Behavioural correlates of stereotypic behaviour in *Rhabdomys dilectus*

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Declaration

I hereby declare that this dissertation is my own unaided work. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

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16 April 2018

Abstract

The specific causal mechanisms of stereotypies are difficult to establish, especially because they do not develop in all individuals of a species living in the same captive environment, and may be affected by other behaviours (e.g. personality) and the life history of the animal. The overarching aim of this study was to investigate the behavioural correlates of stereotypic behaviour in the striped mouse *Rhabdomys dilectus,* and to ascertain whether there are any specific traits associated with stereotypic behaviour in this species. I studied the behaviour of stereotypic and non-stereotypic striped mice in four behavioural assays, including: (1) general home cage behaviour; (2) dyadic encounters to assess social interactions; (3) personality tests to measure inter-individual variation in behaviours; and (4) perseveration tests by means of a plus maze. Results indicated that: (1) stereotypic striped mice showed higher frequency and duration of active behaviour and higher rates of inactivity, whereas non-stereotypic mice displayed longer durations, but fewer occurrences, of inactivity; (2) social motivation was not a predictor of stereotypic behaviour in striped mice; (3) Stereotypic mice showed a proactive coping style typified by spending a longer time in the light compartment after a startle response, a greater manipulation of novel objects in the home cage, and increased activity levels in standard housing. Non-stereotypic mice showed a reactive coping style typified by greater anxiety and fear toward novel objects, and heightened inactivity; and (4) levels of perseveration were higher in stereotypic striped mice. I also found that stereotypic mice that showed higher frequencies and durations of activity also displayed a proactive coping style and were more preservative. In addition, non-stereotypic mice that were inactive for longer showed a reactive coping style and lower levels of perseveration, which suggests inactivity is a possible alternative response to stereotypy in captive environments. In conclusion, stereotypy, activity, personality, and coping style appear to have common underlying, possibly neurobiological, mechanisms. In particular, I hypothesise that dysfunction of the basal ganglia, or suppression of the indirect (striatopallidal) pathway, results in inappropriate repetitive responses and stereotypic behaviour. Further research is needed to measure brain hormones and structure in order to determine the nature of the imbalances and whether they are consistent within and

between species. In addition, investigations are required of factors which may mediate these imbalances, including age of weaning and other genetic influences.

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Chapter 1. Introduction

1.1 Rationale

Captive animals are housed in environments that are vastly different from those in which they have evolved and thus might need to adjust their behaviour in order to cope with the new, often barren and restricted, housing conditions and rearing environments (McPhee and Carlstead, 2010). Sub-optimal conditions in captivity may lead to a number of phenotypic changes in animals, including increased levels of stress, obesity, aggression, and most notably, the performance of stereotypic behaviours (SBs) (Mason, 1991a). SBs result from the chronic impact of captivity on brain development and function, and are induced by a lack of space, physical complexity and/or social stimulation in captive environments (Mason, 2006; Jones et al., 2010a). They manifest in a spectrum of responses, such as pacing and weaving in captive carnivores (Clubb and Vickery, 2006), box walking and cribbing in stabled horses (McBride and Hemmings, 2009) and somersaulting and bar biting in captive rodents (Würbel, 2006). These behaviours are often accompanied by hypothalamic-pituitary-adrenal (HPA) activation and are thought to be caused by frustration, repeated attempts to cope, or central nervous system (CNS) dysfunction (Mason, 1991a; Würbel, 2006; Latham and Mason, 2008). Corticosterone levels are an accepted measure of hypothalamic-pituitary-adrenal (HPA) axis activity, with high levels reflecting increased stress (Touma et al., 2003). Corticosterone has been found to be released from the cerebral cortex in response to a stressor (Charmandari et al., 2005), and thus animals that are more anxious should have higher levels of corticosterone. It is released into the blood in response to a stressful event, is then reabsorbed and later partially eliminated in the faeces. Jones et al. (2011) found that wild-caught *Rhabdomys* proved more fearful and less active than captive-born individuals, and had higher levels of faecal corticosterone metabolites. Fearfulness and inactivity are both traits of reactive copers, and therefore reactive copers can be said to have a higher HPA response to stress.In humans, stereotypic behaviour (SB) is considered to be deliberate because it can be voluntarily subdued (at least for a while), and is performed for self-stimulation and a sense of escape (Mostard, 2011).

The specific causal mechanisms of stereotypies are difficult to establish especially because they do not develop in all individuals of a species living in the same captive environment, and may be affected by diverse triggers, for example the age and personality, of an animal (Mason, 1991a; Mason, 1991b; Joshi and Pillay, 2016a). This indicates that various factors in addition to the prevailing environment, such as genetic predisposition (e.g. bank voles *Clethrionomys glareolus*; Schoeneker and Heller, 2000; striped mice *Rhabdomys* spp; Schwaibold and Pillay, 2001; mink *Mustela vison;* Jeppesen et al., 2004), contribute to the ontogeny of SBs. Stereotypic animals also have certain traits that distinguish them from non-stereotypic animals. These include: (1) a higher motivation to perform specific activities, such as pacing in zoo carnivores, which is linked to a motivation to roam (Clubb and Vickery, 2006); (2) increased interactions with novel environments or novel objects (Wechsler, 1995; Dingemanse et al., 2002; Janczak, et al., 2003; Dingemanse et al., 2007). In contrast, non-stereotypic striped mice are expected to either retreat or become vigilant when confronted with novelty and also show a reactive coping style (i.e. conservation-withdrawal response), resulting in greater anxiety, fear and inactivity (Meagher and Mason, 2012).; and (3) a greater tendency to be perseverative and active, as seen in a variety of species, including orange-wing Amazon parrots *Amazona amazonica* (Vickery and Mason, 2005) and bank voles *Clethrionomys glareolus* (Garner et al., 2003).

The fields of ethology and neurobiology have both vastly contributed to our understanding of SB. Ethology is concerned with external (e.g. limited feeding opportunities) and internal (e.g. energy deficiencies) factors which induce SB (Rushen, 1993). These factors continuously frustrate highly motivated consummatory behaviours in captive environments by preventing these individuals from reaching motivational goals (Rushen, 1993; Toates, 2001). For example, repeated escape attempts in laboratory mice *Mus musculus* lead to bar biting (Nevison et al., 1999; Lewis et al., 2006) and stereotypic digging in Mongolian gerbils *Meriones unguiculatus* is associated with their need to access shelter (Wiedenmayer, 1997). In terms of energy deficiencies, inactivity is often mentioned as a problem in captive animals and may be associated with negative and harmful affective states such as freezing, boredom, depression-like states and ill health

(Meagher, 2011; Meagher and Mason, 2012). Too much activity, on the other hand, is also viewed as a welfare concern in captive animals and is often accompanied by SB (Meagher, 2011).

Neurobiological explanations for SB focus more on the proximal causes of this behaviour, such as structural and functional brain changes and alterations in affected individuals (Mason, 2006). Neuroscientists explain SB in terms of forebrain dysfunctions, particularly in the corticostriatal circuits between the cortex and basal ganglia. Dysfunctions in these circuits inhibit information processing and behavioural flexibility, and the selection of goal-directed cognitive behaviour, which are all believed to underpin SB (Langen et al., 2011a).

Deficits in the inhibitory control mechanisms, which are located in the neural pathways connecting the frontal cortex and basal ganglia and are responsible for the inhibition of inappropriate behaviours, are also suggested as causes of perseveration (defined as the continuation or recurrence of an activity without the appropriate stimulus; Zohar et al., 1995; Turner et al., 2003a). Positive relationships have been found between SB and perseveration in a number of species, such as blue and marsh tits *Parus caeruleus and P. palustris* (Garner et al., 2003), brown bears *Ursus arctos* (Vickery and Mason, 2003), deer mice *Peromyscus maniculatus* (Tanimura et al., 2008); American mink *Neovison vison* (Dallaire et al., 2011), as well as in humans (Zohar et al., 1995). In addition, conditions that lead to the development of SB, such as maternal deprivation (e.g. rhesus monkeys *Macaca mulatta*; Gluck and Sackett, 1974), have also been found to induce perseverative behaviour. Both neurobiological and environmental factors may underlie the association between perseveration and SB, but there is little focus on integrating both these perspectives in the literature in order to obtain a broader understanding.

Ethological and neuroscientific models each focus on discrete explanations for SB and often provide mutually exclusive rather than complementary accounts of this behaviour. A broader perspective that integrates both models is important for at least three reasons. (1) Ethological and neuroscientific perspectives both provide explanations for certain

features of SB. Various experimental findings however are insufficiently accounted for by either perspective. For example, while Garner and Mason (2002) found that one specific process involving the suppression of indirect striatopallidal pathway activity lead to SB in bank voles *Clethrionomys glareolus*, studies of other species, such as marsh tits *Poecile palustris* (Garner et al., 2003) and sun bears *Helarctos malayanus* (Vickery and Mason, 2003) indicated that at least another process is involved in the relationship between SB and perseveration. (2) SB has long been associated with poor welfare (Mason, 1991b; Lawrence and Rushen, 1993), but no clear link has been established between the two. In some environments, stereotypic animals may appear fitter and fare better than non-stereotypic animals living in the same conditions, but not in other environments (Mason and Latham, 2004). More obvious correlates that suggest SB is an aspect of poor welfare include: (a) chronic stress and persistent frustrations (Mason, 2006); (b) permanent brain dysfunction induced by captive environments (Mason, 1991a). A better understanding of the causes of SB, both neurobiological and ethological, may assist our understanding of the welfare correlates of the behaviour. (3) Understanding the neurobiological and ethological mechanisms of SB may contribute to our understanding of a range of domains associated with SB, including perseveration, hyperactivity and personality.

1.2 Stereotypic Behaviour

Stereotypic behaviour describes the abnormal and unvarying repetition of a particular set of behaviours that lack any apparent goal or function (Mason et al., 2007). They are most often the result of chronic exposure to aversive stimuli in captive environments which leads to abnormal brain development and function (Garner et al., 2011). Stereotypies are estimated to occur in 85 million domestic animals and a large proportion of laboratory and zoo animals worldwide (Mason and Latham, 2004). Captive environments create circumstances that are different to those found in nature; these include differences in complexity, foraging, social and exploratory opportunities, space and levels of human interaction (Mason, 1991b; Rushen, 1993). Behaviours normally found in free-living individuals become gradually replaced by abnormal behaviours in captivity (Mason, 1991a; Rushen, 1993; Wiedenmayer, 1997; Mason et al., 2007). Furthermore, SB

represents a significant divergence from the behavioural phenotypes of animals in the nature, and may therefore indicate CNS dysfunction induced by these new restricted environments (Mostard, 2011). SBs are thus assumed to be an indirect response to the deprived environmental conditions in captivity (Mason, 1991a, Joshi and Pillay, 2016b). They are mediated by changes in forebrain function- particularly changes in neural pathways between the basal ganglia and cortex, which are key areas in the inhibiting inappropriate behaviours and maintaining behavioural flexibility (Lewis et al., 2006; Graybiel, 2008). SBs are also thought to be caused by early rearing environments which affect CNS development (Mason et al., 2007).

SBs are the most common types of Abnormal Repetitive Behaviours (ARBs). Examples of ARBs include excessive grooming, stereotyped pacing, somersaulting, head twirling, and bar biting (Mason, 1991a; Mason and Latham, 2004; Mason et al., 2007). They are phenomenologically and aetiologically similar to ARBs in humans, such as obsessive-compulsive disorder (OCD) and autism, suggesting their causes stem from frustrations, numerous attempts to cope, or environmentally induced brain dysfunctions (Latham and Mason, 2010). While some repetitive behaviour may be appropriate in early life, such as repetitive motor actions in the form of swaying or rocking, or compulsive and ritualistic behaviours such as an insistence on certain foods or a bath time ritual (Thelen, 1979), others appear to be abnormal in frequency and may cause disruption in daily functioning (Turner, 1997; Turner, 2002; Garner, 2006). Some SBs however may persist, instead of decrease with age, in children and adults, especially when they are bored or stressed (Schlagger and Mink, 2003). Research on the human disorders autism, OCD and brain injury shares commonality in that these disorders all involve forms of CNS dysfunction, which suggests they have an underlying neurological cause (Latham and Mason, 2004; Garner, 2006; Mason et al., 2007). This dysfunction leads to the impairment of “normal” behaviour and the display of inappropriate inhibited responses to the external environment (Mason and Latham, 2004; Garner, 2006, Mason et al., 2007).

1.2.1 Abnormal repetitive behaviours

ARBs are grouped into two categories (Figure 1) low order motor actions (stereotypic movements, repetitive manipulation of objects), which involve repeated movements; and 2) high order behaviours (compulsions, rituals, insistence on sameness and restricted interests), which have a distinct cognitive component and reflect rigidity and adherence to particular rules or deeply ingrained mental sets (Turner, 1997).

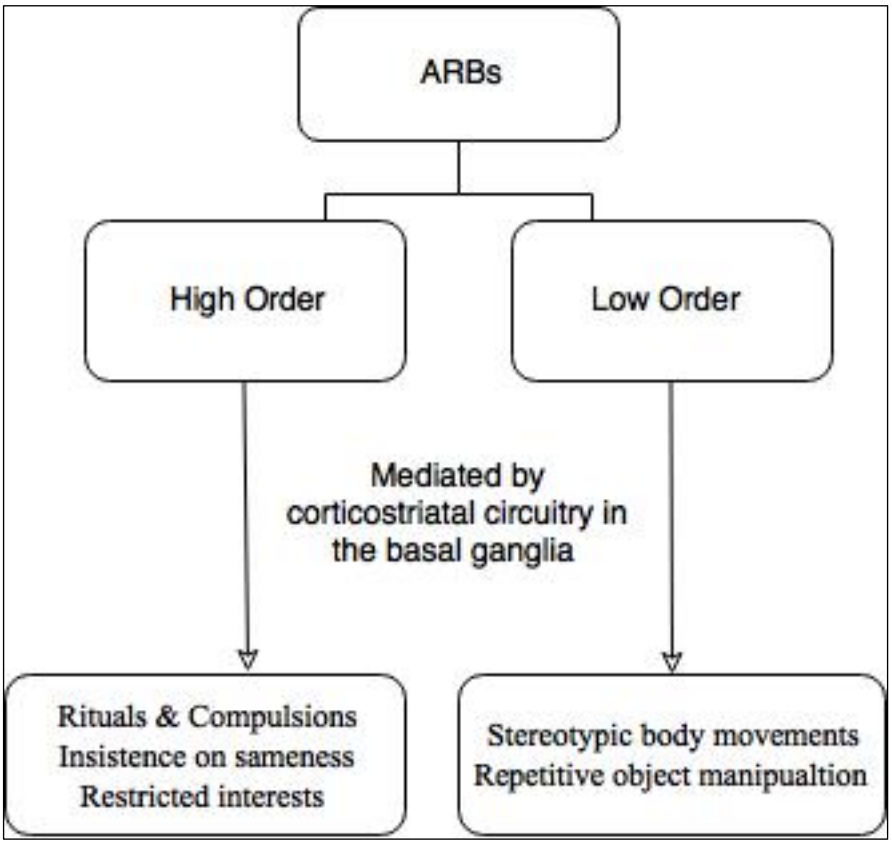

Figure 1: Diagrammatic representation of the two forms of Abnormal Repetitive Behaviours (ARBs) defined by Turner (1997).

Turner (1997) defined a repetitive movement/manipulation as a behaviour repeated at a relatively high rate, pursued in a invariant way, and considered to be inappropriate and abnormal in its manifestation. Head twirling in minks *Neovison vison* (Dallaire et al., 2011), body rocking in rhesus monkeys *Macaca mulatta* (Novak et al., 2006b), head shaking in domestic horses *Equus caballus* (Goodwin, 2002) and vertical jumping in deer

mice *Peromyscus maniculatus* (Symons et al., 2005) are well known low-order ARBs exhibited by animals in captivity (Figure 1).

High-order ARBs reflect an inflexible, almost anxious, adherence to routines and rituals (Figure 1). Lopez et al. (2005) showed that the degree of restrictive and repetitive behaviour in autistic individuals positively correlated with executive function deficits, particularly on tasks that measure cognitive flexibility, such as gambling (guessing) tasks, reversal and extinction learning. Cognitive flexibility has been found to have an inverse relationship with motor stereotypies. For example, extinction learning in bank voles *Myodes glareolus* (Garner and Mason, 2002) and brown bears *Ursus arctos* (Vickery and Mason, 2005) has been significantly inversely correlated with SB. Garner et al. (2003) found that stereotypic orange wing Amazon parrots *Amazona amazonica* with higher motor stereotypy scores showed greater sequential dependency in a gambling task, and a higher tendency to repeat responses (i.e. rigidity) and be perseverative. In sum, animals with high SB levels display stronger tendencies to repeat previously learnt responses. This suggests that a common pathway, most likely neurologically based, may underlie perseveration and stereotypy (Garner et al., 2003). Garner and Mason (2002), for example, demonstrated a correlation between SB and a cognitive task that reflects basal ganglia function. Tanimura et al. (2008) also found that SB and cognitive abnormalities were mediated by corticostriatal circuitry. These findings thus support the hypothesis that high order ARBs, which reflect SB, are correlated and mediated by corticostriatal impairments.

1.2.2 Forms of Stereotypic Behaviour

Stereotypic behaviours can be generally subdivided into (1) locomotor and (2) oral forms of SB (Terlouw et al., 1991; Carlstead, 1998). Locomotor SBs are said to occur as a result of limited space in captivity, which leads to frustrated locomotory behaviour (Carlstead, 1998). This category can be divided further into (1) locomotor movements, such as pacing, and (2) non-locomotory body movements, which include rocking and bouncing (Terlouw et al., 1991). One hypothesis posits that the motivation underlying locomotory stereotypies in carnivores is thwarting of their natural foraging behaviour (Clubb and

Mason, 2003). SBs in carnivores are proposed to represent the appetitive search phase of the hunt (Terlouw et al., 1991; Mason 1993; Mason et al., 2007) and manifest as frustrated pacing behaviour (e.g. tigers *Panthera tigris*; Clubb and Vickery, 2006). Other examples of locomotor stereotypies are route tracing, for example in blue tits *Parus caeruleus* (Garner et al., 2003), which are thought to be motivated by restless escape attempts in these migratory birds. Patterned running in deer mice *Peromyscus maniculatus* is also thought to be motivated by escape attempts (Powell et al., 1999).

Oral stereotypies usually develop due to feeding and dietary restrictions in captivity (Terlouw et al., 1991). They are common in domestic horses *Equus caballus,* which display a wide range of oral stereotypies including chewing, lip-licking, wood chewing, and crib biting (McGreevy, 2004). In nature, horses spend most of their time and energy grazing and foraging, and once enclosed in stables and fed low fibre diets they are forced to alter their natural time budget, resulting in SB linked to frustration (McGreevy et al., 1995). In sum, both forms of SB result from an abnormal interaction between the captive animals and the environment and have both neurobiological and ethological underlying causes.

1.3 Mechanisms of stereotypic behaviour

The diverse manifestations of SB are thought to be underpinned by different brain regions and pathways. Stereotypy development may also be related to the structure of the environment. The development of locomotor stereotypies in bank voles *Clethrionomys glareolus*, for example, may occur due to unsuccessful repeated attempts to climb out of the cage (Wiedenmayer, 1997). The on-going success of enrichments, which aim to reduce stereotypy in captive environments, has proved these behavioural needs can be met, which suggests there are a number of clear causal mechanisms that bring about the onset of stereotypic behaviour (Albin et al., 1989).

The most notable pathway that governs stereotypic behaviour is the cortico-basal ganglia-thalamic pathway, which is primarily involved in motor activities (Garner, 2005; Tanimura et al., 2008). This circuitry involves pathways that project from specific areas

in the cortex to the striatum, then to other basal ganglia nuclei (globus pallidus, substantia nigra), and to the thalamus and finally back to the cortex. In terms of ARBs, studies have linked the striatum, which is part of the basal ganglia, to the neurophysiological processes of stereotypic behaviour (Garner et al., 2003; McBride and Hemmings, 2005; Vickery and Mason, 2005; McBride and Hemmings, 2009). Antelman and Szechtman (1975) showed that injection of the dopamine neurotoxin (6-hydroxydopamine) into the striatum region of the basal ganglia in rats *Rattus rattus* significantly reduced motor stereotypies.

1.3.1 The basal ganglia

The basal ganglia are involved in a variety of functions that include voluntary motor control, procedural learning, routine behaviours, and cognitive and emotional functions (Werry et al., 1983). They have long been thought to play a role in the development of SBs. Amsler (1923) confirmed that the striatum was directly implicated by drug-inducing SB in guinea pigs, and since then many other studies have shown that damage to or dysfunction of the basal ganglia results in perseveration or response inhibition (Turner, 1997; Niehaus et al., 2000; Turner et al., 2003b; Garner, 2006). The basal ganglia are located in the midbrain around the thalamus. The major nuclei of the basal ganglia (the striatum) is composed of the caudate nucleus, the putamen, the globus pallidus, the pars reticula and compacta of the subtantia nigra, and the subthalamic nucleus. The basal ganglia consist of a number of circuits that target primary motor areas as well as pre-motor and pre-frontal cortical areas. Each circuit receives cortical inputs via the striatum and passes the inputs through the basal ganglia, via output nuclei, to the thalamus, and back to a singular cortical area (Ring and Serra-Mestres, 2002). Each corticostriatal circuit consists of two branches, the direct (striatonigral) pathway, and the indirect (striatopallidal) pathway. In a normally functioning system, the basal ganglia select appropriate behaviours through the direct pathway and inhibit unwanted actions through the indirect pathway. In sum, it can be hypothesised that the activation of the indirect pathway or suppression of the direct pathway reduces SBs, whereas the suppression of the indirect pathway will induce them (Langen et al., 2011a). On the other hand, the activation of the direct pathway will lead to hyperactivity and inhibition of this pathway suppresses all behaviour, including SB (Garner, 2006; Lewis et al., 2006). The basal

ganglia system is also modulated by several endogenous neurotransmitters, including GABA and glutamate, dopamine, opiates, and serotonin (Mason and Rushen, 2006). An imbalance in activities of both pathways results in SB (Lewis et al., 2006).

1.3.2 Neurotransmitters associated with stereotypic behaviour

The neurotransmitters dopamine and serotonin are both associated with the expression of SB. Dopamine is implicated in the direct and indirect neural pathways of the basal ganglia and the consequent expression of SB; dopamine is altered by the stress induced by impoverished conditions in captivity (McBride and Hemmings, 2005). Thus, SBs are developed and maintained by the disruption in the neural pathways and structures that utilise dopamine, and these neural pathways can be changed only through environmental manipulations or by way of neurotransmitter injections (Lewis et al., 2006). For example, house mice *Mus musculus* injected with dopamine in the striatum region of the basal ganglia show increased stereotypy levels, while injection with dopamine antagonists resulted in decreased stereotypy levels (McBride and Hemmings, 2005; Langen et al., 2011b). Striatal dopamine is suggested to modulate the balance between direct and indirect pathways of the corticostriatal circuit in the basal ganglia, and therefore also modulate SB by stimulating the direct pathway and inhibiting the indirect pathway. Conversely, blocking dopamine receptors can suppress the direct pathway and decrease feedback to the cortex, thereby resulting in reduced levels of SB (Joel and Doljansky, 2003).

Serotonin is linked to behavioural flexibility and may be implicated in the individual variation in coping styles (Koolhaas et al., 1999; Coppens et al., 2010; Koolhaas, et al., 2010). It is also hypothesised that hypoactivity in serotonin pathways induces spontaneous SB (Koolhaas et al., 2010), as shown in bank voles *Clethrionomys glareolus* in which citalopram, a serotonin agonist, reduced SB (Schoenecker and Heller, 2003). It has also been well established that the pharmacological stimulation of postsynaptic serotonin receptors in rodents leads to stereotypic and repetitive behaviour (Coppens et al., 2010).

1.4 Development of stereotypic behaviour

1.4.1 Genetic transmission of stereotypic behaviour

Not all animals housed in captive environments develop SB. Therefore, factors other than the environment may contribute to the ontogeny of SB (Mason and Latham, 2004). Behaviour can be transmitted to offspring by genetic and non-genetic means (e.g. social learning). It is therefore difficult to study genetic inheritances because the phenotype can arise from either genetic factors or learned influences, which are sometimes difficult to separate. Nonetheless, there is an ever-growing body of evidence which suggests that SBs are genetically transmitted, as shown in bank voles *Clethrionomys glareolus* (Schoeneker and Heller, 2001) striped mice *Rhabdomys* spp. (Jones et al., 2008) and mink *Mustela vison* (Jeppesen et al., 2004; Svendsen et al., 2007). In two separate studies in striped mice, individual striped mice born to stereotypic mothers were four to five times more likely to display SB themselves when compared to mice from non-SB mothers (Schwaibold and Pillay, 2001; Jones et al., 2008). The stereotypic trait however is mostly transferred only through mothers, and mostly in impoverished conditions (Jones et al., 2008), so influences, other than genetic, might be involved in the transmission of SB.

1.4.2 Non-genetic factors

To understand what mechanisms lead to the development of SB in captive animals, researchers tend to examine changes in activity patterns, day-to-day routines, and the environment to make associations between these and SB (Mason, 1991a. Latham and Mason, 2010). Although neurobiological (see above) and impoverished captive environments (Mason, 1991b; Latham and Mason, 2004) underlie the expression of SB, the development of SB is often not apparent, particularly since not all individuals housed in a specific environment develop SB. The differences in development may be related to the age and context of the individual, as in the features of the captive environment such as amount of space and level of complexity (Mason, 1991a). Another correlate of the onset is whether captive animals are wild caught (less probability of developing SB) or captive-born (greater probability of developing SB; Jones et al., 2008). The expression of SB may also be associated with historic triggers, such as traumatic events in the past that contribute to current behaviour and are mediated by changes in forebrain function,

particularly in the structures implicated in inhibiting inappropriate responses, such as the basal ganglia and the cortex (Clubb and Mason, 2007).

From a frustration-linked perspective, it is also suggested that SB develops due to a chronic lack of opportunities to respond appropriately to internal or external stimuli, despite a high motivation to do so (Mason et al., 2007). The failure of negative feedback loops related to motivations can leave the animal in states of high motivation and this in turn leads to frustration related stress and consequently the expression of SB (Rushen and Mason, 2006; Jones et al., 2011). Frustration induced SBs are thought to be a direct result of motivational frustration and are not the consequence of underlying CNS dysfunction (Mason et al., 2007). The SB that result from this type of frustration are associated with the underlying behaviour which the individual is attempting to perform, or to escape from confinement (Mason & Rushen, 2006).

Maternal deprivation in rhesus macaques *Macaca mulatta* for example leads to self-directed SB in the form of self-clasping behaviour, digit sucking, rocking and bouncing due to insufficient tactile stimulation from their mothers (Novak et al., 2006b). Around three years of age, these individuals then developed other kinds of SBs such as somersaults, head bobs, or even self-injurious behaviours. The introduction of a surrogate mother for the young monkey to clasp onto reduced this behaviour (Novak et al., 2006a). Maternal deprivation is common in captive animals and can be a cause of major behavioural changes, but many other factors also play a role. Age of weaning, as in the age at which the youngster is separated from their mother, effects the development of SB with earlier weaning leading to more instances of SB later on in life (Weary et al., 1999; Worobec et al., 1999).

A number of other factors have also been suggested to be contributors to the onset of stereotypic behaviour, such as routine or restricted feeding patterns (Lawrence and Rushen, 1993) and social isolation (Novak et al., 2006a). These possible psychological mechanisms are not the only factors that may lead to stereotypy, and physiological factors have also been found to play a major role. Baxter and Plowman (2001) suggested

that oral stereotypies in giraffes *Giraffa camelopardalis* were reduced by the addition of fibre to their diets, which resulted in increased rumination and decreased SB. Similarly, Cronin et al. (1985) found that non-nutritive sucking in domestic veal calves was associated with hormone secretion in the digestive tract and thus a physiological response was responsible for this behaviour, rather than a psychological mechanism.

1.5 Stereotypic behaviour and coping styles

The coping hypothesis, described by Rushen (1993), states that an animal develops SB in order to cope with the adverse environment in which it is housed. A widely accepted though commonly criticised hypothesis is that coping styles generally form as a response to stress and aversive situations. This leads to an elevation of cortisol levels in the individual. This indicates that the repression of SB leads to an increase in stress levels and that the proposed function of SB is thus to cope with the stress caused by restricted environments (Mostard, 2011). Coping styles include fight/flight escape responses, which activate the sympathetic-adrenomedullary system (Rushen, 1993) and distress responses, which activate the pituitary-adrenocortical system (Koolhaas et al., 2010). They are characterised by a consistent set of neurobiological and behavioural characteristics, most of which are associated with one another. The success of a coping style can be measured by its effectiveness in reducing physiological measures of stress, or by removing aversive stimuli (Wechsler, 1995). A number of negative health consequences can arise if an animal cannot cope with a stressor. These include cardiovascular pathology, ulcers, infectious diseases and stereotypies, all of which could arise from chronic over-activation of various neuroendocrine sectors in the brain related to stress (Koolhaas et al., 1999).

Opponents of the coping hypothesis, however, argue that not all SB develops as a response to stress. It can be triggered by factors that are not viewed as stressful (Appleby, 1999), or may occur independently of the initiating environmental stimulus (van Lierop, 2005). Coping styles can thus be viewed as a potential warning of adversity, but are not a sole indicator thereof (Mason and Latham, 2004). While some studies show that coping can reduce physiological measures of stress, others provide no evidence of stress-reducing effects of SB. Wechsler (1995) showed increased SB in rats sensitised to

amphetamine was associated with decreased plasma corticosterone levels, while Terlouw et al. (1991) conversely found no relationship between post-feeding SB and levels of corticosterone in plasma.

1.5.1 Types of coping styles

Koolhaas et al. (1999) identified two types of coping styles, namely proactive and reactive (Figure 2). This implies that individuals have different ways of adapting to certain environments. Proactive coping styles are characterised by routine behaviour, aggression (i.e. less social motivation), boldness, and behavioural responses independent of environmental stimuli (Janczak et al., 2003; Figure 2). Boldness refers to the greater propensity of an individual to take risks, be quick to approach novel objects, explore in novel environments and show more activity (Wilson et al., 1993). Reactive individuals, on the other hand, are more dependent on environmental cues, less aggressive (i.e. display amicable behaviour and greater social motivation), displaying apathetic behaviours when faced with a challenge, and engaging in more freeze behaviour than proactive individuals (Wechsler, 1995; Janczak et al., 2003; Figure 2). In addition, proactive copers show difficulty in preventing a previously reinforced response, which suggests that proactive individuals are more prone to routine formation and depend on previous experience. For example, Bolhuis et al. (2004) found that proactive piglets are less successful in reversal learning of a T-maze task than are reactive individuals. The piglets also encountered difficulty in inhibiting their previously reinforced response, a food reward, which implies that proactive individuals are dependent on earlier experiences and struggle to abandon previously learnt behaviour once it becomes functionless (i.e. they may be more perseverative than reactive individuals; Bolhuis et al., 2004).

1.5.2 Neurobiological associations of coping styles

From a physiological perspective, stress involves interplay between external events and individual predispositions, such as genetics and early experiences (Ladewig et al., 1993). External stressors lead to elevated cortisol levels, which have been commonly used to characterise stress response in horses (Mal et al., 1991; Clark et al., 1993; Mills et al.,

1997). McBride and Cuddeford (2001) found significantly higher cortisol levels in horses that exhibited oral stereotypies such as crib- biting. In carnivores, particularly leopard cats *Felis bengalensis,* stereotypic individuals have also been shown to excrete higher cortisol levels (Carlstead et al., 1998), and SB such as pacing than those of non-stereotypic individuals (Wielebnowski et al., 2002).

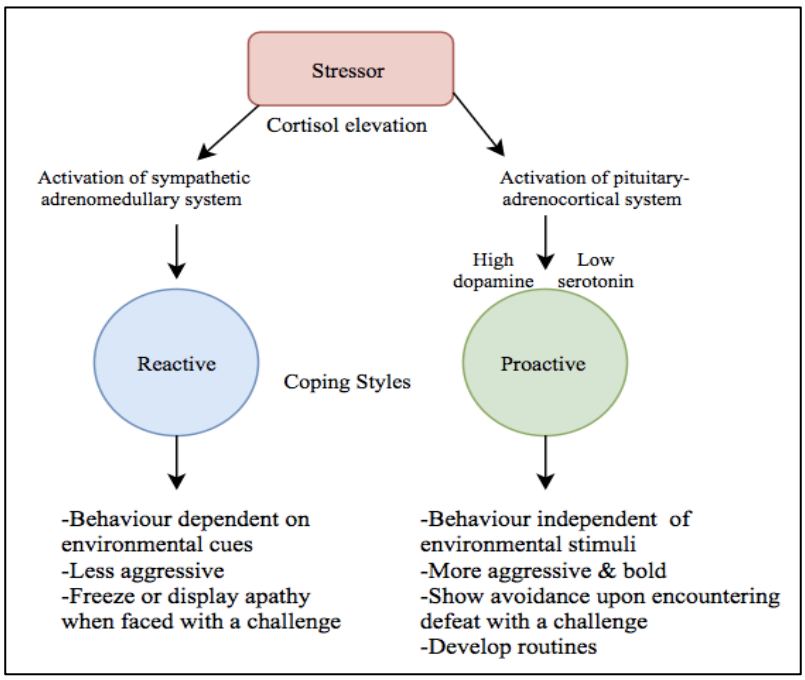

Figure 2. Representation of the two types of coping styles and their characteristics. *Developed from Wechsler 1995; Wielebnowski et al., 2002; Coppens et al., 2010; Koolhaas et al., 2010; Ijichi et al. 2013.*

The underlying mechanism which results in an individual adopting a particular coping style could be attributed to behavioural flexibility (Coppens et al., 2010), which is modulated by neurobiological factors (Koolhaas et al., 2010). A reactive coper is characterised by high reactivity of the HPA system, whereas a proactive coping style is modulated through activation of the sympathetic adrenomedullary system (Figure 2; Wechsler 1995; Koolhaas et al., 1999). Individuals that use passive rather than active coping strategies typically show higher HPA responses to stress, and thus might often be judged to have poorer welfare since corticosteroid levels are one of the most common

welfare indicators. Jones et al. (2011) found that *Rhabdomys* displaying reactive coping traits such as increased fearfulness and reduced activity also had higher levels of faecal corticosterone metabolites, which suggests HPA response is linked to passive coping in this species. Based on my findings and that of Jones et al. (2011) it can thus be said that a reactive coper is characterised by high reactivity of the HPA system, whereas a proactive coping style is modulated through activation of the sympathetic adrenomedullary system (Figure 2; Wechsler 1995; Koolhaas et al., 1999). From a neurobiological perspective, changes in the prefrontal cortex, particularly serotonergic input to the medial prefrontal cortex are responsible for behavioural flexibility and individual variations in coping styles (Koolhaas et al., 2010; Coppens et al., 2010). Low serotonin levels have been implicated in both impulsive actions and aggression in both humans and rodents (Roberts et al., 1994; Fletcher, 1995; Harrison et al., 1997; Crean et al., 2002).

Ijichi et al. (2013) proposed that SB is associated with a proactive coping response to an aversive environment. They suggested that proactive individuals might become stuck in a fixed self-rewarding routine in order to avoid an uncontrollable stressor. Reactive individuals are less likely to develop this routine behaviour and may instead try to cope with stress by developing a depression-like "learned helplessness" state (Koolhaas et al., 2010). Joshi and Pillay (2016a), Yuen et al. (2016) and Yuen et al. (2017) found that stereotypic striped mice were bolder and showed proactive coping styles, while non-stereotypic mice were less bold and showed a reactive coping style. These authors also found that having a proactive style did not predict the onset of SB, which proves that this form of coping style cannot be defined as being a sole indicator of SB.

1.5.3 Commonalities between stereotypic behaviour and coping styles

The characteristics of proactive copers (i.e. routine development, aggression, boldness and avoidance) are also exhibited by stereotypic individuals (Figure 3). On the other hand, the behaviours displayed by non-stereotypic mice are similar to those that define reactive coping styles. The mechanisms that determine whether an individual will adopt a proactive or reactive coping style, and subsequently stereotypic or non-stereotypic behaviour, may be attributed to underlying neurological and environmental factors.

Firstly, both forms of coping styles as well as SB may result due to changes in the prefrontal cortex, which is responsible for behavioural inhibition (Coppens et al., 2010; Koolhaas et al., 2010). Secondly, individuals may display coping styles and SB when they are confronted with an external stressor, and react by either engaging in a proactive or reactive coping response, depending on the individual's personality (Joshi and Pillay, 2016a). Finally, the neurotransmitters dopamine and serotonin are implicated in both stereotypic and proactive individuals (Figure 3). Overall both neuroscientific and ethological factors can play a role in the development of SB and coping styles.

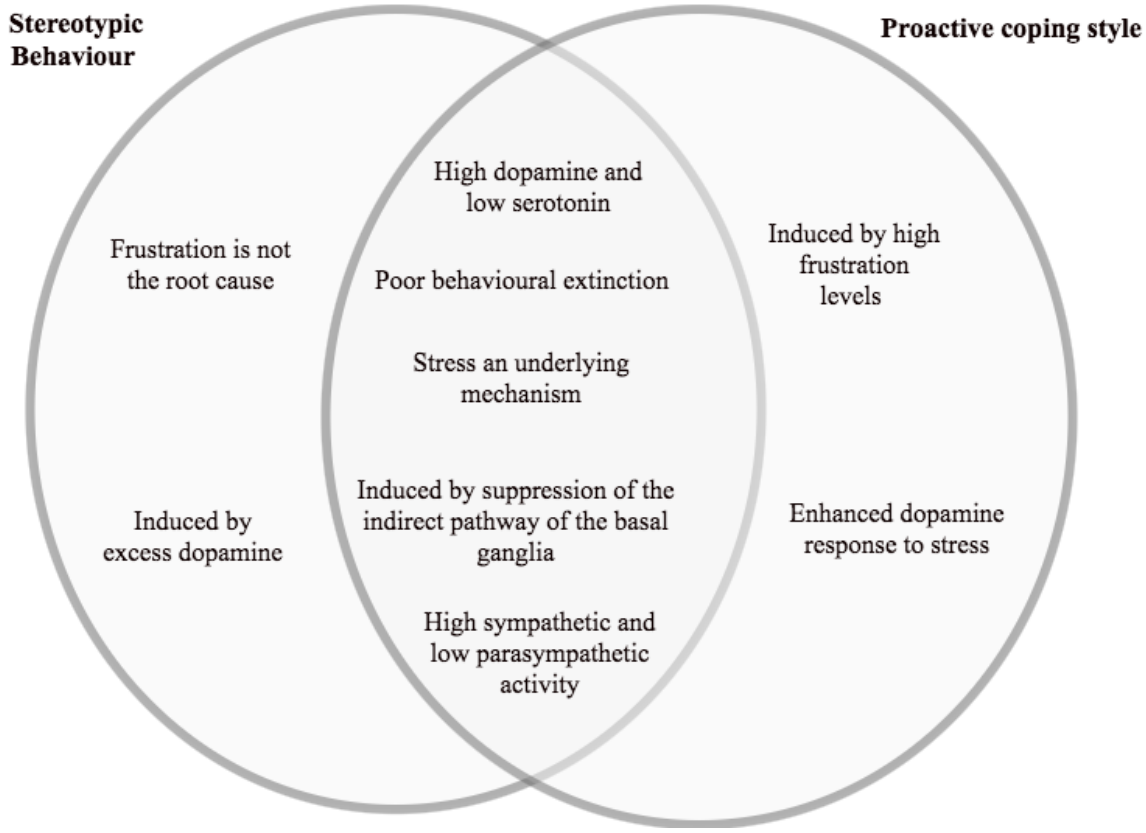

Figure 3: Venn diagram showing overlaps between stereotypic behaviour and coping styles suggesting they are linked. *Developed from Wechsler 1995; Wielebnowski et al., 2002; Coppens et al., 2010; Koolhaas et al., 2010; Ijichi et al. 2013*

1.6 Stereotypic behaviour and inactivity

The most common definition of inactivity is being relatively motionless with no gross movement of the body with an apparent function (e.g. foraging or chewing), but may include slight movements such as head turning or shifting positions (Meagher, 2011). A recent review by Meagher (2011) characterised inactivity in animals into three types, namely those associated with: (1) perceived threats (freezing, tonic immobility and hiding); (2) negative states (ill health, boredom and depression); and (3) positive states (sun basking and post-consummatory activities). Too much inactivity in humans is very often associated with negative affective states, such as physical illness and various forms of depression (Gold and Chrousos, 2002; Meagher, 2011). In non-human animals, however, the subjective affective states associated with inactivity are not well understood and very few studies have focused on inactivity as a behavioural state. Despite this, inactivity is often viewed as a problem in captive animals, especially mammals and birds, with the implication that inactive animals are bored, depressed or ill (Zanella et al., 1996; McPhee and Carlstead, 2010; Meagher, 2011). Too much activity on the other hand is also thought to be a sign of poor welfare, whereby increased rates of behavioural initiation, as in high frequencies of particular behaviours, are thought to predispose SB (Garner and Mason, 2002). Figure 4 below shows the overlaps between SB and inactivity.

When inactivity occurs in long bouts in a relatively safe environment, it is regarded as being "rest" (Lima et al., 2005; Meagher, 2011). Inactivity in free-living animals is often adaptive because it facilitates energy conservation and reduces predation risk (Engel and Schmale, 1972; Hart, 1988). All animals are inactive for at least some of the time, but in captivity, inactivity levels are often much higher than in nature.

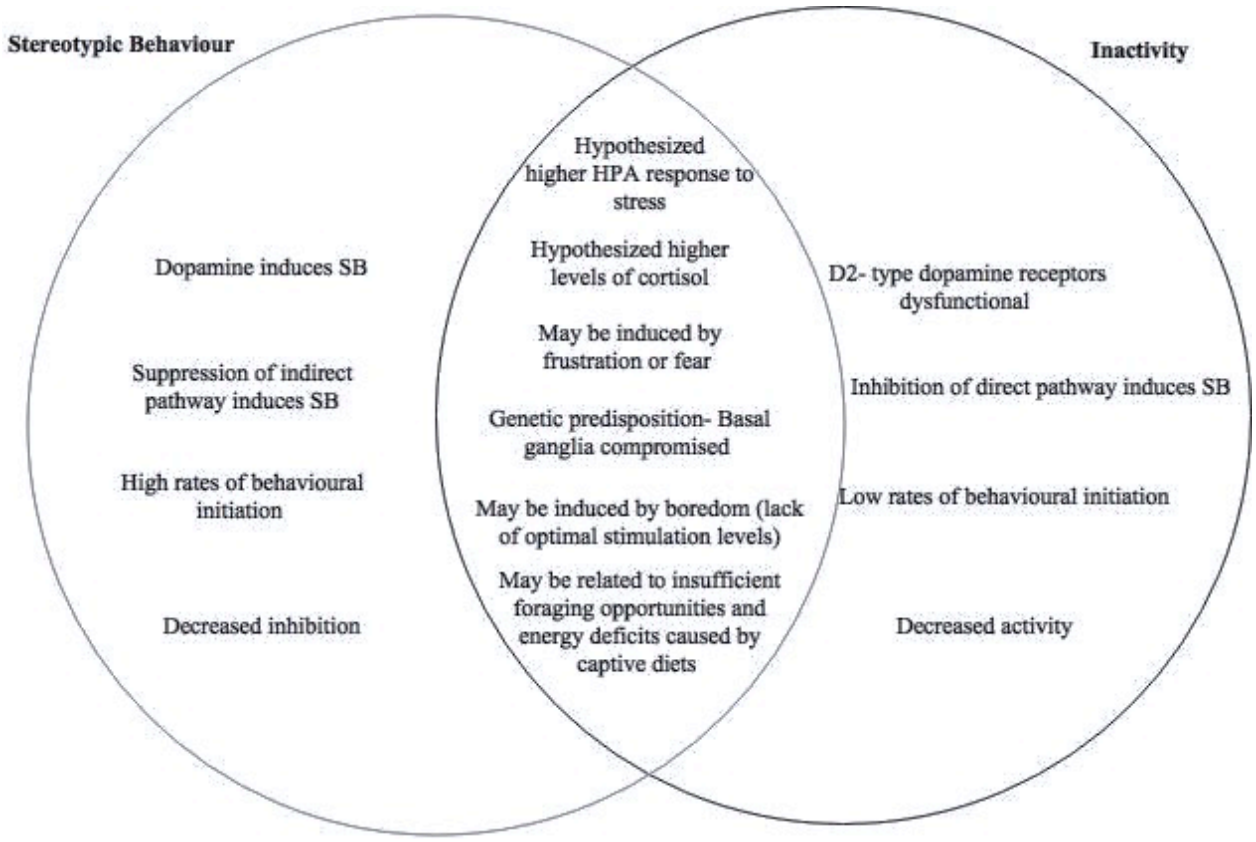

Figure 4: Venn diagram showing overlaps between stereotypic behaviour and inactivity suggesting they are linked. *Developed from Wechsler 1995; Wielebnowski et al., 2002; Coppens et al., 2010; Koolhaas et al., 2010; Ijichi et al. 2013.*

Inactivity in captive leopards *Prionailurus bengalensis*, for example, vastly exceeded that which is observed in nature - 68-90% in captivity (Mallapur and Chellam, 2002) vs 48% in nature (Clubb and Mason, 2007). Captive animals are more likely to engage in "unhealthy" forms of inactivity, such as freezing (e.g. black rats) in response to predator odour (Wallace and Rosen, 2000), depression-like states (e.g. elephants *Loxodonta africana*; Mason and Veasey, 2010), boredom (e.g. chimpanzees *Pan troglodytes*; Celli et al., 2003) and tonic immobility (e.g. rabbits *Oryctolagus cuniculus*; Klemm, 1966) due to smaller environments and a lack of stimulation (Engel and Schamle, 1972).

1.6.1 Inactivity and fear

Fear is a state of compromised welfare that is easily identifiable and often leads to inactivity and SB (Mason, 1991a; Meagher, 2011; Figure 4). Physical location is often

used as an indicator of fear in standardised tests. For example, spending more time in a closed rather than open space in a plus maze is interpreted as a fear response in mice (Carlstead, 1998). Negative and highly aroused affective states associated with inactivity and fear include freezing and hiding. These usually occur in response to a real or perceived threat and are characterised by immobility, rigidity and a reduced heart rate (Meagher, 2011). Freezing in animals is used to quantify fearfulness in behavioural tests and can be induced by exposing, for example, rats to predator odour or other forms of aversive stimuli, such as auditory startles and handling by humans (Bouton and Bolles, 1980; Knox et al., 2012). Tonic immobility (TI) is characterised by motor inhibition and suggested to be an anti-predator response, e.g. in migratory American sparrows *Zonotrichia leucophrys* (Mewaldt and Rose, 1960) and New Zealand white rabbits *Oryctolagus cuniculus* (Zarrow et al., 1961). Hiding is less species-specific and is usually observed in animals attempting to avoid a perceived threat by remaining out of sight, for example cats *Felis catus* (Rochlitz et al., 1998). Freezing, TI and hiding all appear to be reliable indicators of negative highly aroused affective states in animals.

1.6.2 Inactivity and depression or apathy

In other contexts, where increased inactivity occurs and threat and fear levels are low, states such as "depression" and "apathy" have been described as possible explanations for such inactivity (Meagher, 2011). The forced swim test is most widely used to identify depression-like states in non-human animals where remaining immobile and floating instead of actively trying to escape indicate depression (Knox et al., 2012). Learned helplessness accompanied by a decrease in activity (Meagher, 2011) occurs when animals display an absence of active responses to stress (such as escape attempts) and results from exposure to uncontrollable stressors (e.g. forced swim test). The term "apathy" has also been applied to similar behaviour patterns in suboptimal inescapable environments (Wells, 2005; Meagher, 2011).

1.6.3 Inactivity and boredom

The negative affective state of boredom is another potential correlate of both inactivity and SB (Figure 4). Boredom is induced by monotonous environments and a lack of

optimal levels of stimulation (Mason, 1991a; Fureix and Meagher, 2011). In humans, boredom is identified through self-reporting, and therefore this state has been subject to little empirical investigation in non-human animals. Meagher and Mason (2012) proposed an operational definition for boredom based on motivation to obtain stimulation. Animals displaying boredom-like states may have reduced motivation to participate socially with other animals, to move around, or even to feed (Meagher and Mason, 2012). McFarland (1989) found that when the immediate physical needs of free-living animals were met, they could not continue with other activities that would occupy their time, they are left in a state of "limbo". The term boredom and its relationship to inactivity in animals still require validation, however. SBs are commonly performed when little is happening in the environment and arousal is low. Captive mink *Mustela vison*, for example, perform SB in the quiet and calm hours after food delivery (Mason, 1991a). Such SBs are often interpreted as responses to boredom that comes about due to arousal and stimulation falling below optimal limits.

1.6.4 Positive states associated with inactivity

Positive and highly aroused affective states associated with inactivity are likely to be linked to high motivation, particularly in terms of foraging, and reward seeking behaviour (Mineka and Henderson, 1985). Sun basking in animals is a form of inactivity that enables thermoregulation and can thus be classified as a positive affective state (D'Eath et al., 2009, Meagher, 2011). Post-consummatory inactivity, such as inactivity that occurs immediately after copulation or feeding, is also associated with positive affective states (D'Eath et al., 2009). Stallions, for example, become more relaxed and inactive following ejaculation (Waring, 2003). Post-copulation inactivity in animals may be said to bring about the same calming affective state as experienced by humans (Levin, 2007).

1.6.5 Commonalities between inactivity and stereotypic behaviour

The welfare correlates of inactivity are not always obvious. Whereas some forms of inactivity are associated with positive affective states such as relaxation, others are associated with negative states including chronic fear, apathy, or depression. SB, on the other hand, is most often seen as a sign of poor welfare, and is often associated with

hyper activity and suppression of the indirect pathway of the basal ganglia (Garner et al., 2003; Figure 4). Dopamine levels also differ in stereotypic and inactive individuals, with higher dopamine levels inducing SB (Garner et al., 2003) and malfunction of D-2 type dopamine receptors leading to inactivity (Kravitz et al., 2016). In order to determine whether there is a link between SB and inactivity, one can look at commonalities between the two and assess whether there are any correlates. From a neurobiological perspective it is hypothesized that both stereotypic and inactive (negative affective state) individuals have a higher HPA response to stress and higher cortisol levels, suggesting they react to stressful and aversive situations in the same way (Figure 4). They also share an underlying dysfunction in the basal ganglia, which is responsible for the inhibition of inappropriate behaviours (Garner, 2006). From an ethological standpoint, boredom has been posited to play a role in activity (Wood-Gush and Beilharz, 1983) and the development of SB (Mitchell and Etches, 1977). Therefore, by merging the two perspectives, it can be seen that inactivity and SB might both occur due to underlying genetic dysfunctions and high HPA responses to stress, as well as the subjective state of boredom. Individuals may react to these factors in different ways, either by becoming inactive, or alternatively becoming stereotypic.

1.7 Stereotypic behaviour and perseveration

The dorsal striatum in the forebrain, which is involved in the selection and organisation of behavioural patterns and the inhibition of inappropriate behaviour, is considered to play a key role in the relationship between SB and perseveration (Garner at al., 2003; Vickery and Mason, 2005; Garner, 2006). SBs become perseverative if the behaviour switches to automatic processing and becomes centrally controlled (Mason and Latham, 2004). Over time, these behaviours become more rigid and increase in frequency due to repeated failures to cope with an aversive environment. The relationship between SB and perseverations apparently occurs because of conditions in captivity that lead to disruptions in the dorsal striatum in the forebrain, which modifies features of behavioural organisation (Vickery and Mason, 2005). In humans, relationships have been found repeatedly between measures of perseveration and levels of SB in both clinical and non-clinical populations. For instance, in autistic children, individuals who performed poorly

on a two-choice guessing task, a measure of recurrent perseveration, also showed higher rates of SB (Frith & Done, 1983) and, in a sample of adults, perseveration on a rule-changing task correlated positively with scores on an obsessive compulsive inventory (Zohar et al., 1995).

1.7.1 Types of perseveration

SBs are associated with four different types of perseveration.(1) Continuous perseveration is described as the continuous and inappropriate repetition of individual movements (eg. tics in humans & animals), which develop due to impairments in the primary motor branch of the motor loop in the basal ganglia (Garner, 2006). (2) Recurrent perseveration, which is particularly implicated in SB, results from the inappropriate repetition of complex movements or responses and develops due to disruption in the sensorimotor loop (Langen et al., 2011a). (3) Stuck-in-set perseveration is the inappropriate repetition of abstract rules or mental sets which arise from altered functioning in the associative loop (Garner, 2006; Langen et al., 2011a). (4) Affective perseveration is described as the inability to inhibit emotionally motivated responses to reward cues and is associated with impairments in the limbic loop (Hauser, 1999; Langen et al., 2011b). Both corticostriatal loops are then further divided into two pathways, namely the inhibitory indirect pathway, and the excitatory direct pathway (Lewis et al., 2006). The development of ARBs is linked to decreased activity in the indirect pathway, which works to inhibit unwanted behaviour.

1.7.2 Commonalties between stereotypic behaviour and perseveration

Results from studies on captive animals have proposed three reasons why SBs may be linked to perseveration. (1) In a variety of species, a positive relationship has been found between SB and recurrent perseveration. (2) Treatments or conditions that induce SB such as deprivation-rearing, for example in rhesus monkeys *Macaca mulatta* (Gluck and Sackett, 1974) or high dose amphetamine administration, for example in laboratory rats (Evenden and Robbins, 1983) also lead to recurrent perseveration. The barren conditions in captivity may impair brain development in otherwise normally developing individuals with no prior brain dysfunction, which induces perseveration and SB (Novak et al.,

2006a). (3) Correlations exist between SB and local activity of implicated forebrain regions for instance in deer mice *Peromyscus maniculatus* (Lewis et al., 2006). Neuroscientifically, the suppression of the indirect pathway in the basal ganglia, which leads to a lack of behavioural flexibility, has been thought to underpin both SB and perseveration (Garner and Mason, 2002; Figure 5). When captive animals are taught an operant task that leads them to a food reward, stereotypic animals take longer to suppress their learnt responses after the food reward is taken away (Vickery and Mason, 2003). This suggests that stereotypic animals have no deficits in learning a task, but struggle to abandon the behaviour once it becomes functionless (Vickery and Mason, 2003). Figure 5 provides a visual representation of the overlaps between SB and perseveration.

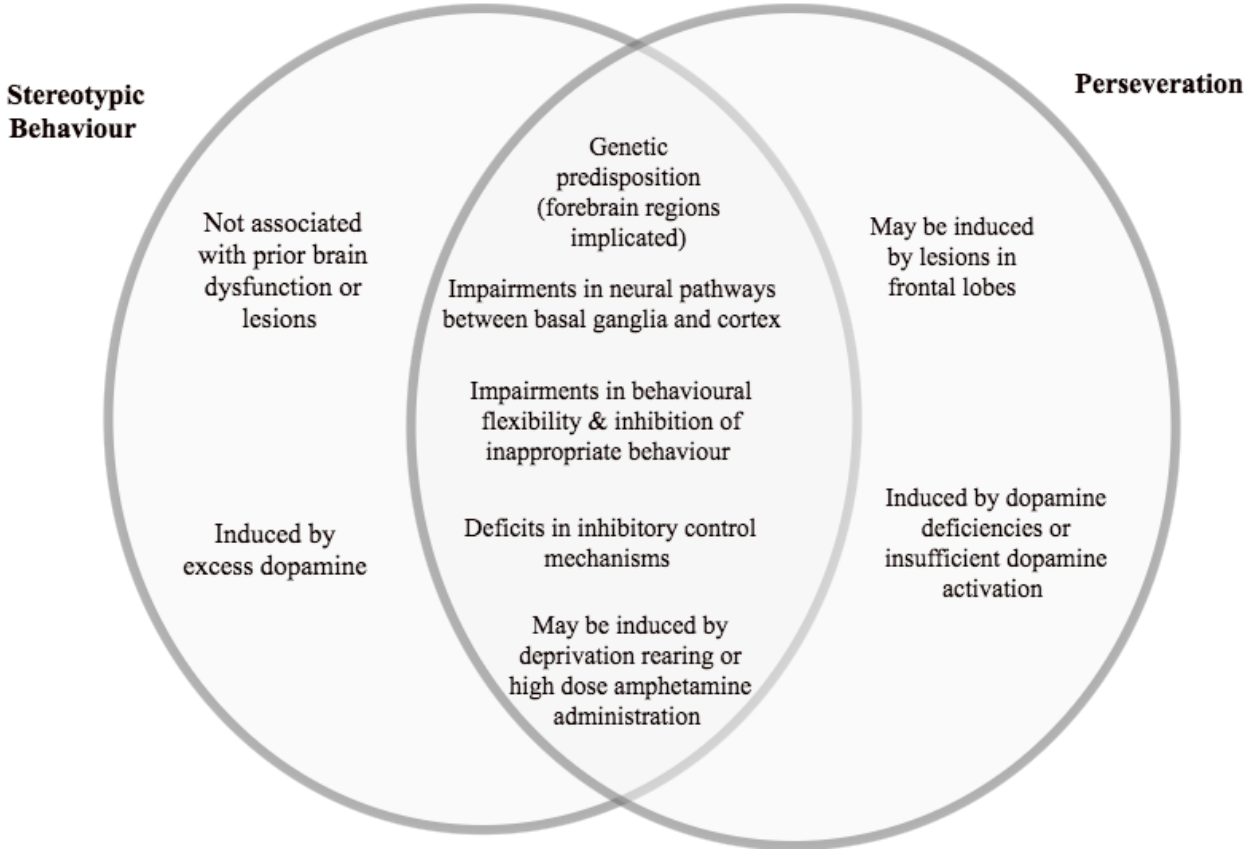

Figure 5: Venn diagram showing overlaps between stereotypic behaviour and perseveration suggesting they are linked. *Developed from Wechsler 1995; Wielebnowski et al., 2002; Coppens et al., 2010; Koolhaas et al., 2010; Ijichi et al. 2013.*

Broadly speaking, both SB and perseveration arise from similar neurobiological mechanisms and environmental circumstances. Both have also been associated with poor welfare and it is thus important to investigate which mechanisms underlie the two in order to predict where certain individuals or environments will be more predisposed to their development.

1.8 Study species

The African striped mouse, genus *Rhabdomys*, is a diurnal murid rodent that is widely distributed across the southern African, occurring in several biomes, such as grasslands, deserts, semi-deserts and forests (Skinner and Chimimba, 2005). Its wide distribution is likely due to high levels of behavioural plasticity (Schradin et al., 2011). Striped mice display a diurnal, bimodal activity pattern, with most activity occurring around the morning and in the evening (Schradin and Pillay, 2004). It is omnivorous and feeds mainly on plants, seeds, and a high proportion of insects during the breeding season (Perrin et al., 1980). This mouse has a light brown pelage with a light underbelly and four distinctive dark stripes along the back (Skinner and Chimimba, 2005). Adult striped mice weigh between 40 and 80g in nature (Brooks, 1982). There is no sexual dimorphism in this genus (Skinner and Chimimba, 2005).

The striped mouse is a seasonal breeder (breeding in spring and summer). Gestation is 22-23 days (Schradin and Pillay, 2003). Litter sizes vary according to context, with females giving birth to approximately five pups in nature (Brooks, 1982) and seven pups in captivity (Pillay, 2000a). Pups are weaned at 16 days of age and reach sexual maturity at approximately five to six weeks old in nature (Brooks, 1982), but often around 60 days in captivity (Pillay, 2000c).

Striped mice are suitable study subjects because they breed readily in captivity, have a short generation time, are easy to house and handle, and more particularly in the case of this study, exhibit a number of different locomotory SBs which are relatively easy to identify. Approximately 50% of striped mice born in captivity become stereotypic (Schwaibold and Pillay, 2001). SBs emerge in early development, sometimes as early as

weaning, but often around 30 days of age and, once present, remain throughout the lifespan of three to four years in captivity (Jones et al., 2010a). SB in striped mice has been found to have a genetic basis (Schwaibold and Pillay, 2001), and stereotypic mothers are five times more likely to produce offspring that display stereotypic behaviours (Jones et al., 2010a).

1.9 Aims, objectives and predictions

The overarching aim of this study was to investigate the behavioural correlates of SB and in stereotypic striped mice *Rhabdomys dilectus.* The objectives are outlined below.

1) The first objective of this study was to determine the frequencies and durations of four behaviours (inactivity, activity, freeze, and stereotypy) in striped mice in order to determine their correlates with SB. I predicted that stereotypic mice would be more active and engage in higher frequencies of all observed behaviours. Non-stereotypic mice, on the other hand, would be less active and engage in longer durations of inactivity.

2) The second objective of the study was to determine whether personality predicted stereotypic behaviour in striped mice by means of novel object and startle tests. I predicted that if SB were correlated with proactive coping strategies, stereotypic mice would be bolder and would therefore spend a longer duration with the novel object upon its introduction to the home cage. They would be less anxious and quicker to recover after a startle. Non-stereotypic mice would conversely be more fearful and anxious according to the coping hypothesis because they are reactive copers, and will thus be less bold and spend less time with a novel object, as well as take longer to recover and emerge from the dark side of the tank after a startle. From a neurobiological perspective, stereotypic mice would be less capable of inhibiting inappropriate behaviours and therefore spend less time recovering from startle in order to re-engage in their stereotypic routine.

3) The third objective was to measure social motivation is striped mice using dyadic encounter experiments. In line with the coping hypothesis, stereotypic mice would be more aggressive and thus less socially motivated in dyadic encounters, while non-stereotypic mice would display more amicable behaviour.

4) The fourth objective was to investigate perseveration in striped mice by means of a plus maze test. I predicted that stereotypic striped mice would be more prone to routine behaviour than non-stereotypic striped mice, due to a lack of behavioural flexibility, which is mediated by underlying neural pathway dysfunctions between the cortex and basal ganglia. From an ethological standpoint, stereotypic mice would be more prone to routine behaviour because they display a proactive coping style and a more active response to stressful situations.

5) The final objective was to link all the behavioural assays mentioned above in order to find correlates of SB. I predicted that stereotypy would be associated with higher activity levels, proactive coping, a bolder personality and higher levels of perseveration due to several common underlying mechanisms. These could include: (1) a dysfunction of the basal ganglia and its pathways around the cortex; (2) abnormality of the transmission of neurotransmitters serotonin and dopamine; and (3) external stressors in the environment, such as a lack of space and stimulation.

Chapter 2. Materials and methods

2.1 Housing and husbandry

The *R. dilectus* used in this study were F1 and F2 captive-born individuals whose parents originated in Pretoria (25◦ 40′ S; 28◦ 30′ E), South Africa. The mice were housed in the Milner Park Animal Unit, University of the Witwatersrand and maintained under partially controlled environmental conditions: 14L: 10D light: dark cycle (lights on at 05h00); 22–24^{0}C; and 30–60% rH. Test subjects (below) were housed individually in clear Lab-o-tec^{TM} cages (L × H × W: 300 mm × 200 mm × 150 mm). Woodshavings (±3 cm) were provided as bedding, with a handful of *Eragrostis* sp. grass (±20 g) and ± 5 g of shredded tissue paper for nesting material. PVC nest-boxes (L × H × W: 100 mm × 100 mm × 150 mm, open at both ends) were also provided in each cage. No other enrichment devices were provided, since SB is reduced in striped mice housed in enriched environments (Joshi and Pillay, 2016b). Epol® mouse cubes and water were available *ad libitum*. Approximately 5 g of fresh fruit and/or vegetables and 5 g of mixed seed were supplied daily per individual.

2.2 Identifying stereotypic and non-stereotypic striped mice

Recordings were made of 60 adult (less than 60 days of age) males and females housed individually so that the stereotypic status of each could be identified. The behaviours of individuals were video-recorded for 15 min a day per individual for 10 days. Recordings were made when striped mice are most active (between 09h00–12h00; Pillay, 2000b); no human observers were present in the room during recordings. The recordings continued until 30 stereotypic (15 female, 15 male) and 30 non-stereotypic (15 female, 15 male) had been identified for use in the study. Stereotypic individuals were those that displayed 10 or more instances of locomotory (i.e. circuit running, cage-lid climbing, wind-screen wiping) stereotypy per observation session, each with three or more repetitions (Jones et al., 2008); non-stereotypic mice displayed no stereotypic behaviours and were used as a comparison with the stereotypic mice. Stereotypic behaviour is an “all or nothing” occurrence in striped mice, and so only the absence or presence of stereotypic behaviours was recorded (see Jones et al., 2008). Following the identification of stereotypic and non-

stereotypic striped mice, all underwent four experimental tests individually in order to identify and categorise restricted and repetitive behaviours.

2.3 Experimental design

The 30 stereotypic and 30 non-stereotypic striped mice underwent four tests in sequence to avoid age-related (ontogenetically) influences on behaviour (Figure 6). Tests included: 1) home cage behaviour (from Day 70 to Day 94); 2) dyadic encounters to measure aggression levels (Day 96); 3) novel object test and startle test (Day 105, 106 respectively) to measure anxiety; and 4) SAchi test in a plus maze (Day 110). All tests were conducted in a separate video-recording room between 09h00–12h00.

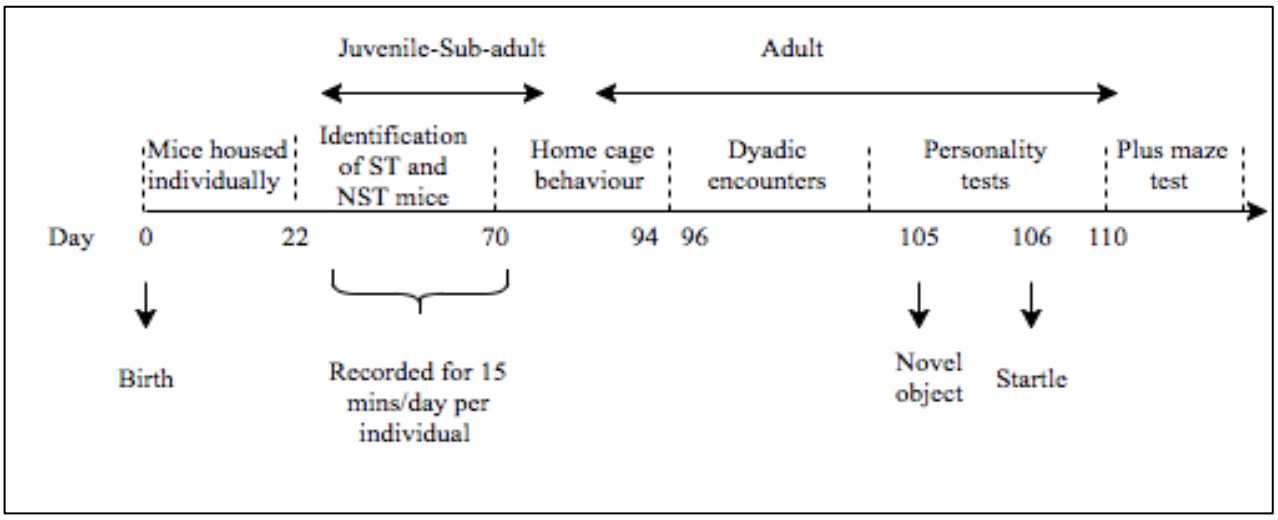

Figure 6. Timeline showing days (age) at which striped mice were exposed to four tests, including home cage behaviour, dyadic encounters, the novel object and startle tests, and the plus maze.

2.4 Home cage behaviour

The subjects were housed singly in clear Lab-o-tec™ cages furnished as described above and their behaviours were recorded for 15 min a day every second day for a total of 12 days. Using Observer software (version 5.0, Noldus Information Technology), the frequency and duration of four behaviours linked to stereotypic behaviour and inactivity

(Table 1) were scored using continuous focal sampling. The data were summed for all days for the data analyses. Again, no human observers were present in the room during these recordings.

Table 1. Ethogram of striped mice behaviours scored in standard laboratory housing

Behaviour	Definition
Stereotypic behaviour	A behaviour repeatedly and invariantly performed 3 or more times in succession (Jones et al., 2008).
Active	Engaging in movement not related to stereotypic behaviour (e.g. exploring, grooming)
Hide	Individual inside the nest box or stationary under woodshavings
Freeze	Individual stops all body movement and is rooted to the spot.

2.5 Dyadic encounters

Two days after the end of the home cage behaviour sampling, dyadic encounters were staged between test subjects and age-matched, same-sex stimulus individuals from the striped mice breeding colony. Dyadic encounters were staged in metal tanks (465 mm × 310 mm × 350 mm, l x b x h) constructed of galvanised steel with a clear Perspex front to facilitate video recording; tanks were capped with wire mesh lids during encounters. The floors of the tanks were covered with a 1 cm layer of woodshavings. In all tests, the stimulus animals weighed less than the test animal, because dominance is mass-dependent in striped mice (Schradin and Pillay, 2005), and I wanted to assess the aggression of test subjects. The mass was balanced between dyad partners and treatment. In the stereotypic individuals dyads, the mass difference was 3-5 g, and in non-stereotypic individual dyad the mass difference was 2-5 g. The motivation of the test subject to dominate and/or interact with the stimulus individual was then recorded. All animals were used only once in experiments.

The tanks were divided equally with a cardboard partition at the start of encounters. A focal and a stimulus mouse were randomly placed on either side of the partition. After an acclimatisation period of three to four minutes, the partition was removed and behaviour

of the dyad was video-recorded for 15 min. I sat quietly in the room approximately two metres from the dyad in order to terminate the dyad should fights become damaging; direct aggression was rare, so none of the dyads had to be terminated. After encounters, the test and stimulus subjects were returned to their cages. Tanks were cleaned with disinfectant soap, water and alcohol between tests to remove the odour of the previous dyad.

The larger focal subject was easily recognisable from video-footage. The frequency of the test subject's aggressive (chase, sparring, lunge, jump on opponent) and amicable (body contact, allogrooming) behaviour (Schradin and Pillay, 2003) was captured using Observer 5.0. Aggression and amicable behaviours are differently motivated (Laviola and Terranova, 1998), so that both must be regarded as describing social motivation. I created an aggression index (AI) as follows:

AI = frequency of aggression/(frequency of aggression + frequency of amicable behaviour) * 100.

2.6 Personality tests

A week after the dyadic encounters, test subjects were next used in two standard personality tests (novel object and startle response), which have both been used to measure high order ARBs. These personality tests are commonly used in studies of striped mice in captivity (Jones et al., 2010b and a, 2016) and in nature (Yuen et al., 2015).

Novel object test. This test was conducted in a glass tank (600 mm × 300 mm × 250 mm) with clear sides, a transparent lid, and the floor was covered with a 1 cm layer of woodshavings. The test subject was allowed to explore the tank without any observers in the room; five minutes later a novel round plastic object (±25 mm in diameter) was placed in one corner of the tank, opposite to where the test mouse was located. The behaviour of the individual was video-recorded for 10 min. The duration of its interaction with the novel object later scored using Observer 5.0. The tank was cleaned with disinfectant soap, water and alcohol between tests and the mouse was then returned to its home cage.

Startle response test. This test took place in a tank (600 mm × 300 mm × 250 mm) which was divided into two equal-sized (300 mm × 225 mm × 300 mm) sections, one half painted black (including the lids) and one half transparent. The halves were separated by a black partition with small opening at the base so that the test mouse could move between both halves. Tanks contained a 1 cm layer of woodshavings. The test mouse was placed in the light side of the tank and allowed to explore for five minutes without any observers in the room. Thereafter, the mouse was startled with a loud handclap next to the tank, upon which it immediately retreated into the dark. The latency of the mouse to return to the light half of the tank was then recorded for a further 5 min using Observer 5.0. The tank was cleaned with water, disinfectant soap and alcohol between tests.

2.7 Behavioural routines

In this test, a four-arm maze was used, which consisted of four enclosed arms (7.5 x 7.5 x 15cm) constructed of clear PVC and connected to a central chamber (10 x 10 x 20cm; Jones et al., 2010a). A mouse was introduced into the central chamber and its behaviour was recorded for 10 min. The frequency of arm entries was recorded as a measure of locomotor activity. The methods of Hlinák and Krejci (2006) were used to calculate Spontaneous Alternation Behaviour scores (SAB) for a series of four-arm entries (a tetrad), as the ratio of actual arms entered to the possible number of arms that could have been entered. For the arm entry sequence 12343, an alternation score for each tetrad was calculated as follows: for the first tetrad (1234), the mouse entered four different arms out of a possible four, giving an alternation score of 4/4 = 1. For the second tetrad (2343), it would have entered three out of a possible four arms, and hence scored 3/4 = 0.75, with the last three entries of the sequence (234) not being considered because these did not constitute a complete tetrad. Total SAB scores for the trial were calculated by averaging SAB scores across all tetrads in a sequence, with low overall scores representing a tendency to enter a more restricted number of arms and to make more repeat visits of the same arm. Sequential analysis was then used assess the predictability of a striped mouse entering a particular arm, following entry into another particular arm. For each individual, the sequence of arm entries was coded into transition matrices with the current behavioural element (an entry into one of the arms) represented in the rows and the preceding arm entered represented in the columns. Using the software Matman (Noldus

Information Technology), I calculated the adjusted residuals (i.e. differences between observed and expected values for each transition frequency) for each matrix and then used the generated χ^2 value (SAchi) for each matrix as an index of routine formation (the higher the χ^2 value, the more predictable a mouse's pattern of arm entry; thus, unlike the SAB score, here high scores mean a more predictable sequence).

2.8 Data analysis

Statistical analyses were conducted using R studio (R version 3.4.3 http://www.R-project.org) and Graphpad Instat 3.0 (www.graphpad.com). All tests were two-tailed and alpha was set at 0.05. The dataset was tested for departure from normality using the Shapiro-Wilk test and visualised using Q-Q plots. The data were non-normal, so appropriate analyses were used. A comparison was made between the behaviours of stereotypic and non-stereotypic striped mice (i.e. stereotypy status) and sex (fixed factors) using a Generalised Linear Model (GLM; glm2 in R studio). The GLM was run with a Poisson error structure and log link function. Comparisons were made of: 1) the frequency and duration of behaviours in home cage, except for stereotypical behaviour (which was only shown by stereotypic striped mice); 2) AI scores in dyad encounters; 3) duration with novel object; 4) latency to enter the light following a startle; and 5) SAchi scores in the plus maze. The overdispersion was ≤ 1 in all tests, indicating almost nil overdispersion.

Spearman rank correlations were conducted to assess the relationship between active, hide, freeze and stereotypic behaviour in the home cage, as well as scores for the novel object, startle, plus maze and dyadic encounter tests, separately for stereotypic and non-stereotypic striped mice. Sex was not a significant predictor of behaviours in the GLM output (see Results), so sex was not considered in correlation analyses. Male and female animals have different life history strategies (Nevison et al., 1999), patterns of hormone secretion (Beatty, 1979; Quiñones-Jenab et al., 1999) and differences in genetic predisposition (de Visser et al., 2007), all of which may contribute to sex differences in terms of object manipulation, startle response, and activity levels. Female rats have been found to show a greater inclination to novelty than males and therefore display higher

levels of exploration and reduced levels of anxiety or fearfulness (Aguilar et al., 2003; Øverli et al., 2006). Striped mice are not sexually dimorphic, and, apart differences in sexual differences in reproductive behaviour (Schradin et al, 2011), males and females do not often show sexual differences in other behaviours. For example, Yuen et al. (2017) did not detect differences in personality tests. In addition, Mackay (2011) found that sex did not influence the duration spent in the clear and dark arms of the plus maze or the frequency with which the arms were entered in the same species. Nonetheless, Joshi and Pillay (2016a) found minor sex differences in the behaviour of striped mice to enrichment.

Correlations were conducted separately for frequency and duration data because they consider different scales and types of measures. Moreover, because the Spearman regression was on conducted multiple comparisons, I adjusted P values using the Benjamini-Hochberg (1995) method.

Chapter 3. Results

3.1 Behaviour in the home cage

Stereotypy status significantly the influenced the frequency of active and hide behaviour (Figure 7), with stereotypic mice showing more frequent active behaviour than non-stereotypic mice ($z = 20.27$, $p < 0.001$), as well as a greater frequency of hide behaviour ($z = 16.62$, $p < 0.001$). There were no significant differences in the frequencies of freeze behaviour between stereotypic and non-stereotypic mice ($z = 0.40$, $p = 0.692$). Sex (Active: $z = -1.36$, $p = 0.174$; Hide: $z = -1.27$, $p = 0.204$; Freeze: $z = 0.42$, $p = 0.675$; Table 2) and stereotypy status*sex (Active: $z = 0.12$, $p = 0.905$; Hide: $z = 0.71$, $p = 0.478$; Freeze: $z = -1.27$, $p = 0.204$) were not significant predictors of the behaviours (Table 2).

Table 2. Median and interquartile (IQ) frequencies for the behaviour of female and male stereotypic and non-stereotypic striped mice

Stereotypic status	**Sex**	**Behaviour**	**Median**	**1st IQ**	**3rd IQ**
Stereotypic	**Female**	Active	48	23	90
		Hide	62	55.5	65.5
		Stereotypy	88	75.5	116
		Freeze	60	29	65
	Male	Active	47	16	65.5
		Hide	55	52	60
		Stereotypy	127	68.5	163
Non-stereotypic	**Female**	Active	8	6.5	10.5
		Hide	21	14	28
		Freeze	45	41	54.5
	Male	Active	5	3.5	9.5
		Hide	12	9.5	21
		Freeze	47	43	59

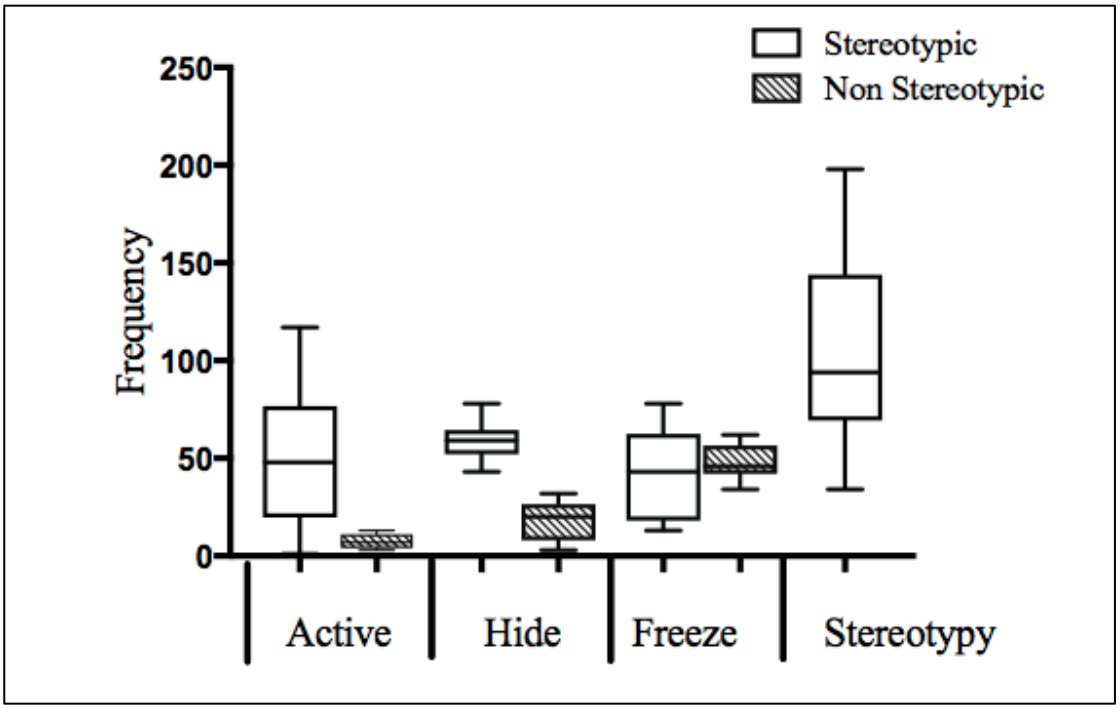

Figure 7. Frequency of behaviours in stereotypic and non-stereotypic striped mice. Boxes indicate inter-quartiles, the horizontal line indicates median and the error bars indicate confidence intervals. No comparisons were done for stereotypy because of its presence only in stereotypic striped mice.

Stereotypy status also influenced the duration of behaviours in the home cage (Figure 8). Non-stereotypic mice displayed longer durations of hide behaviour (z = -200.11, p < 0.001), while stereotypic mice displayed longer durations of active (z = 80.32, p = < 0.001) and freeze (z = 80.12, p = <0.001) behaviour. Sex (Active: z = -1.73, p = 0.084; Hiding: z = -0.43, p = 0.666; Freeze: z = 1.82, p = 0.068; Table 3) and stereotypy status * sex effects (Active: z =0.23, p = 0.818; Hiding: z = 0.174, p = 0.082; Freeze: z = 0.107, p = 0.286) were not significant predictors of behaviours (Table 3).

Table 3. Median and interquartile (IQ) duration (s) for the behaviour of female and male stereotypic and non-stereotypic striped mice

Stereotypic status	**Sex**	**Behaviour**	**Median (s)**	**1st IQ (s)**	**3rd IQ (s)**
Stereotypic	**Female**	Active	1511	1284	1909.5
		Hide	3267	1138	5506.5
		Stereo	3885	2155.5	6374.5
		Freeze	2082	1560	2455.5
	Male	Active	1296	1222.5	1551
		Hide	1866	534	3051
		Stereo	5349	4385	6302.5
		Freeze	2130	1815	2385
Non-stereotypic	**Female**	Active	573	520.5	622.5
		Hiding	9228	9112.5	9616.5
		Freezing	972	588	1188
	Male	Active	558	480	610.5
		Hiding	9300	9076.5	9568.5
		Freezing	999	688.5	1195.5

Although stereotypic behaviour was not statistically analysed, because non-stereotypic mice do not display stereotypic behaviours, stereotypic behaviour was a predominant constituent of the general activity of stereotypic individuals (Figures 7 and 8).

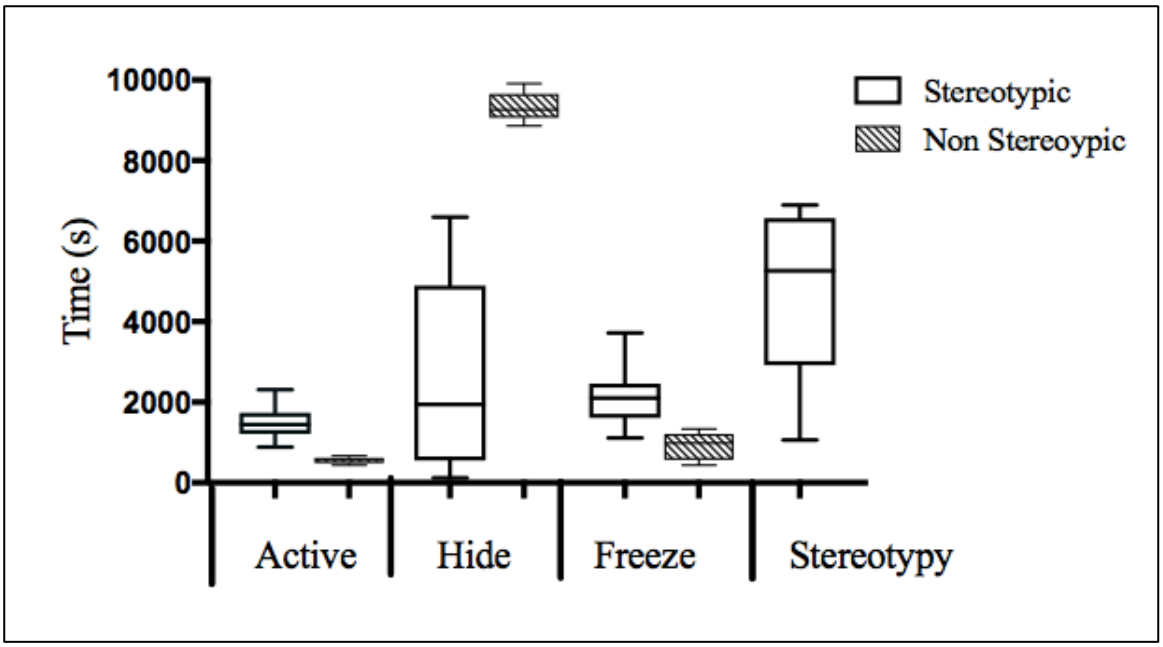

Figure 8. Duration of behaviours (s) in stereotypic and non-stereotypic mice. Boxes indicate inter-quartiles, the horizontal line indicates median and the error bars indicate confidence intervals. No comparisons were done for stereotypy because of its presence only in stereotypic striped mice.

3.2 Dyadic encounters

There was a no significant influence of stereotypy status on the AI index in the dyadic encounters ($z = 1.28$, p = 0.201; Figure 9). Sex ($z = 1.01$, p = 0.313. Table 4) and stereotypy status * sex ($z = -1.85$, p = 0.064) were not significant predictors of behaviours.

Table 4. Median and interquartile (IQ) for aggressive index scores for female and male stereotypic and non-stereotypic striped mice

Stereotypic status	**Sex**	**Median**	**1st IQ**	**3rd IQ**
Stereotypic	**Female**	21	12	33
	Male	13	12	32
Non-stereotypic	**Female**	10	3	13
	Male	21	11.5	28.5

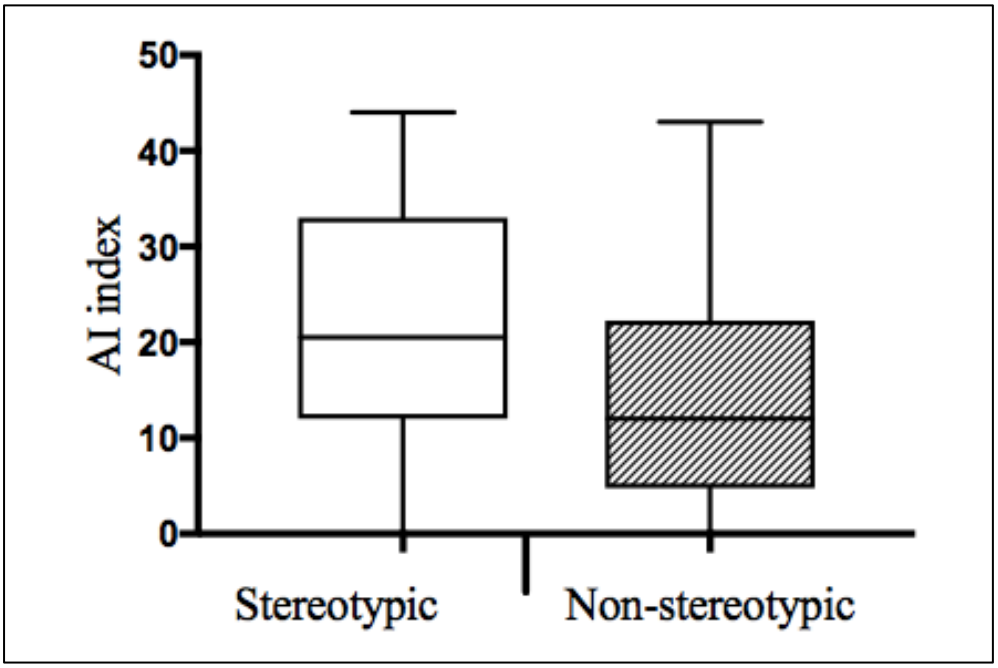

Figure 9. AI index of aggression scores in stereotypic and non-stereotypic mice. Boxes indicate inter-quartiles, the horizontal line indicates median and the error bars indicate confidence intervals.

3.3 Personality

Stereotypy status significantly affected novel object behaviours ($z = 20.92$, $p < 0.001$) and startle response ($z = -21.97$, $p < 0.001$). In the novel object test, stereotypic striped mice spent significantly more time than non-stereotypic striped mice interacting with the novel object (Figure 10a). In the startle response test, stereotypic striped mice spent significantly less time in the dark side of the tank and were quicker to return to the lighter half after being startled than non-stereotypic striped mice (Figure 10b). There were no sex (novel object: $z = 0.10$, $p = 0.992$; startle: $z = 0.11$, $p = 0.912$; Table 5 and 6) and stereotypy status * sex (novel object: $z = 0.213$, $p = 0.831$; startle: $z = 1.26$, $p = 0.209$) effects.

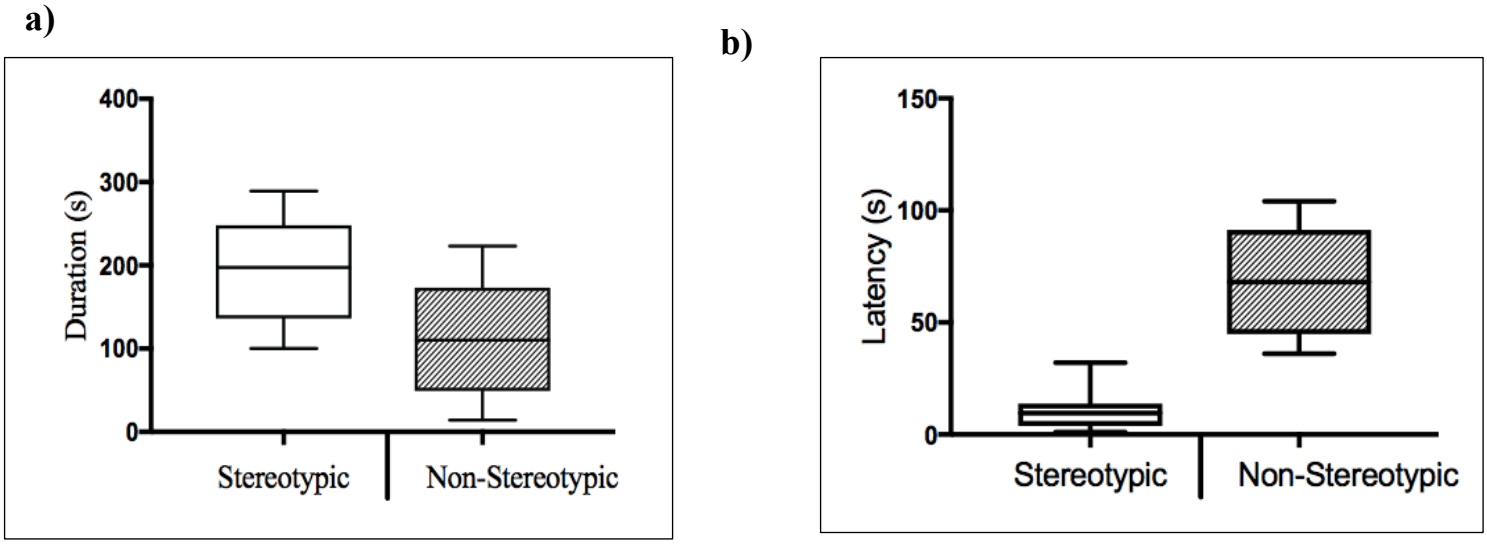

Figure 10. Responses of striped mice in a) novel object (duration with novel object) and b) startle response (latency to resume activity) tests for stereotypic and non-stereotypic striped mice. Boxes indicate inter-quartiles, the horizontal lines indicate median and the error bars indicate confidence intervals.

Table 5: Median and interquartile (IQ) duration (s) spent with the novel object in female and male stereotypic and non-stereotypic striped mice.

Stereotypic status	**Sex**	**Median**	**1st IQ**	**3rd IQ**
Stereotypic	**Female**	206	173.5	232
	Male	195	132.5	252.5
Non-stereotypic	**Female**	5	3.5	11
	Male	10	4.5	16

Table 6. Median and interquartile (IQ) latency (s) to resume behaviour after a startle response in female and male stereotypic and non-stereotypic striped mice.

Stereotypic status	**Sex**	**Median**	**1st IQ**	**3rd IQ**
Stereotypic	**Female**	3.5	5	11
	Male	4.5	10	16
Non-stereotypic	**Female**	50	68	84.5
	Male	48.5	68	84

3.4 Behavioural routines

There was a significant influence of stereotypy status on the SAchi scores in the plus maze test ($z = 8.2$, p = <0.001; Figure 11). Stereotypic striped mice showed higher SAchi scores than non-stereotypic striped mice. Sex ($z = 1.89$, p = 0.091; Table 7) and stereotypy status * sex effects ($z = 0.81$, p = 0.418) were not significant predictors of SAchi scores.

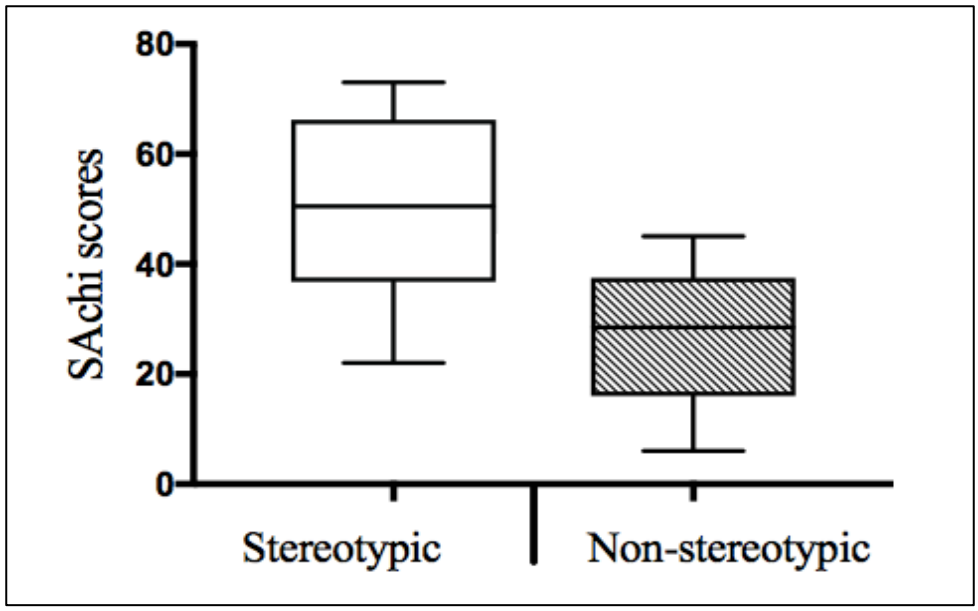

Figure 11. SAchi scores in stereotypic and non-stereotypic mice. Boxes indicate inter-quartiles, the horizontal line indicates median and the error bars indicate confidence intervals.

Table 7: Median and interquartile (IQ) SAChi scores for female and male stereotypic and non-stereotypic striped mice

Stereotypic status	**Sex**	**Median**	**1st IQ**	**3rd IQ**
Stereotypic	Female	52	37	67.5
	Male	49	37	60.5
Non-stereotypic	Female	36	26	38
	Male	23	15.5	34

3.5 Relationship between behavioural variables in the four tests

Spearman rank correlations for the behaviours of stereotypic mice (Table 8) showed positive correlations between the frequency and duration of active behaviour and the following: (i) the duration (s) spent with novel objects in the novel object test; (ii) latency to emerge from the dark compartment in the startle test; (iii) SAchi scores in the plus maze; and (iv) stereotypy. This indicated that active stereotypic mice that spent more time with novel objects also spent longer in the dark half of the tank after being startled, and were more prone to forming routines. The frequency of stereotypy was also positively correlated with scores from these three personality tests. There were also positive correlations between the plus maze, novel object, and startle test, indicating that stereotypic mice that spent more time with novel objects also had higher SAchi scores, and a shorter latency to return to the dark compartment after startle. With regard to home cage behaviour, there were positive correlations between the duration of freeze and frequency of hide and stereotypic behaviour, as well as the frequency of freeze and duration of active behaviour.

Table 8. Statistical output (r, p) for the Spearman rank correlation coefficient analysis for home cage behaviour, AI scores, novel object/ startle values, & SAchi scores in stereotypic striped mice. Values above the diagonal represent correlations for duration and those below the diagonal are frequency correlations. P values are adjusted using the Bejamini-Hockberg method. Values in bold are significant.

		Active	Hiding	Stereotypy	Freeze	AI	Novel Object	Startle	SAchi Score
Active	r	*	0.02	**0.25**	-0.08	-0.01	**0.48**	**0.46**	**0.48**
	p	*	0.106	**0.05**	0.07	0.110	**0.007**	**0.014**	**0.019**
Hide	r	0.09	*	0.16	**-0.46**	0.30	0.06	0.06	0.06
	p	0.210	*	0.060	**0.029**	0.09	0.080	0.082	0.009
Stereotypy	r	-0.02	0.13	*	**-0.38**	0.19	**0.68**	**0.67**	**0.68**
	p	0.322	0.495	*	**0.043**	0.06	**0.005**	**0.005**	**0.005**
Freeze	r	**0.38**	0.12	0.19	*	-0.06	**-0.38**	**-0.38**	**-0.39**
	p	**0.028**	0.182	0.07	*	0.751	**0.034**	**0.037**	**0.029**
AI	r	-0.12	**0.38**	0.02	0.10	*	0.07	0.03	0.06
	p	0.168	**0.042**	0.308	0.196	*	0.07	0.101	0.091
Novel Object	r	**0.77**	0.16	0.18	0.03	0.07	*	**0.99**	**0.99**
	p	**0.014**	0.112	0.084	0.280	0.224	*	**0.005**	**0.005**
Startle	r	**0.78**	0.147	0.196	0.034	0.034	**0.994**	*	**0.994**
	p	**0.014**	0.126	0.057	0.266	0.252	**0.014**	*	**0.005**
SAchi Score	r	**0.77**	0.14	0.17	0.02	0.06	**0.99**	**0.99**	*
	p	**0.014**	0.140	0.098	0.294	0.238	**0.014**	**0.14**	*

Table 9. Statistical output (r, p) for the Spearman rank correlation coefficient analysis for home cage behaviour, AI scores, novel object and startle values, and SAchi scores in non-stereotypic striped mice. Values above the diagonal represent correlations for duration and those below the diagonal are frequency correlations. P values are adjusted using the Bejamini-Hockberg method Values in bold are significant.

		Active	Hide	Freeze	AI	Novel Object	Startle	SAchi Score
Active	r	*	0.14	0.07	-0.42	-0.20	-0.07	0.06
	p	*	0.240	0.320	0.064	0.180	0.300	0.340
Hide	r	**-0.41**	*	0.14	0.16	0.09	**0.59**	**0.59**
	p	**0.030**	*	0.220	0.200	0.280	**0.048**	**0.032**
Freeze	r	0.01	-0.004	*	0.103	0.005	0.02	0.21
	p	0.114	0.120	*	0.260	0.380	0.360	0.160
AI	r	-0.009	**0.41**	-0.06	*	**0.50**	0.22	0.33
	p	0.090	**0.036**	0.108	*	**0.048**	0.140	0.008
Novel Object	r	**-0.40**	**0.76**	-0.05	**0.50**	*	**0.55**	0.30
	p	**0.042**	**0.012**	0.102	**0.024**	*	**0.016**	0.105
Startle	r	**-0.38**	**0.73**	0.09	0.22	**0.55**	*	**0.59**
	p	**0.048**	**0.012**	0.096	0.078	**0.018**	*	**0.016**
SAchi Score	r	-0.23	**0.36**	0.13	0.33	0.30	**0.59**	*
	p	0.072	**0.05**	0.081	0.060	0.066	**0.0001**	*

Spearman rank correlations for non-stereotypic mice showed negative correlations for frequency of hide and the duration of active behaviour, as well as positive correlations for the duration of hide and also: (i) duration spent with novel object; (ii) startle response, (iii) SAchi scores; and (iv) AI scores (Table 9). This indicated that non-stereotypic mice that were inactive (ie. hid) for longer durations, spent less time with novel objects, longer durations in the dark side of the tank after being startled, had lower AI scores, and were less prone to routine formation.

Chapter 4. Discussion and Conclusions

The overarching aim of this study was to investigate the behavioural correlates of SB in stereotypic striped mice *Rhabdomys dilectus*. By integrating the psychological and ethological theories of SB, I aimed to assess these two approaches against the neurobiological literature. I investigated four behavioural correlates of SB, namely inactivity, social motivation, personality, and perseveration. Stereotypic striped mice were expected to show increased activity levels, greater social motivation, increased exploratory behaviour, reduced anxiety upon encountering a novel object or startle sound, and the predisposition to develop routines. Non-stereotypic mice, on the other hand, were expected to show increased levels of inactivity (i.e. hiding), lower levels of social motivation, decreased exploratory behaviour, increased anxiety upon encountering a novel object or startle sound, and a lower predisposition to develop routines.

The first experiment measured the frequencies and durations of four behaviours (active, freeze, hide and stereotypy) in the home cage of the striped mice. Stereotypic striped mice displayed higher frequencies of active and hide behaviour, and longer durations of active and freeze behaviour than non-stereotypic mice. In contrast, non-stereotypic striped mice were typically inactive and engaged in longer durations of hide behaviour. Greater inactivity and longer durations of hide behaviour has also been observed in a variety of animals kept in zoos (Meyer-Holzapfel, 1968). The differences in the frequency and duration of hiding behaviour between stereotypic and non-stereotypic striped mice reflect differences in the functional relationship between frequency of occurrence and duration. Non-stereotypic striped mice hid for longer periods during the observation period and rarely displayed other behaviours, with the result that their hiding frequency was low, but duration was higher. In contrast, stereotypic striped mice changed behaviours more often (i.e. indicating changes in behavioural motivation), resulting in greater frequency and lower duration of hiding behaviour. This corresponds with findings in other animals (e.g. bank voles *Myodes glareolus*) in which increased rates of behavioural initiation (i.e. higher frequencies of behaviour) are suggested as being factors predisposing hyperactivity and stereotypic behaviour (Garner et al., 2003).

The behaviour in the home cages suggests that stereotypic and non-stereotypic mice exhibit different responses to captive environments in terms of their daily activity and possibly energy budgets. From a neurobiological perspective, stereotypic mice were more likely to engage in higher frequencies of activity because of an imbalance in the direct and indirect pathways of the basal ganglia. This is associated with decreased inhibition (i.e. greater frequencies of SB and hyperactivity) and increased behavioural initiation (i.e. greater frequencies of all behaviours, including hiding; Garner, 2006). The pathways in the basal ganglia malfunction due to impoverished conditions in captivity. This results in abnormal behavioural responses and SB (Garner, 2006; Lewis et al., 2006) in individuals prone to developing SB. In general, the activation of the indirect pathway (which inhibits unwanted actions), or suppression of the direct pathway (which elicits desired behaviours) would decrease SB, whereas the suppression of the indirect pathway will induce SB (Langen et al., 2011a). The activation of the indirect pathway or suppression of the direct pathway results in hyperactivity, and the inhibition of the direct pathway suppresses all behaviours including SB, and thus leads to inactivity (Garner, 2006; Lewis et al., 2006). Individuals either become more active/stereotypic, or more inactive depending, on the nature of the environment, basal ganglia impairments and the conditions prior to these behaviours forming, such as early weaning processes and genetic influences (Figure 12) In sum, it can be hypothesised that the activation of the indirect pathway or suppression of the direct pathway reduces SB, whereas the suppression of the indirect pathway will induce them (Langen et al., 2011a).

SB and inactivity are associated with the same underlying mechanisms, which may include a higher HPA response to stress, and an imbalance in neurotransmitter regulation and basal ganglia function (Figure 12). An environmental stressor, such as a lack of physical space, may lead to impairments in the basal ganglia, and, depending on which pathway (direct or indirect) is affected, will result in either stereotypy or inactivity. Another factor, however, possibly personality or coping style, may also determine how the individual responds to an external stressor (Figure 12). An individual with a proactive coping style and bolder personality, for example, would be more likely to have an

imbalance in the indirect pathway, which inhibits unwanted actions and leads to greater activity, resulting in SB (Ijichi et al., 2013). Individuals adopting a reactive coping style are likely to have an imbalance in the direct pathway, and are thus more likely to resort to inactivity rather than SB (Ijichi et al., 2013).

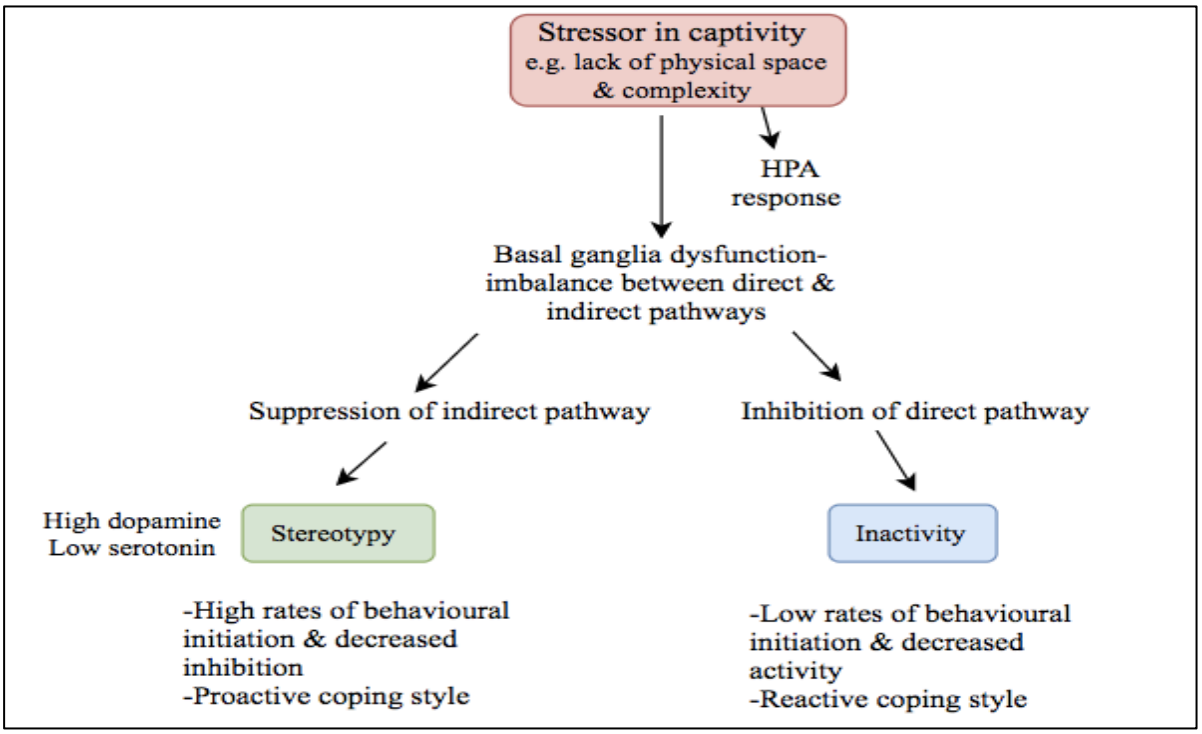

Figure 12. Flow chart of the mechanisms of SB and inactivity.

Individual variation in the prefrontal cortex may contribute to differences in coping styles. Dopamine for example is usually higher in proactive individuals while serotonin, which is involved in behavioural flexibility, is low in proactive and stereotypic individuals (De Boer and Koolhaas, 2003). Thus, individuals with higher dopamine concentrations are more likely to engage in SB as opposed to inactivity in response to aversive environments (McBride and Hemmings, 2005; Langen et al., 2011b). Inactivity may be an alternative response to SB adopted by individuals to barren environments, depending on neurotransmitter make-up and individual coping strategies or personalities (Latham and Mason, 2004; Garner, 2006; Mason et al., 2007; Mostard, 2011). Therefore, because both of these factors are associated with stress, it is possible they are linked to poor welfare in captivity. It is thus questionable as to whether animals that engage in long

durations of active behaviour can be said to fare better than those who are largely inactive in captive environments, since both aspects are linked to neural dysfunction and stressful environments.

In the second test, contrary to my prediction, there was no association between stereotypy status and social motivation. The reason for this could have been because stereotypic mice were not motivated to engage in social behaviour, be it amicable or aggressive, because they were actively engaged in and preoccupied with their stereotypic routine. In neurological terms, the suppression of the indirect pathway in the basal ganglia induced by aversive conditions in captivity would result in high levels of SB which cannot be inhibited. The individual is thus unable to switch readily from one behaviour to another and continuously engages in SB, overriding all other behaviours that would otherwise occur in nature (Mason, 1991a). According to the psychogenic hypothesis (Harvey and Singer, 2009) individuals in captivity attempt to reduce external distractions and demands by engaging in stereotypic behaviour. Therefore the stereotypic mice may have been using SB as a coping mechanism in order to avoid the other individual in the dyad.
Another possible reason for the lack of social motivation in stereotypic mice may have been because they fearful of the other member of the dyad, which correlates with this increased hide behaviour of the stereotypic individuals. This is common in captivity, where normal behaviours, such as exploration, play and sociality, are gradually replaced by abnormal behaviours, such as stereotypic or apathetic behaviours (Mason 1991a; Rushen, 1993). SB has been found to interfere with normal socialisation, and captive environments often impede social interactions (Mostard, 2011). For example, female leopard cats *Prionailurus bengalensis* engage in stereotypic pacing, rather than caring for their cubs in captivity (Wildholzer and Voss, 1978). Non-stereotypic laboratory mice also did not differ in their motivation to engage in social behaviour (Mostard, 2011). This may be because they are reactive copers and thus are less bold, more anxious and more likely to avoid social contact. They may be fearful of novel individuals and thus retreat or remain inactive or hide instead of engaging in social behaviour. In terms of neurological pathways, inhibition of the direct pathway leads to a decrease in all behaviours, including social motivation (Mostard, 2011). Thus, an individual with an imbalance in this pathway

will be less active, less social, and more inclined to hide away from novel objects or individuals.

Welsher (1995) found that non-stereotypic laboratory mice were more likely to avoid novel objects and to display fearful and docile behaviour, while stereotypic mice were less fearful and engaged in risk-taking behaviour in novel environments. Similarly, stereotypic striped mice spent a longer duration with a novel object, indicating a bolder personality (Joshi and Pillay, 2016a). Repetitive manipulation of objects, a low order ARB, is maintained by continuous self-stimulatory reinforcement (Harvey and Singer, 2009) and is thought to compensate for a deficit in external arousal in captive conditions (Turner, 1997). Individuals repeatedly interact with the same object in order to gain sensory stimulation, which leads to automatic reinforcement and in turn maintains ritualistic behaviour. This is a component of the psychogenic hypothesis (Harvey and Singer, 2009) that suggests individuals in captivity attempt to reduce external distractions and demands by engaging in self-stimulatory behaviour and automatic reinforcement in order to cope with external deficits in the environment.

In the startle response test, stereotypic striped mice were quicker to recover and spent a shorter time in the dark (closed) compartment after a startle response, compared to non-stereotypic mice. Individuals that venture faster into the light (open) spaces are regarded as being less anxious than those which remain in the darker components of the box (Dellu et al., 1996). Returning to the light compartment quickly after being startled may be associated with a high order ARB, whereby the compulsion to reengage in repetitive, routine behaviour is stronger than the urge to retreat after being startled (Turner et al., 2003a). This compulsive behaviour is characterised by strict mental rules and is associated with sensory seeking and positive mood states, as proposed in the psychogenic hypothesis (Harvey and Singer, 2009) My findings are comparable with those of a study conducted on great tits *Parus major* by van Oers et al., (2004) in which proactive individuals returned quickly to the feeding table after being startled compared to reactive individuals.

According to the coping hypothesis, proactive individuals are bolder, and less fearful and anxious, which concurs with the behaviour of stereotypic striped mice, which were quicker to retreat from the dark compartment. Non-stereotypic striped mice showed a reactive coping style, being fearful and less bold and therefore more likely to remain in the "protected" darker components of the box. Joshi and Pillay (2016b) found that stereotypic mice had a quicker recovery time and spent a longer duration in the light compartment after a startle response. Jones et al. (2010) also found that shorter duration dark side of the light-dark box corresponded to the development of stereotypic behaviour in striped mice. My findings indicate that the stereotypic routine of these individuals are interrupted for only short intervals before SB being resumed, suggesting that the neural pathways (particularly the dorsal striatum in the basal ganglia), which allow for behavioural flexibility in stereotypic individuals, cannot be easily changed.

My findings suggest that personality and SB have common underlying mechanisms (Figure 13). The mechanisms underlying the differences in these coping styles can be explained by changes in the prefrontal cortex, particularly in terms of serotonergic input to this area (Koolhaas et al., 2010; Coppens et al., 2010). Low serotonin and high dopamine levels are implicated in proactive/stereotypic individuals (McBride and Hemmings, 2005; Mason and Rushen, 2006 ; Langen et al., 2011b). From an ethological perspective, SB is an attempt by the individual to compensate for a lack of arousal in the environment (Harvey and Singer, 2009), which would explain why stereotypic individuals are more likely to engage in repetitive object manipulation and channel actions into stereotypic movement.

Perseveration was scored using a plus maze test, which relies on the natural tendency of mice to alternate arm choices in a T-maze. Perseveration is relatively common in all laboratory mice strains and includes spatial habits and reversal learning tasks (e.g. Lalonde, 2002; Hlinák and Krejci, 2006). Stereotypic striped mice had higher SAB scores in the plus maze test, indicating that their behaviour was more predictable than that of non-stereotypic striped mice. These results suggest that stereotypy in striped mice also reflects a general disinhibition of response selection in the motor system. In humans,

individuals with autism display a strong insistence on sameness, one of the main features of high order ARBs (Latham and Mason, 2004; Garner, 2006). This feature is usually mediated by mental states and compulsions to adhere to a strict routine and thought to be caused by structural alterations in the cortical-basal ganglia circuitry, particularly activation of the direct pathway (Figure 13), and impairments in the secretion of dopamine, both of which are associated with procedural learning, routine behaviours, and habits (Garner, 2006; Mostard, 2011).

It appears that SB and perseveration could be controlled by the same underlying mechanisms, much like SB and inactivity and personality (Figure 13). Both SB and perseveration are associated with basal ganglia dysfunction in the brain cortex (Garner, 2006). It is hypothesised that this dysfunction is linked to personality and coping styles (Ijichi et al., 2013; Joshi and Pillay, 2016b).

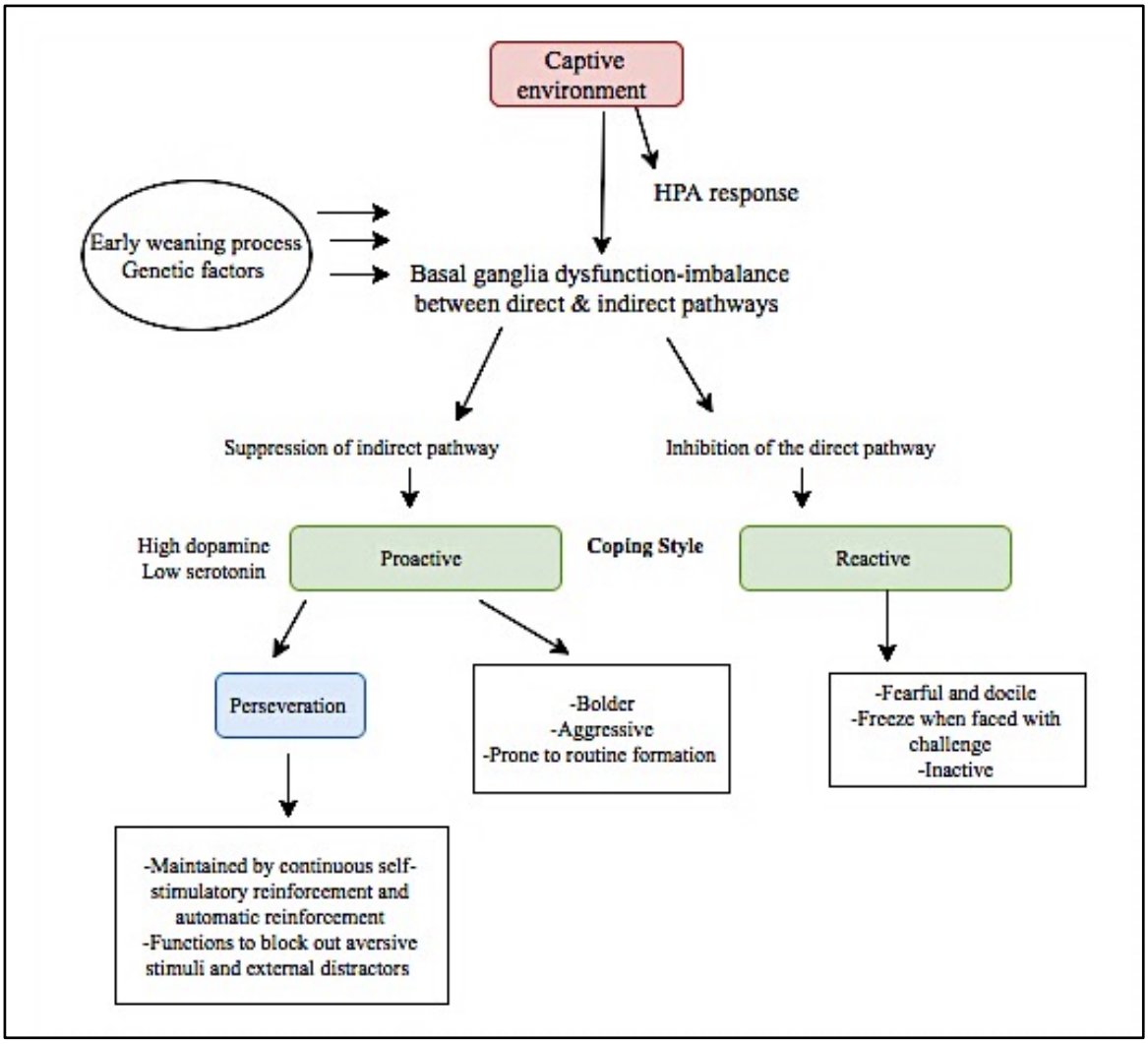

Figure 13. Flow chart showing the links between SB, coping styles, personality and perseveration.

Proactive copers, which are generally stereotypic, are thought to be more prone to routine formation, similar to individuals which engage in perseverative behaviours (Joshi and Pillay, 2016b). Thus, it is possible that the neural pathways in the basal ganglia which utilise dopamine and serotonin may lead to perseveration (Mostard, 2011; Ijichi et al., 2013; Joshi and Pillay, 2016a). Dysfunction of these structures may lead to routine behaviours and SB (Garner et al., 2003; Garner, 2006; Lewis et al., 2006; McBride and Hemmings, 2009).

Correlations between the results of the four different assays were conducted separately for stereotypic and non-stereotypic striped mice. These analyses allowed me to assess the association between the behaviours and also to assess within treatment (i.e. stereotypic and non-stereotypic) variation in behavioural responses. At least four conclusions could be drawn from Spearman rank correlations for stereotypic mice. (1) The duration and frequency of active behaviour, as well as the duration of SB, were positively correlated with the time taken to recover after being startled, suggesting that stereotypic mice which had a quicker recovery time also displayed increased durations of active and SB. Therefore, stereotypy, activity, personality, and coping style may have a common underlying mechanism. (2) There were positive correlations between the frequencies of active and SB and the duration spent with the novel object, suggesting that striped mice which exhibited repetitive object manipulation also displayed higher levels of activity and stereotypic behaviour. Thus, striped mice which engaged in longer periods with the novel object (i.e. those that were more bold) showed higher levels of SB and activity. It is thus possible that the same mechanism underlies activity, stereotypy, and boldness, this most likely being basal ganglia dysfunction described above. (3) Spearman rank analyses showed a positive correlation between SAchi scores and (i) frequency and duration of active behaviour and (ii) the duration of SB, suggesting that striped mice with higher perseveration scores were also more active and displayed longer bouts of SB. Stereotypic mice were more prone to routine formation and predictability, which is a high order ARB caused by various abnormalities in brain structure and function and possibly mediated by environmental impoverishment (Mason 1991a; Garner, 2006. (4) Spearman rank analyses also showed positive correlations between: (i) the duration spent with a novel object; (ii) the latency to merge from the dark compartment in the startle test; and (iii) perseveration scores in the plus maze. This showed that stereotypic mice that exhibited low order ARBs, for example object manipulation in the novel object test and quick recovery in the startle test, were more likely to also exhibit high order ARBs in the form of routine formation in the plus maze test. When feedback between corticostriatal loops in the basal ganglia becomes dysfunctional, the result is inappropriate repetitions of behavioural sets and inability to switch to different behavioural responses, which leads to the maintenance of SB.

Spearman rank correlations between behaviours of non-stereotypic mice indicated two patterns. (1) The duration of hide behaviour was positively correlated with (i) duration of time spent with novel object, (ii) latency to return to light side of tank after startle response, (iii) SAchi scores, and (iv) AI scores. This indicated that non-stereotypic mice that were inactive for longer durations spent a shorter time with novel objects, longer in the dark side of the tank after being startled, had lower AI scores, and were less prone to routine formation, thereby confirming that they are reactive copers (more anxious and fearful, less bold, more inactive). (2) There were positive correlations between novel object and startle scores and SAchi scores, suggesting non-stereotypic striped mice that spent shorter durations with novel objects, also took longer to recover after a startle response and were less prone to routine formation. This further confirms that non-stereotypic mice are reactive copers which display anxiety and fear when confronting novelty, and are less bold than stereotypic mice. Moreover, a common mechanism, particularly dysfunction in the basal ganglia and suppression of the indirect pathway, underlies all of the above correlated factors.

Conclusions

This study sought to establish the correlates of SB in striped mice using neurobiological and ethological theoretical approaches. In sum, stereotypic mice were more active, display a proactive coping style which involved increased boldness and tolerance for novelty, as well as an increased predisposition for routines. Non-stereotypic mice were inactive for longer duration, displaying a reactive coping style, possibly as a consequence of more anxiety and fear, and a lower level of perseveration. Social motivation was not influenced by stereotypy status.

The findings suggest that dysfunction in the basal ganglia and suppression of the indirect pathway is a common mediator that underlies most SB and associated behaviours, including inactivity, coping style, personality, and perseveration. All involve an imbalance between aspects of the corticostriatal circuits, the primary function of which is to control and select goal-directed motor, cognitive and emotional behaviour through the

direct or indirect pathways (Welch et al., 2007). Disruption in the basal ganglia between the striatal and forebrain regions thus leads to SB. The suppression of the indirect pathway of the basal ganglia is the major factor which leads to SB and its associated behaviours, while inhibition of the direct pathway leads to inactivity (Garner, 2006; Mostard, 2011). These disruptions are likely caused by impoverished conditions in captivity and are mediated by genetic factors and life history phenomena, such as early weaning (Mason 1991a; Garner, 2006). Psychogenic factors also play a role in all of the above behaviours, and SB, perseveration, and repetitive object manipulation in particular can be associated with self-stimulatory behaviour and automatic reinforcement in the individual (Harvey and Singer, 2009).

For the most part, the findings in the different behavioural assays are largely consistent with my assumptions about SB. Two findings were unexpected, however, and need to be considered in future studies. Firstly, stereotypy status had no effect on social motivation in striped mice. This is contradictory to previous studies which have shown stereotypic mice are more aggressive (Joshi and Pillay, 2016a). Future research should investigate social interaction abnormalities in striped mice by means of social preferences tests or partition tests in order to confirm whether captivity has a role in reducing social behaviour in mice. Secondly, stereotypic mice showed high frequencies of hide behaviour. This contradicts findings from some studies which state that stereotypic animals are predominantly active and bold (Meagher, 2011; Joshi and Pillay, 2016b). Further observational tests should be conducted to ascertain whether stereotypic mice display reactive traits, and the conditions under which these occur. The scientific literature contains a plethora of information about the causation and correlates of SB (Mason 1991a; Young, 2003; Garner, 2006) but much of this information is contradictory. Therefore, future research should focus on the neurobiological factors which underlie the correlates of SB and should also integrate findings across a variety of techniques in different species in order to improve our understanding of the regulation of SB and the generalisability of the findings of this study.

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