixture of both fluorescent nucleotides hybridized, whereas genes expressed at different levels between both samples display predominant hybridization of one or both fluorescent nucleotides. For more information on microarrays, the technological and statistical concerns, the advantages and disadvantages, see, among others, Feldker et al. (2003), Steinmetz and Davis (2004), and the Nature Genetics Supplement, 2002.[2]

[2] http://www.nature.com/ng/supplements/index.html

The availability of a draft sequence of the mouse genome (Waterston et al., 2002) has not only facilitated fine-mapping of QTLs (see above) but also opened the door to nucleic-acid-based approaches that act to silence gene expression in a sequence-specific manner. One of its latest additions is RNA interference (RNAi). RNA interference, first discovered in the nematode *Caenorhabditis elegans* (Fire et al., 1998), is a process by which double-stranded RNA (dsRNA) silences specifically the expression of homologous genes through the degradation of their related mRNA. Hence, this technique is essentially a knockout approach. The primary advantages of RNAi—especially over the classic knockout technology—are the ease of making dsRNAs that mediate RNAi and the flexibility of inhibition. Hence the user can spatially and temporally control the interference reaction. The disadvantages are that the level of functional reduction is unpredictable and difficult to measure experimentally. These small interfering RNAs can also mediate an interferon response as a secondary effect. The ease of use, however, makes RNAi one of the most promising methods applied in the genetic dissection of complex traits today. For more information on siRNAs, their applications and potential as therapeutics, the reader is referred to Dorsett and Tuschl (2004). To the best of our knowledge, this promising technique has not yet been applied to learning and memory in any organism.

GENE-ENVIRONMENT INTERACTIONS

In the previous sections, we have shown that individual differences in behavior can be explained by genotypic variation. Obviously, this explanation is only partly true; differences in the environment also play an important role. This section focuses on the borderland of both sources of variation: gene-environment interactions.

Generally, the term gene-environment interaction refers to the phenomenon that the behavioral expression of the genotype depends on its environment. The study of gene-environment interactions is becoming more and more prominent in the analyses of complex traits (Barr et al., 2003; Caspi et al., 2002, 2003, 2004; Murphy et al., 2003; Sluyter et al., 2002; Tsuang, 2000; Tully et al., 2004a, b).

A clear example of the importance of gene-environment interactions in the learning and memory field comes from the performance of the previously mentioned NMDA receptor subunit knockouts. When raised under normal laboratory conditions, such mice do not perform well in learning and memory tasks. When exposed to an enriched environment for an extended period, however, the animals improve markedly and do as well as 'normal mice' do in various tasks. This behavioral enhancement is reflected anatomically: the number of connections between hippocampal cells has actually increased. Hence, in such mice, the enriched environment compensates for a genetically engineered memory defect (Rampon et al., 2000).

ENDOPHENOTYPES

Until now, we have not dealt with the intermediate neuronal structures through which genes modulate learning and memory. The intermediate traits, also called *endophenotypes*, are becoming more important because identifying the effect of a gene on a more elementary (neuro)biological trait is easier than identifying its effect on a complex trait, including learning and memory. In animal models, endophenotypes should be continuously quantifiable and meet the following criteria: reliability, stability, heritability, causality, and phenotypic and genetic correlation (de Geus, 2002; de Geus et al., 2001).

The hippocampus is a good place to look for a candidate endophenotype meeting these stringent criteria because many lesion studies have shown this brain structure to be involved in learning and memory. Apparently, the variation in the size of one particular hippocampal structure, the intra- and infra-pyramidal mossy fiber (IIPMF) terminal fields, correlates positively with performance in a radial maze (Crusio & Schwegler, 1991; Crusio et al., 1993; Crusio et al., 1987; Jamot et al., 1994; Schwegler et al., 1990). Hence, animals with larger IIPMF projections generally perform better on spatial learning tasks, as has been shown in different laboratories at different time points. Moreover, this correlation appears to be genetic because the significant correlation between inbred-strain means (see Fig. 2) suggests that the same (set of) gene(s) affect(s) the variation of the IIPMF sizes and spatial memory (Crusio, 2000). These findings strongly suggest that the genetically determined neuroanatomic variations in a defined brain structure, the hippocampus, may explain variation in learning and memory.

CONCLUSION

In recent years, genetic methods have led to the identification of many genes that are implicated in learning and memory processes. This achievement has given rise to considerable optimism that many questions regarding learning and memory will soon be solved. Despite all the progress, however, we would like to sound a word of caution. In our view, most likely many problems regarding learning and memory processes will prove to be unsolvable using single-gene approaches such as knockout and transgenic studies. One reason for this view is that, for instance, different types of memory depend on different brain structures. Why this is so, will have to be tackled on a systems level. As one of us has put it before (Crusio, 1999b):

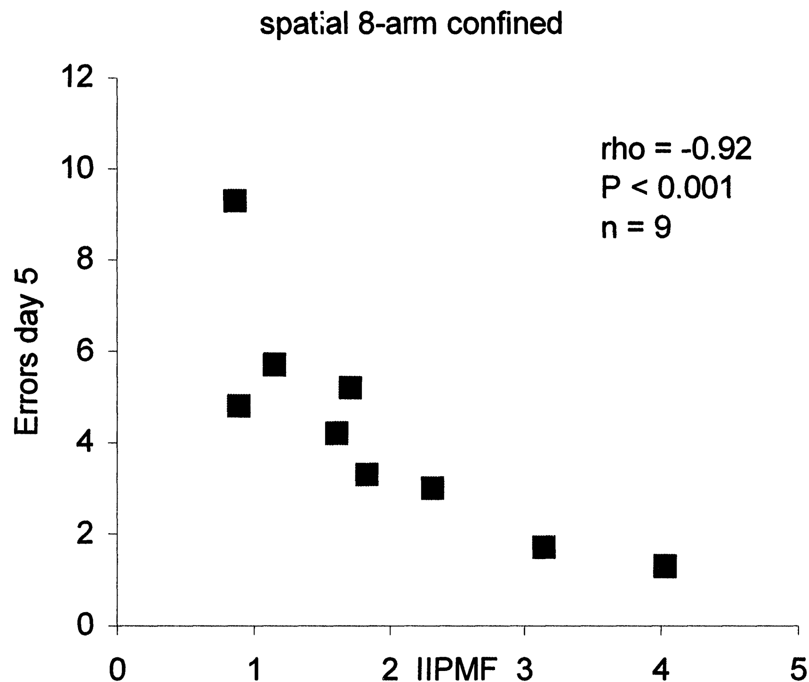

Fig. 2: Correlation between numbers of errors (repeat entrances) on the fifth daily trial in an 8-arm radial maze and hippocampal intra- and infrapyramidal mossy fiber extent (IIPMF). Data from Schwegler *et al.* (1990). Points represent means of 6 animals per strain.

Sooner or later, single-gene analysis will certainly help us to clarify basic cellular mechanisms of information storage and there is very clearly a great potential for exploiting this technique to develop new therapeutic tools. However, defining the function of the hippocampus, or explaining the existence of multiple memory systems would be a very daunting task if it were to be done by single-gene analysis only, and would take reductionism too far. This can be likened to trying to deduce the orbit of the earth around the sun using only knowledge about subatomic particles.

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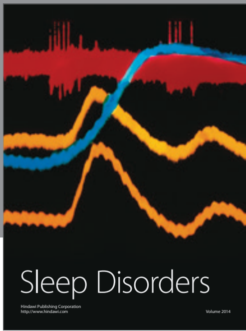

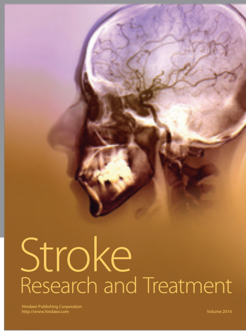

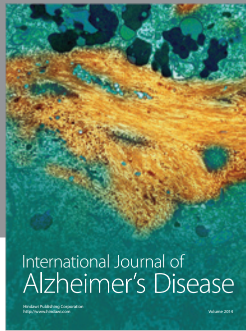

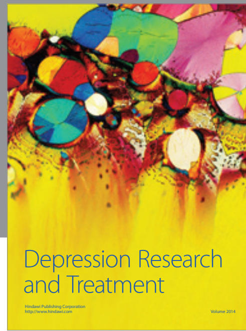

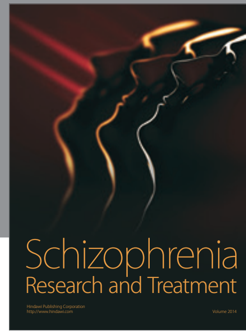

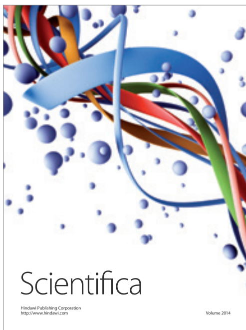

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