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Research Report

Cognitive bias in the chick anxiety-depression model

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ABSTRACT

Cognitive bias is a phenomenon that presents in clinical populations where anxious individuals tend to adopt a more pessimistic-like interpretation of ambiguous aversive stimuli whereas depressed individuals tend to adopt a less optimistic-like interpretation of ambiguous appetitive stimuli. To further validate the chick anxiety-depression model as a neuropsychiatric simulation we sought to quantify this cognitive endophenotype. Chicks exposed to an isolation stressor of 5 m to induce an anxiety-like or 60 m to induce a depressive-like state were then tested in a straight alley maze to a series of morphed ambiguous appetitive (chick silhouette) to aversive (owl silhouette) cues. In non-isolated controls, runway start and goal latencies generally increased as a function of greater amounts of aversive characteristics in the cues. In chicks in the anxiety-like state, runway latencies were increased to aversive ambiguous cues, reflecting more pessimistic-like behavior. In chicks in the depression-like state, runway latencies were increased to both aversive and appetitive ambiguous cues, reflecting more pessimistic-like and less optimistic-like behavior, respectively.

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1. Introduction

Traditional animal models of anxiety and animal models of depression differ in their procedural manipulations and behavioral endpoint measures (Willner, 1991). However, a novel model using chicks that involves separation from conspecifics reveals both anxiety-like and depression-like behavior within a single paradigm on a single behavioral measure (Sufka et al., 2006). The chick anxiety-depression model involves social separation stress that initially produces high distress vocalization (DVoc) rates characteristic of an

anxiety-like state (i.e., panic model; Warnick et al., 2006) that is followed by lower DVoc rates characteristic of a depression-like state (i.e., behavioral despair model; Lehr, 1989). These phases can be pharmacologically dissociated in that diverse compounds possessing anxiolytic effects (e.g., chlordiazepoxide, clonidine, imipramine) attenuate the high DVoc rates during the anxiety-like phase while compounds possessing antidepressant effects (e.g., imipramine, maprotiline and fluoxetine) attenuate the reduction in DVoc rates during the depression-like phase (Sufka et al., 2006; Warnick et al., 2009; see also Lehr, 1989). Additionally, common stress and

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depression biomarkers are present in the model and include elevated corticosterone and interleukin-6 (IL-6) levels (Sufka et al., 2006; Warnick et al., 2009).

A recent study that screened the efficacy of seven compounds targeting novel CNS sites, each of which previously passed antidepressant screening in rodent models, yielded a somewhat different profile than the early preclinical screens. The chick anxiety-depression model identified prasterone, ketamine, mifepristone, CGP36742 and DOV216,303 as possessing antidepressant properties while memantine and antalarmin did not (Sufka et al., 2009). Interestingly, this pattern of effects is in line with early clinical trial outcomes and illustrates the predictive validity of the model by correctly detecting efficacy of five compounds and avoiding two false positives (Wolkowitz et al., 1999; Zarate et al., 2006a,b; Belanoff et al., 2002; Schechter et al., 2005). Collectively, these results not only question the predictive validity of rodent models, but also begin to provide support for the validity of the chick anxiety-depression model as a neuropsychiatric simulation/screening assay. However, the quality of a simulation increases with greater numbers of homologies demonstrated between the animal model and its clinical syndrome (Kalueff and Murphy, 2007; Miczek and de Wit, 2008; Panksepp, 2006; van der Staay, 2006).

Biases in cognitive function have been shown in anxious individuals who display more pessimistic judgments and in depressed individuals who display not only more pessimistic judgments, but also less optimistic judgments (Wright and Bower, 1992; MacLeod and Byrne, 1996; Miranda and Mennin, 2007). Pessimism is defined as an increase in the expectation of negative events whereas optimism is defined as a decrease in the expectation of positive events. An example of a more pessimistic cognitive style has been demonstrated in individuals diagnosed with generalized anxiety disorder (Mogg et al., 2004) and in those suffering from depression (Mogg et al., 2006) who reported a greater number of threat related responses to ambiguous homophones (e.g. die-dye, weakweek) compared to controls. An example of a less optimistic cognitive style has been demonstrated in depressed individuals undergoing treatment for metastatic renal cell carcinoma or metastatic melanoma who report significantly lower levels of treatment specific optimism (i.e., likelihood of being cured) compared to non-depressed matched controls (Cohen et al., 2001).

Cognitive biases related to altered affective states have been studied across a range of species including rhesus macaques, dogs, rats and birds (Harding et al., 2004; Burman et al., 2008; Bethell et al., 2007; Bateson and Matheson, 2007; Matheson et al., 2008; for reviews see Mendl et al., 2009; Brilot et al., 2010). Some of the most successful of these have required animals to learn that cues presented at opposite ends of a stimulus range (e.g., white vs. black) require approach and avoidant behavioral responses that are associated with appetitive (e.g., food) and aversive (e.g., white noise) outcomes, respectively. The animal is then exposed to a novel ambiguous stimulus cue (or cues) that fall within the original stimulus range. Responses to these ambiguous cues can be used to determine whether the animal expects a positive or negative event to occur. Exposure to stressors that impact emotional states is hypothesized to alter cognitive decision

making in such tasks. For example, increased avoidant responses to ambiguous cues associated with a negative outcome reflect more pessimistic-like behavior. In contrast, decreased approach responses to ambiguous cues associated with a positive outcome reflect less optimistic-like behavior (see Fig. 1 for illustration).

Several recent studies have explored cognitive biases associated with stress states in avian models. For example, one study (Matheson et al., 2008) compared the performance of European starlings (Sturnus vulgaris) housed in chronic enriched versus impoverished cages on a temporal generalization task. The starlings were initially trained to discriminate two temporal stimuli (2 s vs. 10 s light cue) paired with instant versus delayed food reward, and were subsequently tested with ambiguous, intermediate-duration stimuli. The probability of classifying an intermediate stimulus as the stimulus associated with instant food (i.e. the better outcome) was lower in starlings housed in impoverished cages. This pattern was interpreted as reflecting reduced optimistic-like behavior associated with depression-like states induced by inadequate cage environments. More recent studies have explored the use of behavioral responses to ecologicallyrelevant stimuli (e.g., predator cues) that are likely to have been important in a species' evolutionary history (Brilot et al., 2009). The potential advantage of such stimuli lies in the reduced requirement for extensive associative training prior to the cognitive bias tests. The current study builds on this approach by using silhouettes of a conspecific chick (or mirror), an owl, and three intermediate ambiguous cues with varying degrees of chick and owl stimulus characteristics (see Fig. 2A). The two unmodified silhouettes are designed to possess a predetermined valence for a social prey species like domestic chicks: the Chick cue is predicted to be positive, whereas the owl (a potential predator) is predicted to be negative. To measure approach/avoidant responses we utilized a straight-alley maze (see Fig. 2B), a paradigm commonly used to quantify chick social reinstatement (Jones and Marin,

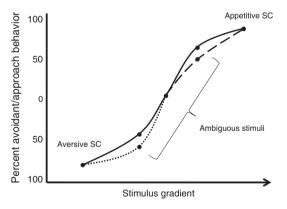


Fig. 1 – Predicted percent of avoidant/approach behavior to a range of stimulus cues (SC). In non-stressed control animals, predicted behavioral responses are indicated by the solid line. Dotted line represents increased avoidant behavior to ambiguous aversive cues and reflects more pessimistic-like behavior. Dashed line represents decreased approach behavior to ambiguous appetitive cues and reflects less optimistic-like behavior.

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