CHAPTER 3

Animal Models for Psychological Disorders

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INTRODUCTION

Psychological phenomena and disorders have been modeled in animals for over a century, and
the studies of, for example, Ivan Pavlov and Burrhus Frederic Skinner have been crucial to our
understanding of both basic psychological processes and psychopathology. A cursory examination
of the index of almost any standard introductory text in psychology reveals how influential animal
research and animal modeling has been for the development of the discipline. In more recent texts,
authors have often chosen to omit the fact that major research findings are based on animal research,
which belittles its contribution. One might surmise that this is either to avoid upsetting the student,
out of ignorance, or out of political correctness. In fact, many clinical practitioners today appear
to be unaware of the origins of the very methodologies that they commonly use in treating patients
(Plous 1996).

Psychological disorders, in particular, are generally associated with negative feelings and emotions
(one rarely becomes depressed by the perception of being successful), and thus the models are
generally associated with negative events for the animal. Therefore, it is not surprising that
psychological studies have been particularly targeted by opponents of animal experiments. This is
rather disappointing in view of the considerable beneficial consequences much of this research has
had on how we treat our fellow animals, and researchers have, therefore, a particular responsibility
to deliver scientific facts and knowledge within this field.
The issue of similarities and differences between the mental lives of animals and humans is, of course, fundamental. Claims of animal consciousness or unconsciousness are difficult, if not impossible, to verify. However, for a model to be useful, it is sufficient that there are similarities along a phylogenetic continuum. It is not mandatory for the animal mind to be as complex as the human mind; anxiety, for example, probably occurs in all mammals and indeed serves a crucial adaptive function. Perhaps Damasio’s differentiation between “core consciousness” (present in most, if not all, animals to varying extents) and “extended consciousness” (limited probably to humans and their closest relatives) may provide a useful framework (Damasio 1999). The latter is associated with the presence of sense of self and identity, theory of mind, and the awareness of one’s mortality. Following this distinction, it would be challenging to attempt to model psychological disorders associated with “extended consciousness,” except perhaps by using nonhuman primates in cognitive research, given that we share important neural substructures. Disorders concerned with “core consciousness” may be more accessible to modeling.

Comparative studies are of great informative significance, but to understand the use of animal models in studies of psychological disorders, it is necessary first to delineate the functions of models. This has been discussed extensively by several authors. Overmier (1999) provides a useful framework for this field, listing the functions of models as “heuristic” (question-generating), “evidential” (theory-testing), and “representational.” It is perhaps the first of these that has had the most impact on psychological science by generating hypotheses of importance to both animal and human mental health. Models derive their usefulness from their ability to establish initial and formal analogies between the two domains, animal and human. Relationships in the one domain help us to generate hypotheses about potential relationships in the other domain (Overmier and Patterson 1988).

In this chapter, the focus will be on behavioral models of psychological disorders that are mainly from the most often-used animals, namely rodents. Psychopharmacological research will only be touched upon within this context. The themes to be discussed include models of anxiety, depression, posttraumatic stress disorder, and schizophrenia, arguably representing the most serious psychological disorders. The discussion cannot be exhaustive, but will cover those models that are considered to have high face validity. There is also, of course, rapid growth in the use of genetically modified rodents in psychobiology, for example, as models of dementia and other cognitive deficits. An exciting new development with important potential is the study of epigenetic mechanisms, whereby gene expression may be modified by environmental factors. In animals, these mechanisms are beginning to be understood (Szyf, McGowan, and Meaney 2008), while in humans, gene–environment interactions are increasingly being recognized as fundamental to a number of psychological processes and disturbances (Rutter, Moffitt, and Caspi 2006).

**ANIMAL MODELS OF DEPRESSION**

Research findings indicate that depressive disorders are associated with underlying biochemical abnormalities, even though most affected individuals blame themselves or are blamed by others for their altered behavior (Trivedi et al. 2008). But is it possible that the behavioral state of clinical depression has an adaptive value? Social withdrawal in the face of adversity will conserve the individual’s energy until recovery from a perceived threat or stressor is possible. Lowering of anhedonic tone and increased neophobia will protect the organism from unidentified threats at a time of general danger (“harm avoidance”). Depression as a phylogenetic adaptation is discussed at length by Keller and Nesse (2006). One of the key features of the depression models here is that they involve aversive experiences and a component of uncontrollability over these events. Thus cognitive factors are central—the organism must be able to perceive that responses and outcomes are independent or noncontingent. For a model of a psychological disorder to be useful, the disorder that is being mod-
Learned Helplessness (LH)

Historically, there have been several animal models of depression that have proved useful in both the heuristic sense and in the development of behavioral and pharmacological treatments in humans. One of the most established of these, and the most cognitively orientated, is the so-called learned helplessness (LH) model of Martin Seligman and his colleagues (Seligman 1975). The model arose from the finding that naïve dogs exposed to a series of inescapable electric footshocks (IS) developed a pattern of behaviors which included a failure to learn to escape or avoid shocks, passivity, and resignation (Overmier and Seligman 1967). A parallel phenomenon could be produced in humans by using uncontrollable noise (Miller and Seligman 1975). The key to inducing helplessness is that the organism must learn that its responses and their consequences are independent—that whatever the animal does, it does not resolve the aversive situation and the outcome is unpleasant. This is also a key concept in later theories of human stress, degree of well-being, and vulnerability to psychosomatic disorders (Eriksen et al. 2005), all associated with clinical depression. In the animal model, it is crucial that the amount of aversive stimulation (e.g., shock) is of a certain intensity and number; in rats this is typically greater than 70 1-mA shocks each of 5 seconds duration with semirandomized inter-shock intervals. Provision of signals, either for danger (shock) or for “safe” periods, modulates the behavioral effects. As we shall see later, qualitatively different effects are produced by a smaller number of shocks.

Helplessness is seen in several species including rats, although the criteria for helplessness might not be the same across species. Importantly, induction of helplessness is preventable by “immunization” (previous experience with controllable shock), and in fact Seligman found it almost impossible to induce helplessness in “street-wise” animals. The importance of such developmental and earlier experiential factors is central to the concept of resilience. Learned helplessness, as first demonstrated, has a relatively limited time span, but later studies have shown that the state is subject to classical conditioning (Maier 2001). Thus, the basic principles of learning may help us to understand how people develop mood disorders. Importantly, the helplessness condition in animals may be treated by learning procedures also effective in humans (behavioral therapy), in addition to biochemical interventions. The learned-helplessness effect also shows hormonal parallels to human depression, such as nonsuppression in the dexamethasone suppression test (Raone et al. 2007).

In the rat model, helplessness is not generally manifested as a failure to avoid shock or in increased escape latencies under simple fixed-ratio 1 (FR1) contingencies (Maier 1990). Rather, it is manifest as increased latencies to escape shock under fixed-ratio 2 (FR2) contingencies; that is, the rat seems to be impaired only in relatively complex situations. Furthermore, it seems that there is considerable individual variation in vulnerability, since not all animals subject to the same experimental procedures develop the condition. Importantly, the escape deficit dissipates over time without further testing. No deficit is found if the period between inescapable shock and testing exceeds four days. The temporal dissipation is parallel to neurochemical changes induced by the inescapable shock procedures (J. Weiss et al. 1981).

Clearly, a method that induces a short-lived “depression” has little face validity for those primarily interested in human clinical depression, in particular the type of major depression resistant to remission. However, the results from Maier (1990) show that the escape deficit in helpless rats may be prolonged by reexposure to the environmental cues associated with IS, but that the effect of reexposure also dissipates over time. Furthermore, the exposure to the cues must occur within a time period during which the escape deficit is normally manifest. Repeated reexposure to the cues of inescapable shock prolongs the deficit for up to 18 days. However, if the animals are exposed to IS cues for long periods of time, they eventually learn that shock will not occur, and the deficit recedes.
Elicitation of a nonspecific stress response by reexposure to conditioned cues does not explain the deficit, since using other stressors has no “reminding” effect.

An ISI (Institute of Scientific Information) search revealed over 2,000 references to learned helplessness since 1968, some 600 of these from rodent studies, suggestive of a substantial influence on depression research. The model has been exploited for the development of both behavioral and pharmacological approaches to the human disorder and has clearly been successful in this regard. However, the use of the model has been criticized and constrained by ethical considerations, and in some countries has come to be regarded as too extreme (Brain and Brain 1998), stimulating explorations of other potential models. Other criticisms of the model have included its reliance on one exposure to an aversive and unnatural stressor. However, within a cognitive perspective, it does not matter what the organism is unable to control, as long as the animal develops “negative outcome expectancies” (Eriksen et al. 2005).

As with any animal model of any disorder, there are considerable inter-strain differences in susceptibility to behavioral or neurophysiological symptoms paralleling depression, but variance is greater in outbred strains. As just one example of strain differences in rats, Holtzman rats seem particularly susceptible to learned helplessness (Padilla et al. 2009). Early adverse experiences also affect sensitivity to stressors, a phenomenon of increasing interest not only with respect to depression research. Generally, manipulation through early handling of animals appears to be protective against later helplessness induction (Costela et al. 1995), while prenatal stress renders the animal more susceptible (Weinstock 2001).

**Chronic Unpredictable Stress (CUS) and Anhedonia**

Anhedonia—a general lack of interest in the pleasures of life—is a core symptom of human depression and may easily be tested in animals. The most common methods for measuring hedonic tone include avidity for sucrose or saccharine consumption (Willner 2005). Most species, including humans, favor carbohydrate sweeteners, and several validated and accepted preference tests have been designed for rodents.

Whereas the learned-helplessness model generally relies on one exposure to an aversive stressor, the chronic unpredictable stress (CUS) model, originally proposed by Roth and Katz (1981), uses a series of different uncontrollable stressors (inescapable shock, forced swim, periods of food and/or water deprivation, and heat stress, to name but a few) over a period of weeks (Katz 1982). Following the final stress exposure, the animals exhibit anhedonia, as indexed by lowered sucrose or saccharine consumption and preference. Importantly, the stress-induced anhedonia found in this model is sensitive to the tricyclic antidepressant, imipramine (Tofranil®), given during the chronic stress phase.

It is reasonable to suppose that the learned helplessness and chronic unpredictable stress models are affecting common neurobiological mechanisms underlying depressive symptomatology. Exposure to inescapable shock leads to a reduction of intracranial self-stimulation in the mesocorticolimbic system, a critical brain area for reward mechanisms (Zacharco and Anisman 1991), and conversely, experience with chronic stress procedures enhances helplessness behavior in rats (Murua and Molina 1992).

**Chronic Unpredictable Mild Stress (CUMS)**

The logic underlying the Katz model was followed up in the chronic unpredictable mild stress (CUMS or, originally, CMS) model originally developed by Willner and colleagues (Willner 2005). The measure of the animals’ expression of a depression-like state was the same—anhedonia—but the procedures used to induce the state were significantly reduced in severity in comparison to the Katz procedures. The logic is that depression is the consequence of daily, mild, nonspecific hassles, rather than exposure to one or more traumatic stressors. As with the Katz model, the animals (rats or mice) are exposed over some weeks to uncontrollable events, none of which are
regarded as particularly stressful by themselves. These include periods of food deprivation followed by restricted access to food; water deprivation; rehousing with strange animals; soiling of the cage bedding; changes from normal light–dark cycles; periods of stroboscopic lighting; and cage-tilt. The hedonic deficit is first observed after one to two weeks of the CMS procedures, and is sensitive to a variety of antidepressant treatments, including electroconvulsive therapy and various clinically effective pharmacological agents, including selective serotonin reuptake inhibitors (SSRIs) (Willner 2005). The hedonic changes seen in rats are not limited to sucrose and saccharine consumption, but also include alterations in sexual behavior (parallel to loss of libido in human depressives; Grønli et al. 2005), sleep patterns (Grønli et al. 2004), and intracranial self-stimulation (Moreau et al. 1992).

The CUMS procedure is finding increasing popularity because it avoids the use of strongly aversive treatments. However, the effects of the procedures are not always apparent, and both its robustness and validity have been questioned (McArthur and Borsini 2006). It seems unclear exactly which, if any, of the elements of CUMS procedures are necessary to produce the anhedonic effect, and some workers have chosen to include nonmild stressors such as intraperitoneal saline injections (e.g., Moreau 1997). In our own studies, we have observed both increases and decreases in hedonic tone using the sucrose test following CUMS procedures (Murison and Hansen 2001). While a decrease in hedonic tone might be a useful index of depression, an increase might be the consequence of environmental enrichment (Fernández-Teruel et al. 1997). Because CUMS-induced anhedonia is not completely robust, researchers using the model with other dependent measures should ensure that an anhedonic state has been achieved. Failure to do so may lead to misleading results and interpretations. Notwithstanding the criticisms concerning the robustness of the CUMS model, it should not be discarded. Detailed parametric studies are needed to identify which components of the procedure are necessary and/or sufficient to induce anhedonia, as well as whether there are interactions with other relevant factors, such as early life events and genetic influences.

One interesting principle question attached to the CUMS model is whether the mild refers to the procedures or the outcome. If CUMS produces an effect similar to the more severe CUS and LH methods, can it really be regarded as mild?

Developmental Models

One of the most renowned series of studies in animal psychology involved the separation of rhesus monkeys from their mothers during infancy, performed by Harlow and his colleagues during the 1950s and ‘60s (Suomi and Harlow 1975). The result of this manipulation was dramatic for the offspring, involving social withdrawal, fear, and a condition with parallels to “anaclitic depression” seen in human infants, a phenomenon described as early as the 1940s (Spitz and Wolf 1946). The Harlow studies have been massively criticized, but critics should be aware of the cultural environment in which they were performed, where close physical contact between human mothers and infants was often publicly discouraged by psychologists and psychiatrists (Blum 2002). Harlow’s observations provided a new understanding of human behavior and development that has been central for understanding psychiatric and psychological disorders.

In rodents, there is a considerable literature on the effects of early manipulations. As long ago as 1956, Seymour Levine showed that early handling or maternal separation of rats permanently altered their emotional and endocrinological state in adulthood (Levine, Chevalier, and Korchin 1956; Levine 2005). Generally, brief daily early handling rendered animals less emotional and “stress resistant” as adults, while either several periods of maternal separation, or a single long maternal separation, rendered the animals “stress sensitive” as adults. Problems with the reliability of this paradigm have arisen from the multiplicity of procedures used: Age at separation, length of separation, and maintenance of body temperature are but a few of the critical factors that have varied (Lehmann and Feldon 2000). The more recent studies of Michael Meaney and his colleagues have tied these effects to specific mother–pup interactions, such as licking and grooming, and arched-back nursing, and have
shown that the effects may also be transmitted across generations (Meaney 2010; Szyf et al. 2005). Interestingly, not all of the effects of low interactions are negative. Recent data suggest that offspring that have been subject to low licking and grooming may be better learners under high-stress conditions as adults, whilst those exposed to high licking and grooming may learn better under low-stress conditions as adults (Champagne et al. 2008).

ANXIETY AND ANXIETY-RELATED DISORDERS

Within its normal range, anxiety clearly represents an adaptive phenomenon, protecting animals against unknown threats. This is in contrast to specific anxiety or fear (and phobias) targeted against “known” threats, acquired through learning or through innate predispositions. Anxiety becomes nonadaptive, or a state of disorder, when it interferes with normal function. Anxiety in animals may be measured by a number of techniques, all with high face validity, although the indices do not always correlate well, probably because of procedural differences.

The oldest, and arguably most reliable, measurement technique is that of open field exploration (Hall 1934), either of the “forced” or “free” types. In the former, the animal (rat or mouse, generally) is placed in the center of an empty arena (typically on the order of 1 × 1m square) and its behavior recorded over a chosen period (from 3 to 15 minutes). Behaviors typically recorded are activity around the peripheral walls of the arena (thigmotaxis), crossings of the central area, vertical activity, grooming, rearing, and defecation. In some studies, defecation has been used as the cardinal measure of anxiety. The disadvantage with the method, as well as the advantage, is the potential for collecting vast amounts of data. “Free” exploration involves placing the animal in a start box attached to the test arena. In addition to those measures mentioned above, the most important score for anxiety is the latency to emerge from the start box into the open field area. In principle, this latter test is similar to the dark–light two-chamber test. The advantages and disadvantages of this measure have been discussed at length elsewhere (Archer 1973), but the test remains popular (Kalueff, Wheaton, and Murphy 2007).

A second popular method for rodents is the elevated plus maze (Pellow et al. 1985; Lapiz-Bluhm et al. 2008). Here, a four-armed maze is placed on legs approximately 1 m above the floor. Two arms are enclosed by high walls, while the remaining two are open. The animal is placed in the center facing either an open or a closed arm according to a predetermined design. Anxiety is measured by the ratio of the amount of time the animal spends in the closed versus open arms, and by the number of entrances made into the open arms. In general, an anxious animal will spend more time in the closed arms, and display less overall activity (Paterson et al. 2010). Today, such behavioral data can be collected through highly advanced computerized programs, thus reducing observational errors and time spent observing.

A third method is the defensive burying situation developed by Pinel and his colleagues (Treit, Pinel, and Fibiger 1981; Lapiz-Bluhm et al. 2008). Many rodent species have a natural tendency to bury objects that they perceive to be aversive. The defensive burying test entails presenting animals with an aversive object, such as a shock probe, a discrete source of an aversive odor (e.g., ammonia), or a flashbulb. Pinel and colleagues have argued that the intensity of burying of the aversive object is an index of anxiety, and the response is modulated by anxiolytic agents. However, it could be argued that this is a test of fear toward an identifiable object, rather than general anxiety.

An interesting and simple method is implicitly based on the association between anxiety and increased vigilance. The “audiogenic immobility reaction” is induced by first habituating an animal to a test chamber with a background of white noise of a given intensity, typically on the order of 80 dB. The habituation session is for a given period of 6 minutes. On the subsequent test session, the background noise is abruptly turned off after the first 3 minutes, and the animal’s behavior is observed for the remaining 3 minutes of silence. The index of anxiety here is the time spent immobile after noise is turned off (so-called freezing behavior) and the amount of vertical activity (rearing; van Dijken et
al. 1992c). However, the animal is not totally immobile; typically, the animal will remain in one position, but with head movements indicative of increased vigilance. This method is noninvasive, easy and cheap to perform, and has also proven useful in combination with other behavioral tests, like the open field test mentioned previously (Fahlke, Eriksson, and Hård 1993).

A final method is the acoustic startle response, an assessment of habituation or sensitization effects to different intensities of brief noise. Animals are exposed to a semirandom series of brief acoustic stimuli of varying intensities (for example 95, 105, and 115 dB), and the startle response (bodily muscle contractions) is measured by movement sensors placed under the restraining tube in which the animal has been placed. This method has been highly standardized and elaborated. For example, in rats and mice, the response is potentiated by fear conditioning (Davis 1986) and sensitized by earlier shock (Richardson 2000; Milde et al. 2003; Armario, Escorihuela, and Nadal 2008). It is debatable whether the pure acoustic startle response is a measure of anxiety or fear, although as we shall see, anxiety disorders are related to increased startle. In humans, the startle response may be measured using the eye blink reflex to an air-puff, and both habituation and sensitization to repeated stimuli may be measured. The test is sensitive to previous stress exposures and pharmacological manipulations.

Nonpharmacological methods of raising anxiety levels in rodents again involve the use of aversive stimulation. An important series of studies with regard to this was performed by van Dijken and colleagues (van Dijken et al. 1992a, 1992b, 1992c). Briefly, rats exposed to a small number of shocks (10; well below the number required to induce a state of learned helplessness) exhibited a long-lasting reduction in exploratory behavior in a forced exploration (open field) test up to 21 days after shock. Interestingly, the effect was the smallest one day after shock and grew over increasing post-shock intervals (note that these were independent groups of animals). A later study showed no differences in locomotion 1 or 4 hours after shock. A marked increase in the audiogenic immobility response was seen 21 days post shock. Importantly, the long-lasting behavioral changes were sensitive to anxiolytic, but not antidepressant, drugs. The progressively increasing effects of the short shock regimen over time differ fundamentally from the transient effects of learned-helpless procedures, which are, in contrast, sensitive to antidepressant drugs. In a direct comparison of the effects of a short shock exposure with the effects of learned-helplessness induction, we have shown that the LH shock failed to produce an increase in the audiogenic immobility response 14 days after shock (Murison and Overmier 1998). This is in contrast to the 10-shock paradigm, the effects of which were observed up to 3 months following shock. Thus, exposure to different amounts of a stressor of the same modality results in qualitatively quite different effects.

Animal models are potentially highly useful in studies of one particular mood or anxiety disorder, namely posttraumatic stress disorder (PTSD). It could be argued that both the learned-helplessness and the short-shock methods described here are indeed modeling PTSD rather than depression and anxiety (which, in humans, are seldom found independently of one another). In humans, both complex (associated with multiple traumatic events) and simple (associated with a single major trauma) PTSD is characterized by increased startle reactivity, flashbacks, and avoidance. Some studies have reported lower than normal levels of plasma cortisol in PTSD (Yehuda and LeDoux 2007). Importantly, not all individuals exposed to trauma develop the disorder; the incidence varies between 20% and 60%. It would clearly be useful to develop a model that would allow us to identify risk factors for PTSD. Prospective animal studies have suggested two such risk factors: initial pre-stress startle amplitude (Rasmussen, Crites, and Burke 2008) and low pre-stress levels of corticosterone and hypothalamic-pituitary-adrenal reactivity (Milde et al. 2003; Cohen et al. 2006).

SCHIZOPHRENIA

Animal modeling of human psychosis, such as schizophrenia, poses a much greater challenge than does modeling of the affective disorders, for a number of reasons. Firstly, anyone with even
limited experience with animals recognizes the face validity of such constructs as fear, anxiety, and even depression, at least in mammalian species. But with schizophrenia, there is a lack of the “initial analogy,” so one must resort to conceptual equivalence rather than material equivalence. Secondly, there is clearly an element of learning involved in acquisition of anxiety and depression, facilitating animal modeling. Thirdly, the affective disorders seem to reflect that a normally adaptive phenomenon has become maladaptive. Fourthly, schizophrenia seems to affect higher cognitive processes—a disturbance in thinking (Andreasen 2000)—and may only become manifest in species capable of these processes. Crow (2000) argues that the condition is human-specific and related to the development of the capacity for language. And finally, the term schizophrenia and the diagnosis of the condition may be insufficiently delineated to model.

In summarizing a Nobel symposium on the subject, Terenius (2000) cautions us that “schizophrenia may eventually be shown to be elicited by a large number of mechanisms at a fundamental level … with a final common outcome.” That is, there might be several etiologies leading to a common proximal process responsible for the condition. This is reflected in the multitude of factors found to be of epidemiological importance in schizophrenia, including seasonal effects, infections during pregnancy, drug abuse, etc. It is also important to note that schizophrenia is characterized by three sets of symptoms: positive symptoms (hallucinations, delusions, racing thoughts), negative symptoms (apathy, lack of emotion, poor or nonexistent social functioning), and cognitive symptoms (disorganized thoughts, memory problems, poor concentration and difficulties in following instructions and completing tasks) that are differentially responsive to the so-called typical and atypical antipsychotic drugs (Arnt et al. 2008).

Even given these limitations, models of schizophrenia serve several purposes. Firstly, they may be heuristic, providing a framework in which to ask questions about etiology. Secondly, they may be predictive, i.e., used to test potential antipsychotic treatments, since animals and humans to a large extent share similar neurochemistries and neurocircuitries of the brain. Advances in neuroimaging technology give us the potential to detect brain functioning in vivo in anesthetized or even unanesthetized animals. However, the use of unanesthetized animals requires that the animals be extremely well accustomed to the restraint procedures that are necessary to hold the animals stationary during, for example, functional MRI testing (Febo et al. 2005).

Schizophrenia is often regarded as a cluster of symptoms reflecting thought disorders that are consequent to a brain dysfunction. Because we do not have access to the animals’ minds, researchers have developed animal models based on (a) epidemiological findings and (b) known therapeutic effects in humans. The latter is represented by the fact that antipsychotic agents are antagonists of dopaminergic function, and that dopaminergic agents induce psychotic symptoms. It has been argued that models based on this have high predictive validity, but no construct validity (Lipska and Weinberger 2000).

One of the most important issues is to determine which aspect of schizophrenia one should choose to use as the dependent variable in an animal model. On the behavioral level, perhaps the most promising involves the phenomena of latent inhibition (Shao et al. 2009) and prepulse inhibition (PPI) of the startle response in rats (Romero et al. 2010). The logic underlying the PPI model is that schizophrenia is associated with a deficit in sensory gating, by which the animal is normally able to filter out most of the information available and to direct attention to salient stimuli. The startle response mentioned previously is sensitive to a number of manipulations that will affect intensity and habituation. PPI involves presenting a lower intensity acoustic stimulus immediately preceding the normal high-intensity startle stimulus. When this occurs, the normal response to the startle stimulus is modulated. In human schizophrenics, there is a deficit in PPI (suggestive of a weakening of sensory gating), which correlates with schizophrenics’ thought disorders (Brenner et al. 2009; Geyer et al. 2001). It is important to note that the deficits in PPI are not specific to schizophrenia, but are also found in other disorders associated with deficits in sensory, motor, or cognitive gating.
Etiological models of schizophrenia have either focused on direct pharmacological manipulations (particularly of the dopaminergic and glutamate systems, which seem to directly mimic the abnormalities of the human schizophrenic brain) or nonpharmacological manipulations aimed at exploring other etiological factors. With respect to the former, dopamine agonists, including apomorphine, reduce PPI in rats, primarily through acting at the D2 receptor, and the effect can be blocked by the typical antipsychotic drug, haloperidol. The effect is also blocked by atypical antipsychotic drugs, such as clozapine.

The PCP model in rats and mice involves glutamate antagonist action, and again is associated with deficits in PPI (Brigman, Graybeal, and Holmes 2010). The effect of PCP is not reversed by typical antipsychotics, such as haloperidol. These models, while having high predictive validity (and thus being useful in development of therapeutic strategies), have little to say about the natural etiology of schizophrenia. Given that it is well established that schizophrenia is associated with dopaminergic abnormalities, it should not be surprising that pharmacological manipulations of the dopaminergic system will induce changes paralleling schizophrenia.

Animal models using brain lesions derive mainly from postmortem findings of abnormalities in structures such as prefrontal cortex in humans (Lotstra 2006). The hippocampal lesion model developed by Lipska and coworkers has contributed significantly to screening and developing antipsychotic treatments (Lipska et al. 2002).

There is considerable interest in the role of early environmental factors in vulnerability to schizophrenia, even if the disorder typically only becomes fully manifest after puberty, with onset at between 18 and 35 years of age in humans. There are a number of hypotheses that damaging factors may already be present early in life. Candidates for the induction of the disorder include prenatal infections (Mednick et al. 1988; Romero et al. 2010) and early stress (Feldon and Weiner 1992). With respect to the former, several studies have shown how viral infections disrupt normal neurodevelopment (for review, see Lipska and Weinberger 2000). With respect to early stress and environmental manipulations, research has focused in particular on the effects of early handling, maternal separation, and isolation rearing on PPI in the adult rat. Ellenbroek’s studies, using rat lines selected for high or low sensitivity to apomorphine, suggest that a single 24-hour maternal separation on day 7 or 10 induces a deficit in PPI (Ellenbroek, van den Kroonenberg, and Cools 1998). In a critical review, I. Weiss and Feldon (2001) claim no evidence of either early handling or maternal separation effects on PPI, but substantial evidence for PPI deficits in adult animals that have been socially isolated in the period from weaning to adulthood. The effect is reversed by both typical and atypical drugs.

“PSYCHOSOMATIC” AND FUNCTIONAL DISORDERS

The term psychosomatic, in its original form, means that psychological factors may influence the initiation and development of somatic dysfunction. In contrast to earlier views, few today would argue that a disease state is “caused” by psychological factors. However, most disease states are multifactorial and accessible to psychological influences, through either direct nervous control or psychoendocrine influences.

Historically, one of the most studied of these is stress-induced gastric erosions. Although these localized bleeding areas of the stomach lining are induced by “physical” stress, such as cold or electric shock (usually in rodents), the severity is strongly influenced by psychological conditions before, during, and after the stress exposure. In 1968, Weiss showed in a series of studies that severity of ulceration was modulated by providing the animals with control over a physical stressor, in this case electric shock (J. Weiss 1968). The Weiss studies provided a framework for later models of the relationship between effort, feedback, and human disease (Ursin, Murison, and Knardahl 1983). In rats, exposure to an earlier uncontrollable shock stress renders the animal more sensitive
to stress gastric erosions, an effect that is related to induction of learned helplessness. This effect is blocked by naloxone and mimicked by morphine. Prior experience with controllable stress and coping, however, appears to reduce the animals’ vulnerability to stress erosions (Overmier, Murison, and Milde 2006).

One has to be cautious in interpreting these stress erosion studies as a model for ulcer. Since the discovery of *Helicobacter pylori*, ulcer disease in humans has been regarded as primarily an infectious disease. However, most clinicians and basic researchers agree that other factors are involved, as evidenced by the facts that so few infected individuals develop ulcer (Weiner and Shapiro 1998; Levenstein 1999; Murison 2001) and that there is a placebo treatment effect in humans (de Craen et al. 1999). Additionally, both older experimental and newer field studies on primates clearly implicate a role for psychological factors in gastric pathology in our closer relatives (Brady et al. 1958; Tarara, Tarara, and Suleman 1995). Others have suggested that gastric erosions of the kind seen in these studies might better be models of erosive prepyloric changes as sometimes observed in patients with functional (nonulcer) dyspepsia (Berstad and Nesland 1987). Gastric erosion studies in animals may also provide a fruitful area for studies of stress–brain–immune interactions. Animal and human studies have shown changes in the bacterial content and adhesion in the gastrointestinal tract in response to stressors (Söderholm et al. 2002; Knowles, Nelson, and Palombo 2008). And Elliott et al. (1998) have reported changes in bacterial population characteristics as a response to induction of gastric erosions.

Other studies of psychological influences on gastrointestinal pathology have focused on animal models of inflammatory bowel disease (IBD). The models employed have included the use of different chemicals like TNBS (trinitrobenzenesulfonic acid), DNBS (dinitrobenzenesulfonic acid), and DSS (dextran sulfate sodium) to induce colitis. Evidence is emerging that vulnerability to, and recovery from, such chemically induced IBD as ulcerative colitis may be influenced by stress (Collins et al. 1996; Gué et al. 1997; Million, Taché, and Anton 1999). In nonhuman primates, the cotton-topped tamarin shows spontaneous colitis, a phenomenon that again has been ascribed to stress (Wood et al. 2000).

In the 1970s, evidence began to mount for brain–immune interactions. In particular, the studies of conditioning of the immune response by Robert Ader and his colleagues (Ader and Cohen 1975) attracted considerable attention. Little credence was given to the phenomenon until both endocrine and nervous mechanisms were identified (Dunn 1995). Even then, there remained doubts as to whether the so well-demonstrated interactions had a biological and clinical significance in animals or in humans. While stress clearly impinges on the immune system, and vice versa, implications of classical conditioning have been little explored. Exton and colleagues have convincingly shown that classical conditioning of cyclosporine-induced immunosuppression in the rat has dramatic effects on longevity following transplant surgery (Exton et al. 2000). Such findings, together with the enormous efforts being made to identify molecular mechanisms, will inevitably lead to the eventual recognition of the importance of the animal work. In a related area, it is also known that conditioning procedures are effective in altering mast cell function in the gut, a finding with implications for colon disease (MacQueen et al. 1989), among other research areas.

Functional disorders are more difficult to model in animals, simply because they are defined by the absence of identifiable organic causes or changes. However, studies by Stam and her colleagues (Stam et al. 1999) have made use of gut recording techniques in rats to investigate how prior life events might affect intestinal motility, a potential model for irritable bowel syndrome, a disorder also associated with significant levels of psychopathology. This functional disorder is, in humans, sometimes also associated with prior infections, which might sensitize the perception of autonomic signals. There is clearly great potential for pursuing animal models in this field. Other functional disorders, such as fibromyalgia and lower back pain, will be more difficult, but not necessarily impossible, to model.
ETHICAL ISSUES

Compared to somatic disorders, psychological disorders are often regarded as low status, despite the huge costs associated with them, both in terms of individual suffering and economic costs for society. Society is obliged to employ all available tools to alleviate these disorders based on clear scientific understanding of the underlying mechanisms. At the same time, psychological researchers must be vigilant with respect to using the most humane end points in their experiments. In psychological studies, these are most often changes in behaviors, and rarely involve somatic changes, even though most scientists recognize the mind–body interaction.

Within psychology, animal research is rather peculiar, in that numbers of animals are kept to a minimum, while human psychological studies tend to involve far larger numbers of subjects than is the case in traditional medical experiments. Reduction of animals in research is one of three (including refinement and replacement) principles (the three Rs) originally proposed by Charles Hume in 1954, leading to a book published in 1959 by Russell and Burch (W. Russell and Burch 1959), and these are highlighted in the education and training of all those using animals in research through the Federation of European Laboratory Animal Science Associations (www.felasa.eu) and other similar organizations. The small numbers of subjects used in animal psychological studies represent both an advantage and a disadvantage. On the positive side, significant findings with small sample sizes are powerful. On the negative side, such findings must be independently replicated, preferably by another group of researchers. It could also be argued that replications should include minor procedural variations to ensure that the phenomenon is truly robust and can be generalized across experiments and environments. When using animals, the purpose must be clearly identifiable, with specific hypotheses and appropriate research designs. Of course, approval from local ethics committees must be obtained prior to beginning any research project. Despite enormous progress in alternative techniques and methods, the reality is that there is still an important need for animal research if we are to gain real insight into the etiology and treatment of human psychological disorders.

CONCLUSION

Typical examples of how animal models have been used in studies of psychological disorders are shown in Table 3.1.

It is clear that animal models have provided insight into the etiology and mechanisms underlying the affective psychological disorders, including depression and anxiety, and these have had an impact on the development of theories and treatment of human disorders. The animal-based cognitive theories of depression have led to an understanding that behavioral therapies may replace, or at least provide an important supplement to, pharmacological strategies (Schwartz and Schwartz 1993). Similarly, cognitive behavioral approaches are proving useful in the treatment of anxiety disorders such as PTSD (Foa 1997).

For human psychosis, the implications of animal research on normal brain development have been crucial in understanding how normal maturation of specific brain areas may be affected by early developmental pathology. By viewing schizophrenia as neurodegenerative, the models at least provide us with an understanding of risk factors and putative mechanisms, and in the longer run, an understanding of the course and interactive mechanisms. The impact on treatment strategies for the future most likely lies within the psychopharmacological domain.

For the classical psychosomatic conditions, in which organic alterations are identifiable, the impact of animal models is to emphasize the need for combining psychological and medical treatments, with the latter to remedy the physical symptoms and the former to prevent relapse. Both for
these, and for the functional disorders, an important lesson from the basic research concerns the importance of changing individuals’ core beliefs concerning their control over the environment. Animal models have been developed for several other psychological disorders not discussed here; for alcoholism (Lovinger and Crabbe 2005) and drug craving (Giorgi, Piras, and Corda 2007); memory disorders (Overmier, Savage, and Sweeney 1999), including age- and dementia-related disorders; attention-deficit hyperactivity disorder (ADHD) (V. Russell 2007); aggression (Huhman 2006); and fears and phobias (Mineka 1985). The reader is directed to recent reviews that deal with these in greater detail than is possible here.

In all animal model research, consideration must be given to genotype–environment interactions. Different strains of animals may be more suitable than others, depending on the disorder one wishes to address, and the rapidly developing field of functional genetics will hopefully provide us with a much richer picture of these interactions. In the meantime, however, even a cursory examination of the basis of the various models reveals extraordinary variations in the strains of animals used and the exact procedures employed. If we are serious in our use of animal models, greater emphasis should be placed on parametric studies, both with respect to strains and species, and to procedures, including husbandry.

**REFERENCES**


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**Table 3.1 Examples of Commonly Used Methods for Induction and Testing in Chosen Animal Models of Psychological Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Induction Method</th>
<th>Test/end point</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Learned helplessness</td>
<td>Learning impairments, neurochemistry</td>
<td>Overmier and Seligman 1967; J. Weiss et al. 1981</td>
</tr>
<tr>
<td></td>
<td>Chronic unpredictable stress</td>
<td>Anhedonia, neurochemistry</td>
<td>Katz 1982</td>
</tr>
<tr>
<td></td>
<td>Chronic mild stress</td>
<td>Anhedonia, neurochemistry</td>
<td>Willner 2005; Murison and Hansen 2001</td>
</tr>
<tr>
<td>Anxiety/PTSD</td>
<td>Footshock</td>
<td>Startle, defensive burying, vigilance</td>
<td>Richardson 2000; van Dijken 1992c; Treit et al. 1981</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Pharmacological manipulations (e.g., dopaminergic system)</td>
<td>Pre-pulse inhibition in startle test</td>
<td>Brigman et al. 2010; Lipska et al. 2002; Feldon and Weiner 1992</td>
</tr>
<tr>
<td></td>
<td>Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal separation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosomatics</td>
<td>Stress</td>
<td>Organic changes (e.g., gastrointestinal inflammation and ulcerations)</td>
<td>Gué et al. 1997; Overmier et al. 2006</td>
</tr>
<tr>
<td></td>
<td>Conditioning of immune responses</td>
<td>Changes in immune parameters; survival rate</td>
<td>Exton et al. 2000</td>
</tr>
<tr>
<td>Functional GI disorders</td>
<td>Stress, early experience</td>
<td>Gastric motility</td>
<td>MacQueen et al. 1989</td>
</tr>
</tbody>
</table>

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