General understanding, neuro-endocrinologic and (epi)genetic factors of stereotypy

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Abstract

Stereotypies are abnormal repetitive, unvarying, and functionless behaviours often performed by captive and domesticated animals as well as by certain classes of psychiatric patients and typically developing children. Stereotypies in animals are associated with poor welfare in past or present and might function as a coping style to reduce stress and frustration. Although the exact causes and/or functions of stereotypic behaviour remain broad and imprecise, there are clues indicating an altered brain development causing neurotransmitter imbalances in the basal ganglia, which disturbs proper inhibition and/or stimulation of certain behaviours. The development of stereotypy also seems to have a strong genetic component although epigenetic factors might be important as well.

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1. Understanding stereotypic behaviour

1.1. Terminology

Many captive animals as well as humans display stereotypies, defined as repetitive, invariant behaviour patterns without an obvious goal or function (Mason, 1991a). However, the definition and included activities remain broad and imprecise. Stereotypies are only apparent in animals in captivity and absent in wild animals living in nature. This seems contradictory for the appearance of stereotypies in humans. This will be an important topic in the discussion in this paper. Usually stereotypies develop in animals kept in barren environments that lack appropriate sensory and motor stimulation and inhibit the performance of highly motivated behaviour patterns (Dawkins, 1988; Hughes & Duncan, 1988; Mason, 1991; Würbel, 2006). At least 85 million domestic animals and a significant portion of wild animals housed in zoos and laboratories are affected by stereotypies (Mason and Latham, 2004). Stereotypies have been viewed as pathological, indicating (previous) distress and poor welfare in captive animals (Broom, 1993).

In humans motor stereotypies are one of the criteria, together with preoccupations, rigidity, and restricted interests, for a diagnosis of an autism spectrum disorder (ASD) in DSM-IV (American Psychiatric Association). They are widely viewed as deliberate behaviors produced for escape or self-gratification (self-stimulation) because they are voluntarily suppressible – at least for a while – and are enhanced by excitement, anxiety, boredom, sensory isolation, or social demands.

1.2. The occurrence of stereotypic behaviour

Stereotypic behaviour among animals is most prevalent in the agricultural sector. In some type of farms, for instance breeding units, almost every individual is stereotypic at a certain point, and this, combined with the massive volume of farm animals on a global scale, makes this sector to contribute for many hundreds of millions of affected individuals worldwide (Mason & Latham, 2004). The second most stereotypic group is probably represented by laboratory animals; the many millions of mice and other animals kept for research ensure that worldwide their stereotypic behaviours are numerous and even in some housing conditions (e.g. single-housed primates), most of the individuals are affected (Novak et al., 2006a-b). A third group of concern includes the growing group of millions of companion animals such as lone-housed, concentrated-fed (i.e. canned food or dry food fed) animals, that live in herds in wild conditions, such as some breeds of dogs and horses (Mills & Luescher, 2006). A fourth group of affected animals are zoo animals although these animals’ housing conditions are mostly of lesser concern than the housing of farm and laboratory animals, they still display
stereotypic behaviours. Research on the behaviour of zoo animals brings some unique advantages due to the great variation in housing, rearing (mother-reared versus human-reared) and species-type across zoos. This means that research on stereotypies among zoo animals might have useful wider implications for other systems and species that are of more serious concern regarding health and welfare.

Stereotypic behaviours are not limited to animals, they are present in humans as well in different populations, ranging from individuals with autism or schizophrenia (American Psychiatric Association) to developing children in general. Stereotypies are a normal phenomenon in normally developing infants, but these kind of stereotypies normally decrease rapidly with aging. However, they may persist in some toddlers (Werry et al., 1983) and in some typically/normally developing children (Mahone et al., 2004; Tan et al., 1997) or adults who, especially when bored or stressed (Schlaggar and Mink, 2003) still engage in hair twisting, drumming, or other mannerisms.

1.3. Stereotypies as phenotypical abnormality

Stereotypies are assumed to be an abnormal behaviour pattern. The argument is that stereotypies cannot be the product of natural selection (they are absent in the wild) nor of selective breeding for captivity (they are not unique to domesticated species). Typically, stereotypic behaviours of captive animals are not seen in nature, and often seem the product of activities present in the wild being constrained by enclosure (Clubb & Mason, 2007). They thus flag a great divergence between the behavioural phenotypes of captive animals and their free-living counterparts, with the former being ‘abnormal’. At least they are abnormal in a statistical sense; the stereotypic behaviour is quite a bit away from the norm and the natural behaviours are lost and/or replaced by captivity-induced behaviours (see also §1.2./1.4./1.5./1.6.). This leads to individuals that genetically may represent wild species but behaviourally have little resemblance with their natural phenotype. For ethology research these individuals are not reliable study objects to study ‘natural’ behaviour.

The above statements, imply that humans with stereotypies are not living, or were not at some point in the past, living in their ‘natural environment’. An orphanage, in this sense, could be considered a ‘non-natural’ environment for example (see §1.6) or in general an environment with large stressors or deficiencies.

Stereotypies can be ‘abnormal’ in a second sense: arising from dysfunction of pathology (see also §1.5. and chapter 2). Evidence for this statement comes from behavioural research on human disorders like schizophrenia, autism, and some types of brain injury. These have in common that they involve forms of CNS dysfunction that impair proper regulation of behaviour, leading the subjects to produce unnecessary, inappropriate ‘uninhibited’ responses to external cues. A lot of these responses are ‘perseverations’; continuations or reiterations of an activity without the appropriate stimulus being present (Mason et al., 2007; Mason & Latham, 2004; Garner, 2006). Perseverative tendencies correlate with stereotypic behaviours, also in human subjects (Mason, 2006). For example when caged animals are taught an operant response to win them a food reward, but this is then made unrewarding (by withholding the treat), the animals with the most stereotypic behaviour take the longest to suppress these now-inappropriate responses. This is quite uncorrelated with their learning abilities or feeding motivations. This implies that stereotypic animals have no problems with learning the task, just with abandoning it when it becomes functionless (Vickery and Mason, 2003, 2005).

These results do not directly demonstrate CNS pathology as they could demonstrate a pre-existing, perfectly normal individual difference in persistence or habit-formation. But there is also evidence suggesting captive wild animals being dysfunctional. It has long been
known that when compared with more natural captive conditions, very barren or socially-
impoverished rearing conditions impair brain development, inducing perseverating and
stereotypic behaviours (Novak et al., 2006a; Lewis et al., 2006b). A more natural captive
environment, in contrast, can ‘protect’ animals from later stereotypic behaviour when they are
subsequently moved to barren housing conditions (Lewis et al., 2006). However, relatively
natural captive conditions still only offer a fraction of the challenges and opportunities that a
‘wild’ environment would offer and therefore would probably not guarantee full normality of
function. This also appears from the fact that captive-born wild animals often display more
abnormal repetitive and stereotypic behaviours than wild-born individuals caught and caged
as adults (Mason et al., 2007; Latham & Mason, 2006). Apart from this, CNS pathology
would help explain the self-damage of some stereotypies as well as the seemingly
unnecessary time and energy devoted to the behaviour. Stereotypy sometimes seems to
represent a net cost to the animal as in the self-biting of clouded leopards (Wielebnowski et al.,
2002), the pacing that sometimes persists despite the injuries it causes (Morris, 1964; Meyer-
Holzapfel, 1968; Mason 1991a) and also the way some stereotypic behaviours seem to
interfere with normal social or parental interactions such as females pacing instead of caring
for their infants (Wildholzer & Voss, 1978) (Mason et al., 2007).

It is important to recognize stereotypic animals as animals with behavioural
abnormalities that could have arisen from severe stress (Cabib, 2006) and thence indicate
severe welfare problems, at present or at least in some point in the past. Further, CNS
dysfunction could diminish the preservation value of such animals, by potentially interfering
with breeding or by the neglect of offspring. It might also reduce the chances of success for
reintroduction in the wild (Vickery & Mason, 2003, 2005; Mason et al., 2007).

1.4. Various types of stereotypic behaviour

The overall definition of stereotypy suggests an invariant, functionless and repetitive
behaviour pattern. This covers many different variants of stereotypy, from pacing leopards to
feather pecking chicken and from wind-sucking horses to nail biting students. In general
stereotypies can be subdivided in oral stereotypies and motor stereotypies. This latter
category can be further divided in locomotory movements, such as pacing, and non-
locomotory body movements, such as body-rocking and repetitive jumping, described as
‘other’ in figure 1.1 This figure shows that different taxa of animals differ in their responses
to captivity and that certain stereotypies are more common among certain groups of species.
The figure shows the prevalence of repetitive behaviour across the four main captive
mammalian orders (Magin et al., 1994). Stereotypic carnivores favour locomotory movements,
while ungulates, and to a lesser extent primates, display mostly oral forms.
The taxonomic distribution of different forms of abnormal repetitive behaviour. ARBs in affected captive animals across 121 species were categorised as: (1) pacing and similar, i.e. locomotory movements; (2) oral, e.g. sham-chewing; (3) other: non-locomotory body movements, e.g. body-rocking, repetitive jumping. Juveniles were excluded, to rule out repetitive behaviours relating to play, as were animals with severe CNS dysfunction. The following were also excluded, to minimize effects of husbandry differences between taxa: food-deprived animals (largely farmed pigs); animals exposed experimentally to ‘intermittent schedules of reinforcement’ (largely laboratory rodents); and animals very prematurely separated from their mothers (largely dairy cattle and laboratory primates). Restraint (largely applying to horses, cattle and horses) was controlled for by scoring swaying/weaving as ‘Pacing’ in tethered subjects. Each species was categorized according to its sole or commonest form (according to time budget data, or in the absence of this, the number of times each form was reported). The occurrence of different ARB categories varied significantly varied with taxon ($\chi^2 = 51.17$, d.f. = 6, $p < 0.001$). (Figure and subscription by Mason et al., 2007)

The correlation between the taxonomic distribution and the dominant type of stereotypy can be ascribed to the natural ethology of the certain taxonomic group. Carnivores for example have to hunt for their food, in wild conditions, which involves a great amount of physical effort and thus energy for locomotor movements. Captivity almost always causes a confinement of this wild behaviour and can lead to the development of a locomotory stereotypy such as pacing. Otherwise ungulates are primarily herbivores and therefore their prevalence for oral stereotypies very likely are derivatives of their natural foraging behaviour. For example, in the wild, horses will spend up to 70% of their time grazing and foraging for food (Mal et al., 1991). Being confined to a stable and feeding on low fibre concentrates tends to decrease the amount of time horses spend on feeding, altering their natural time budget and leaving them frustrated (McGreevy et al., 1995).

Apart from the distinction between ungulate and carnivore preferred stereotypies, there is a wide variety of stereotypies than can be found within one particular species. For example the stereotypies within the species of *Equus caballus* (domesticated horse) ranges from oral stereotypies such as ‘chewing’, ‘lip-licking’, ‘wood-chewing’, ‘crib-biting’ and ‘wind-sucking’ to motor stereotypies such as ‘box-walking’, ‘weaving’, ‘tail-swishing’, ‘door-kicking’, ‘head-tossing/circling/shaking/nodding’ to even self mutilating stereotypies such as ‘self-biting’ and ‘self-rubbing’ (McGreevy, 2004).
From studies concerning human stereotypies, stereotypies can be broadly classified in two categories, *Primary Stereotypies* and *Secondary Stereotypies*, where the first category can be subdivided into three groups: common behaviours (e.g., rocking, head banging, finger drumming, pencil tapping, hair twirling) and two forms with atypical or complex behaviours - head nodding and complex motor movements (e.g., hand and arm flapping/waving), respectively. The category of secondary stereotypies is characterized by the presence of an additional diagnoses with behavioural neurological signs and symptoms, including autistic spectrum disorders, mental retardation, sensory deprivation, Rett syndrome, neurodegenerative disorders, inborn errors of metabolism, drug-induced conditions, infection, tumor, or psychiatric conditions (Harvey & Singer, 2009). However, human stereotypies differ from human impulsive/compulsive disorders as seen in OCD. Impulsive/compulsive disorders, although being repetitive, vary in the form of their motor pattern and are goal-directed (towards an inappropriately repeated goal).

### 1.5. Fundamental causes of stereotypy

There is a wide variety of stereotypic behaviours (as described in §1.4.) which makes it difficult to ascribe all the variants to a single fundamental cause. The suggested pathophysiological mechanisms for stereotypies range from psychological concerns to neurobiological abnormalities. According to Mason et al. (2006a) captive animals perform stereotypic behaviour for the following, non-mutually exclusive, reasons:

1. Internal states induced by the captive environment, and/or cues external to the animal, persistently trigger or motivate a specific behavioural response. And/or:
2. The environment creates a state of sustained stress which affects how [specific brain regions] elicit and sequence behaviour, resulting in abnormal perseveration. And/or:
3. A past, early rearing environment has affected CNS development, again resulting in abnormal behavioural sequencing, with effects evident long past infancy.

Mason et al. also stated that in some cases stereotypy might be further promoted by endogenous effects such as reinforcing consequences resulting from the behaviours and this endogenous reinforcement may again increase through repetition. They further proposed that forms with ‘cause (1)’ be called ‘frustration-induced stereotypic behaviour’, and those with causes (2) and (3), ‘malfunction-induced stereotypic behaviour’. Frustration-induced stereotypic behaviours are driven directly by motivational frustration, fear or physical discomfort and are not the consequence of any underlying dysfunction. The motor patterns that are repeated in this type of stereotypy reflect the nature of the underlying problem, deriving from attempts to replace a missing/inhibited normal behaviour, to escape from confinement, or to otherwise alleviate the problem. Malfunction-induced stereotypic behaviours are products of CNS abnormality, and co-occur with a suite of other effects (e.g., quantifiable changes in brain physiology/anatomy). The forms of motor pattern repeated may sometimes be more arbitrary/less natural, not directly reflecting the problem’s primary cause (e.g., eyepoking in primates removed from their mothers too early) (Mason et al., 2006a). For more information about this last example see the next paragraph (§1.6) about maternal deprivation.

Another hypothesis, described by Harvey and Singer (2009), that partially supports Mason’s fundamental causes comes from the observation of a higher frequency of stereotypic behaviours in situations of altered arousal. This observation has led some investigators to
suggest that movements act to maintain an optimal state of arousal (Zentall & Zentall, 1983). Proponents of a psychogenic mechanism tend to suggest the following possibilities:

1. A form of sensory self stimulation or automatic reinforcement (i.e., the reinforcing factor and the behaviour are one and the same) in which the stimulation is designed to compensate for a deficit of external arousal, e.g., congenital blindness, deafness, autism, or mental retardation, (Zentall & Zentall, 1983; Cunningham & Schreibman, 2008) or deficits that develop when an animal is caged or a human is placed in solitary confinement.

2. An attempt to deplete aversive stimuli, to use up excess attentional capacity, or to reduce external distractions or demands, by channeling thoughts and actions into movements (Hutt, 1970).

3. Substitution behaviours to take the place of imaginative activities (Honey et al., 2007).

4. A component of obsessive-compulsive disorder, (Castellanos et al., 1996; Niehaus et al., 2000; Hansen et al., 1990), general anxiety disorder, perfectionism, or impulse dyscontrol (Niehaus et al., 2000). These later suggestions are based, in part, on studies of the occurrence of common stereotypies in college students.

However, several lines of evidence support a neurobiological basis for stereotypies, including its correlation with the severity of autism and cognitive impairment (Goldman et al., 2009), association with disorders such as Rett syndrome (Temudo et al., 2007), pharmacological induction in animal models and humans, and abnormal findings on neuroimaging (see also chapter 2).

1.6. Maternal deprivation in relation to stereotypy development

The captive environment (controlled by humans) is an environment that in many aspects is in contradiction with and impedes wild behaviours and social interactions. For example the captive environment can change mating behaviour, but also foraging, hunting, resting and locomotor behaviours, which can lead to food (i.e. foraging) deprivation, social deprivation, environmental deprivation (barren cages) lack of physical exercise and to maternal deprivation.

Many farm, laboratory, zoo and companion animals experience some form of maternal deprivation. This is typically via separation from their mothers earlier than would happen in free-living populations, in some cases even while young are still dependent upon milk. For example, dairy calves may be separated from their mothers at only a few hours old (EPA, 2004), for commercial purposes. Yet cattle do not naturally wean their calves until 9-11 months (Reinhardt and Reinhardt, 1981; Veissier et al., 1990; Reinhardt, 2002). Curtailed maternal care is also found in research, companion and zoo animals, although typically less early in development compared to farm animals. Here, infants are usually removed once they have stopped suckling, even though their natural dispersal age would be much later. Maternal deprivation may also occur in a qualitative way, via inadequate maternal care, perhaps caused by inexperience (Goodall and Toms, 2003) or by restrictive environments that limit maternal behaviours.

Maternal deprivation is thus a common part of early experience for captive animals. The first scientific accounts for the lasting effects of maternal deprivation in animals stemmed from the research of Harlow et al. (1969) several decades ago. He studied the long-term effects of maternal deprivation on rhesus macaques (Macaca mulatta). He found that later in life macaques that were reared in isolation developed more whole body stereotypies, such as
rocking and bouncing, as well as self-directed stereotypic behaviours, such as self-clasping and digit-sucking. Later on, at the age of 3, the self-directed stereotypies gave way to other kinds of stereotypic behaviours, such as somersaults, head bobs or even self-injurious behaviour. Other studies have since found similar long-term increases in stereotypic behaviours and self-directed behaviours in peer-reared rhesus macaques and chimpanzees, particularly in individuals reared in incubators during the first few months of life (see Champoux et al., 1991; Spijkerman et al., 1994; Bloomsmith et al., 2002). Similar effects have been seen in human infants. Henry Dwight Chapin was one of the first researchers to examine child development in institutionalized settings (Chapin, 1911) and revealed that 30-100% of infants admitted to institutions during the first year of life died prior to their second birthday (see Gray, 1989). He also found that infants revealed other problems related to early institutionalization – such infants later showed mental, social and behavioural deficits, including stereotyped motor behaviour (Spitz, 1945). Further evidence for maternal deprivation, physical and sensory deprivation (Fisher et al., 1997; Gunnar, 1999; Beckett et al., 2002) as well as nutritional deprivation (Monsen, 2004) causing stereotypic behaviours in humans that persisted even long after the deprivation, came from Romania. During the 1980s, 65,000 children were separated from their parents and placed in orphanages (85% of the infants within their first month of life) (see Chungani et al., 2001). The infants lived in bare rooms, having minimal contact with other infants and adults. During the 1990s thousands of these orphans were adopted internationally, with several hundred being studied by developmental psychologists, which revealed that the orphans continued to exhibit behavioural as well as cognitive and emotional problems long after adoption (Fisher et al., 1997; Beckett et al., 2002).

Although it seems that maternal deprivation is a major cause of behavioural changes, there are many other factors. The age of weaning (the time that young are separated from their mother) affects the development of stereotypic behaviour; the earlier weaning occurs, the more abnormal behaviour young animals will go on to perform (Weary et al., 1999; Worobec et al., 1999; Würbel & Stauffacher, 1997). Further the developmental stage of individuals at weaning and whether the weaning is gradual or abrupt could affect the development of abnormal behaviour (Latham & Mason, 2007).

1.7. Coping hypothesis

Stereotypies develop in sub-optimal captive environments which lack necessary stimuli for normal (brain) development, induce chronic stress, repeatedly expose animals to uncontrollable and unpredictable aversive situations (like visitors in a zoo; the amount of visitors is correlated to the amount of stereotypy performance and corticosteroid metabolites in tigers (Carlstead et al., 1993).

A widely accepted, although frequently contested, hypothesis used to explain stereotypies is the coping hypothesis, which states that animals perform stereotypies to cope with the stress of adverse environments. Several definitions of coping can be given (Wechsler, 1995) but here coping is defined as the behavioural and physiological efforts to master a situation (Lazarus, 1966; Wechsler, 1995). The wild environment and the domestic environment are not the same. Since an animal’s behaviour reflects its environment, its behaviour is expected to be different in the two situations. These differences do not necessarily mean that the domestic environment is causing problems. The differences in behaviour may simply reflect adaptations to the different environments. Behaviour strategies of any animal have evolved because they helped its ancestors to adapt to a changing environment. According to the coping hypothesis, the natural behaviour strategies and
priorities which an animal is likely to have are similar in captive and wild environments and are regulated by similar motivational factors. Contradictions may arise because the strategies and control mechanisms of an animal are adequate in its natural niche but not in a captive context. This is illustrated in figure 1.2.

![Venn Diagram](image)

Figure 1.2: Venn diagram illustrating the relationship between the adaptations possessed by animals and the demands of living in captivity. The greater the amount of circle B that overlaps circle A, the less the contradiction between wild and captive environment, and also the less the threat to the animals' wellbeing and consequential behaviour problems. Adapted by K. Mostard from Fraser et al. (1997).

For example a stabled horse is facing major potential problems such as food deprivation and social deprivation as well as physical activity deprivation. The wild horse spends most of its time foraging, social interacting and napping. In captivity the first two activities are highly restricted. Food is delivered to the horse a couple of times a day in a highly concentrated form while the horse is adapted to spent many hours a day chewing grass. Also the stable walls represent a physical barrier between the horse and its companion horses (if it has any). The horse can smell, see and hear the other horses but is restricted from completing social interaction rituals. Both the impairment of the chewing behaviour and the social interaction completion can cause stress and frustration. Frustration causes physiological changes and the physiological changes can lead to behavioural changes. This leads to the hypothesis that states that stereotypies will develop as a way to cope with the stress/frustration from the environment (deprivations). When a horse is prevented from performing stereotypic behaviour, their cortisol levels rise, which indicates the inhibition of the stereotypy elevates stress and that the 'function' of the stereotypy is to cope with the stress caused by the incompatibility of the captive environment and the behaviour impulses necessary to cope with a wild environment. This coping hypothesis finds support by studies of Cronin et al. (1985) and Pargman and Baker (1980), who suggested that animals perform stereotypies to selfnarcotize in analogy to a ‘runner’s high’ (euphoria during long distance running caused by endogenous opioids).

Whilst the coping hypothesis is a popular explanation for stereotypies, results from studies investigating how stereotypies may reduce physiological responses to stress, based on demonstrable, measurable output (e.g. corticosteroid levels) have been mixed (Mason 1991b).
Therefore the suggested ‘function’ of stereotypy remains controversial. Arguments against the coping hypothesis include that stereotypic behaviour has heterogeneous causes, and that not all forms of stereotypy are responses to stress. For example, stereotypies can be triggered by factors that are not considered adverse or stressful (Kennes et al., 1988) or may occur even separately from the initiating environmental stimulus (Fentress, 1977; Dantzer, 1986).

Mason (1991b) argues that individuals with stereotyping behaviour usually have improved welfare compared with non- or low-stereotyping animals in the same circumstances. Again, this is not always the case as is evident in the review by Latham and Mason (2004), indicating that whilst some stereotypies may enable an animal to cope and hence improve its individual welfare, it is exceedingly unlikely that coping is their sole function and that as in the examples above other functions may exist.

1.8. The importance of understanding stereotypies

It is important to understand the underlying causes and mechanisms of stereotypies for several reasons. First of all, many stereotypies indicate environments that cause poor welfare (i.e. negative effects on emotional states). Even when stereotypic behaviours help animals to cope with suboptimal environments, they are only expressed because more natural, and presumably more effective, activities are not possible. This is not just a problem for the affected animals but it also leads to ethical and practical concerns due to other likely consequences of stress. Zoos, farms, laboratories, companion animals settings and even orphan institutions need to respond appropriately to stereotypies instead of ‘explaining the behaviour away’, or physically preventing or punishing the behaviour, responses which sometimes still occur nowadays. It is important that these kind of institutions understand stereotypies better so they can respond to them appropriately, instead of in ways that mask, or even exacerbate, animals’ and humans’ welfare and wellbeing problems.

Further, stereotypies in animals represent a considerable divergence from the behavioural phenotypes of free-living wild congeners and could indicate CNS dysfunction. This is also of concern in the conservation of species and may hamper suitability of reintroduction into the wild after a period of captivity.

Understanding stereotypies is not only important to improve animal and human welfare and wellbeing but understanding stereotypies could be of great importance for the scientific outcomes of scientific experiments. Normal behaviour plays a key role in facilitating homeostasis, especially by allowing an animal to control and modify its environment. Captive environments may interfere with these behavioural responses, and the resulting stress may alter many physiological parameters. Abnormal behaviours indicate that an animal is unable to adjust behaviourally to the captive environment and, hence, may be expressing abnormal physiology. Therefore captive environments may affect the validity, reliability and replicability of scientific experiments. Validity, because abnormal animals are introduced into experiments while considered ‘normal’ individuals. Reliability of experiments might also be questioned because the introduction of stereotypic individuals increases interindividual variation, and replicability might be affected by an altered number of such individuals between laboratories.

Furthermore, it is important to understand the etiology of stereotypies because stereotypic behaviours can tell much about how ‘normal’ behaviour is organized and controlled, and even about the likely psychological or neurophysiological normality of many of the millions of animals kept by humans worldwide. These animals can perhaps even serve as experimental models for many human mental disorders (instead of being considered as representatives for healthy individuals).
However, interest in stereotypies comes not just from scientific or welfare perspectives but also from economic perspectives. For example, in farmed mink (*Mustela vison*) the frequent performance of stereotypies is associated with reduced pelt value and increased mortality (reviewed by the European Commission, 2001). Further stereotypies can decrease the ‘economic value’ of certain animals, for example horses, not only because stereotypies are aesthetically unattractive (Cooper et al., 2000), but they may also cause problems to the animal’s physical health (Houpt, 1993). Horses can lose weight from the increased energy expenditure caused by stereotypic performance, and athletic ability may also be compromised (Houpt, 1993). Self injurious behaviours are also associated with stereotypy and of course are also economically very unwanted. Stereotypies can also have negative economic consequences in zoos because they can attract criticism by the media and the public (Mason et al., 2006).

Last but not least a better understanding of the underlying causes of the development of stereotypies enables people to use better prevention methods. Nowadays often prevention methods are used that physically prevent an animal from performing the stereotypy but these methods will increase stress levels in the animals and therefore further decrease welfare. Environmental enrichment is another method that is often used and seems to successfully decrease stereotypy performance and improve welfare. When the (physiological and neurological) understanding of stereotypy development further increases and the underlying causes are better understood, better prevention methods can be developed. This will likely include changes in housing condition, management and handling practices of the captive and domesticated animals.

2. Neuroendocrinology of stereotypies

2.1. Stereotypy as coping style

A wide variety of medical, psychological and animal studies demonstrate that individuals may differ in their coping capacities. Coping styles are characterized by consistent behavioural and neuroendocrine characteristics, some of which seem to be causally linked to each other. For animals in general two coping styles are distinguished: active and passive coping. Evidence is accumulating that the occurrence of both coping styles in populations of vertebrates from fishes to mammals reflects a differential vulnerability to stress mediated diseases due to the differential adaptive value of the two coping styles and the accompanying neuroendocrine differentiation (Koolhaas et al., 1999).

Factors that affect an individual’s coping capacity include, among others, early experiences, genotype, development and social support. The term ‘coping style’ can be defined as a coherent set of behavioural and physiological stress responses which is consistent over time and which is characteristic to a certain group of individuals (Koolhaas et al., 1999). The concept of coping styles therefore implies that animals have a differential way to adapt to various environmental conditions. The incapacity to cope with a stressor can have negative health consequences for an animal. Chronic over-activation of various neuroendocrine systems may lead to specific types of pathology. When a coping-style fails to reduce the negative effects of the stressor, different types of stress-pathologies might develop like cardiovascular pathology, ulcer formation, infectious diseases as well as stereotypies (Koolhaas et al., 1999).
2.2. Cortisol and beta-endorphin

When accepting the coping hypothesis for the development of stereotypy, this means that somewhere in the past an animal or person showing stereotypic behaviours was or is experiencing a lot of stress due to its responses to its environment. The physiological concept of stress involves the interaction between external events ('stressors') and individual predispositions (determined by genetic factors and early experience) giving rise to measurable 'stress' responses (Ladewig et al., 1993). Because stressors consistently prompt cortisol production, plasma cortisol concentrations have frequently been used to characterize the stress responses of horses (Alexander et al., 1988; Martinez et al., 1988; Mal et al., 1991; Clark et al., 1993; Milss et al., 1993).

Since it has been proposed that stereotypies arise in response to stress (Mason, 1993), the relationship between plasma cortisol levels and stereotypic behaviour has been investigated in several species, including horses (McGreevy and Nicol, 1995). Furthermore, because opioid antagonists can transiently eliminate stereotypic behaviour (Dodman et al., 1987, 1988), it has been proposed that endogenous opioids, such as beta-endorphin (BE), facilitate and reinforce stereotypies (Dodman et al., 1987; Gillham et al., 1994). This, however, seems to be in contrast with the findings of Cronin et al. and Pragman and Baker who suggested that animals perform stereotypies to release endogenous opioids in analogy to a 'runner’s high' (see §1.7). Pell and McGreevy (1999) investigated the relationships between cortisol, BE levels, and equine stereotypic behaviour. They found no significant differences between the mean cortisol concentrations of stereotypic and normal horses, indicating that their arousal levels were similar. They also found that mean plasma BE levels did not differ significantly between stereotypic and non-stereotypic horses. Still this does not reject the suggestion that endogenous opioids facilitate stereotypic behaviour because it is still possible that stereotypic horses have inherited an increased opioid receptor sensitivity (Gillham et al., 1994) instead of an altered BE expression pattern or release.

However, McBride and Cuddeford (2001) found significantly elevated mean plasma cortisol levels in crib-biting horses that were prevented from crib-biting (oral stereotypy; \( P = 0.05 \)). A similar, though not significant effect was observed in weaving (locomotor stereotypy) horses when prevented from weaving. This suggests that prevention of the stereotypy in a stereotypic individual is stressful. It also showed that plasma cortisol levels were significantly higher immediately prior to the onset of stereotypy followed by a significant reduction post-stereotypy, which suggests, amongst other things, that the performance of stereotypies has a coping function to reduce stress levels in the animal (McBride and Cuddeford, 2001).

In carnivores highly stereotypic individuals excrete higher levels of cortisol than those with lower stereotypy levels (Bildoe et al., 1991; Wielebnowski & Brown, 2000; Shepherdson et al., 2004) while stress-inducing manipulations and stress-relieving ones respectively increase and decrease the levels of both cortisol and pacing in leopard cats (Felis bengalensis) (Carlstead et al., 1993).

However although some studies find an effect on cortisol levels, results are contradictory and not conclusive. More research here is needed.

2.3. The basal ganglia system

The basal ganglia (see figure 2.1) are a set of subcortical nuclei located in the midbrain, around the thalamus. The major nuclei of the basal ganglia are the striatum, which is composed of the caudate nucleus and the putamen, the internal and external parts of the
globus pallidus, the pars reticulata and the pars compacta of the substantia nigra, and the subthalamic nucleus. The basal ganglia are associated with a variety of functions, including voluntary motor control, procedural learning relating to routine behaviors or "habits", eye movements, and cognitive (Stocco et al., 2010), emotional functions (Weyhenmeyer et al., 2007). Currently popular theories implicate that the basal ganglia system is primarily involved in action selection, i.e. in the decision of which of several possible behaviors to execute or not at a given time (Stocco et al., 2010; Chakravarthy, 2010). Traditionally the basal ganglia have been a candidate for explaining repetitive behaviours including stereotypy. Since the findings of Amsler in 1923 that the striatum was directly implicated by drug induced stereotypies in guinea pigs, many other studies confirmed that damage or dysfunction of the basal ganglia results in ‘recurrent perseveration’ or inappropriate response repetition (Garner, 2005; Norman and Shallice, 1986; Sandson and Albert, 1984; Turner, 1997). Alexander et al. (1986) reviewed earlier ideas and studies of basal ganglia function and proposed that the basal ganglia should be viewed as components of multiple parallel, segregated circuits with outputs targeting different cortical areas. Each circuit receives cortical inputs to the striatum (caudate nucleus, putamen (the dorsal striatum) and nucleus accumbens (the ventral striatum)), passing the input through the basal ganglia, via output nuclei (substantia nigra pars reticulata and the medial globus pallidus) to a restricted area of the thalamus and from there back to a single cortical area (Ring and Serra-Mestres, 2002). Corticostriatal loops can be functionally divided into three ‘macro-circuits’, related to the predominant cerebral cortical input to striatum: 1) the sensorimotor circuit, 2) the associative circuit, and 3) the limbic circuit (Groenewegen et al., 2003). Within these macro-circuits, smaller (micro-)circuits can be recognized that serve specific functions within the broader functional domain. Each corticostriatal circuit receives information from different cortical areas and each loop consists of a direct (striatonigral) and an indirect (striatopallidal) pathway. In a normally functioning system the basal ganglia select and amplify wanted behaviours and movements via the direct pathway while they inhibit unwanted actions via the indirect pathway as depicted in figure 2.1 The net result of the activity of the direct pathway is an increase in thalamic activity, whereas activity of the indirect pathway inhibits the thalamus. In general, activation of the indirect pathway or suppression of the direct pathway will reduce stereotypic behaviour, whereas suppression of the indirect pathway will induce them (Langen et al., 2011). In contrast, activation of the direct pathway leads to hyperactivity, not stereotypy, and the inhibition of only the direct pathway suppresses all behaviour including stereotypic behaviour (Garner, 2006; Lewis et al., 2006). Repetitive behaviour is associated with an imbalance between the activities of both pathways as result of either decreased inhibition and/or increased facilitation of behaviour (Lewis et al., 2006, 2007).
2.2. GABA and glutamate

The main inhibitory neurotransmitter in striatum, pallidum, and thalamus is GABA and the main excitatory neurotransmitters in these areas is glutamate. Targeted administration of agents that bind either to the inhibitory GABA-receptors or to the excitatory glutamate sites can be used to manipulate the activity of distinct elements of corticostriatal circuitry. By intervention in one area in the corticostriatal circuitry, the feedbackloop to the cortex can be affected to reduce or induce repetitive behaviour. Muscimol, a specific GABA agonist, induces stereotyped behaviour when administered in the substantia nigra pars reticulate (SNpr) (Scheel-Kruger et al., 1980). GABA receptor stimulation in the globus pallidus (GP), the subthalamic nucleus (STN) and the substantia nigra pars reticulate mediates the efferent output of the striatum (figure 2.1.) (Scheel-Kruger et al., 1980; Langen et al., 2011). Administration of GABA-agonists to the frontal cortex in rats attenuates stereotypic behaviour whereas administration of GABA-antagonists exacerbates stereotypy (Karler et al., 1995). However, the effects of GABAergic drugs administration is not conclusive and can have different effects on behaviour dependent on the topographical site of drug-administration as well as the dose of the particular drug (Scheel-kruiger et al., 1980). The location of administration as well as the dose of a drug can have different neurochemical effect on the corticostriatal feedback loops.
Additional to GABA-ergic agents, glutamatergic agents can also modulate stereotypic behaviour. Striatal administration of an NMDA agonist, a glutamate receptor agonist, can induce stereotypy, whereas NMDA antagonists can reduce drug induced stereotypy (Bedingfield et al., 1997).

2.5. Dopamine

Dopamine has been the primary candidate neurotransmitter underlying the development and maintenance of stereotypic behaviour for some time since Harnack in 1874 demonstrated ‘compulsive gnawing’ in rabbits after injection of apomorphine, which was later recognized as being a dopamine agonist. Since then, many other studies have reported induction of stereotypy through administration of dopamine agonists that are phenotypically similar to environmentally induced (spontaneous) stereotypies for several animal species (Amsler, 1923; Robbins et al., 1990; Cooper and Dourish, 1990). Further, the injection of a dopamine neurotoxin (6-OHDA) into the striatum region of the basal ganglia, showed a significant reduction in environmentally induced stereotypy in rats (Antelman and Szechtman, 1975) and spontaneous stereotypy performance is attenuated by striatal infusion of dopamine D1 receptor antagonists, which are considered to alter the balance of the direct and indirect basal ganglia pathways to overall suppression of the striato-cortical output (Presti and Lewis, 2005). How different agents affect these basal ganglia circuits is illustrated in figure 2.1 and reviewed by Langen et al. (2011): “In the direct pathway, post-synaptic D1 receptors are targeted by dopamine projections from the substantia nigra pars compacta (SNpc). Activation of these D1 receptors increases the overall excitability of the post-synaptic neuron, resulting in amplification of excitatory corticostriatal input and subsequently increased GABA-ergic inhibition of the substantia nigra pars reticulate and the medial globus pallidus, the major inhibitory output nuclei of the basal ganglia. This in turn facilitates activation of thalamo-cortical relay neurons and consequently provides positive feedback to the cortex. In contrast, the blocking of these D1 receptors suppresses the direct pathway, and decreases feedback to the cortex, resulting in less stereotypic behaviour (Joel and Doljansky, 2003; Presti, 2003). In the indirect pathway, activation of post-synaptic dopamine D2 receptors in the striatum reduces excitatory cortical input and thereby decreases inhibition of the globus pallidus externa (GPe). This leads to stronger inhibition of the subthalamic nucleus (STN), thereby decreasing activation of the substantia nigra pars reticulate and the globus pallidus interna (GPI). When these major inhibitory output nuclei are inhibited, the thalamus becomes disinhibited, resulting in increased activity of the cortex (Lewis et al., 2006). Dopaminergic drugs such as apomorphine and amphetamine act on dopamine D2 receptors (Garner, 2006). These agents suppress the indirect pathway and disinhibit behaviour. Conversely, dopamine antagonists, such as haloperidol, reduce or block stereotypies by blocking dopamine D2 receptors (Kjaer et al., 2004).”

Studies further have shown that the ventral rather than the dorsal striatum is critical to stereotypy development. Stress-induced stereotypy has been associated with long-term potentiation (increased and sustained transmission) of the mesoaccumbens dopamine pathway (ventral striatum), as indicated by upregulation of D1 and D2 receptors in the nucleus accumbens (ventral striatum) and downregulation of dopamine D2 receptors in the ventral tegmental area (Cabib et al., 1984; Cabib et al., 1998; Cabib and Bonaventura, 1997; Cabib et al., 2002). Similar results were found in crib-biting horses. Stereotypic (crib-biting) horses had significantly higher D1 and D2 receptor subtypes in the nucleus accumbens (ventral striatum) and significantly lower D1 receptors in the caudatus (dorsomedial striatum) compare with non-stereotypic horses (McBride and Hemmings, 2005).
The dopaminergic system also has an important role in the stress response: The activity of the dopamine system differs across individuals, and a first indirect link between stress and dopamine came from studies showing that individuals with higher reactivity to mild stress (High Responders, HRs) show greater dopaminergic activity compared with individuals with a lower reactivity to stress (Low Responders, LRs). Higher reactivity to stress is measured by a greater (Kabbaj et al., 2000) or longer (Piazza et al., 1991) corticosterone secretion in response to a stressful situation, such as the exposure to a novel setting or to restraint stress. It is also characterized by greater or longer locomotor response to a novel environment (Marinelli, 2005). Thus, animals with enhanced reactivity to stress (HRs) show higher baseline firing and bursting activity of dopamine neurons compared to animals with low reactivity to stress (LRs; Marinelli and White, 2000). Greater neuronal activity is paralleled by enhanced extracellular levels of dopamine in the nucleus accumbens (ventral striatum), both in basal conditions and in response to stress or psychostimulant drugs (Bradberry et al., 1991; Hooks et al., 1991; Piazza et al., 1991; Rouge-Pont et al., 1998).

2.6. Serotonin

Serotonin is a chemical mediator of inflammation. Its secretion and physiological actions mediate stress and pain, affecting both immune and nervous system functions through the hypothalamic-pituitary-adrenal (HPA) axis. Serotonin receptor dysfunction is well characterized in mental disturbances such as depression and anxiety (Smythies, 2004).

Chronic stress has been shown to produce specific downregulation of 5-HT\textsubscript{1a} receptors in the hippocampus (Lopez et al., 1999; Pare and Tejani-Butt, 1996). Mice lacking the 5-HT\textsubscript{1a} receptor gene display increased anxiety in behavioral models such as the open field test or elevated plus maze (Heisler et al., 1998; Parks et al., 1998; Sarnyai et al., 2000; Sibille et al., 2000), and the anxious phenotype is associated with changes in GABA\textsubscript{A}R neurotransmission (Olivier et al., 2001).

Most of what is known about the role of serotonin (5-HT) on stereotypy comes from studies of drug-induced behaviour. From the experiment of Ödberg and Mers (1998) it was shown that the selective 5-HT re-uptake inhibitor (SSRI) fluoxetine exerts a rate-dependent effect on stereotypy. It has an increasing effect on stereotypy performance in low-stereotypic voles but a decreasing effect in high-stereotypic individuals.

Schoenecker and Heller (2001, 2003) investigated the effect of clozapine (which blocks dopamine receptors and acts as a partial 5-HT antagonist) and citalopram (an antidepressant that selectively increases 5-HT transmitter activity) as well as sex differences and the effects of the drugs. They found that clozapine had no effect on stereotypies under undisturbed conditions or after acute stress in males or females. In first instance they found that citalopram did not affect stereotypies under undisturbed condition but that it effectively removed the elevations in stereotypy levels after acute stress. In an additional study however they found a sex difference with the treatment of citalopram. Facilitation of 5-HT neurotransmission by citalopram treatment did reduce the performance of already developed stereotypies in female but not in male bank voles under undisturbed conditions. This may indicate that already established stereotypy in females is related to relatively decreased serotonergic functioning. (Schoenecker and Heller, 2003). Interestingly, it seems that environmental stress plays an important role in the involvement of serotonin in repetitive behaviours because stressor-induced increases in stereotypy are more dependent on serotonin than dopamine functioning (Schoenecker and Heller, 2001, 2003).

Other studies have suggested a higher serotonin release or turnover or over-activity of serotonin receptors in the development of stereotypic or repetitive behaviour. An example
came from Kraemer et al. (1989) where isolated reared primates which showed abnormal repetitive behaviours also had higher levels of 5-hydroxyindoleacetic acid (5-HIAA), the major brain metabolite of serotonin, compared to socially reared controls.

2.7. Effects of environmental enrichment on BDNF

Environmental enrichment is an often used strategy to prevent stereotypic behaviour development. In deer mice this kind of prevention strategy is associated with alterations in neuronal metabolic activity and dendritic morphology (Turner et al., 2003a; Turner et al., 2002), especially in motor areas like motor cortex and striatum. Several studies suggested that these environmental-enrichment induced alterations in neuronal metabolic activity and dendritic morphology might be mediated by neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophin factor (BDNF). Neurotrophins are the key mediators of synaptic plasticity in the CNS. It has been shown that environmental enrichment increases NGF and BDNF levels in several brain areas (Pham et al., 1999; Ickes et al., 2000). Turner and Lewis assessed whether environmental enrichment-related effects on the development of stereotyped behaviour in deer mice was associated with alterations in BDNF and NGF. The results of this study showed that the enrichment-related prevention of stereotypy was associated with a significant increase in BDNF levels in the striatum. These results indicate that areas involved in motor behaviours also show evidence of plasticity after environmental enrichment (Turner and Lewis, 2003b), similar as the cerebral cortex, basal forebrain, hippocampus, and hindbrain, which also showed increased BDNF and NGF levels (Pham et al., 1999; Ickes et al., 2000). This finding is interesting considering the interactions between dopamine and BDNF in the striatum as they can reciprocally potentiate each other (Goggi et al., 2002; Kuppers and Beyer, 2001).

2.8. Common mechanism for stereotypy in animals and humans

Environmental deprivation induced stereotypies in captive and domesticated animals closely resemble the stereotopies of autistic and mentally retarded patients, unmedicated schizophrenic patients, certain classes of simple tic in Tourette’s syndrome and several drug-induced behaviours (Garner and Mason, 2002; Mason and Turner, 1993; Nurnberg et al., 1997; Overall, 1997). Stereotypies in human mental disorders are indicative of profound brain dysfunction involving the basal ganglia, and are associated with pervasive voluntary-motor impairments and psychological distress. Garner et al. (2003) showed that stereotypy in captive Orange-Wing Amazon Parrots (Amazona amazonica) is correlated with poor performance on the same psychiatric task (the ‘gambling task’) as stereotypy in autistic and schizophrenic patients. This task measures recurrent perseveration; the tendency to inappropriately repeat responses. The most stereotypic parrots were most likely to inappropriately repeat themselves at the gambling task; and the most rapidly in performing repeated, but not switched, responses. Similar results were obtained in human patients and they suggest a common disinhibition of the behavioural control mechanisms of the basal ganglia (Garner et al., 2003).
3. Genetic and epigenetic factors in the inheritance of stereotypies

3.1. Genetic predisposition

Many animals, though not all individuals that are housed in sub-optimal environments develop stereotypy (Mason and Latham, 2004). This indicates that factors other than the environment contribute to the ontogeny of stereotypies. The hypothesis of genetic predisposition in the transmission of stereotypy is supported by several studies. Offspring of stereotypic blank voles (*Clethrionomys glareolus*) were more likely to develop stereotypy compared to offspring from non-stereotypic parents (Odberg, 1986; Schoenecker and Heller, 2000). Similar results were observed in studies involving mink (*Mustela vison*) (Jeppesen et al., 2004), striped mice (*Rhabdomys pumilio*) (Schwaibold and Pillay, 2001) and the domestic horse (*Equus caballus*) (Kiley, 1977; Smith, 1984). A hereditary component to stereotypy development in horses is also suggested by evidence that certain thoroughbred bloodlines are more likely than others to perform stereotypies (Hosoda, 1950; Vecchiotti & Galanti, 1986).

Behaviour can be transmitted from parents to offspring by genetic and non-genetic (e.g. social learning) means. Therefore, a methodological problem for studying behavioural inheritance arises if offspring are raised with the parents, since it becomes difficult to separate genetic from learned influences in the behavioural phenotype. In the case of stereotypy, Lewis et al. (1990) found that Rhesus monkeys raised in absence of their mothers showed high levels of stereotypic behaviour (see also § 1.6. about maternal deprivation). They suggested then that the stereotypic behaviour was not learned, at least not from the mother. In contrast, Palya and Zacny (1980) have shown that social influence (i.e. social learning) is important in the development of stereotypy in pigeons, since the incidence of stereotypy increased if an animal’s neighbor showed this behaviour (Schwaibold & Pillay, 2001).

However further evidence for a genetic basis came from a study of Schwaibold & Pillay (2001) which showed that stereotypies in *R. pumilio* were four times more common in the offspring of stereotypic females than in those of non-stereotypic females. Post-natal cross-fostering experiments demonstrated that the pups of stereotypic mothers were significantly more likely to display stereotypic behaviour than pups of non-stereotypic females, regardless of whether they were raised by their own or a non-stereotypic foster mother. These findings of Schwaibold & Pillay suggested that the tendency to develop stereotypic behaviour in captive striped mice is related to its occurrence in the biological mother rather than to social learning. In their study a cross-fostering treatment was used to ascertain the extent of genetic influence on stereotypic behaviour. The reasoning for this was that if genetically-related animals (i.e. the offspring from the same breeding pair) exhibit similar specific behaviours when raised under different environmental conditions (e.g. by a foster mother), the genetic control of the behaviour must be fairly rigid, according to studies of Huck & Banks (1980) and Drickamer & Vessey (1986). Schwaibold & Pillay concluded that the high incidence of stereotypy in fostered individuals whose biological mothers were also stereotypic suggested a genetic basis for stereotypy in striped mice similar as in previous finding of Schoenecker and Heller (2000).

3.2. Maternal and paternal contribution

From the cross-fostering experiment of Schwaibold & Pillay it was found that the development of stereotypy was strongly related to the stereotypy status of the biological mother, and it was thus concluded that stereotypies are genetically rather than socially
transmitted. Jones et al., (2008) built further on this research by assessing the contribution of the father to the development of the stereotypic behaviour. They assessed the genetic transmission of stereotypies to the offspring from both the mother and the father in *Rhabdomys*, a small, diurnal muroid rodent that is widespread and abundant in southern Africa (De Graaff, 1981). Jones et al. established four treatment groups, comprising breeding pairs of combinations of stereotypic (S) and non-stereotypic (NS) females and males; S♀+S♂, S♀+NS♂, NS♀+S♂ and NS♀+NS♂. Based on previous studies, and because the genetic contribution from each parent was expected to be equal and additive (e.g. Schoenecker and Heller, 2000), they predicted that litters with two stereotypic parents would show the highest prevalence of stereotypy, followed by litters with only one stereotypic parent, and litters from non-stereotypic parents having the lowest stereotypy prevalence.

It showed, however, that offspring with two stereotypic parents (S♀+S♂) were not at a greater risk of developing stereotypy than offspring with only a stereotypic mother (S♀+NS♂) (p = 0.567), with about 50% of the offspring in both these treatments displaying stereotypy. Second, significantly fewer (p < 0.001) stereotypic offspring were produced in treatments in which only the mother (NS♀+S♂; 30% stereotypic offspring) or both parents were non-stereotypic (NS♀+NS♂; 10% stereotypic offspring). Third, offspring with at least one stereotypic parent (S♀+NS♂ or NS♀+S♂) were significantly more likely to develop stereotypy than offspring from non-stereotypic parents (NS♀+NS♂; p < 0.001). Fourth, maternal stereotypy (S♀+NS♂) was a better predictor of offspring stereotypy than paternal stereotypy (NS♀+S♂; p = 0.039).

The prediction made by Jones et al. that mothers and fathers contribute equally and additively to stereotypy in their offspring and that therefore stereotypy prevalence would be highest in offspring from S♀+S♂ groups, was not met. The larger maternal than paternal contribution to the development of stereotypic behaviour in the S♀+NS♂ compared with the NS♀+S♂ groups, as well as the lack of difference in stereotypy transmission between the S♀+NS♂ and S♀+S♂ groups, indicate that genetics alone might not explain the observed transmission patterns. The possible explanation of social learning had already shown to be unlikely because the cross-fostering experiments showed that the stereotypic status of the foster mother did not influence the development of stereotypy in fostered offspring (Schwaibold and Pillay, 2001). Further *Rhabdomys* parents, except for suckling, contribute equally to parental care (Schradin and Pillay, 2004) which would mean that if stereotypy was transferred by social learning the maternal influence could not be four times larger. Thus there must be other factors involved in stereotypy transmission than genetics and social learning.

### 3.3. Epigenetics

The cross-fostering experiments of Schwaibold and Pillay were all postnatal cross-fostering experiments. However the prenatal environment appeared to be important as well in the development of behaviour later in life, and gestational effects between conception and birth can have enduring effects on neurobehavioural development (Francis et al., 2003; Szyf et al., 2007) and possibly predispose for a stereotypic phenotype. For example, several rodent studies showed that the offspring of psychologically stressed mothers are more anxious than offspring of mothers that were not stressed during pregnancy (Macri and Würbel, 2006). This could be ascribed to epigenetic changes causing an abnormally up-regulated HPA-axis (Kofman, 2002). Although evidence is mixed for stereotypic animals having higher baseline stress hormone glucocorticoid levels than non-stereotypic animals, it cannot be ruled out that the prenatal environment (in utero) contributes, via epigenetic mechanisms, to a fourfold higher incidence of stereotypy among the offspring of stereotypic mothers. This would also
explain the relatively small paternal contribution to the transfer of stereotypy to the offspring (the genetic paternal and maternal contribution will probably be equal). To proof a epigenetic component in the transfer of stereotypic behaviour the effects of the prenatal and postnatal environment should be investigated. Prenatal cross-fostering in mice, i.e. embryo transfer, have shown to effect behaviour development in studies with two different strains of mice (B6 and BALB mice) that differ significantly in an array of behaviors related to anxiety and learning (Francis et al., 2003). B6 mice that were placed in a BALB uterus and reared by a BALB mother, showed behaviours that were identical to those of BALB mice and significantly different from B6 mice. These prenatal cross-fostered mice had a B6 genotype but a BALB phenotype, thus their behavioural differences must have resulted from non-genetic factors. However, this apparently epigenetic effect did not result entirely from prenatal factors, as the mice that were developing in a BALB uterus but reared by a B6 mother did not show the BALB behavioural phenotype. From the experiments of Francis et al. (2003) it can be concluded that behavioural development relies on epigenetic mechanisms which are influenced, at least, by the postnatal environment. Similar mechanisms may influence the development of stereotypic behaviour as maternal stress also affects adult offspring’s behaviour. Maccari et al. (2003) showed that prenatal restraint stress (PNRS) induces higher levels of anxiety, greater vulnerability to drugs, a phase advance in the circadian rhythm of locomotor activity and an increase in the paradoxical sleep in adult rats. These behavioural effects result from permanent modifications to the functioning of the brain, particularly in the feedback mechanisms of the HPA axis: A prolonged secretion of corticosterone after stress and a reduced number of central glucocorticoid receptors. As stereotypy is a behavioural trait that is linked to stress coping it and elevated stress sensitivity is caused by prenatal stress, it is likely that stereotypy is transferred by a similar epigenetic mechanism.

3.4. Genetic modulation of repetitive behaviour

In addition to the administration of pharmacological agents or inducing lesions, genetic modification is a way to affect CNS function. Gene knockouts can enhance the understanding of certain genes in the development of behaviour, including abnormal/stereotypic behaviour. Data from gene knock-out studies suggest that specific genes may directly and specifically affect or induce repetitive behaviour (reviewed by Langen et al., 2011). Candidate genes include dopamine and serotonin genes as well as a number of other genes.

Berridge et al. (2005) found that dopamine transporter (DAT) knockout mice display a behaviour pattern known as superstereotypy: excessively strong and rigid manifestations of complex and fixed action patterns. The knockout effect of DAT is twofold, leading to hyperdopaminergia (Berridge et al., 2005), i.e. increases in extracellular dopamine levels, and causing an imbalance between the dopamine and serotonin systems in the basal ganglia (Pogorelov et al., 2005). Further the knockout of the dopamine D3 (DRD3) receptor gene lead to narrowly defined changes in behaviour. Joseph et al., (2002) found an increase in spontaneous stereotypy in DRD3-knockout mice compared to wild type mice.

However the field of neuroscience concerning the genes that may potentially affect pathological repetitive behaviour is still in its infancy. Although modifications of dopamine genes seem to be very important in the development of stereotypy, there could be many other genes contributing to it. According to Langen et al., (2011) some of the candidate genes include the GABA A-receptor beta-3 gene (GABRB3), the serotonin receptor 2C gene (HTR2C or 5HT2C), and the disks large-associated protein-3 gene (DAP-3 or SAP90/PSD-
95-associated protein 3 or SAPAP3). Some translational studies already showed the involvement of the knockout of these genes in stereotypy: intensified and stereotyped chewing was seen in 5HT2c knockout mice (Chou-Green et al., 2003); increased repetitive grooming in SAPAP3 knockouts (Welch et al., 2007); and intense circling and tailchasing in GABRB3 gene knockouts (DeLorey et al., 2008; Homanics et al., 1997). All three genes are also linked to neuropsychiatric disorders, in which repetitive behaviour is one of the core features: GABRB3 was linked to autism (DeLorey et al., 2008) even as the HTR2C gene which was also linked to obsessive compulsive disorder (OCD) (Veenstra-VanderWeele et al., 2000), and DAP3 was linked to trichotillomania (pathological repetitive hair-pulling) and obsessive compulsive disorder (OCD) (Züchner et al., 2009).

A problem with knockout translational models however is that the modifications affect the organism as a whole and may have unpredictable, widespread and non-specific effects. Genetic modifications that can be targeted to specific brain regions would provide a better experimental model.

3.5. Stereotypy and fertility

The study of Jeppesen et al. (2003) showed that stereotypies are associated with higher fertility. Stereotypic female farm mink (*Mustela vison*) had increased litter size and a lower mortality rate among the pups compared to non-stereotypic females. The study demonstrated a positive relationship between stereotypies and fertility due to lower body weight in stereotypers. Compared to non-stereotypic females there were also less infertile (including unreceptive) individuals among stereotypic females. It appeared that stereotypic behaviour affects fertility through actions on the animals’ body weight. In general, stereotypic mink are considerably more active than non-stereotypers (Jeppesen et al., 2002) which may very well account for the lower body weight and higher fertility of stereotypers. There was no relationship between weight at weaning and subsequent incidences of the development of stereotypies in the pups but there was a significant negative correlation between already developed stereotypies and body weight indicating that stereotypies may be the cause rather that the result of low body weight (Jeppesen et al., 2003). Jeppensen et al.’s study demonstrated a positive relationship between stereotypies and fertility in female farm mink. The increased fertility is correlated to lower body weight/ increased activity. The precise underlying mechanism is unknown and seems contradictory to the known relationship in for instance (non-stereotypic) humans, where low body weight is associated with infertility.

4. Conclusions and discussion

Stereotypy is the definition of a group of phenotypic different behaviours that share the following three characteristics: morphologically identical movements, which are repeated regularly and have no obvious function. Overall we can state that animal stereotypy has only been observed in animals born in captivity and therefore this abnormal behaviour is probably being caused by the captive environment. The captive environment in most cases is quite different from the wild environment of the specific species and in several cases severely conflicts with the animals’ natural/wild behaviour. Some natural behaviours are impaired due to some kind of deprivation, being it social, environmental, maternal or nutritional deprivation. All these kinds of deprivation, and especially when more types of deprivation are present at the same time, create a possibility for the development of stereotypic behaviour.
Stereotypic behaviour also affects humans. Many mental disorders are accompanied with the performance of stereotypies, as seen in autistic patients, schizophrenics and some other patients with mental disorders. In humans, stereotypy is also associated with deprivations such as maternal deprivation, or food and environmental deprivation, as seen in orphans. The ontogeny and context in which stereotypies are performed are considered to be very heterogenic. Since stereotypies have not been observed in wild animals it is generally assumed that stereotypies in captive and domesticated animals result from poor coping with the environment and could be related to previous or present experience of stress. Therefore stereotypic behaviour in animals is considered to be an important parameter of long-term animal welfare. The performance of stereotypies thereby indicates poor welfare in past or present. A more controversial view explains the stereotypic behaviour as an adaptation that is beneficial for the animal in their domesticated/captive environment. Here stereotypy is regarded to be an evolutionary advantage. Overall however it is seen as an abnormal phenotype with underlying pathophysiologic causes.

As mentioned earlier, stereotypy is only observed in animals born in captivity, but is also present in humans who are not born in captivity (and thus could be considered to be ‘wild’ and living in their natural environment). This seems contradictory and could mean two things: 1) Stereotypy could be present in wild animals, but is not observed (so far). This might be due, amongst others, to a natural selection process early in life in which the stereotypic phenotype is less well adapted for a wild environment. The survival chances of stereotypers are lower and they are not likely to be able to survive into adulthood. This might cause the fact that stereotypy is not observed (yet) in animals living in the wild. 2) On the other hand the presence of stereotypy in humans but (seemingly) absence in wild living animals could indicate that a ‘mismatch’ between the natural ethology and the environment is not only present in captive animals but in some humans too. This is shown by the orphan studies; The more severe the deprivations (found in many ethological areas such as feeding, social interaction, locomotion, mother-child-interaction, explorative behavior etc.) the higher the chances are for the development of stereotypic behavior (and often accomplished mental/psychiatric disorders). The observation of stereotypy in non-orphan-house-raised individuals could suggest the presence of certain deprivations within our society the way it is today. This could mean that the natural human ethology (as it has evolved during thousands of years of evolution) is not completely agreeable with the modern ‘natural’ environment which has changed dramatically in the last 300-500 years due to several industrial revolutions. Therefore it could be stated that although humans do not live in captivity, they might be too far deviated from their natural habitat with corresponding behavioural patterns.

It is suggested that stereotypies develop due to an altered brain development induced by the (deprived/stressful) environment. The most important brain areas involved in this development are the basal ganglia, which stimulate or inhibit the cortex, through respectively the direct and indirect pathway, and in this way alter the performance of motor behaviours. Studies concerning agonistic and antagonistic drugs showed that GABA, glutamate, dopamine and serotonin are the main neurotransmitters that regulate motor behaviour performance and that an imbalance of these neurotransmitters can induce stereotypic behaviour.

Stereotypies also seem to have a strong genetic component, as appears from post-natal cross-fostering experiments. However, the trait is mainly transferred through the mothers and is only observed in animals in captivity and in humans. Thus it can be stated that not only genes cause the development of stereotypy. A plausible explanation for this might be found in the field of epigenetics. To be able to draw conclusions about epigenetic influence additional research is needed. Studies on prenatal cross-fostering experiments are necessary to investigate the effect of the prenatal environment (in utero) on the development of stereotypic behaviour. Although glucocorticoid levels in stereotypic mothers are not raised compared to
non-stereotypic mothers, other (yet unknown) factors could create an ‘anomalous’ environment in utero that might have epigenetic implications for the offspring. The possibility that DNA-methylation and other epigenetic mechanisms in the offspring are influenced by specific factors only expressed (or absent) by stereotypic mothers during the prenatal phase cannot be ruled out. Transplanting embryos of non-stereotypic mothers to the uterus of stereotypic mothers could provide useful information about the extent to which epigenetic mechanisms cause different epigenetic patterns in the DNA of the offspring.

Studying and understanding the causes, etiology and pathology of stereotypic behaviour is important for many reasons. First of all understanding the environmental causes will enable us to create captive environments that better resemble the natural habitat of the animals. This also requires a thorough understanding of the natural/wild behaviour of the specific animal species to be able to ‘create’ a captive/domestic environment that best suits these behaviours. An environment that will allow and stimulate the performance of the natural behaviour will prevent stereotypy development, likely because it will allow correct brain development and basal ganglia functioning. Second, it is of great importance to understand stereotypies to be able to draw the correct conclusions from scientific research on laboratory animals. This is especially important in research areas including psycho-pharmacy, neurology and mental/behavioural disorders but also in fields such as fertility and obesity research. The presence of stereotypic behaviour in experimental animals can jeopardize the validity, reliability and replicability of an experiment, since stereotypic behaviour can interfere with the effects of the tested variable. Third, stereotypic behaviour can have far reaching economic consequences. Economic losses can follow directly out of the second point by accepting wrong hypothesis in science. But also because stereotypic behaviour can have economical consequences when it leads to injuries and depreciation of animals, animal fur, milk, meat and eggs, or reputation damage for zoos, intensive bio-industry, laboratories and orphan and psychiatric institutions. Understanding the development of stereotypy could lead to elimination of this behaviour and thus to prevention of the economic consequences that accompany them.

The fourth reason for spending more attention to stereotypy research, however, is in contradiction with the previous reasons. It is assumed that there is a genetic component in the susceptibility of stereotypy development within a captive/domestic/stressful environment. So a possibility to reduce the occurrence of stereotypies among captive animals is to breed them selectively and select the trait out of the population. However, as the exact cause(s) of stereotypy are very broad and imprecise, it is not sure if it will benefit and enhance the welfare of animals if they are selectively bred to lose the behaviour. Stereotypic animals seem to have higher fertility than non-stereotypic animals which indicates a better adaption to the captive environment. A counterargument here is that this selective breeding strategy is not applicable in human settings were stereotypic behaviour accompanies many psychiatric disorders. Children with psychiatric disorders might have a genetic predisposition for both the disorders as for the development of the stereotypy but, based on orphan observations, it seems to be influenced very strong by the environment. In humans as well as in animals the environment seems to be more important than the genetic predisposition for stereotypy development. Since stereotypy in humans is most observed in persons that also suffer from mental disorders such as autism and schizophrenia this suggests that the stereotypy is a visual observable symptom of the abnormal brain development in these patients. In animals it is not possible to test for mental disorders such as autism-spectrum disorders. So in animals only the visual observable symptoms can be analyzed. However, these animals might also be affected by schizophrenia or autism due to the observed altered brain development and functioning that is associated with stereotypic behaviour in which environmental circumstances seem to play an important role for the development, with a possible genetic predisposition. The same
seems to be true for stereotypic humans: there might be a genetic predisposition but the environment (e.g. orphans) seems to play a crucial role in the abnormal brain development that causes stereotypy (and/or autism/schizophrenia). Even the ‘genetic component’ might be highly or at least partially be influenced by epigenetic mechanisms which also indicates that the environment in which a child/animal develops, is very important for healthy mental development.

The gene-knockout experiments depict especially the dopamine and serotonin related genes as candidate genes for stereotypy development. DAT-Knockouts (Dopamine Transporter) become ‘superstereotypers’, and express a very extreme version of stereotypy. Serotonin receptor and dopamine receptor knockouts also display more stereotypic behaviours. This could suggest that mutations in the genes or certain types of the normal variations of the genes could lead to stereotypy. It might also support the hypothesis that the genes can be influenced by the environment and therefore behavioural changes can occur due to epigenetic mechanisms that alter gene regulation and expression.

Conclusively it can be stated that stereotypy is a serious concern for animals as well as for humans. It indicates serious welfare problems and therefore it is very important to understand its etiology. The environment seems to be the most important variable, so it is important to focus on the environment-brain-development relation. Epigenetics should be considered a possible key mechanism in the trait. A better understanding is not only important for animal welfare and human welfare on an individual basis but it is important for society as a whole. People have lost a large part of their natural habitat especially since the Industrial Revolution era. With the development of technology and individualization of society, humans drift further and further from their ‘wild environment’. Humans have to deal more and more with social deprivation, time-management, stressful jobs etc. and this might have a larger impact than realized on the offspring (and their brain development). Similar as taking wild animal behaviour into account for designing captive environments for animals, it is important when ‘designing’ human society to take natural behaviour of humans into account. This might be an important key to reduce mental disorders in humans in combination with good education about the importance of the ability for the expression of natural behaviour as being a requirement for healthy brain development (maybe already before birth). However, much more research on epigenetics is needed here.

References

Beddingfield, J.B., Calder, L.D., Thai, D.K., Karler, R., 1997. The role of the striatum in the mouse in
behavioral sensitization to amphetamine. Pharmacology Biochemistry & Behavior 56(2), 305-310.


Schradin, C., Pillay, N., 2004. The striped


Schradin, C., Pillay, N., 2004. The striped mouse (Rhabdomys pumilio) from the Succulent Karoo, South Africa:...


