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Association of Cortisol with Neuropsychological Assessment in Older Adults with Generalized Anxiety Disorder

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Abstract

Objectives—Older adults with Generalized Anxiety Disorder (GAD) have elevated diurnal cortisol patterns and show an increased cortisol stress response, which may increase risk for cognitive dysfunction. The current secondary data analysis examined how neuropsychological assessment as a possible laboratory stressor affects cortisol levels in late-life GAD and, in turn, how cortisol levels affect cognitive performance.

Methods—The current sample consisted of 69 individuals with late-life GAD and 39 psychiatrically-healthy group-matched comparison participants. Cognitive performance was measured with a neuropsychological battery and salivary cortisol was collected at several time points. Hierarchical regressions were performed to assess the moderating role of cortisol in the relationship between GAD status and cognitive performance.

Results—The results revealed that older adults with GAD showed significantly lower cortisol levels during neuropsychological assessment, compared to their baseline levels. Further, there was a significant interaction between post-neuropsychological assessment cortisol levels and GAD status on several measures of cognitive performance. The interaction indicated that there is a significant negative relationship between cortisol level and cognitive performance in the GAD participants and no such relationship in the comparison participants.

Conclusions—Our results revealed that participating in a neuropsychological assessment was associated with reduced cortisol in GAD participants, suggesting that refocusing attention such as engaging in cognitive tasks had a cortisol-lowering effect. Further, a higher cortisol level appears to have a detrimental effect on cognitive performance for individuals with GAD but not psychiatrically-healthy comparison participants. The methodological and treatment implications of these findings are discussed.

Keywords

Generalized anxiety disorder (GAD); HPA axis; neuropsychological assessment; cortisol; stress

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Conflicts of Interests

Dr. Lenze reports the following potential conflicts of interest (current and past three years): research funding from Forest Laboratories, Roche, Johnson & Johnson, and Lundbeck; and consulting payments from Fox Learning Systems. The other authors report no potential conflicts.

Generalized anxiety disorder (GAD) is a chronic condition characterized by excessive and uncontrolled worrying with prevalence in older adults ranging from 4 to 7% in recent large-scale epidemiologic studies (Angst, Gamma, Baldwin, Ajdacic-Gross, & Rossler, 2009; Beekman et al., 1998; Grant et al., 2005). Individuals who report high levels of anxiety or who have an anxiety disorder are at increased risk of experiencing cognitive decline (Andreoletti, Veratti, & Lachman, 2006; DeLuca et al., 2005; Sinoff & Werner, 2003). Specifically, poorer cognitive performance has been reported in older adults with GAD (Butters et al., 2011; Mantella et al., 2007). The etiology of cognitive decline in late-life anxiety is still largely unknown, but it is likely multifactorial and probably includes negative effects of an exaggerated biological stress response on brain function (Beaudreau & O'Hara, 2008).

Older adults with anxiety disorders have elevated diurnal cortisol patterns, show increases in cortisol levels in response to stressors, and take longer to return to baseline compared to older adults without anxiety disorders (Chaudieu et al., 2008; Mantella et al., 2008). The release of cortisol from the adrenal cortex is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol displays a normal diurnal pattern with increases in the morning and after meals and returns to basal levels later in the day and at night (Fries, Dettenborn, & Kirschbaum, 2009; Joels, 2006; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Lupien et al., 2005). We previously demonstrated that older adults with GAD experience higher basal diurnal cortisol levels than healthy comparison participants, a sign of elevated HPA axis activity (Mantella et al., 2008).

Neuropsychological assessment itself could be a stressor for older adults, leading to additional increases in cortisol levels (Neupert, Miller, & Lachman, 2006). Alternately, neuropsychological assessment could be cortisol-reducing, if by focusing on the cognitive tasks, individuals with GAD are prevented from worrying, as worry levels are highly predictive of cortisol levels in these individuals (Mantella et al., 2008). These hypotheses are particularly important to understanding cognitive functioning in late-life anxiety disorders.

Further, research on the relationship between cortisol patterns and cognitive functioning in older adults has found increased cortisol levels associated with poorer performance on a wide variety of cognitive assessments (Comijs et al., 2010; Franz et al., 2011; Lee et al., 2007; Lupien et al., 1994, 1998, 2005; Seeman, McEwen, Singer, Albert, & Rowe, 1997; Wright, Kunz-Ebrecht, Iliffe, Foese, & Steptoe, 2005). Poorer performance may be due to the detrimental effects cortisol has on brain structures important for cognitive processing, such as the hippocampus and prefrontal cortex (Bremner et al., 1995, 1997; Franz et al., 2011; Herbert et al., 2006). Thus, persons with GAD may experience changes in cognitive performance from elevated cortisol levels. However, research has also shown a positive association between acute changes in cortisol levels prior to testing and cognitive performance (humans: Beckner, Tucker, Delville, & Mohr, 2006; Cahill, Gorski, & Le, 2003; De Kloet, Oitzl, & Joels, 1999; Herbert et al., 2006; rats: Hui et al., 2004; Roozendaal, Okuda, de Quervain, & McGaugh, 2006a; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006b).

In this study, we explored the association of cortisol levels, reflecting the biological stress response, with performance on a range of cognitive tasks in older adults with GAD and non-psychiatric comparison participants. We addressed the following questions: 1) Do older adults with or without GAD demonstrate an alteration in cortisol level when coming to a laboratory and undergoing neuropsychological assessment?; and 2) Is post-neuropsychological assessment cortisol level differentially associated with neuropsychological performance in older adults with or without GAD? We hypothesized that the GAD group's cortisol levels would be higher during the pre-neuropsychological

assessment compared to their baseline and continue to increase during the neuropsychological assessment. Further, there would be a negative relationship between cortisol levels and cognitive performance in the GAD group.

Methods

Study participants

The subject recruitment and inclusion/exclusion criteria have been previously described (Mantella et al., 2008). Briefly, the sample consisted of community-dwelling adults over the age of 60 who did not have a diagnosis of dementia and scored greater than or equal to 24 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975); 69 participants had a principal diagnosis of current GAD as diagnosed by the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1995), and 39 comparison participants with no lifetime DSM-IV diagnosis were recruited and equated to the GAD group on demographic characteristics. GAD subjects with co-morbid diagnoses (e.g., social and specific phobias, panic disorder, and depression) were included in the current analyses. All study participants provided informed consent prior to any study procedures.

Neuropsychological Measures

The neuropsychological battery was used to assess several cognitive domains. Global cognitive functioning was measured with the MMSE (Folstein et al., 1975), and time to complete the Color-Word portion of the Stroop Neuropsychological Screening Test (Trennery, Crosson, DeBoe, & Leber, 1989) was used as a measure of inhibition. Working memory was assessed with the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). Age-adjusted standard scores were computed for the following neuropsychological outcomes. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998) was used to index language, visuospatial/construction skills, attention, and immediate and delayed memory. The Card Sorting Task from the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001) indexed higher-order executive functioning (i.e., problem-solving, conceptual ability, and mental flexibility).

We measured psychological distress during the neuropsychological assessment using observational ratings. Study staff rated participants' distress (e.g., crying, behavioral signs of anxiety or distress) during the test session using a four point Likert scale (none, mild, moderate, or severe). Inter-rater reliability for this observation was 100% based on five randomly chosen participants who were observed independently by two study staff members. Based on low frequencies of moderate or severe distress, we did not include this variable as a covariate in any of the analyses.

Salivary sampling protocol

Participants provided saliva samples before ($n = 72$) and after ($n = 108$) neuropsychological assessment during the clinic visit. In addition, for two consecutive days prior to the clinic visit participants collected six saliva samples upon waking, 30 minutes later, 1200, 1600, 2000h, and at bedtime (exact times of collection were recorded; for a full explanation of the salivary sampling protocol see Mantella et al., 2008). For each of these time points across the two days, cortisol values were averaged together for a total of six possible at-home measurements. These at-home cortisol measurements were used to create a baseline cortisol measure that corresponded to the participant's clinic appointment. In the event that the participant's appointment time did not directly correspond with an at-home sample time, the two closest time points were used to form the current baseline cortisol measurement. All of

the cortisol data were log-transformed to normalize the data prior to performing the analyses.

Cortisol assay protocol

Standard procedures were used to store and assay the salivary cortisol samples (Salimetrics, State College, PA). The assays were performed in duplicate and the coefficient of variation had to be <10% to be considered reliable (for more information see Mantella et al., 2008).

Statistical Analysis

Group differences on the background characteristics, cortisol levels, and cognitive indices were assessed using *t*-tests for continuous variables and χ^2 tests for categorical variables. We conducted a repeated measures analysis of variance to examine group differences in cortisol patterns across time (baseline, pre- and post-neuropsychological assessment) while controlling for the time of assessment (to adjust for daily fluctuations in cortisol levels) and wake-up time (see Almeida, Piazza, & Stawski, 2009). Lastly, separate hierarchical multiple regressions were performed for each of the cognitive outcomes to determine whether or not cortisol level moderated the relationship between GAD status and cognitive performance. The post-neuropsychological cortisol measurement was used in the regression analyses because cortisol takes approximately 20–30 minutes to become active in the saliva after experiencing a stressor (Engert, et al., 2011; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004) and this measurement would reflect the cortisol level while the participants were taking the neuropsychological battery. The *group mean* centered cortisol measure was used in the regression models to reduce multicollinearity and provide a meaningful zero (Field, 2009; Jaccard & Turrisi, 2003; Tabachnik & Fidell, 2007). The structure of the models was as follows: Step 1- we controlled for the time of assessment, wake-up time, baseline cortisol level, education, and age (if applicable- age was not included as a covariate in the regression models for the cognitive outcomes with age-adjusted scores); Step 2- we entered GAD status and the post-neuropsychological assessment cortisol measure; and Step 3- we entered the interaction between GAD status and the post-neuropsychological assessment cortisol measure (i.e., GAD*cortisol).

Results

Descriptive Analysis

The means and standard deviations for all the variables of interest can be found in Table 1. The groups were similar in age, education level, gender, ethnicity, marital status as well as the time they woke up in the morning. The GAD group exhibited distress during the neuropsychological assessment more often than the comparison group, $\chi^2(1) = 11.25, p < .001$. The comparison group started the neuropsychological assessment session significantly earlier in the day than the GAD group, $t(106) = 2.99, p < 0.01$, but the groups did not differ in the amount of time it took to complete the assessment. In addition, the GAD participants had significantly higher cortisol levels in their home environment (i.e., AUCg) than the comparison group, $t(103) = 4.42, p < 0.001$, as previously reported (Mantella et al., 2008). On the other hand, the groups had similar pre-neuropsychological assessment cortisol levels but the GAD group had significantly *lower* post-neuropsychological assessment cortisol levels than the comparison group, $t(106) = -2.73, p < 0.01$. Lastly, the GAD group had significantly poorer scores than the comparison group on the MMSE, $t(106) = -2.82, p < 0.01$; Letter-Number Sequencing, $t(105) = -2.02, p < 0.05$; DKEFS Card Sort-Correct Sorts, $t(105) = -2.03, p < 0.05$; RBANS Immediate Memory Index, $t(105) = -2.25, p < 0.05$; and Delayed Memory Index, $t(104) = -2.16, p < 0.05$; the results of the full neuropsychological evaluation has been published previously (Butters et al., 2011).

Effects of neuropsychological assessment on cortisol levels

We compared the baseline cortisol level estimate (described earlier) to the pre- and post-neuropsychological assessment cortisol levels, in the GAD and comparison groups using repeated measures analysis of variance controlling for the time of day that testing occurred and wake-up time. There was a significant time by group effect, $F(2,65) = 9.78$, $p < 0.001$, but a non-significant time, $F(2, 65) = 2.81$, $p = 0.07$, and group effect, $F(1, 66) = 1.18$, $p = 0.19$. The time by group interaction was characterized by a significant difference in baseline cortisol levels ($p < 0.001$) but no differences in the pre- and post-neuropsychological assessment cortisol levels between the two groups (see Figure 1). This indicates the GAD group's cortisol levels were significantly higher than comparisons in their home environment but not different from the comparison group in the assessment environment. Further, contrasts revealed no differences across the three cortisol measurements within the comparison group. However, baseline cortisol estimates for participants with GAD were significantly higher than the pre- ($p < 0.05$) and post-neuropsychological ($p < 0.001$) assessment cortisol levels. On the other hand, the post-neuropsychological assessment cortisol levels for the GAD participants were not significantly lower than the pre-neuropsychological assessment cortisol levels (although they continued to decrease).

Due to missing data in the pre-neuropsychological cortisol measurement, we imputed the missing values and reran the previous analyses with the imputed data. The results were the same.

The relationship between GAD status, cortisol and cognitive performance

There were no significant effects of post-neuropsychological assessment cortisol levels, group status, or the interaction between group status and cortisol levels on performance for the following cognitive measures: Stroop Color-Word Time, Visuospatial/Construction Index, Attention Index and Delayed Memory Index. There was a significant main effect of group status on MMSE and DKEFS Card Sort Correct Sorts performance where the comparison group performed significantly better than the GAD participants. Further, there was a significant negative relationship between cortisol level and performance on the DKEFS Card Sort Correct Sorts. Table 2 presents the results of the hierarchical multiple regressions for the models with a significant (or approaching significance) interaction between GAD status and cortisol on cognitive performance.

The results for the RBANS Total Index score, Immediate Memory Index score, Language Index score, and Letter-Number Sequencing performance are presented in Table 2. Step one was significant for the Language Index score and Letter-Number Sequencing performance accounting for 11 and 15% of the variance in performance, respectively. Step one was not significant for the RBANS Total and Immediate Memory Index scores. Step two was significant for Letter-Number Sequencing performance accounting for 9% of the variance in performance. Importantly, the interaction between group status and cortisol levels was significant (or approaching significance) for all four neuropsychological measures, accounting for 3 to 12% of the variance in performance. To better understand these interactions, we graphed the interaction as described by Cohen, Cohen, West, & Aiken (2003; see Figures 2A–D). The interactions were characterized by a significant negative relationship between cortisol levels and performance in the GAD group on all four measures. There was a positive relationship between cortisol levels and performance on the RBANS Total, Immediate Memory, and Language Indices in the comparison group but no relationship on Letter-Number Sequencing performance.

We created an area under the curve with respect to ground (AUCg: Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) measure from the six at-home cortisol measurements

and reran all of the regression analyses using this measure as a covariate in place of the baseline cortisol estimate. As can be seen in Table 2, the only difference was that the significant cortisol by GAD status interaction for the letter-number sequencing task was no longer approaching significance using the AUCg measure as a covariate.

Discussion

The goals of the current study were to address the following two questions: 1) Do older adults with or without GAD demonstrate an alteration in cortisol level when coming to a laboratory and undergoing neuropsychological assessment?; and 2) Is post-neuropsychological assessment cortisol level differentially associated with neuropsychological performance in older adults with or without GAD? Our examination of the relationship among cortisol level and both the experience of undergoing neuropsychological assessment as well as the performance in older adults with GAD revealed two findings: (1) participation in the neuropsychological assessment reduced cortisol level to the level of the non-psychiatrically ill comparison group, and (2) higher cortisol level was associated with poorer cognitive performance. In contrast, in the comparison group, cortisol level was positively related to performance on the RBANS Total, Immediate Memory, and Language Indices. This latter finding is consistent with recent data suggesting that acute changes in cortisol prior to testing enhances memory performance (Beckner et al., 2006; Cahill et al., 2003; De Kloet et al., 1999; Herbert et al., 2006; Hui et al., 2004; Roozendaal et al., 2006a, 2006b). The two observations within the GAD participants have important methodological and treatment implications, discussed below.

Effects of neuropsychological assessment on cortisol levels

We hypothesized that the GAD group's cortisol levels would be higher during the pre-neuropsychological assessment compared to their baseline and continue to increase during the neuropsychological assessment. Although the GAD group had a higher cortisol level in their home environment compared with the comparison group, the level was significantly reduced, to the level of the psychiatrically-healthy comparison group, at the time of in-laboratory neuropsychological assessment. Examining pre- and post-assessment cortisol levels compared to baseline, the GAD group's levels were significantly lower at the start of neuropsychological assessment and their cortisol level continued to decrease by the end of the assessment. In other words, the experience of going to a laboratory and undergoing neuropsychological assessment was cortisol-lowering rather than cortisol-elevating for older adults with GAD. We have previously shown that high worry levels are predictive of elevated cortisol levels in older adults with GAD (Mantella et al., 2008), and another group has shown that cortisol rises in anxious elderly people in response to a worry-producing stressor (Chaudieu et al., 2008). Thus, our findings of a cortisol-lowering effect of neuropsychological assessment could be explained by a focus on the cognitive tasks undercutting the effects of worry on the biological stress response of anxious older adults. A methodologic implication is that cortisol levels obtained in-laboratory may not accurately reflect anxious participants' levels at home. An important treatment implication is that strategies to increase older anxious adults' cognitive focus to tasks at hand (via cognitively challenging activities or mindfulness therapies which aim to increase present-centeredness) may have a cortisol-lowering effect; since cortisol reduction may improve neuropsychological status (Lenze et al., 2012), and thus, such strategies could improve cognitive function. We caution that this study was not specifically designed to test cognitive challenge as a cortisol-lowering treatment strategy, and these findings should be considered preliminary. Future research should examine this potential treatment implication, which if confirmed, could provide a behavioral strategy to reduce cortisol and its deleterious effects on brain and cognitive function in anxious older adults.

The relationship between GAD status, cortisol and cognitive performance

Consistent with our hypothesis, we found an inverse relationship between cortisol levels and cognitive performance in individuals with GAD but not in our comparison participants. That is, in participants with GAD, higher cortisol levels were associated with poorer performance on measures of global cognitive function, language, executive functioning and episodic memory. The negative association of cortisol with cognitive performance is in line with previous research findings that higher levels of cortisol are associated with smaller hippocampal volume and slower axonal transport in the prefrontal cortex (Lupien, McEwen, Gunnar, & Heim, 2009). The hippocampus is one of the most important brain structures involved in both mediating the stress response (McEwen, 1999) and acquiring and consolidating new episodic memories. Furthermore, the hippocampus is a target of stress hormones, having one of the highest concentrations of receptors for glucocorticoids (Kim & Diamond, 2002). The findings of Mantella and colleagues (2008) showed that GAD participants experience higher cortisol levels throughout the day compared to psychiatrically healthy comparison participants. Assuming that this cortisol exposure is chronic in GAD participants, it would be expected to impair the acquisition and consolidation of new information (De Kloet, Joels, & Holsboer, 2005; Joels, 2006; Sandi & Pineo-Nava, 2007). Thus, our findings support the hypothesis that elevated cortisol is one pathway by which anxious older adults have impaired cognitive function, is consistent with findings in studies of community-dwelling older adults (Comijs et al., 2010). Further, given that the GAD participants' cortisol levels were lower in the lab setting than at-home, suggests lab-based neuropsychological assessments may underestimate the level of cognitive impairment experienced by individuals with anxiety or other conditions of high stress and therefore high cortisol.

Further, Eysenck and colleagues' (2007) attentional control theory suggests that anxious individuals have less processing capacity and focus more on task irrelevant stimuli; ultimately depleting resources to devote to the current cognitive task (see also Tohill & Holyoak, 2000; Waltz, Lau, Grewal, & Holyoak, 2000; Wegner, 1994). In addition, the attentional control theory suggests that an individual with GAD would need to exert more effort in order to perform a task at the same level as a non-anxious individual (Eysenck et al., 2007). Future research could include a simple rating of effort after each of the neuropsychological tasks to assess this concept.

Limitations

Several limitations to this study should be noted. First, we do not have a measure of how difficult the neuropsychological battery was for the participants or how much effort they put forth in performing the tasks. However, as a group, they performed in the average range based on test norms, suggesting that the level of difficulty was similar for both the experimental comparison and normative sample groups. Further, we are presuming (based on the DSM-IV definition of GAD) that individuals with GAD are chronically stressed. Although the current dataset had one measure of distress during the neuropsychological assessment, it would be beneficial to have subjective measures of stress (e.g., perceived stress, daily hassles, or major life events) to determine the role of self-reported stress on cognitive performance in individuals with GAD. Lastly, the cognitive data used in this analysis are cross-sectional and we are therefore unable to determine whether cortisol levels are associated with changes in memory performance over time.

Conclusions

In conclusion, the findings suggest that engaging in the cognitive challenge of a neuropsychological battery was cortisol-lowering for older adults with GAD. Further, we found that there was a negative relationship between cortisol levels and cognitive

performance in late-life GAD participants but not in the psychiatrically healthy comparison group. These findings highlight the need for future research in at least two areas: first, if focusing on a cognitive task is cortisol-lowering, then therapies that teach anxious older adults to be more present-focused and/or able to shift attention away from worry to engaging in or performing cognitive tasks (e.g., cognitive training or remediation) may reduce HPA axis hyperactivity, with potential benefits for brain health and cognition. Second, if HPA axis dysfunction (marked by elevated cortisol) adversely affects cognitive performance, then a pharmacological or behavioral correction of this dysfunction may ameliorate cognitive impairment in late-life anxiety.

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Dr. Kerri Rawson is now a postdoctoral researcher in the Department of Psychiatry at Washington University School of Medicine.

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Figure 1. Cortisol Patterns for Generalized Anxiety Disorder and Comparison Participants at Baseline, Pre- and Post-Neuropsychological Testing.

2A.

Figure 2.

Figure 2A. Interaction Between Group Status and Cortisol for the RBANS Total Index Score

Figure 2B. Interaction Between Group Status and Cortisol for Immediate Memory Performance.

Figure 2C. Interaction Between Group Status and Cortisol for the Language Index Score.

Figure 2D. Interaction Between Group Status and Cortisol for Letter-Number Sequencing Performance.

Table 1

Means and Standard Deviations for all Variables of Interest by Group Status.

	GAD (n=69)	Control (n=39)
	Mean (SD)	Mean (SD)
Background Characteristics		
Age	72.78 (7.42)	74.67 (6.03)
Education	13.91 (2.36)	14.56 (2.95)
Female	69.60%	66.70%
White	84.10%	94.90%
Married	55.10%	64.10%
Observed distress during NP testing (% with) ***	85.50%	56.40%
Wake-up time	645h (1h30min)	645h (1h15min)
Time of Testing		
Pre-NP **	1200h (2h)	1100h (1h30min)
Duration	1h15min (15min)	1h15min (15min)
Cortisol Measures (log)		
Baseline Estimate	0.68 (0.69)	0.51 (0.50)
AUCg ***	3.30 (0.40)	2.94 (0.40)
Pre-NP	0.44 (0.77)	0.54 (0.68)
Post-NP **	0.23 (0.62)	0.55 (0.57)
Cognitive Measures		
MMSE **	28.09 (1.62)	28.95 (1.36)
Letter Number Sequencing *	10.75 (2.33)	11.95 (2.46)
DKEFS- Correct Sorts *	11.94 (2.86)	13.13 (3.01)
Stroop Color-Word Time	119.02 (4.09)	118.10 (4.66)
RBANS Total	95.51 (14.38)	100.49 (14.05)
Language	99.88 (13.17)	98.64 (12.08)
Visuospatial/Construction	92.16 (18.47)	94.67 (15.36)
Attention	100.72 (16.21)	105.00 (15.18)
Immediate Memory *	96.76 (15.19)	104.03 (17.46)
Delayed Memory *	93.61 (16.19)	100.13 (12.61)

Note: Asterisks indicate group differences;

*
p < .05;**
p < .01;***
p < .001; NP = neuropsych

Table 2
Association Between Post-Neuropsychological Testing Cortisol Levels, Group Status, and Cognition.

	RBANS- Total		RBANS-Immediate Memory Index		RBANS- Language Index		Letter-Number Sequencing	
	Baseline Est.	AUCg	Baseline Est.	AUCg	Baseline Est.	AUCg	Baseline Est.	AUCg
Step 1								
Time of Testing	0.11	0.08	0.17	0.11	0.14	0.06	0.16	0.12
Wake time	0.05	0.04	0.05	0.05	0.08	0.11	-0.05	-0.09
Cortisol	0.04	-0.10	0.07	-0.09	0.11	0.05	0.07	-0.01
Education	0.23 [*]	0.22 [*]	0.23 [*]	0.18	0.32 ^{**}	0.34 ^{**}	0.13	0.11
Age	-----	-----	-----	-----	-----	-----	-0.33 ^{***}	-0.32 ^{***}
R ² Change								
	0.06	0.07	0.07	0.06	0.11 [*]	0.12 [*]	0.15 ^{**}	0.14 ^{**}
Step 2								
Group	0.20	0.12	0.26 [*]	0.21	-0.08	-0.08	0.34 ^{**}	0.29 ^{**}
Cortisol	-0.05	0.03	-0.06	0.02	-0.03	-0.03	-0.12	-0.06
R ² Change								
	0.03	0.01	0.05	0.03	0.01	0.00	0.09 ^{**}	0.06 [*]
Step 3								
Group ^a Cortisol	0.32 [*]	0.25 [~]	0.46 ^{***}	0.41 ^{***}	0.25 ^f	0.25 [~]	0.23 [~]	0.20
R ² Change								
	0.06 [*]	0.04 [~]	0.12 ^{***}	0.10 ^{***}	0.03 ^f	0.04 [~]	0.03 [~]	0.02
Overall R ²								
	0.15	0.12	0.24	0.19	0.15	0.16	0.27	0.28

Note: standardized coefficients for each step are displayed for ease of interpretation. a0=GAD; 1=Control

^f p = 0.064;
[~] p < 0.057
^{*} p < 0.05;
^{**} p < 0.01;
^{***} p < 0.001