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Review

Neotic preferences in laboratory rodents: Issues, assessment and substrates

Robert N. Hughes*

Department of Psychology, University of Canterbury, Ilam Road, Private Bag 4800, Christchurch 8020, New Zealand

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Abstract

Neotic preference refers to the extent to which animals prefer stimuli of differing novelty value. Degree of novelty is determined by within- and between-trials habituation and amount of temporal (novelty) and spatial change (complexity) in stimulation which in turn will determine the amount of curiosity-based approach (neophilia) or fear-based avoidance (neophobia) of novel stimuli. Tests of genuine neotic preferences enable direct assessments of responsiveness to temporal and spatial changes and include measurements of novel versus familiar locations (such as novelty-related location preferences), responsiveness to stimulus complexity (such as object exploration) and learning for exploratory rewards (such as light-contingent bar-pressing). Effects of brain lesions and peripherally administered drugs have implicated several brain areas and neurotransmitters that subserve memory, fear and reward in neotic preferences namely the hippocampus and ACh (memory), the amygdala, GABA and 5-HT (fear), and the mesolimbic DA reward system. However, more attention should be paid to the complexity of interactions between different brain and neurotransmitter systems and improvements in methodology before conclusions should be drawn about the neurobiological basis of neotic preferences.

Keywords: Neotic preference; Novelty; Location preferences; Stimulus complexity; Exploratory rewards; Memory; Hippocampus; ACh; Fear; Amygdala; GABA; 5-HT; Brain reward; Mesolimbic DA system; Rats; Mice

Contents

*Tel.: +64 3 364 2879; fax: +64 3 364 2181.
E-mail address: rob.hughes@canterbury.ac.nz.

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1. Introduction

"Neotic" preference (Corey, 1978) refers to active choices of stimuli in terms of their novelty value. Novelty requires that at least two options are available when a choice is made and involves selection of either a novel or a less novel ("familiar") option. A third possibility is a significant preference for neither novelty nor familiarity, which could reflect a decrease in responsiveness to either. A tendency to choose a more novel option is often referred to as "neophilia" (Cowan, 1977) whereas choice of the more familiar has generally become known as "neophobia" (Barnett, 1958). A preference for neither could thus arise from either reduced neophilia, or elevated neophobia (but not to the point where novelty is primarily avoided).

Tests of neotic preference have become increasingly popular as ways of assessing drug and brain lesion effects on underlying behavioral and associated neurobiological processes in laboratory rats and mice, and some other species. To a large extent, this is due to the fact that they are quick, relatively simple and cheap to apply, compared with procedures that involve training. Because learning is not required, they also avoid the need to electrically shock or deprive animals of food or water and thus avoid possible confounding effects of drugs or lesions on performance or motivational states that are not directly related to the behavioral processes under investigation. Being examples of "unconditioned behavior", most tests of neotic preference discourage to a lesser extent responses that are incidental to the behavior of principle interest than tests of "conditioned behavior" or learning, and thus enable detection of reactions to drugs and other influences that might ordinarily go unnoticed (Maxwell, 1971). In more recent times they have become especially favored in the study of anxiety or fear (Kelley, 1993), and memory (Ennaceur and Delacour, 1988).

The aim of the present paper is to re-acquaint readers with the origin of interest in neotic preference, some of the issues that surround it, and to provide an account of some of the ways it has been measured in the most commonly used laboratory animals, namely rats and mice. Particular attention will be paid to earlier research and ideas that are still important for modern interests and approaches to the investigation of neotic preferences, but for which awareness is not always evident in many more recent studies. There will also be a brief discussion of some possible neurobiological substrates for the behavior as suggested from selected studies of brain lesion and drug effects. It is not intended to provide an exhaustive account of the many research reports relevant to each section of this paper as there are already a number of excellent reviews on record which will be referred to when appropriate. Rather, representative examples will be provided that hopefully illustrate the points to be made.

2. Novelty

It has long been recognized that "novelty" is not a quality of stimuli per se and "cannot be distinguished (from other stimuli) by physicochemical properties" (Berlyne, 1960, p. 20), but is an expression that refers to "an interaction between stimulus and perceiver" (Dember, 1960, p. 348) with respect to an organism's past experiences with the stimuli in question. Unlike objectively measurable qualities such as brightness, shape and texture of stimuli, novelty is defined in terms of the extent to which stimuli have been previously experienced and is specific to individuals. To provide novelty for an experimental subject indicates that, as far as can be ascertained, the subject has not encountered the identical situation immediately beforehand. While this can be relatively easily determined for laboratory animals, it is much more difficult to do so for feral species in their normal environments, or for human beings. Amount or degree of novelty will depend on the extent to which the situation differs from what has been previously experienced, which in turn will depend on such factors as the time between successive exposures to the situation, the duration of each prior exposure, and the number of prior exposures. It is therefore apparent that reference to a novel stimulus implies a description of an

organism's past interactions with that particular stimulus. These interactions provide a store of neural information with which new stimuli are compared, and any discrepancies that occur will determine precisely how the stimulus is reacted to in order to reduce such discrepancies (Bardo et al., 1996). Consequently, it is clear that memory is essential for recognizing novel stimuli.

2.1. Habituation to novelty

Organisms' interactions with their environment determine the extent to which stimuli lose their novelty value through the process of habituation which is the decremental responsiveness that occurs as a result of repeated stimulation (Harris, 1943) and is often regarded as a primitive form of non-associative learning (Thorpe, 1956). Complex responses, such as active choices of novel stimuli, habituate more rapidly and take longer to spontaneously recover in the absence of eliciting stimuli than simpler orienting or reflexive responses, probably because of differences in numbers of association neurons intervening between stimuli and responses (Thompson and Spencer, 1966). In the case of habituation to novelty, decrements in responsiveness to novel stimuli occur as a function of the number of exposures to and time in contact with them.

Even though they have sometimes been viewed as having a common substrate (Carlton, 1969), there is evidence of differences between habituation to novelty and habituation of a reflexive response (such as the acoustic startle reflex) in terms of their ontogeny (Williams et al., 1975), and neural and neurochemical substrates (Corey, 1978; Hughes, 1984; Williams and Hamilton, 1974). For example, acoustic startle appears to be mediated by mechanisms operated by a number of transmitters (including glutamate and serotonin, 5-HT) in the lower brainstem, especially the pontine reticular nucleus (Koch, 1999), whereas habituation to novelty probably involves mainly cholinergic activity in the hippocampus (Douglas, 1975; Thiel et al., 1998) along with input from the frontal cortex (Cohen et al., 2002). It therefore seems likely that habituation to novelty and habituation of reflexive responses are not identical phenomena.

Habituation to novelty can occur both within testing sessions and between them. For example, the tendency for rats to choose the more novel of two T- or Y-maze arms on successive occasions (spontaneous alternation behavior) declines with successive alternation opportunities (Richman et al., 1987). While habituation of motor activity emitted in a novel open field may occur during trials and between successive daily trials (Walsh and Cummins, 1976), without any way of distinguishing between responsiveness to component stimuli of differing novelty, it is difficult to decide if the observed activity declines are genuine changes in neotic preference alone (see Section 3 later in this paper). However, when such distinctions are possible, neotic preferences are determined by the operation of habituation to novelty that occurred prior to testing (thereby enabling distinctions to be made between currently familiar and novel stimuli), and also by habituation that occurs during testing, thus leading to a within-session decline in interest in novel stimuli. (For a recent comprehensive review of habituation in rodents, see Leussis and Bolivar, 2006.)

When habituation of an orienting or reflexive response has occurred, reappearance of the response will follow presentation of a novel stimulus (Thompson and Spencer, 1966). Although this phenomenon, known as "dishabituation" (Gray, 1975), was originally viewed as a special case of "sensitization" whereby a novel or intense stimulus can facilitate a non-habituated response, it now seems likely that they are separate processes (Marcus et al., 1988). At the behavioral level, dishabituation involves reappearance of the original response whereas sensitization produces a more intense response than the original. The tendency for rats that have been habituated to an explored stimulus to then subsequently investigate a novel stimulus presented in the same environment has been referred to as "dishabituation" (e.g., Singh, 2001). References to dishabituation apply particularly to studies of odor discrimination (Brown, 1988; Schellinck et al., 1995). While strictly speaking such terminology may be appropriate especially with activity (rather than choice) measures of responsiveness to novel stimulation (Aoyama and McSweeney, 2001; Terry, 1979), in the case of active choices of novel stimuli it is debatable if it is more informative than merely describing them as investigation of novelty, particularly since habituation (and presumably dishabituation) of neotic behavior may be a different phenomenon from habituation of orienting or reflexive responses (see above).

2.2. Changes in stimulation

Central to the term "novelty" is the idea that some type of change in stimulation has occurred between successive experiences. However, change can also be an inherent quality of certain forms of stimulation encountered during a single experience. This was recognized by Dember and Earl (1957) when they coined the terms "temporal" and "spatial" changes in stimulation. Temporal changes were seen as involving a discrepancy between one exposure to a stimulus and another, and encompassed what is usually referred to as novelty. The authors stressed that a temporal change would only arouse attention (and subsequent behavior) if it provided a discrepancy between what the subject expects to observe and what actually is observed. A particularly notable example of this is "surprisingness" (Berlyne, 1960) whereby, in addition to arousing attention, a discrepancy between what is expected and what is observed can generate intense emotion, such as the excitement or even fear displayed by chimpanzees when confronted with the model of a severed human or chimpanzee head (Hebb, 1949, p. 243). On the other hand, Dember and Earl (1957) said that spatial changes resulted from spatial dishomogeneity or discontinuity within a

stimulus array and included the concept of stimulus "complexity" as well as certain other "collative variables", (such as incongruity) described by Berlyne (1960, 1963). Complexity refers to the degree of variation or diversity within a stimulus pattern which is determined by the "number of distinguishable elements" and "dissimilarity between elements" (Berlyne, 1960, p. 38). However, since perception of the spatial changes in such a pattern implies sensory scanning of its elements, this is equivalent to movement of the stimulus over time and is thus psychologically equivalent to temporal changes in stimulation (Dember and Earl, 1957). It therefore follows that choices of stimuli on the basis of their complexity characteristics effectively register neotic preferences.

2.3. Approach and avoidance of novelty

Responsiveness to novel stimuli can be in the form of approach (neophilia) or avoidance (neophobia) depending on the degree of novelty generated (Barnett, 1958; Berlyne, 1950). In other words, intense novelty may elicit avoidance whereas mild novelty elicits approach (Welker, 1961). Montgomery (1955) recognized that novel stimuli can evoke fear as well as curiosity thereby causing an approach-avoidance conflict. In fact, at one time, it was proposed that fear was the common reason for both approach and avoidance of novelty, namely high fear led to avoidance, but low fear led to approach (Halliday, 1966; Lester, 1967b). However, there is little conclusive evidence for this point of view (Russell, 1973, 1983). In most situations, the extent of avoidance and approach would obviously depend on the degree of novelty generated by the stimuli encountered. It is therefore likely that a curvilinear relationship exists between increasing conflict and decreasing novelty (see Fig. 1) which would ultimately determine whether approach or avoidance mainly prevailed.

Little conflict should occur with either maximum or minimum novelty as neophobia would accompany the former, whereas indifference to the stimuli would be associated with the latter. Neophilia would occur somewhere between the two extremes of conflict presumably at the point where approach sufficiently outweighed avoidance. The sequence of avoidance, approach and then disinterest is generally accepted for most neotic behavior (Corey, 1978). Some authors have suggested that positions adopted on a neophobia–neophilia scale might be used for drawing distinctions between different species in levels of curiosity (Glickman and Sroges, 1966) and foraging specialization (Day et al., 2003) as well as intra-species individual differences in the magnitude of a neophobia-related glucocorticoid response to novelty that might negatively impact on rats' life expectancy (Cavigelli and McClintock, 2003).

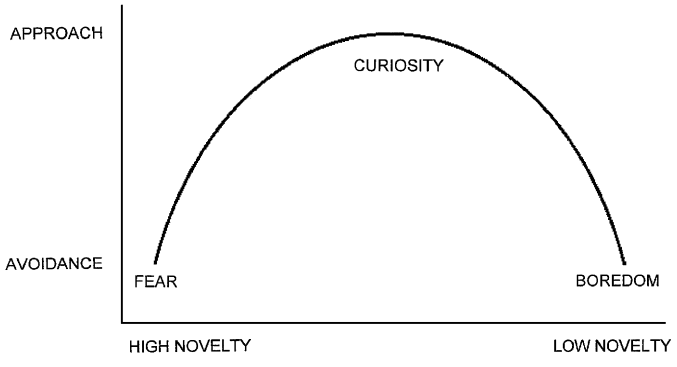

Fig. 1. Possible relationship between decreasing novelty and avoidance or approach of novel stimuli as determined by fear, curiosity or "boredom".

The extent of approach and avoidance that occurs in response to the presence of a novel stimulus can also depend on the degree of novelty of the context in which the stimulus appears. For example, Cowan (1974) reported that feral rats would not avoid a novel object in an unfamiliar environment, but would avoid the same object if it appeared in a familiar environment. Similar observations have been made with other feral species (Harris and Knowlton, 2001). Hebb (1949) had also earlier noted that greater fear was generated for chimpanzees when confronted with situations that combined novel and familiar stimuli. To some extent observations such as these might be due to there being less opportunity to retreat from a novel object to a familiar area when the context is also novel (Corey, 1978). However, contrary to feral animals, laboratory rats have been shown to show preferences for novel objects in familiar but not unfamiliar environments (Besheer and Bevins, 2000; Sheldon, 1969). Conversely, the novelty of experiencing a familiar stimulus in an unfamiliar environment can produce a more intense response than the environment on its own. This was demonstrated by Hennessey et al. (1977) when they showed that increases in plasma corticosterone were greater in rats presented with a familiar tone in an unfamiliar environment than when either the tone was first presented, or when the environment was encountered without the tone. Obviously the novelty of the context in which a novel or a familiar stimulus is experienced can determine the level of sympathetic arousal, as well as the extent of avoidance and approach.

As an aside, "fear" and "anxiety" are often treated as equivalent in rodent tests of neotic preference. A distinction between the two for mice has been suggested by Belzung and Griebel (2001) who equated fear with "normal" or "state anxiety" that arises from experience with aversive novel stimuli. They distinguished this from "pathological" or "trait" anxiety which they ascribed to the particular genetic strain of the species. However, for the remainder of this review, the term "fear" will be preferred to "anxiety". This is because, while fear is an adaptive response to an unconditioned threat (such as an unfamiliar environment), anxiety represents an "abnormal" emotional response to the learned threat of a stimulus which, on its own, may be quite harmless. According to this terminology, unless there are conditioned fear stimuli present, most

neophobic responses will be determined by fear, rather than anxiety.

3. The assessment of neotic preference

By involving active, preferential choices, neotic preference is distinguished from the practice of imposing unavoidable novel stimulation on experimental subjects. Neotic preference is thus particularly relevant to the study of curiosity-motivated or intrinsic exploration in non-human animals since it potentially enables more accurate assessments of investigation of novel stimuli for their own sake by allowing subjects to freely choose between novel and familiar environments or stimuli. (For reviews of exploration see Archer and Birke, 1983; Corey, 1978; Fowler, 1965; Hughes, 1997; Renner, 1990). Such curiosity has been described as "diversive" (Berlyne, 1954) and comprises the general novelty seeking that will occur in response to insufficient variation in stimulation, or boredom (Loewenstein, 1994), in contrast to "specific" curiosity that involves the search for specific information, such as the solution of puzzle. However, it is conceivable that, although approach of a novel stimulus might appear to be an example of intrinsically motivated diversive exploration, it could at times be directed towards some specific extrinsic goal. For example, if a rat prefers to visit the more novel of two T-maze arms on the second of two successive trials, rather than curiosity, this behavior could reflect an attempt to find an escape route that could not be found on the first trial (Hughes, 1997).

Exploratory tasks involving neotic preference comprise "free" tests of exploration (Welker, 1957) based on "relative novelty" (Hennessey and Levine, 1979) and contrast with "forced" tests (Welker, 1957) whereby subjects are thrust into an unfamiliar environment characterized by "absolute novelty" (Hennessey and Levine, 1979), such as an open field, from which there is no retreat. Consequently, it is more difficult to determine if activity-based "exploratory responses" such as ambulation, rearing and sniffing that typify most rodent tests of forced exploration arise from curiosity alone, or are extrinsically motivated by some other influence such as fear and associated attempts to escape (Hughes, 1997), or food-seeking. In addition, there is evidence that experiencing inescapable novelty is more stressful (Hennessy et al., 1979) than novelty that can be freely chosen (Misslin et al., 1982). However, even though choices of novel versus familiar environments or stimuli may appear to be more valid reflections of curiosity than activity emitted in forced tests, there is no guarantee that extrinsically derived motives are not the reasons for the choice behavior observed. As mentioned above, attempts to escape could at times be responsible as indeed might be other influences such as food- or mate-seeking. But, on balance, there is probably a greater likelihood of choices of the more novel of two or more stimuli in tests of free exploration being curiosity-based, than behavior emitted in forced-test situations. To a large extent, this might depend on the precise nature of the free test applied, as will become evident in subsequent sections of this paper. (For a comprehensive review of the measurement of exploratory behavior in general rather than neotic preferences specifically, see Harro, 1993.)

Most tests of neotic preference involve active selection of a specific stimulus or environment that differs in novelty, such as entering or occupying one of two spatially similar chambers, responding to visual stimuli of varying complexity, encountering a novel object in a less novel environment, or working for access to an environment or stimulus that functions as a primary reinforcer, such as solving a maze task or pressing a bar.

3.1. Location preferences

Tests of novel location preferences usually involve an animal being faced with two or more locations that differ in novelty in terms of its previous experiences with each. As these tests consist of providing free access to both novel and less novel locations, they more closely approximate real-life settings whereby animals venture out from the relative safety of their familiar home territory to explore new stimuli or areas (Hughes, 1997). A common procedural characteristic that all tests of location preferences share is a period of familiarization with at least one location prior to any assessment of neotic preference being made. Then, when ultimately faced with locations of differing novelty value, whether the preference is for the more novel (neophilia), the more familiar (neophobia) or neither will be determined by the degree of novelty of each generated for the individual. And while neophilia is generally assumed to be curiosity-motivated, the possibility that alternative extrinsic influences could be operating must not be underestimated. A lack of preference for either novelty or familiarity could give rise to interpretative difficulties because, as mentioned earlier, this might reflect either indifference-based decreased neophilia, or increased neophobia. Nevertheless, the introduction of procedures involving location preferences signified a major improvement in ways for measuring free choices of novel stimuli and in distinguishing between neophilic and neophobic responses.

3.1.1. Exploration boxes and the like

A number of procedures have been developed that were based on the principle of allowing animals to freely move between a familiar (or living) area and one not previously encountered. Many of these originate from a study of 50 years ago in which rats were confined for 24–26 h to one of two spatially identical rectangular boxes, namely the "home box" (Fehrer, 1956). They were then allowed access to the adjacent "exploration box" by means of an opening in the wall separating the two boxes. All rats showed a preference for occupying this more novel environment (Fehrer, 1956).

Over 40 years ago, the present author devised a test of neotic preference based on Fehrer's (1956) procedure that consisted of confining fed and watered rats to one half of an exploration box, and then later allowing them access to both this familiar half and a mirror-image novel half (Hughes, 1965a, 1968). In general, rats will show significant preferences for visiting and occupying the novel half following as little as 2 h of prior confinement. The initial apparatus which consisted of three novel and three familiar wooden compartments was later modified to comprise a clear Perspex box with two novel and two familiar compartments (Hughes and Swanberg, 1970) in order to reduce the time required for familiarization with the half to which the rats were confined. This box has been recently reduced to one novel and one familiar compartment to enable periods of 24 h to intervene between familiarization and measurement of neotic preference so that drug-attenuated forgetting can be assessed (Hughes, 2006). As the procedure enables neotic preferences to be observed that are relatively uncontaminated by motor activity, it is useful for assessing drug effects especially when preference and activity are affected in different ways (Robbins, 1977). Consequently, it has been adopted either directly or in principle for a number of drug and lesion studies with rats (e.g., Dalrymple-Alford, 1994; Hughes, 2006; Hughes and Pither, 1987; Kirkby, 1978; Velley et al., 1988). The general procedure has also been modified for the study of "novelty-seeking behavior" by mice in an exploration box comprising three novel and three familiar compartments (Misslin and Ropartz, 1981a) and very successfully applied to the study of drug and lesion effects in this species (e.g., Cigrang et al., 1986; Griebel et al., 1991; Misslin and Ropartz, 1981a, c). Although attempts to identify the specific stimuli that animals use in distinguishing between novel and familiar locations have not been a general feature of most studies, rats and mice appear to utilize mainly olfactory cues in this particular type of apparatus (Hughes, 1991; Misslin and Ropartz, 1981b).

Other procedures based on the principles underlying Fehrer's (1956) approach include a central chamber opening into novel and familiar compartments (Hall et al., 1997), a darkened box opening into an open field that subjects can freely enter and leave (Glickman et al., 1964; Valle, 1972), an open field with holes in the wall through which rats could inspect the experimental room (Kelley et al., 1986), a novel alley attached to a nest box or home cage (Blanchard et al., 1974; Graf, 1974; Mitchell et al., 1993), a novel alley leading off a runway (Cohen and Stettner, 1968), and a symmetrical Y maze with one novel arm (Cox and Tye, 1975; Dellu et al., 2000). A variant of movements between a darkened box and an open field is an emergence test which involves measuring a rat's latency to emerge from its home cage positioned within an open field (Paré et al., 2001). While qualifying as tests of neotic preference, this and other emergence tests (e.g., Hascoët et al., 2001) exploit the animals' neophobic tendencies as a way of assessing their levels of fear. Movements of animals into a novel alley or chamber from their home cage or after 24 h or more confinement to what effectively becomes their home environment probably more closely approximate what happens in "natural" situations and thus better reflect genuine neophilia than behavior following much shorter periods of confinement.

Under some circumstances, novel areas can be deliberately avoided thereby suggesting the operation of neophobia. This occurs especially when animals are confronted with fear-inducing situations such as the effects of electric shock (Haywood and Wachs, 1967) and drugs with central or peripheral actions that animals can find aversive (Horsburgh and Hughes, 1981; Hughes, 1987). These latter outcomes have provided serious challenges to the view that effects of drugs which antagonize the central action of acetylcholine reduce neophilic behavior because of interference with habituation to novelty (Carlton, 1968) or memory (Meyers, 1965). Examples of significant preferences in rats for the less novel of two locations following treatment with the antimuscarinic, scopolamine, show that the subjects are perfectly able to distinguish between the options but prefer the more familiar because of a possible neophobic reaction to the drug's aversive action (Hughes, 1982). This ability to distinguish between neophilic and neophobic responses is a particularly useful feature of providing animals with locations that differ in novelty.

3.1.2. *Spontaneous alternation behavior (SAB)*

Because conventional two-trial SAB involves a choice between the arms of a T or Y maze, one of which had been entered on an immediately preceding "familiarization" trial, the phenomenon clearly qualifies as a test of novelty-related location preference. As the phenomenon has been extensively reviewed elsewhere (Dember, 1961; Dember and Fowler, 1958; Dember and Richman, 1989; Hughes, 2004b; Lalonde, 2002; Richman et al., 1987), it is not necessary to discuss all of the issues surrounding it again, except to mention that the frequency of alternation is negatively related to inter-trial interval length and the number of successive alternation opportunities (Dember, 1961), and positively related to the length of time animals are confined to the maze arm first entered. SAB is also greater after forcing animals to enter one arm through the presence of a barrier across the other arm (Dember and Fowler, 1959) because of the extra novelty (and thus incentive to enter the alternate arm) provided by removal of the barrier (Hughes, 1966). Such types of observation further supported a neotic basis for SAB.

At one stage, two-trial SAB was a popular measure of habituation to novelty especially in attempts to establish the neural and neurochemical bases of the phenomenon (e.g., Carlton and Markiewcz, 1971; Douglas and Isaacson, 1966; Douglas and Raphelson, 1966). In more recent times it has featured extensively as a measure of short-term memory (especially in pharmacological investigations) on the basis that subjects must remember which maze arm it entered on the first trial, so that it can alternate on the

second. However, without modification, its value in this respect is limited because of methodological difficulties in distinguishing between drug effects on attention, memory and performance (Hughes, 2004b). Although the general assumption would be that SAB is an example of neophilic behavior, failure to alternate may not always indicate a reduction in neophilia. As with neotic preferences observed in exploration boxes, what might appear to be an inability to distinguish, novelty-wise, between the two options, could actually be due to an increase in neophobia. In other words, an increase in fear might lead to a tendency to avoid the novel option to some extent. This would of course be most evident if significant repetition rather than alternation prevailed thereby indicating that the animal was able to distinguish between the maze arms, but preferred to visit the less novel of the two, as has been shown with hyperemotional rats (Douglas et al., 1969; O'Connell, 1974), and occasionally following treatment with cholinergic antagonists (Hughes and Daley, 1977; Meyers and Domino, 1964) and catecholaminergic agonists (Adkins et al., 1969). Both of these groups of drugs are known to have aversive stimulus properties (Berger, 1972). It is also possible that seemingly neophobia-induced repetition could be due to the subject having associated removal from an aversive environment with the arm visited previously, as might be the case for significant repetition in domestic hens and pigeons (Hughes, 1989). Alternatively, handling the subject to remove it from the arm entered could be aversive and thus lead it to alternate so as to avoid this experience again, or else cause it to freeze thereby reducing SAB rates because of increased time between choices (Gerlai, 2001). So, while two-trial SAB has become a popular test in drug and lesion studies, its simplicity of application is to some extent compromised by difficulties in interpretation.

As with location preferences in exploration boxes, subject-generated olfactory cues seem to play a major part in enabling rats to distinguish between the novelty characteristics of the two maze arms, although extra-maze directional cues are probably more important (Douglas, 1966). While later research has confirmed the involvement of both types of cue (Richman et al., 1969, 1970), olfaction played no part (in favor of direction) in SAB recorded in two T mazes set orthogonal to each other (Dember et al., 1966). In this study, rats entered the maze arm on their alternation trial that was in the opposite direction to the maze stem for their first trial. Although Douglas (1966) discounted any role for intra-maze visual cues in SAB, subsequent research demonstrated that they can indeed play a part (Hughes, 1966; Richman et al., 1970).

More recently, two-trial SAB has been superseded in popularity by continuous alternation, especially in pharmacological studies of memory (Hughes, 2004b). Continuous SAB usually involves 8-min unrestrained trials in a symmetrical Y maze during which sequences of entries into the three arms are recorded (e.g., Maurice et al., 1994; Sarter et al., 1988). Although choices of each arm are assumed to be determined by their novelty in relation to that of arms previously visited, neotic comparisons at any one time are less clearly identifiable, and inter-choice manipulations of novelty value are extremely difficult (if not impossible) to achieve. It therefore seems likely that two-choice SAB is a less disputable measure of genuine novelty-related location preferences.

3.1.3. Responsiveness to change

As a direct result of an attempt to distinguish between two opposing explanations for the origin of intrinsic exploration, Dember (1956) devised a test of neotic preference in which rats were allowed to see into a black and a white arm of a T maze (via the presence of transparent barriers across each arm entrance), before one of the arms was changed to opposite brightness. The barriers were then removed and it was noted which arm the rats entered first. Dember observed that the changed (or novel) arm was their preferred choice even though they were faced with two arms of identical brightness. The challenge for rats faced with this situation is not unlike what characterizes some reinforced delayed non-matching to sample tasks (Dudchenko, 2004).

Although responsiveness to brightness change proved to be a robust phenomenon in rats (Fowler, 1958; O'Connell, 1964; Walk, 1960) and other animals (Hughes, 1965b; Platt and James, 1967), it suffered from the limitation of being restricted to a nominal scale of measurement which was wasteful and ethically questionable because of the large numbers of subjects required for observing the effects of brain lesions and drugs (e.g., Łukaszewska, 1993; Markowska and Łukaszewska, 1981). Therefore, to provide better measurements of neotic preference as a way of studying memory (since the rats must remember which arm has changed from what it was previously), the present author also recorded total entries of and time spent in a novel Y-maze arm (compared with the "familiar" or unchanged arm) during a 3-min observation period (Hughes, 2001). This was later reduced to 1 min (Hughes, 2002) since it had been established that indifference to both arms occurs after this interval (Hughes, 2001). The introduction of repeated-measures experimental designs as well as ordinal scales of measurement also significantly reduced the numbers of subjects needed for studies involving invasive procedures (Hughes, 2003, 2004a; Hughes and Neeson, 2003). In addition, it has been recently shown that responsiveness to change is not confined to brightness, but will also occur with changes in tactile stimulation (Hughes and Kleindienst, 2004).

While it is clear that, during a 1-min observation period, rats will choose to enter and occupy the novel arm more often and for longer than the "familiar" arm, it is equally clear that rats spend most of their time in the "neutral" stem of the apparatus. This is exemplified by re-analysis of data from the first experiment of a recent study (Hughes and Maginnity, 2007) in which the mean ± SEM percen-

tages of their time (during a 1-min "retention" trial) that eight male and eight female hooded rats spent in the novel arm, the familiar arm and the stem, respectively, were 18.42±2.77, 9.08±2.18 and 72.5±4.40s. As shown by a repeated measures ANOVA, the differences between time spent in each Y-maze location were significant ($F = 84.20$, df = 2,28, $P < 0.0001$). Neither the sex difference nor the location × sex interaction was significant. Although the rats spent significantly more of their time in the novel rather than the familiar arm ($t = 2.55$, df = 15, $P < 0.025$), their greatest preference was clearly for occupying the stem which was the most familiar of the three options since, unlike either arm (that contained a new insert, one of which was of a different brightness from that experienced during the rats' 6-min "acquisition" trials with free access to both arms), it was the same as it had been earlier. However it is possible that these results were due to the animals' ability to visually inspect the brightness characteristics of each arm without actually entering them. But a similar re-analysis of nine male and 10 female hooded rats' responsiveness to a change in the tactile properties of the floor of a Y-maze arm, that could only be detected by actually entering both arms (Hughes and Kleindienst, 2004), revealed a similar outcome. In this case the mean±SEM percentages of the rats, time spent in the novel arm, the familiar arm and the stem were 21.29±1.36, 15.06±1.13 and 63.65±2.15s, respectively. Again the differences between the percentages were significant ($F = 182.69$, df = 2,34, $P < 0.00001$) with the rats obviously spending most of their time in the stem even though the novel arm was significantly preferred to the familiar ($t = 4.90$, df = 18, $P < 0.0001$). The sex main effect and the location × sex interaction were again not significant. It is therefore clear that rats from both studies preferred the familiar stem to either the novel or familiar arm thereby supporting the observation that, in some situations, animals may respond less to novelty when it is provided within a familiar context (Cowan, 1974). Nevertheless, in spite of this qualification, responsiveness to change has considerable potential for investigating neotic preference and may be preferable to SAB especially if such preference is used for measuring retention in studies of memory (Hughes, 2004b).

3.2. Responsiveness to stimulus complexity

Neotic preference can also be determined by the extent to which animals attend to the components of stimulus patterns or arrays through choice of or engagement with these components. Such attention is evident from preferences for visual patterns or reactions to environmental constituents that vary in complexity. Preferences may be in the form of spending more time in close proximity to one visual pattern than another (Dember et al., 1957), or by investigating some components of an experimental environment more often or for longer periods of time than others (Anderson, 1994). Because complexity involves variations in numbers of and dissimilarity between stimulus elements (Berlyne, 1960), studies of the role of reactions to visual patterns that vary in complexity, investigation of novel objects, and hole-board exploration will all be viewed as conceptually similar in terms of expressing neotic preferences.

3.2.1. Preferences for visual complexity

The first reports of responsiveness of rats to visual complexity came from Berlyne and Slater (1957) and Dember et al., (1957). The former authors found that rats preferred to enter a Y-maze arm that led to an area containing cards with black and white symbols drawn on them, than an equivalent empty area. Dember et al. (1957) gave rats the opportunity to visit two adjacent circular alleys joined to form a figure of eight. The walls of the alleys were lined with black and white stripes that were vertically positioned for one, and horizontally positioned for the other. The authors reported that the rats spent more time in the alley with vertical stripes, which was defined as the more complex of the two because it produced more spatial changes in stimulation (from black to white) per length of rat then did horizontal stripes. Interestingly, Dember et al. (1957) also found that, over several days of testing, any change in preference was virtually always from the less to the more complex alley, and not the reverse. This finding was later supported by May (1968) who gave rats choices of T-maze arms that varied in visual complexity. It is therefore possible that an initial preference for less complexity might have represented a neophobic response that declined with repeated exposures and was replaced by neophilia. Because Lester (1967a) observed that rats' initial preferences for vertical black and white lines declined with repeated testing to no preference for either vertical or horizontal stripes, it would seem that, as for other types of response to novelty, neophilia is eventually replaced by habituation-induced indifference.

Following the studies of Berlyne and Slater (1957) and Dember et al. (1957), preferences for the more complex of two or more visual stimuli were reported a number of times in rats (Leyland et al., 1976; May, 1968; Sackett, 1967; Walker and Walker, 1964) and other species (Eastment and Hughes, 1968). However, more recently there has been less interest shown in measures involving preferences for visual complexity. To some extent this could be due to a trend to approximate situations that are more "natural" for rats and mice for which vision is not the predominant sensory modality they use in exploring their environment. As olfactory, tactile and egocentric position cues obviously play a much larger part than visual cues for such primarily nocturnal animals, it may be preferable to provide them with test situations that are not solely reliant on vision. Most procedures based on novelty-related location preferences require the use of senses in addition to or instead of vision, as do other tests of complexity.

3.2.2. Object investigation

Because the presence of objects within an exploratory environment increases the number and dissimilarity of component stimulus elements, they effectively contribute to levels of stimulus complexity in the manner described by Berlyne (1960). Although measurements of animals' investigation of novel objects featured in some earlier studies (Berlyne, 1955; McCall et al., 1969), they have become more popular in recent times (Anderson et al., 2003; Pisula and Siegel, 2005; Renner et al., 1992a) particularly in the context of drug testing (Heyser et al., 2004; Nicholls et al., 1992; Renner et al., 1992b), and comparative studies of curiosity and neophobia (notably in parrots, Huber et al., 2001; Mettke-Hofmann et al., 2002, 2005).

Interactions with novel objects have typically been measured by numbers of contacts and time spent with them (Anderson, 1994; Zimmerman et al., 2001), but few have described the precise nature of the interactions (Renner, 1990). Studies in which object exploration was defined purely in terms of visits to areas where the objects were located (e.g., Cowan and Barnett, 1975; Powell et al., 2004; Williams et al., 1966) were no doubt examples of novelty (or complexity)-related location preferences, as well as responses to complexity per se. However, it should be kept in mind that "spatial locomotion and interaction with objects are separable entities" (Renner, 1990, p. 19). This conclusion was based on Renner's own observations of, for example, experience-dependent changes in the behavioral complexity of interactions with objects in the absence of both comparable changes in amount of contact with them, and locomotion (Renner and Rosenzweig, 1986). It is therefore conceivable that experimental manipulations of visits to locations containing novel objects and manipulations of interactions with them could produce different outcomes.

Neophilia is fairly convincingly demonstrated when novel objects are approached and investigated. However, in contrast to preferences for a familiar rather than novel location, it is more difficult to conclusively state that non-approach of objects constitutes neophobic avoidance rather than unresponsiveness, unless perhaps both familiar and novel objects are available at the same time (Powell et al., 2004). In this latter respect, an interesting development of object investigation is the "playground" maze that involves observing rats' responses to a single novel object interspersed amongst familiar objects in a familiar circular arena (Nicholls et al., 1992). A related procedure is a test of recognition memory devised by Ennaceur and Delacour (1988) that consists of exposing rats to one or two objects and then noting their reactions to a novel object presented at the same time as one of the original objects. This task is effectively a delayed non-matching to sample test based on rats' tendencies to explore novel stimuli (Dudchenko, 2004). A further development of the test introduced a spatial component by measuring rats' ability to locate the new position of one of two objects that it had encountered in a preceding trial (Ennaceur et al., 1997, 2005). As subjects in both these tests are confronted with a temporal change in the form of a new object or a familiar object in a new location, the underlying memory component (and also in the playground maze) is similar to what characterizes responsiveness to brightness change described in Section 3.1.3 which has been described as an index of recognition memory (Becker et al., 1992; Poucet and Buhot, 1989) and appears to be guided by spatial cues (Hughes and Maginnity, 2006).

Recently there has been some interesting progress in the use of object investigation for studying what appears to be episodic memory in mice, namely, evidence favoring the animals' ability to remember the temporal order of object presentations as well as recognize novel objects and their previous location (Dere et al., 2004, 2005). This procedure clearly has considerable potential for the study of memory.

3.2.3. Hole-board exploration

Hole-board tests were originally devised by Boissier and Simon (1962, 1964) and involve recording the frequency and duration of head dipping by rats and mice into holes in the floor of an arena underneath which various objects can be placed. The hole-board test is therefore really a type of object investigation task, although head dipping into empty holes will also occur, but not as frequently as when objects are available (File and Wardill, 1975). In some earlier versions of the test there was the possibility of photocell light beams used for recording head dipping being broken by accidental insertion of animals' tails or feet into the holes (Boissier and Simon, 1967), thereby contaminating results with their locomotor activity. However, this problem was addressed by reducing the number of available holes from 16 to 4 (File and Wardill, 1975) thereby improving the capability of the test for measuring relatively uncontaminated responsiveness to complexity and thus neotic preference. Locomotor activity and head dipping appear to occur relatively independently in this modified version (Durcan and Lister, 1989) which has featured in most subsequent research (e.g., Brennan et al., 1984; Kamei et al., 2004; Takeda et al., 1998).

As with object investigation, neophilia can be reasonably well identified, in this case through head dipping, but it is more difficult to distinguish between neophobia and indifference in failures to head dip. There is also the possibility that head dipping could involve attempts to find an escape route rather than reflect a genuine interest in objects underneath the holes (Renner, 1990) particularly in the light of head dipping by rats in the absence of objects (File and Wardill, 1975), and tunnel entries by mice in a tunnel board (Ahtee and Shillito, 1970).

3.3. Performing for exploratory rewards

It has been known for some quite considerable time that laboratory animals are capable of learning responses when

the only incentive to perform is the opportunity to experience temporal or spatial changes in stimulation. The first studies of exploration-reinforced learning were those of Harlow and associates who demonstrated that rhesus monkeys would solve mechanical puzzles with no other reward than completion of the task itself (Harlow, 1950; Harlow et al., 1950). These observations were later extended to show that monkeys could learn visual discrimination tasks that were reinforced by opportunities to look outside the experimental apparatus and view the experimental room (Butler, 1953), a moving toy train (Butler, 1954) or a monkey colony (Butler and Alexander, 1955).

3.3.1. Performing for access to novel locations

About 20 years before Harlow's studies, Nissen (1930) had demonstrated the strong incentive value of exploration for rats by showing that they would cross the electrified grid of a Columbia Obstruction Box (Jenkins et al., 1926) to gain access to a complex maze that they could enter and explore. Although it became popular to account for such findings by the development of secondary or conditioned drives and reinforcers based on primary needs (Fowler, 1965), it was later shown that rats, in a two-compartment apparatus, would learn to press a lever merely to gain access to one compartment from the other (Myers and Miller, 1954). This study was followed by demonstrations of rats learning position habits and brightness discrimination tasks in a Y maze when reinforced by the opportunity to explore a checkerboard maze (Montgomery, 1954; Montgomery and Segall, 1955). In a series of subsequent studies it was shown that rats were also able to learn position habits and brightness discriminations when novel objects in one of the arms of a T maze served as exploratory incentives (Leaton, 1965, 1968a, b, 1969). Further evidence for the reinforcing effects of novelty and complexity was found in a report of faster running speed by hamsters to a goal box that contained novel objects (especially when they were changed between trials), rather than an empty goal box (Schneider and Gross, 1965). It was also shown that the speed of shifting from eating in a start box to entering an adjacent chamber was faster for food-deprived rats when the chamber was novel and complex, than when it was less so in these respects (Timberlake and Birch, 1967).

An interesting advance in the study of novelty rewards in specific locations has been the recent development of novelty-reinforced place conditioning in rats. This procedure is based on the observation that rats can learn to associate a particular location with a rewarding or aversive experience, such as a drug effect, and then subsequently prefer (or avoid) that place in the absence of the earlier experience (Carr et al., 1989). Bevins and Bardo (1999) paired exposure to a non-preferred compartment with access to a novel object and found that their rats subsequently preferred this compartment in the absence of the object. This finding has been confirmed in several investigations of effects of drugs (Besheer et al., 1999; Bevins, 2001; Bevins et al., 2002) and social isolation (Douglas et al., 2003). Novelty-reinforced place conditioning may also be useful in the assessment of losses in the reward value of novelty as a measure of anhedonia that can accompany depression and drug withdrawal (Bevins and Besheer, 2005). However, as the procedure involves establishing an association with a place in which a novel object is provided, versus a place without an object, perhaps any later preference for the former place is due to the change experienced from object present to object absent, rather than to place conditioning. This possibility should be addressed in future research even though in either case memory is obviously required.

3.3.2. Performing for temporal changes in stimulation

There have been many reports of rats and mice performing for changes in stimulation in an operant chamber that involve bar-pressing for light onset (Hurwitz, 1956; Kish, 1955) or light offset (Glow and Russell, 1974), and increases (Berlyne et al., 1964; Girdner, 1953) or decreases in ambient illumination of the experimental chamber (Robinson, 1961), i.e., light-contingent bar pressing (for a review of earlier literature see Lockard, 1963). It was also shown that there were no differences in reinforcing effectiveness of the changes between light increases or decreases, irrespective of the light levels involved (McCall, 1965). Reinforcing effects similar to light changes have also been described for changes in auditory stimulation (Barnes and Kish, 1961; Berlyne et al., 1966; Glow and Russell, 1974).

Although there seems little doubt that bar pressing for sensory change demonstrates genuine neophilia of a predominantly intrinsic origin, an alternative interpretation was that the reinforcement mainly involved animals' ability to control their environment, rather than to experience a change (Glow et al., 1972; Glow and Winefield, 1978). However, this idea does not seem to have been considered further by subsequent researchers.

While neophilia is relatively easy to identify when animals respond for a light or sound change, there is more difficulty in distinguishing between neophobia or fear of the change and mere disinterest in it when animals fail to respond. A more definitive example of neophobia would be bar pressing for a familiar rather than novel change (Berlyne et al., 1966), especially if this occurred in the presence of some aversive experience. Although bar pressing for sensory change was once very enthusiastically received, its popularity has declined quite significantly. This might be due to its reliance on learning and thus replacement by less demanding "unconditioned" procedures, although novel-object place conditioning is clearly making some impact. As with other forms of behavior reinforced by exploratory rewards, bar pressing for change suffers from the disadvantage of requiring longer periods

of testing to establish effects of independent variables on neotic preference than is the case for procedures involving more spontaneous responses to novel or complex stimuli. Nevertheless, it should not be entirely ignored, as it remains a procedure with considerable potential for expressing and exploiting genuine neotic preferences that are relatively uncontaminated by activity levels.

4. Some neurobiological substrates of neotic preferences

Neophilic neotic preferences that indisputably arise from curiosity or intrinsically motivated exploration are undoubtedly a reflection of the rewarding properties of novelty. If so, it seems likely that they would be mediated by the same central mechanisms that subserve other forms of reward. Bardo et al. (1996) have therefore suggested that the mesolimbic dopamine (DA) system may play a major role in processing of the reward value of novelty as it does for drugs of abuse and other forms of reinforcement. However, as mentioned earlier, whether a novel stimulus is avoided, approached or ignored will be determined by the degree of novelty it generates. Whether or not a novel stimulus is recognized as such will depend on the amount of prior habituation or familiarization that has taken place before testing, and thus involvement of short-term working memory as, for example, in conventional two-trial SAB, or longer-term reference memory, as in novel-object place conditioning. In addition to the memory demands of a specific test, the precise nature and sign of the neotic preferences exhibited will also depend on levels of fear generated for the subjects (see Section 2.3 above). In other words, while memory will determine whether or not a stimulus is recognized as novel, the type of response made towards it will depend on both the fear and the interest it invokes. Therefore, it is to be expected that the extent to which lesions or drugs target the CNS mechanisms mediating memory and fear in particular will determine how neotic behavior is affected, depending on which one of them is the predominant cause of results of the specific test applied. In some instances, lesion or drug effects on neotic preferences could also reflect interference with sensory processing or attentional mechanisms that may be independent of changes in memory or fear. It is well beyond the scope of this present paper to review the huge volume of research dealing with lesion and drug effects on memory, fear and reward per se, as there are already many other excellent reviews on record, e.g., memory and fear (Bannerman et al., 2004; Gold and Greenough, 2001; Pratt, 1992), brain reward mechanisms (Ikemoto and Panksepp, 1999; Kelley and Berridge, 2002; Wise and Rompre, 1989). Instead, the following sections will be confined to selected examples of studies involving effects of surgical, electrolytic, cytotoxic or excitotoxic lesions, and peripherally administered drugs on neotic preferences that may help understand the importance of these processes for particular types of neotic response.

4.1. Memory and habituation

Memory is quite clearly fundamental to any neotic behavior as it determines the extent to which a stimulus is perceived as novel. In many cases, degrees of novelty will depend on how much memory-related habituation has occurred. Therefore, as habituation and recognition of novelty obviously involve memory systems within the brain, the next section will comprise a discussion of effects of brain lesions and drugs that act on central memory processes.

4.1.1. Effects of hippocampal lesions

Lesions of the hippocampus and associated structures and pathways that comprise the medial temporal lobe memory system (Squire and Zola-Morgan, 1991) have been shown to reduce responsiveness to novelty as reflected in such outcomes as chance level SAB (Douglas, 1989) and impairments of object recognition (Winters and Bussey, 2005), object location (Ennaceur et al., 1997; Mumby et al., 2002) and novelty-related location preferences (Misslin et al., 1981). Given the important role of the hippocampus in memory (Bannerman et al., 2004; Gold and Greenough, 2001), it is not surprising that many of the decreases in novelty preferences following hippocampal lesions have been ascribed to disturbances of memory function or habituation to novelty (Douglas, 1989), although impaired attention or sensory processing could play a part in some instances (Hughes, 1982). It is also possible that reduced preferences for novelty expressed as decreased SAB in rats with lesions to the associated septal area (Douglas and Raphelson, 1966) might be a neophobic response to the elevation of fear that can follow such a procedure (Slotnick et al., 1974), although Gray (1979) proposed that septal lesions reduce rather than increase fear. And more recent evidence indicates that impaired memory involved in preferences for novelty may be specific to the novel stimulus when presented in a different location, rather than to the ability to discriminate between novel and familiar stimuli experienced in the same location (Mumby et al., 2002).

It has been suggested that relationships between hippocampal memory processes and neotic preferences may specifically involve a novelty detection network whereby current experiences are compared with encoded details about previous experiences (Johnson and Moberg, 1980; Knight and Nakada, 1998; Mumby et al., 2002). If such comparisons result in a "mismatch" with stored information, then detection of novelty would be registered and accordingly responded to (Lisman and Otmakhova, 2001). Consequently, damage to the hippocampus may interfere with mismatching and thus the ability to detect or respond to novelty (Honey et al., 1998; Save et al., 1992). However, it is possible that involvement of the hippocampus itself in comparator functions may be more specific to novel spatial arrangements of stimuli, while responsiveness to novel stimuli themselves could depend to a greater

extent upon surrounding cortex (Jenkins et al., 2004; Wan et al., 1999). Although the hippocampus certainly appears to be an important component of a novelty detection network, its precise role in this respect in relation to memory functions in general remains to be further clarified. Nevertheless, there have been some recent promising advances that may throw light on the issue. These include the study of hippocampal phosphorylated cAMP response element-binding protein levels (Moncada and Viola, 2006; Winograd and Viola, 2004), *N*-methyl-D-aspartate receptors (Nakazawa et al., 2002), and associated brain areas such as the amygdala (Moses et al., 2002).

In most investigations of brain lesion effects on neotic preferences that target memory, it is not possible to distinguish between lesion effects on attentional and memorial processes because acquisition, retention and retrieval of information must all inevitably follow the surgical procedure. However, this is less of a problem in the assessment of drug effects.

4.1.2. Effects of cholinergic drugs

Drugs that are known to either disrupt or enhance memory usually decrease or increase preferences for novelty, respectively. The most extensively investigated agents in these respects have been antagonists and agonists of the neurotransmitter acetylcholine (ACh), which plays a major role in hippocampal memory functions (Gold, 2003). Systemic administration of the cholinergic antagonists, scopolamine and atropine, is well known to affect rodents' neotic preferences in the form of decreases in two-trial SAB (Douglas and Isaacson, 1966), novelty-related location preferences (Horsburgh and Hughes, 1981), responses to brightness change (Łukaszewska, 1993), novel object exploration (Renner et al., 1992b) and head dipping in a hole board (Brodkin, 1999; Williams and Hamilton, 1974). On the other hand, while effects of cholinergic agonists have been less extensively investigated, in some studies they have been shown to have the opposite effect to antagonists, namely increased two-trial SAB with physostigmine (Egger et al., 1973; Squire, 1969), improved novel object recognition with nicotine (Puma et al., 1999) and, with tetrahydroaminoacridine, increased preferences for a novel location (Hughes, 2006) and improved novel-object recognition in aged rats (Scali et al., 1997). However, physostigmine failed to have any effect on rats' preferences for a novel location (Hughes, 1992; Hughes and Trowland, 1976).

A number of other compounds that are known to enhance memory such as glucose (Messier, 2004) and the NMDA partial agonist, D-cycloserine (DCS, Flood et al., 1992) can also enhance preferences for novelty. For example, glucose has been shown to increase novelty-related location preferences (Hughes, 2006) and responsiveness to brightness change in rats (Hughes, 2003; Hughes and Neeson, 2003) as well as improving object recognition (Messier, 1997). Likewise, DCS will increase rats' responsiveness to a brightness change in a sex-related dose-dependent manner (Hughes, 2004a), and object investigation (Kart-Teke et al., 2006). Intraseptal infusions of NMDA agonists and antagonists have also been shown to, respectively, increase and decrease novel object investigation in rats (Puma et al., 1998). As it seems likely that ultimate facilitation of cholinergic activity probably accounts for the effects on memory of glucose (Messier, 2004), DCS (Izquierdo and Medina, 1995) and many other drugs, this could be the reason for their enhancement of preferences for novelty.

Although peripheral administration of drugs to animals is obviously a very imprecise way of targeting neurotransmitters in specific brain areas, it does have the advantage over lesions of enabling post-acquisition administration (Breen and McGaugh, 1961), thereby allowing distinctions to be drawn between drug effects on attention/encoding and consolidation/retrieval, as has occurred in some recent studies of neotic preferences in rats with glucose and DCS (Hughes, 2003, 2006; Hughes and Neeson, 2003), and NMDA antagonists (de Lima et al., 2005; Winters and Bussey, 2005). Consequently, as with effects of hippocampal lesions, some earlier examples of decreased preferences for novelty in rats following pre-acquisition treatment with cholinergic antagonists (Douglas and Isaacson, 1966; Łukaszewska, 1993; Williams and Hamilton, 1974) could have been due to impairments of attention or sensory processing rather than memory or habituation deficits. Nevertheless, the results of most lesion and drug studies are consistent with involvement of cholinergic memory mechanisms in neotic preferences.

4.2. Fear

Even though an animal may recognize a stimulus as novel, it may not necessarily prefer to approach and investigate it. In other words, fear-based neophobia can supersede neophilia if the degree of novelty is too great, or if some other unrelated influence has generated high levels of fear. It is also possible that lower levels of fear may detract from the intensity of a neophilic response. The following section will therefore address the effects on neotic preferences of lesions and drugs that are believed to modify central fear-related mechanisms.

4.2.1. Effects of amygdaloid lesions

Lesions to structures in the amygdaloid complex have been shown to increase preferences for novelty in mice in the form of lack of avoidance of a novel location shown by control subjects (Misslin and Ropartz, 1981c), and decreased latencies to approach novel objects (Sargolini et al., 1999**).** As the amygdala is heavily implicated in the mediation of fear responses (LeDoux, 1995), it seems likely that these effects arose from attenuated fear and thus a reduced neophobic tendency to avoid novel stimuli. It is possible that damage to the amygdala was responsible for increased hole-board exploration following lesions of the basal forebrain (Johanssen and Hansen, 2001) because of

reduced neophobia although, as the authors pointed out, their lesions also impinged on other emotion systems, namely the septal and ventral striatopallidal systems. But a direct relationship between amygdaloid lesions and reduced fear need not always be the case as the amygdala has been implicated in other functions as well, such as memory (Amaral, 2003; McGaugh et al., 1996) and olfaction (Buck, 1996). However, although either of these functions could play a part in neotic preferences, amygdaloid lesions would be expected to reduce rather than increase preferences for novelty if impaired memory rather than attenuated fear were the reason for the results. While the literature describing effects on rodent neotic preferences of lesions to the amygdala and associated areas is not extensive, there are a number of reports of lesion effects on monkey preferences, most of which support the general view that amygdaloid damage leads to enhanced novelty seeking (e.g., Aggleton and Passingham, 1981; Mason et al., 2006) probably through reduced fear or cautiousness (Mason et al., 2006).

Although the amygdala has received most attention in the context of neotic preferences, other brain structures could also be important. For example, although (as discussed in Section 4.1.1) hippocampal lesions usually decrease preferences for novelty, this effect could depend on which part of the structure is damaged. When confined to the ventral region (Kjelstrup et al., 2002), they can decrease fear (Deacon et al., 2002) in a similar fashion to amygdaloid lesions. It has accordingly been proposed that the ventral region is involved in the regulation of fear or anxiety-like responses, while memory functions of the structure are associated mainly with the dorsal region (Bannerman et al., 2004), a proposition for which there is recent evidence (Bertoglio et al., 2006).

4.2.2. Effects of benzodiazepine, GABAergic and serotonergic drugs

It is commonly assumed that changes in the behavior of rodents following treatment with benzodiazepine agonists (such as chlordiazepoxide and diazepam, for which the amygdala appears to be an important site of action, Caldji et al., 2000; Burghardt and Wilson, 2006) are invariably due to reduced fear or anxiety arising from the drugs' anxiolytic action. In fact, the terms "anxiolytic" and "benzodiazepine" have become virtually interchangeable (Rosenberg et al., 1994). The anxiolytic action of benzodiazepine agonists is generally accepted as mainly involving enhancement of the inhibitory activity of GABA at $GABA_A$ synapses chiefly in the amygdala, although other receptors and other structures (such as the hippocampus and lateral septum) are undoubtedly implicated (Gray and McNaughton, 2000; Millan, 2003). The drugs might therefore be expected to enhance preferences for novelty by attenuating fear of novel stimuli. And indeed there is some evidence supporting this. For example, chlordiazepoxide increased preferences for a novel location in BALB/c mice (Griebel et al., 1993) and the time rats spent investigating a novel object in a playground maze (Nicholls et al., 1992, 1994), an outcome also shared by the $GABA_A$ agonist muscimol (Nicholls et al., 1994), and diazepam increased investigation by rats of a novel object in a novel open field (Delini-Stula and Hunn, 1988). Both diazepam and chlordiazepoxide have been shown to increase the number and duration of head dips by mice in a holeboard (Takeda et al., 1998). Even though $GABA_A$ receptors (especially α_2- $GABA_A$ receptors, Möhler et al., 2002) are generally seen as more important for fear-attenuating effects of GABA agonism, long-term treatment with the $GABA_B$ agonist, baclofen, has also been shown to improve rats' ability to detect spatial novelty (Tang and Hasselmo, 1996), although the same drug had earlier reduced investigation of a novel object (Nicholls et al., 1994).

However, there are a substantive number of reports that fail to support an attenuated fear interpretation of benzodiazepine agonist effects on neotic preferences. These demonstrated either reduced preferences for novelty or no effect of the drugs. For example, chlordiazepoxide either decreased preferences for a novel location in rats (Hughes, 1972a; Hughes and Syme, 1972), or had no effect on the response in C57 mice (Griebel et al., 1993). Diazepam and the partial benzodiazepine agonist, alpidem, had no effect on this response in either C57 or BALB/c mice (Griebel et al., 1993), while another agonist, Ro 19-8022, had no effect in the former strain but increased preference for a novel location in the latter strain (Griebel et al., 1993). Diazepam has also been shown to reduce rats' preferences for a novel location to the point that familiarity was preferred (Hughes, 1981) thereby suggesting that this result, and a similar outcome for chlordiazepoxide (Hughes, 1972a), could have been due to increased neophobia. But this is unlikely in view of a co-existing reduction in fear-related emergence latencies from the darkened into the illuminated side of a shuttle box with the former drug (Hughes, 1981), and enhanced rather than diminished familiarity preferences with repeated exposures to chlordiazepoxide (Hughes and Greig, 1975). It is also possible that some examples of decreases in memory-dependent preferences for novelty were due to the amnesic effects of benzodiazepine drugs (Lister, 1985; Thiebot, 1985). And while benzodiazepine antagonists might be expected to decrease such preferences, flumazenil had no effect on novel object investigation by rats in a playground maze (Nicholls et al., 1994). The amount of conflicting experimental evidence on record makes it impossible to account for all effects of benzodiazepine agonists on neotic preferences simply by attenuated fear and thus decreased neophobia arising from facilitation of GABA activity. However, heightened fear also appears to be related to increased 5-HT activity (Wise et al., 1972) possibly via modulation of GABA activity in the amygdala (Stutzmann and LeDoux, 1999). In view of the secondary changes in serotonergic activity that follow activation of GABA-benzodiazepine receptors (Leonard, 2003), perhaps the influence of fear in determining a neotic preference might

depend on 5-HT. Consistent with this view, a number of 5-HT agonists, such as flesinoxan, fluprazine and eltoprazine, have been shown to reduce preferences for a novel location in Swiss mice (Griebel et al., 1990, 1993) thereby suggesting increased neophobia. However, rather than leading to expected increases in preferences for novelty, the 5-HT antagonists mianserin and ritanserin produced similar results to agonists (Griebel et al., 1993), and two other antagonists, zacopride and (S)-UH-301, and some other agonists, such as S 20244 and S 20500, have failed to have any effect on the response (Griebel et al., 1993; Moreau et al., 1992). More recently, the 5-HT re-uptake inhibitor, fluoxetine, and the antagonist mianserin have been shown to increase and decrease, respectively, occupation of a novel location in BALB/c mice (Belzung et al., 2001).

While studies of effects of 5-HT agonists and antagonists on neotic preferences in rats are not as numerous as studies with mice, they also tend to reflect a similar lack of consistency in outcomes. For example, the 5-HT (and noradrenalin, NA) re-uptake inhibitor, imipramine, decreased the time spent in a novel Y-maze arm (Cox and Tye, 1975), but had no effect on preferences for a novel location in an exploration box (Hughes and Pither, 1987). Another 5-HT agonist, lysergic acid diethylamide-25, decreased bar-pressing for light onset (Lowe and Williams, 1972) and, with higher doses, the time spent in a novel chamber (Adams and Geyer, 1982, 1985), but increased this latter measure with lower doses (Adams and Geyer, 1985), and had no effect on preferences for a novel location (Hughes, 1973). The involvement of 5-HT in neotic preferences of rats is complicated by a recent report of a negative relationship between levels of the transmitter in the brainstem and nose pokes in a hole board, but a positive relationship between the two in the amygdala (Ray et al., 2006).

As is the case for benzodiazepine and GABA receptors, the effects of drugs that target 5-HT activity are too inconsistent to enable evaluation of the role of central fear mechanisms in determining neotic preferences. To some extent inconsistencies could have arisen from differences in species, strain and particular receptor subtypes that were affected. While it is possible that some outcomes were indeed due to attenuation or accentuation of fear, the receptors and transmitters involved also affect other processes which in some cases could be the reason for any reported changes in neotic preference. For example, 5-HT is heavily implicated in memory (Meneses, 1998, 1999) and could directly (or through its interactions with relevant brain systems operated by acetylcholine, glutamine, GABA and DA, Buhot et al., 2000) affect the memory rather than fear components of neotic preferences. Thus, changes in serotonergic activity from the effects of receptor subtype-specific agonists and antagonists of 5-HT might in some cases lead to either enhanced or impaired memory that could be responsible for the associated changes in neotic preferences.

4.3. Reward characteristics of neotic responses

Acceptance of the reward value of novelty in curiosity or intrinsically motivated exploration assumes involvement of the central pathways that mediate other types of reward (Bardo et al., 1996), as well as the essential memory mechanisms. Consequently, the next section will deal with effects on neotic preferences of lesions and drugs known to influence activity of the mesolimbic DA reward system.

4.3.1. Effects of mesolimbic lesions

Manipulations that disrupt functioning of the mesolimbic DA system would be expected to reduce the neophilic novelty seeking- or curiosity-related reward basis of novel stimuli and thereby decrease neotic preferences. Lesions of the nucleus accumbens and other parts of the DA system have accordingly been shown to decrease SAB (Taghzouti et al., 1985; van Kuyck et al., 2003), novel object exploration (Fink and Smith, 1979) and preferences for a novel location (Pierce et al., 1990). Such findings are consistent with the view that depletion of forebrain DA reduces the rewarding properties of novelty (which has been related to DA release in the nucleus accumbens, Bardo et al., 1996). The nucleus accumbens appears to be involved in reinforcement generally, as suggested by reports that rats will self-administer DA and self-stimulate when the cannulae and electrodes are implanted in the structure (Guerin et al., 1984; Olds and Fobes, 1981). However, it is possible that some cases of impaired neotic behavior following nucleus accumbens lesions could be due to memory rather than reward deficits because the structure has been implicated in the ability of mice to recognize a change in location of an object (Mele et al., 2004). And it should be kept in mind that the DA reward system comprises and has connections with structures in addition to the nucleus accumbens (including the ventral tegmental area, amygdala and prefrontal cortex, Kelley and Berridge, 2002) that are implicated in other behavioral processes.

4.3.2. Effects of dopaminergic drugs

In contrast to lesion studies, effects on neotic preferences of drugs that enhance the action of DA do not appear to convincingly support the proposition that novelty-seeking behavior is related to activity of the mesolimbic DA reward system (Bardo et al., 1996). There are a number of earlier studies that demonstrated a reduction rather than the predicted increase in neotic preferences following treatment with a range of DA agonists. For example, decreased preferences by rats and mice for a novel location have been shown with amphetamine (Ågmo and Belzung, 1998; Cox and Tye, 1975; Wimer and Fuller, 1965), methamphetamine (Hughes and Greig, 1976; Misslin and Ropartz, 1981a), methylphenidate (Dyne and Hughes, 1970; Heyser et al., 2004; Hughes, 1972b; Hughes and Greig, 1976; Hughes and Syme, 1972) and apomorphine (Misslin et al., 1984). Caffeine, which appears to have indirect DA agonist

properties through antagonism of adenosine (Garrett and Griffiths, 1997), has also been shown to decrease novel location preferences (Hughes and Greig, 1976). Consistent with these outcomes was the observation that apomorphine decreased novel object exploration in mice (Adriani et al., 2000). While amphetamine was reported to have no effect on preference for the most novel of three compartments (Bardo et al., 1989) or on novel object exploration in rats (Nicholls et al., 1992; Russell and Pihl, 1978), this drug has been shown to decrease their object investigation in a novel alley (Robbins and Iversen, 1973) and novel object exploration in mice (Adriani et al., 2000). However conversely, the selective D4 receptor agonist, RO-10-5824, increased object investigation in C57 but not DBA mice (Powell et al., 2003) and amphetamine increased the reinforcing properties of illumination changes in a light-contingent bar-pressing setting (Glow and Russell, 1973a, b).

Some studies of the effects of DA antagonists supported interference with the mesolimbic DA reward system, namely, decreased preference for a novel location with haloperidol in rats (Bardo et al., 1989) and with thioridazine in mice (Misslin et al., 1984), but others have demonstrated a lack of effect of sulpiride and tiapride on the same response (Misslin et al., 1984). Although sulpiride and SCH23390 also failed to affect novel object exploration (Adriani et al., 2000), haloperidol interfered with this response in mice (Roullet et al., 1996). Chronic treatment with this latter drug and with risperidone has recently been shown to have no effect on hole-board exploration in rats (Karl et al., 2006). Haloperidol has also been reported to decrease bar-pressing by rats for light onset, but increase this response when the reinforcement was flickering light (Lowe, 1976). Because the effects of DA agonists on neotic preferences have generally been contrary to expectations derived from the view that novelty seeking is determined by activity of the mesolimbic DA reward system (Bardo et al., 1996), the effects of DA antagonists should also be interpreted within this context. Thus it has been suggested that suppression of neotic preferences by DA agonists in some situations might reflect "a non-specific activation of behavioral systems that are incompatible with true exploratory behavior directed at novel stimuli" (Bardo et al., 1996, p. 28). However, most of the pharmacological evidence fails to convincingly support modification of the mesolimbic DA system as the reason for dopaminergic drugs' effects on neotic preferences especially when agonist-induced decreased preference can occur simultaneously with decreased locomotor activity (Misslin et al., 1984), thereby suggesting the converse of activation. Nevertheless, it is certainly possible that, at times, both DA agonists and antagonists may have led to neophobia arising from their possible aversive stimulus properties that can also determine effects of other drugs (Berger, 1972). This is especially likely when familiarity preferences followed treatment with dopaminergic drugs (Dyne and Hughes, 1970; Hughes and Greig, 1976; Misslin and Ropartz, 1981a), thus indicating maximum novelty avoidance (Hughes, 1982).

4.4. Discussion of lesion and drug effects

Although the above brief (and limited) examination of studies of lesion effects was confined to parts of the brain that are more closely identified with activity of the hippocampus, amygdala and the nucleus accumbens, lesions in other areas are also known to affect neotic preferences. For example, caudate-putamen lesions decreased neophobic responses to a novel object in mice while having no effect on preference for a novel location (Cigrang et al., 1986). This latter result contrasted with an earlier report of increased time exploring a novel location by rats following caudate nucleus lesions, an outcome that was ascribed to a deficit in their ability to acquire sensory information (Kirkby, 1978). Increased neophobia in the form of decreased time spent in a novel location has been shown to be associated with lesions in the locus coeruleus of the midbrain tegmentum (Velley et al., 1988) from where originates the most important noradrenergic innervation of the forebrain. And lesions of a major efferent pathway from the locus coeruleus, the dorsal noradrenergic bundle, have also been shown to decrease SAB that was accounted for by impairments of fear habituation (Pisa and Fibiger, 1983) or habituation to novelty (Pisa et al., 1988). However, in such cases it is difficult to conclude if the resulting interference with forebrain NA activity, and thus changes in neotic behavior, arose from increased fear, impaired habituation, or impairments of attention or arousal, both of which have been associated with activity of the locus coeruleus and dorsal noradrenergic bundle (Aston-Jones et al., 1999; Carli et al., 1983). It is also possible that there were deficits in the ability to integrate memory with environmental sensory information that has been suggested as another function of locus coeruleus noradrenergic activity (Sara et al., 1994). Responses to novelty may also be mediated by possible NA action on D4 receptors (Aston-Jones et al., 1991) that are widely distributed in the frontal cortex and hippocampus (Wedzony et al., 2000). Both of these areas are important for reactions to novelty and habituation (Cohen et al., 2002). These examples along with those discussed in Sections 4.1–4.3 illustrate the complex interrelationships between a number of brain areas and the different behavioral processes that can determine the characteristics of a specific neotic response.

Although in many cases the effects of drugs on neotic preferences support conclusions derived from lesion studies regarding modification of underlying processes, there is really too much inconsistency in the findings to enable firm conclusions to be drawn. This is particularly so for drugs that act on possible fear-related systems operated chiefly by GABA (and associated benzodiazepine receptors) and 5-HT, and drugs that act on the mesolimbic DA reward

system. Research in these areas should be more directly guided by increasing awareness of the need to consider specific receptor subtypes when assessing the effects of drugs on particular neurotransmitter systems. For example, any involvement of DA in reward-based neotic preferences may be specific to D4 receptors, as suggested by studies of D4 receptor-knock-out mice (Dulawa et al., 1999). And the importance of genetic factors (in the form of strain and sex) should not be overlooked. Although sex differences in rodents' reactions to drugs are well known (Claassen, 1994) and have been consistently reported for around four or five decades (e.g., Irwin et al., 1958; Vesell, 1968), examination of recent issues of any neurobehavioral or behavioral pharmacological journal will reveal that the vast majority of rodent research continues to involve male subjects exclusively. While sex-related drug effects may reflect differences in absorption, metabolism or pre-drug basal levels of responding, they may also be indicative of hormonally based sex differences in central organization, such as the activity of DA in the striatum and nucleus accumbens (Becker, 1999). Although there is much more consistency in effects of drugs that directly or indirectly influence cholinergic attentional, memory and habituation mechanisms, there is still the need in this area to more seriously consider receptor subtypes along with the strain and sex of experimental animals.

Given the overwhelming complexity of the nervous system and the many interactions that can occur between different neurotransmitters and neural systems, combined with the various behavioral processes that can underlie a neotic preference, it would be a gross oversimplification to try and account for the phenomenon by a single neurobiological substrate. This is reinforced by reports of changes in neotic preferences in rats and mice following treatment with drugs that are less closely associated with the neural and transmitter systems discussed above. For example, neotic preferences can be affected by lithium (Kurz and Levitsky, 1983; Syme and Syme, 1974), arginine vasotocin (King et al., 1982), CGS 15943A (Griebel et al., 1991), cholecystokinin (Crawley, 1984) and melatonin (Kopp et al., 1999). However, significant progress in clarifying the specific role of different brain areas and transmitters and how they interact with each other would inevitably follow a more noticeable move away from the rather gross neurobiological and pharmacological procedures that have characterized much of the earlier research. Ablations and peripheral administration of drugs are unlikely to provide the degree of precision achievable by stimulation of, drug injection into and recording from specific brain structures by means of implanted electrodes and cannulae. Greater use of these methods combined with informative post-experimental examinations of brain tissue, such as autoradiography (Sokoloff, 1981) and *c-fos* expression (Sagar et al., 1988) as used by Jenkins et al. (2004), could conceivably contribute to a better understanding of which central processes are crucial for neotic preferences.

5. Conclusion

In general, as measures of behavior directed specifically to novel stimuli, tests of neotic preference are less questionable and more "natural" than "forced" tests of exploration based primarily on assessments of motor activities that may or may not have an intrinsic exploratory function. Consequently, in recent times, there has been increasing use of neotic preferences for studying their underlying behavioral and neurobiological processes without the need to train animals which could introduce confounding effects of deprivation and electric shock. The study of neotic preferences in laboratory rodents has required consideration of such core issues as the meaning of the term "novelty", distinctions between and determinants of novelty avoidance (neophobia) and approach (neophilia), the various ways in which preferences can be measured in terms of responsiveness to temporal and spatial changes in stimulation, the essential role of memory and habituation, and the extent to which preferences are a reflection of fear (arising from novelty per se or some extraneous influence) and curiosity- (or novelty seeking-) based reward properties of novel stimuli.

During the course of this review, a recurring concern has been the extent to which a curiosity-based preference for novelty is influenced by an animal's level of fear. This was particularly apparent in the consideration of effects of drugs that are either assumed to increase or decrease fear (Section 4.2.2), and when aversive stimulus properties of these or other drugs can lead to novelty avoidance. Therefore, the challenge for researchers is to determine when an experimental outcome is due to a specific influence on neotic preference rather than to an effect on fear or some other process. There has been awareness of this problem for some considerable time. For example, even though the dangers of interpreting the effects of benzodiazepine agonists on tests of exploration in terms of the drugs' anxiolytic properties was pointed out over 20 years ago (File 1985), indices of neotic preference are still commonly adopted as tests of "anxiety" (although, as suggested in Section 2.3, most are probably more appropriately regarded as indices of "fear"). The possibility that a drug's motor stimulant or sedative properties could be responsible for an effect on novelty responding independent of either fear of neotic preference is an obvious possibility in choices requiring a high level of locomotion. As responsiveness to novelty varies in an inverted U-shaped fashion, it may also be difficult to determine if a treatment has decreased preferences for novelty through either an increase or a decrease in fear (Lister, 1991). So, how might distinctions be drawn between effects on fear and effects on curiosity-based neotic preference? One possibility is to simultaneously record more physiologically based measures of fear, such as defecation, urination or plasma cortisol levels, although this may be impractical in many situations. Another option is to supplement a test of neotic preference with other tests that have been more

reliably shown to reflect fear. This approach has at times made it possible to determine if changes in neotic preference following a particular manipulation were primarily due to changes in fear. For example, use of an emergence test enabled fear (or neophobia) to be ruled out as the reason for reduced novelty-related location preferences following daily treatment with chlordiazepoxide (Hughes and Greig, 1975), but supported fear being responsible for diminished responsiveness to brightness change in rats treated with benzylpiperazine during adolescence (Aitchison and Hughes, 2006). A third way of distinguishing between fear and curiosity is to develop tests that enable distinctions to be behaviorally drawn within a single session, as has been attempted by Ohl et al. (2001). These authors have modified the standard hole-board test of neotic preference to also include simultaneous measurement of open-field and (for rats tested in groups) social affinity measures. It is claimed that indices of anxiety (e.g., time on the hole board), exploration (e.g., holes explored), locomotion (crossing of lines on the floor around the hole board), social affinity (e.g., latency to first contact the group), physiological arousal (defecation and self-grooming) and risk assessment (stretched body posture) can all be recorded at the same time. This type of approach shows considerable promise and is to be encouraged. However, in the meantime the exclusive use of tests of neotic preference for assessing fear is unlikely to lead to definitive outcomes unless supplemented with other behavioral and physiological assessments of fear responses.

While brain areas and transmitters that subserve memory, fear and reward obviously play a part in the mediation of neotic preferences, with the possible exception of memory mechanisms, the extent of their involvement is difficult to ascertain from the effects of lesions and drugs because of the significant number of inconsistent findings. To a large extent this might be due to insufficient attention being paid to the complex interactions between the relevant central processes involved, combined with the need (especially in drug studies) to more carefully consider receptor subtypes and the species, strain and sex of experimental animals. The use of more precise neurobiological and pharmacological procedures discussed in Section 4.4 could help elucidate the nature of and interactions between the contributing central processes.

At a purely behavioral level, whether or not a stimulus is recognized as novel will depend on the operation of a memory-based novelty detection process and pre-test habituation. But whether the same stimulus is avoided, approached or ignored will be largely determined by fear, curiosity and the amount of prior and within-trial habituation. If neotic preferences are to be used as indices of any one of these processes, the possible confounding influences of one or more of the others must somehow be taken into account before meaningful conclusions can be drawn. Probably the best way of dealing with this problem would be through the development of better forms of assessment that enable clearer distinctions to be made between contributions of the different processes along the lines suggested above. A satisfactory solution is highly desirable because, in spite of the concerns outlined, unconditioned tests of neotic preference will continue to be applied to the effects of drugs in particular because of their simplicity, speed of administration and avoidance of the need to electrically shock or deprive animals in order to teach them to perform.

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