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Extraversion modulates cortisol responses to acute social stress in chronic major depression

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ABSTRACT

Background: Chronic Major Depressive Disorder (CMDD) is a common, disabling illness that is often complicated by high reactivity to social stress. To further elucidate the nature of this reactivity, the current study evaluated whether the personality dimensions of neuroticism and extraversion influenced cortisol responses to a social challenge in CMDD patients vs. controls.

Methods: Fifty participants with CMDD and 58 healthy controls completed the Trier Social Stress Test (TSST) using a standard protocol. Neuroticism and extraversion were measured using the Revised NEO Personality Inventory. Hierarchical linear regressions assessed associations between independent variables neuroticism and extraversion and dependent variable cortisol area-under-the-curve increase (AUCi) in response to the TSST in the two study groups.

Results: The extraversion-by-group interaction was a significant predictor of cortisol AUCi, while no significant findings related to neuroticism were found. Simple slopes analysis revealed a significant negative association between extraversion and AUCi in the CMDD group, but not in healthy controls. Post-hoc analysis of the raw cortisol data over time found that CMDD participants with higher extraversion scores had significantly higher pre-challenge cortisol levels than did other study participants, however this did not explain or confound the AUCi results.

Conclusions: In participants with CMDD but not in controls, higher levels of extraversion were associated with higher pre-challenge cortisol levels and decreased cortisol reactivity during the TSST, however these two findings were statistically independent. These findings underline the importance of considering personality factors when studying stress biology in CMDD patients. Extraversion may prove to be an important intermediate target for both research and clinical work in this complex, heterogenous and often treatment-resistant population.

1. Introduction

Up to 35% of individuals with Major Depressive Disorder (MDD) go on to develop Chronic Major Depressive Disorder (CMDD) (Boschloo et al., 2014; Waugh and Koster, 2015), defined as a major depressive episode lasting at least two years.[1] CMDD is a major public health concern, given its association with higher levels of functional impairment, increased risk of suicide, greater comorbidity with other psychiatric illnesses, and poorer response to treatment relative to acute depression (Boschloo et al., 2014; Robison et al., 2009; Torpey and Klein, 2008). Despite the high morbidity associated with CMDD, patients with CMDD are often excluded from pathophysiological and/or clinical trial research (Fried, 2015), largely as a result of their high co-morbidity rates which contribute to heterogeneity. As a result, little is known about the etiology and pathophysiology of CMDD, and few individualized treatment approaches have been developed for this population.

One potential research strategy to deal with co-morbidity and illness heterogeneity is to focus on dimensional measures of behaviour and

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[1] While the chronic specifier of MDD was taken out of the DSM-V, the diagnosis of Persistent Depressive Disorder (dysthymia) does not sufficiently capture the severity of depression in the present study. This, and the fact that the current data was collected prior to the DSM-V launch led us to use the diagnostic criteria of CMDD from previous versions of the DSM. A similar approach has recently been used by other authors (Ten Have et al., 2018).

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psychopathology that cut across multiple categorical diagnoses. Indeed, this is the strategic approach that informs much of the work emanating from the current Research Domain Criteria (RDoC) framework (Insel et al., 2010). We implemented this approach in the current study of CMDD, focusing on personality dimensions relevant to social stress responsivity. We chose this focus based on the well-established role of social stress in triggering and maintaining depression over the lifespan (Slavich and Irwin, 2014; Waugh and Koster, 2015). Our specific strategy was to examine whether cortisol responses to the Trier Social Stress Test (TSST) were modulated by the personality dimensions of neuroticism and extraversion in CMDD patients and in healthy controls. Neuroticism and extraversion are two of the primary personality dimensions in the Five-Factor Model of Personality (Costa and McCrae, 1992). A core feature of neuroticism is the tendency to experience negative and/or unstable thoughts and emotions, while extraversion encompasses positive emotions and social interactions. Separate lines of research have shown that high neuroticism and low extraversion are associated with a chronic course of MDD on the one hand (Duggan et al., 1990; Robison et al., 2009; Rhebergen et al., 2012; Scott et al., 1992; Weissman et al., 1978; Wiersma et al., 2011), and altered stress responsivity on the other (Bibbey et al., 2013; Childs et al., 2014; Phillips et al., 2005; Xin et al., 2017). We thus hypothesized that neuroticism and/or extraversion would play an important role in shaping the cortisol stress response to a social challenge in patients with chronic depression. For the current study, our general working hypothesis was that neuroticism and/or extraversion would modulate cortisol responses to a social stressor differentially in CMDD patients vs. healthy control participants. As this was the first study to examine the role of personality in shaping cortisol responses to a social stressor in a depressed population, we did not have clear *a priori* hypotheses about the specific nature of these differences. Our general goal was to assess, in a preliminary way, whether these personality measures could have value as potential intermediate targets for future research and clinical work in this complex, heterogenous and often treatment-resistant population.

2. Methods

2.1. Participants

Participants with CMDD were recruited from a tertiary care teaching hospital via posters and direct referrals between 2008 and 2010. The Structured Clinical Interview for DSM-IV Axis I Disorders (Version 2.0/Patient Form; SCID-I/P; First et al., 1995) was completed to confirm the diagnosis of CMDD, i.e. a major depressive episode without remission for a minimum of 2 years (Blanco et al., 2010). The SCID-I/P is a semi-structured interview that establishes major DSM-IV Axis I diagnoses. In addition, each subject scored 18 or higher (the cut-off for moderate depression used by our clinic) on the 29-item version of the Hamilton Depression Rating Scale (HDRS-29; Williams et al., 1988). This version of the HDRS includes all seventeen items in the original HDRS (Hamilton, 1960) as well as the “atypical” symptoms, such as increased appetite and hypersomnia, that are often reported by chronically depressed individuals (Horwath et al., 1992; Stewart et al., 1993; Benazzi, 1999). We considered both the HDRS-29 and HDRS-17 as potential co-variates in our statistical analyses to reflect the full symptom profile of CMDD patients, while enabling more direct comparisons to prior MDD research that has been based primarily on the HDRS-17.

The normal control group was recruited via posters and newspaper advertisements. Absence of psychiatric history was confirmed based on the SCID-I/P. Controls were included if they were not on any psychotropic medication at the time of data collection and if they scored seven or less on the HDRS-29.

Exclusion criteria for all participants included major medical illnesses, medical conditions and/or medications likely to confound cortisol levels including ischemic heart disease, heart arrhythmias, current steroid treatment, acute substance abuse, pregnancy, bipolar disorder, acute suicidal ideation and a history of psychotic symptoms.

We concluded a priori that a drug-free study would be desirable but impractical in this population. However, we did require that participants be on stable doses of psychotropic medications for a minimum of one month before study entry to limit the effect of acute medication changes on the study results. A similar approach has been used in prior biological studies of the CMDD population (e.g. Spinhoven et al., 2017).

All participants provided written informed consent and the project was approved by the Centre for Addiction and Mental Health (CAMH) research ethics board.

2.2. Procedure

2.2.1. Visit 1: clinical assessment

To assess clinical symptoms, participants were administered the SCID-I/P and the HDRS-29 by a trained research assistant. To assess personality, participants were administered the Revised NEO Personality Inventory (Costa and McCrae, 1992) which generates dimensional data based on the Five Factor Model (FFM) of personality. The FFM evaluates subjects on personality domains of Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness. The NEO PI-R consists of 240 self-report items answered on a five-point Likert format, with separate scales for each of the five domains. NEO domain scores are standardized by converting raw scores to T scores; T-scores < 45 are considered to be in the low range, 45–55 in the average range and > 55 in the high range (Oswald et al., 2006). Stability estimates for the domains are high in both normal (e.g., Costa and McCrae, 1992) and depressed samples (Trull and Goodwin, 1993; Santor et al., 1997; Costa et al., 2005). These latter studies demonstrated that while personality scores can be influenced by ongoing depressive symptoms, the rank order of the domain scores is robust following clinical improvement, suggesting that there are both state and trait effects on these measures. Of great interest, the effect of anti-depressants on personality is largely distinct from their effect on depressive symptoms, and may involve different brain pathways (Tang et al., 2009).

While the complete NEO inventory was completed by participants, it was decided *a priori* to focus on the personality domains of neuroticism and extraversion for the current project as these have been the primary focus of the prior literature cited above. Furthermore, neuroticism and extraversion have repeatedly exhibited prognostic utility in treatment trials of samples including both acute and chronic MDD (Quilty et al., 2008; Thibodeau et al., 2015).

2.2.2. Visit 2: the trier social stress (TSST) (Kirschbaum et al., 1993)

Trained undergraduate student volunteers, research assistants, and physicians conducted various components of the social stress protocol.

After a preparatory phase, subjects were led into a room that mirrored a standard interview room with various props (including a video camera, microphone and stand) and an “expert committee” of three people dressed in lab coats sitting behind a table. Participants were explained that the task included 10 min to prepare a 5-min job application speech for the expert committee, after which the committee would assign them a second task, which would also be 5 min in duration. The participants then prepared the speech in a separate room. After participants completed the public speaking task, they were to complete a difficult mathematical problem that consisted of serially subtracting 13 from 1022 for 5 min. Once the stress challenge was completed, there was a recovery phase in a separate room. Salivary cortisol samples were taken before subjects were given specific information about the social stress test (-35 min, -20 min), just prior to entering the room to complete the public speaking and mathematical challenge (0 min), and post-stressor ($+20$, $+40$, $+60$, and $+80$ min). For all participants, the TSST was administered between time times of 1400 and 1830 to control for circadian effects on cortisol secretion.

Salivary samples were obtained by having participants lightly chew on cotton wool salivettes (Sarstedt, Montreal, Quebec). Cortisol levels were determined in saliva, in duplicate, by RIA using radioimmunoassay kits (ICN Biomedical Inc, Costa Mesa, CA.). The intra- and extra-assay variability was less than 10%. Saliva samples were stored until analysis at a minimum of −20 °C.

2.3. Statistical analyses

To compare basic demographic and personality variables across the CMDD and healthy control groups, we applied independent samples *t*-tests for continuous variables and X^2 tests for categorical variables.

2.3.1. Prediction of cortisol AUCi

Given our primary interest in HPA reactivity as opposed to tonic cortisol release, cortisol responses during the TSST were measured using area-under-the-curve increase (AUCi), which measures the reactivity of the HPA axis following a challenge (Pruessner et al., 2003). Pending a non-normal distribution of AUCi values, log transformations were implemented.

A recent meta-analysis (Liu et al., 2017) and our own prior results (Chopra et al., 2009) point to gender differences in the cortisol stress response with the TSST. In light of this, we included gender as a covariate in step 1 of all regression analyses. To establish whether to include age and/or body mass index as covariates in the final models, preliminary univariate regression analyses were completed using either age or BMI as the predictor variable and AUCi as the dependent measure. For a given regression model, either or both of these potential confounders were included if they were significant at $p < .05$ based on these univariate tests. In our analyses of the main study hypothesis, hierarchical linear regressions were used. After controlling for gender and other potential covariates at step 1, step 2 included personality scores (either neuroticism or extraversion), group (CMDD vs. healthy controls), and the respective personality X group interaction term as predictor variables.

Pending the discovery of a significant interaction predicting AUCi, the simple slopes of the two-way interaction were investigated as specified by O'Connor (1998). Using this approach, the variables included in the two-way interaction (i.e. the dependent variable, the two main effects and their interaction) and gender would be residualized on the remaining variables in the model and entered into the program created by O'Connor (see http://flash.lakeheadu.ca/~boconno2/simple.html).

3. Results

3.1. Sample characteristics

As shown in Table 1, the study sample consisted of 50 patients with CMDD and 58 normal controls. There was no significant difference in the proportion of females between groups. When compared to the normal control group, the CMDD group was significantly older and had a higher mean body mass index. As expected, the mean neuroticism t-score of the depressed group was significantly higher than that of the control group (70.3 +/−11.0 vs. 46.6 +/−10.0 respectively; $t(106) = 11.70$, $p < .001$), while the mean extraversion t-score was significantly lower in the CMDD group relative to the control group (38.1 +/− 11.3 vs. 51.9 +/− 9.5 respectively; $t(106) = 6.95$, $p < .001$). T scores

Within the CMDD group, the mean age of onset of depression was 19.8 (± 11.7) years, and the mean duration of the current episode was 13.8 (± 13.2) years. Of the depressed sample, 72% were on psychiatric medication at the time of data collection. Based on our exclusion criteria, none of the healthy controls were on psychiatric medication.

The mean HDRS-29 and HDRS-17 depression scores in the CMDD group were 34.1 +/− 8.5 and 20.8 +/− 4.4 respectively, consistent with a moderate severity of depression (Zimmerman et al., 2013).

Table 1
Demographic characteristics of chronically depressed subjects and healthy controls.

Variable	Depressed (*N* = 50)	Control (*N* = 58)	Group Comparison P value
Female, No. (%)	29 (58.0)	29 (50.0)	0.41
Current Age in years, mean (SD)	41.6 (8.2)	37.1 (7.9)	0.005
Current BMI (kg/m^2), mean (SD)	27.6 (5.3)	25.4 (4.7)	0.03
Age of onset of depression in years, mean (SD)	19.8 (11.7)		
Duration of current episode in years, mean (SD)	13.8 (13.2)		
Currently taking psychiatric medication, No. (%)	36 (72.0)		
HDRS-29 item, mean (SD)	34.1 (8.5)		
HDRS-17 item, mean (SD)	20.8 (4.4)		

Notes: SD = standard deviation. HDRS = Hamilton Depression Rating Scale.

Within the CMDD group, there was a significant positive correlation between neuroticism scores and HDRS-17 scores (r = .33, p = .02) but not HDRS-29 scores (r = .23, p = .11). There was a significant negative correlation between extraversion scores and scores for both the HDRS-29 (r = −0.36, p = .011) and HDRS-17 (r = −0.32, p = .026).

3.2. Normality of AUCi scores

Across all participants, AUCi scores were not normally distributed (Kolmogorov-Smirnov statistic = 0.09, df = 107, p = .029), while the respective log transformed scores were (Kolmogorov-Smirnov statistic = 0.045, df = 107, p = .20). The log transformed AUCi scores were thus used in all subsequent analyses.

3.3. Assessment of potential confounding variables

When all 108 study subjects were considered together, preliminary univariate analyses showed no significant association between AUCi and either age or BMI. Within the CMDD group, there was no significant association between AUCi and age of onset of depression, duration of the current episode, or use of psychotropic medication. As a result, none of these demographic/clinical variables were included in the regression models that follow.

3.3.1. Regression model including neuroticism

The regression model predicting AUCi with neuroticism t-score, group (CMDD vs. control) and their interaction, controlling for gender, was not significant. No further analyses with neuroticism were thus conducted.

3.3.2. Regression model including extraversion

Fig. 1 plots the relationship between extraversion T scores and cortisol AUCi in the CMDD and normal control groups. As summarized in Table 2, the regression model predicting AUCi with extraversion t-score, group, and their interaction, controlling for gender, was significant ($F = 2.77$, $df = 4$; $p = .031$). The main effect of extraversion was significant, while the main effect of group was not. Of particular interest, the extraversion-by-group interaction was significant (standardized $\beta = 1.64$, $t = 2.43$, $p = .017$). The simple slopes of the significant two-way interaction were investigated as specified by O'Connor (1998). This indicated that the simple slope was significant in the CMDD group (β = −0.40, t = −2.38, p = .019) but not in the normal control group (β = 0.15, t = 1.28, p = .20).

3.3.3. Supplemental post-hoc tests

To help interpret the significant results described above, which were based solely on the post-challenge AUCi scores, we extended our post-

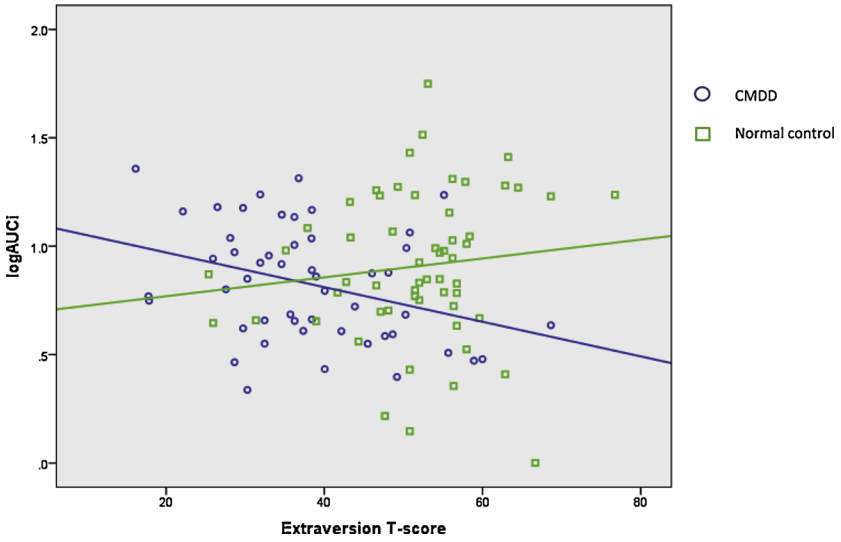

Fig. 1. Relationship between Extraversion T- scores and cortisol AUCi (log transformed) in the CMDD and normal control groups. The simple slope was significant in the CMDD group (at p = .019) but not in the control group.

hoc analyses in several ways to better explore the raw TSST data over time. Firstly, we plotted the raw cortisol data over all seven TSST time points for both the CMDD and normal control groups. As shown in Fig. 2A, visual inspection of this raw data suggested that pre-challenge cortisol levels were higher in the CMDD group. To test this statistically, we ran a repeated- measures ANOVA for the pre-challenge phase of the TSST (based on times −35, −20 and 0 min.), using diagnostic grouping (CMDD vs. control) as the independent variable while controlling for gender as before. The results of the between-subject comparisons indicated that the CMDD group did in fact have higher cortisol values than did the control group over the pre-challenge phase (F = 6.03, df = 1,105, p = .016). Next, given our significant AUCi findings related to extraversion, we calculated separate median extraversion scores in the CMDD and normal control groups respectively, and designated each study participant as being above or below-the-median relative to their respective group. This established subgroups above and below the respective median for CMDD, and above and below the respective median for normal controls. We then plotted the raw cortisol values in these four subgroups over the entire TSST protocol (Fig. 2B). As shown, the CMDD subgroup with above-the-median extraversion scores had higher pre-challenge cortisol levels than did each of the other three subgroups. To assess this difference statistically, we ran another repeated measures ANOVA based on the three pre-challenge cortisol values (-35,-20 and time 0 relative to the social stressor), this time using the new extraversion-based subgrouping rather than diagnosis alone (CMDD vs. control) as the independent predictor variable. Results confirmed a significant between- groups effect for the raw cortisol levels across these 3 time points (F = 4.36, df = 3,104, p = .006). Pairwise post-hoc comparisons further confirmed that pre-challenge cortisol levels were higher in the CMDD subgroup with above-the-median extraversion scores than in each of the three other subgroups considered separately. None of the other three subgroups differed from one another on this measure. This confirmed that CMDD patients with higher extraversion scores were driving the increase in pre-challenge cortisol levels observed in the CMDD group overall.

In light of these pre-challenge differences, one possible explanation for the main findings related to AUCi is that CMDD participants with higher extraversion scores had lower AUCi levels because of a ceiling effect i.e. having higher baseline cortisol levels may have limited their ability to react to the social challenge with a robust cortisol response. To examine this statistically, we repeated the main regression analysis summarized in Table 2, now adding the mean pre-challenge cortisol level (the sum of the −35, −20 and time 0 values) as a new co-variate. Results indicated that mean pre-challenge cortisol levels did have a significant negative association with AUCi levels overall (β = −.13, t = −2.79, p = .006), however the extraversion X group interaction remained a significant predictor of AUCi in this model (β = .012, t = 2.21, p = .029). This suggests that the significant extraversion by group interaction in predicting AUCi was not explained or confounded by the pre-challenge cortisol levels.

Visual inspection of Fig. 2B suggests that CMDD participants with above-the-median extraversion scores had a blunted rise in cortisol immediately following the TSST, with a rapid return to baseline levels. While this is consistent with the initial AUCi findings, AUCi incorporates both the acute rise in cortisol and the return of cortisol values back towards baseline after the social challenge. To better assess the acute rise in cortisol across subgroups, we next calculated a

Table 2
Results of the linear regression analysis predicting cortisol AUCi (log transformed) with extraversion, group and their interaction, controlling for gender. The overall model was significant (F = 2.77, df = 4, p = 0.031).

Predictor variable	Standardized β	t	p	95% CI	R Square	R Square Change	Sig F Change
Block 1					0.020	0.02	0.141
Gender	−0.14	−1.43	0.157	−0.205, 0.034			
Block 2					0.098	0.078	0.035
Gender	−0.19	−1.94	0.055	−0.240, 0.003			
Extraversion t-score	−0.96	−2.68	0.009**	−0.042, −0.006			
Group	−0.83	−1.90	0.06	−1.056, 0.023			
(depressed or control) Extraversion-by-group	1.64	2.43	0.017*	0.003, 0.025			

* $p < 0.05$.
** $p < 0.01$.

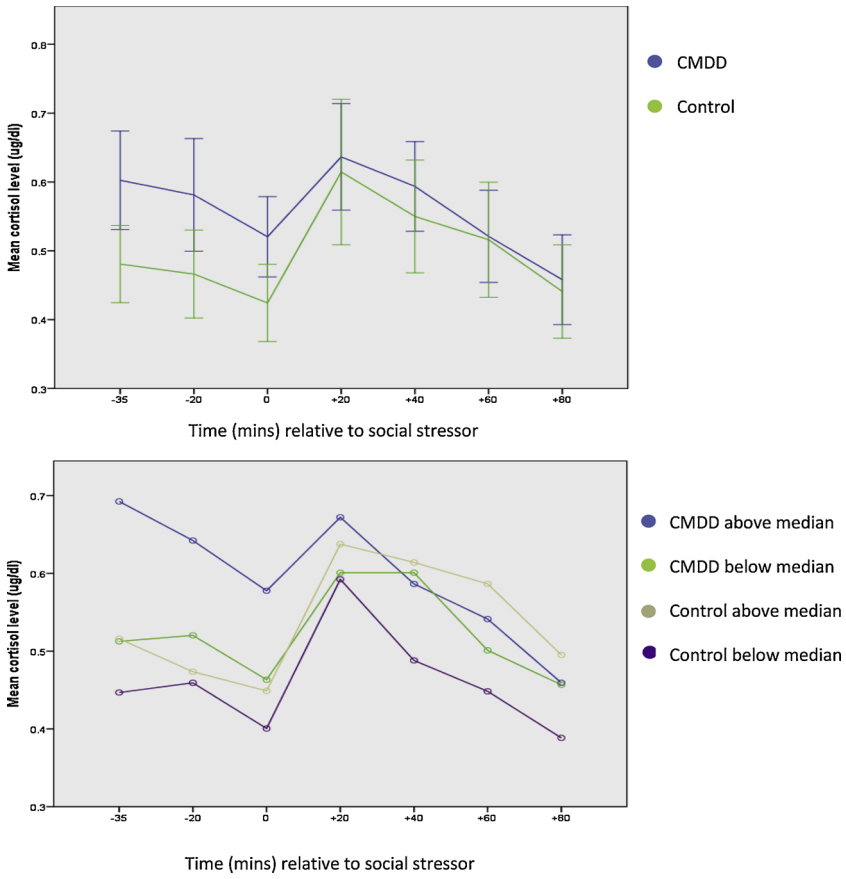

Fig. 2. A. Raw cortisol values (+/−95% confidence intervals) over time in the CMDD and normal control groups. **B.** Raw cortisol values over time in the four subgroups defined by the median extraversion scores in the CMDD and control groups respectively.

percentage cortisol change score for each subject from time 0 to time +20 min. based on the formula ((time +20 value-time 0 value)/time 0 value)*100. The respective mean % change scores (+/−SD) across the four subgroups were: CMDD above-the-median 12.8 +/−41.7%; CMDD below-the-median 43.7+/−61.4%; normal control above-the-median 58.5% and normal control below-the-median 54.1+/−82.3%. Pairwise post-hoc comparisons indicated that the acute % rise in cortisol was significantly less in the CMDD group with above- the-median extraversion scores than in each of the two control subgroups, but was not different from levels in the lower- extraversion CMDD subgroup. The Pearson correlation between pre-challenge cortisol levels and the % increase in cortisol levels from time 0 to time + 20 min was significant in the overall sample ($r = -0.26$, $N = 108$, $p = .007$) and in the overall CMDD group ($r = -.30$, $N = 50$, $p = .03$), but not in the normal control group ($r = -.19$, $N = 58$, $p = 0.15$). Among CMDD participants, this correlation was significant for CMDD participants with below-the-median extraversion scores ($r = -.40$, $N = 25$, $p = .05$) but not in the CMDD subgroup with higher extraversion scores ($r = .04$, $N = 25$, $p = .84$). This latter finding further supports the argument that blunted cortisol responses to the social challenge in CMDD patients with higher extraversion scores was not a ceiling effect attributable to high baseline cortisol levels. On the other hand, in CMDD patients with below-the-median extraversion scores, post-challenge cortisol responses were strongly influenced by pre-challenge cortisol levels. It may be that in CMDD patients with higher extraversion scores, factors other than cortisol feedback play a greater role in the acute hormonal response to social stress.

3.3.3.1. Possible confounding by HDRS scores. As described above, there was a significant negative correlation between HDRS scores and Extraversion in the CMDD group. To help determine whether the key AUCi findings related to extraversion were confounded by depression severity, we performed a separate post-hoc linear regression in the CMDD group including HDRS-29 scores, gender and Extraversion as co-variates. Extraversion remained a robust predictor of AUCi ($t = -3.15$, $p = .003$) after controlling for gender and HDRS-29 scores. The same overall result was found when we used HDRS 17 scores instead of HDRS-29 scores. In summary, for the CMDD participants, extraversion was a significant predictor of AUCi while depression severity was not.

3.3.3.2. Influence of childhood trauma. Given that childhood trauma is a major contributor to chronicity in depression (Wiersma et al., 2009), and has significant effects on HPA functioning (Carpenter et al., 2007), we also examined whether childhood trauma contributed to the current results. Childhood trauma was measured at baseline using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). The CTQ is a 28-item self-report instrument to rate the severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse. We first ran a series of univariate regressions predicting AUCi with each of the five CTQ subscales as well as total CTQ scores. This showed a significant negative association between sexual abuse scores and AUCi (standardized $\beta = -.20$, $t = -2.06$, $p = .042$), while the other results were non-significant. Next, we repeated the main analysis, now including sexual abuse scores as a further co-variate. Results indicated that the study group by extraversion interaction remained significant, while sexual abuse was not significant, in this model. We conclude that early adversity did not have a major influence on our main findings.

4. Discussion

As a group, CMDD patients tend to have significant deficits in interpersonal functioning and to report increased sensitivity to daily

interpersonal events (Bora and Berk, 2016; Davidson and Thase, 2007; Zobel et al., 2010). To gain a better understanding of this vulnerability, we investigated whether cortisol responses to the Trier Social Stress Test were modulated by the personality dimensions of neuroticism and extraversion in CMDD patients and healthy controls. The main finding was that higher extraversion scores predicted decreased cortisol stress responses following the social challenge in participants with CMDD, while there was no significant relationship between these same two variables in normal controls. Post-hoc analysis of the raw cortisol data over time found that the subgroup of CMDD participants with above-the-median extraversion scores had significantly higher pre-challenge cortisol levels than did other participants, however this did not explain or confound the post-challenge cortisol results. Similarly, consideration of other potential confounders such as depression severity and childhood trauma did not influence the significant extraversion by group interaction. Given that extraversion had a robust ability to predict post-challenge cortisol responses in participants with CMDD after controlling for several potential confounding variables, and can independently predict treatment response in depressed patients (Bagby et al., 1995), extraversion may prove to be an interesting intermediate target for future work in complex, heterogenous CMDD populations.

While there is no prior research linking extraversion or neuroticism with cortisol stress responses in CMDD or other depressed populations, such studies have been done in healthy control samples. In comparing our normal control data for neuroticism and extraversion with other studies that used the TSST or similar social stress test protocols, our negative findings are similar to those of Schommer et al (1999), Oswald et al (2006) and Bibbey et al (2013). However two studies reported that higher neuroticism was associated with lower cortisol responsivity (Bibbey et al., 2013; Xin et al., 2017). Extraversion has also been linked to cortisol reactivity in some studies of normal controls (Childs et al., 2014; Xin et al., 2017), although the overall pattern of responses across different studies is difficult to interpret pending more data.

Xin et al. (2017) have suggested that highly extraverted individuals tend to engage in active coping styles that result in reduced cortisol stress reactivity after encountering a stressor. While the overall level of extraversion was low in our CMDD sample, it is plausible that on a relative basis, CMDD patients with higher extraversion scores have better social coping skills than do other CMDD patients. Childs et al. (2014) proposed that higher extraversion may confer resilience to negative environmental stimuli resulting in reduced cortisol reactivity. In the current sample, CMDD patients with higher extraversion scores might have experienced less rejection sensitivity during the TSST compared to less extraverted CMDD patients, with secondary effects on cortisol levels, although we did not measure this directly.

The post-hoc finding that CMDD patients with above- the- median extraversion scores had significantly higher pre-challenge cortisol levels than did other participants merits further consideration. While in theory, high baseline cortisol levels can establish a ceiling effect and thus limit cortisol levels following an acute stress, the significant extraversion by group interaction in predicting AUCi post challenge was not significantly affected by pre-challenge cortisol levels. It would appear that extraversion has significant but distinct moderating effects on both anticipatory and post-challenge cortisol levels in the CMDD population. This, and the rapid return of cortisol levels to baseline in the higher extraversion CMDD group post-challenge, suggest that these individuals may be particularly adept at matching their cortisol secretion to moment–to-moment conditions, with less carry over effects and a more rapid recovery profile than for other individuals with CMDD. Why this pattern was seen in participants with CMDD but not in controls with relatively high extraversion cannot be determined from the current data.

The overarching clinical problem that stimulated the current line of research was the relative dearth of studies on the etiology and pathophysiology of CMDD, despite its high prevalence and enormous costs at a personal and societal level (Boschloo et al., 2014; Robison et al., 2009; Torpey and Klein, 2008). The lack of understanding of the causes of CMDD makes it difficult to treat at an individual patient level. To address this challenge we used an RDoC approach focused on a dimensional process (personality) that is well suited for CMDD patients. In using an RDoC strategy, one major goal is the identification and development of intermediate targets that have a more proximal and specific relationship with brain circuitry and pathophysiology than do categorical diagnoses. Although in need of replication and extension in other samples, the robustness of the current results in the face of several potential confounders supports the possible use of extraversion as an intermediate target for both clinical and research work in complex CMDD populations. Of great interest, a prior meta-analysis concluded that extraversion contributes to depression overall, but has a more important effect for chronic forms of the illness (Kotov et al., 2010). It would be of interest to determine whether treatments designed to enhance extraversion, even independently of mood *per se*, might have particular benefits for the CMDD population. As mentioned above, antidepressant medications have an effect on personality measures, including extraversion, that is largely independent of depressive symptoms (Tang et al., 2009). Future clinical trials in CMDD might thus benefit from the inclusion of extraversion as an intermediate target and potential mediator of positive treatment responses.

The limitations of this study include the fact that most CMDD subjects were on psychotropic medications. For ethical and pragmatic reasons we were unable to study a drug free CMDD population. However, controlling for medication status did not influence the primary findings. Despite the fact that clinical and demographic variables were non-significant predictors of the cortisol stress response in the current study, it is possible that we did not have the power to sufficiently account for potential covariates. Furthermore, several potential confounders such as menstrual status and oral contraceptive use (Kirschbaum et al., 1999), a past history of substance abuse or dependence (Sher et al., 2006) and suicidal ideation and behavior (Melhem et al., 2016; O'Connor et al., 2017), were not included in our analysis. Finally, only cortisol responses related to the TSST were included in the current analyses. Diurnal cortisol measures and cortisol responses to pharmacological challenges would provide a greater understanding of the extent and at which level HPA activity is influenced by personality factors in CMDD.

As previously mentioned (see Section 2.1), our basis for diagnosis of CMDD was a major depressive episode without remission for 2 years. Persistent depressive disorder (dysthymia) is the current diagnosis used for various forms of chronic depression; it represents a consolidation of the DSM-IV-defined CMDD and dysthymic disorder. In spite of the removal of the chronic specifier of MDD from the DSM-V, we chose to use the DSM-IV-defined CMDD diagnosis as it better captured the severity and chronicity of our CMDD sample. Furthermore, our data was collected prior to the DSM-V launch. In light of this, our findings may not be generalizable to all patients diagnosed with persistent depressive disorder based on DSM-V.

4.1. Future directions

To help determine the specificity of the current findings for CMDD relative to other depressed populations, it would be of great interest to implement the current protocol in a single study that including both a CMDD and more acute MDD group.

Regarding other biological factors that might help explain the current results, Hellerstein et al. (2015) have shown that behavioural activation is highly effective in addressing residual functional impairments in CMDD patients. This may have particular relevance for the current findings in that extraversion has been associated with individual differences in brain dopamine activity (Depue and Collins, 1999), the same biological substrate associated with the behavioural approach and activation system (Gray, 1970). Recent evidence suggests that extraversion and the behavioural activation system tap a single

latent factor tied to approach and dopamine functioning (Quilty et al., 2014). Future studies to examine brain dopamine functioning and social stress responsivity in CMDD and other depressed patients would thus be of great interest.

In conclusion, the current study found that cortisol reactivity to acute psychosocial stress varied as a function of extraversion in CMDD patients but not in healthy controls. Neuroticism did not emerge as a significant predictor of cortisol reactivity in either group. Given the recent research emphasis on intermediate phenotypes, findings from the current study support the RDoC approach in considering basic domains of human functioning such as personality, to better understand and treat complex psychiatric disorders such as CMDD.

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Conflict of interest

All authors declare no conflict of interest.

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