Genetic dissection of mouse exploratory behaviour

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Abstract

A large variety of apparatus and procedures are being employed to measure mouse exploratory behaviour. Definitions of what constitutes exploration also vary widely. The present article reviews two studies whose results permit a genetic dissection of behaviour displayed in an open-field situation. The results agree that factors representing exploration and stress/fear underlie this type of behaviour. Both factors appear to be linked to neuroanatomical variation in the sizes of the hippocampal intra- and infrapyramidal mossy fibre terminal fields. Multivariate analysis of genetic correlations may render important insights into the structure of behaviour and its relations with neuroanatomical and neurophysiological systems. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

It has already been shown years ago [24] that the full genetic variation that is potentially available for a phenotype will only get expressed in ecologically meaningful situations. Therefore, if we want to understand behaviour in the context of an animal's natural habitat, then we have to attempt to study it either in the field under natural circumstances or in the laboratory under semi-natural conditions [1]. Exploratory behaviour is most often studied in the laboratory, using a large variety of methods: the field is clearly open for standardisation.

Exploration is usually evaluated by measuring the behaviour displayed by animals placed in some kind of arena. Such open-fields exist in many varieties, square, circular, or rectangular, and in many different sizes. The procedures employed are manifold, too. The exposition to the novel environment may be forced (the animal is placed in the apparatus without possibility of escape) or free (the subject is given the choice when to enter the arena). The duration of the behavioural measurement may vary from a few minutes [19] to 20 min [36] or more. Generally, only a few behavioural measures, such as activity and defecation, are taken [19,35]. Others, however, have advocated using an ethogram to quantify exploratory activity. With the help of an ethogram, seemingly continuous behaviour is described as a sequence of successive, mutually exclusive, and distinct motor-posture patterns that represent species-specific units of behaviour which may be quantified subsequently by measuring their frequency and/or duration. Complex behavioural responses are thus regarded as organised appearances of the behavioural units. Ethograms of behaviour displayed in open fields have been devised, among others, for rodents [36] and paradise fish [21].

2. Defining exploration

Mice are attracted by novel stimuli and they spend long periods exploring when exposed to a novel environment, even when satiated in every aspect. Although seemingly simple, some confusion exists on the precise definition of exploratory behaviour. Most authors merely equate exploratory behaviour with 'activity', 'open-field behaviour', or even treat it as the opposite of 'emotionality' (whatever that may be). This is a moot

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point. Some authors feel that even the more sharply defined locomotor activity in a runway or an open-field contains a non-exploratory component and they distinguish between 'general activity' and exploratory activity (e.g. [20,26,42]). In addition, animals, and rodents in particular, often show a behavioural repertoire in an open-field that is infinitely richer than just locomotion and defecation (see [36] for an extensive ethogram of the mouse). Although almost all behaviours are 'activities', not all of them can be classified as exploratory.

The concept of exploration is closely associated with that of novelty [4], which may involve some quality never previously experienced or familiar items arranged in an unfamiliar way. O'Keefe and Nadel [28] defined novelty within the framework of their cognitive map theory as follows: 'an item or place is novel if it does not have a representation in the locale system' and exploration as 'a direct response of the animal to the detection of a mismatch by the locale system' (p. 241). The locale system is their term for the cognitive mapping system, presumably located in the hippocampus, that contains mental representations of stimuli previously perceived. In other words, the hippocampal system supposedly signals a lack of information about the current environment. Consequently, one of the processes thought to be associated with exploratory activity is what is called latent learning or exploratory learning [28,29]. Latent learning occurs without overt reinforcement. If a satiated animal is allowed to explore a novel environment (for instance, a maze) and subsequently made hungry or thirsty, then the animal will quickly learn to go to the proper place to find food or water, more quickly than an animal lacking such previous experience [5]. Thus, animals acquire information about their surroundings by means of exploratory movement.

In conclusion then, we have formulated previously the following definition of exploration: 'exploration is evoked by novel stimuli and consists of behavioural acts and postures that permit the collection of information about new objects and unfamiliar parts of the environment' [18].

The biological significance of exploration emerges clearly: entering and exploring new places promotes dispersion and improves the chances of finding life necessities (food, shelter, escape routes, etc.). Simultaneously, such behavioural activity will render an animal vulnerable to predation. In accordance with this, we have previously shown that exploratory behaviour in mice [15,18] as well as in paradise fish [21] has a genetic architecture consisting of large additive genetic variation combined with ambidirectional dominance. Such genetic underpinnings are diagnostic for a past history of stabilising selection, where an intermediate expression of the phenotype is more favourable than either higher or lower extremes [6].

Several good reviews of the different methods for evaluating exploration are available [2,4,41] and this subject will therefore not be discussed further here. Instead, as the subject of this special issue, test standardisation, is only meaningful if accompanied by a thorough understanding of the behaviour involved, I would like to concentrate here on a dissection of mouse exploratory behaviour into its underlying components. An excellent method for doing this is the multivariate analysis of genetic correlations between phenotypes. In addition, this method might reveal possible relations of the behaviour in question with other, neuroanatomical or physiological variables.

3. Genetic correlations

A weakness inherent in correlational studies is that a phenotypical correlation between characters does not necessarily reflect a functional relationship. On the other hand, if two independent processes, one causing a positive relationship, the other causing a negative relationship, act simultaneously upon two characters, the effects may cancel each other so that no detectable correlation can emerge. These problems can to a large extent be avoided by looking at the genetic correlations, that is, at correlations between the genetic effects that influence certain characters. These are the products of either genes with pleiotropic effects or of linkage disequilibrium. By using inbred strains that are only distantly related, the probability that a linkage disequilibrium occurs may be minimised so that a possible genetic correlation will most probably be caused by pleictropy, that is, there exists a (set of) gene(s) influencing both characters simultaneously. Thus, for these characters, at least part of the physiological pathways leading from genotype to phenotype must be shared and a causal, perhaps also functional, relationship must exist. It is this special property that renders the genetic–correlational approach so uniquely valuable. A more technical discussion of phenotypical and genetic correlations has been presented elsewhere [7,9].

4. Hippocampal mossy fibres and exploration

Although many different theories exist that address the question of the proper function of the hippocampus, most agree, more or less, that this structure is intimately involved with the processing of information about the environment [32]. This notion is supported by evidence from lesion studies [22], pharmacogenetic findings [38,39], and electrophysiological data, such as the observation that dentate synapses become potentiated during exploratory learning in rats [27].

The information collected during exploration is mainly of a spatial nature [28]. According to O'Keefe and Nadel's 'cognitive map' theory [28], the information acquired permits the animals to construct an internal representation of the spatial properties of their environment in their hippocampus. Thus, if a novel environment is entered, the hippocampus, acting as a comparator, detects this novelty and initiates exploratory behaviour, thereby enabling the animal to collect more information about that environment. The animal will gradually become familiarised with it and exploration will wane (habituation). It is known that hippocampal lesions produce hyperactivity, without habituation becoming evident [28].

Given the foregoing, we may hypothesise that sizeable anatomico–behavioural correlations do, in fact, exist. Furthermore, as selective forces have acted on the hippocampus indirectly by affecting behaviour, it is to be expected that such correlations will have an important genetic component. Finally, negative correlations are to be expected between the size of the hippocampal intra- and infrapyramidal mossy fibre (IIPMF) projection and exploration. The reasoning behind this is as follows. The IIPMF projection, which connects the dentate granular cells with the basal dendrites of the CA3 pyramidal neurons, varies strongly between inbred mouse strains [3] and this variation is heritable to a large extent [10,40]. In a number of experiments concerning spatial learning tasks in radial mazes, it has been shown that larger IIPMF facilitate acquisition in such tasks [12,14,33]. Furthermore, mice possessing the larger IIPMF projections show larger behavioural changes when observed in the open-field for a second time [11]. Taken together, this strongly suggests that larger IIPMF facilitate the processing and/or storage of spatial information. Consequently, we may expect that animals with larger IIPMF will habituate faster to a novel environment and, overall, show lower levels of exploratory activity.

5. Genetic dissection of exploratory behaviour and hippocampal neuroanatomical variation

Two experiments have been published in which exploratory behaviour and hippocampal mossy fibres were analysed employing genetic correlations [16,30] and in what follows their results will be briefly presented.

In the first study, Crusio et al. [16] carried out a diallel cross, in which five different inbred strains were intercrossed in all possible combinations, producing 25 genetically different populations with a total of 150 males being analysed. At the age of 3 months, all animals were observed directly and continuously for 20 min in a rectangular open-field, measuring $109 \times 49 \times$

49 cm, with a triangular object fixed against the back wall. Subsequently, the subjects were processed for histology and morphometry. The sizes of their IIPMF were expressed as a percentage of the total of the CA3 and CA4 areas [16]. Employing a bivariate extension [8] of the Hayman ANOVA for diallel crosses [23], additive genetic correlations were estimated between different components of exploratory behaviour and the IIPMF. As predicted, many substantial genetic correlations were found between the IIPMF and the behavioural responses to novelty displayed in an open-field. The value of the genetic approach becomes apparent when comparing phenotypical and genetic correlations. In a number of instances, environmentally-induced covariations were shown to counteract genetic correlations. This cancellation of effects resulted in many non-significant phenotypical correlations (i.e. correlations between the 150 individual values) and no apparent relationship between the IIPMF and exploration. However, to aid in the interpretation of the large correlation matrices thus obtained they were factor analysed (Table 1). This factor analysis of the matrix of additive-genetic correlations revealed a close relationship between the IIPMF and two of the three behavioural factors extracted.

The second factor (Table 1) is dominated by grooming (both frequency and duration) and can be interpreted as self-maintaining behaviour, but the first and third factors are more important for the present discussion. The first factor shows positive loadings for behavioural variables that can help the mouse to obtain information about its environment (wall-leaning, object-leaning, locomotion, and rearing) and appears to represent exploration. As hypothesised above, the IIPMF show a negative loading on this factor. Finally, the third factor has a positive loading on defecation, a behaviour that is usually seen as indicating stress or

Table 1
Factor analysis of the matrix of additive-genetic correlations between behaviour in the open-field and the size of the intra- and infrapyramidal mossy fibre terminal fields in mice in a 5×5 diallel cross

Variable	Factor I	Factor II	Factor III
Wall-leaning	1.11	0.38	
Object-leaning	0.95		
Locomotion	0.78		
Gnawing	0.75	−0.58	0.39
Grooming freq.		1.03	
Grooming dur.		1.01	
Sniffing		0.78	0.51
Defecation	−0.34		0.96
Rearing	0.60		−0.66
IIPMF	−0.40		−0.86

Factors obtained after an orthoblique Harris–Kaiser rotation [31]. Inter-factor correlations |0.22|. Only loadings with a value |0.30| are shown. After Crusio [16].

fear [43]. Rearing-up loads negatively on this factor, in contrast to the similar movement, wall-leaning. A possible reason for this is that rearing-up, away from the cover provided by the wall, is a behaviour to be avoided as it may make animals more vulnerable to predators. The IIPMF show a negative loading on this factor too. It appears that animals with larger IIPMF projections show lower levels of exploration and are not very fearful. This may mean that, within a 20-min observation period, animals with large IIPMF projections collect information in such an efficient way that their levels of exploration and fear are lower than in other mice; the open-field has rapidly become less novel to them. This result is in agreement with our hypothesis that larger IIPMF projections facilitate efficient information processing.

One of the strongest additive–genetic correlations found between the IIPMF and behaviour was that with rearing, although only a low and non-significant phenotypical correlation was obtained. Yet, the sizeable, positive additive–genetic correlation (0.48) implies that there exist pleiotropic genes that influence these two phenotypes in the same direction. Selective pressures on rearing should thus provoke neuroanatomical changes in the hippocampus. This hypothesis was tested by examining the inbred selection lines SRH (selection for rearing: high) and SRL (selection for rearing: low), which had been developed by van Abeelen [37,38]. As expected, SRH mice possessed IIPMF terminal fields that were larger than those of SRL mice [13]. Subsequently, the serendipitous appearance of a mutation in the C57BL/6J inbred strain permitted a further test of the relationship between the IIPMF and rearing. The C57BL/6J//Nmg subline displayed a marked drop in the frequency with which this behaviour is displayed in an open-field when compared with the original C57BL/6J subline. Again, as expected on the basis of the positive genetic correlation between rearing and the IIPMF, the mutated subline was shown to have smaller IIPMF [17,25].

The results of the latter two experiments convincingly confirm the validity of the results of the diallel cross. Unfortunately, this experimental design requires a large investment in resources and effort in order to breed and test animals from many different groups. The main alternative for the diallel cross as a tool for the genetic dissection of neural and behavioural phenotypes is the estimation of genetic correlations, using a battery of inbred strains. In this approach, we 'magnify' individual differences by studying animals from different inbred strains and looking for correlations between the means obtained for different variables (see [12] and references therein for some illustrative examples). This latter approach was taken by Roullet and Lassalle [30]. They observed 48 animals from 12 isogenic groups (9 inbred strains and 3 Fl hybrid groups, aged 8–9 weeks;

Table 2
Factor analysis of the matrix of correlations between strain medians of behaviour in the open-field and the size of the intra- and infrapyramidal mossy fibre terminal fields in mice from 11 isogenic groups

Variable	Factor I	Factor II
CSC	0.94	
Wall-leaning	0.93	
PSC	0.86	
Rearing	0.64	
Defecation		0.97
IIPMF	0.43	−0.59

Factors obtained after an orthoblique Harris–Kaiser rotation [31]. Inter-factor correlation −0.40. Only loadings with a value |0.30| are shown. Original data from Roullet and Lassalle [30].

2 males and 2 females per group) during 5 min in a circular arena (diameter 40 cm). Several behaviours were measured that were also evaluated in the previous study: leaning, rearing, defecation, and locomotor activity. The latter variable was subdivided into two separate variables: central sector crossings (CSC) and total sector crossings (SC). As in our earlier study, animals were processed for histology and morphometry of the IIPMF after the end of the behavioural experiment. Taking the median values presented in their Table 2 ([30], pp. 66–67), the correlation matrix between these behavioural and neuroanatomical variables was calculated and a factor analysis of this matrix was performed (Table 2). To remove the dependency between the variables CSC and SC, the latter variable was replaced by the number of peripheral sector crossings (PSC = SC − CSC). Although correlations between strain means are not technically identical to genetic correlations, they are lower bound estimates of these [9].

As Roullet and Lassalle [30] did not measure grooming behaviour, it is not very surprising that the solution obtained shows two factors only. Factor II resembles Factor III from the earlier study, being characterised by loadings for defecation and the IIPMF with opposite signs. Factor I is similar to Factor I from the diallel cross, being characterised by locomotor activity (both CSC and PSC), wall-leaning, and rearing. Two major differences become apparent, however. First, rearing loads only on Factor I, but not on Factor II. Second, the IIPMF have a positive loading on Factor I, as opposed to a negative one in the earlier study. One possible explanation for this is that Roullet and Lassalle used inbred strains, as well as three different F1 hybrids. Dominance effects have been found for exploratory behaviour [15,18], but not for IIPMF sizes [10]. As a result, the correlations between the group medians will not accurately reflect additive–genetic correlations [7,9]. The reanalysis of Roullet and Lassalle's [30] data was therefore repeated, but this time omitting

Table 3
Factor analysis of the matrix of correlations between strain medians of behaviour in the open-field and the size of the intra- and infrapyramidal mossy fibre terminal fields in mice from nine inbred strains

Variable	Factor I	Factor II
CSC	0.93	
Wall-leaning	1.00	
PSC	0.94	
Rearing		0.86
Defecation		−0.81
IIPMF		0.78

Factors obtained after an orthoblique Harris–Kaser rotation [31]. Interfactor correlation 0.54. Only loadings with a value $> |0.30|$ are shown. Original data from Roullet and Lassalle [30].

the medians of the hybrid groups. The results are presented in Table 3.

Factor II now closely resembles Factor III from the diallel study: positive loadings for rearing and the IIPMF coupled with a negative loading for defecation. Factor I now joins locomotor activity and wall-leaning. Again, we find some differences between the two studies. In Table 3, the IIPMF and rearing do not load on Factor I, as was the case in the earlier study (cf. Table 1). This, however, may be readily explained by the fact that Roullet and Lassalle [30] observed their animals for 5 min only. This would leave scant time to habituate to the novel environment, as opposed to our earlier study in which animals were observed for 20 min. Spatial memory could therefore hardly play a role in this situation, and no correlation with the IIPMF would be expected. Rearing mainly occurs in later stages of these 20 min (unpublished observations) and seems to be particularly inhibited by novelty: hence the absence of a sizeable loading on Factor 1. It may be worth noting that whether F1 hybrids are included or not, the IIPMF-rearing correlation is, again, one of the strongest correlations found.

6. Conclusion

The studies discussed above confirm the early findings of Whimbey and Denenberg [43] that exploratory behaviour as displayed in an open-field is multifactorial, with exploration and fear/stress being the main motivational systems underlying the behavioural variation observed. It might be noted that although in the diallel cross a strong genetic correlation between locomotion and defecation was observed (data not shown), this did not appear in Roullet and Lassalle's strain study. In addition, these variables loaded on different factors in both studies. These findings render doubtful

the often-used concept of 'emotionality', defined by high defecation and low locomotor activity [19,35]. Evidently, studying the behaviour in more detail by observing more elements from the ethogram, as was done in the experiments discussed in the preceding sections, makes it possible to dissect the underlying mechanisms into more detail.

In recent years, linkage studies have attempted to identify quantitative trait loci (QTL) in order to uncover the polygenes underlying behavioural variation. Flint and colleagues [19] localised three QTL on chromosomes 1, 12, and 15 for mouse 'emotionality' and concluded that a simple genetic basis underlies this complex psychological trait. This conclusion appears premature at the least. Apart from the caveat that there might be genes with effects under the detection threshold of the methods employed in their study, a follow-up experiment [35] failed to replicate their earlier results. In both studies a QTL was found on chromosome 1, but careful comparison of the data (Fig. 1 in [19] and in [35]) shows that the confidence intervals of these putative loci do not overlap, so that extending the reasoning of these authors in extremis would mean that no genes at all influence these phenotypes: clearly an absurd conclusion. The genetic architecture of exploratory behaviour emerging from quantitative-genetic analyses [15,18], combined with the results of the factor analyses presented here, clearly point in the direction of a complex genetic basis for this complex phenotype.

Genetic methods are increasingly being applied to elucidate brain-behaviour relationships. Usually, however, these approaches utilise identified, single genes through the production of transgenic or knock-out mice [34]. In the present brief overview, I have attempted to show that quantitative-genetic methods, using polygenic variation caused by unidentified genes, may also be used fruitfully to provide answers to such questions. In this way, a close involvement of the hippocampus in the regulation or modulation of behavioural factors underlying mouse behaviour as exhibited in an open-field could be shown to exist. It should perhaps be emphasised here that this relationship could not be demonstrated at the phenotypical level, but was revealed only after analysing the genetic correlations.

In conclusion, then, it appears that multivariate analyses of genetic correlations, are a very powerful approach with which behaviour can be dissected in its underlying components. In the context of the present special issue, it will be abundantly clear that the more exact understanding of behaviour that this genetic dissection may render can be very valuable for the design of standardised behavioural tests that can provide meaningful measures.

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