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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).