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Review article

Pacing stereotypies in laboratory rhesus macaques: Implications for animal welfare and the validity of neuroscientific findings

Colline Poirier*, Melissa Bateson

Institute of Neuroscience, Medical School, Newcastle University, UK

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ABSTRACT

Stereotypic behaviours are commonly observed in captive animals and are usually interpreted as a sign of poor welfare. Stereotypies have also been linked with brain abnormalities. However, stereotypies are a heterogeneous class of behaviours and mounting evidence indicates that different stereotypies can have different causes, and can be linked to different affective states. As a consequence, the implications of a specific stereotypy in a specific species cannot be safely inferred from evidence on other stereotypies or species. Here we review what is known about pacing behaviour in laboratory rhesus macaques, a common stereotypy in this species. Our review highlights the current lack of understanding of the causal factors underlying pacing behaviour. According to current knowledge, the welfare of pacing macaques could be either better, worse or equivalent to that of non-pacing individuals. It is also unclear whether pacing results from brain abnormalities. Since rhesus macaques are widely used as a model of healthy humans in neuroscience research, determining if pacing behaviour reflects an abnormal brain and/or poor welfare is urgent.

1. Introduction

Stereotypies are repetitive, unvarying and apparently functionless behaviours (Mason, 1991a). They are typically displayed by animals in captivity but not in the wild. For this reason they are considered as abnormal behaviours and often used as an indicator of poor welfare. Despite several decades of research, the causal factors underlying stereotypies are still unclear. Stereotypies have been hypothesised to be an index of current frustration or chronic stress, the product of a damaged brain, a satisfying way to perform a natural behaviour in an artificial environment, or an efficient way to cope with stress (Mason and Latham, 2004). While some of these hypotheses are not necessarily mutually exclusive (e.g. current frustration vs. abnormal brain), others seem contradictory (e.g. current frustration vs. a satisfying way to perform a natural behaviour). Traditionally, stereotypies have been considered as a homogeneous group of behaviours, leading investigators to lump different stereotypies together (e.g. Baker et al., 2012; Lewis et al., 1990; Waitt and Buchanan-Smith, 2001). However, accumulating experimental evidence supports the idea that even within a single species different stereotypies can have different causes (Dallaire et al., 2011; Pomerantz et al., 2012a) and can be linked to different affective states (Novak et al., 2016; Pomerantz et al., 2012b). To better understand the mechanisms underlying stereotypies and their relation with animal welfare, it is therefore crucial to investigate each stereotypic behaviour separately.

Understanding the cause of stereotypies is particularly important in laboratory animals. Indeed, beside welfare concerns, if some stereotypies are the product of an abnormal brain, the use of stereotyping animals in research might compromise the validity, reliability and replicability of scientific findings (Garner, 2005). As a case study, we review here the scientific evidence related to pacing behaviour in laboratory rhesus macaques (*Macaca mulatta*), one of the main animal models used to understand human brain mechanisms. Pacing is a stereotypic behaviour consisting of the repetitive walking of an individual in the exact same pattern (either back and forth or in circle) (Gottlieb et al., 2013; Lutz et al., 2003) and is the most frequent stereotypy displayed by laboratory rhesus macaques (hereafter macaques) (Lutz et al., 2003). After reviewing data supporting the different potential causes of pacing in this species, we consider the implications of the different hypotheses from welfare and biomedical perspectives.

2. Potential causes of pacing behaviour

Pacing behaviour is highly prevalent in cage-housed macaques. For instance, pacing was displayed by 78% of singly-housed individuals in a large research colony (Lutz et al., 2003) and is also frequent in socially-housed caged macaques (personal observations). In contrast, pacing is nearly absent in macaques housed in large enclosures such as those

* Corresponding author at: Institute of Neuroscience, Newcastle University, Framlington Place, Newcastle-upon-Tyne, NE2 4HH, UK.
E-mail address: colline.poirier@ncl.ac.uk (C. Poirier).

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encountered in modern zoos and some breeding facilities (Pomerantz et al., 2013; Claire Witham, personal communication). Thus captivity alone does not explain pacing behaviour in macaques. Small cages differ from large enclosures not only in terms of space but also in terms of environmental and social complexity. Following from these differences, three alternative causes could explain pacing behaviour: pacing could be the consequence of stress, boredom or, based on the form of the behaviour, a need to walk.

2.1. Stress

2.1.1. Links between pacing and stress

In accordance with its use in the stereotypy literature, we use 'stress' in this review to mean the unpleasant emotional reaction resulting from the overstimulation of an individual (this definition allows us to distinguish stress from boredom, see Section 2.2). The initial idea that pacing behaviour displayed by macaques might be caused by stress comes from the multiple reports that pacing behaviour emerges for the first time soon after macaques raised in a social group (including their mother) are moved to a small, barren, individual cage for research purposes (Capitanio, 1986). The separation from previous social partners, the move to a new location, the space restriction and the absence of social partners are all potential sources of stress. The emergence of pacing behaviour when macaques are singly-housed for the first time could thus be a consequence of this stress.

Exposure to an unpleasant situation is known to increase pacing frequency. When confronted with a foreign macaque during an experimental session, single-housed individuals responded by pacing, cooing and pilo-erection (Mitchell et al., 1966). Placing a macaque in a transport box and then in an unfamiliar cage induced increased pacing and somersaulting compared to the frequency of these behaviours in the home cage just before the move (Mitchell and Gomber, 1976). The mere cue of an up-coming transient separation of cagemates (placing a transport box in front of the homecage) was also found to increase pacing frequency (Willott and McDaniel, 1974). The role of stress has been further demonstrated by the fact that injection with a high dose of the anxiogenic drug FG7142, which is known to produce unpleasant arousal in humans (Dorow et al., 1983), increased the frequency of pacing in macaques (Major et al., 2009). While all these studies link increased pacing behaviour with stress, one recent study provided inconsistent results. Peterson et al. (2017) used a classical test to induce fear and anxiety in macaques, the human intruder test. These authors found that the presence of an unknown human being in front of the home cage induced an increase in threatening and anxious behaviours, but a decrease in pacing behaviour. This study highlights the lack of a systematic association between stress and increased pacing behaviour.

An additional problem is the fact that all these studies lack the necessary controls to distinguish whether pacing is a specific response to negatively-valenced (i.e. unpleasant) events or whether it is a more general response to arousing events, irrespective of their valence. From a welfare point of view, this potential absence of specificity is important because it means that even if a new experimental/husbandry procedure induces an increase in pacing frequency, one cannot conclude that the procedure had a negative impact on the welfare of the individuals, since it might have been the source of a positively-valenced aroused state.

Furthermore, our own observations of macaques housed in big cages (15 m^3) furnished with several shelves, suggest that exposure to arousing events, independently of their valence, induces an increase in agitated locomotion rather than pacing (unpublished data). Agitated locomotion can be defined as 'moving rapidly between locations, often via jumps, with a stiff un-relaxed gait'. This behaviour differs from pacing in that it is much more flexible (the path can vary) and not necessarily repeated. However, it is possible that in small cages this behaviour appears stereotypic due to the lack of options in the paths individuals can walk, making it visually indistinguishable from true pacing. Interestingly, the literature cited above (Major et al., 2009; Mitchell and Gomber, 1976; Mitchell et al., 1966; Willott and McDaniel, 1974) comes from macaques housed in very small cages (below 1.3 m^3). It is thus possible that existing literature linking unpleasant events and pacing could be reinterpreted as showing a link between arousal and agitated locomotion. Whether pacing can be induced by stressful events might thus need to be revisited and the specificity of the response to negatively-valenced events needs to be established.

2.1.2. Coping mechanisms

In an attempt to further assess whether pacing is caused by stress, we now examine its possible function. Stereotypic behaviours observed in captive animals are not natural behaviours. As a consequence, they are unlikely to have been subjected to natural selection and do not necessarily have an adaptive function. If pacing in macaques is caused by stress, one possibility is thus that it has no function. In this case, pacing behaviour would represent a mere behavioural manifestation of stress (or of general arousal). However, an alternative hypothesis has been proposed (Mason, 1991a): some stereotypic behaviours might represent an active coping strategy to mitigate the damaging effects of stress. The mere repetition of some motor acts is known to be calming in humans. While the most common example is parents rocking their babies, people who pace have also reported the calming effect of this specific behaviour (see examples in Mason and Latham, 2004). Such a property would self-reinforce the behaviour, explaining its repetitive nature and would also explain why it increases in stressful situations: pacing might be an efficient way to cope with stress.

In the wild, macaques and other primates cope with stress using social behaviours (Cheney and Seyfarth, 2009; Gust et al., 1993; Schino et al., 1988; Young et al., 2014). Social behaviours are obviously absent in singly-caged macaques. It is thus possible that pacing replaces social behaviours as a coping mechanism in single housing. When pair-housed with another individual, macaques previously singly-caged displayed numerous social behaviours and performed abnormal behaviours less frequently (Baker et al., 2014, 2012; Doyle et al., 2008; Schapiro et al., 1996). Although results specific to pacing were not provided in these studies (data were pooled across any type of abnormal behaviours in Baker et al., 2014, 2012; Schapiro et al., 1996 and were restricted to locomotor stereotypies in Doyle et al., 2008), pacing was likely to be the main abnormal behaviour since individuals involved in these studies were raised with their mother or with peers and pacing is known to be the most frequent stereotypy displayed by this population of animals (Lutz et al., 2003). However, Doyle et al. (2008) reported that the decrease of locomotor stereotypies did not persist in time, despite a sustained increase of social behaviours. In the UK, pacing is also frequent in mother-raised macaques housed in pairs or in small groups of individuals with no history of single housing (personal observation). Together, these data indicate that single-housing is not the sole cause of pacing and suggest that pacing and social behaviours have distinct functions.

The coping hypothesis has been recently tested more directly in macaques using a corticosteroid approach (Pomerantz et al., 2012a). Acute stress in healthy subjects is known to activate the hypothalamic-pituitary-adrenal (HPA) axis, inducing a sharp increase of corticosteroids (cortisol in macaques) followed by a subsequent return to baseline when the source of stress disappears. When the source of stress persists, efficient coping behaviours allow the corticosteroid level to return rapidly to baseline levels. In the absence of any coping mechanisms, corticosteroid levels remain high for a prolonged period and can have detrimental effects on the health and well-being of an individual (e.g. loss of muscle mass, hypertension, immune and/or reproductive suppression, and even death) (Sapolsky et al., 2000). A behaviour is thus usually interpreted as an efficient coping mechanism if a high frequency of the behaviour is associated with a low level of corticosteroids, but as a mere manifestation of stress if a high frequency of the behaviour is associated with a high level of corticosteroids (e.g. Cheney and Seyfarth, 2009; Gust et al., 1993; Ninan et al., 1982; Watson et al.,

1999). Using such approach on macaque stereotypies, Pomerantz et al., (2012a) reported a negative correlation between self-directed stereotypies (mainly hair pulling) and cortisol levels, but not between locomotor stereotypies (mainly pacing) and cortisol levels. They concluded that self-directed stereotypies (but not locomotor ones) are an efficient coping mechanism. However, chronic unmitigated stress can end up blunting the sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in low basal corticosteroid levels and the absence of a corticosteroid increase after a stressful event (Fries et al., 2005; Heim et al., 2000). Therefore, an alternative interpretation of Pomerantz and colleagues' data is thus that the HPA axis of macaques displaying high levels of self-directed stereotypies has been compromised by previous intense and/or chronic stress, preventing cortisol from rising during the intruder test. Similarly, the absence of a correlation between locomotor stereotypies and cortisol levels could have several alternative explanations: (1) locomotor stereotypies might be unrelated to stress; (2) they might be a manifestation of stress, but the fact that some individuals have developed a blunted HPA axis sensitivity might have prevented the stereotypies from being positively correlated with cortisol levels; (3) locomotor stereotypies might be an efficient way to cope with stress, their frequency reflecting how much stress is experienced and coped with by an individual, resulting in a lack of association between the stereotypy and cortisol levels. Combined with the fact that a high level of corticosteroids can also be induced by positively-valenced arousing events (Otovic and Hutchinson, 2015; Ralph and Tilbrook, 2016), this analysis illustrates the difficulty of testing the coping hypothesis using a corticosteroid approach.

2.2. Boredom

In humans, boredom has been defined as a negative affective state resulting from the under-stimulation of an individual (Berlyne, 1960). Based on the hypothesis that this emotional state also exists in non-human animals, it has been suggested that stereotypies might be a mechanism for alleviating boredom (Mason and Latham, 2004; Wemelsfelder, 2005). Since living in a small cage is unlikely to provide the amount of stimulation a macaque experiences in the wild, it is possible that pacing is a form of self-stimulation.

Under this hypothesis, stimulation via cage enrichment is expected to prevent or at least reduce pacing behaviour. Physical enrichment with toys, foraging devices and mirrors have been tested many times in macaques (for a review, see Lutz and Novak, 2005): usually, pacing and other whole-body stereotypies initially decrease when the enrichment device is first introduced; however, with time, the interest of macaques wanes, the frequency of interaction with the item decreases and the amount of whole-body stereotypies re-increases (e.g. Novak et al., 1998). As mentioned above, social enrichment by housing macaques in pair after they have been previously singly-housed also tends to induce a decrease of abnormal behaviours while social affiliative behaviours increase (these studies did not distinguish different types of stereotypies) (Baker et al., 2014, 2012; Doyle et al., 2008; Schapiro et al., 1996). However, the decrease in abnormal behaviours may not persist in time despite a sustained increase in affiliative behaviours (Doyle et al., 2008), suggesting that the stereotypies do not simply replace social interactions as a source of stimulation in single-housed macaques.

In the previous experiments, despite physical and social enrichment attempts, individuals were still housed in a small and relatively barren environment. In the UK, several research settings have recently refurbished their macaque facilities, and macaques are now housed in pairs or in small social groups in relatively big cages (more than 8 m^3) and are provided with multiple physical enrichment elements (daily foraging opportunity, wooden shelves, swings, ropes, objects to manipulate changed on a regular basis and natural light). Despite these efforts, many macaques moving from the breeding centre to research laboratories still develop pacing behaviour soon after arrival. This indicates that either the available space and/or the enrichment are still insufficient, or that pacing is not exclusively caused by a lack of stimulation.

2.3. Need to walk

While the stress and the boredom hypotheses have been proposed to explain different types of stereotypic behaviours in various species, the walking hypothesis is specific to pacing behaviour since it is inspired by the form of the behaviour (repetitive walking along the same route). In small cages, the length and number of paths that a macaque can walk is much more limited than in large enclosures. Pacing behaviour could thus be a substitute for ranging, expressed when macaques are housed in a small space. This hypothesis comes from studies of pacing behaviour in carnivores. In this order, natural ranging behaviour of various species predicts pacing frequency in captivity (Clubb and Mason, 2003). A similar effect has been recently reported in primates: Pomerantz et al., (2013) found that the amount of pacing across different species of zoo-housed primates was positively correlated with the daily distance a species would travel in the wild.

Based on this hypothesis, one would expect pacing to disappear when macaques previously housed in small cages are moved to larger cages. However, earlier attempts to decrease pacing frequency in macaques by increasing the size of their cage have reported mixed results. Small changes in cage size (from 0.33 to 0.69 m3) have failed to show consistent changes (Line et al., 1990). Moving a single-housed macaque from a small cage (0.75 m3) to a very large one (261.3 m3) has been shown to completely suppress pacing and other stereotyped behaviours (Draper and Bernstein, 1963); however, observations were made for only 5 min after the move, preventing conclusions about the long-term effectiveness of such a manipulation. In another study, macaques were moved from a small (1.24 m3) to a relatively big cage (6.77 m3) and the short and long-term effect of the manipulation on whole-body stereotypies (including pacing but also flipping, bouncing and rocking) was investigated (Kaufman et al., 2004). During the first month following the cage move, the frequency of whole-body stereotypies did not change, while after 8 months in the bigger cage, it halved relative to before the move (note however that the difference was not statistically significant, possibly because of the very high inter-individual variability combined with a low number of subjects (n = 8)). It should be noted that these results were obtained from macaques with a long history of pacing. It has been suggested that once a stereotypic behaviour has become established, it can become a habit and for this reason be much more difficult to eliminate (Mason and Latham, 2004). This latter idea could potentially explain why a move to a larger cage does not systematically abolish pacing.

2.4. Damaged brain and abnormal perseveration tendency

Under the stress, boredom and walking hypotheses, the cause of pacing is constant during the lifetime of the individual (even if pacing has become a habit, it would still be mainly induced by its primary cause). However, another hypothesis that fully decouples the cause of stereotypy emergence (i.e. when it is displayed by an individual for the first time in its life) from its maintenance has also been proposed: the 'perseveration hypothesis' (Mason and Latham, 2004). Perseveration can be defined as "the continuation or recurrence of an … activity without the appropriate stimulus" (Sandson and Albert, 1987, 1984, cited in Mason and Latham, 2004). Under this hypothesis, the stress caused by a major traumatic event would damage the central nervous system, inducing abnormal perseveration tendencies. These abnormal perseveration tendencies would induce the abnormal repetition of a normal behaviour, and would explain the maintenance of the stereotyped behaviour over the whole life of an individual, even when the source of the original harm has disappeared. In the case of pacing macaques, the move from the breeding centre to research laboratories

and the associated loss of previous social partners could be the source of major stress that causes brain abnormalities and consequently pacing behaviour. After emergence, pacing would become mainly unrelated to the internal state or the external environment of the individual. This hypothesis could explain the afore-mentioned failures to abolish or even sustainably decrease pacing frequency in macaques.

2.4.1. Links between stereotypies and perseveration

Human beings suffering from various psychiatric disorders (schizophrenia, autism, Tourette syndrome, obsessive compulsive disorder) display abnormal repetitive behaviours. Perseveration tendency of these subjects measured in the lab has been consistently found to be correlated with the amount or severity of their abnormal repetitive behaviours in their everyday life (e.g. Frith and Done, 1983; Lucey et al., 1997; Turner, 1997). In various animal species, experimental paradigms have been developed to measure the perseveration tendency of individuals; here too, this tendency has been repeatedly found to be correlated with the frequency of stereotypies displayed by individuals in their home cage (e.g. Garner et al., 2003; Garner and Mason, 2002; Mcbride and Hemmings, 2005; Vickery et al., 2003).

2.4.2. Links between stereotypies/perseveration and basal ganglia abnormalities

The basal ganglia are cerebral structures playing a central role in the sequencing and execution of movements. They interact with other brain structures via loops (Fig. 1). One loop links the putamen (in the dorsal striatum) with the pre-motor and motor cortex (primary motor cortex and supplementary motor area) and supports automatic behaviour. A second loop links the caudate nucleus (in the dorsal striatum) with the ventro-medial pre-frontal cortex and is responsible for goal-directed behaviours (Balleine and Doherty, 2010). A third loop involved in the motivational control of movement links the nucleus accumbens (in the ventral striatum) to limbic structures (amygdala, hippocampus, anterior cingulate, medial orbitofrontal cortex).

Abundant evidence links abnormalities in cortico-basal ganglia loops and abnormal repetitive behaviours and perseveration tendencies. For instance, magnetic resonance imaging studies in human subjects suffering from trichotillomania (repetitive hair-pulling), fragile X syndrome (characterised by mental retardation and numerous stereotypies), Tourette's syndrome (characterised by repetitive motor tics), obsessive compulsive disorders and autism have revealed structural abnormalities in the basal ganglia and abnormal functional connectivity in the basal ganglia loops (Banca et al., 2015; Gothelf et al., 2008; Mahone et al., 2016; O'Sullivan et al., 1997; Sears Lonnie et al., 1999; Worbe et al., 2015, 2012). Lesions in ganglia loops can also induce abnormal perseveration in humans (Sandson and Albert, 1984). In other animal species, pharmacological studies have shown that injection of various drugs (including dopamine, glutamate receptor, GABA and opiate agonists) into the striatum and other basal ganglia nuclei can induce stereotypic behaviours (Bedingfield et al., 1997; Cools and van Rossum, 1970; Ernst and Smelik, 1966; Scheel-Kruger et al., 1978). Infusion in the striatum of a dopamine or glutamate receptor antagonists induced a dose-dependent reduction of spontaneous stereotypic jumping in mice without altering non-stereotypic motor behaviour (Presti et al., 2003). Decrease of rodent spontaneous stereotypies by environmental enrichment has also been shown to be mediated by structural and functional changes in the striatum (Bechard et al., 2016; Turner et al., 2003, 2002; Turner and Lewis, 2003). These findings indicate that basal ganglia are causally linked with pharmacologically-induced stereotypies but also with spontaneous stereotypies performed by some captive animals.

2.4.3. Links between basal ganglia abnormalities and stress

A possible link between stress and abnormalities in basal ganglia loops comes from rodent data (reviewed in Cabib, 2006). In rats and mice, aversive experience induces a release of dopamine in the pre-frontal cortex and/or the nucleus accumbens (in the ventral striatum), depending on the severity, the duration and the repetition of the stress stimulus (Puglisi-Allegra and Cabib, 1997). The dopamine release in the nucleus accumbens is down-regulated by the pre-frontal release of dopamine (McFarland and Kalivas, 2001). The repeated exposure to an unavoidable stressful stimulus induces an imbalance of the pre-frontal and nucleus accumbens dopamine releases (Cabib and Puglisi-Allegra, 1996, 1994; Imperato et al., 1993, 1992; Ventura et al., 2002). The direction of this imbalance depends on complex gene by environment interactions (Cabib et al., 2002; Cabib and Puglisi-Allegra, 1996; Ventura et al., 2002, 2001). An imbalance that favours the pre-frontal dopamine release has been linked to a depressive phenotype (helplessness, anhedonia) and a decreased sensitivity to stereotypy-inducing drugs; such imbalance can be restored by anti-depressant drugs (Karler et al., 1998; McFarland and Kalivas, 2001; Prasad et al., 1999; Ventura et al., 2002). An imbalance that favours the nucleus accumbens dopamine release is related to escape attempts, an increased sensitivity to stereotypy-inducing drugs and an increase of spontaneous stereotypies in the home cage (Alcaro et al., 2002; Cabib et al., 2002; Cabib and Bonaventura, 1997; Ventura et al., 2002). These neurobiological findings support the hypothesis that stereotypies and a depressive phenotype might be two alternative ways for individuals to respond to chronic stress (Fureix et al., 2016; Ijichi et al., 2013; Mason, 1991b).

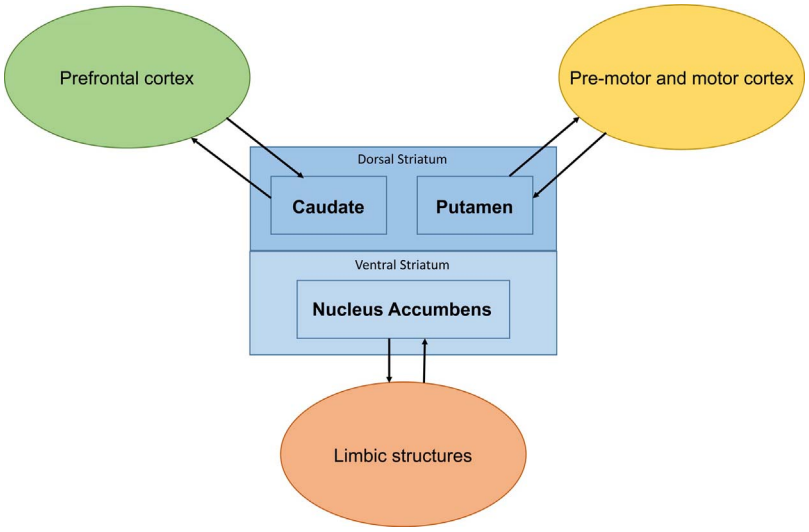

Fig. 1. Schematic representation of the different basal ganglia loops. The main basal ganglia structures are in blue.

2.4.4. Limitations of the 'basal ganglia hypothesis'

The above data show quite convincingly that chronic stress can provoke malfunction of the basal ganglia loops and that such malfunction can induce abnormal perseveration tendencies and stereotypies. However, they do not demonstrate that each stereotypy, in each species, is supported by such mechanisms. For instance, some stereotypies (route tracing) displayed by mice in their home cage have been found to be correlated with perseveration measures but others (barmouthing) have not (Novak et al., 2016).

In macaques, individuals raised in isolation have been shown to display numerous stereotypies (including pacing), to have many abnormalities in the basal ganglia and to be more perseverative than mother-raised individuals (Martin et al., 1991; Sánchez et al., 2001). However, studies of isolated macaques did not identify which aspect of the isolation paradigm was responsible for the numerous characteristics of the isolated individuals (other factors than stress could be responsible for the results) and did not distinguish the different stereotypies. Thus far there has been only a single attempt to determine if different types of spontaneous stereotypies are linked to basal ganglia abnormalities and perseverative tendency in macaques (Pomerantz et al., 2012a). Integrity of basal ganglia function was assessed behaviourally by the time taken by individuals to extinguish a learned response that had been made unrewarding (perseveration tendency measure). In this study, fine motor (mainly cage bar biting/licking) and self-directed (mainly hair pulling) stereotypies, but not whole-body (mainly pacing) stereotypies were found to be positively correlated with the number of trials necessary to extinguish the acquired behaviour. While this negative result suggests that pacing in macaques is not related to basal ganglia abnormalities, it should be interpreted with caution. Previous work on carnivores has shown that the strength of the relationship between perseveration and stereotypies depends on the precise task used to quantify perseveration (Campbell et al., 2013). Moreover, perseveration tasks only represent an indirect way to assess the normality of the basal ganglia loops and it has been suggested that extinction tasks, as used in the macaque study, only assess abnormality of one of the three basal ganglia loops (the prefrontal one) (Langen et al., 2011). The brain damage hypothesis thus requires further testing via direct neurobiological assessment of the integrity of the basal ganglia loops.

2.5. Potential origins of inter-individual variability in pacing

Among individuals housed in a similar environment, a significant proportion of macaques do not pace (Lutz et al., 2003). In paired-housed macaques, it is not uncommon to see only one member of the pair pace (personal observation). Among pacing macaques, the frequency of the stereotyped behaviour also varies between individuals. Do some potential causes better explain this inter-individual variability than others?

Using an epidemiological approach, several groups have tried to identify the risk factors associated with stereotypies in macaques (Gottlieb et al., 2015, 2013; Lutz et al., 2003; Vandeleest et al., 2011). While one of these studies provided results specific for pacing (Lutz et al., 2003), the others grouped several motor stereotypies together. However, as pacing was the most frequent stereotypy, these results are possibly valid for pacing behaviour. The general picture emerging from these studies supports the hypothesis that pacing/motor stereotypies are caused by stress. For instance, the number or frequency of likely-to-be-stressful procedures experienced by an individual (blood draws, research projects, room moves) were found to be a risk factor for developing stereotypies. Rearing conditions was also found to be a risk factor in one of these studies: macaques raised in sub-optimal conditions displayed more motor stereotypies when subsequently cage-housed than macaques raised in more naturalistic conditions (Gottlieb et al., 2013). This result is interesting since numerous data suggest that early-life adversity can decrease stress resilience of primates (reviewed in Parker and Maestripieri, 2011). Gottlieb and colleagues (Gottlieb et al., 2013) also found an additional effect of personality, determined when macaques were 3–4 months old: macaques characterised by an active personality when young displayed more motor stereotypies when adult. We cannot exclude the possibility that the behavioural needs of an individual with an active personality are more difficult to fulfil in a small cage than those of an individual with a less active personality, inducing more stress in the former. However, this latter result fits rather well with the walking and boredom hypotheses: an active personality could explain a higher need to walk or a higher susceptibility to boredom in these individuals.

Unfortunately, all the epidemiological data come from macaques housed in small cages where pacing behaviour might have potentially been confounded with agitated locomotion (see Section 2.1.1). Future epidemiological studies where pacing and agitated locomotion can be disambiguated are necessary to shed light on the cause of these two behaviours.

2.6. Conclusions on causes of pacing

This section illustrates our lack of understanding of the causal factor or factors responsible for pacing behaviour in macaques. We have described four possible explanations for pacing that are compatible with the experimental evidence. While we have presented these hypotheses as alternatives, they are not necessarily mutually exclusive, and we cannot exclude the possibility that pacing is caused by a combination of causal factors. In the next section, we discuss the welfare and biomedical implications of the different hypotheses. To limit the complexity of the discussion, we only consider the potential implications of each alternative explanation, under the parsimonious hypothesis that pacing has one single cause.

3. Implications of pacing

3.1. Welfare implications

Can pacing be interpreted as a sign of poor welfare in pacing macaques? We argue that without knowing the cause(s) of pacing behaviour and why some individuals pace while others exposed to the same environment do not, it is impossible to answer this question. Table 1 summarizes the different possibilities.

If pacing is a manifestation of stress, pacing macaques are likely to have poor welfare and pacing might be a useful indicator of what is perceived as stressful by macaques. However, the welfare of non-pacers under this hypothesis is more difficult to interpret (Mason and Latham, 2004). They might not be stressed because they are stress-resilient individuals, or alternatively they might be 'depressed'. Indeed, as mentioned earlier, stress-induced imbalance of dopamine release in the prefrontal cortex and the ventral striatum can lead to stereotypies or alternatively to depressive behaviour in rodents (Cabib, 2006). A depressive phenotype characterised by frequent inactivity, withdrawn symptoms and a hunched posture has also been described in several species of macaques (Hennessy et al., 2014; Willard et al., 2014) and can be induced experimentally by repeated social stress (Perera et al., 2011). It has been suggested that this depressive behaviour is more

Table 1
Welfare implications (compromised versus uncompromised welfare) of presence and absence of pacing behaviour according to the different alternative hypotheses for pacing.

Hypothesis	Pacers	Non-pacers
Manifestation of stress	compromised	?
Efficient way to cope with stress	uncompromised	?
High need to walk/boredom	?	uncompromised
Abnormal brain/perseveration	?	uncompromised

noticeable when human beings are absent and might require video recordings to be detected (Hennessy et al., 2014). It would be useful to know whether this depressive behaviour is displayed at different frequencies by pacing and non-pacing individuals.

If pacing is an efficient way to cope with stress, the welfare of pacers is unlikely to be compromised (note that if pacing is only partially efficient for coping with stress, then it becomes equivalent to a manifestation of stress). However, here again, the welfare of individuals that do not pace is unclear. They might not experience stress (stress-resilient individuals) or experience it and cope with it using a different strategy. In these two cases, their welfare is unlikely to be compromised. Alternatively, non-pacers could experience stress and not cope with it, in which case their welfare would be compromised. This last hypothesis comes from a meta-analysis examining the prevalence of stereotypies in a range of species (Mason and Latham, 2004). This analysis revealed that stereotypies are more likely to occur in environments known to induce poor welfare, but that within these environments, individuals displaying stereotypies are usually those whose welfare was the least compromised. Whether this is the case for pacing behaviour in rhesus macaques is unknown.

If pacing is caused by a particularly high need to walk in particularly active individuals or a high need to do anything in individuals particularly prone to boredom, then the subsequent question is 'does pacing fulfil this need?' If not, animals might be frustrated as a result of incompletely satisfied motivational state. To answer this question, data linking pacing behaviour in macaques and independent assessment of the individuals' affective states are necessary. However, due to its form (repetitive walking), the behaviour is likely to fulfil at least partially these needs and as a consequence the welfare of pacers is unlikely to be severely compromised. Under the walking and boredom hypotheses, the absence of pacing in some individuals would reflect a less active personality (Gottlieb et al., 2013). The welfare of non-pacers would thus not be compromised.

Finally, if pacing is caused by a past traumatic event that induced brain damage and hence abnormal perseveration tendencies, the welfare consequence of these impairments is unclear. On the one hand, humans beings displaying numerous stereotypies have reported to either not be aware of them or to enjoy them (Mason and Latham, 2004). On the other hand, impaired inhibitory control of behaviour might be a source of frustration. Non-pacers are likely to be stress-resilient individuals in which case their welfare is unlikely to be compromised.

3.2. Biomedical implications

Distinguishing between the different potential causes of pacing is crucial from a biomedical research perspective. Pacing is displayed by the vast majority of singly-housed macaques and by a significant proportion of pair-housed macaques, these two types of housing (single and pair) being by far the most common ways to keep macaques in research laboratories across the world. If pacing is due to an acute major stressor having caused brain damage resulting in abnormal perseveration, such macaques are unlikely to be adequate models of the healthy human brain and the validity of some research findings built on data collected in such individuals might potentially be compromised. Limiting neuroscience experiments to individuals that do not pace is also problematic since under this hypothesis, non-pacers are likely to represent a sub-population of stress-resilient individuals. Focusing on this sub-population could compromise the generalizability of the results to stress-sensitive human beings.

If pacing is a manifestation of stress and if the welfare of pacing macaques is severely compromised, pacing individuals are unlikely to be good model of a healthy human brain either. Stress is known to affect the mammalian brain at multiple levels, from molecular mechanisms to the functional network of brain regions, from sensory to highly cognitive processes (McEwen et al., 2015; Teicher et al., 2016). Effects of stress are not limited to the brain but extend to other body parts as well as to the behaviour of stressed individuals (McEwen, 1998). Under the hypothesis that pacing is a manifestation of stress, pacing macaques are therefore unlikely to be suitable experimental models in any biomedical domain (except when one is interested in the effect of stress). Furthermore, as discussed in the previous section, it is unclear whether non-pacing macaques are unstressed or 'depressed'. If they are depressed they are unlikely to be suitable experimental subjects either, except as animal models of depression. If non-pacers are unstressed, they are likely to represent a sub-population of stress-resilient individuals, since they have been exposed to the same stressful conditions as pacing macaques. The implications in terms of generalizability of data coming from these specific individuals would thus be similar to that under the previous hypothesis that pacing is due to brain damage.

If pacing is an efficient way to cope with stress, and non-pacers do not experience stress or cope with stress in a different way, data from pacers and non-pacers are likely to be valid models of healthy human beings (who commonly experience stress in their every-day life). If non-pacers are individuals that experience stress but do not cope with it, this sub-population is unlikely to be a valid model.

Finally, if pacing reflects a high need to walk or boredom, it is likely to fulfil at least partially this role, and even if the need is not completely fulfilled, the welfare impact of consequent frustration is likely to be moderate. In this case, data coming from pacing and non-pacing macaques are likely to be representative of various levels of frustration/well-being in the healthy human population.

The biomedical implications of pacing behaviour also depend on methodological aspects of the research performed on macaques. Neuroscience research involving macaques usually reports data from a very small number of subject (2–3). One of two alternative strategies is used: either data from the different individuals are pooled and average results are reported and interpreted, or results from each individual are reported and only common results between individuals are interpreted. Considering the high prevalence of pacing behaviour, the majority of neuroscience studies are likely to have reported results from pacing macaques. If an averaging strategy was used, results are likely to be (partially) biased by the ones coming from the pacing subject(s). In the individual-subject approach (no averaging), results should not be biased by pacing if at least one experimental subject was not pacing.

4. General conclusions

This review illustrates how little we know about the causal factors underlying pacing and whether this behaviour has an adaptive function or not. While it is a possibility that pacing is a reliable indicator of poor welfare in individuals displaying the behaviour, there are at least three alternative hypotheses: (1) pacing might be unrelated to current stress (while agitated locomotion would be); (2) pacing might be a non-specific sign of high arousal, preventing us from distinguishing the valence of the emotional state of pacing individuals (stress versus excitement); (3) pacing might be an efficient way to cope with stress.

This review has highlighted the difficulty of measuring stress and more generally affective states in non-verbal animals and the limitations of the approaches currently used by welfare researchers. One way to tackle this problem might be to use approaches developed by other fields such as epidemiology (Gottlieb et al., 2013; Lutz et al., 2003), cognitive psychology (Bethell et al., 2012; Paul et al., 2005; Pomerantz et al., 2012b) and/or neurobiological studies of stress (Cabib, 2006; Shively and Willard, 2012). Considering the prevalence of pacing behaviour among macaques used as models of the healthy human brain and the risk that this behaviour might be the sign of an abnormal brain, neuroscientists might be interested in collaborating with welfare researchers to answer these questions. From an applied science perspective, we conclude that pacing should not currently be used as a reliable sign of poor welfare in pacing individuals. Additional sources of evidence pertaining to the affective states of pacers and non-pacers are

required in order to use pacing as a welfare indicator. However, based on the possibility that pacing could indicate that some individuals are suffering, the mere presence of this behaviour in a macaque colony should motivate further studies to ensure that the welfare of the pacing and non-pacing animals is not severely compromised.

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