



Review

Animal models of human psychopathology based on individual differences in novelty-seeking and anxiety

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ABSTRACT

The role of individual factors in behavioural neuroscience is an important, but still neglected area of research. The present review aims to give, first, an outline of the most elaborated theory on animal behaviour, and second, an overview of systematic approaches of historic and present animal models of human psychopathology based on individual differences. This overview will be focused on animal models of unselected subjects (i.e. natural variance of a specific behaviour within a given population) and selected breeding for a specific behaviour. Accordingly, an outline of the personality model from Gray and McNaughton of individual behaviour in animals is given first. Then, a comprehensive overview of past and current animal models in novelty-seeking (i.e. psychomotor activation and exploration behaviour) based on systematic individual differences and its relationship to addiction is presented. Third, this will be followed by a comprehensive overview of individual differences in previous and present animal models for anxiety. Finally, critical aspects of such approaches in animal research are discussed, and suggestions are given where to go from here.

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Abbreviations: BrdU, 5-bromo-2'-deoxyuridine; 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine, serotonin; 8-OH-DPAT, 8-hydroxy-2-di-N-propylamino-tetralin; ACTH, adrenocorticotropic hormone; AHA, Australian high avoidance; ALA, Australian low avoidance; APO-SUS, apomorphine-susceptible; APO-UNSUS, apomorphine-unsusceptible; BAS, Behavioural Activating System; BIS, Behavioural Inhibition System; BNST, bed nucleus of the stria terminalis; CRH, corticotropin-releasing hormone; DA, dopamine; DNA, deoxy-ribonucleic acid; DOPAC, 3,4-dihydroxyphenylacetic acid; DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; EAE, experimental autoimmune encephalomyelitis; FFFS, Fight/Freezing/Flight System; Floripa H, Floripa high; Floripa L, Floripa low; GABA, γ -aminobutyric acid; GR, glucocorticoid receptor; HAB, high anxiety-related behaviour; HDS, high DPAT sensitive; HOA, high open arm; HPA, hypothalamus-pituitary-adrenal; HR, high responder; HRA, high rearing activity; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LAB, low anxiety-related behaviour; LDS, low DPAT sensitive; LOA, low open arm; LR, low responder; LRA, low rearing activity; MDMA, 3,4-methylenedioxymethamphetamine ("ecstasy"); mRNA, messenger ribonucleic acid; NA, noradrenaline; NMDA, N-methyl-D-aspartate; PAG, periaqueductal gray; p-ERK1/2, phosphorylation of extracellular signal-regulated kinase1/2; PVN, nucleus paraventricularis; QTL, quantitative trait loci; RHA, Roman high avoidance; RHA/Verh, Roman high avoidance (Switzerland); RLA, Roman low avoidance; RLA/Verh, Roman low avoidance (Switzerland); SHA/Bru, Syracuse high avoidance; SLA/Bru, Syracuse low avoidance; SSRI, selective serotonin reuptake inhibitor; THA, Tokai high avoider.

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1. Introduction

Quantitative individual behavioural differences were not systematically addressed until the late 18th century when interest was directed to the ‘personal equations’ used by astronomers for measuring stellar transits. Then, scientists discovered not only differences between individuals, but also that the individual’s ‘personal equation’ also varied over time, suggesting that the rather large individual differences were not invariant. These differences involved visual as well as auditory reaction times, and attention and vigilance also played a role (Anastasi 1958, cited from Brush, 1991). Today, one of the major challenges of personality research is to understand the causes of individual differences and their consequences in terms of fitness, adaptive capacity, and individual vulnerability to diseases. Animal research has also been used to investigate individuality. Thus, there is a range of methods that can be applied in different species (for review see Gosling, 2001). In this literature, individuality is defined as a collection of behavioural or physiological traits, both innate and acquired, that distinguish one individual from near relatives, which as far as possible share the same genetic and environmental background.

The role of individual difference factors in behavioural neuroscience is an important, but still neglected area of research. One problem is the need for higher numbers of participants or subjects than the commonly used approach. Accordingly, research issues requiring many subjects (e.g., dose–response effects) are often neglected in favour of less demanding inquiries. In the last years, however, the necessity of an individual approach for research on biology/behaviour relationships has become more and more important. Despite the progress in examining biopsychological processes in humans, behavioural neuroscience in animals remains indispensable. For example, do animals show substantial differences in behaviour, physiology, or pharmacological reactivity? What are the relationships between these parameters and how consistent are they? What are the key domains of individual behavioural differences that have physiological relevance? More importantly, can these domains predict *a priori* the outcome of experimental manipulations? To what extent do certain stable characteristics of the organism shape physiological outcomes, before and after experimental manipulations? These questions are important to answer if animal

models of diseases are to be developed in order to investigate in depth individual susceptibility to diseases or psychiatric disorders.

The present review aims, first, to give an outline of some of the most important theories of individual behaviours in animals and humans, and second, an overview of all systematic approaches of historic and present animal models of human psychopathology based on individual differences in novelty-seeking and anxiety, to the best knowledge of the authors. It was our intention to include all systematic animal models relating to anxiety and novelty-seeking within one review for the first time. Finally, critical aspects of studying individual behaviour in animals are discussed, and suggestions are given where to go from here.

2. Theories of individual behaviour

It is out of the scope of this work to provide a comprehensive overview of the most relevant biopsychological theories of individual behaviour in animals (e.g., Depue and Lenzenweger, 2005; Gray and McNaughton, 2000; McNaughton and Corr, 2004; White and Depue, 1999), and human personality (Cloninger, 2003; Zuckerman, 1984; for overviews see Amelang et al., 2006; Hennig and Netter, 2005; McAdams, 2001; Pervin and John, 2001). But one of the most influential theories on the neurobehavioural system of approach and avoidance behaviour by Gray and subsequent developments by him and others shall be briefly described. A selection of the most critical parts of this personality theory shall be roughly outlined to which the following findings on approach, avoidance, and their respective biological correlates can be related to. The theory by Gray (1982), Gray and McNaughton (2000), and the modifications from McNaughton and Corr (2004) has been depicted because it appears as the most elaborated animal theory of anxiety/fear and novelty-seeking behaviour.

2.1. The personality model from Gray and McNaughton

In accordance to his teacher Hans-Jürgen Eysenck, Jeffrey Alan Gray stated that personality differences are based on distinct brain systems. However, Gray (1981) postulated that these different systems are also characterised by distinct sensitivities for cues of reward and punishment, thus proposing the ‘reinforcement

sensitivity theory". Gray (1981) also postulated two alternative dimensions of personality, anxiety and impulsivity, of which both have certain relationships to the three personality dimensions (extraversion–introversion and neuroticism) previously postulated by Eysenck.

Gray's theory (1982) of the Behavioural Inhibition System (BIS), Behavioural Activating System (BAS), and the Fight/Freezing/Flight System (FFFS) has been substantially revised by Gray and McNaughton (2000) and further revised by McNaughton and Corr (2004). Two of these systems, BAS and FFFS, are Behavioural Activating Systems. The third system, BIS, serves to interrupt and/or inhibit purposeful behaviour and simultaneously controls possible behavioural options. The theory suggests that the two personality dimensions anxiety and impulsivity are mediated by individual differences in the sensitivity of BIS and BAS to react upon their corresponding stimuli. For a summary see also Amelang et al. (2006).

A clear distinction between fear and anxiety has been postulated later on (Gray and McNaughton, 2000; McNaughton and Corr, 2004), which had not been evident in the initial theory (Gray, 1982). The authors postulate that "fear has the function of moving the animal away from danger" (McNaughton and Corr, 2004, p. 286) resembling the defensive avoidance system, whereas "in an approach–avoidance conflict situation, anxiety has the function of moving the animal toward danger" (McNaughton and Corr, 2004, p. 286) resembling the defensive approach system. Thus, they suggest defensive direction to be the critical factor, which is not shared by the view of the Blanchards, or Depue and coauthors, namely that certainty versus uncertainty of threat plays the major role. Conversely, McNaughton and Corr (2004) critically comment that the differentiation between fear and anxiety is not dependent on the conditioned or unconditioned nature of the stimuli (see the literature for the defensive burying test first reported by Pinel and Treit, 1978). The fear system is insensitive to anxiolytic drugs, while anxiety involves inhibitory behaviour, and enhanced risk assessment. Accordingly, the core features of anxiety are sensitive to anxiolytic drugs, which also enhance exploration behaviour and novelty-seeking.

The theory of the "Neuropsychology of Anxiety" by Gray and McNaughton postulates behavioural (i.e. fear and anxiety) and neural distinctions between panic (periaqueductal gray; PAG), phobia (hypothalamus/amygdala), anxiety (amygdala/septo–hippocampal system), obsession (cingulate), and complex anxiety such as social anxiety (prefrontal cortex). The defence system involving fear and anxiety is categorically different and sometimes even opposite, depending on coherent and hierarchical structures. The basis of their neural hierarchical system of defence behaviour stems from the concept of Deakin and Graeff (1991) and Graeff (1994). Thus, the neural hierarchy is ordered from high (prefrontal cortex) to low (PAG) brain complexity and each level is associated with specific classes of behaviour. It is argued that neural control of fear relative to anxiety is more elaborated at lower levels of the neural system, whereas anxiety is considered to be relatively more elaborated at higher brain levels (McNaughton and Corr, 2004).

The theory views substantive affective events as falling into just two different types, positive and negative. In the revised theory (Gray and McNaughton, 2000; McNaughton and Corr, 2004), the FFFS and the BAS depict these two antagonistic systems. The FFFS is reacting to all types of aversive stimuli (unconditioned and conditioned). The activation of the FFFS subsequently leads to avoidance behaviour of the negative stimulus. Conversely, the BAS reacts to all types of rewarding (unconditioned and conditioned) and the omission of punishing events is assumed to be mediated by this system. Activation of the BAS finally leads to behavioural approach of the positive stimulus. Both systems are activated by

stimuli and situations of major novelty. The BIS is crucial if the FFFS and the BAS are simultaneously activated. This system functions as a mediator, which cannot be activated directly by aversive stimuli. The BIS is activated in conflicts between goals, namely approach–avoidance, approach–approach, and avoidance–avoidance decisions. On the one hand, the BIS inhibits prepotent behaviour (i.e. avoidance and approach), and on the other hand elicits behaviour that serves to resolve the conflict. Thus, the theory comprises a two-dimensional defence system. For example, approach to threat corresponding to anxiety (e.g., open arm approach) and avoidance of threat corresponding to fear (e.g., open arm avoidance) can be typically observed in an elevated plus-maze. This view is similar to Depue and Lenzenweger (2005), who claim that behavioural inhibition will not allow the individual to explore the environment to discover if the situation is threatening. Thus, increased attentional scanning of the uncertain surrounding, and cognitive worrying about possible outcomes may resolve the uncertainty when a rat enters an open arm: Caution, slow approach, heightened attentional scanning, and enhanced cognitive activity are optimal, whereas freezing is not. The elevated plus-maze is a widely used behavioural paradigm that presumably measures anxiety-like/avoidance behaviour and which has been extensively used as an animal model for anxiety. During a typical elevated plus-maze test, animals will actively avoid the open arms in favour of the closed arms. In contrast, in the case of fear conditioned stimuli, the motor response is not escape, but rather freezing or behavioural inhibition (LeDoux, 2000; Phelps and LeDoux, 2005).

One prerequisite of the theory is the defensive distance which has been defined by the Blanchard and Blanchard (1990) and which corresponds with the real distance. For a particular individual in a particular situation, defensive distance is equal to the real distance. But, in a more dangerous situation, a greater real distance will be required to achieve the same defensive distance. Accordingly, another individual in the same situation may require a smaller real distance to achieve the same defensive distance, which could be interpreted as one individual being less anxious than the other. Thus, the defensive distance is subject to individual dispositions, and a subjective cognitive construct of the degree of perceived threat.

The smallest defensive distance would result in defensive avoidance behaviour of sudden attack, involving the lowest neural level (PAG), intermediate defensive distances are followed by flight or freezing, and very large defensive distances result in normal non-defensive behaviour, mediated by the highest neural level (prefrontal cortex). The smallest defensive distance is labelled panic, for example, a rat that is facing a cat. Intermediate defensive distances can be equated with phobic avoidance. In contrast, the smallest distance in the anxiety-mediated defensive approach results in defensive inactivity. In rats, this freezing behaviour is characterised by total immobility except for respiratory activity. At intermediate approach distances, if perceived threat is medium, an undrugged rat is likely to engage in risk assessment behaviour. For example, risk-assessment in an elevated plus-maze typically occurs when the rat is on the middle section of the apparatus, that is, neither on the potentially threatening open arms nor on the relatively safe closed arms. An animal given an anxiolytic drug will decrease risk assessment (which again increases approach to the source of threat). Thus, the drug does not alter specific observable behaviours consistently but produces changes in behaviour that are consistent with decrease in defensive distance. Finally, at very large distances, defensive behaviour disappears and normal non-threat behaviour is shown.

Another critical issue in the theory by Gray and McNaughton is neuropsychopharmacology. Neurotransmitters such as serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (NA) are known

to provide a modulatory and diffuse input to the entire defence system, and other parts of the brain. Particularly 5-HT is thought to be involved only in the defensive approach system (i.e. anxiety). Accordingly, fear-related behaviours are not sensitive to anxiolytic drugs, whereas 5-HT_{1A} receptors seem to be important for anxiety. Recent evidence supports the view that there is a neurochemical rather than a neuroanatomical dissociation between learned fear and anxiety (Fendt et al., 2005; Schweimer et al., 2005; Sullivan et al., 2004).

Overall, the theory by Gray (1982) is one of the most comprehensive works relating to anxiety/fear and approach behaviour. The major revisions by Gray and McNaughton (2000), and McNaughton and Corr (2004) show that the theory is constantly incorporating up-to-date evidence, integrating a remarkable body of evidence of neurophysiological, neurochemical and behavioural data. However, it is not clear whether the assumptions based on experimental animal research are also valid for the explanation of human personality dimensions (Amelang et al., 2006).

3. Individuality in animal models

For a number of decades it has been the aim of several research groups to establish methodologies to assess behavioural traits in animals and to differentiate between conspecifics of a given species. “Trait” is defined here as a pattern of a specific behaviour, which differs between individuals, but which is relatively constant within subjects over time and situations (Amelang et al., 2006). This term is usually used in animal behavioural research instead of “personality” in humans. Nonetheless, there is a wide range of animal behaviours suggested to reflect personality dimensions in humans such as, for example, avoidance behaviour in chimpanzees (Yerkes and Yerkes, 1936), neuroticism in horses (Morris et al., 2002), nervousness in response to other animals in chickens (Hasuo, 1935), response to females in newts (Halliday, 1976), exposure to a mirror and aggression in the midas cichlid (Francis, 1990), assertiveness in the spotted hyena (Gosling, 1998), dominance behaviour in baboons (Sapolsky and Ray, 1989), or social ability in rhesus monkeys (Capitani, 1985), and others. Probably the most studied dimensions of individual differences of behaviour in animals, however, relate to anxiety, activity, and exploratory behaviour (for a review see Gosling, 2001).

Mice and rats are the major experimental animals in the field of behavioural neuroscience, and various approaches have been pursued to analyse dimensions of anxiety and exploratory behaviour. They extend from systematic behavioural differences in normal animals to the recently established genetic models. There are at least four methodological approaches when analysing individual behaviour of a cohort. First, a simple and effective approach is to correlate values of individuals on two dimensions which provide information about the extent of a relationship between individuals (e.g., anxiety-like/avoidance behaviour and corticosterone in the blood). Second, a cohort of animals is exposed to a behavioural test. The individuals are then divided into at least two subgroups according to their behaviour (e.g., high and low responder), that is, using a median split, or extreme groups of a given population (e.g., upper and lower quartiles). Subsequently, additional assays of various types are performed. Third, selective breeding for behavioural dispositions has been carried out scientifically since the first half of the 20th century. There, the most common behavioural dimensions were lines bred for learning and memory experiments, psychomotor activation, addiction models, and emotionality. The fourth approach consists of the comparison of different strains of inbred mice or rats, as well as

inbred strains versus outbred stocks, and finally of genetically manipulated animals.

The advantages of an individual-oriented approach of animal behaviour are various. First, variance between individuals can be systematically explained. Second, systematic relationships between different behaviours or between behaviour and biological functions can be measured more closely. Third, behavioural screening can be used for the prediction of pharmacological or behavioural reactivity in other tests. Fourth, differential animal behaviour, with state or trait characteristics, can also be applied to analyse the susceptibility to disease models. Fifth, the approach makes it feasible to determine an array of behaviours in a broad range of species that resemble human personality dimensions; this then allows one to draw comparisons between animals and humans (Gosling, 2001). The various reasons for the expression of individual differences, even in genetically identical animals, are summarised elsewhere in an overview by Lathe (2004), but are not the focus of the present studies.

It is commonly accepted that animal models make use of ‘selective’ breeding for a specific trait. However, there has been no uniform term coined denoting animals stemming from a given sample population. Some authors have used the term ‘normal’ as a means to filter outliers from sample populations based on the presence of strongly deviant behaviour (Karl et al., 2003). But this term may not fully account for the rat models introduced here, although this term is also often used to denote animals that are naive to behavioural tests and pharmacological manipulations. Other terms such as ‘intact’ or ‘healthy’ are also in use. However, they are more restricted and lay the focus more on health-related issues. One needs to be cautious as such terms require (A) definitions of the terms ‘healthy’ and ‘intact’, respectively, and (B) subsequent extensive health monitoring, which not all laboratories are capable of. For the rats used here, it would not be possible to know if they were all ‘healthy’ or ‘intact’ until the end of the experiments, although the weight of the rats provides a crude evaluation of the health status. The term ‘unselected’ may also appear somewhat misleading since the rats used in given approaches have usually been selected for sex, age, stock, and breeder. Nonetheless, the term ‘unselected’ appears to be the most appropriate expression since it basically comprises all individuals from a sample population, without inferring anything about their health status (‘healthy’, ‘intact’), or claiming that they are ‘normal’.

The present overview will be limited to dimensions of anxiety-related behaviour and psychomotor activation (Table 1), and will not cover strain differences in rodents (Broadhurst, 1960). Accordingly, a comprehensive overview of previous and current animal models for systematic individual differences in psychomotor activation and its relationship to addiction are introduced first. This will then be followed by a comprehensive overview of individual differences in animal models for anxiety. It must be noted that the present review is not exhaustive due to the vast amount of publications available. However, utmost caution was exerted to include all relevant aspects of the respective models.

4. Individuality in novelty-seeking models

4.1. Psychomotor activity and exploratory behaviour: unselected animals

4.1.1. High responder (HR) and low responder (LR) rats

Piazza et al. (1989) provided substantial evidence to demonstrate that (A) individuals within an animal laboratory differ widely in their reactivity to forced novelty exploration and (B) that this difference may be useful to predict individual differences in sensitivity to drugs of abuse. They showed that unselected male

Table 1

Rat animal models based on systematic individual differences in novelty-seeking (psychomotor activity and exploration) and anxiety: behavioural categorisation criteria, differences in other behaviours, psychopharmacology, and physiology/pharmacology (please see text for more details)

	Criteria for categorisation	Behaviour	Psychopharmacology	Physiology/Pharmacology
Psychomotor activity and exploratory behaviour				
Unselected breeding				
High responder (HR) and low responder (LR) rats	Horizontal locomotion upon forced novel circular corridor exposure for 120 min	Self-administration of amphetamine (HR > LR) Cognitive function in Y-maze (HR < LR) Light–dark box anxiety-like avoidance (HR < LR) Speed of food consumption after deprivation (HR > LR) Locomotion up to 16 months of age (HR > LR)	Locomotor sensitisation after amphetamine treatment (HR < LR) Sustained elevated plasma corticosterone after novel environment exposure in HR Opposite effects of corticosterone administration in LR (increase) versus HR rats (decrease) to reinforcing value of amphetamine self-administration Stress-induced accumbal DA release (HR > LR) Extracellular DA release in nucleus accumbens after tail pinch stress (HR > LR)	Basal DOPAC:DA ratio in nucleus accumbens, prefrontal cortex (HR > LR) Basal 5-HT and 5-HIAA levels in striatum, nucleus accumbens, prefrontal cortex collapsed (HR < LR) Cholecystokinin, somatodendritic release of DA in ventral tegmental area (HR < LR) Preprodynorphin and preproenkephalin in nucleus accumbens (HR > LR) Neurogenesis in adult dentate gyrus (HR < LR)
High rearing activity (HRA) and low rearing activity (LRA) rats	Vertical activity (rearings) upon forced novel open field exposure for 10 min	Exploratory activity in novel object test (HRA > LRA) Habituation upon repeated open field exposure (HRA > LRA) Step-in latencies after shock in inhibitory avoidance test (HRA < LRA) Pellets intake and reference memory errors in radial maze (HRA < LRA) Working memory errors in radial maze (HRA > LRA)	Increased rearings and centre time in open field after muscarinic antagonist stimulation (HRA > LRA) Earlier nicotine-induced rearing and locomotor sensitisation in HRA	Ventral and dorsal striatal DA activity (HRA > LRA) 5-HT in medial prefrontal cortex (HRA < LRA) Increased hippocampal extracellular cholinergic activity in rats with “superior” versus “inferior” rearing habituation in both novel and familiar open field
Low exploratory (LE) and high exploratory (HE) activity rats	Exploration box test combining several behaviours to one exploration index based on the second test day for 15 min	Sucrose intake and preference on day 1 (HE < LE) Anxiety-like behaviour profile in elevated plus-maze (LE > HE) Freezing during fear conditioning (HE > LE) Forced swim test immobility (HE < LE), swimming (HE > LE)	Denervation of locus coeruleus noradrenergic projections induced various differential effects on spontaneous, amphetamine-stimulated, and amphetamine-sensitised behaviour	Baseline and amphetamine-induced extracellular striatal DA (HE > LE) 5-HT reuptake inhibition induced increased 5-HT transporter binding and extracellular 5-HT in medial prefrontal cortex (HE < LE) and increased hippocampal extracellular 5-HT (HE > LE) Basal neuronal activity and BDNF mRNA altered between HE and LE

Selected breeding

<p>Apomorphine-susceptible (APO-SUS) and apomorphine-unsusceptible (APO-UNSUS) rats</p>	<p>Apomorphine (1.5 mg/kg, s.c.) treatment followed by gnawing response during novel gnawing box exposure for 45 min</p>	<p>Basal and novel open field locomotor activity (APO-SUS > APO-UNSUS) Two-way active avoidance (APO-SUS < APO-UNSUS) Startle response (APO-SUS > APO-UNSUS) Flee behaviour in resident-intruder test (APO-SUS > APO-UNSUS)</p>	<p>Amphetamine-induced locomotion (APO-SUS > APO-UNSUS) α-Noradrenergic and DA receptor agonist induced locomotion (APO-SUS > APO-UNSUS) Stress-induced plasma ACTH, acute plasma free corticosterone (APO-SUS > APO-UNSUS), and prolactin response, Fos-like immunoreactivity nuclei in the PVN (APO-SUS < APO-UNSUS) Basal plasma ACTH (APO-SUS > APO-UNSUS), basal plasma free corticosterone (APO-SUS < APO-UNSUS)</p>	<p>α_2- and β_2-adrenoceptor agonist relaxation in mesenteric resistance arteries (APO-SUS < APO-UNSUS) Hippocampal novelty-induced dynorphin B expression (APO-SUS \neq APO-UNSUS) Hippocampal mineralocorticoid receptors, CRH mRNA expression, synaptic density in the PVN (APO-SUS > APO-UNSUS) Body weight, striatal, hippocampal, adrenal tissues weight (APO-SUS > APO-UNSUS), bulbus olfactorius (APO-SUS < APO-UNSUS) IFN-γ mRNA:IL-4 mRNA ratio in naive splenocytes (APO-SUS < APO-UNSUS) Disease IgE response to parasitic infection (APO-SUS > APO-UNSUS) Susceptibility for EAE, infections, and periodontitis (APO-SUS > APO-UNSUS)</p>
<p>High responder (HR)-bred and low responder (LR)-bred rats</p>	<p>Summing horizontal locomotor and vertical rearing activities in a novel activity box for 60 min</p>	<p>Horizontal and vertical activity in a novel activity box (HR-bred > LR-bred) Open arm times and latency in elevated plus-maze (HR-bred > LR-bred) Light-dark box anxiety-like avoidance profile (HR-bred < LR-bred) Activity profile and centre time in open field (HR-bred > LR-bred) Novel object contact (HR-bred > LR-bred) Anxiety-like behaviour before puberty and as adults (HR-bred \neq LR-bred)</p>	<p>Activity in open field after benzodiazepine treatment (HR-bred > LR-bred) Corticosterone stress response before puberty and as adults (HR-bred \neq LR-bred)</p>	

Table 1 (Continued)

	Criteria for categorisation	Behaviour	Psychopharmacology	Physiology/Pharmacology
Anxiety-like/avoidance behaviour Unselected breeding High open arm (HOA) and low open arm (LOA) rats	Open arm time during first exposure to an elevated plus-maze for 5 min	Retest reliability for a period of 24 h or 120 days Avoidance of aversive objects in unconditioned object burying test (HOA < LOA) Active avoidance learning in a shuttle-box (HOA > LOA) Freezing during fear conditioning and when testing (HOA < LOA) Ultrasound separation vocalisation as pups (HOA > LOA) and ultrasound vocalisation during fear conditioning (HOA < LOA) Body temperature following handling stress (HOA > LOA)	Reduced immobility in forced swim test upon D-cycloserine (only LOA) Post-mortem p-ERK1/2 levels in amygdala upon D-cycloserine treatment after forced swimming (HOA < LOA) Chronic dioscorea treatment after ovariectomy decreased anxiety-like behaviour and IL-2 levels in cerebral cortex (only LOA) Chronic dioscorea treatment after ovariectomy increased anxiety-like behaviour and IL-2 levels in prefrontal cortex (only HOA)	Post-mortem 5-HT levels in ventral striatum (HOA > LOA) Post-mortem IL-2 mRNA levels in striatum (HOA < LOA) and prefrontal cortex (HOA > LOA)
Selected breeding Maudsley reactive and non-reactive rats	Absolute number of fecal boli on 2 min trials in an open field on four consecutive days		Refer to text and original literature due to abundance of literature	
Roman high avoidance (RHA/Verh) and Roman low avoidance (RLA/Verh) learning rats	Learning to actively avoid foot shocks of four consecutive avoidance responses within the first 10–20 trials of the first session in a two-way shuttle-box	Horizontal (locomotion) and vertical (rearing) activity, exploratory activity, self-grooming (RHA/Verh > RLA/Verh) Freezing (RHA/Verh < RLA/Verh) Anxiety-like behaviour in open field, elevated plus-maze, black/white box test, light/dark open field test (RHA/Verh < RLA/Verh) Stress responsivity, anxiety-like behaviour to novelty (RHA/Verh < RLA/Verh) Novelty-seeking (RHA/Verh > RLA/Verh) – acoustic startle response (RHA/Verh < RLA/Verh) Effects of neonatal handling on adult emotional-related behaviour and hormonal stress reactivity (RHA/Verh ≠ RLA/Verh)	Amphetamine induced behavioural sensitisation (RHA/Verh only) Altered 5-HT and 5-HIAA in the cortex, hypothalamus, hippocampus, pons/medulla following shock stress (RHA/Verh ≠ RLA/Verh) DA levels in the striatum following shock stress (RHA/Verh < RLA/Verh)	ACTH, corticosterone, prolactin, VP mRNA in PVN (RHA/Verh < RLA/Verh) GR in hippocampus and pituitary (RHA/Verh > RLA/Verh) Dopaminergic (nucleus accumbens), GABAergic (cortex) neurotransmission (RHA/Verh > RLA/Verh) Splenic T-lymphocyte and natural killer cell activity (RHA/Verh < RLA/Verh) Response to serotonergic reuptake inhibitors in frontoparietal cortex (RHA/Verh > RLA/Verh) Catabolism of progesterone-derived, anxiolytic neurosteroids in the frontal cortex and BNST (RHA/Verh > RLA/Verh) VEP augmenting and reducing (RHA/Verh ≠ RLA/Verh) QTL (RHA/Verh ≠ RLA/Verh)

Floripa high (H) and low (L) rats	Locomotion in the centre of a novel open field for 5 min	Anxiety- (plus-maze, light-dark box) and depressive-related (immobility during forced swimming) behaviour (Floripa H < Floripa L) Voluntary oral alcohol intake (female Floripa H < female Floripa L)	Not known	Not known
High anxiety-related behaviour (HAB) and low anxiety-related behaviour (LAB) rats	Open arm time in elevated plus-maze for 5 min	Open arm time up to 16 months of age (HAB < LAB) Time spent and distance travelled in centre of open field and modified hole board (HAB < LAB) Pups ultrasound isolation calls (HAB > LAB) Freezing behaviour, ultrasound vocalisation during social defeat (HAB > LAB) Active social interaction, light-dark box (HAB < LAB) Baseline fear-sensitised acoustic startle response (HAB < LAB) Voluntary oral alcohol intake (HAB < LAB) Depressive-related floating (HAB > LAB) and struggling (HAB < LAB) behaviour during forced swimming Awake time (HAB < LAB), non-REM sleep (HAB > LAB) Social discrimination not observed in LAB	Attenuation of stress-induced elevation of plasma corticotropin, corticosterone, and improvement of depressive-related behaviour during forced swimming by repetitive transcranial magnetic stimulation only in HAB Chronic SSRI treatment improved depressive-related behaviour during forced swimming only in HAB CRH type 1 receptor antagonist attenuated stress-induced sleep disturbances especially in HAB SSRI-induced attenuation of CRH-stimulated increase in ACTH and corticosterone secretion and decrease of hypothalamic vasopressin mRNA only in HAB Treatment with vasopressin V ₁ receptor-antagonist into the PVN decreased anxiety-like (plus-maze) and depressive-related (forced swimming) behaviour in HAB	HPA axis activation following mild stress (HAB > LAB) or social defeat (HAB < LAB) mRNA expression and release of vasopressin in the PVN (HAB > LAB) Basal V _{1a} -binding sites in lateral septum (HAB > LAB rats) Polymorphisms in the promoter region of the vasopressin gene in HAB Fos expression in specific brain areas following social defeat (HAB ≠ LAB)
Other approaches	See text for details			

Sprague–Dawley rats differed in their response to a novel environment, which predicted individual differences in response to the psychostimulant drug amphetamine. In detail, a random cohort of rats was tested individually in a novel circular corridor for 2 h. Based upon locomotor activity levels measured by photocell counts, the animals were subjected to a median split, which categorised each animal as either high responder (HR) or low responder (LR). Then, these animals were tested for intrajugular self-administration of amphetamine. While HR rats acquired self-administration of amphetamine, LR rats did not. The relationship between amphetamine and reactivity to a novel environment was further supported by a positive correlation between the magnitude of the response to novelty and their subsequent reactivity to systemically injected amphetamine as indicated by locomotor activity and self-administration. That is, HR animals with a more rapid locomotor response to intraperitoneal amphetamine also more rapidly acquired self-administration. The two groups also responded differently with respect to behavioural sensitisation, which occurred when amphetamine was repeatedly administered. While LR rats developed sensitisation, the HR group did not. In fact, HR rats behaved as if they had been sensitised, that is, the locomotor response of LR rats during the first 30 min of each test showed a progressive increase and reached the stable high level of HR rats by the fourth amphetamine injection. The authors concluded that an individual's propensity to develop amphetamine self-administration can be predicted by its reactivity to a new environment (Piazza et al., 1989, 2000).

A number of subsequent studies from this same group revealed additional differential characteristics in the two subgroups (reviewed by Dellu et al., 1996). The differences in psychomotor activation appeared to be consistent over at least one half of a rat's life span, as indicated by a longitudinal study. Thus, HR and LR rats screened at the age of 2 months still showed comparable differences after 3 and 16 months but not at 24 months of age (Dellu et al., 1994; Piazza et al., 1990). In another longitudinal study, poor cognitive functions were followed in HR rats: at the age of 25 months, which is a rather old age for rats, they showed memory impairments in a Y-maze discrimination task relative to LR rats (Dellu et al., 1994). In a free exploratory paradigm, HR rats visited a novel arm in a Y-maze more often than LR rats, despite fewer overall visits of all arms by HR animals. The latter rats also had a reduced latency to emerge into the light area and a higher frequency of visits in the aversive illuminated compartment in a dark–light emergency test as compared to LR rats (Dellu et al., 1993); this is indicative of less anxiety-like/avoidance behaviour in HR rats. Also, natural reinforcers such as food were consumed faster in deprived HR rats compared to LR rats. In contrast, food consumption under normal conditions was comparable in both subgroups, indicating that basic metabolic processes are probably not involved (Dellu et al., 1996).

Additionally, neuroendocrine differences were observed. Initially, both subgroups showed similar increases in plasma corticosterone levels after 30 min in response to continuous mild stressor exposure of a novel environment. However, while the concentrations fell to baseline in LR rats thereafter, corticosterone levels in HR rats were sustained even 2 h after the onset of continuous stressor exposure (Piazza et al., 1991a). According to the authors, this may be due to the fact that HR rats explored more and thus exposed themselves to greater stress. Furthermore, corticosterone administration in LR rats increased while in HR rats it decreased the reinforcing value of intracardiac amphetamine self-administration. These results indicate that stress-related activity of the hypothalamus–pituitary–adrenal (HPA) axis (review by Hübener and Staib, 1965) may be important for substance-induced addiction (Piazza et al., 1991a).

Neurochemical characteristics have also been observed. As an index of basal dopaminergic activity, the levels of dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), were measured. In HR rats, the DOPAC:DA ratio was higher in the nucleus accumbens and lower in the prefrontal cortex. Further, they showed lower levels of 5-HT and the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) in the prefrontal cortex, nucleus accumbens, and the dorsal striatum compared to LR rats (Piazza et al., 1991b). Both subgroups also differed in their reactivity to a tail pinch stressor. Extracellular DA concentrations in the nucleus accumbens peaked at about 30 min after the end of tail pinch stress in both subgroups. However, while DA release was always lower in LR than HR rats and returned to baseline levels, they remained high at least 2 h after stress exposure in HR rats (Rougé-Pont et al., 1993). When analysing basal neurochemical differences between HR and LR rats, HR rats appear to have a lower expression of factors that exercise an inhibitory regulatory output on dopaminergic neurons in the ventral tegmental area, e.g. cholecystokinin and a lower somatodendritic release of DA. In contrast, HR rats exhibited a higher expression of factors that have an excitatory control on dopaminergic cells, e.g. preprodynorphin and preproenkephalin in the nucleus accumbens (Lucas et al., 1998). Other evidence suggests individual differences in tail-pinch stress-induced accumbal DA release to be modulated by corticosterone (Rougé-Pont et al., 1998). HR rats showed a higher and longer stress-induced accumbal DA release compared to LR rats which became similar to each other after corticosterone blockade (Rougé-Pont et al., 1998). Finally, these rats differed in their levels of neurogenesis in the adult dentate gyrus evaluated by the incorporation of 5-bromo-2'-deoxyuridine (BrdU) in progenitors, since cell proliferation in LR rats was twice as high as compared to HR animals (Lemaire et al., 1999).

Taken together, HR and LR rats are the first subgroups of unselected animals that showed systematic variation in their behaviour, endocrinology, and neurochemistry. These studies have inspired and influenced the following differentiation of unselected rats.

4.1.2. High rearing activity (HRA) and low rearing activity (LRA) rats

The abovementioned HR and LR rats are thought to reflect the expression of a trait (Dellu et al., 1996), which may be comparable to the sensation-seeking trait in humans (Zuckerman, 1984). These classifications have often been applied to study mechanisms of stress and addictive susceptibility in animal models (for reviews see Cools and Gingras, 1998; Dellu et al., 1996). It was recently shown that rearing in a novel open field can also be used to systematically differentiate between unselected male outbred Wistar rats (Thiel et al., 1998, 1999). These subgroups are termed high rearing activity (HRA) or low rearing activity (LRA) rats (Fig. 1). It is known that spontaneous (i.e. undrugged) rearing and locomotor activity in a (novel) open field are often positively correlated (Borta and Schwarting, 2005a; Thiel et al., 1999). Screening procedures using locomotion (HR and LR), or rearing (HRA and LRA) gauge similar, but probably not identical mechanisms. It has been suggested, for example, that spontaneous locomotor activity largely reflects exploratory behaviour, whereas rearing may also be determined by emotionality (Gironi Carnevale et al., 1990; Thiel et al., 1998). Interestingly, a stronger rearing response of HRA rats probably also reflects reactivity to novelty, since such rats also showed more exploratory activity in a novel object test (Pawlak and Schwarting, 2002; Fig. 2). This study also showed that exploration of novel objects was not related to horizontal locomotion. Furthermore, differences between HRA and LRA rats disappeared with repeated exposure to the same environment, which was due to stronger habituation in HRA rats

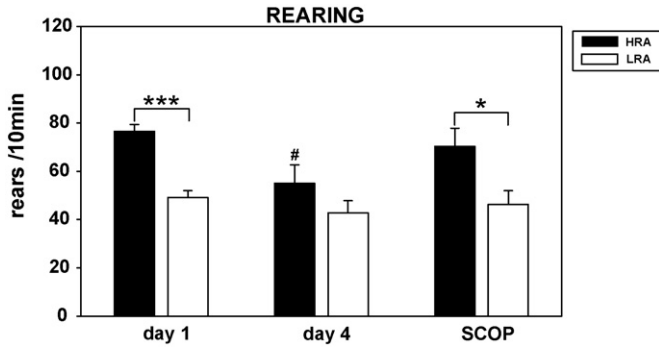


Fig. 1. Rearing behaviour in the open field measured as the number of times (means \pm S.E.M.), the animals reared on their hind legs. On four consecutive days (days 1–4; days 2, 3 not shown), the rats were tested in the undrugged state (10 min each); then, on the fifth day, they received an injection of 0.5 mg/kg scopolamine (SCOP; i.p.) and were again exposed to the open field. Based on number of rearings in a novel open field (day 1), the animals were assigned to two subgroups, with either high (HRA; black bars) or low rearing activity (LRA; open bars). * $P < .05$, *** $P < .001$ represent significant difference between HRA and LRA rats; # $P < .05$, represents within-group changes between scopolamine and behaviour on day 4. Adapted from Thiel et al. (1999).

(Thiel et al., 1998, 1999; Fig. 1). Nevertheless, the HRA and LRA designations appear to reflect a stable trait, since they can still be observed when such rats are again tested in other novel open fields (Pawlak and Schwarting, 2005a).

Finally, differences in open field rearing behaviour seen in HRA and LRA rats did not correspond to anxiety-related profiles in an elevated plus-maze (Borta, 2006; Borta and Schwarting, 2005b; Ho et al., 2002; Pawlak and Schwarting, 2002; Schwarting et al., 1998; Thiel et al., 1999). So far, there was only one study showing that anxiety-like/avoidance behaviour in an elevated plus-maze was higher in the HRA compared to LRA rats (Borta and Schwarting, 2005a). On the other hand, HRA and LRA rats differed in an inhibitory avoidance test, since HRA had shorter retention scores, that is, HRA rats showed lower step-in latencies after shock experience than LRA rats (Borta and Schwarting, 2005a).

In a radial maze task, food-deprived HRA rats consistently needed less time to obtain and consume all pellets than LRA rats, which was due to faster locomotion on the arms and less time spent at the food pits. During the initial days of training, they were

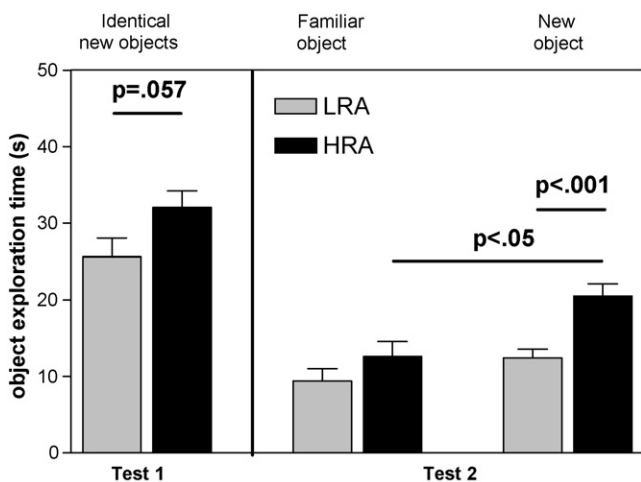


Fig. 2. Data reflect means \pm S.E.M. of exploration time (s) in a novel object test with two novel identical objects (Test 1), and one familiar and one novel object (Test 2). Each test lasted 3 min, with a 15 min intertrial interval. High (HRA; black bars) or low rearing activity (LRA; light bars). Adapted from Pawlak and Schwarting (2002).

also more efficient in obtaining all food pellets available. Furthermore, HRA rats visited more arms and made relatively less reference memory errors than LRA rats. This allowed them to forage food quickly, but was paralleled by more working memory errors than in LRA rats (Görisch and Schwarting, 2006).

The trait hypothesis of stable activity behaviour is further supported by pharmacological and neurochemical data, showing that HRA and LRA rats also differ in their behavioural reactivity to cholinergic drugs. Evidence was obtained in a psychopharmacological study, which found a stronger psychostimulatory activation of rearing activity and centre time but not horizontal locomotion to the muscarinic antagonist scopolamine in HRA rats (Thiel et al., 1999; Fig. 1). Additionally, rearing behaviour sensitised earlier in systemically nicotine-treated HRA than LRA rats, and a sensitised locomotor response to the cholinergic agonist nicotine was initially observed only in HRA rats, and became apparent for LRA rats only after retesting the animals (Pawlak and Schwarting, 2005a; Fig. 3). When comparing these subgroups in an unbiased

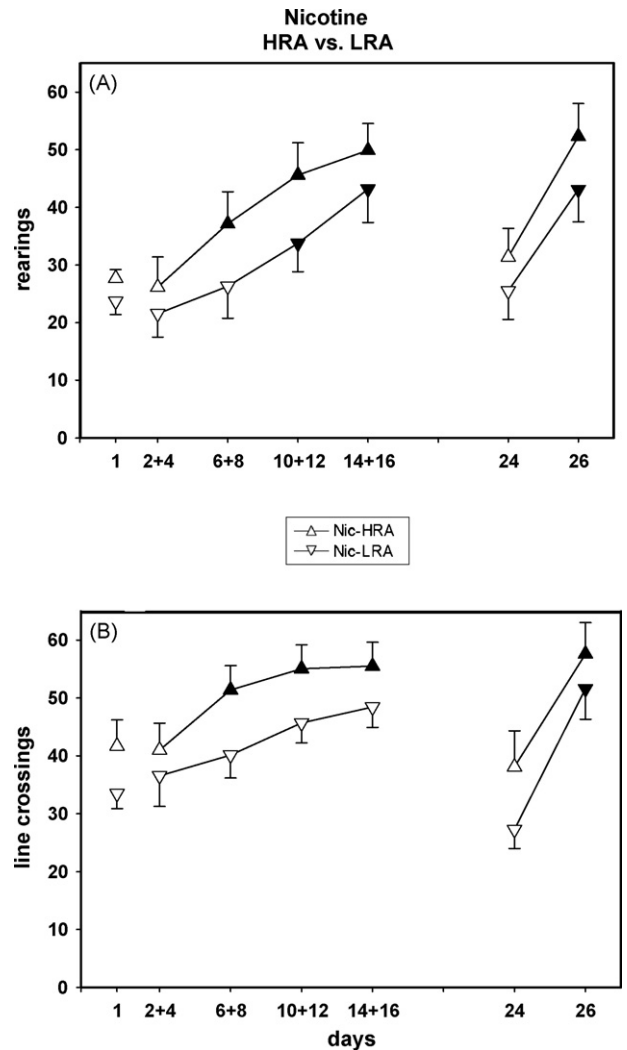


Fig. 3. Rearing activity (A) and locomotor activity (B) during sensitisation behaviour of high (Nic-HRA; triangles) and low rearing activity (Nic-LRA; inverted triangles) nicotine-treated rats. Behaviour was recorded during baseline (day 1, drug-naive animals in the entire apparatus), during repeated systemic i.p. treatments with nicotine (days 2 + 4, 6 + 8, 10 + 12, 14 + 16), in a test of conditioned sensitisation (saline only; day 24), and in a final test for expression of sensitisation (nicotine; day 26). Differences within groups (versus day 2 + 4) are indicated by filled symbols ($P < .05$). Data reflect means \pm S.E.M. Adapted from Pawlak and Schwarting (2005a).

model of conditioned place preference, rearing behaviour in the nicotine treatment quadrant was initially higher in HRA than in LRA rats (Pawlak and Schwarting, 2005a). In contrast, HRA versus LRA rats did not differ in voluntary or forced consumption of oral nicotine, or water (Pawlak and Schwarting, 2002).

Neurochemically, HRA rats exhibited higher ventral and dorsal striatal DA activity than LRA rats and lower 5-HT levels in the medial prefrontal cortex, but exhibited no group differences in the hippocampus or amygdala (Thiel et al., 1999). When differentiating rats into “superior” versus “inferior” learners according to their habituation characterised by rearing activity to re-exposure to an initially novel open field, the superior rats showed increased hippocampal cholinergic activity in the novel environment and also 24 h later during open field re-exposure (Thiel et al., 1998). Behavioural activity in an open field, however, was not related to brain (striatum, prefrontal cortex, hippocampus, amygdala), or peripheral (adrenal glands, spleen) mRNA (messenger ribonucleic acid) levels of cytokines (interleukin(IL)-1 β , IL-2, IL-6, tumour necrosis factor- α) measured post-mortem (Pawlak and Schwarting, 2005b).

Finally, relating rearing behaviour to the course of an immune-mediated disease in clinic modeling randomized trials of sepsis in rats may offer a first approach to translational disease research (Bauhofer et al., 2001). Recently, rearing activity in an open field appeared to be affected more in active animals depending on the mortality rate in a sepsis model. Measures of high and low responder for locomotion and rearings showed interaction effects over time pointing at a differential role for baseline activity towards recovery from sepsis (Bauhofer et al., submitted for publication). In general, these results support previous evidence on individual differences to disease susceptibilities (e.g., Sajti et al., 2004).

4.1.3. Low exploratory (LE) and high exploratory (HE) activity rats

A recent model of the group by Harro et al. distinguishes between rats with low exploratory (LE) and high exploratory (HE) activity using an exploration box test (Harro et al., 1995). This test uses three unfamiliar objects and one familiar aliment (a glass jar, a cardboard box, a wooden handle, and a food pellet), which remain in the same place throughout repeated test days (Harro et al., 1995; Otter et al., 1997). The test is unique in the sense that it provides a relatively dichotomous distribution of male Wistar (and Sprague–Dawley) rats on the second, but to a lesser extent on the first, day of exposure to the apparatus (Altoa et al., 2005), with high retest reliabilities for five consecutive test days (Mällo et al., 2007). Interestingly, an array of behavioural measures (e.g., horizontal and vertical activity, exploration of the three unfamiliar objects) is used as an index of exploration considering both the elements of inquisitive and inspective exploration (i.e. exploration of the environment as a whole versus exploration of particular items; Harro et al., 1995).

These exploratory activities were found to be moderately correlated with indices of anxiety- and depression-related behaviours (Mällo et al., 2007). Furthermore, Sprague–Dawley HE animals showed lower sucrose intake and preference than LE rats during the first testing. Wistar LE animals exhibited an anxiety-like behavioural profile in an elevated plus-maze compared to HE animals, which became even more pronounced on the following test day. However, HE animals displayed higher levels of freezing behaviour during fear conditioning on day 1 only, while the freezing levels in the LE group remained almost unchanged compared to the following testing day. Finally, in a forced swim test, only in HE animals the immobility time was decreased and swimming was increased on the second day of testing (all results from Mällo et al., 2007).

The LE and HE rats have been investigated particularly with regard to reactivity to monoaminergic neurotransmission. For example, treatment with the neurotoxin DSP-4 (*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine), which is selectively toxic for the locus coeruleus noradrenergic projections had different effects on spontaneous, amphetamine-stimulated (Altoa et al., 2005), and amphetamine-sensitised (Altoa et al., 2007) behaviour in LE and HE animals. In addition, DSP-4 locus coeruleus partial denervation also decreased post-mortem 5-HIAA and DA and its respective metabolite levels in the nucleus accumbens, and DOPAC content in the frontal cortex only in LE rats (Altoa et al., 2007). Hence, the authors suggest that in LE, but not HE rats, the baseline dopaminergic activity in the nucleus accumbens is dependent on intact noradrenergic projections from the locus coeruleus. Further, all reductions in these measures were normalised by repeated amphetamine treatment (Altoa et al., 2007). More specifically, in vivo microdialysis studies have revealed that LE rats also had lower extracellular DA levels in the striatum in baseline conditions as well as in response to amphetamine administration; however, in contrast to post-mortem analyses (Altoa et al., 2007) no difference in dopaminergic activity between LE and HE animals was detected in the nucleus accumbens (Mällo et al., 2007). Finally, in vivo baseline extracellular levels of 5-HT were similar in both groups in the medial prefrontal cortex and dentate gyrus (Mällo et al., 2008). However, LE animals had significantly higher levels of 5-HT transporter binding in the medial prefrontal cortex and a larger increase in extracellular 5-HT levels after administration of the 5-HT reuptake inhibitor citalopram into this area by retrograde dialysis, while showing a lower increase in extracellular 5-HT in the dentate gyrus during citalopram perfusion (Mällo et al., 2008).

Finally, molecular analyses revealed that LE rats showed higher levels of neuronal activity measured by relative oxidative metabolism (cytochrome *c* oxidase) in dorsal raphe and inferior colliculi. In contrast, HE rats had higher metabolic activity in entorhinal cortex (Matrov et al., 2007), and higher levels of BDNF mRNA in the prefrontal cortex (Mällo et al., 2008).

4.2. Psychomotor activity and exploratory behaviour: selective breeding

4.2.1. Apomorphine-susceptible (APO-SUS) and apomorphine-unsusceptible (APO-UNSUS) rats

In this test, male rats are treated with the DA receptor agonist apomorphine and the drug-dependent gnawing response is measured. This differentiation resulted in the selectively bred apomorphine-susceptible (APO-SUS) and apomorphine-unsusceptible (APO-UNSUS) lines (Cools et al., 1990; Ellenbroek et al., 2000). The APO-SUS rats show a strong, stereotyped gnawing response (>500/45 min), whereas APO-UNSUS show only a weak gnawing response (<10 counts/45 min). Follow-up studies have shown that the phenotypical expression of these rats depends on genetic and early and late environmental factors (review by Ellenbroek and Cools, 2002).

The basis for these two lines was a bimodal distribution in a number of different behaviours in outbred Wistar rats. Although the apomorphine stereotypy test is the paradigm used to selectively breed APO-SUS and APO-UNSUS rats, it is important to realise that there are at least two alternative methods to select animals with the same neurobiological structure from an outbred Wistar population (Cools and Gingras, 1998; Ellenbroek and Cools, 2002). The first is to observe their reactivity to novelty in a relatively large novel open field (160 cm \times 160 cm), i.e. a table without external cues (including walls). Using this test, HR and LR rats are identified based on their locomotor response to novelty, which showed close resemblance to those described by Piazza et al.

(1989), including the time to habituate to the environment (Cools et al., 1990). The second alternative is the resident–intruder test, where the experimental (intruder) rat is allowed to enter the home cage of a much larger (resident) rat that is temporarily constrained in a small cage. Following removal of the constraining cage, the resident rat can freely interact with the intruder. In this test, freezing and fleeing of the intruder serve as the critical variables (Cools et al., 1990). This test allows the separation of rats that primarily flee (FLEE rats) and rats that primarily freeze (NON-FLEE rats). The focus in the following section will lie on APO-SUS and APO-UNSUS rats, however, since they appear to have been studied most thoroughly.

With regard to other behaviours, the APO-SUS rats fulfilled the criteria for HR rats in a novel open field and fled more in the resident–intruder test (Cools et al., 1990). Moreover, APO-SUS rats had an increased startle response and a diminished prepulse inhibition of the acoustic startle compared to that of APO-UNSUS animals (Ellenbroek et al., 1995). The latter are also marked by relatively high two-way active avoidance performance and lower baseline locomotor activity (Cools et al., 1993a).

Based on various data, it is suggested that APO-SUS rats could have an increased vulnerability to cardiovascular diseases such as hypertension (Ellenbroek and Cools, 2002). One indication is that APO-SUS rats were less sensitive to the relaxation effects of the β_2 -adrenoceptor agonist salbutamol and the α_2 -adrenoceptor agonist clonidine in mesenteric resistance arteries (Smits et al., 2002). They are also more susceptible to the locomotor-activating properties of amphetamine (Cools et al., 1997). Moreover, when agents are locally applied to the nucleus accumbens, APO-SUS rats showed stronger phenylephrine-induced (α -noradrenergic agonist) locomotor activity and more stable ergometrine-induced (DA receptor agonist) induced locomotor activity (Cools et al., 1990). The reported differences extend beyond the dopaminergic system and its major neuroanatomical correlates, since they involved also dynorphin B in the hippocampus. In this brain area, novelty-induced dynorphin B was differently expressed in APO-SUS compared to APO-UNSUS rats (Cools et al., 1993a). Dynorphin B seems to be important for information flow signaling environmental novelty (van Abeelen, 1989).

APO-SUS and APO-UNSUS rats also differ in parameters related to the HPA axis, since APO-SUS rats have more hippocampal mineralocorticoid receptors, more corticotropin-releasing hormone (CRH) mRNA expression, and a higher synaptic density in the nucleus paraventricularis (PVN) of the hypothalamus (Mulders et al., 1995a; Rots et al., 1995, 1996). Additionally, APO-SUS rats showed higher basal plasma levels of adrenocorticotropic hormone (ACTH), but lower basal plasma levels of free corticosterone (Rots et al., 1995). When stressed, a stronger and longer-lasting increase in ACTH and acutely higher (later on a lower) corticosterone plasma levels became evident in APO-SUS compared to APO-UNSUS rats paralleled by a reduced prolactin response (Rots et al., 1995, 1996). Furthermore, mild open field stress induced fewer Fos-like immunoreactive nuclei in the PVN in APO-SUS rats (Mulders et al., 1995b). Finally, APO-SUS rats have a higher body weight (Rots et al., 1995; Smits et al., 2002), which was also reported for striatal, hippocampal, and adrenal tissues in contrast to the olfactory bulbs (Cools et al., 1990). Overall, the authors suggest a reduced feedback in the HPA axis in APO-SUS rats.

Interestingly, these two lines have also been characterised concerning some immune functions. Ellenbroek and Cools (2002) and Cools and Gingras (1998) state that APO-SUS rats showed alterations in various cellular immune functions, such

as higher number of macrophages in the thymus (Cools et al., 1993b), lower amounts of peripheral number of natural killer cells, T-lymphocytes and higher counts of B-lymphocytes, as well as more regulatory T-lymphocytes in the spleen, but original data have not been published for any of these results to the best of our knowledge. Nonetheless, APO-UNSUS compared to APO-SUS rats were more vulnerable to develop experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (Cools et al., 1993b). Additionally, APO-SUS rats showed a much stronger immunoglobulin (Ig)E response by B-lymphocytes in the presence of IL-4 to a parasitic infection (Kavelaars et al., 1997). Accordingly, cytokine responses of splenocytes revealed that the ratio of mRNA expressions for interferon (IFN)- γ and IL-4 was smaller in naive APO-SUS than in APO-UNSUS rats. Among other cytokines, IL-4 provides help for B-lymphocyte differentiation and humoral immune responses. Overall, APO-UNSUS rats appear to have an increased susceptibility to inflammatory (i.e. EAE) and a lower vulnerability for infectious diseases, respectively (Kavelaars et al., 1997). Further support for this humoral B-lymphocyte-driven dominance came from a study that investigated the extent of periodontitis (Breivik et al., 2000). According to the model of Breivik et al. (1996), a B-lymphocyte-driven dominance greatly increases the susceptibility for periodontitis. In agreement with this, APO-SUS rats appeared to be much more susceptible to developing periodontitis than APO-UNSUS rats.

Together, comprehensive analyses of the two bred rat lines, APO-SUS and APO-UNSUS, revealed extensive behavioural differences that appear to reflect complementary differences in the central and peripheral nervous system, and in the endocrine and immune system.

4.2.2. High responder (HR)-bred and low responder (LR)-bred rats

The abovementioned HR versus LR model is an established paradigm for studying systematic variation in spontaneous novelty-seeking behaviour and susceptibility to drug abuse in unselected rats (Piazza et al., 1989). The research group of Akil also found spontaneous differences in anxiety-like/avoidance behaviour and reactivity to contextual and psychosocial stressors in unselected Sprague–Dawley rats (Kabbaj and Akil, 2001; Kabbaj et al., 2000, 2001). They also observed differences in the levels of central immediate early gene *c-fos* expression implicated in emotionality under basal conditions and upon stress challenge (Kabbaj and Akil, 2001; Kabbaj et al., 2004). These differences were observed not only in the mesolimbic DA circuitry, but also in neural structures implicated in stress, anxiety and emotional reactivity, including the amygdala, hippocampus, hypothalamus and prefrontal cortex (Kabbaj, 2004; Kabbaj et al., 2004).

Further, reduced expression levels of glucocorticoid receptors (GR) in the hippocampus of HR unselected rats were found (Kabbaj et al., 2000), which would diminish the GR-mediated negative feedback on corticosterone, thereby explaining the prolonged corticosterone response reported by Piazza et al. (1991a). The increase in hippocampal GR expression in LR compared to HR rats was shown to be related to enhanced anxiety-like/avoidance behaviour in an elevated plus-maze, as blockade of the GR hippocampal receptors increased exploration and decreased anxiety-like/avoidance behaviour in LR rats (Kabbaj et al., 2000). Basal gene expression differences have also been shown for CRH, with increased CRH mRNA levels in the hypothalamic PVN, and reduced levels in the central nucleus of the amygdala of HR rats (Kabbaj et al., 2000). Analysis of hippocampal gene expression of HR and LR rats has also been addressed using deoxy-ribonucleic acid (DNA) microarrays. DNA microarrays allow a quick and

simultaneous analysis of several thousands of gene expressions on mRNA level produced by recently transcribed DNA sequences. Kabbaj et al. (2004) identified large numbers of differences between these rats both, basally and in response to social defeat in a resident–intruder paradigm, including genes involved in intra- and extracellular signaling, receptor activity, and neurogenesis. This evidence is supported by the qualitatively different pattern of the immediate early gene *c-fos* activation in HR rats exhibiting higher *c-fos* expression than LR rats in the dorsal striatum and other areas upon exposure to a novel situation (Kabbaj and Akil, 2001).

It was repeatedly shown that unselected HR rats are more prone for self-administration of and reactivity to psychostimulants, including cocaine, and amphetamines, than LR rats (review by Bardo et al., 1996). Further, chronic social defeat evens out individual differences in cocaine self-administration so that HR and LR are no longer distinguishable, and finally both groups exhibited substantial levels of drug-taking behaviour (Kabbaj et al., 2001). The results suggest that some animals (HR) might seek drugs because of their high propensity for novelty-seeking, while others (LR) might seek drugs as a reaction to social stress (Kabbaj et al., 2004). The neural and molecular levels of these mechanisms that lead to vulnerability to addictive behaviour remain to be elucidated (Kabbaj et al., 2004).

Recently, the group of Akil has started a breeding programme. They confirmed their previous evidence and extended the findings to selectively HR-bred and LR-bred rats, which stem from a colony of outbred Sprague–Dawley, reporting on several behavioural measures in the eighth generation of these two lines (Stead et al., 2006). The HR-bred and LR-bred animals were differentiated by summing horizontal locomotor and rearing activities in a novel activity box for 60 min. The results showed that the phenotype is strongly heritable, that measures of novelty-seeking and spontaneous anxiety-like/avoidance behaviour remain correlated, that maternal factors have only small effects on activity scores but do modulate spontaneous anxiety-like/avoidance behaviour, and that activity in an open field after 10 days of oral benzodiazepine treatment is higher in HR-bred than in LR-bred animals (Stead et al., 2006). In contrast to their previous findings (Stead et al., 2006), no differences in anxiety-like behaviours were found in HR-bred and LR-bred rats in a light–dark box test (Ballaz et al., 2007). Moreover, LR-bred animals exhibited increased anxiety-like behaviour on re-exposure to an elevated plus-maze but only if both trials were preceded by a light–dark box test (Ballaz et al., 2007). Finally, novelty-induced locomotion did not change over time, but prenatal stress reduced anxiety-like behaviour in LR-bred rats compared to unstressed LR-bred controls (Clinton et al., 2008). Prenatal stress differentially impacted on corticosterone stress responses: LR-bred pups (25-day old) showed an exaggerated corticosterone stress response upon forced novel open field exposure, whereas HR-bred rats produced an exaggerated corticosterone stress response only as adults, when comparing each group with their respective prenatally unstressed control group (Clinton et al., 2008).

Together, this body of evidence on novelty-seeking, drug self-administration, stress responsiveness, and spontaneous anxiety-like/avoidance behaviour suggests that unselected HR and LR, and HR-bred and LR-bred rats respond differentially to rewarding stimuli, exhibit fundamental differences in emotional reactivity, and interact differently with their environment across numerous conditions. The recently selectively bred lines may be helpful as an additional stable tool to elucidate further the mechanisms that underly the differential behaviour related to novelty-seeking, and intake of psychostimulants.

5. Individuality in anxiety models

5.1. Anxiety and fear as two distinct behavioural systems

The use of the word “anxiety” dates back to Middle High German, and “fear” dates back to the Old German period (Paul, 2006). Both words were used in different context: “Fear” often in combination with, for example, religious issues, and “anxiety” linked with misery, pain, and affliction (Paul, 2006). Personality researchers nowadays have acknowledged that anxiety and fear are two distinct behavioural systems (Depue and Lenzenweger, 2005; Gray and McNaughton, 2000; McNaughton and Corr, 2004; White and Depue, 1999). The categorical distinction between fear and anxiety derives from detailed analyses of defensive responses and their regulation (e.g., Blanchard and Blanchard, 1988; Graeff, 1994). For example, the studies of Depue and Lenzenweger (2005) argue for the independence of anxiety and fear within the literature on personality traits, showing that the relationship between neuroticism (anxiety) and harm avoidance (fear) is approaching zero. Additionally, one of the most reliable indices of conditioned fear in animals is behavioural inhibition (Davis et al., 1997; Panksepp, 1998; Phelps and LeDoux, 2005), which is not the case for stimulus-induced anxiety-like behaviour (Davis et al., 1997). In parallel, other personality psychologists (Tellegen and Waller, 1992), behavioural neuroscientists (e.g., Andreatini et al., 2001; Deakin and Graeff, 1991; Graeff et al., 1996) and clinical psychologists (e.g., Barlow, 2002; Yehuda and Hyman, 2005, but see Marks and Nesse, 1994) also postulate that anxiety and fear are different emotions.

5.2. Anxiety-like/avoidance behaviour: unselected animals

5.2.1. High open arm (HOA) and low open arm (LOA) rats

One approach to systematically analyse variance in an unselected cohort of male rats has been successfully employed for elevated plus-maze behaviour (Pawlak and Weyers, 2006; Schwarting and Pawlak, 2004). There, the animals are divided by a median split upon their first exposure to the apparatus into those that spend less time on the open arms (LOA; previously termed high anxiety (HA) rats), and those that spend more time on the open arms (HOA; previously termed low anxiety (LA) rats). Significant retest reliability for a period of 24 h or 120 days provides evidence for a relative stability of this dimension (Schwarting and Pawlak, 2004; Fig. 4). The HOA Wistar rats showed less avoidance behaviour of aversive objects in the unconditioned object burying test (Ho et al., 2002; Fig. 5) and faster active avoidance learning in a shuttle-box (Ho et al., 2002). In comparison to LOA rats, they also showed less freezing behaviour in a standard fear conditioning paradigm on the conditioning and test day, respectively (Borta et al., 2006; Fig. 6). Finally, LOA and HOA rats did not differ regarding immobility in the forced swim test, an animal model related to depression (Ho et al., 2002).

These results suggest that the performance of active coping behaviour might be different between LOA and HOA rats in escapable stress, but not of passive coping in inescapable stress (forced swim test). This indicates that the individual anxiety-like/avoidance level has certain correlations with the ability to cope with environmental challenges. These differences seem not to be due to pain reactivity (Borta and Schwarting, 2005a). Furthermore, there are indications for positive correlations between ultrasound vocalisation of pups and their adult behaviour in an elevated plus-maze: Pups which utter more ultrasounds during separation spent more time on the open arms as adults, that is, they showed less anxiety-like/avoidance behaviour (Schwarting and Pawlak, 2004). When these subgroups were tested in a standard fear conditioning

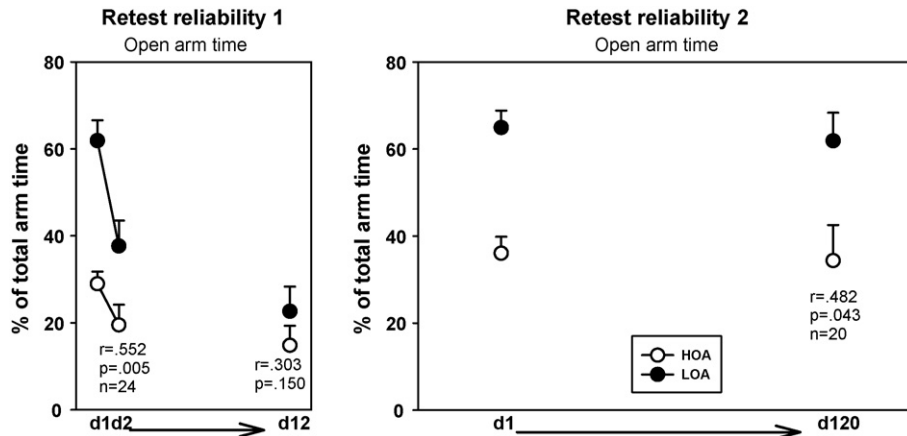


Fig. 4. Time in the open arm of an elevated plus-maze (expressed in percentage of total test time; mean + S.E.M.) in rats which were tested either on day 1 (1st exposure) and retested on days 2 and 12 (left side), or in rats which were retested 120 days after the 1st exposure. The correlation coefficients (Spearman) reflect comparisons between the given test day and the 1st exposure (d1). Based on the amount of open arm time during the 1st test (d1), the animals were assigned either to the LOA or HOA subgroup. Adapted from Schwarting and Pawlak (2004).

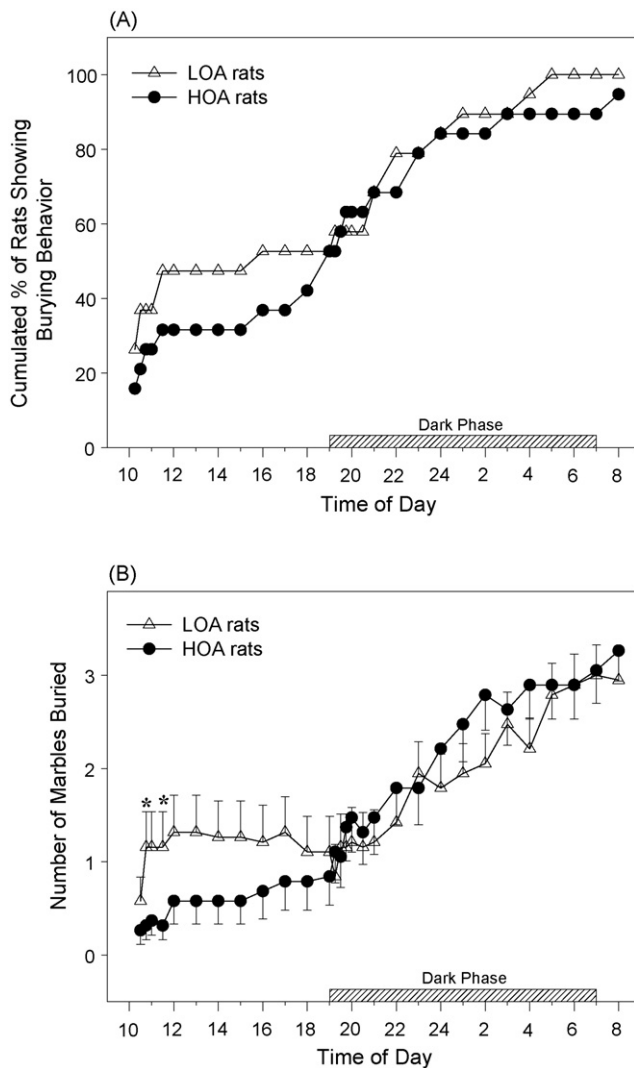


Fig. 5. Time course of cumulated % of rats showing unconditioned object burying behaviour (A) and the number (mean + S.E.M.) of marbles buried (B). Four marbles coated with Tabasco sauce were introduced into the rat's home cage at 10 h. *Indicates a difference ($P < .05$), compared with high open arm (HOA) rats at that time point. Adapted from Ho et al. (2002).

paradigm, adult LOA rats now emitted more calls, and with higher peak frequency, than their HOA counterparts (Borta et al., 2006). On the subsequent testing day, ultrasound call differences between groups were no longer detectable (Borta et al., 2006).

Interestingly, behaviour of all studies except one (Borta and Schwarting, 2005a) consistently showed no relationships between anxiety-related profiles in an elevated plus-maze and vertical psychomotor activation (rearings) in a novel open field, or activity box, performed in different laboratories, with different experimenters, and with different animal providers (Borta and Schwarting, 2005b; Ho et al., 2002; Pawlak and Schwarting, 2002; Schwarting et al., 1998; Thiel et al., 1999).

Concerning pharmacological reactivity, differences following a single systemic injection of the amphetamine analogue 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") 15 days after drug treatment became evident during active avoidance learning. There was a significant interaction between treatments and subgroups, since the number of avoidances in vehicle-treated LOA rats was lower than in vehicle-treated HOA rats. Furthermore, MDMA-treated HOA rats showed less avoidance behaviour than vehicle-treated HOA rats (Ho et al., 2004; Fig. 7). A more recent study (Ludwig et al., 2008) showed that HOA and LOA rats also responded differently to a regimen of repeated MDMA treatments. Additionally, HOA rats showed higher phasic rectal body temperature following handling stress (Ho et al., 2004).

Analyses of post-mortem neurochemistry revealed relationships between open arm time in an elevated plus-maze and 5-HT in the brain. Animals with higher anxiety-like/avoidance behaviour had lower tissue levels of 5-HT in the ventral striatum but not in other brain areas (Schwarting et al., 1998; Fig. 8). Furthermore, there were no differences between the two groups of animals with respect to NA or DA levels (Schwarting et al., 1998). Differences were obtained on neuroimmunological levels showing that LOA rats had higher striatal, and less prefrontal IL-2 mRNA – but not IL-1 β , IL-6, and TNF- α mRNA – compared to HOA rats (Pawlak et al., 2003; Pawlak et al., 2005; Fig. 9). These results indicate that the relationship between anxiety-like/avoidance behaviour, and central cytokines is site- (striatum, prefrontal cortex), and cytokine-specific (IL-2 mRNA). Subsequent striatal microinjection studies supported the otherwise correlative link between IL-2 and anxiety-related behaviour (Pawlak and Schwarting, 2006a,b; Karrenbauer et al., 2007). In addition, anxiety-like/avoidance levels in half of a female rat sample were increased by ovariectomy. After chronic treatment with dioscorea, a Chinese medicine, a decrease in

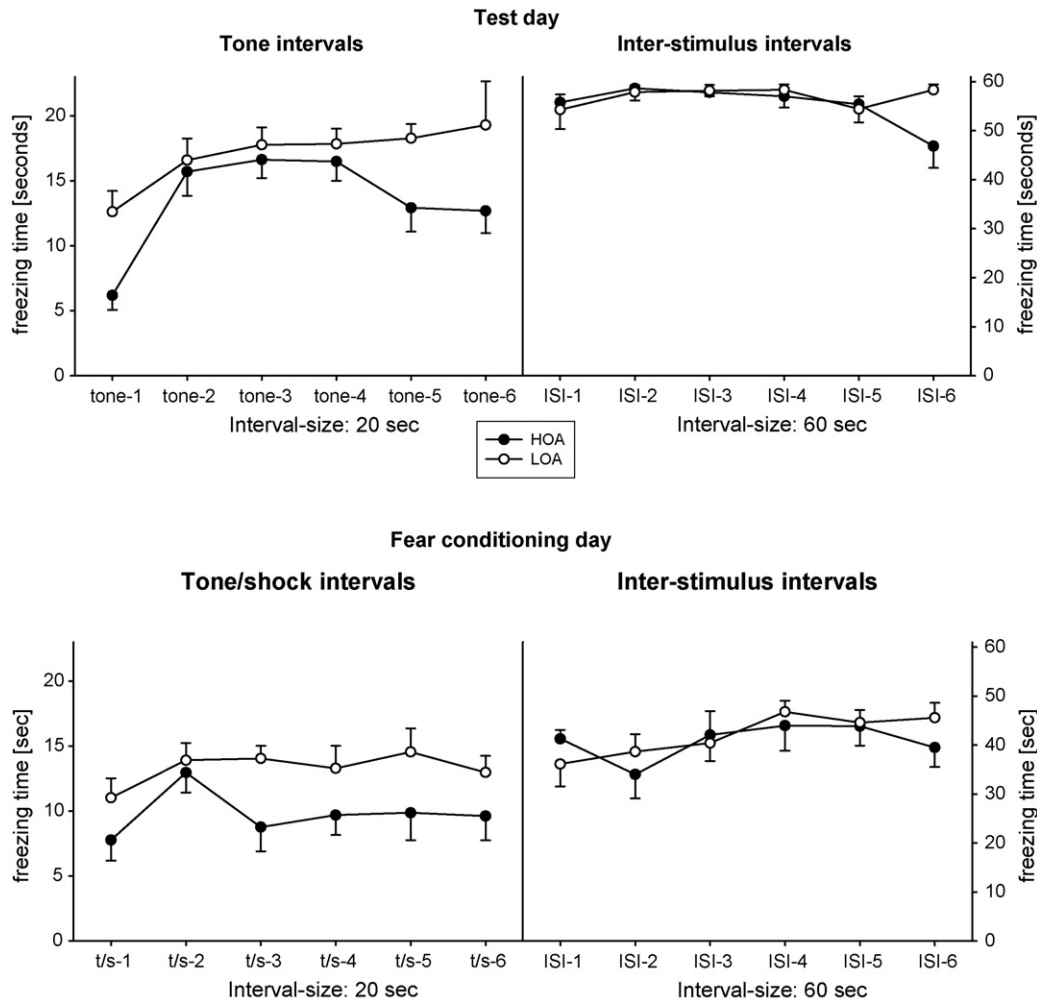


Fig. 6. Freezing behaviour (in seconds) during fear conditioning (top) and during testing (bottom) expressed separately for the six tone/shock (A; t/s-1 to t/s-6), or tone intervals (B; tone-1 to tone-6), and the six inter-stimulus intervals (A, B; ISI-1 to ISI-6). Open circles: rats with low open arm (LOA) time ($n = 10$), full circles: rats with high open arm (HOA) time in an elevated plus-maze. Adapted from Borta et al. (2006).

anxiety-like/avoidance behaviour and IL-2 levels in the cerebral cortex was observed in the LOA ovariectomised rats, whereas administration of dioscorea increased anxiety-like behaviour and IL-2 levels in the prefrontal cortex in HOA ovariectomised rats (Ho et al., 2007). Finally, D-cycloserine, a partial agonist of glycine binding site on N-methyl-D-aspartate (NMDA) receptors, was found to suppress the immobility in the day-2 trial of the forced swim test in LOA rats (Wu et al., 2008; Fig. 10). In parallel, post-mortem analyses showed that LOA but not HOA rats had increased levels of phosphorylation of extracellular signal-regulated kinase 1/2 (p-ERK1/2) in the amygdala following D-cycloserine treatment (Wu et al., 2008; Fig. 10). These findings indicate different sensitivities of p-ERK1/2, IL-2, and behavioural responses to the treatment of D-cycloserine and dioscorea between HOA and LOA rats, suggesting that the activity of NMDA receptor-mediated ERK1/2 signaling and cytokine (IL-2) function in the brain are related to individual behavioural differences of anxiety.

Taken together, the HOA and LOA Wistar rats can be distinguished in a number of behavioural paradigms, and in their pharmacological reactivity, neurochemistry, and physiology. Our approach takes advantage of the fact that there are existing systematic stable natural variances that may resemble conditions of a wide spectrum of behaviours and their related physiology. We suggest this approach to be particularly suitable to display a

continuum of a population, including extremes on both ends, rather than following a rigid selective dichotomy because our results often also showed substantial individual correlations between parameters when analysing all animals of a given sample.

5.3. Anxiety-like/avoidance behaviour: selective breeding

5.3.1. Maudsley reactive and non-reactive rats

Hall (1934) was the first who intensively analysed individual behavioural differences in rats in an open field. He assessed defecation and urination as the critical variables. Subsequently, Hall (1938) bred lines on the basis of such defecation rates. His work was taken up again by Broadhurst in London in the 1950s. These studies produced two Wistar lines that were differentiated according to their emotional reactivity in the open field, assessing their defecation rate (Broadhurst, 1957, 1960, 1962, 1975), aiming to model the human personality dimension of emotionality. These lines were termed Maudsley reactive (defecation high) and non-reactive (defecation low) rats and were maintained for males and females, respectively. Several hundreds of studies dealt with the differences between these two lines as well as some other lines derived from them showing behavioural differences in other dimensions (Blizard, 1981; Broadhurst, 1975; Eysenck and Broadhurst, 1964). The results can be summarised in the most simple

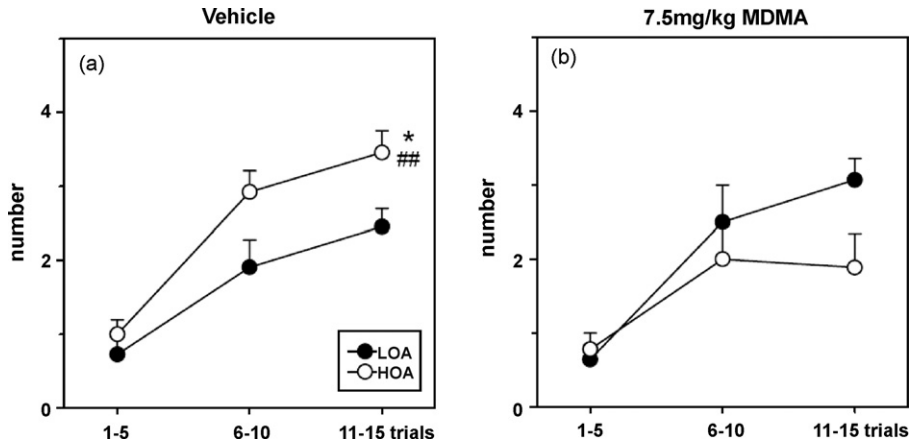


Fig. 7. The number of avoidances (mean + S.E.M.) during three consecutive blocks of five trials each in an active avoidance learning test. Fifteen days before, the animals had received either an i.p. injection of vehicle (left) or 7.5 mg/kg MDMA. *Indicates a difference ($P < .05$) between low (LOA; full circles) and high open arm (HOA; open circles) rats, and ## indicates a difference ($P < .01$) between vehicle- versus MDMA-treated HOA rats. Adapted from Ho et al. (2004).

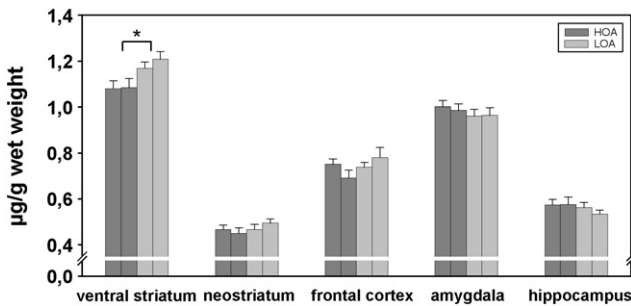


Fig. 8. Analyses of post-mortem neurochemistry of 5-HT in the brain. For each group and brain area, two bars are given, which refer to data of the left and brain hemisphere, respectively. Rats with low open arm (LOA) compared to high open arm (HOA) had higher tissue levels of 5-HT in the ventral striatum but not in other brain areas (mean + S.E.M.). * $P < .05$, represents significant difference between HOA and LOA rats (unpaired t -tests). Adapted from Schwarting et al. (1998).

form that Maudsley reactive rats yielded higher scores in several tests of anxiety-like/avoidance behaviour than non-reactive animals. However, there were also some tests showing no differences in tests for anxiety and activity. One critical reason for these ambiguous outcomes could relate to the cross-breeding of the Maudsley lines with non-genetically selected lines (Paterson et al., 2001). The disparate results and their implications for the Maudsley reactive versus non-reactive lines have been discussed (Blizard and Adams, 2002; Paterson et al., 2001). Although this approach was useful to study individual differences in anxiety-like/avoidance behaviour, it has not been pursued intensively in recent years.

5.3.2. Roman high avoidance (RHA) and low avoidance (RLA) learning rats

A number of breeding lines were selected for learning to actively avoid foot shocks in a two-way shuttle-box. However, only few breeding lines underwent intensive examinations. Probably the best known selective breeding lines are the Syracuse high and

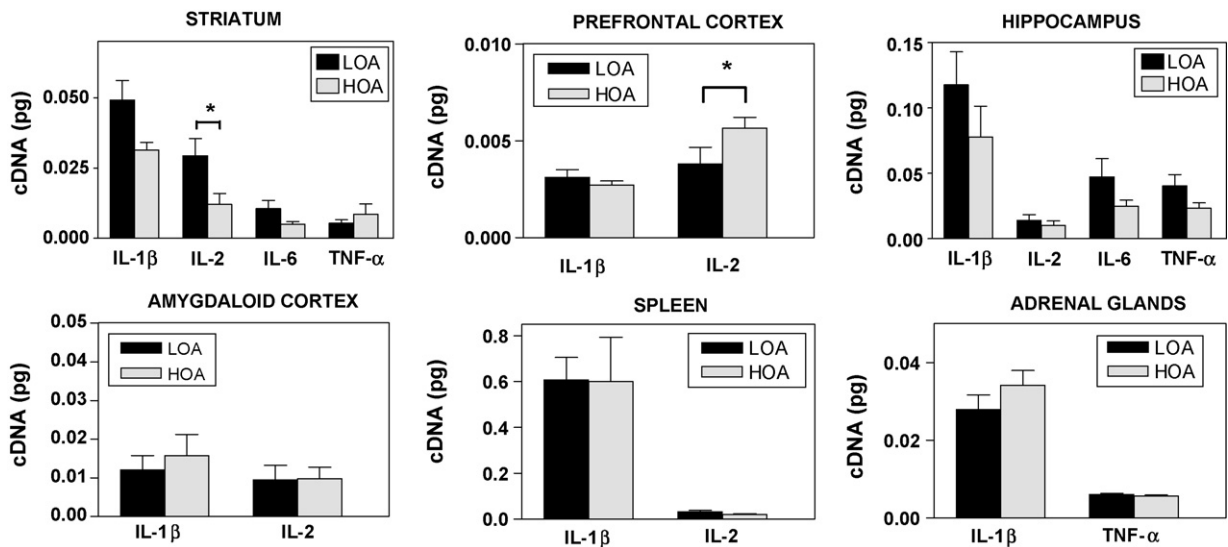


Fig. 9. Cytokine expression levels in different central and peripheral tissues of animals with high open arm (HOA) or low open arm (LOA) behaviour. Based on the percentage of open arm time, LOA compared to HOA rats expressed higher levels of IL-2 mRNA in the striatum, and lower IL-2 mRNA expression in the prefrontal cortex. Other cytokines did not differ between the two subgroups. * $P < .05$, represents significant difference between HOA and LOA rats. Data are expressed as mean + S.E.M. Adapted from Pawlak et al. (2003, 2005).

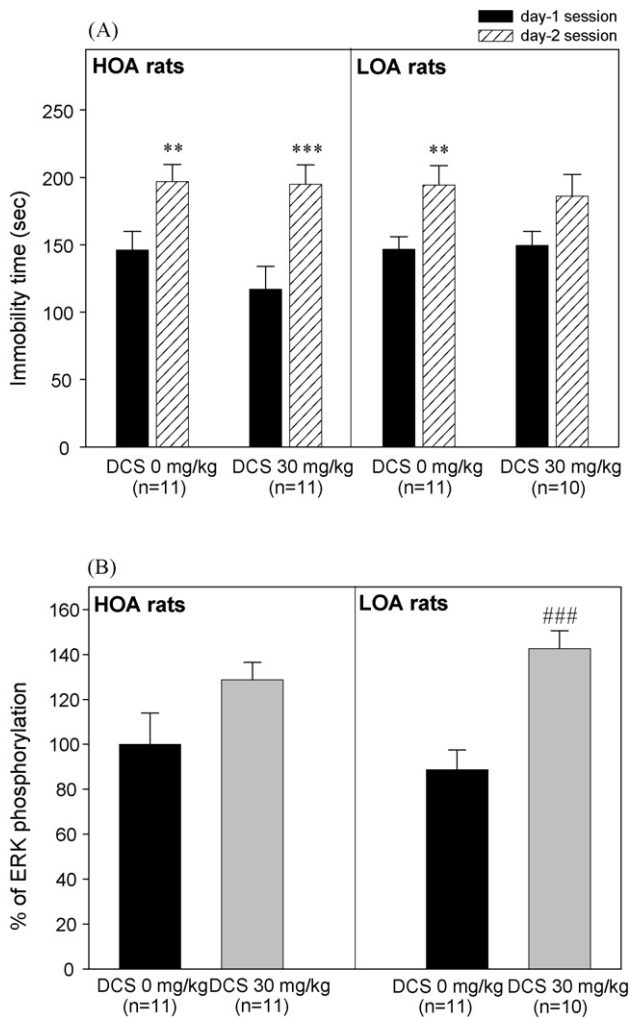


Fig. 10. Role of anxiety level in the effects of D-cycloserine (DCS) on the immobility of rats in forced swim test and the activation of ERK1/2 (p-ERK1/2) in the amygdala. Thirty minutes after the treatment of DCS (30 mg/kg, i.p.), the immobility in the day-2 trial of the forced swim test is suppressed (A) but the p-ERK1/2 level in the amygdala is increased in LOA (low open arm) but not HOA (high open arm) rats (B). Data are expressed as mean \pm S.E.M. ** $P < .01$, *** $P < .001$, compared to the day-1 session. ### $P < .001$, compared to the rats treated by vehicle in the LOA subgroup. Adapted from Wu et al. (2008).

low avoidance (SHA/Bru and SLA/Bru) Long-Evans rats (Brush, 2003; Brush et al., 1979), and the Roman high avoidance (RHA) and low avoidance (RLA) Wistar rats (Bignami, 1965). In addition, there are the Australian high and low avoidance (AHA and ALA; Bammer, 1983) Sprague–Dawley rats. The unidirectionally Tokai high avoider (THA; Shigeta et al., 1990) Jcl–Wistar rats were selected using a nondiscriminated free-operant lever-press avoidance procedure. This latter strain and the AHA/ALA lines have not been in use since the middle 1990s. Since the RHA and RLA strains may appear to be more relevant to the present topic, they will be described in more detail in the following.

The RHA and RLA colonies were divided and selectively bred for several generations, but their characteristics remained similar to the original animals (Driscoll and Bättig, 1982). Similarities (defecation frequency, Pavlovian aversive conditioning), differences (activity level, sensory and aversion thresholds to electric shock, HPA axis), and conflicting results (inhibitory avoidance learning) between RHA and RLA and SHA/Bru and SLA/Bru strains have been observed (Brush, 1991). Initially, the breeding lines were intended as psychogenetic animal models to study differences in

learning and memory (Willig et al., 1991). It was shown, however, that these rats also differ in a number of emotion-related behavioural and neuroendocrine characteristics. Thus, there appears to be less fear and anxiety-like behaviour in RHA rats compared to RLA lines (Castanon et al., 1995; Driscoll et al., 1998; Steimer and Driscoll, 2003; Yilmazer-Hanke et al., 2002).

A modified form of this strain of male rats, stemming from a Swiss laboratory and termed RHA/Verh and RLA/Verh, have been genetically selected since the early 1970s for good and poor performance in a two-way, active avoidance paradigm (Driscoll and Bättig, 1982). These strains were selectively bred on the basis of differences in learning to actively avoid foot shocks of four consecutive avoidance responses within the initial 10–20 trials of the first session in a two-way shuttle-box (Driscoll and Bättig, 1982). RHA/Verh and RLA/Verh rats subsequently showed substantial differences in anxiety-like behaviour and emotionality (i.e. tendency to freeze repeatedly, decreased exploratory activity, and increased self-grooming). On the basis of these behavioural differences, RLA/Verh rats can be regarded as more emotional than their RHA/Verh counterparts (Steimer and Driscoll, 2003). The RLA/Verh rats adopt a more passive (or reactive) coping style when confronted with a novel environment (Steimer and Driscoll, 2003; Steimer et al., 1997b; Walker et al., 1989, 1992). In an open field, elevated plus-maze, black/white box test, and in a light/dark open field test, RLA/Verh rats exhibited more anxiety-like behaviour than their RHA/Verh counterparts, whereas in a social interaction test no substantial differences were observed (Steimer and Driscoll, 2003). This latter finding was paralleled by other reports obtained in Bordeaux which failed to show differences in social interaction in RHA and RLA sublines (Chaoulloff et al., 1994). In contrast, RHA/Verh rats were less responsive to stress, showed less anxiety-like/avoidance behaviour in novel situations and appeared to be impulsive novelty-seekers (Driscoll et al., 1998). Some behavioural differences could already be observed within the early postnatal period, but the typical pattern of these sublines may develop fully only after puberty (Steimer and Driscoll, 2003). These RHA/Verh and RLA/Verh rats provide some of the rare data on behavioural and physiological responses to novelty and/or other stressful situations during the early pre-weaning period (Steimer and Driscoll, 2003).

The profile of more anxiety-like behaviour of RLA/Verh rats corresponds to altered neuroendocrine and vegetative reactivity to mild stressors (Gentsch et al., 1982; Steimer et al., 1997a,b; Walker et al., 1989), i.e. differences in vasopressin, oxytocin and CRH action at the level of the amygdala (Roosendaal et al., 1992; Wiersma et al., 1997; Yilmazer-Hanke et al., 2002), decreased GR in the hippocampus in the RLA/Verh rats (Walker et al., 1989), reduced dopaminergic neurotransmission in the nucleus accumbens and decreased cortical γ -aminobutyric acid (GABA)ergic neurotransmission in RLA/Verh rats (Corda et al., 1997), higher basal vasopressin mRNA expression in the hypothalamic PVN in RLA rats (Aubry et al., 1995), similar basal 5-HT output in the frontoparietal cortex, stronger responses to serotonergic challenges in this brain area in RHA/Verh rats (Giorgi et al., 2003), altered metabolism of 5-HT, but not DA, in the cortex, hypothalamus, hippocampus and pons/medulla following shock-stress (Driscoll et al., 1983), with amphetamine induced behavioural sensitisation in RHA rats, but not in RLA animals after repeated treatment (Corda et al., 2005), lower activity of T-lymphocytes and natural killer cell activity in the spleen of the RHA line (Sandi et al., 1991), and various other neurochemical alterations (e.g., Driscoll et al., 1998; Steimer and Driscoll, 2005). The studies also revealed an increased catabolism of progesterone-derived, anxiolytic neurosteroids in the frontal cortex and bed nucleus of the stria terminalis (BNST) of RHA/Verh rats, which may also explain some

differences in emotional reactivity of these two lines (Steimer et al., 1997a). They, as well as inbred strains derived from them, also differ in their respective coping style, responses to novelty, startle response and sensation seeking (Escorihuela et al., 1999; Schwegler et al., 1997; Steimer et al., 1997b). These sublines also differ in quantitative trait loci (QTL; indicating a significant relationship between the phenotype, i.e. anxiety-related behaviour, and a genetic trait, of which the genomic location is known) (Fernández-Teruel et al., 2002).

Taken together, these two lines differ in a number of behavioural and physiological measures. Genetic analyses underlying these differences are under scrutiny. Thus, even more detailed data can be expected from RHA and RLA rats.

5.3.3. Floripa high (H) and low (L) rats

A new approach to study individual anxiety-related mechanisms based on open field behaviour was recently introduced by Ramos et al. (2003). Earlier, their results identified and mapped QTL for emotional-related behaviour, by use of an intercross between Lewis and Spontaneously Hypertensive rats (Ramos et al., 1999). The major locus for locomotion in the centre of an open field was identified on rat chromosome 4, and to a lesser extent, on chromosome 7, but both QTL were found in females only.

The subsequent aim was then to create an alternative genetic model that would help to corroborate the existence of these loci in males and females. In order to create a starting population with maximal genetic variability, Ramos et al. (2003) intercrossed three rat lines (Wistar, Hooded, Lewis). They started a bidirectional selection which resulted in the development of two new rat lines termed Floripa (short form for Florianópolis, the city of the laboratory) high (H) and low (L) based on their locomotion in the centre of a novel open field recorded for 5 min. That is, Floripa H rats showed more locomotion in the centre of a novel open field than their counterparts. At the fourth generation, the new outbred lines differed substantially with respect to the selected trait. At each generation, all rats were also tested in an elevated plus-maze and a light–dark box, with the two lines differing also in these two tests for anxiety-like/avoidance behaviour, that is, Floripa H rats showed less anxiety-like/avoidance behaviour than the Floripa L line. In addition, Floripa H rats showed less depressive-like behaviour (immobility) in the forced swim test compared to Floripa L animals (Hinojosa et al., 2006). Finally, Floripa L female rats consumed more ethanol than their Floripa H counterparts at concentrations of 6% and 10% in a two-bottle choice protocol (Izídio and Ramos, 2007).

These results suggest that behavioural measures from different tests for emotionality/anxiety are, at least in part, genetically related. When considering measures of locomotion in all tests, females were generally more active than males. They also defecated less in the open field and showed less anxiety-like/avoidance behaviour than males in the black and white box, although no sex differences were found for the selected trait or for anxiety-like/avoidance measures in an elevated plus maze (Ramos et al., 2003). This genetic approach may be useful as a tool to test the importance of the genetic loci of the two aforementioned chromosomes 4 and 7 putatively associated with emotionality.

5.3.4. High anxiety-related behaviour (HAB) and low anxiety-related behaviour (LAB) rats

Two successful breeding lines of male and female Wistar rats with high anxiety-related behaviour (HAB) or low anxiety-related behaviour (LAB), assessed by an elevated plus-maze, started in the beginning of the 1990s (reviews by Landgraf and Wigger, 2002, 2003). They represent the most recent breeding lines in the fields of anxiety and to some extent also of depression research. These

animals have been characterised in their behaviour (Henniger et al., 2000; Liebsch et al., 1998b), neuroendocrinology (Wigger et al., 2004), psychopharmacology (Keck et al., 2003), cognition (Ohl et al., 2002), vegetative system (Liebsch et al., 1998a), somnology (Lancel et al., 2002), and molecular structure (Murgatroyd et al., 2004).

With regard to behaviour, HAB rats spent about less than 5% of their total arm time on the open arms of an elevated plus-maze (5 min test), whereas LAB rats spent there more than 50%, without any overlap between the two lines (Landgraf and Wigger, 2002). The arm criteria used are different from those of many other laboratories in that an entry is counted when both forepaws of the rat are placed into the respective arm (Wigger et al., 2001). Further, both lines showed stable emotional differences during their entire lifetime with lower open arm exploration until 16 months of age for HAB rats compared with LAB rats (Wigger et al., 2001). Indices of differences in anxiety-like levels were not only detectable in an elevated plus-maze test. For example, in an open field (Liebsch et al., 1998b) and the modified hole board test (Ohl et al., 2001), the ratio of time spent and distance travelled in the centre, compared to the border zone, was lower in the HAB compared to the LAB line. Accordingly, in other tests of unconditioned anxiety-like/avoidance behaviour like the social interaction test and black–white box, HAB and LAB rats also exhibited different behaviour; the former entering the white compartment less often and spending less time in it, and also spending less time in active, but not passive, social interaction (Henniger et al., 2000; Salomé et al., 2002). There is evidence that both lines do not differ in their locomotor activity analysed with a radiotelemetric system in their home cages (Liebsch et al., 1998a). Additionally, HAB compared to LAB pups emitted more ultrasound isolation calls which are suggested to measure emotionality of newborn rats (Wigger et al., 2001). This is in contrast to the higher ultrasound vocalisation in HOA compared to LOA unselected rats (Schwartz and Pawlak, 2004). Finally, adult HAB rats showed more freezing behaviour and emitted more ultrasound vocalisation in a social defeat situation than their LAB counterparts (Frank et al., 2006).

To test for social discrimination, a social recognition test was applied (Engelmann et al., 1995) by placing a stimulus novel juvenile rat into the home cage of the male rat and by recording the amount of investigation directed to the juvenile. Then, the now familiar juvenile rat was removed from the cage, and after a fixed period of time it was placed back into the home cage of the experimental male along with another novel juvenile animal. Both, HAB and LAB rats were able to discriminate between the two juveniles after a 30 min interexposure interval (Liebsch et al., 1998b), indicating an intact social short-term memory. However, this behaviour seems to be differentially coded in HAB and LAB rats. After several years of breeding, HAB rats had kept this learning and memory ability, while it was erased in LAB rats. According to Landgraf and Wigger (2002), this represents the only shift in a behavioural measure observed over the years of breeding in these lines.

Surprisingly, LAB rats exhibited a higher baseline fear-sensitised acoustic startle response compared to HAB rats, although the two rat lines did not differ in freezing duration during the inter-stimulus intervals in the startle experiment (Yilmazer-Hanke et al., 2004). The number of neurons for CRH and neuropeptide Y in amygdaloid nuclei did not reveal any differences between the two lines, which is in contrast to findings in the aforementioned Roman rat lines (Aguilar et al., 2002; Yilmazer-Hanke et al., 2002). The authors explain the behavioural discrepancies between anxiety-like and fear-like behaviours by analysis of QTL in rats providing support for an involvement of different genes that either influence the anxiety-like behaviour on

the open arms of an elevated plus maze (on chromosome 5) or the acoustic startle response (on chromosome 10); however, these data were obtained in RHA/Verh and RLA/Verh rats (Fernández-Teruel et al., 2002).

Relating to drug consumption, there are contradictory findings to the hypothesis of the positive relationship between more anxiety-like behaviour and higher ethanol consumption. While Spanagel et al. (1995) showed a higher voluntary oral self-administration of ethanol for rats with more anxiety-like/avoidance behaviour, Henniger et al. (2002) observed more ethanol intake for LAB compared to HAB rats. These differences could be due to the fact that Spanagel et al. (1995) used unselected rats and lower amounts (2% and 4%) of ethanol solutions than Henniger et al. (2002) who used 5%, 10%, and 20% concentrations.

Crossfostering experiments failed to reveal behavioural differences between regularly and cross-fostered HAB and LAB rats, indicating that the extremely divergent anxiety-like/avoidance levels of HAB and LAB rats are maintained during their whole lives and are determined genetically, rather than being learned. Crossbreeding of HAB and LAB rats resulted in offspring showing anxiety-like/avoidance behaviour on an elevated plus-maze yielding open arm times between regular bred HAB and LAB rats, providing further evidence for a genetic basis of differences for anxiety-like/avoidance behaviour in HAB and LAB rats (Wigger et al., 2001). In the forced swim test, which may signal depression-related behaviour and clinical efficacy of antidepressant drugs, HAB rats floated more and struggled less than LAB rats (Keck et al., 2001), which is indicative of more depressive-related behaviour in HAB rats.

Repetitive transcranial magnetic stimulation attenuated stress-induced elevation of plasma corticotropin and corticosterone concentrations, and induced changes in stress coping abilities in HAB rats only, allowing these animals to reach performance of LAB rats (Keck et al., 2001). Pharmacological long-term treatment over a period of 8 weeks with the selective serotonin reuptake inhibitor (SSRI) paroxetine, ameliorated depressive-relevant behaviour of HAB rats to the levels of higher struggling and floating of LAB rats (Keck et al., 2003). Interestingly, when comparing HAB and LAB rats with the HOA and LOA rats, different behavioural patterns emerged. In contrast to basal differences of HAB and LAB rats, exposure to the forced swim test revealed no significant differences between the subpopulations of unselected HOA and LOA rats (Ho et al., 2002).

An analysis of sleep-wake behaviour of HAB and LAB rats revealed differential patterns, with the former spending less time awake and more time in non-REM sleep (Lancel et al., 2002). This sleep pattern of HAB animals is in contrast to what is usually observed in patients with anxiety and depression. However, a CRH type 1 receptor antagonist attenuated stress-induced sleep disturbances particularly in HAB rats (Lancel et al., 2002). A biotelemetry system revealed comparable levels in body temperature, with baseline day and night peak values very similar between HAB and LAB rats (Liebsch et al., 1998a).

The two rat lines were also shown to differ in their endocrine susceptibility to mild emotional stress (5 min of forced open arm exposure on an elevated plus-maze) with a hyperactive HPA axis in HAB rats (Landgraf et al., 1999). In addition, although novelty exposure failed to differentially stimulate HPA axis activity, LAB rats responded to social defeat with a higher release of ACTH and corticosterone stress hormones than did HAB rats (Frank et al., 2006). However, a previous study did not find any differences in the number of CRH immunoreactive neurons between the two lines (Yilmazer-Hanke et al., 2004). In contrast to the previous observations that HAB and LAB rats have similar vasopressin plasma levels (Landgraf et al., 1999), the same group later reported

an increased expression and release of vasopressin in the PVN in HAB rats that may be responsible for their altered behaviour and neuroendocrine profile in anxiety-like/avoidance behaviour (Wigger et al., 2004). Further, HAB rats showed paroxetine-induced attenuation of CRH-stimulated increase in ACTH and corticosterone secretion (Keck et al., 2003). In parallel, a reduction in hypothalamic vasopressin mRNA expression was found in HAB but not LAB rats (Keck et al., 2003). Specifically, treatment with a vasopressin V₁ receptor-antagonist into the PVN decreased anxiety-like/avoidance and depressive-like behaviour (Wigger et al., 2004), although basal V_{1a}-binding sites were higher only in the lateral septum when compared to LAB rats (Keck et al., 2003). Moreover, molecular analyses have identified polymorphisms in the promoter region of the vasopressin gene, suggesting that vasopressin appears to play a critical role in anxiety-like/avoidance behaviour of HAB rats (Murgatroyd et al., 2004). Interestingly, these results were also recently supported by another group, suggesting that vasopressin in combination with oxytocin plays an important role in fear behaviour, which is mediated by a neuronal network between the basolateral amygdala and the cerebral cortex (Huber et al., 2005). Finally, as indicated by regional Fos expression, exposure to a resident in a social defeat paradigm particularly activated distinct regions of the amygdala and hypothalamic areas in HAB rats, and specific forebrain (e.g., nucleus accumbens) and brainstem areas in LAB rats (Frank et al., 2006).

In summary, HAB and LAB rats are useful lines to further study anxiety-like/avoidance and, to a certain extent, depression behaviour. The lines have been extensively characterised also in other labs, and may thus provide more information about the genetics of anxiety and depression in the future.

5.3.5. Other approaches

A number of less well known approaches for anxiety have been proposed, but they have not been extensively studied. Briefly, Fujita et al. (1994) gave an overview of the Tsukuba high- and low-emotional strains of Wistar rats. The lines were based on testing in a runway apparatus over three consecutive days. The authors suggested that the Tsukuba high-emotional rats are reminiscent of human “introverted” behaviour, while the Tsukuba low-emotional rats could be regarded as “extroverts” because the latter line showed more activity in novel situations or during aggressive encounters than the former rats (Fujita et al., 1994).

Selective breeding for high and low sensitivity to the hypothermic response induced by the 5-HT_{1A} receptor agonist 8-hydroxy-2-di-N-propylaminotetralin (8-OH-DPAT) has established two rat lines: High DPAT sensitive (HDS) and low DPAT sensitive (LDS) rats. The HDS rats differed from LDS rats on several behavioural measures reflective of anxiety-like or depressive-like behaviour, including reduced social interaction, reduced responding in a conflict task, and exaggerated immobility in a forced swim test. However, they did not differ from LDS rats in an elevated plus-maze task (Overstreet et al., 2003).

Another approach for open field activity was developed for mice (DeFries et al., 1978). Balb/cJ and C57LB/6J inbred mice were divided based on open field activity tested on two consecutive days. However, both lines have not been followed-up since the middle 1990s. Such mouse models of individual behaviour may still be of interest for practical reasons (i.e. lack of availability of genetically modified rats). However, most relevant behavioural paradigms were developed with rats, whereas modified versions have been applied to mice. It is still not clear if these mouse models are qualitatively comparable to those of the rat.

Basis of the nervous pointer dog approach was the breeding of two lines of pointer dogs (Dykman et al., 1969). The phobic line

(male and female nervous pointer dogs) was characterised by extreme fearfulness, avoidance of humans, and diminished exploratory behaviour compared to the normal line (Lucas et al., 1981). Since the beginning of the 1990s, work with these two canine lines has practically ceased, although most of the results resembled evidence obtained from rodents and humans.

Finally, current thinking holds that genotype has a major influence in determining personality traits (Bouchard, 1994), although research has developed from assuming single gene causation to more complex polygenic models of personality traits (e.g., Noblett and Coccaro, 2005). In the field of behavioural genetics, a wide array of research tools is available to determine the role of genetics in behaviour of laboratory animals. These tools include selective breeding, recombinant inbred strains, as well as the use of mutant or transgenic strains. Genetically modified models such as knockout or transgenic animals to mimic human psychopathology are still available almost only for mice. Nonetheless, it has been possible to assess single genes or a conglomeration of genes that may be relevant for the expression of behaviour also in humans. Research on these models has increased dramatically over the last years. Overviews are given by Bucán and Abel (2002), Clément et al. (2002), Finn et al. (2003), Flint (2003), Gordon and Hen (2004), and Gross and Hen (2004).

5.4. Summary

In previous years it became clear that an approach based on individual differences is not only necessary in humans, but is also critical in animal models. There are a number of approaches to model human psychopathology based on individual differences in trait anxiety and novelty-seeking behaviour in animals (i.e. rat and mice). These approaches vary considerably, however, at least some of them aim at reliable results with repeated testings and most (if not all) of them attempt to extract stable relationships between different paradigms of anxiety-like/avoidance and exploratory behaviour. These different approaches, ranging from unselected normal to selectively bred rodents and genetically manipulated animals, have almost exclusively been conducted apart and independent from each other, but it appears desirable and reasonable to compare these different strains (genetic variation minimised by inbreeding), stocks (genetically heterogeneous by crossing two or more strains), and lines bred for specific behaviours to examine both the commonalities and the distinctions between them. A first approach has already been attempted with the mouse phenome project, which is a database encompassing physiological characteristics, gross and microscopic anatomy, disease susceptibility, robust behavioural traits, metabolic parameters, and gene expression profiles (Paigen and Eppig, 2000).

Together, as probably most researchers would agree, none of the neurotransmitter systems discussed above (e.g., DA, 5-HT, NA) are specific for novelty-seeking or anxiety. Research in the recent years has shown that each of these neurotransmitters can be linked to other personality traits (Amelang et al., 2006). Moreover, Riemann and Spinath (2005) summarise evidence of genetic polymorphism in the respective neurotransmitter systems and personality dimensions, and come to the conclusion that the assumptions for specific relationships between neurotransmitter and personality traits cannot be maintained. Thus, rather complex interactions between these systems have to be assumed, or as Depue (1995) pointed out: “Models of personality traits based on only one neurotransmitter are clearly too simplistic and will require the addition of other modulating factors. (...) Therefore, simplistic amine models of behaviour may be viewed as important

building blocks for more complex future modeling of personality traits” (pp. 429–430).

6. Conclusion

In the future, the individual approach to study behaviour of laboratory animals has to play a more important role than before. Likewise as shown in research with humans and experienced in encounters in daily life with humans, animals also simply do not react uniformly to the same stimulus. It is a must to distinguish between individual subjects, and to select subgroups of animals in a given population that are particularly reactive and are thus readily transformed in different emotional states than animals that are less responsive to external stimuli. Thus, the introduced animal models of individuality provide a critical method to develop a much needed individualised approach to the treatment of diseases (Woodcock, 2007).

The various reasons for the expression of individual differences, even in genetically identical animals, would deserve attention, but are out of scope here. Nonetheless, there are several genetic and non-genetic aetiological sources of early origin of individuality, which have been summarised by Lathe (2004) and shall be briefly mentioned. For the genetic part, imprinting errors which lay down and maintain early developmental patterns (e.g., masculinisation via androgens, aggressiveness changes with perinatal stress) appear to impact on individuality. In addition, while new point mutations are rare (Keightley and Hill, 1992), the mammalian genome is loaded with repeat elements including minisatellites (or variable numbers of tandem repeats) and transposable elements. A number of non-genetic factors that are suggested to be sources of diversity include epigenetic inheritance, the intrauterine position, nutrition in utero, non-hormonal communication (twin effects), maternal stress and infection, endocrine factors during the estrus cycle and during pregnancy and lactation. Thus, Lathe (2004) concludes that all these factors listed above are likely to contribute, at least in part, to the development of individual behavioural characteristics in otherwise genetically identical animals. Finally, postnatal effects such as early life experiences, including social stress, impact on behavioural and physiological parameters and social status, with the latter also influencing subsequent behaviour and physiology (Sapolsky, 2005).

7. Suggestions for future research

At first sight, the open field and the elevated plus-maze, on which most approaches of individuality in rodents are based, appear to be thoroughly characterised and effective for understanding clinically relevant problems, but a number of issues remain to be addressed. One stems from the lack of sufficient studies on long-term effects of drugs. Another issue concerns a need for more precise validity of the models for human disorders as postulated by Willner (1991), and Willner and Mitchell (2002). It may also be necessary to develop further animal models to examine hitherto unknown relationships concerning cognitive influences on emotional behaviour that have not been systematically addressed in rodents. For example, Paul et al. (2005) recently suggested a novel approach to look at cognitive aspects of anxiety-related behaviour. They suggest to train rats in an operant discrimination task (2 or 4 kHz tone) to discriminate stimuli predicting a “good event” (e.g., food) or a “bad event” (e.g., no food and an unpleasant tone). Thus, to get food the animal has to press a lever (2 kHz discrimination stimulus; “good event”); to turn off the unpleasant tone the animal has to put its nose into a hole (4 kHz tone discrimination stimulus; “bad event”). The authors argue that the trained animal would then react in a follow-up test dependent

upon its emotional state. To test the animal, it is put either into a positive or a negative emotional state according to different experimental setups and then presented with an ambiguous stimulus ranging between 2 and 4 kHz tones. The specific reaction may reflect their present emotional state. For example, in a negative state the animal would interpret the ambiguous test tone to be similar to a tone of 4 kHz which preceded the “bad event”. The interpretation could be in parallel to patients with depression or anxiety who interpret ambiguous stimuli in a negative way, and exhibit reduced expectations when exposed to positive events.

Like humans, animals do not react in the same manner to an identical stimulus. Accordingly, it appears sensible to filter subgroups of animals which are particularly reactive, and in which reliably emotional states can be induced, or in which traits can be gauged reliably. These differential models are interesting with regard to anxiety and its potential treatments. In this respect it seems also appropriate to take into account evidence from personality research in order to gain better insight into differential mechanisms. In the end the usually great variance in apparently similar animals is still one of the most neglected problems. As pointed out in this work, much of this variance is systematic in nature.

There are limitations and pitfalls of studying individual differences in behaviour. Many breeding programmes derive colonies from one behavioural parameter (e.g., locomotor activity) that appears to have little translational value to human personality traits or psychopathology. Such paradigms may be very insensitive with limited construct and predictive validity. For example, several rat lines used in the study of emotionality differ not only in approach/avoidance behaviours thought to be indices of anxiety but also in general locomotor responses to stress, with extreme lines reacting either actively or passively to various stressful situations (Ramos and Morméde, 1998). Therefore, we suggest the following points to further improve the translational value of the already existing animal models: long-term assessment of the effects of acute versus chronic drug treatment to mimic clinical aspects more closely; developing tools going beyond a dichotomous differentiation of subpopulations by making use of more than one behavioural variable to distinguish between two, or more extreme, subgroups; assessing protective factors; taking into account cognition; assessing long-term effects of genetically modified animals (they show great variance too!); aetiologically oriented studies including transient and conditional (tissue-specific) knockouts to specifically analyse developmental aspects and to elucidate the origin of individuality.

Nonetheless, it is impressive how valuable the individualised animal approach has already been to understand biological mechanisms underlying individually expressed behaviour of emotion and motivation. We believe that an extended individualised approach in animal research is an optimal way to develop a personalised approach in medicine. The heterogeneity of psychiatric conditions (and other diseases) should be taken into account when further modeling behaviour. Far too often the scientific community speaks about animal models “of” a broad psychobiological construct (e.g., anxiety, novelty-seeking), but it should be emphasised that these are animal models “for” some aspects of this behaviour. That is, caution needs to be exerted when claiming a model to display the full construct. All the models discussed above display aspects of these broad constructs, but it should be clear that existing models are not capable of displaying the wide array of psychiatric conditions. Thus, a new generation of animal models should mimic specific symptoms more in depth in translational research, rather than trying to model fully developed psychiatric conditions. Clinicians also do not treat “the” anxiety or “the” fear, but aspects of these emotions. Hence, such work

requires extensive communication between all disciplines, but especially between basic and clinical researchers who also pay attention to the outliers of their research. About a century ago, William Stern stated that the 20th century would be the epoch of the individual. For the 21st century, the time is ripe to extend this epoch to the scientific analysis of the individuality of animals.

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