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Depression and cortisol responses to psychological stress: A meta-analysis

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Summary The purpose of this meta-analysis is to examine the association between depression and cortisol responses to psychological stressors. A total of seven studies comparing plasma or cortisol responses to psychological stressors in clinically depressed (MDD) and non-depressed (ND) individuals ($N=196$: 98 MDD, 98 ND; 83 men, 113 women; mean age = 40 years) were included. Sample size-adjusted effect sizes (Cohen's *d* statistic) were calculated and averaged across baseline (before stressor onset), stress (stressor onset up to 25 min after stressor offset), and recovery (more than 25 min after stressor offset) periods. Overall, MDD and ND individuals exhibited similar baseline and stress cortisol levels, but MDD patients had much higher cortisol levels during the recovery period than their ND counterparts. There was also a significant time of day effect in which afternoon studies were more likely to reveal higher baseline cortisol levels, blunted stress reactivity, and impaired recovery in MDD patients. This blunted reactivity-impaired recovery pattern observed among the afternoon studies was most pronounced in studies with older and more severely depressed patients.

1. Introduction

Psychosocial stressors are associated with the onset (Daley et al., 2000; Kendler et al., 1999; Lewinsohn et al., 1999), symptom severity (Hammen et al., 1992), and course of major depressive disorder (MDD) (Kendler et al., 1997). One possible mechanism linking stress and MDD is altered hypothalamic-pituitary-adrenal (HPA) functioning (Carroll et al., 1981; Holsboer et al., 1984; Nemeroff et al., 1984; Halbreich et al., 1985; Pfohl et al., 1985; Gold et al., 1986; Gold et al., 1988a,b; Young et al., 1993). The entire HPA system is designed to allow organisms to adapt to physical and psychosocial changes in their environments. In humans,

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perceived stress activates the central nervous system (CNS), causing the release of corticotropin releasing hormone (CRH) from the hypothalamus, adrenal corticotrophic hormone (ACTH) from the anterior pituitary, and cortisol from the adrenal cortex. In turn, elevations in cortisol levels typically inhibit the HPA system via negative feedback mechanisms in the hippocampus (Jacobson and Sapolsky, 1991; Munck et al., 1984; Sapolsky et al., 1986).

The temporal dynamics of HPA responses to stressors typically consist of three phases: (1) basal activity, which reflects unstimulated, non-stressed HPA activity, (2) a 'stress reactivity' phase in which cortisol increases from baseline (i.e. pre-stressor) levels following the onset of a stressor, and a 'stress recovery' phase in which cortisol levels return to baseline levels following the offset of the stressor (McEwen, 1998). Each of these phases reflects different physiological processes, with mineralocorticoid receptors (MCRs) regulating cortisol levels during periods of low HPA activity (e.g. evening), and GCRs regulating cortisol responses to stress and cortisol levels during periods of high HPA activity (e.g. morning).

A substantial literature has documented the link between MDD and abnormalities in HPA activity (Carroll et al., 1981; Holsboer et al., 1984; Nemeroff et al., 1984; Halbreich et al., 1985; Pfohl et al., 1985; Gold et al., 1986, 1988a,b; Young et al., 1993). Most of what is known about HPA functioning in depressed individuals is based on studies of basal HPA activity (Halbreich et al., 1985; Asnis et al., 1987) and pharmacological challenge studies designed to test the negative feedback mechanisms in the HPA axis, such as the dexamethasone suppression test (Carroll et al., 1981). Some findings have suggested that a subset of individuals with MDD have elevated basal cortisol levels coupled with blunted ACTH responses and cortisol elevations in response to dexamathasone administration (Holsboer et al., 1984; Gold et al., 1986; Young et al., 1993).

Although the pharmacological literature on HPA activity in depressed patients has yielded important findings for the field of psychoneuroendocrinology, it is not without limitations. First, dexamethasone is a synthetic glucocorticoid, and the levels of dexsamethasone used in pharmacological challenge studies are specifically designed to mimic the highest extreme of glucocorticoid functioning in order to suppress subsequent endogenous cortisol release (Carroll et al., 1981). Such high levels of glucocortcoids may not accurately reflect the magnitude of endogenous HPA responses to psychosocial stressors. Further, dexamethasone specifically probes glucocorticoid but not mineralocorticoid receptor function, and poorly crosses the blood-brain-barrier (De Kloet et al., 1998). Finally, in contrast to psychological stressors, many pharmacological and neuroendocrine challenge tests ignore suprahypothalamic (e.g. limbic) input. Thus, psychological stress challenges offer the advantage of reflecting endogenous activity of the entire HPA system.

There is also evidence that HPA activity may differ between individuals, as well as between situations. Not all MDD patients are cortisol non-suppressors, suggesting that there may exist significant variability in HPA response patterns amongst MDD patients. Potential sources of variation include: (1) individual characteristics such as age and gender (Seeman and Robbins, 1994; Kudielka et al., 2004; Otte et al., 2005), (2) depression characteristics such as subtype (Gold et al., 1995), severity (Carroll et al., 1981; Meador Woodruff et al., 1990), hospitalization status (Maes et al., 1994), and early life stress or PTSD comorbidity (Heim et al., 2000; Yehuda et al., 2004), and (3) stressor characteristics such as type of stressor (e.g. public speaking vs. cognitive task) and duration (Dickerson and Kemeny, 2004). Finally, the effect of depression on HPA responses to stress may depend on the time of day or HPA phase examined (e.g. basal activity, stress reactivity, stress recovery).

The primary purpose of this meta-analysis is to quantify the association between MDD and HPA responses to and recovery from psychosocial stressors. A secondary goal is to identify potential moderators of the depression and HPA stress response association. The large majority of empirical studies have used cortisol rather than ACTH. Therefore, only studies using cortisol responses to stress are included in this meta-analysis.

2. Methods

2.1. Studies

Several factors were considered when selecting studies for review. First, only studies comparing MDD using structured diagnostic interviewing based on a clinical diagnosis (e.g. DSM or RDC criteria) to ND individuals were included to ensure construct validity. Second, because pediatric and adolescent MDD may be biochemically distinct from adult forms (Kaufman et al., 2001), only studies with adult samples were included. Third, since physical illness may produce abnormal neuroendocrine

stress responses, only studies examining physically healthy individuals were used. Fourth, because the purpose of this review and meta-analysis was to compare cortisol responses to psychological stressors between MDD and ND individuals, only studies that included manipulated or measurable psychological stressors (e.g. laboratory stressors, naturalistic stressors) were included in this review. Finally, effect sizes must have been calculable for both baseline and stress time periods.

Online databases (Medline, PsycInfo) and reference lists were searched in January, 2004 to identify all studies comparing plasma, urinary, or salivary cortisol responses between MDD and ND individuals to psychological stressors. Search terms included 'cortisol,' 'stress,' 'depression,' and 'depressive'.

Abstracts were initially reviewed by the first author to determine eligibility (e.g. non-review article, adult human population, etc.). Following this initial cursory review, 19 empirical studies were randomly assigned for further independent review by one of the two authors (Davis and Mohr). Thus, every study was reviewed independently by two authors. As a result of this review process, 11 studies were excluded: one study because of a non-independent sample (Heim et al., 2002), three studies for not having a depressive symptom measure reflecting MDD symptomatology (Ely and Mostardi, 1986; van Eck et al., 1996a; Grossi et al., 2003), six studies because of an inability to calculate effect sizes (Hall and Johnson, 1988; Griffiths et al., 1997; Roy et al., 2001; Sayal et al., 2002; Strickland et al., 2002; Vedhara et al., 2002), and one study for not providing an objective measure or manipulation of stress (Jacobs et al., 1984). There was 100% agreement on study inclusion and exclusion.

The final sample included eight studies reported in eight separate journal articles. Out of the eight studies selected for inclusion, seven were laboratory studies and one was a field study. Since laboratory and field studies have been shown to yield different cortisol stress responses (van Eck et al., 1996b), only the laboratory studies were included in the formal meta-analyses. Comparison of the results of the laboratory studies to the field study are discussed later.

2.2. Materials

Studies judged to meet inclusionary criteria were coded by the first author to assess characteristics of the participants (e.g. *N*, mean age, % male, medication usage), depression characteristics (e.g. hospitalization status, depression severity, other Axis I disorder), and stress characteristics (e.g. time of day, duration of stressor, and type of stressor).

For each study, demographic and medical information such as mean age, gender composition (% male), and medication use were coded. Medication usage was coded with a categorical variable where 1 = no medication, 2 = medication washout, 3 = only non-endocrine medications, 4 = mixture of endocrine and non-endocrine medications, 5 = unclear, and 6 = no report.

For each study, depression characteristics such as symptom severity, hospitalization status (inpatient vs. outpatient), and comorbid PTSD (present vs. not-present) were coded when this information was available. Depression severity was coded as the mean Hamilton depression rating scale (HDRS) (Hamilton, 1960). Hospitalization status was dummy-coded into outpatient (e.g. community and/or outpatient) and inpatient (e.g. exclusively inpatient or inpatient/outpatient mixed) samples.

Laboratory stress studies were categorized into morning and afternoon studies based on the time of day each study commenced. The total duration of the stressor was calculated in minutes. In addition, the type of stressor task in each study was coded using a classification system developed by Dickerson and Kemeny, and is described elsewhere (Dickerson and Kemeny, 2004). With this system, stress tasks were classified into two categories: public speaking tasks (PS) (e.g. Trier Social Stress Test (Kirschbaum et al., 1993)) and exclusively cognitive tasks (CT).

2.3. Procedures

Standardized mean difference (Cohen's *d*) effect sizes were calculated based on average group differences between MDD and ND groups at baseline, stress, and recovery (Cohen, 1988; Lipsey and Wilson, 2001). An advantage to Cohen's *d* statistic is that it corrects for small sample size bias. Baseline effect sizes were operationalized as the average of Cohen's *d* statistics before the onset of a stressor. All stress effect sizes were calculated by averaging the Cohen's *d* statistics for samples collected after the onset of the stressor and less than 25 min after stressor offset because cortisol appears in the bloodstream approximately 25 min after a stressor occurs (Kirschbaum and Hellhammer, 1989). For the recovery analyses, cortisol samples collected at least 25 min after the termination of the stressor were considered 'recovery' samples, and were averaged into a recovery effect size.

Table 1 Study characteristics and effect sizes.

Study (first author)	MDD			ND			Depression characteristics	HDRS	Time of day	Stress characteristics	Effect size (d)		
	n	M:F	Age	*n*	M:F	Age	Hospital		Hour	Stressor	Baseline	Stress	Recovery
Laboratory studies													
Breier	7	3:4	41 (11)	10	6:4	33 (9)	I	-	1400	CT	0.70	0.85	-
Croes	11	5:6	46 (10)	11	5:6	46 (8)	I	29.45	1400	CT	1.06	−0.59	-
Gotthardt	20	5:15	47 (6)	20	8:12	47 (4)	n/s	22.50	1300	CT	1.11	−0.11	1.02
Heim	23	0:23	33 (3)	12	0:12	29 (2)	O	19.91	1300	PS	−2.06	3.42	2.08
Ravindran	18	9:9	38 (4)	23	9:14	35 (3)	O	23.60	0800	CT	−1.42	−1.06	-
Trestman	9	9:0	53 (4)	12	12:0	48 (3)	I	27.30	1400	CT	2.05	−1.14	2.00
Young	10	6:4	33 (11)	10	6:4	34 (12)	O	20.00	1600	PS	1.04	0.73	0.60
Naturalistic study													
Peeters	47	19:26	40 (11)	39	16:23	44 (12)	O	24.00	-	Naturalistic	−0.70[a]	−3.84	-

M, male; F, female. I, inpatient; O, outpatient. CT, cognitive task; PS, public speaking task.
[a] Note: this effect size represents differences between depressed and non-depressed individuals in basal cortisol levels, as opposed to baseline cortisol levels.

Effect size calculation was based on the following order of preference: (1) means and standard deviations (e.g. extracted from text of article or figures, or obtained directly from author), (2) inferential statistics (Hedges and Olkin, 1985; Rosenthal, 1991), (3) verbal statement in text (e.g. 'significant effect' assumed $p<0.05$, 'no significant effect' assumed effect size $d=0.00$).

2.4. Statistical analyses

To control for the effect of baseline differences in baseline cortisol levels on subsequent cortisol stress reactivity, baseline effect sizes (Cohen's *d*) were calculated reflecting baseline cortisol differences between MDD and ND individuals. As our primary interest was in the effect of depression on cortisol stress responses relative to cortisol baseline levels, baseline effect sizes were included as covariates in the subsequent meta-analyses. Two independent meta-analyses were conducted: one for stress reactivity and one for stress recovery.

The effect sizes for each study were then weighted by their inverse variance. Using a random effects maximum likelihood (REML) model, 95% confidence intervals (CI) for the weighted effect sizes were calculated (Lipsey and Wilson, 2001). The *Q* test was used to test the homogeneity of variance of the effect sizes. When heterogeneity between studies was found, the effects of potential moderators such as characteristics of participants, depression, and/or stressors were explored using regression analyses.

3. Results

3.1. Characteristics of selected studies

Seven laboratory stress studies with 98 MDD and 98 ND individuals were included in the meta-analyses (Breier et al., 1989; Trestman et al., 1991; Croes et al., 1993; Gotthardt et al., 1995; Ravindran et al., 1996; Heim et al., 2000; Young et al., 2000) (Table 1). Though not included in the formal meta-analyses, an additional study examining stress responses of 47 MDD and 39 ND participants in the field study will be discussed separately (Peeters et al., 2003). Studies reviewed in this meta-analysis are marked with asterisks in the reference list.

A total of 196 participants (83 men, 113 women), with mean age of 40.32 years (range = 18–68) were included in the formal meta-analysis (Table 1). None of the studies controlled for menstrual cycle, one study controlled for menopausal status (Heim et al.,

2000), and two studies verified that participants were physically healthy (Gotthardt et al., 1995; Young et al., 2000). All studies controlled for medication usage in one of three ways: (1) no medication use (Trestman et al., 1991; Young et al., 2000), (2) medication wash-out period (Breier et al., 1989; Gotthardt et al., 1995; Ravindran et al., 1996), or (3) restricting medication use to non-endocrine medications (Croes et al., 1993; Heim et al., 2000).

Of the seven studies included in the meta-analysis, depression was diagnosed using DSM-III (Breier et al., 1989; Croes et al., 1993), DSM-III-R (Gotthardt et al., 1995; Ravindran et al., 1996), DSM-IV (Heim et al., 2000; Young et al., 2000), or RDC criteria (Trestman et al., 1991). In terms of comorbid psychiatric conditions, one study had three patients with anxiety disorders in its MDD sample (Young et al., 2000) and one study had 11 patients with PTSD in its MDD sample (Heim et al., 2000). The average HDRS score across studies was 23.48 (range: 19.91–29.45), reflecting a moderate to severe level of depressive symptomatology. Out of the seven studies, three used outpatient samples (Ravindran et al., 1996; Heim et al., 2000; Young et al., 2000), three used inpatient samples (Breier et al., 1989; Trestman et al., 1991; Croes et al., 1993), and one study did not specify the hospitalization status of their depressed participants (Gotthardt et al., 1995).

With one exception (Ravindran et al., 1996), all of the studies were conducted in the afternoon. The average duration of stress was 25 min (range: 10–45 min). Of the seven laboratory studies, four provided sufficient data to calculate effect sizes at recovery.

Of the seven laboratory stress studies, two used PS tasks (Heim et al., 2000; Young et al., 2000) and five used CT tasks (Breier et al., 1989; Croes et al., 1993; Gotthardt et al., 1995; Ravindran et al., 1996; Trestman et al., 1991;). The PS tasks were variations of Trier Social Stress Test (TSST). The CT tasks included anagrams with uncontrollable noise (Breier et al., 1989), a computer vigilance task (Gotthardt et al., 1995), mental arithmetic with auditory distraction (Trestman et al., 1991), and mental arithmetic with (Croes et al., 1993) and without forced failure (Ravindran et al., 1996). None of the studies assessed whether the stressor was successful in eliciting perceived stress per se. However, four out of seven laboratory studies provided some type of mood measure in response to the stressor (e.g. depressed mood visual analogue scale, lack of control rating scale, perceived success, helplessness, and control scale, and mood visual analogue scales) (Breier et al., 1989; Croes et al., 1993; Gotthardt et al., 1995; Trestman et al., 1991; Young et al., 2000). The studies that did report mood reactivity found inconsistent results, with some studies finding depressed patients to be more mood reactive than non-depressed patients (Breier et al., 1989; Young et al., 2000), and others finding no differences between groups (Croes et al., 1993; Gotthardt et al., 1995; Peeters et al., 2003). The naturalistic study found that MDD patients were less responsive to stress in terms of negative affective responses when compared to their ND counterparts, despite having higher levels of negative affect overall (Peeters et al., 2003).

3.2. Baseline results

Including all seven laboratory studies in the analysis, there was no significant effect of depression on baseline cortisol levels, $d=0.36$, SEM$=0.55$, $p=0.58$ (Table 2). However, a homogeneity test revealed that the effect of depression on baseline levels of cortisol varied significantly across studies, $Q\ (6)=74.99$, $p<0.0001$.

Table 2 Summary of results: average effect sizes at baseline, stress, and recovery.

Variables	Effect sizes			
	d	SE	±95%CI	*Z*
Baseline				
Average ES at baseline	0.36	0.55	(−0.73, −1.45)	0.65
Time of day (morning vs. afternoon)	0.34	0.16	(0.03, 0.65)	2.15*
Morning	−1.42	0.36	(−2.08, −0.76)	−4.23****
Afternoon	0.83	0.18	(0.48, 1.18)	4.68****
Stress				
Average ES at stress (unadjusted for baseline)	0.27	0.52	(−0.75, 1.28)	0.51
Recovery				
Average ES at recovery (unadjusted for baseline)	1.39	0.35	(0.70, 2.08)	3.94***

$p<0.10$. *p, <0.05; **p, <0.01; ***p, <0.001; ****p, <0.0001.

Since cortisol levels are typically highest in the morning and lowest in the afternoon, we reasoned that the time of day of each study might be a significant source of this variability. One study was conducted in the morning (Ravindran et al., 1996), and the remainder were conducted in the afternoon. Results of ANOVA revealed that the time of day had a significant effect on the relationship between depression and baseline cortisol levels, Q (1) = 25.88, $p < 0.0001$. Specifically, results revealed that MDD patients had much lower baseline cortisol levels than their ND counterparts in the morning study ($d_{AM} = -1.42$, $SE_{AM} = 0.36$, $p < 0.0001$). In contrast, in afternoon studies, MDD patients had moderately higher baseline cortisol levels than their ND counterparts ($d_{PM} = 0.83$, $SE_{PM} = 0.18$, $p < 0.0001$).

3.3. Stress reactivity

To validate that the stressors used in the studies included in the meta-analysis were successful in eliciting cortisol responses, we first analyzed cortisol stress responses among ND individuals only. Results revealed an average effect size[1] of $d = 1.05$, $SE = 0.28$, $p < 0.01$, suggesting that cortisol levels significantly increased in response to the stressors in ND individuals, though the magnitude of cortisol stress responses in ND individuals differed between studies, Q (6) = 52.72, $p < 0.0001$. Cognitive stressors elicited greater cortisol responses than public speaking tasks ($d_{cognitive} = 1.28$ vs. $d_{public\ speaking} = 0.64$). Thus, the stress procedures utilized by the studies included in the meta-analysis were valid elicitors of cortisol responses in ND individuals[1].

All subsequent analyses were run comparing MDD and ND individuals. Two questions were addressed by the stress reactivity analyses: (1) do MDD patients display higher cortisol levels at stress than their ND counterparts, and (2) if so, do these differences remain after controlling for any baseline effects? To address the first question, effect sizes at stress, unadjusted for baseline differences between MDD and ND individuals were analyzed (Table 2). Across all seven studies, MDD and ND individuals did not differ significantly in unadjusted cortisol levels at stress, with an average effect size of $d = 0.27$, SEM = 0.52, $p = 0.61$; Range: −1.14–3.42. However, results of a homogeneity test suggested that the effect of depression on cortisol stress levels varied significantly between studies, Q (6) = 62.82, $p < 0.0001$. Results revealed that MDD patients had much lower stress cortisol levels than their ND counterparts in the morning study ($d_{AM} = -1.06$, $SE_{AM} = 0.34$, $p = 0.002$). Since afternoon studies tended to observe higher baseline cortisol levels in MDD patients, if MDD and ND individuals were equivalently reactive to stress, one would expect MDD patients to also have higher cortisol levels at stress than their ND counterparts. This was not the case; among afternoon studies, there was no effect of depression on stress cortisol levels ($d_{PM} = 0.29$, $SE_{PM} = 0.18$, $p = 0.11$). Thus, there is evidence supporting a relatively blunted pattern of cortisol stress reactivity among MDD patients in afternoon studies.

To address whether MDD patients exhibited greater cortisol stress levels after controlling for baseline effects (i.e. stress reactivity), we included baseline effects and time of day as covariates (Table 3). Results of these analyses revealed that the greater the effect of depression at baseline, the smaller the effect of depression at stress, $\beta = -1.11$, $SE = 0.17$, $p < 0.0001$. In other words, higher baseline cortisol levels in MDD patients at baseline were associated with more blunted cortisol stress responses in MDD than ND patients. Even after controlling for baseline effects, there remained a significant effect of time of day on the depression and stress reactivity association, $\beta = 3.86$, $SE = 0.53$, $p < 0.0001$, suggesting that afternoon studies were more likely to find greater stress reactivity in MDD patients than the morning study. Moreover, there existed significant heterogeneity between studies in the effect of depression on cortisol stress responses, Q (6) = 62.82, $p < 0.0001$. Therefore, we explored potential moderators of this association in subsequent analyses.

As age, gender, and medication use have been independently associated with alterations in HPA activity (Seeman and Robbins, 1994; Kudielka et al., 2004; Otte et al., 2005), we examined whether these characteristics influenced the relationship between depression and cortisol stress reactivity (Table 3). Age had a significant effect on the relationship between depression and cortisol stress responses, Q (2) = 48.90, $p < 0.0001$. Specifically, as the age of the samples increased, individuals with MDD tended to exhibit more blunted responses to the stressor than their ND counterparts ($p = 0.05$). There were no significant effects of gender or medication use on the relationship between depression and cortisol stress responses.

We also examined whether characteristics of the depression, such as symptom severity, hospitalization status (e.g. inpatient vs. outpatient), PTSD

[1] In this case, effect sizes reflect differences in cortisol levels from baseline to stress, such that positive values reflect increases in cortisol levels from baseline to stress, and negative values reflect decreases in cortisol levels from baseline to stress.

Table 3 Summary of results: predictors of cortisol stress reactivity and recovery.

Predictors	Coefficients			
	β	SE	±95%CI	Z
Stress reactivity				
Baseline cortisol ES	−1.11	0.17	(−1.44, −0.79)	−6.73****
Time of day (morning vs. afternoon)	3.86	0.53	(2.82, 4.91)	7.25****
Participant characteristics				
Age	−0.07	0.04	(−0.14, 0.02)	−1.92*
Gender distribution (% male)	0.76	1.06	(−1.32, 2.85)	0.72
Depression distribution (% male)				
Symptom severity (HDRS)	−0.11	0.06	(−0.23, 0.01)	−1.80
Hospitalization status (inpatient vs. outpatient)	−0.30	0.39	(−1.05, 0.46)	−0.77
PTSD comorbidity	0.84	1.64	(−2.37, 4.05)	0.51
Anxiety disorder comorbidity	0.81	0.50	(−0.18, 1.79)	1.60
Stress characteristics				
Duration	0.00	0.01	(−0.02, 0.03)	0.22
Public-speaking tasks	0.75	0.51	(−0.25, 1.74)	1.46
Cognitive tasks	−0.75	0.51	(−1.74, 0.25)	−1.46
Stress recovery				
Baseline cortison ES	−0.20	0.17	(−0.53, 0.13)	−1.17
Participant characteristics				
Age	0.06	0.04	(−0.02, 0.14)	1.44
Gender distribution (% male)	1.62	1.18	(−0.69, 3.93)	1.38
Depression characteristics				
Symptom severity (HDRS)	0.27	0.11	(0.05, 0.49)	2.37*
Hospitalization status (inpatient vs. outpatient)	1.50	0.66	(0.21, 2.79)	2.27*
PTSD comorbidity	4.95	2.13	(0.78, 9.12)	2.32*
Anxiety disorder comorbidity	−0.81	0.53	(−1.84, 0.22)	−1.55
Stress characteristics				
Duration	0.00	0.02	(−0.05, 0.05)	−0.13
Public-speaking tasks	−0.65	0.63	(−1.89, 0.59)	−1.03
Cognitive tasks	0.65	0.63	(−0.59, 1.89)	1.03

p, <0.10; *p, <0.05. **p<0.01; ***p, <0.001; ****p, <0.0001.

comorbidity, or other anxiety disorder comorbidity might influence the relationship between depression and cortisol stress reactivity. Among the six studies with HDRS scores, there was a statistically non-significant trend for studies with more severely depressed samples to observe more blunted cortisol stress responses in MDD vs. ND individuals ($p=0.07$).[2] However, there was no significant effect of hospitalization status on the relationship between depression and cortisol stress reactivity. There was also no significant effect of PTSD diagnosis or other anxiety disorders on the relationship between depression and cortisol stress responses. In addition, there was no significant effect of stressor duration or type (e.g. PS vs. CT) on the relationship between depression and cortisol stress responses.

3.4. Stress recovery

Of the seven studies included in the meta-analysis, only four (^{N}recovery=125 individuals) provided sufficient information to examine differences between MDD and ND individuals in cortisol stress recovery. Two questions were addressed by the stress recovery analyses: (1) do MDD patients display higher cortisol levels at recovery than their ND counterparts, and (2) if so, do these differences remain after controlling for any baseline effects? To address the first question, we first examined recovery effect sizes unadjusted for baseline effects. MDD patients had higher unadjusted cortisol levels at recovery (based on samples collected≥25 min stressor offset) than ND individuals, $d=1.39$, SE=0.35, $p<0.0001$ (Table 2), with

[2] Though we were not likely to detect effects, as the Residual Q in the age effects analysis was not significant ($Q(3)=1.29$, $p=0.73$), since age and depression symptom severity were confounded, we tested the independent effects of both variables on depression effects on cortisol stress reactivity. Neither age ($\beta=-0.04$, SE=0.05, $p=0.39$) nor symptom severity ($\beta=-0.07$, SE=0.07, $p=0.31$) effects on depression and cortisol stress reactivity were statistically significant, though both remained in the same direction.

significant heterogeneity between studies, $Q(3) = 7.93$, $p < 0.05$.

Next, because we were interested in recovery levels relative to baseline effects, baseline effects were included as a covariate. Since all stress recovery studies were conducted in the afternoon, time of day was not included as a covariate. Results revealed that baseline effect sizes were not associated with the effect of depression on cortisol stress recovery, suggesting that the higher stress recovery cortisol levels in MDD than ND individuals was not due to the fact that MDD patients started out with higher baseline cortisol levels.

There were no significant effects of age ($p = 0.15$) or gender ($p = 0.17$) on the relationship between depression and cortisol stress recovery (Table 3). Greater depression severity (i.e. higher HDRS scores) ($p = 0.02$) and inpatient status ($p = 0.02$) were associated with elevations in cortisol levels during recovery from stress in MDD individuals compared to their ND counterparts. Moreover, though based on one study, presence of PTSD comorbidity was also associated with higher baseline-adjusted stress recovery cortisol levels in MDD patients compared to ND individuals ($p = 0.02$). There was no significant effect of comorbid anxiety disorders on the association between depression and cortisol stress recovery. There were also no significant effects of stressor duration or type on the association between depression and cortisol stress recovery.

3.5. Naturalistic study

One study compared cortisol responses between MDD and ND individuals in a naturalistic setting (Peeters et al., 2003) (Table 1). In this study, participants were instructed to provide self-reports of mood and events, as well as collect salivary cortisol samples 10 times per day for 6 days. Results revealed no differences between MDD and ND participants in basal cortisol levels. However, depressed participants exhibited blunted cortisol responses to naturalistic stressors. In addition, MDD participants also exhibited blunted negative affect response to negative events, despite reporting higher levels of negative affect overall than ND individuals. Finally, depressed women showed larger cortisol responses to negative events than depressed men.

4. Discussion

The purpose of this meta-analysis was to review and quantify the findings of studies examining the pattern of cortisol responses to psychological stressors in depressed individuals. We compared responses between MDD and ND individuals at two phases of stress: stress reactivity and stress recovery. Our results suggest that MDD and ND individuals differ in their cortisol response patterns to stress. Specifically, in MDD individuals, cortisol activity is characterized by blunted stress reactivity and impaired stress recovery. Put another way, depressed individuals exhibit a relatively flat and unresponsive pattern of cortisol secretion. Overall, this 'flattened' pattern is consistent with studies demonstrating flattened diurnal activity (i.e. lower morning cortisol, higher afternoon cortisol) among MDD patients compared to their ND counterparts (Carroll and Mendels, 1976; Young et al., 1994). In contrast, ND individuals show a more dynamic and responsive pattern of cortisol activity, with greater stress reactivity and more rapid recovery following stress. In addition, the results of the naturalistic study supported those observed in the laboratory stress studies, as both revealed evidence of blunted cortisol stress reactivity.

There also existed significant sources of variation in cortisol response patterns between studies. Results of this meta-analysis demonstrate that situation- and person-specific characteristics, such as time of day, age, and depression severity, moderate the effect of depression on cortisol stress responses. Studies conducted in the afternoon were more likely to find higher baseline cortisol levels and greater stress reactivity in MDD than ND

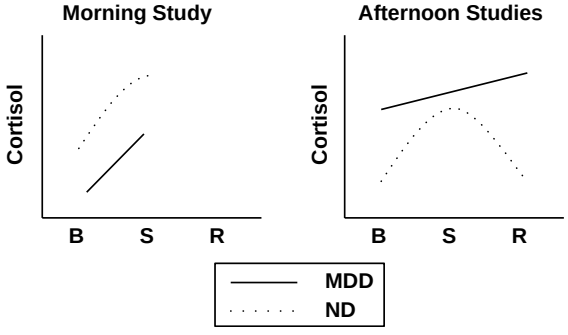

Figure 1 This figure is a schematic representation of the meta-analysis results. In the morning study, MDD patients have lower baseline and stress cortisol levels than their ND counterparts. In contrast, among afternoon studies, MDD patients had higher cortisol levels at baseline and recovery than their ND counterparts. Though there were no significant differences between MDD and ND individuals in cortisol levels at stress, after adjusting for baseline effects, MDD patients exhibited relatively blunted cortisol responses to stress. MDD = major depressive disorder, ND = non-depressed. B = baseline, S = stress, R = recovery.

individuals than the study conducted in the morning (Fig. 1). Results also revealed that the blunted cortisol stress reactivity observed in MDD patients was most pronounced in older and/or more severely depressed patients, although these two variables may have been confounded in our analyses. Similarly, poor stress recovery was most pronounced in more severely depressed and/or hospitalized MDD patients, as well as MDD patients with comorbid PTSD.

These results suggest that both age and depression severity may operate in the same direction, with older and more severely depressed individuals exhibiting a flatter response to psychosocial stressors than their younger and less severely depressed counterparts. However, these results do contrast with those found in a recent meta-analysis of the effects of age on cortisol responses to challenge which demonstrated greater cortisol reactivity in older than younger, non-depressed; otherwise healthly participants (Otte et al., 2005). One possible explanation for the discrepancy in results is that, since we were interested in cortisol responses to stress (i.e. change from baseline), we covaried out the baseline effects, whereas the aforementioned meta-analysis of age effects did not. In addition, in pharmacological challenge studies, endogenous 'reactivity' to exogenous, pharmacological challenge is more analogous to the stress recovery phase of the stress response. In other words, what is referred to as 'reactivity' in the pharmacological literature is actually a reflection of an individual's ability to 'recover' from the challenge, or turn off his or her own production of cortisol via negative feedback.

Consistent with pharmacological studies demonstrating that DST non-suppressors represent a subset of severely depressed, often hospitalized individuals (Carroll et al., 1981; Maes et al., 1994), we found evidence for more blunted cortisol responses and impaired recovery among more severely depressed and/or hospitalized MDD patients. Our results suggest that depression severity may have a dose-dependent effect on a flattening of cortisol responses. Another alternative is that severely depressed patients may represent a qualitatively distinct sample of depressed individuals, characterized by HPA abnormalities. This interpretation would be consistent with results of pharmacological challenge tests finding that a subset of depressed patients are DST non-suppressors (Carroll et al., 1981).

Though based on results of one study, results of this meta-analysis revealed that presence of comorbid PTSD was associated with poorer recovery among MDD patients than ND individuals. Given the small number of studies in this meta-analysis, one might question whether the inclusion of a significant sample of depressed patients with comborbid PTSD might unduly bias the direction and/or magnitude of effects. This point is especially poignant given that the study with PTSD patients had the largest absolute effect sizes at every time point. However, re-running the meta-analyses without the PTSD comorbid patients did not change the results or conclusions presented in this review. Overall, while interesting, more data are needed before firm conclusions can be drawn about the effect of PTSD comorbidity on depression and cortisol stress responses.

This meta-analysis has several limitations. First, it is based on a small number of individuals within an even smaller number of studies, which precluded the examination of potentially meaningful sources of the variability between studies in cortisol responses to stress. This limitation was most pronounced for the stress recovery meta-analysis, as it was based on four studies. Nevertheless, we observed several significant effects, particularly for age and depression severity. Second, with the exception of the naturalistic study, the remaining studies were limited to assessments of baseline, and not basal cortisol activity. It is possible that the 'baseline' assessments actually reflected the stress of coming to the laboratory as well as anticipatory stress. Another limitation of this meta-analysis is that cortisol, typically total plasma cortisol, was the only hormone assessed, yet it represents just one component of a complex HPA axis. Total plasma cortisol does not represent the bioactive, or 'free' portion of cortisol that is available to bind to target receptors and produce physiological effects (Kirschbaum and Hellhammer, 1989). Thus, a more complete picture of HPA activity and responsivity to stress in depressed individuals could be achieved by including other HPA hormones, as well as their relative balance to cortisol, parsing 'free' cortisol from total cortisol levels, and testing the sensitivity of target cells to glucocorticoids (Raison and Miller, 2003). Finally, based on these data, we are unable to determine whether the relatively flat pattern of stress responsivity precedes, accompanies, or follows a depressive episode. Only prospective, longitudinal studies of stress and depression can adequately address this issue.

In summary, we found evidence that depression was associated with blunted cortisol stress reactivity and impaired stress recovery in certain subgroups of MDD patients. Furthermore, this relatively unresponsive pattern of cortisol activity

was most pronounced in older and more severely depressed individuals. The results of this study provide a foundation for further investigations in this important area of psychoneuroendocrinology.

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