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Multimodal evidence of regional midcingulate gray matter volume underlying conflict monitoring

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ABSTRACT

Functional neuroimaging studies have long implicated the mid-cingulate cortex (MCC) in conflict monitoring, but it is not clear whether its structural integrity (i.e., the gray matter volume) influences its conflict monitoring function. In this multimodal study, we used T1-weighted MRI scans as well as event-related potentials (ERPs) to test whether the MCC gray matter volume is associated with the electrocortical marker (i.e., No-go N200 ERP component) of conflict monitoring in healthy individuals. The specificity of such a relationship in health was determined in two ways: by (A) acquiring the same data from individuals with cocaine use disorder (CUD), known to have deficits in executive function including behavioral monitoring; and (B) acquiring the P300 ERP component that is linked with attention allocation and not specifically with conflict monitoring. Twenty-five (39.1 ± 8.4 years; 8 females) healthy individuals and 25 (42.7 ± 5.9 years; 6 females) individuals with CUD underwent a rewarded Go/No-go task during which the ERP data was collected, and they also underwent a structural MRI scan. The whole brain regression analysis showed a significant correlation between MCC structural integrity and the well-known ERP measure of conflict monitoring (N200, but not the P300) in healthy individuals, which was absent in CUD who were characterized by reduced MCC gray matter volume, N200 abnormalities as well as reduced task accuracy. In individuals with CUD instead, the N200 amplitude was associated with drug addiction symptomatology. These results show that the integrity of MCC volume is directly associated with the electrocortical correlates of conflict monitoring in healthy individuals, and such an association breaks down in psychopathologies that impact these brain processes. Taken together, this MCC–N200 association may serve as a biomarker of improved behavioral monitoring processes in diseased populations.

1. Introduction

Cognitive control mechanisms are engaged to guide behavior in the face of uncertainty, when the goals or response tendencies come into conflict with one another. Continuous monitoring of these moment-to-moment representations of action tendencies for potential conflicts (i.e., conflict monitoring) is crucial for goal directed behavior (Botvinick et al., 2001). Functional neuroimaging studies have consistently implicated the activity of the dorsal and posterior portions of the medial prefrontal cortex, specifically the mid-cingulate cortex (MCC), in detecting pre-response conflict between intended actions and their outcomes (Botvinick et al., 2004; Bush et al., 1998). However, the association of the MCC's function in monitoring conflict with its structural integrity is not well understood.

In studies utilizing electroencephalographic (EEG) recordings, amplitude of the N200 event-related potential (ERP) in response to incongruent (i.e., conflict-ridden) stimuli is considered as a reliable biomarker of conflict monitoring (Yeung et al., 2004) and of conflict detection (van Veen and Carter, 2002). The N200 is a negative-going fronto-central ERP deflection occurring 200–400 ms following the onset of a stimulus, and is more pronounced in response to high-conflict events (Donkers and van Boxtel, 2004). For example, in a Go/No-go task, the tendency to inhibit a response (for No-go cues) conflicts with the prepotent tendency to respond (for Go cue) and in turn elicits an enhanced (i.e., more negative) N200 amplitude (Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2003).

By employing techniques such as dipole source modeling (Bekker et al., 2005; Huster et al., 2010) and current density reconstruction (Enriquez-Geppert et al., 2010), source localization studies have reported the engagement of medial cortical regions encompassing the MCC in the generation of the No-go N200. However, a direct association between the structural integrity [i.e., the gray matter (GM) volume] of

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the MCC and the intact engagement of conflict monitoring processes in healthy individuals is not yet known.

Therefore, the main goal of the current study was to ascertain whether the GM volume of the MCC region is associated with the ability to monitor conflict, as quantified using the N200 amplitude that is elicited by the No-go trials in a Go/No-go task. To determine the specificity of such an association in healthy individuals, we investigated the GM volume–N200 relationship in a neuropsychological disorder known to be associated with structural and functional impairments in the cingulate cortex: cocaine use disorder (CUD). Indeed, previous reports in CUD have shown reduced prefrontal GM volume (Franklin et al., 2002; Matochik et al., 2003), impaired executive function including conflict monitoring as assessed with fMRI (Connolly et al., 2012; Hester and Garavan, 2004) and anomalies in the No-go N200 amplitude (Sokhadze et al., 2008). Thus, we hypothesized deficits in prefrontal GM volume and blunted N200 amplitude to negatively impact the fidelity of the GM volume–N200 association.

Moreover, to ascertain the specificity of the relationship of N200 with the MCC GM volume, we also extracted the No-go P300, a positive ERP component occurring 250–500 ms following stimulus presentation and maximal at fronto-central scalp locations in No-go trials, which has been linked to stimulus characterization and attention allocation (Picton, 1992; Soltani and Knight, 2000) as well as response inhibition (Falkenstein et al., 2002; Strik et al., 1998) and even motor related activation (Salisbury et al., 2004). Here, we did not expect the GM volume in the MCC to be associated with the P300 amplitude.

2. Methods

2.1. Participants

Participants were 25 healthy individuals and 25 individuals with CUD, recruited through advertisements in local newspapers and by word-of-mouth. Although some data from these participants have already been published elsewhere (Goldstein et al., 2008; Parvaz et al., 2012b), the current study focuses exclusively on previously unreported data from these participants. All participants underwent full physical and neurological examinations, including the inclusion/exclusion criteria, by a neurologist and a diagnostic interview by a clinical psychologist, the details of which can be found in our previous publications (Goldstein et al., 2008; Parvaz et al., 2012b).

All individuals with CUD met DSM-IV criteria for either current cocaine dependence (N=22) or abuse (N=3) and reported some cocaine use in the last 30 days. Study groups were matched on the distributions of gender and race, and on age, education, socio-economic status, depression and non-verbal intelligence (Wechsler, 1999) (Table 1). However, controls showed significantly higher verbal intelligence (Wilkinson, 1993) compared to CUD ($t(48) = 2.13$; $p = 0.038$: Table 1). Only 6 controls were current or past smokers compared with the majority ($n = 23$) of cocaine users, and this represented a significant difference ($\chi^2 = 22.03$; $p < 0.001$). Among current smokers, however, the number of cigarettes smoked per day did not differ between the groups (Table 1). Cigarette smokers were not required to abstain to avoid acute nicotine withdrawal effects. Participants were fully informed of all study procedures and risks and provided written consent in accordance with the local Institutional Review Board.

All participants underwent an electroencephalography (EEG) as well as a structural magnetic resonance imaging (MRI) scan in a random order. Due to image quality (primarily due to motion artifact), the structural MRI scans of 4 healthy controls and 1 individual with CUD were removed from the analysis. However, the usable subsample (21 healthy controls and 24 individuals with CUD) did not differ ($p > 0.65$) from the entire group of participants in any demographic and/or drug use variables delineated in Table 1.

Also, as part of this study, participants completed the Multidimensional Personality Questionnaire (MPQ; Patrick et al., 2002). The personality measures were scored for the 3 main personality dimensions of the MPQ: Positive Emotionality (or extraversion), Negative Emotionality (or neuroticism) and Constraint.

2.2. Task paradigm

Participants completed a Go/No-go monetary reward paradigm, for which the data from Go trials have been published previously (Goldstein et al., 2008; Parvaz et al., 2012b). The current study is exclusively focused on results from the No-go trials on this task. Briefly, the task included six blocked sequences, each consisting of 9 Go and 9 No-go trials for each of three blocked monetary reward conditions: 45¢, 1¢, and 0¢, yielding 54 Go and 54 No-go trials per condition. Participants were instructed to press a button as quickly but as accurately as possible, only upon seeing the target stimulus (S2) after a Go S1 stimulus and to refrain from pressing the button upon seeing S2 after a No-go S1 stimulus. Feedback was presented as $0.45, $0.01, and $0.00 for correct responses/non-responses or an "X" for incorrect responses/non-responses. Participants could receive up to $50 contingent on their task performance.

2.3. Psychophysiological recording

Electroencephalogram (EEG; Neuroscan Inc., Sterling, USA) recordings were obtained during the Go/No-go task using a 64 silver–silver chloride electrode cap positioned according to the International 10/20 system. Electrooculogram (EOG) electrodes at left supra- and infra-orbital sites and the right and left outer canthi recorded the blinks (and vertical eye movements) and horizontal eye movements, respectively. EEG recordings were sampled at 1000 Hz, band pass filtered at 0–70 Hz, while the electrode impedances were kept under 10 kΩ. Performance accuracy for the No-go events (correct response-inhibition, and incorrect response-commission) was recorded during all task trials and conditions. Only trials with successful response-inhibition were used for ERP analysis (approximately 99% of total No-go trials; see Table 2). Post-task ratings of interest, excitement and frustration indicated that both groups were engaged in the task, the detailed analyses of which have been presented earlier (Parvaz et al., 2012b).

2.4. EEG data reduction

The continuous EEG was first filtered using a band pass filter (0.1–30 Hz), re-referenced to linked mastoid electrodes and divided into epochs extending from 200 ms before the onset of No-go S1 stimulus to 800 ms after. All epochs were then subjected to a baseline correction with respect to the 200 ms pre-stimulus baseline, and artifact rejection procedures. After artifact rejection, there was a minimum of 25 epochs per task condition (minimum of 75 No-go epochs across all money conditions). Only the No-go trials with correct response inhibitions were averaged separately for each group (individuals with CUD and healthy controls).

Peak amplitudes were isolated using temporospatial principal components analysis (PCA) [Matlab (Mathworks Inc., Natick, MA) based EP-Toolkit (version 2.23)] (Dien, 2010). Temporospatial PCA assesses variance first across time (to identify peak latency) and then across space (to identify topography) to maximize the separation of overlapping ERP components (Dien et al., 2005) across all participants in each group separately. A temporospatial factor was identified for each ERP component (i.e., N200 and P300) based on a specific peak latency (i.e., a single peak latency value per group) and scalp topography for each group. The factor with negative polarity and frontal topography with peak latency of 200–300 ms was identified as N200 (Folstein and Van Petten, 2008), while the one with positive polarity and fronto-central topography of 250–600 ms was identified as P300 (Picton, 1992).

Table 1
Demographics and drug use-related measures of all study participants.

	Test (χ2, t, or Z)	Control (N = 25)	Individuals with CUD (N = 25)
Demographics			
Gender: male/female	0.4	17/8	19/6
Race: Caucasian/African-American/other	4.8	6/15/4	1/20/4
Age (years)	1.7	39.1 ± 8.4	42.7 ± 5.9
Education (years)	1.6	14.0 ± 1.9	13.2 ± 2.1
Non-verbal IQ: Wechsler Abbreviated Scale of Intelligence: Matrix Reasoning Scale	0.9	11.1 ± 2.7	10.3 ± 3.3
Verbal IQ: reading subscale of the Wide Range Achievement Test 3 (WRAT 3)	2.13*	100.68 ± 10.4	94.28 ± 10.84
Depression: Beck Depression Inventory II (Beck et al., 1996)	1.5	4.1 ± 4.3	6.6 ± 7.2
Drug use			
Cigarette smokers (current or past/nonsmokers)	22.0*	6/19	23/2
Daily cigarettes [current smokers: $N = 4/18$ (controls/CUD)]	0.65	4.5 ± 9.0	7.0 ± 6.6
Age of onset of cocaine(years)	–	–	22.6 ± 6.2
Duration of use of cocaine (years)	–	–	15.0 ± 6.3
Duration of current abstinence (days)	–	–	3.0 ± 3.4
Cocaine use during last 30 days: days/week	–	–	3.2 ± 2.1
Cocaine use during last 12 months: days/week	–	–	3.2 ± 2.0
Urine status for cocaine on study day: (positive/negative)	–	–	15/10
Total score on the Cocaine Selective Severity Assessment Scale	–	–	12.5 ± 9.9
Severity of Dependence Scale (0–15)	–	–	3.3 ± 4.3
Cocaine Craving Questionnaire (0–45)	–	–	14.4 ± 9.9

χ^2 tests were used for categorical variables; Mann–Whitney U for all drug-related variables (continuous non-normally distributed variables) and *t*-tests for all comparisons between the groups; values are frequencies or means ± standard deviation (S.D.).
* $p < 0.05$; race: other (Hispanic/Asian/biracial).

Table 2
Task accuracy and No-go N200 and P300 amplitudes for healthy controls and individuals with CUD for all monetary conditions.

		No-go accuracy (%)	N200 (μV)	P300 (μV)
Healthy controls	$0.00	99.70 (0.69)	−2.49 (0.42)	2.49 (0.53)
	$0.01	99.85 (0.51)	−2.33 (0.45)	2.46 (0.54)
	$0.45	99.93 (0.37)	−2.54 (0.46)	3.14 (0.65)
Individuals with CUD	$0.00	99.33 (1.40)	−1.33 (0.20)	2.01 (0.40)
	$0.01	99.26 (1.69)	−1.33 (0.19)	2.12 (0.48)
	$0.45	99.41 (1.03)	−1.52 (0.17)	2.28 (0.49)

Mean (SEM).

For quantitative analysis, the peak amplitude was extracted for a group of electrodes around the maxima of the ERP component (Pandey et al., 2012), such that the N200 was extracted from Fz, FC1, FCz, FC2, and Cz and the P300 from FCz, C1, Cz, C2, and CPz, as reported previously (Folstein and Van Petten, 2008; Sokhadze et al., 2008) (Table 2). The grand-averages for each condition, group and selected electrodes as well as the PCA factors and their scalp topographies can be inspected in Fig. 1.

2.5. Structural MRI

MRI acquisition was performed using a 4-Tesla Varian/Siemens scanner, with a self-shielded whole-body SONATA gradient set. A T_1-weighted anatomical MRI scan was obtained from all participants using a 3D-MDEFT (3 dimensional modified driven-equilibrium Fourier transform) sequence (Lee et al., 1995) (TE/TR = 7/15 ms, $0.94 \times 0.94 \times 1.00\ mm^3$ spatial resolution, axial orientation, 256 readout and 192×96 phase-encoding steps, 16 minute scan time). The MDEFT is particularly effective for tissue differentiation producing the most precise characterization of GM tissue compared to other sequences (Tardif et al., 2009). A T_2-weighted hyperecho scan was also obtained to rule out any gross morphological abnormalities. Structural scans were obtained from these participants within 1 week (2.19 ± 2.12 days) of completing the psychophysiological recordings and clinical interviews, with no differences between the groups in this time gap ($p > 0.5$).

Data preprocessing was performed using the statistical parametric mapping (SPM8) suite (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab version 7.0 (Mathworks Inc., Natick, MA). Voxel-based morphometry (VBM), a whole-brain, fully automated, unbiased, and operator-independent MRI analysis technique commonly used to detect regionally specific differences in brain tissue composition using a voxel-wise comparison across participants (Ashburner and Friston, 2000), was conducted with the VBM toolbox (VBM8) (Gaser, C, University of Jena, Department of Psychiatry, Germany; http://dbm.neuro.uni-jena.de/vbm.html).

As part of the toolbox pipeline, the MDEFT scans were (1) checked for scanner artifacts and gross anatomical abnormalities for each participant; (2) realigned for the origin to be at the anterior commissure; (3) corrected for bias-field inhomogeneities; (4) segmented into different tissue classes (gray matter, white matter and cerebro-spinal fluid); (5) spatially normalized by linear (12-parameter affine) and non-linear transformations using Diffeomorphic Anatomical Registration using Exponential Lie algebra (DARTEL) template in the standard Montreal Neurological Institute (MNI) space; and, (6) modulated with the Jacobian determinants to correct for differences in head size. Finally, the images were smoothed with a 10 mm^3 full-width at half-maximum Gaussian kernel.

2.6. Data analysis

2.6.1. Behavior and ERP analyses

The distribution of the PCA factor amplitudes was negatively skewed and therefore, the variables were normalized using the logarithmic transformation as previously suggested by Tabachnick and Fidell (2007) and Howell (2007). This transformation enabled the use of a mixed 3 (money: 45¢, 1¢ and 0¢) × 2 (group: controls and individuals with CUD) repeated measures analysis of variance (ANOVA) for ERP PCA factor amplitudes. In all parametric analyses, the Greenhouse–Geisser correction was applied for cases where Mauchly's test showed

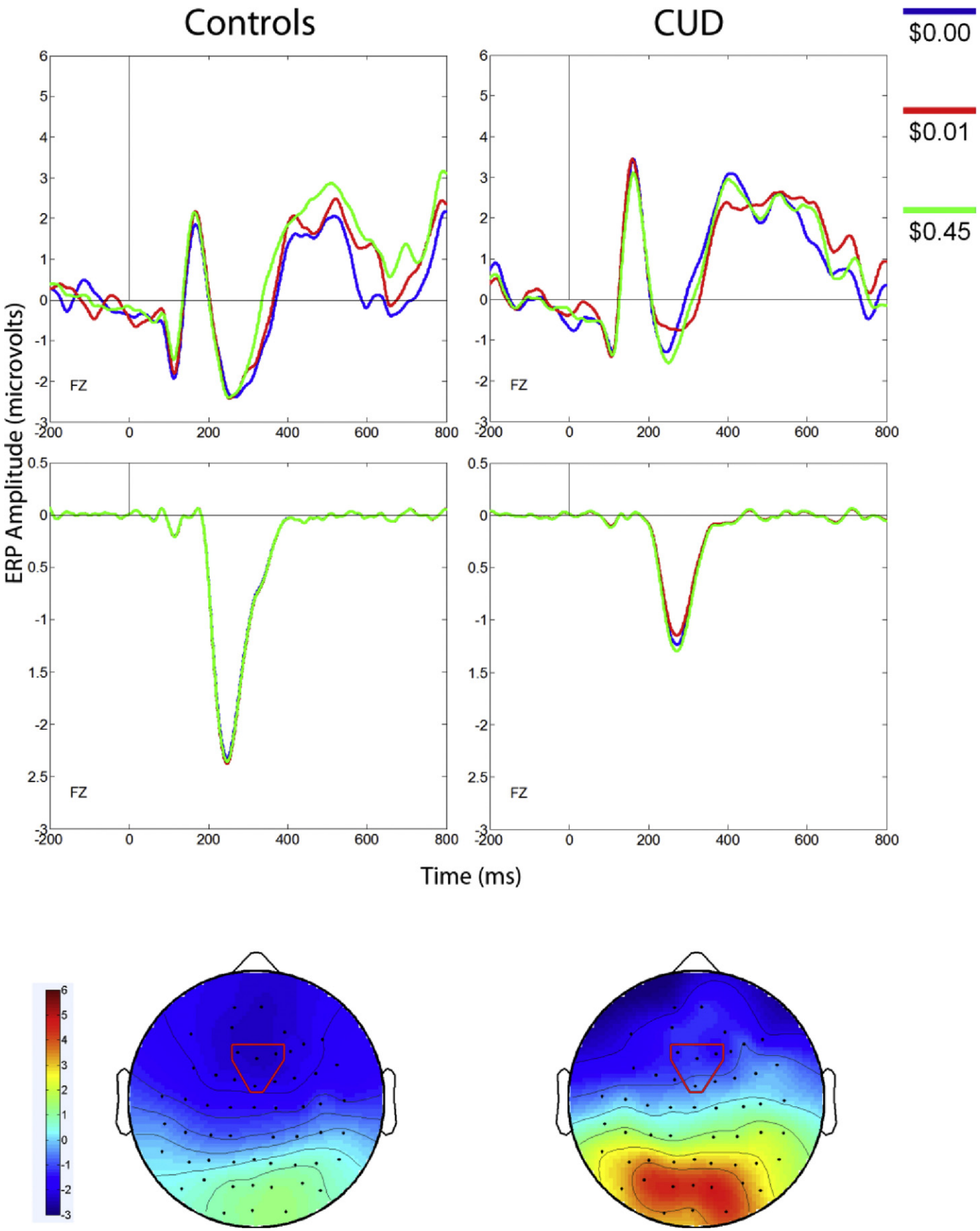

Fig. 1. ERP waveforms and scalp topographies. (Top) Grand averaged ERP waveforms for controls and CUD at Fz electrode during −200 ms before to 800 ms after the cue stimulus (S1) for each monetary reward condition (45¢, 1¢, and 0¢) during the 'No-go' trials (middle). The N200 temporospatial factors isolated using PCA, separately for each study group (bottom). The scalp topography of No-go N200 PCA factor averaged across the monetary conditions. The triangular region shows the electrodes used for extraction of the No-go N200 amplitudes.

the assumption of sphericity was not met. Significant effects were followed with post-hoc comparisons and the significant effects from the ANOVA and non-parametric tests were then correlated with specific drug use variables (presented in Table 1) to investigate associations between metrics of conflict monitoring and drug-related symptoms in CUD.

Finally, given our previous findings regarding electrocortical differences based on recency of drug use (Dunning et al., 2011; Parvaz et al., 2012b), we performed supplemental analyses of the electrocortical data in which individuals with CUD were further compared as a function of cocaine urine status: those who tested positive for cocaine in urine (CUD+; N=15) versus those who did not (CUD−; N=10).

2.6.2. ERP–GM volume regression analysis

Based on the known role of the cingulate cortex in conflict monitoring, and in consideration of our hypotheses, an anatomical bilateral mask was created in Pick Atlas that encompassed the entire (including posterior) cingulate cortex (BAs 23, 24, 25, 26, 29, 30, 31, 32 and 33). Consequently, masked regression analyses were performed in SPM8 with the transformed peak N200 amplitudes as a covariate of interest regressed against regional GM volumes in each voxel of the bilateral cingulate cortex across all participants and separately in healthy controls and individuals with CUD. Age, verbal IQ (ascertained using the reading subscale of the Wide Range Achievement Test 3; Wilkinson, 1993) and gender of each participant were included in the model as a nuisance variable. That is, the averaged N200 amplitude across all monetary conditions (see Results below) was regressed against participants' masked GM maps controlling for age, IQ and gender of the participants. Statistical maps were thresholded at $p < 0.05$ voxel-level family-wise error (FWE)-corrected at the voxel-level. To check the strength of the significant correlations, whole-brain (without the anatomical masks) regression analyses were carried out in SPM8 and cluster-level inference was used. Participants' individual cluster volumes were extracted and assessed for outliers and for subsequent between-group comparisons. The extracted GM volumes were normally distributed and therefore parametric tests were used for analyses. In CUD, the volumes were correlated with drug-use variable to assess their association with the pattern of use and clinical symptoms. We have previously used a similar approach to perform a hypothesis-driven VBM "functional–structural" correlation to assess reward sensitivity in CUD and reported the association of reward-mediated P300 amplitude with the structural integrity of prefrontal brain regions (Parvaz et al., 2012a).

3. Results

3.1. ERP comparisons

The PCA factor identified as N200 appeared maximally at frontal electrodes at 247 ms in controls and at 272 ms in individuals with CUD (Fig. 1). The 3 × 2 mixed ANOVA for N200 amplitude revealed a significant group main effect [$F(1,48) = 5.67$, $p = 0.021$: enhanced N200 amplitude in controls compared to individuals with CUD], but neither the money main effect [$F(2,47) = 1.75$, $p = 0.18$] nor the money by group interaction [$F(2,47) = 0.53$, $p = 0.59$] reached significance. For P300 (centroparietal; at 422 ms in controls and at 474 ms in individuals with CUD), the money main effect [$F(2,47) = 0.76$, $p = 0.47$], the group main effect [$F(1,48) = 0.29$, $p = 0.59$], and the money by group interaction [$F(2,47) = 0.28$, $p = 0.75$] did not reach significance.

Taken together, unlike the P300, the N200 was uniquely more pronounced in controls compared to individuals with CUD across all money conditions. Due to the lack of N200 amplitude differences between the money conditions, the normalized N200 peak amplitudes were averaged across money conditions for all subsequent analyses.

3.2. Task behavior

The Mann–Whitney U Test for the task accuracy on No-go trials revealed a significant group difference in the task accuracy for the 45¢ condition ($Z = 2.30$, $p = 0.021$) but not for 0¢ ($Z = 0.81$, $p = 0.42$) and 1¢ conditions ($Z = 1.58$, $p = 0.13$). Thus, the task behavior for the highest monetary reward condition showed that individuals with CUD found it more difficult to refrain from responding in the No-go trials compared to healthy controls. Moreover, across all participants, the overall task accuracy (i.e., No-go accuracy across all monetary conditions) was significantly correlated with the averaged N200 amplitude ($r_s = 0.307$, $p = 0.03$).

3.3. ERP and gray-matter correlations

To evaluate whether the N200 was associated with the GM volume of the cingulate cortex, we performed a regression analysis within the anatomical mask of the cingulate cortex, controlling for the effects of age, using the N200 amplitude response (averaged across all money conditions in No-go trials) as the covariate of interest. There were no significant correlations at the set significance threshold level or at a reduced threshold of $p < 0.01$ uncorrected when considering the whole sample of 45 participants. When performing the analyses only within controls, however, results at cluster-level revealed that the N200 amplitude was significantly and negatively correlated with GM volume in the medial MCC (BA 24; cluster size = 2462 voxels; x = −2, y = −18, z = 40; $Z = 4.89$, $p_{FWE} = 0.006$). These results survived even when the regression was performed at the whole-brain level (without the mask) (BA 24; cluster size = 2738 voxels; x = −2, y = −18, z = 40; $Z = 4.89$, $p_{FWE} = 0.035$) (Fig. 2). The extracted GM volume of this MCC cluster differed between the groups [controls > individuals with CUD; $t(44) = 2.25$, $p = 0.029$]. The No-go P300 responses, in contrast, showed no significant correlations with the GM volume at the set significance threshold level (or at the reduced $p < 0.01$ level) in the CUD group or across all participants, even when analyses were constrained within anatomically marked cingulate regions only.

To ascertain if this MCC–N200 association is unique to healthy controls, we set up an additional regression model where we specified regressors for group, N200 amplitude, and an interaction term between group and N200 amplitude. Indeed, the group by N200 interaction within the masked cingulate region was significant in a similar MCC cluster (cluster size = 1773 voxels; left MCC: x = −5, y = −14, z = 36; $Z = 3.79$, $p_{FWE} = 0.034$), suggesting that the relationship between N200 amplitude and regional GM volume of the MCC significantly differed between the groups. Taken together, these results suggest a unique MCC–N200 correlation in healthy controls, which is absent in individuals with CUD, who manifest decreased GM volume in the MCC and attenuated N200 No-go amplitudes.

3.4. Correlations

The scores on the MPQ subscales did not correlate significantly with any of the dependent variables (overall task accuracy, averaged N200 amplitude, MCC GM volume). Moreover, the correlations between the drug-use variables and the dependent variables in CUD revealed that drug withdrawal was significantly associated with both behavioral (i.e., overall task accuracy; $r_s = -0.504$, $p = 0.012$; Fig. 3A) and electrocortical (i.e., N200 amplitude; $r_s = 0.424$, $p = 0.039$; Fig. 3B) correlates of conflict monitoring in individuals with CUD. Lastly, the total brain volume did not significantly correlate with age, verbal IQ, and drug-use variables.

3.5. Consideration of potential confounds

The effect of smoking history (past or current smokers vs. non-smokers) on the dependent variables was ascertained using

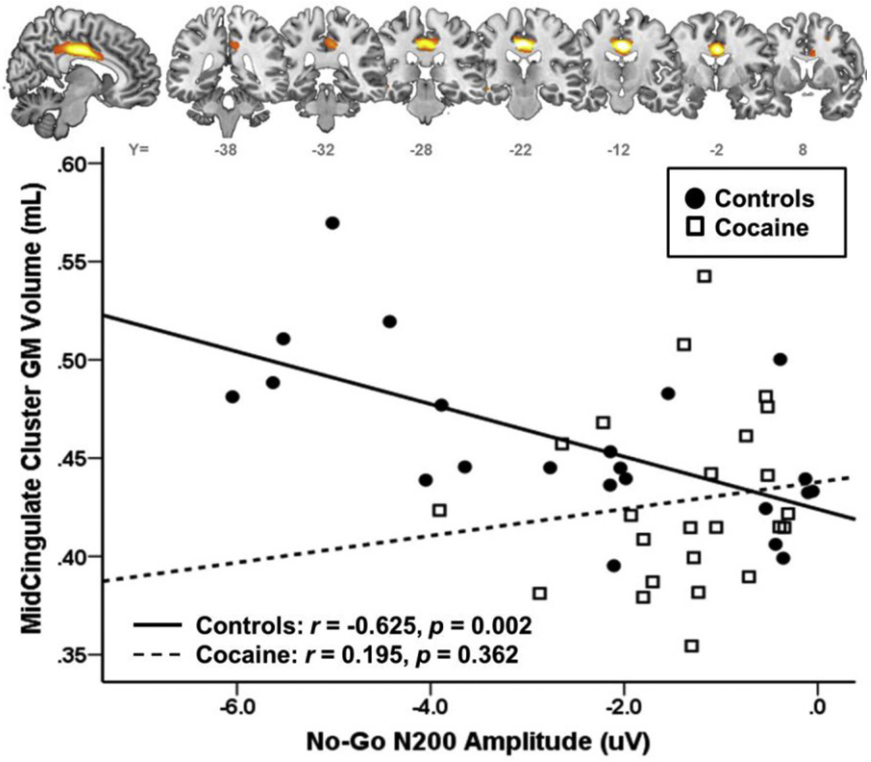

Fig. 2. Correlations between midcingulate volume and N200 amplitude. Midcingulate–N200 correlation in healthy individuals (solid line) and in individuals with CUD (dashed line). The GM volume was extracted from the midcingulate cluster (hot) that was significantly correlated with N200 amplitude in healthy controls within a whole brain regression model.

independent *t*-tests separately for each study group (overall task accuracy: $t < |0.84|$, $p > 0.41$; N200 amplitude: $t < |1.58|$, $p > 0.13$; midcingulate GMV: $t < |1.05|$, $p > 0.30$; this analysis was not conducted across the entire sample given the almost parallel distribution with study group). Furthermore, for current smokers (4 controls/18 individuals with CUD), the dependent variables were not associated with number of cigarettes smoked per day or years of nicotine use ($r < |0.34|$, $p > 0.12$). In terms of the urine status on the study day (15 CUD+ and 10 CUD−), the analysis showed that cocaine urine status in individuals with CUD did not significantly impact the dependent variables ($t < |1.08|$, $p > 0.29$) and, therefore, these variables were not entered as covariates in the relevant ANOVAs.

4. Discussion

In this multimodal neuroimaging study, we examined whether the structural integrity of the cingulate cortex is associated with the functional viability of conflict monitoring mechanisms. For this purpose, the No-go N200 ERP component was used as an electrocortical marker of conflict monitoring (Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2003). Our novel results showed a significant association between the No-go N200 amplitude and the GM volume of the MCC, the region that is reportedly activated under high conflict situations (Botvinick et al., 2001; Botvinick et al., 2004), such that higher GM volume in the MCC correlated with the electrocortical metric of better conflict monitoring in healthy individuals. Suggesting specificity of this correlation in health, the results further showed lack of such an association in individuals with CUD, a clinical population with impairments in action monitoring (Hester and Garavan, 2004). Indeed, the CUD group showed reduced task accuracy and predictably reduced N200 amplitude, accompanied by reduced GM volume of the same MCC region, all of which typify the impaired conflict monitoring in these individuals. Moreover, the less pronounced the N200 amplitude, the higher the drug withdrawal in the CUD group, supporting a direct effect on conflict monitoring of short-term abstinence from acute drug use. Taken together, this novel study underscores the relationship between the structural integrity of the MCC and the adequate functioning of conflict monitoring processes in healthy controls, which is disrupted in drug addicted individuals possibly due to processes underlying withdrawal from recent drug use.

The MCC–N200 association in healthy controls is anticipated given previous ERP source localization and functional neuroimaging studies. For example, ERP studies employing sophisticated statistical techniques have identified medial frontal regions, including the MCC, as generators of the N200 ERP component (Bekker et al., 2005; Huster et al., 2010). Similarly, previous EEG and fMRI studies have consistently linked the activity in the MCC with the N200 amplitude in high-conflict task situations (Ursu et al., 2009; van Veen and Carter, 2002). However, our current results extend these above studies by showing for the first time that increased structural integrity of the MCC also contributes to the increased viability of the N200 amplitude, a well-known electrocortical metric of resolving conflict. Providing support to our results, a recent multimodal study has highlighted the impact of the MCC's asymmetrical morphology (i.e., gyral and sulcal folding) on the N200 amplitude (Huster et al., 2014) suggesting a role of the MCC morphological integrity in neuropsychological functioning related to cognitive control.

It is interesting to note, however, that although the MCC cluster in the current study encompasses a considerable region in the MCC, the peak of the cluster is slightly posterior to the coordinates that are typically reported in EEG source localization studies (Enriquez-Geppert et al., 2010; Nieuwenhuis et al., 2003); an exception is the Bekker et al. (2005) study that showed a more posterior region (similar to the current cluster) as the generating source for the No-Go N200 amplitude. However, it should also be noted that the goal of the current study was not to localize the neural generators of the No-Go N200 amplitude;

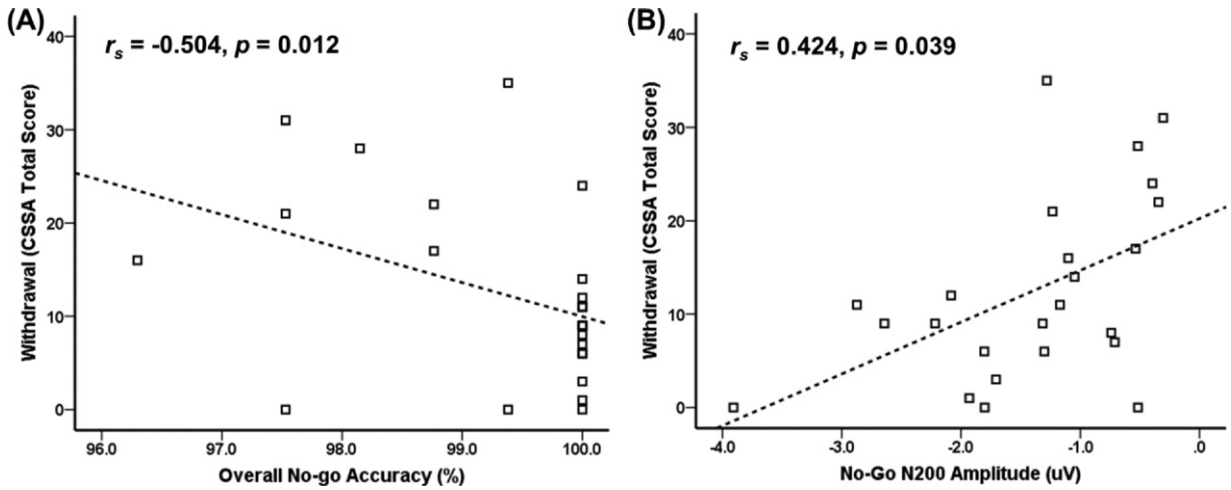

Fig. 3. Drug use symptoms and conflict monitoring. In individuals with CUD, drug withdrawal was associated with both (A) behavioral (i.e., overall task accuracy on No-go trials) and (B) electrocortical (i.e., the No-go N200 amplitude) correlates of conflict monitoring, such that heightened withdrawal symptoms were associated with attenuated N200 amplitude as well as decreased task accuracy in CUD.

rather it was to study whether the structural integrity of the MCC region was associated with the fidelity of the No-go N200 response.

The specificity of MCC–N200 association in healthy controls is established by its absence in individuals with CUD; a group that manifested lower task accuracy, anomalies in the N200 component and decreased GM volume of the MCC, all of which pointing to a general impairment in conflict monitoring in these individuals. Previous neuroimaging studies have consistently shown reduced regional GM volume – including that of MCC – across most individuals with substance use disorders (Franklin et al., 2002; Gallinat et al., 2006; Matochik et al., 2003; Mechtcheriakov et al., 2007; Yuan et al., 2009). Similarly, addiction-related ERP studies have also shown reduced N200 amplitude across individuals with substance use disorders (Luijten et al., 2011; Realmuto et al., 1993; Sokhadze et al., 2008). We, for the first time, examined the correlation between the regional MCC volume and the electrocortical correlate of conflict monitoring and reported its absence in individuals with CUD. Thus, deficits in MCC GM volume, less pronounced N200 amplitude, and the absence of the association between the two likely reflect over-arching task monitoring impairments in individuals with CUD, as affirmed by the lower task accuracy in these individuals.

As expected, the GM volume of the MCC did not correlate with the P300 amplitude, providing further evidence for the specificity of the MCC–N200 association. The lack of this relationship was expected because P300 in the current context is not elicited due to response inhibition, rather it was elicited in response to the warning stimulus (S1; cue to indicate Go or No-go, where response-inhibition is not yet engaged).

The current findings in individuals with CUD are not surprising, and potentially could underlie their addiction-related deficits in adaptive decision making and self-control, especially when the decision to stop drug use conflicts with the drive to keep using (Goldstein and Volkow, 2011), as indeed suggested by the association between the withdrawal symptoms and the N200 amplitude (and task accuracy) across all individuals with CUD. Although a direct relationship between acute drug-mediated states and the N200 amplitude has never been previously shown, an earlier study has reported a recovery of N200 latency in longer-term abstinent individuals with CUD (Porjesz and Begleiter, 1993), suggesting that addiction-related anomalies in N200 may be associated with recent drug use and state-dependent characteristics and may recover after protracted abstinence. Note that although N200 latency could not be statistically analyzed in the current study because temporospatial PCA yields only a single factor latency per group, the temporal PCA suggested that individuals with CUD might have delayed N200 peak latency compared to healthy controls.

It should also be noted that in addition to conflict monitoring, No-go N200 has also been explained as a marker of frontal inhibition mechanism, which is active on No-go trials (Falkenstein et al., 1999; Jodo and Kayama, 1992). This notion is further strengthened by the report of enhanced N200 in response to successful inhibition in stop-signal trials with zero delay; trials that are functionally equivalent to No-go trials (Kok et al., 2004). However, in the study by Nieuwenhuis et al. (2003) the N200 was evoked in Go trials when the frequency of presentations of No-go trials was quite high, which indicated that the N200 might reflect conflict arising from competition between the execution and the inhibition of a response. This suggestion was recently supported by an ERP study of a combined Go/No-go and Stop-signal task (Enriquez-Geppert et al., 2010), highlighting growing evidence that implicate No-go N200 in conflict monitoring. Some studies have also argued that other frontocentral ERP components are also sensitive to conflict detection, such as N450 in the Stroop task (West et al., 2004) generated in the anterior cingulate cortex (Liotti et al., 2000; West, 2003). Therefore, it can be speculated that neural substrates underlying conflict monitoring generate negative ERP components, the latencies of which are dependent on the idiosyncrasies of the task (e.g., N200 in No-go tasks and N450 in the Stroop task).

Limitations of this study include differences in cigarette smoking history between the two groups, the effect of which on the current results could only be partially ascertained due to its parallel distribution with the study groups. Moreover, the relatively small sample size and gender bias (both study groups predominantly consisted of male participants) also served as limiting factors in the wider generalizability of the current results. Therefore, future studies may recruit a much larger and a more balanced sample to robustly study whether the history of cigarette smoking and gender mediate the MCC–N200 relationship in controls. It will also be important to test if the current findings generalize when using other task paradigms that target conflict monitoring such as the Stroop and the Flanker tasks. Although the current study reports the lack of MCC–N200 relationship in a specific psychopathology of cognitive control, i.e., drug addiction, future studies may extend these findings by investigating this relationship in other neuropsychiatric disorders in which impairments in conflict monitoring are also pronounced (e.g., intermittent explosive disorder, binge eating). Future studies may also examine whether the N200 amplitude can track the severity of recent drug-use symptoms in individuals with other substance

use disorders (or relevant symptoms in other disorders of conflict monitoring, such as food craving in obesity), or whether it can objectively quantify the impact and efficacy of therapeutic interventions that would focus on reduction of acute drug-use symptoms.

5. Conclusions

Thus, this multimodal study for the first time demonstrates a direct association in healthy individuals between the structural integrity of the MCC and the N200 amplitude, a well-known functional marker of conflict monitoring. Our results further attest to the specificity of this relationship in healthy individuals by highlighting its absence in individuals with CUD. The CUD group instead showed decreased gray matter MCC volumes and reduced N200 amplitude, with the latter deficit correlating with withdrawal. Taken together, this novel study underscores the relationship between the structural integrity of the MCC and the adequate functioning of conflict monitoring processes in healthy controls, which is disrupted in drug addicted individuals possibly due to the processes associated with withdrawal from recent drug use.

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Appendix A. Supplementary Material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2014.05.011.

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