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# Behavioral inhibition is associated with airway hyper-responsiveness but not atopy in a monkey model of asthma

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## Abstract

**Objective—**To determine whether indicators of behavioral inhibition and cortisol responses to stressful situations, obtained in infancy, were associated with asthma-related measures (atopy and airway hyper-responsiveness) approximately two years later.

**Methods—**Measures reflecting inhibited temperament and cortisol response following a 25-hr separation from mother and relocation to a novel room were obtained for 21 rhesus monkeys (mean age 109 days, range 91–122). Inhibited temperament was measured by reduced emotionality and increased vigilance Atopy and airway hyperresponsiveness were assessed after two years (age range 19–35 months) using skin tests to common aeroallergens and inhaled methacholine challenge, respectively.

**Results—**No associations were found between atopy and either behavioral inhibition or cortisol levels ($p > 0.56$). Low emotionality was associated with airway hyper-responsiveness ($r = 0.47$, $p = 0.03$) and a trend was found for blunted cortisol responsiveness and airway hyper-responsiveness ($r = 0.42$, $p = 0.06$).

**Conclusions—**Inhibited temperament and blunted cortisol responsiveness may be related to the development of airway hyperresponsiveness that is common to both non-atopic and atopic asthma phenotypes, and may indicate risk for non-atopic asthma specifically.

### Keywords

asthma; behavioral inhibition; cortisol; temperament; atopy; airway hyper-responsiveness

## INTRODUCTION

Asthma has long been recognized as having a significant psychosocial component (1) and a variety of studies have suggested that inhibited temperament in children and anxiety and depression in adults is associated with asthma. These suggestions come from three types of studies. First, comparisons have often been made between individuals with and without asthma. For example, compared to controls, Kim, Ferrara & Chess (2) reported that children with asthma showed a temperamental pattern characteristic of “slow-to-warm-up” children – children that are inhibited (shy or reserved) in unfamiliar situations – and Ortega et al. (3)

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reported that adolescents with a history of asthma were significantly more likely to have an anxiety disorder. A second set of studies has examined factors associated with severity of disease, such as demonstrating that the relationship between anxiety and asthma was strongest for those with “severe” versus “non-severe” lifetime asthma (4). Third, and perhaps most powerfully, a few studies have employed a prospective methodology. Jonas et al. (5) followed more than 5000 adults for 13 years, and found that, among nonsmokers with no respiratory symptoms at baseline, the relative risks for developing asthma were strong and significant for those with high anxiety or high depression. Similarly, in a three-wave study of 11,000 Finnish adults (6), men that were high in neuroticism had significantly greater odds of developing asthma. Together, these studies point to a possible role of inhibited temperament in asthma. Some of this research has identified a link explicitly (e.g., 2), but other studies described above are consistent with the idea that inhibited temperament early in life, because it is strongly linked to later anxiety, depression, and neuroticism (7–10), may be associated with later development of asthma.

While the retrospective and prospective studies described above are compelling, many relied on self- or parent-reports of asthma, and the definition of asthma used was often very broad. The designs of these studies also do not generally permit understanding of whether inhibition/anxiety precedes asthma, is a consequence of it, or whether both the psychological factors and the asthma phenotype are manifestations of an underlying third cause, such as central and autonomic nervous system organization. Moreover, none of the cited studies distinguished between atopic and non-atopic asthma. The proportion of asthma cases attributable to atopy has been widely debated; however, a recent report (11) using a representative sample from the US determined that about half of all asthma cases were associated with an atopic response (defined as an outcome of a skin-testing procedure). This result has raised questions about the relative lack of attention paid to non-atopic asthma (12). While there are many similarities between atopic and non-atopic asthma, differences have been noted; apart from the obvious difference in aeroallergen involvement, non-atopic asthma tends to appear at relatively older ages, and people with non-atopic asthma show greater bronchial reactivity to challenge with methacholine, a receptor agonist in the parasympathetic nervous system (13, 14). Moreover, a recent Danish study suggests that the increased prevalence of asthma worldwide may be due primarily to non-atopic asthma - between 1986 and 2001, prevalence for non-atopic asthma increased 4.2-fold, but for atopic asthma, the increase was only 1.4-fold (15).

Because behavioral inhibition is associated with autonomic reactivity (16–18), one might expect that inhibited temperament would be related to the feature that is common to both forms of asthma, and that is commonly indexed by measuring responsiveness to autonomic challenge, namely airway hyperresponsiveness (AHR). The relation of inhibition to atopy, however, is unclear. On the one hand, studies that included measures of behavioral inhibition suggest there might be a relationship for measures related to atopy, such as hay fever (19), eczema (20), and dermatitis (21). On the other hand, while Kim et al. (2; described above) reported that children with asthma were more likely to show inhibition, control children that had eczema, allergic rhinitis, or both, did not show this temperamental pattern.

One mechanism by which temperament could influence immune processes relevant to atopy and AHR involves regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Little is known about the characteristics of this altered regulation, however. On the one hand, fearful/inhibited temperament has been linked to blunted cortisol reactivity in boys (22), and several studies have reported HPA dysregulation in people with asthma and other atopic disorders, often taking the form of a blunted cortisol response to stress (23, 24) or reduced basal levels at various points in the circadian cycle (25, 26). Blunted basal and stress levels of cortisol

could be achieved through enhanced negative feedback in the HPA system (27), which can be revealed through greater suppression of endogenous cortisol concentrations in response to a dexamethasone challenge. On the other hand, dysregulation might take the form of glucocorticoid desensitization. In fact, Rosenkranz et al. (28) showed that peripheral blood lymphocytes of late-phase responders were less sensitive to suppression by GCs during an antigen challenge. Reduced sensitivity to GCs could result in decreased suppression of inflammatory processes in asthma, and might be revealed by a relative failure to suppress endogenous cortisol levels in response to dexamethasone. Because AHR has an inflammatory component (29), it is unclear to what extent cortisol responsiveness and regulation might be related specifically to the airways response, to the atopic response, or to both.

One strategy for understanding whether temperament and HPA function could be risk factors for atopy and AHR would be to use an animal model. Rhesus monkeys provide an excellent model for the study of asthma and related outcomes (30, 31), and have been useful in studies of airways remodeling and asthma pathogenesis (32, 33). Moreover, nearly three decades of research suggest great similarity in temperament between human and nonhuman primates. For example, behavioral manifestations of various temperament dimensions are similar between the two species. Inhibited (sometimes referred to as anxious or fearful) temperament in rhesus monkeys is often indicated by vigilant behavior and reduction in vocalization in unfamiliar and novel situations (34), while in humans inhibited temperament is typically manifested as responses that are characterized as shy, emotionally reserved, withdrawn, and timid in the presence of strangers (35). These behavioral similarities are paralleled by similarities in measures of brain activity in both species (34). In addition, we have demonstrated with adult rhesus monkeys that reduced basal plasma cortisol levels are associated with natural variation in a personality dimension that is associated with anxious responding during challenging situations (36). A monkey model could also help identify causal pathways – whether inhibition precedes or follows asthma, or if both are related to a common underlying third variable.

The present study examines the relationship, in rhesus monkeys, between temperament and plasma cortisol concentrations assessed in infancy, and airway responsiveness and atopy measured approximately two years later. An atopic response to skin testing and measures of AHR have been used to diagnose and characterize asthma in both human (37, 38) and nonhuman (31) studies. Based on the literature, we expected that measures reflecting inhibited temperament (reduced emotionality and increased vigilance) in a novel, stressful situation would be related to AHR. We also expected that a blunted cortisol response to a stressor would be predictive of atopy, and possibly, AHR. In addition, we examined cortisol levels in response to dexamethasone administration to identify possible mechanisms by which HPA regulation might influence atopy and/or AHR.

## METHODS

### Subjects

Subjects for the current report were 21 (14 females) juvenile rhesus monkeys (*Macaca mulatta*), ranging in age from 19 – 35 months. These animals were drawn from a larger pool of monkeys (n=79) that were screened for a study of asthma, and the final sample includes every animal that a) was skin-tested, b) was given a pulmonary function test, and c) participated in the infant BioBehavioral Assessment (BBA) program (see below). At the time of screening, investigators were unaware that any animals had participated in the BBA program. All subjects were born and reared with their mothers at the California National Primate Research Center (CNPRC) in either indoor or outdoor cages. Preliminary analyses revealed no effects of sex or rearing history on the outcome measures; consequently data

from all animals were combined for analysis. All procedures were approved by the UC Davis Institutional Animal Care and Use Committee, and followed the Guide to the Care and Use of Laboratory Animals (39). UC Davis and the CNPRC are accredited by AAALAC.

## BBA program

At a mean age of 108.6 days (range: 92–122 days), animals participated in CNPRC's BBA program (40, 41). Briefly, infants were removed from their home cages, separated from their mothers, and housed individually in a novel, indoor location for a 25-hour period, during which each infant experienced several situations that were designed to assess infants' behavioral and physiological reactivity. At the end of the 25-hr testing period, animals were returned to their mothers and to their original home cages.

Behavioral inhibition in humans is typically assessed as responses to unfamiliar environments or people, and in such situations, inhibited children are usually described as being vigilant, showing subdued affect, and withdrawing to the proximity of their caregivers (16, 42). For the present analysis, we selected relevant measures from two assessments in the BBA program: Emotionality from the focal behavioral observations, and Vigilance from the temperament assessments.

**Focal behavioral observations—**After the animals had been in their temporary individual cages for at least 15 minutes, behavioral data were collected for five minutes from each animal in a predetermined random order. Inter-observer reliability for recording of behaviors (which are described in 41) was established at better than 85% agreement between two independent observers. Data reduction for measures of behavioral responsiveness and temperament (see next section) was accomplished via exploratory and confirmatory factor analyses using MPlus statistical software (43) in order to derive reliable scales that could be used as outcome measures. Factor analytic procedures (which utilized data from more than 1,400 infants collected over a 5-year period), and all indices of factor model fit, are described in detail in (41). Briefly, an exploratory factor analysis, using weighted least squares with robust standard errors, identified a two-factor solution, which was given a promax rotation. Separate confirmatory factor analyses were performed on separate data sets, and fit was excellent based on traditional fit statistics (see 41). Scales were constructed by summing z-scores for the items that loaded on a given factor. Cronbach's alphas ranged from 0.6 to 0.8. The final scales were then z-scored and labeled ''Activity'' (comprising the proportion of time animals were locomoting; proportion of time animals were not in a hang position from the side or top of the cage; rate of environmental exploration; and whether animals ate food; drank water; and were in a crouched posture) and ''Emotionality'' (rate of vocalizing [coos and barks]; and whether the animal displayed threats, lipsmacks, and self-scratch).

**Temperament ratings—**At the end of the 25-hr. period, observers rated each animal using a 1–7 scale for each of 16 trait adjectives. These ratings provide overall summaries of the observers' experiences with the animals throughout the testing period, during the behavioral observations, the handling of the animals for blood sampling, the transport of the animals to testing cages, etc. For each trait, agreement between independent raters was significantly greater than chance using chi-square ($p<0.001$) when different observers' ratings were allowed to vary from each other by one point. Exploratory and confirmatory factor analyses were performed as described above (details in 41, 44) and utilized maximum likelihood estimation and promax rotation. Fit indices revealed a close fit (41). Factor scores were calculated by summing the z-scores for all adjective items loading on a given factor, and then z-scoring each scale. Cronbach's alpha values for the scales ranged from 0.6 to 0.9.

The four scales, named for the adjective with the highest factor loading, were: Confident (active, bold, confident, curious, playful), Gentle (calm, curious, flexible, gentle), Vigilant (vigilant, not depressed, not tense, not timid), Nervous (fearful, nervous, timid, not calm, not confident). The principal measure of interest was Vigilance. While behavioral inhibition may also appear to be related to other temperament factors such as nervousness, and while, in fact some of these factors are correlated with each other (e.g., the correlation between vigilant and nervous in this sample is $r = -0.721$), correlational analyses, multiple regressions, and logistic regressions (not shown) confirmed that in nearly all cases, the strongest relationships to all of the outcome measures were indeed with Vigilance.

**Plasma cortisol concentrations—**Blood was sampled via femoral venipuncture following manual restraint on four occasions during the 25-hr. assessment period: two hours after maternal separation (1100 hrs: Sample 1); five hours later (1600 hrs: Sample 2); at 0830 on Day 2 (Sample 3); and at 0900 on Day 2 (Sample 4). Immediately following Sample 2, animals were injected with 500ug/kg dexamethasone i.m., and immediately following Sample 3, animals received 2.5 I.U. ACTH, i.m.; thus, Samples 3 and 4 reflect pharmacologic treatments designed to assess regulation of the hypothalamic-pituitary-adrenal axis. 0.5 ml of whole blood from each sample was centrifuged for 10 minutes at 3000 RPM at 4° C. Plasma was removed and decanted into tubes for storage at −80° C, and was later assayed in duplicate using commercially available kits (Diagnostics Products Corporation, Los Angeles, CA). Inter- and intra-assay coefficients of variation were 5.8% and 7.9 %, respectively. Because we were interested in testing hypotheses specifically about blunted cortisol responses to stress (after 23), we averaged the cortisol measures from the first two blood samples, and used this value in the analyses (preliminary analyses revealed that these samples did not differ significantly from each other). Sample 3 values were used to determine whether cortisol's influence may be due to enhanced negative feedback or to glucocorticoid desensitization. Values from Sample 4 were not used, inasmuch as we had no specific hypotheses about adrenal responsiveness to ACTH challenge.

## Skin testing

Intradermal skin testing was done according to published procedures (31). Briefly, hair was clipped from an area of the thorax, and 8 separate intradermal injections (0.1 ml each) were made. The 8 injections consisted of PBS alone (negative control), PBS with histamine (positive control), and six test antigens: house dust mite, cockroach, mold, trees, weeds, or grasses. Wheal diameters were measured after 20 minutes. A skin-test positive response was defined as a wheal diameter for any test antigen that was greater than or equal to that halfway between the diameter of the wheals produced by the positive- and negative-controls (31). By this definition, 8 animals were atopic, and 13 were not.

## Airway responsiveness testing

Airway responsiveness to doubling concentrations of inhaled methacholine aerosols was quantified using previously published procedures (31). Briefly, each animal was anesthetized with propofol (0.1 mg/kg/min), intubated, and placed in a head-out body plethysmograph with the intubation tube attached to a pneumotachograph assembly. Airways resistance was assessed using a forced oscillatory technique (31, 45). Methacholine was administered as an aerosol at a set tidal volume and breathing frequency (15.0 ml/kg and 20.0 bpm) using a compressed air nebulizer in series with a positive pressure ventilator. We used repeated 30-sec challenge periods separated by 240-sec data collection periods, beginning with saline followed by doubling concentrations of methacholine starting at 0.0625 mg/ml and ending at the concentration that gives a 150 percent increase over baseline airways resistance (EC150). Responses by the 21 animals ranged from 0.39 to 32.0 mg/ml.

### Statistical analysis

The principal behavioral measures were Emotionality and Vigilance, and the hormonal measure was the mean concentration of cortisol from the first two blood samples. Because of its non-normal distribution, the measure of AHR was subjected to a $\log_{10}$ transformation. Bivariate correlation coefficients were calculated between predictors and both outcome measures (atopy, AHR), followed by multiple linear regression for the AHR measure, and logistic regression for the measure of atopy. We conducted an additional analysis, using logistic regression, of AHR by dichotomizing this measure, inasmuch as experience with more than 70 animals has suggested that hyper-responsive individuals as a group have EC150 values of about 3.0 or lower, and show little within-group variation in response during asthma induction. Examination of the distribution of EC150 responses for this cohort revealed that 10 animals (designated hyper-responders) had EC150 of 0.39 to 3.21 mg/ml, and 11 animals (normals) had EC150 of 4.98 to 32.0 mg/ml. In the logistic regression analyses, we emphasized classification of the cases based upon the three predictors. By chance, 61.9% of cases (13 of 21) would be classified for the atopy measure, and 52.4% (11 of 21) for the AHR measure. Finally, to identify possible mechanisms by which glucocorticoids could affect AHR and/or atopy, we conducted analyses of variance on the dex-suppressed levels of cortisol in relation to the measure of atopy and the dichotomized measure of AHR.

## RESULTS

Vigilance and Emotionality were uncorrelated in the present sample (r=0.067, p=.77), which precluded construction of a single scale of behavioral inhibition. Cortisol levels were also not correlated with Vigilance (r=0.078, p=.74) or Emotionality (r=0.309, p=.17).

### Atopy

Bivariate correlation coefficients were all non-significant between the three principal BBA predictors and the measure of atopy (all $p > 0.56$; Table 1, row 1). Because we originally defined atopy somewhat conservatively, however, we redefined atopy similar to Sears et al. (46), as a wheal diameter at least 2mm larger than the negative control for the skin test. By this definition, 13 animals (compared to 8 for the original definition) were atopic. Bivariate analysis again revealed that no measure was correlated with BBA predictors (all $p > 0.31$; Table 1, row 2). Logistic regression revealed that the three predictors were unrelated to either the original measure of atopy (Chisquare(3)=1.13, p=0.77) or the revised measure (Chisquare(3)=1.18, p=0.76). Classification analysis revealed that the three predictors resulted in 66.7% correct classification of the cases for either model; as described above, chance classification was 61.9%. To identify whether measures of HPA regulation were related to the original measure of atopy, we conducted an analysis of variance on the two cortisol values. Although the dex-suppressed values were higher for atopic animals, neither the main effect nor interaction effect achieved statistical significance (both p>.38). Both the stressed and dex-suppressed values of cortisol are shown in Figure 1A.

### AHR

In contrast to the results for atopy, animals that showed hyperresponsive airways (lower values for EC150) displayed less Emotionality (p=.03), and blunted cortisol responsiveness (p=.06; Table 1, row 3). The correlation between the airways response and Vigilance was in the expected direction but was not significant (r=−0.235, p=.31). Inclusion of the three predictors in a multiple regression analysis resulted in a significant model fit (F(3,17)=3.59, p=.04), with an adjusted $R^2$=0.28. A similar pattern of results was found for the dichotomized measure of hyperresponsiveness (Table 1, row 4; note that the correlation for cortisol is now statistically significant). Finally, the logistic regression involving the

dichotomized measure of AHR revealed a significant model fit (Chisquare(3)=15.99, p=.001) and correct classification of 95.2% (i.e., 20 of 21) of the cases (chance classification was 52.4%). Maximal classification was obtained only when all three predictors were in the logistic model; for example, although Vigilance was not significant in any bivariate analysis, removal of this measure decreased classification from 95.2% to 66.7%, suggesting that it was the combination of low Emotionality and Vigilance, which together are hallmarks of behavioral inhibition, that was the important construct. Figure 2 shows mean values for the Emotionality and Vigilance measures for hyper-responders and normal-responders. Analysis of variance for the two cortisol values using the dichotomized measure of AHR revealed a trend for AHR (F(1,19)=3.26, p=.09), with hyper-responders showing lower cortisol concentrations. The interaction of sample and AHR response type was non-significant (p=.17). Means for both cortisol measures are shown in Fig. 1B.

## DISCUSSION

Indicators of behavioral inhibition (reduced emotionality, and to a lesser extent, greater vigilance) and blunted cortisol responsiveness were associated with the airways response that is common to both atopic and non-atopic asthma, but not with the atopic response in the animals. Our inability to find relationships between inhibition and atopy suggests that behavioral inhibition may not be related to the allergic component of asthma, a suggestion that is at variance with other reports described above that did find relationships between inhibition-related measures and atopy (19–21). The results are, however, consistent with the initial study by Kim et al. (2). While we acknowledge that further research is needed, we propose that behavioral inhibition may be a marker for non-atopic asthma.

The mechanisms by which inhibited temperament may influence AHR cannot be determined by the present analysis. Airway hyperresponsiveness is a complex condition, with evidence implicating several underlying factors, including abnormalities in smooth muscle, inflammation, and neural control (29). Studies of behavioral inhibition in humans and monkeys have revealed that this temperamental pattern is associated with autonomic reactivity during stressful situations (16–18) and with reduced cellular immune function measured *in vitro* (47). Either of these mechanisms might link temperament with airway responses, and both bear prospective investigation.

In the present study, measures of inhibition and cortisol were obtained in infancy, while the asthma-related measures were obtained approximately two years later. While there is generally good continuity in inhibited temperament across time (16), the behavior of some individuals does normalize. Unfortunately, we did not have contemporary measures of behavior to assess the animals' functioning at the time of the skin-testing and methacholine challenge. It is possible, for example, that stronger relationships between behavioral function and AHR (or even the skin test data) may have been found among a subset of animals whose current (as well as infant) functioning reflected inhibition.

We examined the cortisol response to stress and to an overnight dexamethasone suppression test to determine whether an HPA-related mechanism may be involved in either the atopic response or AHR. All analyses for atopy were non-significant, but there was a significant blunting of stress-related cortisol in hyper-responders compared to normal responders. This may be due to reduced activation of the HPA system in response to stress, or to enhanced negative feedback associated with a greater number or efficiency of glucocorticoid receptors. Although non-significant, dex-suppressed cortisol concentrations were also lower for hyper-responders, a result consistent with the negative feedback interpretation. If AHR is associated with enhanced negative feedback, however, then this finding is counterintuitive to glucocorticoids' anti-inflammatory effects – one would expect a greater anti-inflammatory

effect, not a reduction. It seems likely, therefore, that the altered HPA regulation suggested for the hyper-responders extends beyond simple enhancement of negative feedback, and involves other mechanisms not examined in this study.

We recognize the limitations of the present analysis, and urge caution in interpretation. Sample size was relatively small for an “individual differences” analysis, and may have been underpowered to find an effect on atopy. Moreover, retrospective analysis such as this runs the risk of generating spurious results owing to capitalization on chance associations in the data. Nevertheless, the fact that the results for AHR are consistent with human data that were obtained using a variety of approaches, both prospective and retrospective, provides more confidence in the results. We also note that, inasmuch as this was a retrospective study, we did not have measures of AHR at the time of the BBA assessments. Consequently, we do not know the respiratory status of the behaviorally inhibited animals at 3–4 months of age. Unfortunately, the animals are too small at that age to perform the methacholine challenge test as described. We do know, however, that the animals showed no obvious wheezing or respiratory difficulties that required veterinary intervention at the time of biobehavioral assessment. Regardless of whether the present measures of behavioral inhibition reflect existing pulmonary function or predict later-developing hyperresponsiveness, the present data do suggest that biobehavioral measures that are relatively easy to obtain can identify animals at-risk for hyperresponsive airways.

The rhesus monkey provides an excellent model system to understand the pathophysiologic mechanisms associated with asthma (30), and we believe that the present analysis extends the usefulness of this model into examination of the role of psychosocial factors in the development of asthma. While the present study does not elucidate whether inhibition precedes asthma, follows it, or whether both are manifestations of a third underlying variable, the monkey model could be extremely valuable in addressing this issue, as well as enabling prospective studies to test hypotheses about specific developmental mechanisms, and to attempt interventions that might forestall the development of asthma. In addition, this model is valuable because it permits one to create animals with specific temperamental characteristics. For example, prenatal stress results in offspring that display an inhibited temperament (48) and impaired cellular immunity, as well as evidence of glucocorticoid resistance in immune cells (49). Having a ready source of animals with a risky temperamental phenotype for prospective investigation could be extremely useful in understanding the immune and neural mechanisms associated with AHR and atopy.

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## Acronyms

| | |
|---|---|
| **AHR** | airway hyperresponsiveness |
| **HPA** | hypothalamic-pituitary-adrenal |
| **GC** | glucocorticoid |
| **BBA** | BioBehavioral Assessment |
| **ACTH** | adrenocorticotrophic hormone |

**EC150** concentration of methacholine that gives a 150% increase over baseline airways resistance

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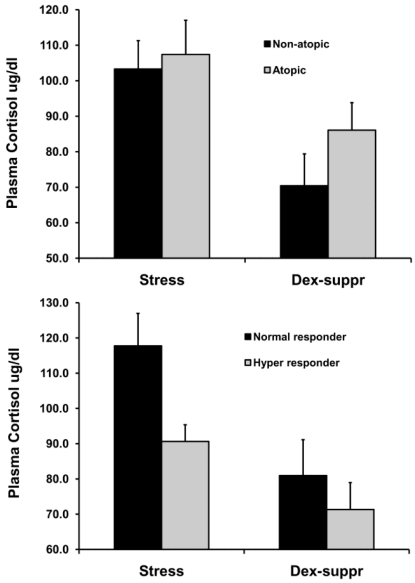


**Figure 1.**

Mean (+/− SEM) plasma cortisol concentrations for stressed samples and samples obtained following overnight dexamethasone suppression. A) Cortisol concentrations based upon original definition of atopy (see text); all results are non-significant. B) Cortisol concentrations based upon dichotomized measure of airways hyper-responsiveness (see text). Left panel of B shows significant effect for stress samples; group differences for dexamethasone-suppressed samples are non-significant.

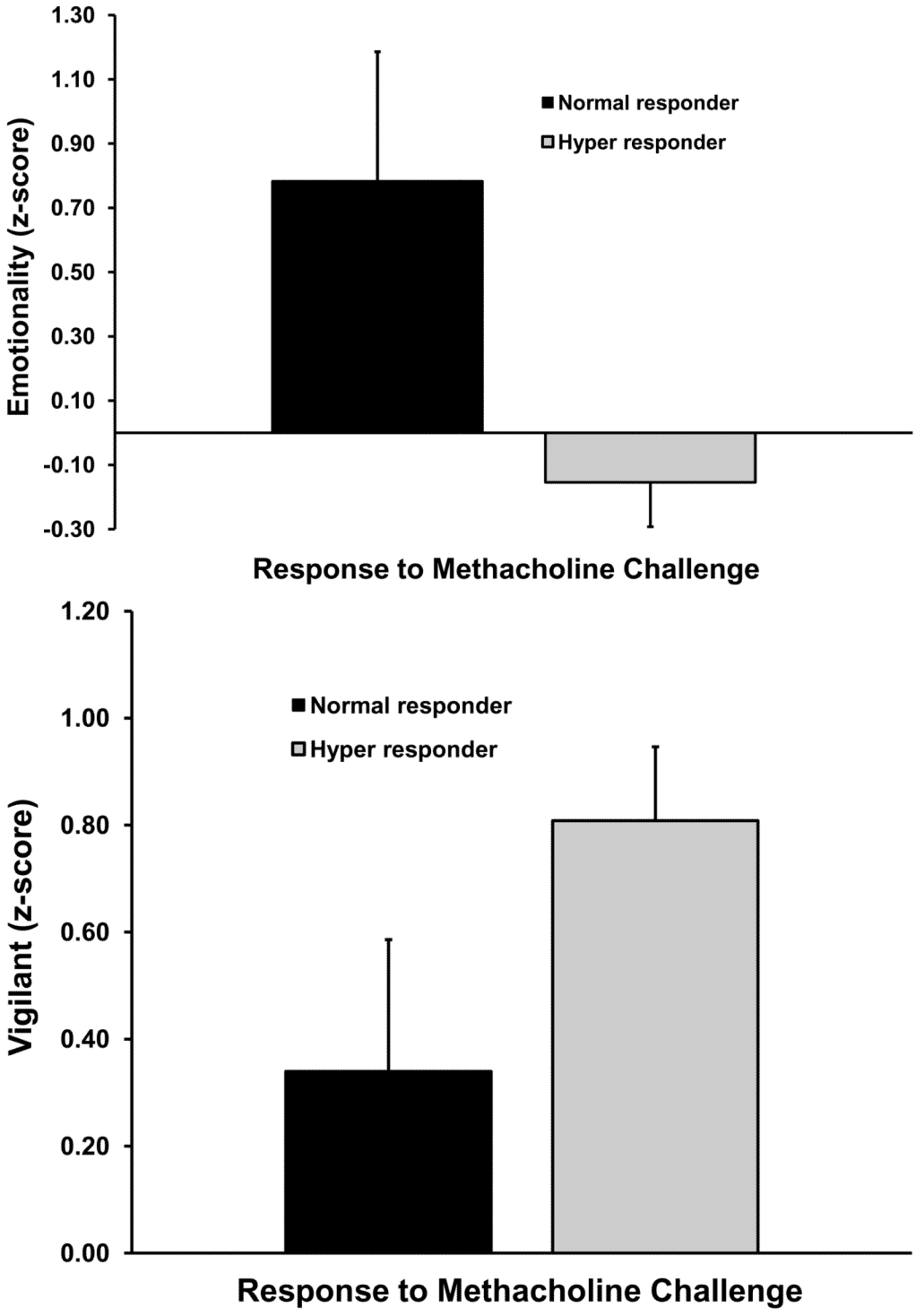


**Figure 2.**
Mean (+/− SEM) values of A) Emotionality (p=.06) and B) Vigilance (not significant) for monkeys that displayed a hyper-responsive or normal response to methacholine challenge (see text for definition). Cortisol concentrations are displayed in left panel of Figure 1B.

## Table 1

Pearson product-moment correlation coefficients between biobehavioral data and measures of atopy and airway hyper-responsiveness (AHR).

| | Emotionality | Vigilance | Cortisol |
|---|---|---|---|
| Atopy (original) | −0.134 | 0.127 | 0.074 |
| Atopy (revised) | 0.061 | 0.231 | 0.014 |
| AHR (continuous) | 0.470, p=.03 | −0.235 | 0.423, p=.06 |
| AHR (hyperresponders) n=21 for all correlations | −0.420, p=.06 | 0.347 | −0.502, p=.02 |

Revised measure of atopy follows Sears et al. 2003; for hyperresponsiveness measure of AHR, 0 = normal responder, 1 = hyperresponder -- see text for details. Note that this classification is the reverse of the continuous measure, which accounts for the differences in signs.