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The Role of Behavior in Translational Models for Psychopathology: Functionality and dysfunctional behaviors

D. Caroline Blanchard^{a,*}, Cliff H. Summers^{b,c}, and Robert J. Blanchard^{a,d}

^aPacific Biosciences Research Center; 1993 East West Road, Honolulu, HI 96822, USA

^bDepartment of Biology, University of South Dakota, Vermillion, SD 57069, USA

^cNeuroscience Group, BBS, Sanford School of Medicine, University of South Dakota, Vermillion, SD 57069, USA

^dDepartment of Psychology, University of Hawaii, Honolulu, HI 96825, USA

1. Translational research; a very short history

In the history of science, there have been at least three major motives for research aimed at understanding natural phenomena. One, perhaps more important in an historic context but still occasionally encountered, is to justify some philosophical, religious, or aesthetic viewpoint. Another, perhaps most characteristic of the majority of contemporary researchers, is the intrinsic interest of the phenomenon. A final motive is to understand a phenomenon or process in order to put that knowledge to use against human problems; to “translate” understanding into effective strategies to control organisms, processes, or events. To neuroscience researchers broadly, and behavioral neuroscience researchers in particular, it is obvious that this “translational” motive is currently on an up-cycle.

For many researchers, struggling to come to grips with this development, a translational focus is regarded as a recent phenomenon. In fact, it is not: Both government and private funding for research, and the agencies charged with directing and overseeing this funding, have long been aimed at solutions to human problems. This can be seen in the creation of National Institute of Health (NIH) and National Science Foundation (NSF), both largely in response to problems arising during crisis (war or incipient war) conditions, reflecting the desire to use research to deal with these problems. Even the European Science Foundation, a consortium of 72 research organizations from 30 countries founded in 1974, is in part guided by the funding priorities developed by the NIH and NSF mandates (European Medical Research Councils, 2007). In the years after World War I, NIH was created partly in response to medico-chemical events emerging in that war (Office of NIH History, n.d.). While NSF was created after WW II, in large part to deal with the technology of the Cold War, its origins lay in the days leading up to WW II, when the need for new and more powerful weapons was becoming apparent (National Science Foundation, n.d.).

And now, there is another “War”: This is often more broadly conceived as an economic crisis in the United States, Europe, and Japan, which has had ramifications for most of the world, as well as for the neuroscience research community (Amara et al, 2011). However a

*Corresponding author: D. Caroline Blanchard; Phone: +1-808-956-8067; Fax: +1-808-956-9612; USA.

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major, perhaps *the* major, component of this crisis is due to the rapidly increasing burden of health care. Around the world, health care costs increased for every nation monitored during the period from 2000 to 2007 (World Health Organization, 2010). In the US, health care costs increased by over 1,000%, from 1980 to 2010. General inflation increased by about 260% over the same period, and population by about 37%, indicating that the inflation-adjusted rise in per capita health care cost was nearly $\times 3$ over this period. In 2010, the proportion of the US gross domestic product accounted for by health care was over 17.5%; and above 10% for countries including Afghanistan, Costa Rica, Cuba, Georgia, Kiribati, Lesotho, Liberia, Moldova, Palau, Rwanda, Sierra Leone, Tuvalu, as well as most of the wealthier countries of Europe (World Health Organization, 2013). Health care costs for treatment of chronic diseases in the US constituted over 75% of national health expenditures; a figure of particular interest in the present context, in that a high proportion of behavioral or mental pathologies are chronic in nature. In terms of Disability Adjusted Life Years (DALY) neuropsychiatric disorders are by far the most problematic medical condition in the United States (TedxTalks, 2013), with economic impacts that are certain to continue until effective methods for treatment, or, better yet, prevention, are found.

If history is any guide, a major push for translational research is likely to last about as long as do the high profile problems giving rise to this push. As one example, funding for NASA, the National Aeronautics and Space Administration, beginning abruptly in 1958 with the successful launch of Sputnik by the then Soviet Union, rose sharply through the decade of the 60s, peaking in 1966, as the success of the US space program *vis-a-vis* the Soviet Union was becoming apparent. It was not reduced below 2% of the federal budget until after the first moon walk in 1969, but has since steadily declined to the current level of less than 0.5% of the federal budget (Budget of NASA, n.d.). By this criterion, success in dealing with important problems, a translational emphasis for behavioral neuroscience research is here to stay for a long time. The issue is how to make the process more effective. In particular, as behavioral aspects of neuropsychiatric disorders emerge as consequences of a process of brain abnormality that may have taken a long period to develop (TedxTalks, 2013), even early stage identification of such conditions through behavior change may be too late for optimal intervention in the abnormal brain process. This situation emphasizes the need for recognition of biomarkers of neuropsychiatric conditions, enabling early intervention, and for understanding the biology of the abnormal process, to enable effective intervention or even prevention.

2. Animal models

Animal models are a core feature of much—likely most—research on neuroscience-relevant psychopathology. Legal prohibitions and ethical strictures severely limit the use of invasive or damaging research using human subjects but, with many qualifications, permit these procedures on a range of nonhuman species. Even so, the use of animal models in research has never enjoyed universal acceptance. On the pragmatic end of these objections, there is a view, widespread for those involved with some neurodevelopmental and psychiatric disorders, that nonhuman animals can never express the full range of abilities, and thus disabilities, of humans. They argue that with or without disorders, nonhuman animals cannot provide adequate models for many human behaviors. The most pragmatic objection is that whether or not appropriate animal models are theoretically possible, there simply are no adequate animal models for some important disorders, particularly those that focus on changes in subjective experience.

Yet the need for animal models in biobehavioral research is clear. In addition to the ability to use a wider range of manipulations, life span and developmental timing are also important issues (Groothuis & Trillmich, 2011), becoming crucial in research on developmentally-

relevant manipulations that might take decades to produce their full pattern of results in humans. Cost, and the ability to control the genetic, environmental, and experiential factors of interest as well as others that are not being directly manipulated, are additional reasons that experimental research often requires animal models. In consequence, attention to the quality, including validity, specificity, and comprehensiveness, of animal models is a crucial component of the effectiveness of translational research in behavioral neuroscience (van der Staay et al, 2009).

3. Conceptualizing validity of animal models

McKinney and Bunney, in 1969, proposed a set of criteria for assessing the validity of animal models, that has been expanded and modified over time, particularly by Paul Willner (Willner, 1984; 1991; Willner and Mitchell, 2002). The original McKinney and Bunney compilation stressed similarity between the model and the condition being modeled, in terms of etiology, biochemistry, symptomatology and treatment, and also emphasized the need for objective and reliable measurement of the behaviors being evaluated. They also noted the need for independent observers/researchers to agree on how these behaviors should be interpreted. The McKinney and Bunney criteria were grouped by Willner into three categories: 1) Face validity, largely relating to similarities between the symptomatology of the disorder and the behaviors seen in the animal model; 2) predictive validity, relating to the success of predictions made from the model, loosely related to the McKinney and Bunney notion of similarity in treatment effectiveness; and 3) construct validity, relating to the model's theoretical rationale (Willner, 1984). While recognizing the value of both etiology and biochemistry as components of a valid model, Willner notes that for conditions such as depression, the disease focus of both the McKinney and Bunney treatment, and of Willner's writing, both etiology and biochemistry are imperfectly understood, making them less useful as criteria for validation of models.

It is important to note that much of the early, and also current, attention to questions of validity of animal models has been explicitly directed at animal models of depression (Willner, 1984; Hendrie and Pickles, 2012), a disorder characterized by imperfectly understood etiology and biological mechanisms, as well as by a range of potentially important behavioral symptoms, also imperfectly understood. This focus has expanded to include attention to other conditions such as schizophrenia, drug abuse/addiction, and autism; again, disorders characterized by imperfectly understood etiology and biological mechanisms, as well as by a range of potentially important behavioral symptoms, also imperfectly understood. In contrast, one of the very highest profile diseases of recent years, HIV/AIDS, while also having a number of poorly understood behavioral aspects, and serving as the topic of an intense research effort stretching over 30 years, has had relatively little attention devoted to analysis of the validity of the animal models on which this research was largely done. The reason for this difference is clear: The etiology of AIDS, infection by a specific (albeit rapidly mutating) virus, was established relatively early in the AIDS epidemic (Gallo, 2006), resulting in a straightforward model about which little discussion of model validity was necessary.

Model validity becomes potentially problematic and an important focus of concern, if and only if the etiology and biology of a condition are not well understood. If there does appear to be a focal cause for a disorder and clear biological markers for it, then that cause is typically characterized and verified in research that involves the condition itself, as indexed by its biomarkers in addition to other criteria. If this condition and its biomarkers are found in a nonhuman species, this is indeed an animal model, but one that requires little or no additional verification. For conditions without clear biomarkers and with a more complex etiology involving an interaction of genetic and environmental/experiential conditions,

particularly those for which multiple conditions on both the genetic and experiential sides may be relevant, the validity of animal models is more questionable, and research aimed at establishing this becomes more difficult. When these conditions are combined with symptom profiles that are largely or exclusively behavioral in nature, as is the case for depression, anxiety, drug addiction, schizophrenia, autism, obsessive-compulsive disorder (OCD), anorexia, and some others, the need to find or produce, analyze, and evaluate animal models of the disorder becomes paramount.

The difficulties in carrying out this task can be seen in analyses of the shortcomings of each of the three validity categories outlined by Willner (Willner, 1984; 1991; Willner and Mitchell, 2002).

4. Construct validity

Construct validity is sometimes treated as the most important of the three criteria for validity outlined by Willner (Sarter and Bruno, 2002); a position with which Willner appears to agree (Willner and Mitchell, 2002). While the concept of construct validity is itself interpreted in different ways, it potentially involves any and all elements that define or characterize the disorder, for example in terms of its presentation in the Diagnostic and Statistical Manual (DSM) or the International Classification of Diseases (ICD). The focus of construct validity may fall on different elements of the concept, but for psychopathologies it typically includes substantial attention to predisposing factors and antecedent conditions, ranging from genetics through exposures to toxic and/stressful exposures, to specific precipitating events. Biomarkers are included, if these are available.

Behavior may be included as one component of the pattern of similarity of a model to factors contributing to the concept/definition of the target condition but behavioral parallels are often treated as specifically related to face validity. One possible rationale for this exclusion is that antecedent conditions relevant to model validity can sometimes involve the same, rather than similar, factors, such as the use of particular drugs to induce addiction, or manipulations of genes that have an established relationship to the disorder, an identity of factors that is not easily applied to behavior. More commonly, however, the model manipulations used do not involve identity, but instead some degree of similarity for core aspects of characterization, based on descriptive studies of the disorder, or on theoretical interpretations of its causes. Some examples of these include the use of threatening or painful events to elicit behaviors or behavior changes that are presumed to be related to anxiety; chronic stressors used to induce changes that are treated as measures of depression; and manipulations based on specific clinical findings such as the connection between maternal infection/inflammation during pregnancy and a behavioral phenotype in the offspring of that pregnancy. The rationale for such use is straightforward: Anxiety disorders often do involve traumatic or painful experience; depression is often linked to previous or current stressful events; gestational infection or inflammation does increase odds ratios for schizophrenia (Meyer and Feldon, 2010) or autism (Patterson, 2011). On the other hand, each such condition can occur without any notable experience of the type described, or indeed without any experience that has as yet been specifically linked to that disorder. Also, while all of these conditions do appear to have substantial genetic components, the search for specific genes that may be involved in each has thus far not yielded a clear or comprehensive picture for any of them. These considerations suggest that although construct validity may involve the most broad-based consideration of parallels between model and target, for many or most psychopathologies these parallels involve broad brush-strokes, rather than specific details.

5. Predictive Validity

Predictive validity has been used to circumvent these difficulties in the establishment of animal models. Jeffrey Gray's (1978) suggestion that anxiety is what anxiolytics reduce is perhaps the best known example of validation based on drug effects believed to be so well-established that they could be used to define animal models for a field of research. While this specific approach to anxiety has since given way to a number of measures based (very) broadly on the view that anxiety is an important component of defensiveness to potentially threatening situations or stimuli, the use of drugs as part of the definition of some pathological behavioral states remains a common strategy, typically falling under the rubric of "predictive validity" if a validity issue is explicitly discussed.

Both drug-induction and drug-reduction are used to assess predictive validity in animal models. For depression, most such usages involve the ability of established antidepressants to normalize behaviors that are induced or changed by some type of condition or manipulation that produces a potentially depressogenic or depression-relevant pattern. For other conditions, such as schizophrenia, drug induction of behaviors that can then be used as measures of the disorder are more common. Thus amphetamine and other dopamine agonists have been used to produce behaviors to serve as models of schizophrenia, (Kety 1972), based on views of the involvement of striatal dopamine systems in the disorder (Simpson et al, 2012); while ketamine, an NMDA receptor antagonist is used on the basis that it that can induce hallucinations, a major positive symptom of schizophrenia (Nowak et al, 2012). Notably, when predictive validity is utilized as the major criterion for asserting the validity of a particular animal model, the behaviors that serve as the dependent variables in this model may be very diverse and sometimes of clearly secondary interest. Thus immobility in the forced-swim test is more commonly used as a measure of depression (Castagne et al, 2011), but has also been used as a model for the negative symptoms of schizophrenia (Chindo et al, 2012). In general, use of drug effects, positive or negative, as a major criterion for validity of animal models is associated with reduced emphasis on an independent analysis of the behaviors being altered by the drug. In general, simplistic interpretations of the predictive validity concept tend to deflect attention from complex biochemical and behavioral etiologies and outcomes by focusing these factors on mechanisms produced or alleviated by a single drug, or class of drugs.

6. Behavior: Face Validity?

Behavioral similarities, described as providing 'face validity', have typically been the least appreciated criteria for animal models. Interestingly, this skepticism does not seem to importantly reflect the genuine differences in body action patterns for a number of behaviors: It is immediately obvious that many of the "normal" actions of rats, mice, or other nonhuman animals are substantially different, on a basic movement-description level, from the human actions having exactly the same function. Humans, locomoting, typically use a single pair of appendages, whereas almost all other mammals use two pairs, and nonmammalian species may use a variety of mechanisms. Copulation in humans is extremely varied, but in rats, mice, and indeed most primates, it is largely limited to a single type of approach that, while certainly one of those utilized in humans, is less common in that species. Human mothers typically carry babies in their arms; mothers of many mammal species carry them held by the mouth, and many others, such as most ungulates, do not carry their babies at all. Yet no one is likely to argue that, despite the utilization of different body parts, and different types of approach/contact to relevant others, locomotion, copulation, and maternal retrieval of babies cannot be appropriately modeled in a range of nonhuman species. The core similarity here appears to be functionality, that locomotion involves

moving from one place to another, copulation involves sexual contact, and carrying an infant or inducing it to move share a function of changing its location.

Other similarities or dissimilarities between animal and human behavior reflect motivational or incentive states. A statement that depressed people seldom kill mice (attributed to Paul Willner and confirmed in a personal communication) suggests, jokingly, a problem with the use of mouse killing as an animal model of depression. An interesting aspect of this problem is where the rat-human disjunction is seen to exist. It is not that rats kill mice by biting them, which they do; whereas were depressed people to do so, a bite would, one imagines, be less often the mechanism of choice. Instead the comment suggests that similarities in the presumed motivation underlying a behavior are crucial to interpretation of that behavior: Mouse killing by rats suggests a motivation/incentive for the putatively depressed rat that is presumed not to be valid for depressed people; although, parenthetically, we might suggest irritability or defensive aggression as potentially bridging motives. This view, that some motivation or incentive state is the crucial factor in behavioral similarities, may underlie ready acceptance of such activities as locomotion, copulation, and maternal retrieval of babies by nonhuman animals as valid models of human activities: They are easily seen as involving similar motivations or incentives and, usually, similar and specifiable outcomes, implying functional parallels, for both species. We understand what the animal is doing and accept it as a valid model of human behavior, because we recognize why the animal is doing it. This recognition may be intuitive, such as “She is carrying her baby back to the nest” in which the intuition involves recognition –undoubtedly based on some previous experience of this event in either animals or humans-- of salient features of the situation; or, it may come about only through a potentially lengthy series of analyses of not only the behavior itself -- about which more later -- but also of the situation and important stimuli in it, the age/sex/species/condition of the animal involved, and the outcome of that behavior for this animal. As a general rule, the more that these factors and the relationships among them are understood for a specific behavior, the clearer will be the motives and incentives associated with that behavior, as well as its normal functioning in the conditions in which the species evolved.

The concept of “face validity” may also be denigrated specifically because the “face” is so much less important as a component of behavior in the laboratory rodents that typically serve as subjects in animal models of biobehavioral disorders, than in humans (Figure 1: Patterson, 2011). As might be expected for largely nocturnal species, rodents tend to utilize other modalities than vision for conspecific communication and their facial expressions are undoubtedly somewhat impoverished. Impoverished, yes, but perhaps not missing altogether. Facial expressions do differ systematically for rodents in particular circumstances, such as in response to pain (Langford et al, 2010). Additional analyses provide some clues as to the specific functions of these facial “expressions”. In attacking resident mice there are several consistent differences in facial muscle movements, as opposed to those of the intruder mice that are being attacked (Figure 2: Defensor et al, 2012). Degree of eye opening is the most salient difference, with the resident's eyes narrowing to a slit while those of the intruder are wide open. This difference can be linked to the differential consequences of the encounter for the two: If the resident bites the intruder, its bites are aimed at non-facial targets such as back and flanks, whereas intruder bites at the resident are made almost exclusively on the resident's face and head (Blanchard et al, 1979; Brain, 1979). Eye narrowing, and associated changes such as bunching up of muscles in the nose and cheek adjacent to the eyes, as well as flattening of the ears, may all be parsimoniously interpreted as protective of vulnerable sites on the face and head, in a situation in which such bites are likely (Defensor et al, 2012). While the narrowed eyes of the attacker and the wide-open eyes of the intruder may have some degree of resemblance to eye conformation in angry vs. fearful humans (Ekman, 1972) and this resemblance may

suggest evolutionary connections between facial changes that are adaptive in protecting specific structures and their eventual use as functional communicatory systems, it is important to note that there is presently no evidence that they are used for communication in mice.

Such examples provide a useful corrective to attempts to assess the validity of animal models purely in terms of specific motivations or incentives. Instead, they support the value of a more basic and more objective analysis involving functional outcomes of particular behaviors in specific situations. This view does not suggest that analyses of motives, or incentives are irrelevant: Both of these are interesting, legitimate, and highly informative aspects of a particular behavior pattern and may ultimately add to an understanding of that behavior and its relationship to antecedent events and subject characteristics. However, they are not essential components of a functional analysis; and may not be relevant to the interpretation of that behavior as emitted in a particular model species. For these reasons, we suggest that adaptive functioning, based on the general evolutionary history of the animal, responsive to subject, stimulus, and situational characteristics, and characterized in terms of its immediate and longer-term outcomes, can constitute a highly efficient basis on which to evaluate parallels between behaviors in an animal model, and those of people.

7. The functionality of dysfunctional behaviors

Understanding the normal function of a pathological behavior is difficult. A psychopathology is, by definition, aberrant; different than the behaviors typically seen in related situations in the same species. Pathological behaviors may be broadly discordant with respect to typical, and presumably evolutionarily adaptive, behaviors in a number of different ways: Too much, as for many aspects of anxiety and defensiveness; too little, as for social behaviors in autism or schizophrenia; too bizarre, as in the thinking patterns of florid schizophrenics or individuals in the manic phase of bipolar disorder; either too much or too little, as for sleep in depression; poorly connected to the stimuli/situations that normally influence these behaviors, as in virtually all of the above; nuanced, with selective omission or enhancement of some but not all behavioral elements, as for OCD. In psychopathology the motive for performing a particular behavior may be different than the typical motivation associated with that action; as in OCD where repetition of behavioral elements appears to be as much motivated by desire for an anxiety-reducing sequence completion as by the achievement of a functional outcome such as locking a door (Zor et al, 2011). In line with the view that functionality is the basic criterion for assessing behavior parallels between animal models and human behavior, it is notable that functionality is also a core criterion for psychopathology: Pathological behaviors are almost always less functional than the behaviors typically seen in a particular situation.

An emphasis on evaluation of behaviors and their outcomes in the context of a detailed description of antecedent and subject characteristics suggests an analytic end-run around the problem of functionality for dysfunctional behaviors. What behaviors should –and typically would – be functional for a particular combination of stimulus/situational factors, and subject characteristics? Indeed, how can it be determined that relevant parameters of these factors have been taken into account? The problem is somewhat analogous to that faced by comparative psychologists in the study of learning; that conditions that might be optimal for one species might not be optimal for another, very different, species. The solution to understanding adaptive variation in learning (Bitterman, 1960) was the procedural examination of systematic variation, providing a range of situations and stimuli to clarify the relationships of these to behavior, and thus permit comparisons across species. This call for systematic variation rather than standardization has recently been repeated by Richter et al, (2009).

A still more inclusive view of this approach can be found in Tinbergen's 'four questions' (1. mechanism, 2. development/ontology, 3. function and 4. Evolution/phylogeny: Tinbergen, 1963) outlining what needs to be known in order to achieve a comprehensive understanding of a particular behavior. These "questions" add issues of subject species (phylogeny) and age (ontogeny) to the mix, permitting an integration of this information with an analysis of the function(s) of the behavior in question for subjects of that type and age. This approach suggests that a substantial part of the problem in recognizing where functional behavior patterns may be distorted in psychopathology may be due to lack of detailed information concerning the normal patterns of behavior seen in many crucial contexts of the lives of animals, compared to those seen in similar contexts, in people. It suggests that when these "normal" behaviors, in their full range of nuanced expression, are adequately characterized, their parallels from nonhuman mammals to people become clearer, as do deviations from those parallel behaviors on both levels.

8. Defensiveness: Fear, Anxiety, and Depression

One recent example incorporating systematic variation in situational and stimulus conditions is focused on defensive behaviors; potentially related to fear, anxiety, and depression. Defensiveness involves a crucial set of behaviors including avoidance, flight, freezing, risk assessment, etc. that have evolved in the context of the myriad dangers that confront members of virtually every animal species. Specific behavioral components of defensiveness have been characterized in rodents in a variety of situations involving different sets of threat stimuli and situations (reviewed in Blanchard et al, 2005), for subjects of different ages (Hubbard et al, 2004); and in association with different 'coping strategies' (Benus et al, 1991) outlining the relationships between these, and the particular responses they typically elicit.

These same relationships between threat situations/stimuli and specific behaviors have also been evaluated in human self-reports, responses to scenarios, and behaviors in computer-based "games"; with findings indicating that many of the specific defensive behaviors shown by rats and mice under particular combinations of threat stimulus and situational characteristics are also seen in the behaviors that people select or demonstrate under similar circumstances (Blanchard et al, 2001; Perkins and Corr, 2006; Shuhama et al, 2008). As noted in Table 1 (Table 3 from Perkins and Corr, 2006) these relationships have proved to be very consistent across human subjects, as well as between people and rats.

The translational relevance of these relationships has additionally been demonstrated in significant correlations between particular choices of human subjects on defensive behavior scenarios and the scores of these same subjects on trait anxiety and psychoticism scales (Perkins and Corr, 2006), and the approach has also been extended into the realm of personality analysis (Perkins et al, 2010), and utilized to examine fear- and anxiety-related behaviors in a military training setting (Perkins et al, 2007). On a more theoretical level, some components of the relationships between threat stimuli/situations and behaviors have been incorporated into a neuropsychological view of fear and anxiety (McNaughton and Corr, 2004) and utilized in computer tasks in association with analyses of brain activity (Mobbs et al, 2009). Finally, risk assessment, including scanning of the environment and hyperattentiveness to stimuli that might indicate threat along with disruption of ongoing behaviors, was identified in the animal model as particularly associated with generalized anxiety (Blanchard et al, 1989). Video or still photographs of human faces instructed to respond to an ambiguous threat displayed the scanning components of this pattern (eye darts and head swivels) and were labeled by naïve observers as reflecting anxiety, rather than fear or other specific emotions (Perkins et al, 2012), providing an additional case where adaptive functioning appears to be involved in the specific elements of facial expressions. Thus in

humans, this expression/facial action does reflect emotionality, and indeed may serve to communicate this emotion to observers. Notably, while facial 'expressions' as reflected in a still photograph may or may not be associated specifically with anxiety or other emotion in mice, the rodent facial actions of scanning the environment and hyperfocus on ambiguously threatening stimuli do appear to be functionally similar to these human facial actions. Darwin's (1872) treatment of facial expressions as functional in communicating intent to another animal, while undoubtedly true and useful in many cases, should not obviate analyses of such expressions as potentially functional even without the element of communication.

While such studies represent a promising beginning, they have hardly scratched the surface of the enormously complex set of stimulus, situational, and experiential factors that influence the adaptiveness/functionality of specific behaviors to threat, nor have they yet provided any comprehensive data on the actual behaviors manifest in different anxiety (and perhaps depressive) disorders that may map onto these relationships

Defensiveness may also be related to depression. Many traditional models of depression, including the tail suspension test and the forced swim test, focus on a lack of perseveration of escape behaviors, while others evaluate behaviors presumably related to anhedonia. Both of these are reasonable in the context of the many specific symptoms that are variably associated with depression (DSM-TR). However, Hendrie and Pickles (2012) have recently suggested a more integrated view, suggesting that a number of behavioral measures seen in both animal models of depression and many depressed humans, including hunched posture, avoidance of eye contact, reduced competition for food/sex and sleep disruption may be specifically adaptive for more subordinate members of highly social species. These behaviors may enable individuals at lower positions on a social hierarchy to avoid or reduce attack by conspecifics, constituting a particularly useful chronic strategy when the option of flight from the social group is relatively nonfunctional. This interpretation is consonant with findings from an expanding literature on chronic defeat (e.g. Yan et al, 2010; Markham et al, 2010), and on chronic social stress in subordinate animals (e.g. Blanchard et al, 2001). Notably, depression is significantly correlated with the experience of being bullied (Hunt et al, 2012), an experience that may provide the closest common parallel in humans to the condition (i.e. chronic attack by conspecifics) that Hendrie and Pickles (2012) suggest as an interpretation for some of the criterion behaviors in measures of depression in animal models.

Both of these cases, defensive behaviors as models for anxiety and fear, and defeat/submissiveness as a model of depression, make the interesting point that behaviors seen as aberrant and pathological may nonetheless have a great deal in common with patterns that are adaptive under somewhat similar circumstances, potentially representing a misplaced or extreme reaction rather than one that is totally unrelated. This suggests the value of research aimed at providing a more comprehensive characterization of the behaviors and behavior changes on the clinical level, aimed at providing a more thorough characterization of precisely which aspects of the psychopathology are nonfunctional and maladaptive, a point made also by Hendrie and Pickles (2012). Such an endeavor, clearly relevant to the nosology of psychopathologies such as depression, clearly constitutes a valuable undertaking --as reflected in ongoing revisions of the Diagnostic and Statistical Manual of the American Psychiatric Association—even aside from its role in the construction and evaluation of animal models. The additional point here is that for some animal models, behaviors have been described in sufficient detail that crosstalk between analysis/classification of the target human psychopathology and these animal model-based descriptions might optimally go in both directions, not unidirectionally as now, only from a set of diagnostic criteria in people to modeling attempts utilizing nonhuman species.

9. An Animal Model of Autism

These considerations suggest that animal models are optimally based on research in which not only behaviors but also relevant situations and stimuli; the relationships between these and the behaviors; and the outcomes of these combinations have been described, resulting in insights into the normal functioning of that behavior. How does such a model bring us closer to the goal of understanding the biology of this behavior, and its potential relationship to related psychopathology? Recent developments in animal models of autism provide a potential test case for the ability of an animal model based on only behavioral parallels to reveal significant behavioral and biological aspects of the condition that it models.

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders defined solely by behavior, with these aberrant behaviors involving three clusters: reduced reciprocal social interaction; deficits in communication; and ritualistic, repetitive or stereotyped behaviors (APA, 2000; Baird et al, 2003). There is clear evidence for a strong influence of genetic factors in ASD, but this appears to involve multiple genes (Geschwind, 2011), with only a small proportion of instances of ASD being attributable to alterations of single genes (McMahon et al, 2006), as well as responsivity to environmental factors (Landrigan 2010).

These combinations, with a wide range of genetic factors potentially interacting with a wide range of environmental/experiential factors, has made analysis of the etiology of ASD very difficult, a difficulty that is exacerbated by the lack of any established biomarker of the disorder (Lord, 2010). Notably, a number of specific tests, typically involving social behavior, have been used to evaluate ASD-relevant behavior profiles in laboratory animals, with findings indicating that several mouse strains provide a robust and consistent pattern of reductions in social behaviors or preferences (Moy et al, 2004, 2006, 2007; Nadler, 2004). The specific strain that, based on its consistent autism-relevant behavior phenotype, has come to serve as the focus for much of this work, is the BTBR T+tf/J (BTBR) mouse (Moy et al, 2006; Defensor, 2011). BTBR mice typically show reduced, or absent, preference for social stimuli in a three chamber test of social preference (Moy, et al., 2006, Defensor, et al., 2011); aberrant behaviors during forced confrontation with another mouse (Defensor et al, 2011), a wide-ranging pattern of reduced sociality when maintained in groups in a Visible Burrow System (Pobbe et al, 2011); changes in communication (ultrasonic vocalizations and scent marking; Scattoni et al, 2011; Wöhr et al, 2011) and increases in several repetitive and stereotyped behavior patterns such as grooming, grooming stereotypy; and object exploration (Mcfarlane et al, 2008; Pearson et al, 2011).

Social systems and their impacts on behavior and even body structure have been a focus of much ethological analysis (e.g. Blanchard, 2010; Estes, 1991). However, the laboratory-based study of sociality and species-typical social patterns has generally lagged behind that of more easily manipulated systems such as defense, ingestion, or sexual behavior. In addition to confirming that BTBR mice are deficient in social behavior compared to most other mouse strains, the development of tests to measure sociality in these animals has provided insights into some additional points of mouse (rodent?) sociality, such as the finding that mice react differently to another mouse approaching from the front (generally remaining in place to interact) vs. approach from the back, that more often elicits flight. These differences suggest (Arakawa et al, 2007), that the approached mouse regards frontal approach as more prosocial than approach from the back; a target site for biting in mice (Blanchard et al 2003). While BTBR mice show less approach of any kind to another mouse, this deficiency is more marked for frontal approach (Blanchard et al, 2012), as it is in oxytocin receptor knockout mice, which also show reduced sociality (Pobbe et al, 2012). Another point at which one mouse's reaction to specific behavior by another is different for

the BTBR mouse involves a direct nose tip –to– nose tip approach/stance. This is common in C57Bl/6J controls, but very much reduced in BTBR mice: When mixed BTBR/C57Bl/6J pairs are used, the BTBR mouse jerks its head away from the nose tip –to– nose tip approach by the C57Bl/6J partner (Defensor et al, 2011). As this stance involves direct eye contact, its avoidance in the BTBR mouse is in agreement with consistent findings of reduced eye contact in autistic individuals (Senju and Johnson, 2009).

10. Autism-relevant brain changes in the BTBR mouse

A view that behavior stems directly from the situationally-responsive activities of brain systems, reflecting their development and current functioning, suggests that there may be brain system or other biological differences between BTBR mice and strains such as C57BL/6 mice, the latter representing a centrist position with respect to sociality (reviewed in Meyza et al, 2012). The discovery that levels of the glycosaminoglycan, heparan sulfate (HS) are strikingly reduced in the lateral ventricle subventricular zone of the BTBR mouse (Meyza et al, 2012) provided a candidate for this mutual aberration (Figure 3). The heparan sulfate proteoglycan consists of a core protein to which HS chains consisting of variably sulfated repeating disaccharide units are attached. In the subventricular zone these interact with growth factors and cytokines, to modulate cell proliferation, differentiation, and migration (Kreuger et al., 2006), as well as responsivity to inflammation (Axelsson et al., 2012). The magnitude and composition of heparan sulfate are influenced by a variety of genes (Yoneda et al., 2012), and postnatal conditional knock-out of the *Ext1* gene, which is involved in HS synthesis, produces a robust reduction in social behaviors, as well as other behaviors providing potential parallels to the diagnostic criteria for autism (Irie, et al, 2012).

The hypothesis that heparan sulfate systems may be involved in autism has been supported by recent findings of a reduction in HS in the subventricular zone of the lateral ventricles in 4 pairs of individuals diagnosed with autism, and age and sex matched typically developing (TD) individuals (Figure 3: Pearson et al, 2013). This reduction was marked in the autistic individuals of the three younger pairs, despite a sharp and consistent drop in HS levels of TD individuals with aging. Although the HS levels of the 60 year-old autistic individual were also low, the TD value was low as well, with no difference of the two. In the present context, a particularly interesting aspect of this finding is that reduced heparan sulfate in the subventricular zone was first noted for BTBR mice; then hypothesized, sought, and confirmed, in tissue from autistic individuals: An animal model identified solely on a pattern of behavioral parallels to diagnostic criteria for a disorder predicted a potential biomarker for that disorder.

10. Some Suggestions for the Creation of Animal Models Involving Behavior

As these examples –anxiety, depression, autism-- suggest, behavioral animal models may have substantial translational validity, extending to suggestions of biomarkers for particular psychopathologies. This translational validity may be greatly enhanced by an understanding of the normal functions of the behaviors involved, an understanding that is facilitated by a wide-ranging description of these behaviors and their normal outcomes in relevant situations. For many behaviors, such a systematic description would necessarily involve a substantial program of research; to the extent that any individual research program may not have the time and means to investigate the range of information needed for an adequate description and functional analysis of a particular behavior.

A partial solution to this problem may involve a deep acquaintance with the literature – particularly the ethological literature-- relating to that behavior, under both natural and

contrived situations, and optimally involving both wild and lab strains for a given species, to provide an understanding of its functional role, in a given species. As an example, longer-term studies of rats, or mice, in groups (e.g. Blanchard et al, 1989; 2003; Calhoun, 1961) suggest that social intolerance, associated with higher levels of mortality from fighting, is generally greater for mice than for rats. This fits with direct observations that mice are less inhibited than rats about biting ventrum sites on a conspecific opponent, a site where wounds are especially likely to be lethal, (Blanchard et al, 2003), suggesting that mice have fewer adaptations for sociality than do rats. Even within a species, strain differences in behavior (e.g. O'Leary and Cryan, 2013) enable a substantially enhanced basis for choice of subject or control strains, and for evaluation of the resulting data.

Additionally, systematic variation of situations and stimuli to determine how the focal behavior may respond to these, should include natural or seminatural habitats in addition to purely contrived tasks. Such habitats can provide a great deal of information relevant to assessment of longer-term outcomes of behaviors under conditions more similar than are lab cages to those in which a species evolved; information that in many cases can be evaluated in conjunction with findings from relevant field studies. Although the drawbacks of such tasks include complexity, expense, reliance on skilled labor for behavior analysis, and the difficulty of manipulating specific variables within a test situation or adequately visualizing/recording subtle movements of individual subjects, such work is often necessary to provide the foundation and justification for subsequent development of tasks with a more limited focus. While the development of new, automated, apparatuses for measuring behaviors in complex situations is a welcome development, care and caution are required for a sensitive match between the output of these systems and behaviors of interest.

If the seminatural situation provides a “zoom out” to encompass the larger picture, then a complementary “zoom in” component might involve detailed analyses of sequences of movements/behaviors under conditions designed to specifically assess functionality. Such conditions might include situational features (familiar or not? your place or mine? Is there a way out of here?) along with variation in the subject's previous experience (e.g. previous defeat or other trauma?) and current states (nursing pups? hungry? just saw a cat?) as potentially relevant to functionality; information facilitating an overview of the link between that behavior and psychopathologies to which it may be relevant.

11. Some problems and potential solutions

Programs such as the above are wildly at variance with contemporary demands for “high throughput” measures. However, success in understanding how a given behavior functions may be expected to result in the identification of specific actions that can then be measured in optimally-relevant situations, producing translationally valid measures that may, or may not, meet criteria for “high throughput”: Valid measures are better than fast ones. Another potential problem with such programs is that detailed behavior analyses, not combined with biological manipulations, may not be seen as a legitimate component of behavioral neuroscience, and receive less immediate attention in consequence. However, such studies have “legs” –the impact of classic descriptive analyses (e.g. Leyhausen, 1979; Pellis and McKenna, 1995; Rogers and Johnson, 1995) may be very durable, and very important in the creation of more valid animal models.

For neuroscientists, the complexity of brain elements is taken for granted. That there should be dozens of receptors for some specific neurotransmitters, or that a single important brain molecule should have an enormous number of potential functional configurational variations, (Kreuger and Kjellen, 2012; Olsen and Sieghart, 2009) are encompassed without astonishment. Yet there remains widespread acceptance of a view that behavior should be

simple and either intuitively obvious or acceptable with minimal prior validation; needing little verification or analysis other than that provided by a history of frequently responding to drugs of interest, or to conditions assumed to provide a parallel to putative etiological factors in DSM or ICD.

In contrast, we maintain that behaviors may be as complex and nuanced as are the biological systems that produce them, and that understanding these behaviors may require researchers to, at least initially, embrace more complexity – and more detailed descriptions and analyses-- than has been typical in the past. The expected reward for these complex undertakings is an understanding of how crucial behavior systems are functional under conditions broadly similar to those in which a given species evolved, leading to the creation of simplified tests in which specific behaviors can be unambiguously interpreted. A basic premise here is that functional behaviors –those that are adaptive in terms of the general evolutionary history of the animal – will show substantial, albeit in many cases imperfect, conservation over (mammalian or closer) phylogeny, and that identification of these functional bases will enormously facilitate the creation of meaningful parallels between animal models and human behaviors, including those relevant to psychopathology. In addition, such functional analyses may also contribute to an understanding of a baseline of “normalcy” and possibly to new approaches to the identification of aberrance, on both the animal model and the clinical levels, with the goal of improving understanding, not only of animal models, but also of what it is that is specifically pathological about a particular psychopathology. For a given condition, achievement of these interacting goals should go a long way toward resolving issues of the validity of the model of interest.

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Highlights

The health care burden of psychopathologies demands research relevant to solutions

Animal models of psychopathologies are a weak link in the translatability of such research.

Their weakness reflects the lack of an adequate conception of the organization of behavior.

The adaptive functions of behavior may enable identification of cross-species parallels....

.....permitting cross-talk between model and psychopathology that aids understanding of both

Figure 1. From Patterson, 2011

Figure 2. Facial expressions of a resident and intruder mouse. Note narrowed eyes and nose bulge of resident compared to intruder.

Figure 3.

Heparan sulfate (HS) in the hypocellular layer (layer II) of the lateral ventricle subventricular zone (LV-SVZ) is decreased in autistic individuals. HS in the LV-SVZ was also reduced in the BTBR mouse, a model of autism, compared to C57BL/6J controls. Note: the mouse LV-SVZ does not have the same four layer cellular organization as the human brain.

Tissue from coronal sections of the LV-SVZ. DAPI (cell marker: blue), Laminin (red) and heparan sulfate (green) immunofluorescence in age- matched typically developing (a) and autism-diagnosed (b) males. (c) and (d) are slides from the same anterior-posterior area in a C57BL/6J mouse and a BTBR mouse, respectively. Yellow reflects co-localization of HS and LAM.

Table 1

Summary of specific findings published in Blanchard et al (2001) along side those of Perkins and Corr, 2006. Modified from Perkins and Corr, 2006.

Predictions by Blanchard et al., 2001	Findings of Blanchard et al, 2001	Findings of Perkins and Corr, 2006
1. The frequency with which risk assessment is selected will relate positively to ambiguity of threat stimuli	.89 **/.86 **	.89 **/.85 **
2. The frequency with which flight is selected will relate negatively to ambiguity of threat stimuli	-.50/-.63 *	-.56/-.59 *
3. The frequency with which defensive attack is selected will relate negatively to ambiguity of threat stimuli	-.53/-.29	-.54/-.44
4. The frequency with which flight is selected will relate positively to escapability of threat	.10/.04	.12/.13
5. The frequency with which defensive attack is selected will relate negatively to escapability of threat	-.76 */-.65 *	-.87 **/-.89 **
6. The frequency with which defensive attack is selected will relate negatively to distance of stimuli	-.59 */-.64 **	-.62 */-.69 *
7. The frequency with which hiding is selected will relate positively to availability of a hiding place	.59 */.63 *	.33/.30
8. Flight is most likely in the face of threats that are escapable and clearly dangerous	Suggested post hoc	$B = -.325/-.414$ **

*
 $p < .05$

**
 $p < .01$