Abstract

Stereotypies that develop spontaneously in nonhuman primates can provide an effective model for repetitive stereotyped behavior in people with neurodevelopmental or obsessive-compulsive disorders. The behaviors are similar in form, are similarly affected by environmental conditions, and are improved with similar treatment methods such as enrichment, training, and drug therapy. However, because of a greater number of commonalities in these factors, nonhuman primates may serve as a better model for stereotyped behavior in individuals with autism or intellectual disability than for compulsions in individuals with obsessive-compulsive disorder. Because animal models may not be exact in all features of the disorder being studied, it is important to investigate the strengths and weaknesses of using a nonhuman primate model for stereotyped behavior in people with psychological disorders.

Key Words: autism; neurodevelopmental disorders; model; nonhuman primate; obsessive-compulsive disorder; stereotypies

Introduction

Stereotypies

Stereotypies can be defined as repetitive, unvarying, and seemingly functionless behavior patterns that are reported to occur in a variety of species (Mason 1991). They are a heterogeneous group of behaviors that vary in form, frequency, and situation and include behaviors such as pacing, rearing, and head twirling in mink (Mason 1993a); stereotyped walking and swimming bouts in polar bears (Wechsler 1991); repetitive jumping in bank voles (Cooper and Nicol 1991); crib-biting and weaving in horses (Dallaire 1993); chain chewing in pigs (Dantzer 1986; Wiepkema and Schouten 1992); self-clasping, rocking, eye poking, and pacing in nonhuman primates (Capitanio 1986; Erwin and Deni 1979); and rocking, eye poking, and hair twirling in humans (Berkson and Davenport 1962; Forehand and Baumeister 1971a; Foster 1998). These behaviors often lack variability in response to environmental change, and in humans, they tend to be inappropriate relative to general developmental level (Berkson 1983). Stereotypies also vary in causal factors, whether induced by environmental conditions, drug administration, or psychiatric disorders (Mason 1993b). In some cases, stereotypies may have resulted from the associated pain or discomfort of clinical disorders. In other cases, they may have resulted from psychopathological disorders or poor rearing conditions (Novak et al. 2012). Determining whether or not a behavior is a stereotypy can be difficult. Often there is a continuum between stereotypies and normal behavior patterns; stereotypies may be incorporated into normal behavior patterns, and many normal behavior patterns are stereotyped. Therefore, in some cases drawing a line between normal and abnormal behavior can be arbitrary (Mason 1993b).

Nonhuman Primate Model for the Human Condition

Stereotypies that develop spontaneously in animal populations can serve as valuable models for behavioral disorders in humans; they provide additional tools for investigating the physiological, developmental, and environmental impact on the behavior. Nonhuman primates are an especially valuable model for behavioral disorders in the human population, because, unlike rodent models, nonhuman primates have a prolonged developmental period, higher cognitive processing, complex social interactions, a more diversified behavioral repertoire, and they share a closer evolutionary history. In this regard, captive nonhuman primates with abnormal stereotyped behaviors may serve as a potential model for humans with psychiatric or neurodevelopmental disorders who display similar behaviors. Although the form of the behavior may not necessarily be equivalent across species, it is reasonable to consider that similar mechanisms may be involved (Ridley and Baker 1982). However, animal models are useful only to the extent that they generalize to the human condition being studied (Suomi 1986). To be effective, an animal model should include, among other criteria, face validity (e.g., similarity in behavioral output), construct validity (e.g., similarity in cause or origin), and predictive validity...
Assessing Behavior in Human and Nonhuman Primates

Behavior can be assessed in a number of ways in both human and nonhuman primates, ranging from direct report to behavioral assessment and physiological measures. However, the method of choice depends both on the question being asked and on the capabilities of the individual. One method of assessing behavior in human research is by self-report of individuals or groups, which allows the person to give a direct account of internal states (Diener et al. 2003; Miguel et al. 1995). However, results from self-report may be potentially problematic because the subject might not be able to correctly identify internal states or may intentionally give an incorrect response (Brune M. et al. 2006). In cases where individuals are not capable of providing a self-report, information can also be obtained from family, friends, or caregivers (Diener et al. 2003; Fisher et al. 1997; Wieseler et al. 1985) or by direct observation of behavior (Berkson and Davenport 1962; Forehand and Baumeister 1970). Additionally, physiological measures can be used to study internal states associated with stereotyped behavior. For example, heart rate was measured in school children during stereotypical leg-swinging (Soussignan and Koch 1985) and in severely mentally handicapped children during complex repetitive hand movements (Young and Clements 1979). Measures of cortisol were also collected from plasma in a study of patients at a developmental center who exhibited stereotyped behavior (Sandman et al. 1990). Because direct self-report measures are not possible in many human subjects, such alternative methods can be informative when assessing behavior.

Using animal models for studying behavior in humans can have some challenges, in part because mental states are difficult to measure or verify. Although self-report cannot be used with nonhuman primates, cognitive bias testing, a relatively novel form of assessing the internal state of an animal, is a potential measure (Mendl et al. 2009). In a study of 16 capuchin monkeys, those displaying high levels of stereotypic head twirls exhibited negative cognitive bias, whereas pacing was not correlated with cognitive bias, suggesting that some behaviors may be more indicative of the animal’s affective state than others (Pomerantz et al. 2012). Additionally, investigators often rely on ratings obtained from individuals familiar with the animals (Stevenson-Hinde and Zunz 1978) or by direct observation. Behavioral assessments, which involve observation and data collection by trained human observers, are routinely conducted at primate facilities. These assessments often help to identify individuals exhibiting stereotypies (Baker et al. 2007; Lutz et al. 2003; Vandeleest et al. 2011) or to assess the impact of interventions on abnormal behavior (Baker et al. 2009; Novak et al. 1998). As with humans, physiological measures can also be used in nonhuman primates to study internal states associated with stereotyped behavior. For example, heart rate was measured in rhesus macaques to assess self-biting behavior (Marinus et al. 1999), and fecal cortisol was measured in capuchin monkeys to test the association between stereotypies and stress (Pomerantz et al. 2012). Because self-report measures are not possible in nonhuman primates, alternative methods are necessary when assessing behavior.

Stereotypies in Nonhuman Primates

Stereotypies have been observed in a variety of nonhuman primate species, including prosimians (Tarou et al. 2005), New World monkeys (Berkson et al. 1966), Old World monkeys (Goosen 1981; Lutz et al. 2003; Mitchell 1968; Vandeleest et al. 2011), and apes (Berkson and Mason 1964a; Davenport and Menzel 1963; Nash et al. 1999; Pazol and Bloomsmith, 1993). These stereotypes can take a variety of forms, including both whole-body and self-directed movements. Whole-body stereotypes may include behaviors such as pacing, bouncing, rocking, flipping, and swinging (Davenport and Menzel 1963; Lutz et al. 2003; Pazol and Bloomsmith 1993; Vandeleest et al. 2011), whereas self-directed or fine-motor stereotypes may include behaviors such as eye poking, digit sucking, hair pulling, and self-grasping (Davenport and Menzel 1963; Lutz et al. 2003). In some studies, stereotypes have been experimentally induced through procedures such as drug administration (Levin et al. 1990; Scraggs and Ridley 1978), lesioning (Bauman et al. 2008; Malkova et al. 1997), or restrictive rearing practices (Harlow and Harlow 1962a, 1962b). However, these behaviors are also reported to occur spontaneously in animals socially housed in zoos (Bollen and Novak 2000; Marriner and Drickamer 1994), as well as in mother-reared laboratory animals (Lutz et al. 2003). In one survey of 108 zoos, 14% of the primates were reported to exhibit some form of abnormal behavior, with apes exhibiting the highest percentage (40%), followed by Old World monkeys (14%), New World monkeys (6%), and prosimians (7%) (Bollen and Novak 2000). In a similar survey conducted at the St. Louis Zoological Park, eight species of zoo primates exhibited stereotyped behaviors such as pacing, rocking, twirling, saluting, coprophagy, urophagy, and regurgitation (Marriner and Drickamer 1994). Studies of abnormal behavior in laboratory primates have reported that as high as 89–100% of singly housed macaques exhibited some form of abnormal behavior (Bayne, Dexter, Suomi 1992; Camus et al. 2013; Lutz et al. 2003), and more than 25% were reported to exhibit motor stereotypes such as pacing (Lutz et al. 2003; Vandeleest et al. 2011). Abnormal stereotypic behavior can be considered pathological in nonhuman
primates if it occupies a substantial portion of the animal’s time budget, interferes with biological functions, or induces tissue damage (Bayne and Novak 1998).

Alternatively, displacement behaviors are relatively benign repetitive behaviors that occur normally in nonhuman primate populations and consist mostly of self-directed activities such as scratching, self-grooming, yawning, and body-shaking (Maestripieri et al. 1992). These behavior patterns often occur in situations where they would not be expected, and they are often associated with uncertainty and anxiety (Troisi 2002). For example, low-ranking Japanese macaques (Macaca fuscata) were more likely to scratch than their high-ranking counterparts (Troi et al. 1991), and socially housed chimpanzees responded to neighbor vocalizations with an increase in scratching and yawning (Baker and Aureli 1997). Similarly, the rate of self-grooming in long-tailed macaques (Macaca fascicularis) increased when female macaques were within one meter of the dominant male macaque. This was interpreted as a conflict situation; the female macaques were attracted to the male, but at the same time, they risked attack. Therefore, the self-grooming may have been used as a displacement activity (Troisi and Schino 1987).

**Stereotypies in Human Primates**

Many human stereotypies are similar to those exhibited by nonhuman primates in terms of motor output such as rocking (Beckett et al. 2002; Mitchell and Etches 1977), pacing (Walsh 1994), and digit sucking (Foster 1998; Ozturk and Ozturk 1977; Troster et al. 1991). However, there are also clear species differences in the form and expression of some stereotyped activities. Although both human and nonhuman primates can show idiosyncratic abnormal activities, these activities are typically more complex in people (Goosen 1981). Such complex stereotyes may include rocking while flicking the hand in front of the face or rubbing a finger against the thumb of the same hand (Hutt et al. 1965), hair twirling (Foster 1998; Rago and Case 1978), repetitive manipulation of objects (Troster et al. 1991), and complex hand movements (Young and Clements 1979).

**Stereotypies in the General Human Population**

Stereotypies can and do occur in the general human population. In some cases, the sequence of the development of stereotypies parallels the sequence in motor development (Wolff 1967). For example, infants exhibit rhythmical stereotypies such as rhythmical kicking, rocking, bouncing, and arm waving during their first year of development, and this tends to occur on a standard developmental trajectory (Thelen 1979). In a sample of more than 470 children, 19.1% were reported to rock and 6.3% were reported to head roll, often when alone in the crib or playpen (Sallustro and Atwell 1978), and 5–15% of infants were reported to exhibit head banging behavior (de Lissovoy 1961; Sallustro and Atwell 1978). Digit sucking is another example of a developmental stereotypy, which is reported to occur in normal children who were weaned from the breast early, schedule-fed, and/or left alone to fall asleep (Ozturk and Ozturk 1977). Although stereotypies such as head banging, digit sucking, and rocking tend to decline as the infant gets older (Werry et al. 1983), some behaviors such as digit sucking can continue into early childhood (Foster 1998).

As with nonhuman primates, humans also exhibit displacement behaviors that can occur in potentially stressful situations where they would otherwise not be expected. Such behaviors can consist of self-directed activities such as self-touching, scratching, and self-grooming (Troisi, 2002). For example, hair and face manipulation, as well as foot and leg rocking, were reported in college students participating in a psychology study and in the classroom (Rago and Case 1978; Woods and Miltenberger 1996), and stereotypic leg swinging was observed in school children during passive and active learning situations (Soussignan and Koch 1985). Motor stereotypies such as finger, foot, or forehead tapping were also reported in dental patients sitting in a waiting room (Barash 1974), a situation that may also be considered stressful. Because such stereotypical patterns of behavior in the normal population tend to occur on a normal developmental trajectory, do not interfere with normal interactions or behaviors, and do not cause the individual distress, they will not be the focus of this article.

**Stereotypies in People with Neurodevelopmental or Obsessive-Compulsive Disorders**

Although stereotypies do occur in the general population, these abnormal repetitive behaviors are more pronounced and disruptive in individuals with neurodevelopmental or psychiatric disorders such as autism, intellectual disabilities, and obsessive-compulsive disorder (OCD). Repetitive behaviors associated with these disorders can be organized into two classifications that may consist of separate and distinct symptoms: lower-order motor movements, such as stereotypies or repetitive manipulation of objects, and higher-order behaviors, such as rituals, preoccupations with aspects of the environment, or compulsions that result from irresistible impulses to perform a seemingly irrational act with the aim of preventing or reducing anxiety or distress (Lewis et al. 2007; Turner 1997; Turner 1999).

**Autism**

Autism is a neurodevelopmental disorder whose central features include impaired social interaction and communication as well as stereotyped patterns of behavior (American Psychiatric Association 2013). In one study of 32 adults with autism, all of the subjects exhibited at least one form of stereotypy (Bodfish et al. 2000). Motor stereotypies such as head banging, body rocking, and hand flicking are common stereotyped patterns of behavior in autistic individuals (Prior and Macmillan 1973). The stereotypic behavior is often
different across autistic individuals, and each individual may have a preferred or characteristic pattern, such as rocking while flicking the hand in front of the face, rubbing a finger against the thumb of the same hand, rapidly rotating the hands, repetitively shrugging the shoulder, or bouncing on the feet (Hutt et al. 1965). Compulsive behaviors have also been reported in this population. In a study of 32 adults with autism, 94% displayed at least one compulsive behavior (Bodfish et al. 2000) such as checking; counting; hoarding; the need to touch, tap, or rub; and self-injurious behavior (McDougle et al. 1995).

Intellectual Disability

Diagnostic criteria for intellectual disability include below-average intellectual functioning along with deficits in the ability to be independent and handle common demands in life when compared with others of a similar age and background (i.e., adaptive functioning) (American Psychiatric Association 2013). Although stereotypic behaviors are not diagnostic criteria, they are commonly associated with this disorder; stereotypies tend to be negatively associated with IQ (Ando and Yoshimura 1978). In a residential institution for adults with learning disability, 57% of residents with a mild learning disability and 63% of residents with a severe disability exhibited some form of stereotypy (Walsh 1994). Similarly, in a study of 210 residents of a facility for individuals with intellectual disability, 60.9% were reported to exhibit stereotypies (Bodfish et al. 1995). Examples of stereotyped behaviors in this population include swaying, rocking, twirling, eye poking, shaking, nodding, head rolling, head banging, and pill rolling (Berkson and Davenport 1962; Mitchell and Etches 1977). The most common stereotypies exhibited by adults with learning disabilities include body rocking, hand motions, pacing, and rubbing/scratching (Walsh 1994). Compulsions have also been reported to occur in this population. In one study, 40% of intellectually disabled residents exhibited compulsive behaviors such as ordering (e.g., arranging objects), closing doors, and hand washing (Bodfish et al. 1995).

Obsessive-Compulsive Disorder

OCD is a disorder in which the individual has obsessions or persistent thoughts, images, or urges that cause anxiety and compulsions or repetitive acts that aim to reduce the anxiety. The obsessions or compulsions cause marked distress (American Psychiatric Association 2013), and the individuals generally recognize their symptoms as senseless and often struggle to stop performing the compulsive rituals (Zohar and Insel 1987). Such compulsive acts in OCD may include cleaning/washing, checking, and repetitive rituals (Miguel et al. 1995).

Cause or Origin of Repetitive Behavior

Inadequate Rearing

An inadequate rearing environment has consistently been shown to adversely affect stereotypical behavior in nonhuman primates. This association has been studied extensively in macaques and chimpanzees. Early research by Harlow and Harlow (1962a, 1962b) demonstrated the intense, negative impact of isolation rearing on infant rhesus macaques. Macaques and chimpanzees reared in isolation exhibited high levels of stereotyped behaviors such as rocking, swaying, and digit sucking (Davenport and Menzel 1963; Mitchell 1968), often within the first month of life (Baysinger et al. 1972). Stereotypies in isolation-reared rhesus macaques were significantly greater than those exhibited by control animals that had been reared with their mother and peers (Lewis et al. 1990). Even infant rhesus macaques reared in partial isolation, where they could see and hear, but not touch, other monkeys, displayed stereotypic behaviors such as self-sucking, rocking, self-clutching, and pacing (Cross and Harlow 1965; Suomi et al. 1971). In contrast, macaques reared in the wild and later individually housed did not exhibit rocking behavior (Suomi et al. 1971). Stereotypies often continue in the behavioral repertoire as the animal grows older. For example, after leaving the nursery and being housed in a social group, nursery- and peer-reared rhesus macaques showed higher levels of stereotypy than did mother-reared animals (Feng et al. 2011). Stereotypic behaviors associated with nursery rearing in macaques include motor stereotypies (e.g., pacing, swinging, flipping, rocking, and bouncing) (Gottlieb, Capitanio, McCowan 2013), digit sucking (Lutz et al. 2003), and self-directed abnormal behavior (e.g., self-clasping, eye poking, self-sucking, repetitive cage licking, and feces smearing) (Bellanca and Crockett 2002). Similarly, hand-reared chimpanzees showed significantly more rocking and self-sucking behaviors than did mother-reared animals (Nash et al. 1999), and in two surveys of zoo primates, past rearing history (i.e., hand-rearing) had a greater impact on stereotypies than present environmental conditions (Bollen and Novak 2000; Marriner and Drickamer 1994).

Studies regarding restrictive rearing or housing in human infants and children are typically retrospective, based on situations where the individuals were placed in an orphanage or in a residential institution. As with nonhuman primates, human infants restrictively reared in impoverished facilities also developed stereotypies. For example, before adoption, up to 84% of children who spent time in a Romanian orphanage exhibited stereotyped behaviors such as rocking or repetitive hand movements (Beckett et al. 2002; Fisher et al. 1997; Hoksbergen et al. 2005). Those placed in foster care showed significantly lower levels of stereotypies, and the reduction was greatest in those with earlier or longer placement in foster care (Bos et al. 2010).

Environmental Restriction Later in Life

Low stimulus input later in life can also foster the development or expression of stereotypies. For individuals experiencing an inadequate environment lacking in stimulation, stereotypies may impart some benefit and function as a
form of “do-it-yourself enrichment,” helping to improve well-being in a suboptimal environment (Mason and Latham 2004). In rhesus macaques, stereotypies have been associated with environmental restriction such as single housing (Lutz et al. 2003; Gottlieb, Capitanio, McCowan 2013); those housed singly exhibited more repetitive locomotion, stereotypy, and self-directed behavior than did monkeys housed in social groups (Bayne, Dexter, Suomi 1992). Similarly, chimpanzees removed from their social group and placed in individual cages also showed an increase in stereotyped behaviors (Brent et al. 1989). Single housing at an early age or for an extended period of time were shown to be risk factors for stereotyped behaviors such as pacing, flipping, eye poking, hair pulling, and self-grasping (Lutz et al. 2003; Vandeleest et al. 2011), and singly housed rhesus macaques expressed 1.34 times as much motor stereotypy as did pair-housed animals (Gottlieb, Capitanio, McCowan 2013). Simply being housed in an indoor environment is also associated with stereotypies (Gottlieb, Capitanio, McCowan 2013). For example, six chimpanzees showed higher levels of repetitive stereotypy (e.g., rocking or swaying) when placed in a small enclosed cage than when housed in their outdoor home cage. When manipulable objects were provided, the occurrence of stereotyped behaviors (e.g., abnormal limb postures, eye poking, and thumb sucking) was reduced. In this example, both general arousal and the ability to perform alternative activities had an impact on the performance of stereotyped behaviors (Berkson et al. 1963).

As with nonhuman primates, an environment lacking sensory input can also result in increased stereotyped behavior in individuals with neurodevelopmental disorders. For example, stereotypes were positively correlated with age and time in an institution (Berkson and Davenport 1962), and in a study of 60 adult residents of a state hospital who exhibited stereotypical behavior, 92% of the staff ranked self-stimulation as the most common consequence of their behavior (Wieseler et al. 1985). In two studies of individuals with intellectual disabilities, one with 14 adult men and one with 55 children, stereotypes increased when the subjects were placed in a restricted environment such as an empty room or a crib and decreased when they were placed in a less-restrictive environment with opportunities for locomotion and manipulation (Berkson and Mason 1963; Warren and Burns 1970). Similarly, the behavior of 12 intellectually disabled subjects was recorded in two situations: when they were located in a 6 × 6 foot chamber and when they were housed in a residential ward. The six subjects with a higher IQ (mean = 26) exhibited significantly more stereotyped rocking while in the chamber setting. However, in the six subjects with a lower IQ (untestable range), there was no effect of location on rocking. These results suggest that subjects with a higher IQ were more responsive to their environment (Forehand and Baumeister 1971a). The impact of environment on behavior was further demonstrated in a study of 46 children with intellectual disabilities. Those that lived in an institution (n = 23) were compared with children living at home but on a waiting list for institutionalization (n = 23) to reduce the variability between the two populations. Stereotyped and self-stimulating behaviors (e.g., head rolling, hand waving, and hand mouthing) were greater in the institutionalized population than the population living at home. In contrast, the home population exhibited greater social behavior (Kaufman 1967). Environmental restrictions also occur intrinsically in autistic and intellectually disabled children because they are less interactive with the environment and/or receive less environmental stimulation (Prior and Macmillan,1973; Walsh 1994). This intrinsic form of restriction may also have led to stereotypies in these populations.

Environmental Overstimulation

Stereotypies may also be used as a mechanism to maintain homeostasis in an overstimulating environment. This theory is centered on the idea that there is an optimal level of stimulation. If there are deviations in either direction from the optimal level, the individual will compensate behaviorally to regulate the stimulation (Zentall and Zentall 1983). Therefore, stereotypic rhythmic patterns may be, in part, a homeostatic response to environmental stimuli (Guess and Carr 1991). Because stereotypies are highly predictable, such repetitive activities may help to reduce anxiety (Baron-Cohen 1989) or to reduce awareness of environmental stimuli. For example, autistic children who were taught to respond to a signal that produced a reward were slower to respond when they were exhibiting stereotypical behavior (Lovaa and Simmons 1967), and human infants were less responsive to tickling when they were repetitively sucking on a pacifier than when they had no pacifier in their mouth (Wolff and Simmons 1967).

Stereotypies may therefore serve as an arousal-reducing response to situations of frustration or aversive stimuli. For example, when chimpanzees were exposed to white noise, a buzzer, or a stimulus object that rocked and produced a grinding noise, they responded with an increase in repetitive stereotyped movement such as rocking or swaying (Berkson et al. 1963; Berkson and Mason 1964a). The rocking or swaying increased as the decibels of the white noise increased, with the highest rates occurring with the buzzer sound (Berkson and Mason 1964a). Common husbandry events such as feeding, sedations, and location changes may also be stressful and have an impact on stereotypies. For example, macaques exhibited motor stereotypes such as pacing, swinging, and bouncing before feeding. When the feeding time was made predictable, the subjects were less likely to perform stereotypes (Gottlieb, Coleman, McCowan 2013). When feeding time was delayed, the stereotyped behavioral patterns were prolonged (Watt and Buchanan-Smith 2001). Similarly, the risk of displaying motor stereotypes in rhesus macaques significantly increased with the number of sedations and blood draws (Lutz et al. 2003; Vandeleest et al. 2011), and motor stereotypy in rhesus macaques increased by 3% for each relocation to a new room (Gottlieb, Capitanio, McCowan 2013). When events such as routine husbandry activities were predictable, levels of stereotypies were decreased (Gottlieb, Coleman, McCowan 2013).
This relationship between stereotypies and environmentally induced anxiety, frustration, or stimulation has also been demonstrated in people with neurodevelopmental and obsessive-compulsive disorders. For example, in a study of six autistic children, levels of stereotypy (e.g., rocking, head shaking) increased as the environment increased in complexity, from an empty room, to a box of wooden blocks placed in the room, to the addition of an adult sitting passively in the room. In this example, stereotypies may have helped reduce levels of arousal as the environment increased in complexity (Hutt and Hutt 1965; Hutt et al. 1965). In intellectually disabled individuals, frustration of goal-directed behavior (e.g., lever pressing) (Forehand and Baumeister 1971b) and noise (Forehand and Baumeister 1970; Levitt and Kaufman 1965) resulted in increased stereotyped behaviors, with the behavior increasing as the noise level increased (Levitt and Kaufman 1965). Anxiety is also commonly associated with OCD (Abramowitz and Arch 2014; O’Connor et al. 2006); almost 90% of subjects with OCD reported anxiety before their compulsive behavior or when the behavior was prevented (Miguel et al. 1995).

### Treatment

#### Environmental Enrichment

Improving environmental conditions is one way in which stereotypies can be reduced in both human and nonhuman primates. For example, infant nursery-reared rhesus monkeys exhibited lower levels of stereotypy when they had stimulation from a mobile surrogate than when they were provided with a stationary surrogate (Mason and Berkson 1975). Providing even more stimulation in the form of a canine companion also resulted in a reduction of stereotyped rocking in a group of 17 chimpanzee infants (Pazol and Bloomsmith 1993). In older animals, additional environmental enhancements such as foraging opportunities can also promote an improvement in behavior. For example, the provisioning of straw, food puzzles, and forage materials reduced abnormal behavior in chimpanzees and rhesus macaques (Baker 1997; Bayne, Dexter, Mainzer, et al. 1992; Bloomsmith et al. 1988); as foraging increased, abnormal behaviors, including stereotypies, decreased (Bayne, Dexter, Mainzer, et al. 1992). Even simple chew toys placed in the cage resulted in reduced levels of abnormal behavior such as feces painting, hair pulling, and pacing (Brent and Belik 1997; Kessel and Brent 1998).

In addition to the contents of the cage, cage location and cage size can also have an impact on stereotyped behavior. For example, a greater proportion of life lived outdoors significantly decreased the risk of motor stereotypies in rhesus macaques (Vandeleest et al. 2011), and motor stereotypy decreased by 20% for every year that an animal spent outdoors (Gottlieb, Capitanio, McCowan 2013). Increased cage size also reduced stereotyped locomotion in rhesus macaques (Draper and Bernstein 1963; Paulk et al. 1977); however, this did not occur in all situations (Bayne and McCully 1989; Kaufman et al. 2004; Line et al. 1990), suggesting that a single environmental change may not always be sufficient.

Social housing may be considered to be the best form of environmental enrichment for nonhuman primates; social interactions routinely vary, and they are less likely to produce habituation than inanimate forms of enrichment. For example, group-housed squirrel monkeys exhibited less stereotyped behavior than did their singly housed counterparts (Spring et al. 1997), and rhesus macaques group-housed in corn cribs exhibited significantly less repetitive locomotion, stereotypy, and self-directed behavior than did singly housed animals (Bayne, Dexter, Suomi 1992). Similarly, when singly housed baboons were moved to outdoor social groups, levels of abnormal behavior, including eye poking, flipping, and pacing, were reduced (Kessel and Brent 2001), and reductions in abnormal behavior were also observed when rhesus macaques were placed into compatible social pairs (Baker et al. 2012; Eaton et al. 1994).

As with nonhuman primates, environmental enrichment also reduced stereotyped behavior in both children and adults with autism and intellectual disabilities. For example, complex hand movements in intellectually disabled children decreased when the environment was enriched with play materials such as puzzles, dolls, and animals (Young and Clements 1979), and when institutionalized intellectually disabled adults were presented with pictures to look at or objects to manipulate, allowing for an alternate activity, they showed reduced levels of stereotypies (Berkson and Mason 1964b; Forehand and Baumeister 1970). Outdoor access also resulted in reduced levels of stereotypies in intellectually disabled adults; in the outdoor environment, levels of stereotypy decreased while locomotion increased (Berkson and Mason 1963). Similarly, when 13 autistic children were provided with multiple sensorimotor stimuli, including olfactory enrichment, music enrichment, and exposure to different textures and toys, they showed a significant reduction in autism severity scores in comparison with the control group that did not receive the enrichment, and there was also a significant increase in the number of parents reporting an improvement in autism symptoms (Woo and Leon 2013). In addition, when two autistic children were provided free access to toys, they showed a reduction in stereotyped scratching (Sidener et al. 2005). These results demonstrate that environmental changes or improvements can have a positive impact on resulting behavior across species.

#### Behavioral Treatment and Training

Behavioral treatment and training can also be effective in reducing stereotyped and repetitive behaviors. In the human population, functional assessment methods have been used to identify environmental variables that reinforce or maintain stereotypies in order to devise procedures to reduce the behavior (Bloomsmith et al. 2007). Sensory extinction is a behavioral method that involves eliminating the relationship between a behavior and its sensory outcome (Rapp and
et al. 1999; Rapp et al. 2000). Sensory extinction was also sustained by automatic reinforcement and sensory stimulation. Providing gloves for them to wear reduced the sensory stimulation as well as the hair pulling and manipulation (Rapp et al. 1999; Rapp et al. 2000). Sensory extinction was also used to reduce stereotypic vocalizations produced by two autistic children. In comparison with baseline (earphones alone), earphones plus white noise to mask the sounds of stereotypic vocalizations resulted in a decrease in the vocalizations (Aiken and Salzberg 1984). An alternative training procedure, differential reinforcement of other behavior, is a strategy in which reinforcement is provided when the target behavior has not occurred during a specified period of time. This method was used both in the classroom setting and in individual sessions to reduce repetitive behavior exhibited by intellectually disabled children. In this paradigm, the children were rewarded with praise, candy, or tokens if they did not exhibit a given stereotyped behavior during a predetermined interval. If the behavior was exhibited, the timer was reset for that interval. Results showed a decrease in repetitive behavior, suggesting that training with differential reinforcement of other behavior is an effective means of reducing stereotyped behavior (Repp et al. 1976). Another method of reducing abnormal behavior is with noncontingent reinforcement, the delivery of a reinforcer on a schedule that is independent of the behavior. This procedure was used with three individuals who exhibited abnormal behavior, two diagnosed with intellectual disability and one diagnosed with autism. The reinforcers were provided on a fixed-time schedule and consisted of access to a bucket of toys and attention from the staff. In all three cases, the aberrant behavior was reduced to near-zero levels (Britton et al. 2000). Cognitive behavioral therapy is a form of training that is often used for individuals with OCD. With this training, a person is repeatedly exposed to the stimulus that makes him or her anxious or uncomfortable and then is trained to resist the urge to carry out the responding compulsion and to wait for the resulting anxiety to subside. In a study of children aged 7 to 17 years with OCD, the use of cognitive behavioral therapy in conjunction with medication resulted in a significant improvement in their obsessive-compulsive scale score when compared with medication alone (Franklin et al. 2011), and in a similar study of adult participants with OCD, those receiving cognitive behavioral therapy showed a clinically significant treatment effect in contrast with those receiving medication alone (O’Connor et al. 2006). However, even though this treatment method is effective, some patients may experience a relapse (Abramowitz and Arch 2014).

As with human subjects, training has also been effective in reducing stereotyped behaviors in nonhuman primates. Although a functional analysis approach may be effective in treating stereotyped behaviors in individual primates, it can be time-consuming and not cost-effective for larger numbers of animals. Instead, nonhuman primates are often trained through positive reinforcement to cooperate with husbandry procedures or to perform behaviors that are incompatible with the stereotyped behavior. Training involving behaviors such as holding a target, stationing, or presenting body parts has resulted in decreased levels of abnormal and stereotyped behavior in rhesus macaques, baboons, and chimpanzees (Baker et al. 2009; Bourgeois and Brent 2005; Coleman and Maier 2010; Pomerantz and Terkel 2009). In a study of 12 chimpanzees trained to hold targets and present body parts, this decrease was observed throughout the day, even outside of the training sessions (Pomerantz and Terkel 2009). In a larger study of 63 rhesus macaques, positive reinforcement training resulted in an overall reduction in stereotyped abnormal behavior, but the reduction occurred only in the animals that exhibited the highest levels of abnormal behavior (Baker et al. 2009). Therefore, positive reinforcement training focusing on husbandry-related or incompatible behaviors can help to reduce stereotyped behaviors in nonhuman primates, but the training may be more effective in some individuals than in others.

Drug Therapy

Altered brain functioning has been associated with the development and expression of stereotypies in both human and nonhuman primates. Pharmacological studies have linked dopaminergic, serotoninergic, and opioid systems to stereotypic behavior, leading to treatment options for nonhuman primates and for individuals with psychiatric and neurodevelopmental disorders.

Dopamine

Dopamine is a neurochemical that has been associated with stereotypical behavior in both human and nonhuman primates. Dopamine and dopamine agonists have been demonstrated to induce stereotypies, whereas blocking dopamine receptors with antagonists decreased stereotypies (Lanovaz 2011). In a study of 24 adult residents of a state developmental center who had severe or profound mental retardation, the 12 subjects who exhibited stereotyped behavior had significantly lower levels of homovanillic acid, a dopamine metabolite, than those who did not stereotype (Lewis et al. 1996). In addition, the administration of amphetamine or the dopamine agonist apomorphine resulted in increased levels of stereotyped behavior (Koizumi 1985; Kramer et al. 1967), and the administration of cocaine, a serotonin-norepinephrine-dopamine reuptake inhibitor caused repetitive involuntary movements (Daras et al. 1994). Cocaine addiction, as well as dopaminergic treatment, has also resulted in repetitive behavior known as “punding,” a stereotyped behavior characterized by complex, non-goal-oriented, repetitive activities (Fasano et al. 2008; Spencer et al. 2011). Dopamine antagonists have been used as a treatment to reduce stereotypical
behavior in individuals with neurodevelopmental disabilities. For example, chlorpromazine reduced rocking in subjects with severe mental retardation (Aman et al. 1984), haloperidol was reported to reduce stereotypies in autistic children in two double-blind studies (Campbell et al. 1978; Cohen et al. 1980), and thioridazine clinically (but not statistically) reduced stereotypies in a group of 20 severely mentally retarded patients (Singh and Aman 1981).

As with humans, in nonhuman primates, the administration of amphetamine or the dopamine agonist apomorphine resulted in increased levels of stereotyped behavior. This has been reported to occur in monkeys (Levin et al. 1990; Lewis et al. 1990; Sams-Dodd and Newman 1997; Schlemmer et al. 1980; Scrapps and Ridley 1978) and chimpanzees (Berkson and Mason 1964a), and the behavioral response can persist, even when it seems unlikely that any drug remains in the system (Castner and Goldman-Rakic 1999). Similarly, cocaine caused repetitive stereotypies such as head swinging and whole body rocking and swinging in squirrel monkeys (Saka and Mason 1987). Dopamine antagonists have also been utilized as a treatment to reduce stereotypical behavior in nonhuman primates. For example, chlorpromazine reduced abnormal behavior in four rhesus monkeys reared in partial isolation. When treated, three of the four monkeys showed a significant reduction in self-disturbance behaviors (e.g., self-mouth, self-bite, self-clasp, huddle, rock, and stereotypy) (McKinney et al. 1973). These results demonstrate an association between dopamine and stereotypical behavior in nonhuman primates and in humans with autism or intellectual disability.

Serotonin

Serotonin is a neurotransmitter that is also implicated in repetitive behaviors. For example, in child and adolescent subjects with autism, those with the long allele (L group) of the serotonin transporter gene promoter polymorphism (5-HTTLPR) showed increased severity in stereotyped and repetitive mannerisms when compared with those with the short allele (S group) (Brune CW et al. 2006). Serotonin has also been implicated in repetitive behaviors associated with OCD. When subjects were given metachlorophenylpoperazine, a serotoninergic agonist, the OCD symptoms were exacerbated (Hollander et al. 1992; Zohar and Insel 1987; Zohar et al. 1987). In addition, in a double-blind study of 24 hospitalized patients with OCD, there was a significant correlation between 5-HIAA (a serotonin metabolite) level in cerebrospinal fluid and improvement of obsessional symptoms scores (Thoren et al. 1980). Serotonin has been further implicated in in studies using drug therapy to reduce stereotypies. For example, fluoxetine, a selective serotonin reuptake inhibitor, was tested on a group of 39 children with autism spectrum disorder in a double-blind placebo crossover study. Fluoxetine administration resulted in a significant reduction in repetitive behaviors and a clinically meaningful, although not statistically significant, effect on global autism symptoms (Hollander et al. 2005). Fluvoxamine, a selective serotonin uptake inhibitor, was also tested on thirty adults with autistic disorder in a 12-week double-blind placebo-controlled study; by week 8, a significant reduction in repetitive behaviors was reported (McDougle et al. 1996). Similarly, clomipramine, a 5-HT uptake inhibitor, reduced body and object stereotypy in adults with intellectual disabilities (Lewis et al. 1995) and decreased obsessive-compulsive ratings in children and adolescents with OCD (Leonard et al. 1989). In these studies, however, the ratings used to determine improvement in OCD symptoms largely measure distress and the ability to control the symptoms (Hollander et al. 1992) or obsessions with thoughts or ideas (Leonard et al. 1989; Zohar et al. 1987), conditions that cannot easily be modeled in an animal population.

In nonhuman primates, fluoxetine was tested on a group of captive vervet monkeys exhibiting stereotypic behavior such as head-tossing, weaving, somersaulting, and saluting. By week 6, the group receiving fluoxetine exhibited significantly fewer stereotypies than did the “no treatment” group (Hugo et al. 2003). However, this effect has not been reported in all studies (Fontenot et al. 2009).

Opiates

One theory of the opiate hypothesis is that repetitive abnormal behavior is associated with a release of β-endorphin that reinforces the behavior (Sandman et al. 1990). In adult human patients with intellectual disabilities, the plasma concentration of β-endorphin was significantly higher in the groups with self-injurious and stereotypic behaviors when compared with the control group that exhibited neither types of behavior (Sandman et al. 1990). As a treatment, naltrexone, a long-acting opioid antagonist, was demonstrated to improve behavior and reduce stereotypies in subjects with autism or intellectual disabilities. In two open-trial studies of naltrexone on children with autism, the autistic score, which includes stereotypical behavior, significantly improved (Campbell et al. 1988; Panksepp and Lensing 1991). Similarly, in a placebo-controlled study of six children with autism, the administration of naltrexone resulted in an improvement of the social interaction and stereotyped behavior score (Williams et al. 2001). Naltrexone was also used to treat two subjects diagnosed with profound mental retardation and autistic disorder in an ABAB-designed study; in this case, treatment significantly reduced stereotyped body rocking (Smith et al. 1995). These results support the theory that stereotyped behavior stimulates the release of endorphins, which may function as positive reinforcement (Smith et al. 1995). However, not all studies support the opiate hypothesis regarding stereotyped behavior (Boďif and Kolmen et al. 1995; Willemsen-Swinkels et al. 1995a; Willemsen-Swinkels et al. 1995b), suggesting that there may be individual differences in responsiveness to naltrexone.

In nonhuman primates, a positive relationship between intact plasma beta endorphin and severity of abnormal behavior has been reported in pig-tailed and long-tailed macaques (Crockett et al. 2007). However, opioid antagonists such as naloxone have not yet been examined as treatments for stereotypies.
Conclusions

Nonhuman primates exhibiting stereotyped behaviors may serve as excellent models for humans with neurodevelopmental or obsessive-compulsive disorders. Although stereotypic behavior includes a diverse range of repetitive behaviors, there are important similarities between stereotypies displayed by nonhuman primates and their human counterparts. For example, the form of the behavior is similar; both human and nonhuman primates exhibit repetitive behaviors such as motor stereotypies and self-directed behaviors. Additional similarities are noted with respect to the cause or origin of the behavior (e.g., environmental restriction or overstimulation) and the types of interventions, whether enrichment, training, or drug therapy (see Table 1 for a summary). However, because of a greater number of commonalities in these factors, nonhuman primates may serve as a better model for the stereotyped behaviors in autism and intellectual disability than for the compulsions in OCD. Because no animal model is exact in all aspects of the condition being studied, it is important to further investigate the use of nonhuman primates in the study of neuropsychiatric and developmental disorders in the human population.

Acknowledgments

This work was supported by Grant R24OD01180–15 to Melinda Novak at Harvard Medical School and P51OD011133 to Texas Biomedical Research Institute (SNPRC).

References


