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# Nuance and behavioral cogency: How the Visible Burrow System inspired the Stress-Alternatives Model and conceptualization of the continuum of anxiety

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## HIGHLIGHTS

- Bob Blanchard used the Visible Burrow System (VBS) to model highly nuanced behavior.
- The Stress Alternatives Model (SAM) was inspired by results from VBS experiments.
- The SAM explores dynamic stress responses and anxiety through dichotomous choices.
- Nuanced behaviors are helpful in parsing complex behavioral conditions like anxiety.
- An anxiety gradient exists spanning contextual settings in SAM experimentation.

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## ABSTRACT

By creating the Visible Burrow System (VBS) Bob Blanchard found a way to study the interaction of genetics, physiology, environment, and adaptive significance in a model with broad validity. The VBS changed the way we think about anxiety and affective disorders by allowing the mechanisms which control them to be observed in a dynamic setting. Critically, Blanchard used the VBS and other models to show how behavioral systems like defense are dependent upon context and behavioral elements unique to the individual. Inspired by the VBS, we developed a Stress Alternatives Model (SAM) to further explore the multifaceted dynamics of the stress response with a dichotomous choice condition. Like the VBS, the SAM is a naturalistic model built upon risk-assessment and defensive behavior, but with a choice of response: escape or submission to a large conspecific aggressor. The anxiety of novelty during the first escape must be weighed against fear of the aggressor, and a decision must be made. Both outcomes are adaptively significant, evidenced by a 50/50 split in outcome across several study systems. By manipulating the variables of the SAM, we show that a gradient of anxiety exists that spans the contextual settings of escaping an open field, escaping from aggression, and submitting to aggression. These findings correspond with increasing levels of corticosterone and increasing levels of NPS and BDNF in the central amygdala as the context changes. Whereas some anxiolytics were able to reduce the latency to escape for some animals, only with the potent anxiolytic drug antalarmin ($CRF_1$R-blocker) and the anxiogenic drug yohimbine ($\alpha_2$ antagonist) were we able to reverse the outcome for a substantial proportion of individuals. Our findings promote a novel method for modeling anxiety, offering a distinction between low-and-high levels, and accounting for individual variability. The translational value of the VBS is immeasurable, and it guided us and many other researchers to seek potential clinical solutions through a deeper understanding of regional neurochemistry and gene expression in concert with an ecological behavioral model.



## 1. Introduction

Animal behavior is always far more complex than we initially imagine. That complexity is derived from the environmental stimuli and internal physiology that motivate it, gene-by-environment interactions,

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evolutionary history, and adaptive significance for the individual behaving [1]. Despite these levels of complexity, numerous experimental protocols depend on extremely simplified stimuli ("painful, novel, or sudden") and outcomes, to produce high throughput designs for assessing translational relationships with human disorders [2]. Studies such as these have recently been determined to have limited clinical validity [3–5]. Context and small discrepancies in behavior (nuance) often make distinctive differences in specific neural activity and the adaptive value of the response for the individual [6–20]. Lorenz suggested that the full range of behavior in contextually appropriate naturalistic settings was necessary to understand the underlying mechanisms [21]. Behavioral paradigms and experimental designs created to study the neurochemical correlates of these nuanced and distinguishing behaviors came from the critical analyses of innovators like Bob Blanchard.

The Blanchards recognized the critical nature of nuanced behavior in their work on animal models of anxiety [16,18,22–37]. Anxiety is ostensibly a continuum of apprehensive behavior extending from subtle reactions related to stressors in the environment. Anxious states are therefore constructed along a stress/fear gradient that spans from foreboding to terror [2,39–40]. The complex nature of anxiety and anxious behavior comes from the potentially unlimited possibilities for stimuli to elicit a response. The high variability of stimuli produces highly variable responses, with a dramatic range of response magnitudes, especially related to neural and physiological activity. Anxiety covers a spectrum of related conditions that include general anxiety, social anxiety, panic, posttraumatic stress disorder (PTSD), and other related syndromes which carry a substantial societal and individual burden, affecting as much as 25% of the population [41]. They are highly comorbid with each other and with other psychiatric conditions, particularly mood disorders. Social anxiety alone has an estimated incidence of approximately 18%, and comorbidity as great as 80% with major depression [41].

Parsing this continuum between normal situational anxiety and that which leads to serious psychiatric disorders in an ethologically valid manner is no small task, as the experimenter must tie the complex and poorly understood symptomatology in humans to observable behaviors in animals. McKinney and Bunny proposed such validity criteria, which were later revised by Willner [42–45]. In addition to relating human symptoms to animal behavior (face validity), effective models should also utilize treatments which produce parallel results in humans and their animal homologues (predictive validity), and relate the symptoms and treatments to the systems involved (construct validity). In anxiety and depression, construct validity proves to be one of the hardest standards to meet, as the bio-behavioral inputs are multifaceted and poorly understood. This is revealed by often contradictory findings in studies [3–5,26] modeled upon experiments which seek to explain a single gear in a large and duplicitous machine. Recent clinical trials suggest that the predictive power of most single niche tests for psychological disorders in animal models is low [3–5]. A new focus, then, must be aimed where behavioral parallels between disorders and models converge, including nuance within a larger picture of behavioral complexity, as it becomes the crucial element in assessing model validity [12].

To model such complexity and accomplish ethological validity, Bob Blanchard recognized a need for systems which model behavior in a semi-natural context, accounting for many of the factors which Tinbergen and Lorenz had laid out many years before. He set out to create such a system, where behavior could be observed in a malleable social context, with variables offering the chance to study neural and endocrine correlates of behavior for individuals in differing social status. The Visible Burrow System (VBS) provided a unique experimental paradigm and apparatus that allowed for highly nuanced behavior within a laboratory setting and detailed evidence for a rodent's psychosocial state, as well as the opportunity to examine the neural and endocrine cascade effects that connect the behavior with potential predictive and construct validity [2,19,46–50]. For defensive behaviors and those related to social anxiety, the escape response in the VBS showed the most broadly homologous potential for mammalian taxa which could be modeled with laboratory animals. Escape behaviors provide a direct and active response compared to those stimulated by novel conditions and exploratory capacity [26]. Conceptions of the importance of social stress and stress coping strategies helped pave the way for understanding how dichotomies in behavior may be predictive of psychosocial disorders [51–54]. The inspiration of the ethologically and ecologically valid Visible Burrow System model combined with the prospect that dichotomous stress coping strategies could be predictive of psychological disorders led us to develop the Stress-Alternatives Model (SAM), a conceptual model and apparatus for assessing anxious and depressive behaviors and their effects on decision-making, which allows for parsing anxious behavior into contextual niches along an anxiety gradient [55].

## 2. Visible Burrow System

The Visible Burrow System (VBS) was created about 25 years ago, with the express purpose of providing a semi-natural situation affording many of the crucial features of a typical natural environment, in which groups of rodents could live for substantial periods of time. It was based in part on much earlier studies in which unfamiliar conspecific intruders had been introduced into large groups of laboratory rats for the purpose of polarizing the aggressive tendencies of the colony male(s) vs. the defensiveness of the intruder [11]: However, these initial studies had not used the VBS' combination of 'open space' (maintained on a 12:12 h light–dark cycle) with chambers and tunnels (maintained under red light; not visible to the rodent subjects used). This addition of chambers and tunnels, in total areas of about the same dimensions (about 1 m on a side) as the earlier tests, greatly enhanced the range of possible behaviors, and enabled a finer analysis of the behavioral effects of dominance-subordination relationships among male rats in these groups. Blanchard & Blanchard [2] detailed the reduced eating, drinking, and offensive aggression of subordinate males, with particular attention to differences of these animals with reference to space. Subordinates tended to remain largely in the tunnels/chambers, especially while the dominant male of each group utilized the open or 'surface' area. This, it did freely, as did females, with much of the copulatory behavior within the group in this location. A second focus of this study involved analysis of changes in behavior for group members as a function of status, following a brief (15-min) presentation of a cat in the open area.

Cat presentation was followed almost immediately by flight to the burrows by any rat located in the open area. Circa 22-kHz ultrasonic cries were made by animals in the burrows, remaining strong for 30 min to about an hour after cat presentation. As these cries declined, individual rats gradually began to approach the open area through the tunnels, peeping out very briefly to scan, and then retreating to the depths of the tunnels. However, no rat re-emerged onto the surface for at least 5–6 h, and the first to emerge was invariably the colony dominant male. Many of the remaining animals had not emerged by the end of the 20 h video recording period, a factor that obviously contributed to decreases in levels of the sorts of normal activities that tended to occur on the "surface".

Approaches to the surface through tunnel entry points involved a head poke and visible scanning in which the animal's head moved from side to side, clearly affording a look at all of the surface area. During its initial full-body re-emergence the dominant colony male continued to limit its exposure to the open area by "corner runs". These utilized a feature of the original burrow systems, that the tunnels and chambers were arranged along two adjacent sides of the open area, such that a tunnel entry point nearest the inside corner was only a very short distance from the entry nearest the same corner on the adjacent wall. Moreover, these "corner runs" were very rapid, as had been the prior instances in which subjects in the burrow system peeped out onto the surface area. In both cases, some visual scanning of the surface could be accomplished in a time that afforded little opportunity for the cat,