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Original article

Cognitive control and network disruption in remitted depression: a correlate of childhood adversity

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Abstract

Individuals in a major depressive episode often display impairment in cognitive control, and this impairment exists outside of the acute phase of illness. Impairment in cognitive control also has been associated with exposure to childhood adversity (CA). The current study examined whether exposure to CA can explain variance in a component of cognitive control—inhibitory control—independent of diagnostic status in young adults with and without a history of depression. Healthy control individuals ($n = 40$) and individuals with remitted major depressive disorder ($n = 53$) completed a task measuring inhibitory control, reported level of CA and completed a scanning session to assess gray matter volume and resting state connectivity in regions associated with cognitive control. The results demonstrate that higher levels of CA were associated with poorer inhibitory control, reduced right middle frontal gyrus gray matter, decreased connectivity of salience and emotion networks and increased connectivity in cognitive control networks, even after controlling for diagnostic status, residual depression symptoms and current stressors. Together, the results suggest that inhibitory control impairment and intrinsic connectivity changes may be characterized as developmental sequelae of early stress exposure.

Key words: cognitive control; inhibitory control; stress; childhood adversity; depression

Introduction

Individuals in a major depressive episode demonstrate impairment in cognitive control (Snyder, 2013). Although there is some evidence that impairment is related to level of symptom severity (Snyder, 2013), impairment also has been observed when symptoms are in remission, indicating some level of stability in cognitive control impairment (Hasselbalch *et al.*, 2011; Bora *et al.*, 2013; Peters *et al.*, 2015; Stange *et al.*, 2016). Evidence from non-depressed samples suggests that impairment in cognitive control, and alterations within associated neural networks, may result from exposure to childhood adversity (CA; Pechtel and Pizzagalli, 2011; Marshall *et al.*, 2016). Given the strong association between CA and depression (Heim *et al.*, 2008; Liu, 2017), this stable cognitive control impairment observed in depressed individuals may be due to CA. The current study examined whether exposure to CA can explain variance in a component of cognitive control—inhibitory control—independent of diagnostic status in young adults with and without a history of depression.

Cognitive control is a broad term describing cognitive processes that allow individuals to evaluate objectives, determine optimal choice parameters and carry out goal-directed

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behavior (Miller, 2000; Banich, 2009). These processes are a set of related abilities including inhibiting automatic responses, flexibly switching behavior and updating the contents of working memory (Miyake *et al.*, 2000; Miyake and Friedman, 2012). Cognitive control is essential for the ability to effectively respond to a changing environment and guide behavior in novel situations (Banich, 2009). The neural network most closely associated with cognitive control (the cognitive control network; CCN) includes regions of the frontal and parietal lobes (Miller and Cohen, 2001; Cole and Schneider, 2007; Menon, 2011). Recent work suggests that, in addition to the CCN, cognitive control is dependent on cooperative functioning of a number of intra- and interconnected networks, including the default mode network (DMN) and the salience and emotion network (SEN; Sridharan *et al.*, 2008; Hermans *et al.*, 2014; Young *et al.*, 2016).

Cognitive control impairment is associated with depression (Snyder, 2013) and has been observed in the remitted phase of illness, suggesting that it is not entirely state-dependent and may function as a vulnerability factor (Hasselbalch *et al.*, 2011; Bora *et al.*, 2013; Peters *et al.*, 2015; Stange *et al.*, 2016). There is also evidence that more impairment may indicate a distinct course of illness. Greater cognitive control impairment is associated with greater number of previous episodes (Kessing, 1998; Paelecke-Habermann *et al.*, 2005) and prospectively predicts response to treatment (Crane *et al.*, 2017; Dawson *et al.*, 2017). Identifying factors that may contribute to cognitive control impairment may therefore contribute to our understanding of this course of illness.

One factor that may contribute to variability in cognitive control impairment in major depressive disorder (MDD) is exposure to CA (Pechtel and Pizzagalli, 2011). In both healthy and clinical samples, exposure to CA has been associated with cognitive control impairment (Marshall *et al.*, 2016), memory difficulties (Majer *et al.*, 2010) and broader cognitive difficulties (Bos *et al.*, 2009, Gould *et al.*, 2012). Alterations in function, connectivity and structure of the CCN, DMN and SEN also have been observed in individuals who experienced CA (Pechtel and Pizzagalli, 2011; McEwen and Morrison, 2013; Philip *et al.*, 2013; Duncan *et al.*, 2015; Demir-Lira *et al.*, 2016). Given the role of cognitive control in regulating emotions (Joormann and Vanderlind, 2014; Langenecker *et al.*, 2014), of particular note are findings that CA has been associated with reduced gray matter volume (GMV) in prefrontal regions and medial temporal regions that are implicated in processing and regulating emotions (Tomoda *et al.*, 2009; Carballedo *et al.*, 2012). CA has also been associated with increased connectivity between the SEN and DMN, suggesting that CA may result in enhanced emotional responding and reduced emotion regulation (Burghy *et al.*, 2012; Herringa *et al.*, 2013; Marusak *et al.*, 2015). Together, this body of work suggests that exposure to CA may lead to widespread alterations in the development of neural systems, which manifest in many ways, including as cognitive control impairment. It remains unknown, however, whether CA is associated with cognitive control impairment and network alterations independent of the effect of depression. Establishing the presence of these relationships, while controlling for diagnosis, in a sample of both healthy control and remitted depressed individuals would suggest that cognitive control impairment may be characterized as a developmental sequela of CA, regardless of diagnosis.

The primary hypotheses of the current study were that CA, after covarying for diagnostic status, current residual symptoms and current life stress, would be associated with (i) impairment in inhibitory control, a component of cognitive control, and (ii) in a dimensional fashion, with alterations in cognitive neural networks in a sample of healthy individuals and individuals with a history of depression. Based on previous associations with CA, we hypothesized that CA would be positively associated with cross-network SEN and DMN connectivity (Burghy *et al.*, 2012; Herringa *et al.*, 2013; Marusak *et al.*, 2015). Based on previous findings in remitted depressed samples, we also expected diminished within-network CCN connectivity (Stange *et al.*, 2017). Finally, we hypothesized that CA would be associated with decreased GMV in lateral and medial prefrontal regions, and medial temporal regions (e.g. hippocampus; Tomoda *et al.*, 2009; Carballedo *et al.*, 2012).

Method

Participants

Study procedures were approved by the University of Michigan (UM) and University of Illinois at Chicago (UIC) Institutional Review Boards. Participants were recruited via flyers and online postings. All participants provided written informed consent. Participants first completed a battery of cognitive, self-report and diagnostic measures and then an magnetic resonance imaging (MRI) scan. Participants were eligible for the study if they met criteria for one of two groups: (i) individuals with remitted MDD (rMDDs) and (ii) healthy control individuals (HCs). Eligibility was determined using the diagnostic interview for genetic studies (DIGS; Nurnberger *et al.*, 1994), which was conducted with the participant, and family interview for genetic studies (FIGS; Nurnberger *et al.*, 1994), which was conducted with a parent, guardian or close sibling. Each of these measures have demonstrated good reliability and validity (Maxwell, 1992; Bucholz *et al.*, 1994). rMDDs met criteria for one or more past major depressive episodes and scored below 10 on the Hamilton depression rating scale (HDRS; Hamilton *et al.*, 1960) at the time of the diagnostic interview. Individuals who met criteria for substance abuse or dependence within the past six months were excluded. HCs did not meet current or past criteria for any Axis I or II psychiatric disorder. All participants were free from psychotropic medications for at least 30 days prior to the scan. The initial sample was 106 participants. Participants were excluded from all analyses for having an unclear diagnosis (R/O psychosis and substance abuse; $n = 1$), conversion from healthy to mood disorder during the study ($n = 4$) and incomplete questionnaires ($n = 8$). The final sample consisted of 53 rMDDs (18 UM, 35 UIC) and 40 HCs (15 UM, 25 UIC). Participants were between 18 and 23 years of age and were 69.9% female (see Table 1 for demographic and clinical characteristics). Additional participants were excluded from imaging analyses for movement ($n = 4$) and missing the scanning session ($n = 4$). Criteria for participant exclusion from analyses for movement were the following: motion of 1.5 mm or more in any direction over three consecutive TRs, any TR to TR movement exceeding 0.5 mm, greater than 2 mm movement over an entire 8 min scan or evidence of outlier status as a movement deviation value across the entire time series in relation to the rest of the sample (Power *et al.*, 2012; Jo *et al.*, 2013).

Measures

CA. The childhood trauma questionnaire (CTQ) was used to assess the frequency of emotional, physical and sexual abuse as well as emotional and physical neglect prior to the age of 18 (Bernstein *et al.*, 1994). The CTQ demonstrates high test–retest reliability and convergent validity with interview measures of CA (Bernstein *et al.*, 1994; Bernstein *et al.*, 1997).

Table 1. Demographics and study variables by group

	HC ($n = 40$)	rMDD ($n = 53$)	Test of difference between conditions
	M (s.d.) / N (%)	M (s.d.) / N (%)	
Age	20.68 (1.64)	21.09 (1.51)	$t(91) = -1.28$, $P = 0.20$
Female	28 (70.0%)	37 (69.8%)	$X^2(1, N = 93) = 0.00$, $P = 0.98$
Education	14.60 (1.41)	14.57 (1.41)	$t(91) = 0.12$, $P = 0.91$
Race/Ethnicity			$X^2(1, N = 93) = 0.27$, $P = 0.60^A$
African American/Black	1 (2.5%)	3 (5.7%)	
Asian	4 (10.0%)	9 (17.0%)	
Indian	3 (7.5%)	1 (1.9%)	
Caucasian/White	30 (75.0%)	34 (64.2%)	
Middle Eastern	0 (0%)	1 (1.9%)	
More than one race	0 (0%)	2 (3.8%)	
Hispanic	2 (5.0%)	3 (5.7%)	
CTQ – total	28.44 (4.83)	34.55 (10.57)	$t(76.90) = -3.72$, $P < 0.001$
Life events occurrence scale – disruption	2.25 (3.11)	4.99 (4.92)	$t(88.53) = -3.28$, $P = 0.001$
Parametric go/no-go – percent correct inhibition trials	60.67 (14.72)	58.77 (15.17)	$t(91) = 0.60$, $P = 0.55$
Hamilton depression rating scale	0.48 (0.96)	2.43 (2.89)	$t(60.47) = -4.44$, $P < 0.001$
Number of previous major depressive episodes	0	2.06 (1.88)	
Age of onset of first major depressive episode	n/a	16.18 (3.86)	
Years in remission	n/a	3.00 (1.81)	

Note. [A]Test of difference between conditions for race/ethnicity is a comparison of Caucasian and all minority groups combined.

Recent life stress. To assess life stress within the past month, participants completed the life events occurrence scale-revised (LEOS-R; McKee *et al.*, 2005). This scale assesses the number of mild to moderate recent stressors (e.g. move, start a new job, fight with friend) as well as the level of disruption caused by each stressor to estimate level of current life stress.

Inhibitory control. Inhibitory control was assessed using the parametric go/no-go (PGNG) task (Langenecker *et al.*, 2007). In this task, letters of the alphabet are rapidly presented on a computer screen. Participants are instructed to respond, as quickly and as accurately as possible, to letters pre-designated as targets, while inhibiting prepotent responses to targets repeated on subsequent trials and to static non-targets. Task performance was measured by the percent correct on inhibitory trials (PCIT; trials in which inhibitory control is required to withhold a prepotent response). The PGNG has demonstrated good construct validity and retest reliability (Langenecker *et al.*, 2007; Votruba and Langenecker, 2013). The PGNG was administered in the first portion of the scanning session as well as during another study visit. To obtain a measure of inhibitory control, PGNG performance was averaged across the two sessions.

Functional MRI acquisition. The UM and UIC resting state functional MRI (fMRI) sequences were different. At UM, an eyes-open resting state scan was acquired over eight minutes on a 3.0 T GE Signa scanner (Milwaukee, WI) using T2*-weighted single shot reverse spiral sequence with the following parameters: 90° flip, field-of-view 20, matrix size = 64 × 64, slice thickness = 4 mm, 30 ms echo time, 29 slices. Eyes-open, resting scans at UIC were collected over 8 min on a 3.0 T GE Discovery scanner (Milwaukee, WI) using parallel imaging with ASSET and T2* gradient-echo axial EPI with the following parameters: 90 degree flip, field-of-view 22, matrix size = 64 × 64, slice thickness = 3 mm, 22.2 ms echo time, 44 slices. At both sites, high-resolution anatomic T1 scans were obtained for spatial normalization and for GMV estimates; motion was minimized with foam pads, a visual tracking line (UIC only) and/or cross (UIC and UM) on the display, and by conveying the importance of staying still to participants, with TRs of 2000 ms and a total of 240 TRs.

Functional connectivity MRI preprocessing

Several steps were taken to reduce potential sources of noise and artifact. Slice timing was completed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/doc/) and motion detection algorithms were applied using mcflirt from the FSL package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Movement parameters did not differ between groups (Stange *et al.*, 2017), nor were any movement parameters related to CTQ, Disruption ($rs < |0.25|$). Co-registration of structural images to functional images was followed with spatial normalization of the co-registered T1-spgr to the Montreal Neurological Institute (MNI) 152 brain template. The resulting normalization matrix then was applied to the slice-time-corrected time series data, resulting in T2* images with 2 mm isotropic voxels. These normalized T2* time series data were then spatially smoothed with a 5 mm Gaussian kernel. GMV was estimated following segmentation with DARTEL (VBM within SPM8) and application of an 8 mm Gaussian kernel and conversion to 2 mm isotropic voxels.

Physiologic correction was performed by regressing out the top 5 principal components from white matter and cerebral spinal fluid sequentially (Behzadi *et al.*, 2007). Motion parameters of deviations in translation and rotations in x, y and z planes were regressed out (along with first temporal derivative and squares of parameters) within first level models (Jo *et al.*, 2013). Global signal was not regressed due to colinearity issues with gray matter signal, problematic misestimates of and likelihood of artificial anticorrelations (Fox *et al.*, 2009) and non-linear effects on distance-micro-movement relationships (Jo *et al.*, 2013). Lastly, time series were band-pass filtered over the range 0.01–0.10 Hz.

Regions of interest (ROI) for each seed were defined and verified in MNI space on the average anatomy of the first 55 scans collected within this study, with a 2.9 mm radius (19 voxels in a spherical configuration). Coordinates were derived from prior studies; three bilateral seeds for the SEN (amygdala +/− 23, −5, −19 mm; sgACC +/− 4, 21, −8; anterior insula +/− 36, 13, 5; Drevets *et al.*, 1997; Deen *et al.*, 2011; Jacobs *et al.*, 2014), one bilateral DMN seed [posterior cingulate cortex (PCC), −5/5, −50, 36; Jacobs *et al.*, 2014] and two bilateral CCN seeds [dorsolateral prefrontal cortex (DLPFC) - PFClp; +/−45, 29, 32; inferior parietal lobule (IPL) - PGa: +/−52, −50, 49; Yeo *et al.*, 2011] were used. Time course data were averaged from each seed region for each hemisphere and for each participant. Correlation coefficients were calculated between mean time course for seed regions and all other voxels of the brain, resulting in three-dimensional correlation coefficient images (r images), transformed to z scores using a Fisher transformation and compared in SPM8.

Statistical analysis

The primary behavioral analysis was a linear regression in SPSS, with a $P < 0.05$, of CTQ predicting PCIT in the PGNG, with diagnosis, current depressive symptoms and current disruption as covariates. The primary imaging analysis was a multiple regression model within SPM8, using CTQ as the primary predictor and site, group, sex, age, recent events disruptions and movement parameters (functional analyses only) as covariates. Total GMV was used as a covariate in the VBM analyses. There were no differences by site in overall GMV. For connectivity analyses, we used an adjusted threshold based upon 3dClustSim height and extent models with 10 000 simulations (and an applied gray matter mask based upon our data (154369 voxels). For six bilateral seeds and one GMV analysis, the family-wise error rate for the entire experiment is 0.13 (13 analyses, each set at $P < 0.01$ WB), with a per analysis whole-brain adjusted threshold of $P < 0.01$ based upon $P < 0.005$ and $k > 57$ from 3dClustSim (Dec 2016) and the -fwhm option (the -acf option was not used).

Results

Group characteristics

Diagnostic groups did not significantly differ on demographic characteristics or inhibitory control. Compared to individuals in the HC group, individuals in the rMDD group reported significantly greater levels of CA, disruption due to recent life stress and current depressive symptoms. Demographic and study variable group comparisons are displayed in Table 1. CTQ scores ranged from 25 to 44 in the healthy control group and from 25 to 71 in the rMDD group. In each group, scores indicated CA ranging from none to severe (Bernstein and Fink, 1998). Site comparisons of demographic and study variables are presented in Supplementary Table S1. Sites did not differ on characteristics, with the exception that CA was significantly higher at UIC compared to UM.

CA and inhibitory control

Across all individuals, CTQ was significantly correlated with PCIT such that greater levels of CA were associated with poorer inhibitory control, $r(93) = -0.23$, $P = 0.02$. (see Figure 1 for scatterplot and Table 2 for correlation matrix). In a linear regression model, diagnosis, symptoms and disruption did not significantly predict PCIT. In contrast, when added to the model, CTQ significantly negatively predicted PCIT (see Table 3)[1]. When added to the model, sex, age and site did not alter the pattern of results.

SEN connectivity and CA

Across individuals, CTQ was correlated with both increased and decreased connectivity in a number of regions for each of the bilateral seeds (see Supplementary Table S2 for each of the combined relationships with bilateral seeds). The main results of these connectivity differences related to CTQ are illustrated in Figure 2A–C. The most prominent effects across two and three

Table 2. Zero-order correlations among primary study variables

All individuals	PCIT	CTQ	Disruption
PCIT	–		
CTQ	−0.23*	–	
Disruption	−0.10	0.00	–
HDRS	−0.08	0.06	0.27**
HCs	**PCIT**	**CTQ**	**Disruption**
PCIT	–		
CTQ	−0.18	–	
Disruption	−0.23	0.12	–
HDRS	0.05	−0.02	.11
rMDDs	**PCIT**	**CTQ**	**Disruption**
PCIT	–		
CTQ	−0.26^{t}	–	
Disruption	−0.02	−0.17	–
HDRS	−0.09	−0.07	0.21

Note. PCIT = Percent correct inhibition trials on the parametric go/no-go task; CTQ = Childhood Trauma Questionnaire; Disruption = Disruption subscale of the Life Events Occurrence Scale-Revised; HDRS = Hamilton Depression Rating Scale.
$^{t}P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.01$

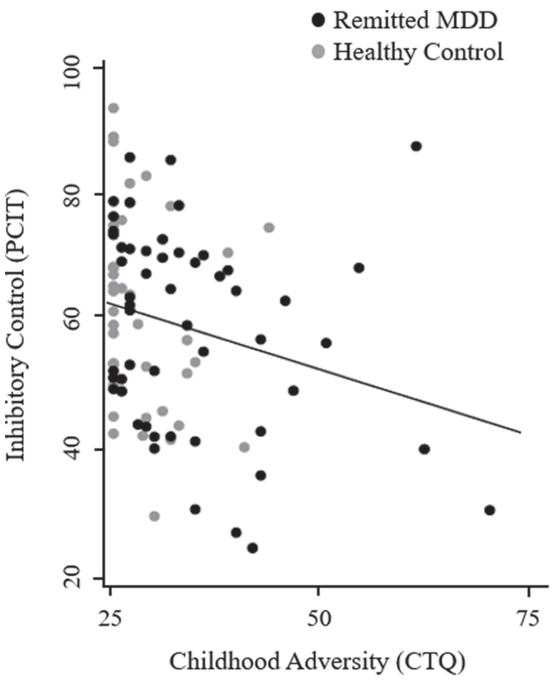

Fig. 1. Scatterplot showing the inverse association between CA, measured by the childhood trauma questionnaire (CTQ), and inhibitory control, measured by percent correct on inhibition trials (PCIT) of the parametric go/no-go test.

Table 3. Regression model testing the hypothesis that CA predicts inhibitory control

Predictors	B	SE	95% CI	β	t	p
Model without CTQ						
Diagnosis	−0.61	3.45	−7.47, 6.25	−0.02	−0.18	0.86
HDRS	−0.16	0.31	−0.77, 0.46	−0.06	−0.50	0.62
Disruption	−0.26	0.38	−1.01, 0.49	−0.08	−0.69	0.50
Model with CTQ						
Diagnosis	2.32	3.60	−4.82, 9.47	0.08	0.65	0.52
HDRS	−0.19	0.30	−0.79, 0.42	−0.07	−0.62	0.54
Disruption	−0.35	0.37	−1.09, 0.39	−0.10	−0.94	0.35
CTQ	−0.42	0.18	−0.78, −0.06	−0.26	−2.33	0.02
Model	ΔR^2	ΔF	p			
Without CTQ	0.01	0.41	0.75			
With CTQ	0.07	5.42	0.02			

Note. Outcome is the percent correct inhibition trials on the parametric go/no-go task; CTQ = Childhood Trauma Questionnaire; Disruption = Disruption subscale of the Life Events Occurrence Scale-Revised; HDRS = Hamilton Depression Rating Scale.

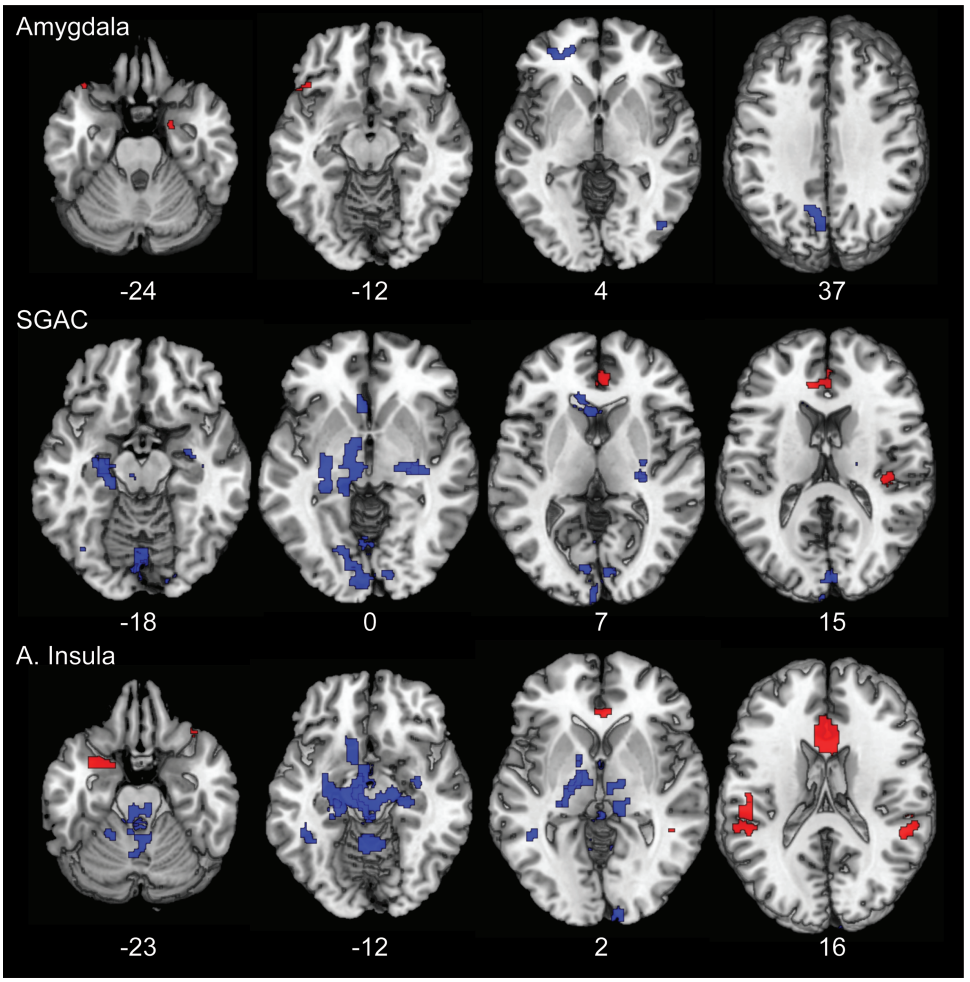

Fig. 2. Connectivity associated with CTQ for SEN seeds. Red indicates nodes of increasing connectivity association and blue illustrates decreasing connectivity association. Z coordinates are noted.

SEN seeds were increasing CTQ associated with greater SEN seed connectivity with the rostral anterior cingulate, bilateral posterior insula and superior temporal gyrus. Increasing CTQ was also associated with lower connectivity between at least two of three of the SEN seeds and bilateral hippocampus, thalamus, cerebellum and ventral subgenual cingulate and orbital frontal cortex.

CCN connectivity and CA

Across individuals, CTQ was positively associated with connectivity between a CCN seed to bilateral middle frontal gyrus, inferior parietal lobule, anterior inferior temporal gyrus and lateral orbital frontal gyrus. CTQ was inversely correlated with connectivity between CCN seeds and left subgenual cingulate,

orbital frontal cortex and right precuneus (Figure 3, Supplementary Table S3).

DMN connectivity and CA

Across individuals, CTQ was positively associated with connectivity of the posterior cingulate seed with bilateral motor and sensory strip regions and mid cingulate, as well as inversely correlated with left superior frontal gyrus (SFG; Figure 4, Supplementary Table S4).

GMV and CA

GMV was significantly lower in rMDD relative to HC [$F(1,81) = 5.29$, $P = 0.02$]. Males had larger volumes than females [$F(1,81) = 11.53$, $P = 0.001$]. Weighted GMV (by site) was inversely correlated with CTQ at the trend level ($r = -.22$, $P = .06$). After covarying for site, sex, age, weighted GMV and group, CTQ was negatively correlated with GMV in the right middle frontal gyrus and left superior temporal gyrus and positively correlated with GMV in mid-cingulate (Figure 5, Supplementary Table S5).

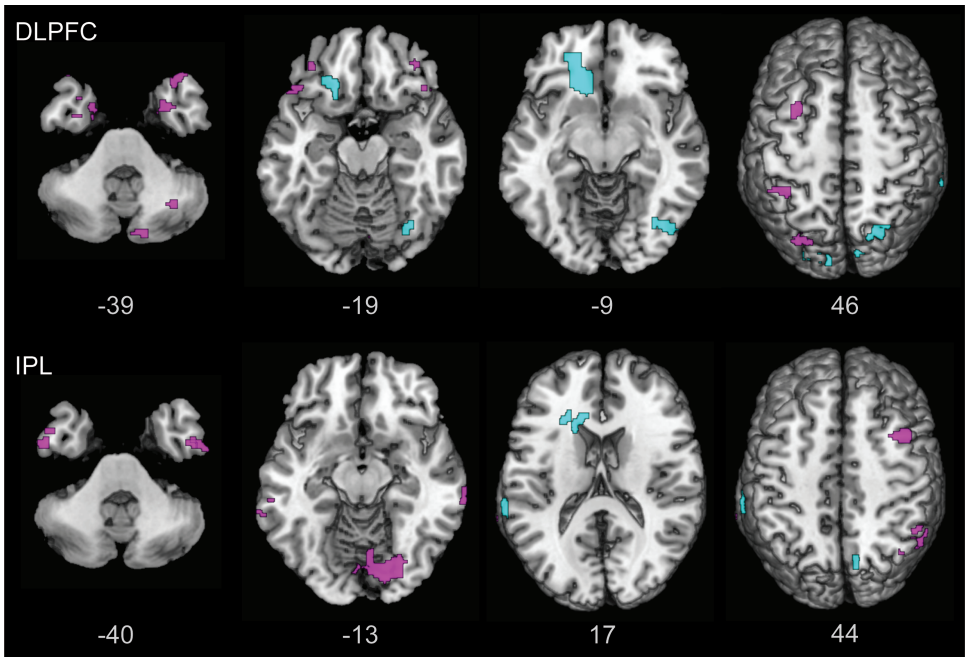

Fig. 3. Connectivity associated with CTQ for CCN seeds. Violet indicates increasing connectivity association and cyan illustrates decreasing connectivity association. Z coordinates are noted.

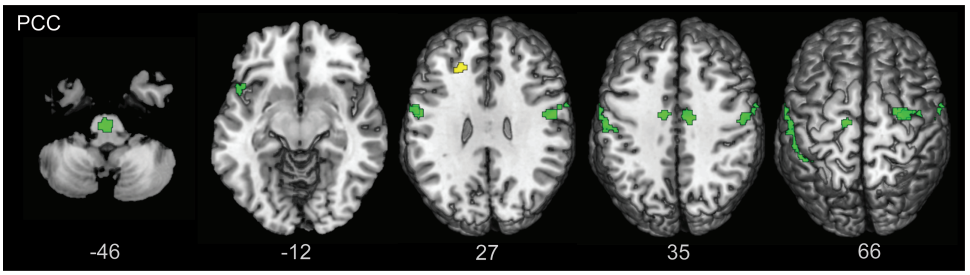

Fig. 4. Connectivity associated with CTQ for DMN seed. Green indicates nodes of increasing connectivity association and yellow illustrates decreasing connectivity association. Z coordinates are noted.

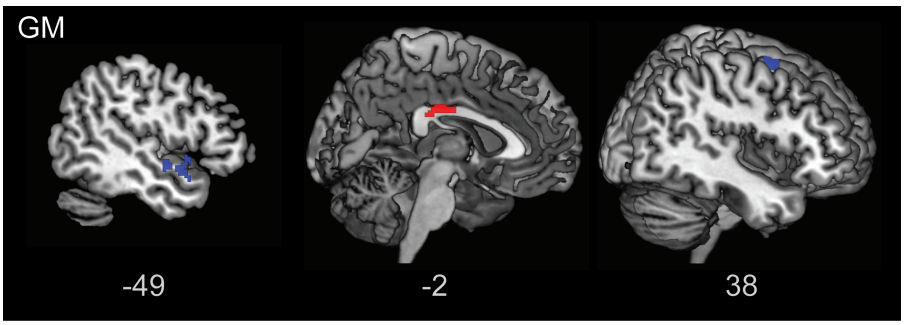

Fig. 5. GMV associated with CTQ. Red areas illustrate increasing GMV, and blue areas depict decreasing volume with higher CTQ scores. X coordinates are noted.

Discussion

The goal of the current study was to identify whether CA is associated with impaired inhibitory control and alterations in networks associated with inhibitory control. Importantly, this study assessed these associations while controlling for diagnosis in a sample of individuals with and without a history of depression. Results demonstrate that a higher level of CA is significantly associated with poorer inhibitory control across all individuals, and this relationship remains after controlling for diagnostic status, residual depression symptoms and current stressors. Moreover, at an exploratory level, prominent resting state connectivity alterations were also evident in each of the three major intrinsic networks assessed, although more so in SEN than in CCN or DMN. Decreased subgenual cingulate and anterior insula seed connectivity to medial temporal and posterior midline subcortical structures was observed with increasing CA. Increasing CA was associated with increasing connectivity of DLPFC and IPL seed connectivity to similar CCN regions and decreasing connectivity to orbital frontal cortex and subgenual cingulate. Together, results suggest that inhibitory control impairment and intrinsic connectivity changes may be characterized as developmental sequelae of CA, independent of diagnostic status.

The inverse relationship between CA and inhibitory control in the current study is similar to prior evidence using broader measures of cognitive control in a heterogeneous patient sample (Gould *et al.*, 2012), measures of working memory and recognition in healthy individuals (Majer *et al.*, 2010) and measures of memory and cognitive control in school-aged children (Bos *et al.*, 2009). Results of the current study are also consistent with those obtained by Marshall *et al.* (2016); their findings suggest that inhibitory control impairment is a consequence of CA in individuals with bipolar disorder as well as in healthy controls. Together, these pieces of evidence suggest that although inhibitory control deficits are often observed in patient populations relative to controls, diagnostic status may not be the primary factor related to this weakness. Instead, inhibitory control impairment may result from exposure to CA during critical developmental years. Given that increased impairment in inhibitory control and other components of cognitive control are associated with greater number of previous episodes (Kessing, 1998; Paelecke-Habermann *et al.*, 2005) and predictive of response to treatment in MDD (Crane *et al.*, 2017), CA may set the stage for inhibitory control impairments contributing to a distinct course of depression. Prospective research is needed to examine whether inhibitory control impairment may be a mechanism by which CA contributes to course of depression.

We also investigated potential influences of CA on resting state intrinsic networks. Previous research has demonstrated network disruptions associated with CA (Pechtel and Pizzagalli, 2011; McEwen and Morrison, 2013; Philip *et al.*, 2013; Duncan *et al.*, 2015; Demir-Lira *et al.*, 2016). We have previously reported network disruptions related to depression in relation to ventral striatum, reward and personality traits (DelDonno *et al.*, 2017), hippocampus and memory (Rao *et al.*, 2016) and cognitive control and rumination (Stange *et al.*, 2017). The current study is the first to examine whether network alterations beyond those accounted for by rMDD diagnosis may be attributed to CA. In the present study, we provide evidence of alterations that are evident within and across networks. Given the large number of findings and the relative sensitivity of resting state-fMRI, we highlight only key results here.

The predominant pattern was of disrupted connectivity using SEN seed regions. We identified several areas of convergence across anterior insula and subgenual cingulate seeds such that increasing CA was associated with decreased connectivity with midline thalamic, putamen and brain stem regions as well as hippocampus. CA has previously been reported to predict reduced thalamic connectivity with SEN, transdiagnostically (Philip *et al.*, 2016). Other studies have also reported altered hippocampal, midline and limbic resting state connectivity in individuals with CA (Insana *et al.*, 2015). Overall, there is consistent evidence for disruptions in SEN connectivity associated with CA, across populations and independent of diagnosis.

In the present report, we also found CA was related to increased intrinsic connectivity in the CCN. There was increased connectivity between the DLPFC seeds and left lateralized DLPFC, IPL and precuneus. There was also increased connectivity between IPL seeds and right lateralized DLPFC and IPL. Ventral temporal regions also exhibited increasing connectivity with CCN seeds with higher levels of CA. There was also an inverse relationship between CA and connectivity of the DLPFC nodes with left subgenual anterior cingulate and medial orbital frontal cortex. The findings of increased connectivity within the CCN were contrary to our hypothesis. One possible explanation for these results is that individuals who are exposed to CA could develop greater connections between regions of the CCN to compensate for impairments in inhibitory control. A much larger sample with targeted stratification on CA and inhibitory control could enable probing the relationships among these key variables in the pathology and course of MDD across development.

Broadly, results of the present study indicate that CA is associated with increased connectivity within SEN and CCN, as well as decreased connectivity between CCN and SEN. Resource allocation models of neural control of behavior suggest that when functioning optimally, the SEN and CCN do not act independently, but instead coordinate activity to efficiently guide behavior (Hermans *et al.*, 2014). When the SEN is highly engaged, catecholamines are released at higher rates and bind to key regions of the CCN, resulting in decreased CCN engagement and inhibitory control impairment (Arnsten, 2009). Thus, results of the current study may indicate that with high levels of CA, there is inefficient coordination of activity both within and across these networks.

The present study also found that CA was positively associated with connectivity of the PCC to bilateral sensory-motor regions and a mid-dorsal cingulate region. This is similar to previous reports of altered connectivity in the DMN in healthy young adults (Lu *et al.*, 2017). Associations between CA and blood-oxygen-level dependent (BOLD) responses to the anticipation of aversive stimuli in the motor cortex and left insula were reported by another group (Duncan *et al.*, 2015); thus, one possibility is that the sensory-motor findings in the present study may represent an increase in intrinsic connectivity between the DMN and aversion-related networks in individuals with higher CA. In the present report, CA was inversely correlated with connectivity of the DMN to the left SFG. The SFG is involved in emotion regulation (Ochsner and Gross, 2005), particularly inhibition of negative affect (Phan *et al.*, 2005). Thus, findings in the present report suggest that CA is associated with increased DMN connectivity to emotion regulation regions.

The current report also illustrates reduced connectivity between SEN seeds and several DMN regions, including precuneus and hippocampus, with increasing CA. This is consistent with previous reports of altered DMN and SEN connectivity in trauma-exposed youth (Marusak *et al.*, 2015). However, based on

evidence of reduced connectivity between SEN regions such as the amygdala and DMN regions such as the medial PFC (Burghy *et al.*, 2012; Herringa *et al.*, 2013; Cisler, 2017), we were surprised not to replicate this effect using our amygdala seed or to find converging evidence using our bilateral PCC seed. However, these studies consisted of adolescents and our sample consisted of young adults.

The present study found that CA was negatively correlated with GMV in right middle frontal gyrus, which is consistent with previous findings in a community sample (Tomoda *et al.*, 2009) and in individuals with a family history of depression (Carballedo *et al.*, 2012). The middle frontal gyrus plays a key role in inhibitory control as well as other components of cognitive control (Langenecker and Nielson, 2003; Langenecker *et al.*, 2004; Niendam *et al.*, 2012; Ryan *et al.*, 2015). When combined with behavioral results indicating that CA is associated with inhibitory control, VBM results suggest that CA may contribute to altered development of the middle frontal gyrus, which manifests as impaired inhibitory control.

There are some limitations that are critical to review. The sampling at two sites has both positive and negative ramifications. As the demographics of the samples were comparable at both sites and equivalent in diagnostic characteristics, results may be more generalizable to the real world than one-site studies. The differing imaging sequences across sites might have inadvertently led to some unusual group by site effects. However, we saw no evidence of group by site interactions for connectivity or GMV in the regions that were reported. To control for any unexplained site differences, the imaging results reported are after covarying for site. Processing imaging data, particularly given inherent smoothness, individual differences and smoothing filters reduces spatial sensitivity. As a result, slight deviations in observed foci may be observed (e.g. foci noted in white matter in Figure 4 may be a false positive for location and/or signal). Additionally, the -fwhm adjustment with a cluster forming threshold of $P < 0.005$ has the potential to lead to inflated type I error rates and results should be interpreted with caution. Another limitation of the current study is that CA was measured with a retrospective self-report and there have been challenges to the veracity of such reports (Harkness and Monroe, 2016). However, collecting such information from young adults with rMDD rather than active MDD could reduce both retrospective bias and bias associated with negative mood. Finally, the rMDD group reported more CA than the HC group, even though the average level for both groups was in the mildly elevated range compared to published normative data.

Conclusion

In summary, the current study demonstrates that CA is associated with impaired inhibitory control and begins to illustrate the underlying nature of these potential weaknesses, with alterations in three primary networks—CCN, SEN and DMN. The association between CA and increased connectivity within the SEN suggests heightened salience of emotion in individuals with high levels of CA, and that CA may lead to dramatic changes in the underlying synchronization and functioning of these networks and related nodes. The positive association between CA and DMN connectivity with somatosensory, aversion-related networks further supports this idea. The association between CA and increased connectivity within both the SEN and CCN, as well as reduced connectivity between the SEN and CCN, suggests that CA may contribute to inefficient network coordination. In general, results suggest that CA may contribute to an altered developmental trajectory of networks, which manifests as impaired inhibitory control, amongst other possible sequelae. Our finding of an association between CA and inhibitory control impairment, independent of diagnosis, suggests that future research on the role of inhibitory control impairment in depression should consider the influence of CA. Finally, given research suggesting that impairment in cognitive control is associated with a distinct course of illness and response to treatment (Kessing, 1998; Crane *et al.*, 2017; Dawson *et al.*, 2017), future research may benefit from examining whether CA, and associated inhibitory control impairment, contributes to a distinct course of depression.

Notes

1. When added to the model, an interaction between CA and diagnostic group was not significant, $B = 0.11$, $P = 0.84$, 95%CI [−0.94, 1.17], indicating that the relation between CA and inhibitory control did not significantly differ across groups.

Supplementary data

Supplementary data are available at *SCAN* online.

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