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# Abnormal proactive and reactive cognitive control during conflict processing in major depression

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**Abstract**

According to the Dual Mechanisms of Control framework, cognitive control consists of two complementary components: *proactive control* refers to anticipatory maintenance of goal relevant information whereas *reactive control* acts as a correction mechanism that is activated when a conflict occurs. Possibly, the well known diminished inhibitory control in response to negative stimuli in Major Depressive Disorder (MDD) patients stems from a breakdown in proactive control, and/or anomalies in reactive cognitive control. In our study, MDD patients specifically showed increased response latencies when actively inhibiting a dominant response to a sad compared to a happy face. This condition was associated with a longer duration of a dominant ERP topography (800-900 ms post-stimulus onset) and a stronger activity in the bilateral dorsal anterior cingulate cortex, reflecting abnormal reactive control when inhibiting attention to a negative stimulus. Moreover, MDD patients showed abnormalities in proactive cognitive control when preparing for the upcoming imperative stimulus (abnormal modulation of the cued negative variation component), accompanied by more activity in brain regions belonging to the default mode network. All together, deficits to inhibit attention to negative information in MDD might originate from an abnormal use of both proactive resources and reactive control processes.

*Keywords: Major Depressive Disorder – Proactive control – Reactive control – ERP topographic mapping analysis*

## Introduction

Although Major Depressive Disorder (MDD) is primarily characterized by persistent low mood, recurrent negative thoughts and anhedonia, it is also accompanied by core cognitive deficits at the level of information processing. These impairments are most pronounced for negative information, with specific difficulties in inhibiting attention to task-irrelevant negative information (Joormann, Yoon & Zetsche, 2007), leading to depressed mood. Depressive feelings have been associated with disregulated cortico-limbic interactions accompanied by changes in dorsal neocortical activation, specifically the dorsolateral prefrontal cortex (DLPFC, Brodman Area (BA) 9/46), the dorsal anterior cingulate (dACC, BA 24), the inferior parietal cortex (IPC, BA 40) and the striatum (Mayberg, 1997). However, it remains unclear whether this dorsal activation is either decreased or increased during cognitive control operations engaged during the processing of emotional stimuli in currently or remitted depressed patients (Joormann & Gotlib, 2008). While some studies reported hyperactivity in these dorsal regions in depressed patients during cognitive control operations (Chiu & Deldin, 2007; Harvey et al., 2005; Holmes & Pizzagalli, 2008a; Luu, Flaisch, & Tucker, 2000; Liotti, Woldorff, Perez, & Mayberg, 2000), other studies found depression-related hypoactivity in these same areas, including the DLPFC and the dACC (Holmes & Pizzagalli, 2008b; Vanderhasselt & De Raedt, 2009). This discrepancy might stem from the fact that these studies focussed on different aspects of cognitive control, including proactive and reactive mechanisms (Braver, Gray, & Burgess, 2007).

Recent theoretical accounts (Braver, 2012) have proposed that cognitive control is not exclusively related to reactive mechanisms in response to an imperative stimulus (e.g. conflict), but that specific proactive processes may also play a role in conflict monitoring (and more generally goal-directed behavior). According to the Dual Mechanisms of Control framework (DMC) (Braver et al., 2007; Braver, 2012), proactive control refers to anticipatory

or preparatory processes (i.e. activating and maintaining online goal-relevant information) aimed at enhancing coping with conflict before it actually takes place. This proactive control depends on contextual information (Miller & Cohen, 2001) and serves to guide the information processing system towards goal relevant information before the onset of the imperative stimulus. On the other hand, reactive control refers to a correction mechanism that is activated when an ambiguous or conflict stimulus occurs (Jacoby, Kelley, & McElree, 1999). Reactive control mechanisms are essential to mobilize additional processing resources in order to eventually resolve this conflict. According to the DMC, although these two components of working memory and cognitive control likely operate at different moments during conflict monitoring (e.g., early/sustained selection and late/transient correction for proactive and reactive mechanisms, respectively), they both depend on the integrity of a dorsal brain system comprising the DLPFC and dACC area.

Although most studies have focused on reactive modes of cognitive control in samples of depressed patients, some studies have also demonstrated abnormalities in proactive control associated with negative mood. An earlier study from West, Choi, & Travers (2010) observed that negative affect (measured using a Beck Depression Inventory) in healthy individuals was associated with attenuated proactive and reactive cognitive control (using a counting Stroop task). Moreover in clinically depressed patients, an abnormal contingent negative variation (CNV) during the engagement of preparatory processes has been observed (Ashton, Marshall, Hassanyeh, Marsh, & Wright-Honari, 1994; Heimberg et al., 1999; Giedke & Heimann, 1987). This slow cue-locked cortical potential, which is maximal over frontocentral sites, reflects anticipatory attention and effortful processing (Brunia & van Boxtel, 2001). Possibly, diminished inhibitory control in response to a (task-irrelevant) negative stimulus (as typically seen in depression) might stem from a breakdown in proactive control, which normally operates before the conflict is actually experienced (Braver, 2012). It appears therefore

important to investigate both proactive and reactive modes of cognitive control in currently depressed patients.

In a recent Event Related Potential (ERP) study (Vanderhasselt et al., 2012), a new experimental paradigm to disentangle the respective contributions of these two cognitive control components during conflict monitoring wasused: : the Cued Emotional Conflict Task (CECT). Based on the presentation of a cue that informed participants about which S-R mapping to use later (either press, actual or opposite) when seeing a face stimulus. using EEG methods, the amount of proactive control could be assessed during this time period preceding the onset of the imperative face stimulus (target). Derived from the DMC framework (Braver et al., 2007; 2012), proactive control was conceptualized as the active maintenance in working memory of a specific task goal. This is harder in the case of “opposite” and “actual” than “press”, given that active emotion face discrimination is required in the former case, while only simple face detection is required in the latter case. Critically, the face had either a happy or sad expression, enabling to compare conflict processing of positive vs. negative information, respectively.

The aim of the current study was to investigate proactive and reactive control mechanisms by comparing behavioral performance (RT) and electrophysiological effects (by means of ERP measurements) in MDD patients and healthy controls during the CECT task. MDD patients were hypothesized to have selectively increased response latencies when encountering sad (compared to happy) faces that are preceded by the cue “opposite”, because of a selective impairment in inhibiting a response to negative information in favor of the concurrent/alternative positive response. Using high density ERP, we evaluated whether such a condition-specific behavioral deficit, if present in MDD, mainly results from selective abnormalities during proactive control (i.e. cue-related ERP activities), or instead during reactive control (i.e. ERP time-locked to the faces), compared to a group of matched healthy

control participants. To address these questions, an advanced ERP topographic mapping analysis (Michel & Murray, 2012; Murray, Brunet, & Michel, 2008; Pourtois, Delplanque, Michel, & Vuilleumier, 2008) was used, combined with a standard distributed source localization method.[1] Using this data analysis, possible abnormalities in either proactive or reactive control during conflict monitoring in MDD can be delineated. Moreover, this study aims to gain insight into the brain networks involved in these processes and their potential alteration in MDD, with a specific focus on lateral and medial prefrontal cortex given the implication of these regions in proactive and reactive cognitive control effects.

## Methods

### Protocol

Participants who agreed to participate in the experiment were contacted by phone, and were screened on inclusion/exclusion criteria. Participants deemed to be eligible after this screening were invited for a clinical structural interview in the lab. Participants meeting all inclusion criteria were subsequently invited for an ERP session. Participants were asked not to smoke at least two hours before the start of the experiment. They gave their written informed consent and received 20 Euros for their participation. The study was approved by the medical ethics committee of the Ghent University hospital.

### Participants

Twenty individuals meeting the DSM-IV criteria for major depressive disorder (MDD) (13 females, mean age: 38.40, *SD*: 13.14), and 20 matched non-depressed (ND) individuals (15 females, mean age: 41.25, *SD*: 14.64), participated in this study.

[1] The added value of this data-driven clustering analysis is that it enables revealing condition-specific differences in the configuration of the ERP electric field (i.e. topography), which are difficult to capture otherwise using a standard peak analysis (i.e. latency or amplitude variations of specific ERP components evidenced at a few electrode positions), especially when substantial differences in the amplitude of the global ERP signal between groups (MDD vs. ND) can occur.

The MDD ambulatory patients were recruited from a local Belgian psychiatric clinic and were diagnosed with MDD (four patients had a comorbidity with anxiety disorder; anxiety symptoms were secondary to a depressive illness). Prior to testing, the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1997), a structured clinical interview, were administered to examine the severity of the current MDD episode. The exclusion criteria for MDD patients were: (1) the presence of other mood disorders; (2) use of anti-psychotics, monoamine oxidase inhibitors, tricyclic antidepressants and/or benzodiazepines; (3) a history of neurological conditions such as epilepsy, a brain trauma, loss of consciousness during more than 5 minutes; (4) a history of electroconvulsive therapy (ECT); (5) the abuse of alcohol during the last year; (6) a current or past substance dependence; (7) a current or past psychotic episode; and finally (8) the presence of learning disorders. Patients who had either serotonergic or noradrenargic antidepressants were included, but only if these patients received their medication for at least 2 weeks on a steady basis prior to testing. Healthy subjects were included in the control group for comparison purposes with the MDD patients if they were free of medication during the time of testing, and presented no evidence of current or past psychopathologic disorders (assessed using the MINI and HAM-D), or self-reported neurologic disorders or head injuries. This ND sample was matched with the depressed participants at the group level on sex, age and education.

All participants were native Caucasian Dutch speakers, had normal or corrected vision and were right handed. Demographic and clinical characteristics of the participants are outlined in Table 1.

**Stimuli and task**

In the Cued Emotional Conflict Task (CECT) each trial starts with 1 out of 3 single written word cue presented in random order (see Figure 1, see Vanderhasselt et al., 2012 for

details): “actual” to press a key corresponding to the emotional expression of the upcoming target face; “opposite” to respond to the opposite emotional expression of the target face; “press” to press a separate key when a face appeared, regardless of the emotional expression of the face (simple detection required). Fourteen faces (7F/7M) from the Karolinska Directed Emotional Faces data set (Lundqvist, Flykt, Öhman, 1997) were used. Each of these faces was shown in a happy and a sad expression, in order to control for physical characteristics of the faces. Faces were followed by a blank screen that remained until a response was made. Participants were instructed to answer as quickly and as accurately as possible with one out of three fingers of their right dominant hand. Participants first completed 30 practice trials using 5 faces not shown during the experimental blocks, followed by 6 blocks of 36 trials. Each block consisted of 6 trials of each cue/face combination, presented in random order.

**Questionnaires**

Depressive symptoms were measured using the BDI-II (Beck, Steer, & Brown, 1967) and the HAM-D (Hamilton, 1960). The BDI-II is a 21-question, multiple-choice, self-report inventory, examining the severity and the occurrence of cognitive, affective, somatic and vegetative symptoms of depression during the last two weeks. The HAM-D is a semi-structured interview, evaluating the severity of depression. The interview consists of 21 items and explores depressed mood, vegetative (e.g., insomnia, fatigue, anorexia) and cognitive symptoms and comorbid anxiety disturbances.

**EEG recording**

Continuous EEG was acquired using a 128-channel (pin-type) Biosemi Active Two system (http://www.biosemi.com) referenced to the CMS-DRL ground with an analog bandpass. The data was digitized at a 24-bit resolution with a Least Significant Bit (LSB) value of 31.25 nV and a sampling rate of 512 Hz, using a low-pass fifth order sinc filter with a -3dB cutoff point at 102 Hz. ERPs of interest were computed offline following a standard

sequence of data transformations (Picton et al., 2000): (1) -250/+1500 ms segmentation around the onset of word (cue) stimulus and -500/+2000 ms segmentation around the onset of the face (target) stimulus (2) pre-stimulus interval baseline correction (from -250 ms to the cue onset, and from -500 ms to target onset), (3) vertical ocular correction for blinks (Gratton, Coles, Donchin, 1983) using the difference amplitude of two electrodes attached above and below the left eye, (4) artefact rejection [*M*=84.47 trials, *SEM*=1.98 amplitude scale (μV) across participants: no difference between ND (*M*=86.32 trials, *SEM*=2.56) and MDD patients (*M*=82.63 trials, *SEM*=3.04) was evidenced; $t$=0.93, $p$=.36], (5) averaging of trials, separately for each group (ND vs. MDD) and experimental condition (n=6), and (6) 30 Hz low pass digital filtering of the individual average data.

**Topographical analyses**

In order to capture ERP differences between ND and MDD patients, a detailed topographic mapping analysis of the ERP data was performed, following a conventional data-analysis scheme (Michel et al., 2001; Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005a; Pourtois, Thut, de Peralta, Michel, & Vuillemier, 2005b). To precisely characterize topographic modulations over time and across conditions, a standard spatial cluster analysis was used. This pattern analysis efficiently summarizes a complex ERP data set into a smaller number of dominant field configurations, previously referred to as functional microstates (Lehman & Skrandies, 1979). The rationale and basic principles of this temporal segmentation method have been extensively described elsewhere (e.g., Murray, Brunet, Michel, 2008). Following standard practice, a topographic pattern analysis was first performed on the grand-average ERP data from stimulus onset until 2000 ms after stimulus onset (1000 consecutive time frames at 512 Hz sampling rate), using a standard K-means cluster method (Pascual-Marqui, 2002). The optimal number of topographic maps explaining the whole data set was determined objectively using both cross validation (Pascual-Marqui, 2002) and Krzanowski-

Lai criteria (Tibshirani, Wallther, & Hastie, 2001). The dominant scalp topographies (identified by the previous analysis) were then fitted back to the ERP data of each individual subject using spatial fitting procedures to quantitatively determine their representation across subjects and conditions. This procedure thus provides fine-grained quantitative values, such as the duration or strength (Global Field Power – GFP), which are critical estimates of the significance of a given topography, not available otherwise in a classical component analysis (Picton et al., 2000). The resulting duration or strength (GFP) values were entered in mixed ANOVAs with the between-subject factor group (ND vs. MDD) and the within-subject factors emotion (happy, sad) and condition (actual, opposite, press). These analyses were carried out using CARTOOL software (Version 3.34; developed by D. Brunet, Functional Brain Mapping Laboratory, Geneva, Switzerland). Given that the cue locked CNV (as a function of the amount of proactive control to be exerted, see below) has typically been associated with amplitude changes in previous ERP studies (see Brunia et al., 2001), the CNV component was expected to vary in amplitude. On the other hand, no such prediction can be made regarding the expression of the reactive component (likely affecting the amplitude or latency of the ERP signal time-locked to the onset of the imperative face stimulus).

**Source localization analyses**

To estimate the likely neural sources associated with the dominant electrical field configurations identified by the previous analyses, a specific distributed linear inverse solution was used, namely standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002).[2] A direct comparison between the inverse solution results for the

[2] sLORETA is based on the neurophysiological assumption of coherent coactivation of neighboring cortical areas (known to have highly synchronized activity, see Silva, Amitai, & Connors, 1991) and, accordingly, it computes the "smoothest" of all possible activity distributions (i.e. no a-priori assumption is made regarding the number and locations of the sources). Mathematical validation of this distributed source localization technique has been demonstrated (Sekihara, Sahani, & Nagarajan, 2005). sLORETA solutions are computed within a three-shell spherical head model co-registered to the MNI152 template (Mazziotta et al., 2001). The source locations were therefore given as (x, y, z) coordinates (x from left to right; y from posterior to anterior; z from inferior to superior). sLORETA estimates the 3-dimensional intracerebral current density distribution in 6239 voxels (5 mm resolution), each voxel containing an equivalent current dipole. This 3-dimensional solution space in which the inverse problem is solved, is restricted to the cortical gray matter (and hippocampus). The head model for the inverse solution uses the electric potential lead field computed with a boundary element method applied to the

opposite-sad and actual-sad condition (MDD patients) was performed separately for the cue and target-related activity, using paired t-tests. To reveal significant effects, we used a stringent non-parametric randomization test (relying on 5000 iterations) using a corrected $p<.05$ value.

## Results

Because of technical problems, data from one healthy participant (n=19) and one patient from the MDD group (n=19) were omitted from the analyses of the behavioral and electrophysiological data.

### Demographics and self-report data

Table 1 summarizes demographic, clinical, and self-report data. Groups did not differ on any demographic variable (*p*s>.05).

### Behavioral data

We refer to Figure 2 for an overview of median RT data for correct responses. Accuracy rates ranged between 90.69% and 96.88%, with no difference between groups, *t*s<1.65 & *p*s>.1. Therefore, only trials for which participants made a correct response were included in the analysis. The *Cue* (opposite, actual, press) x *Emotion* (sad, happy) x *Group* (ND, MDD) ANOVA with the median RTs as dependent variable revealed a three-way interaction, $F(2, 35)=4.41$, $p=.02$, $\eta_p^2=.20$ (also all the main effects were significant, *F*s>9.89, *p*s<.005, as well as the interaction between *Cue* x *Group*, $F=9.03$, $p<.001$, and *Cue* x *Emotion*, $F=11.36$, $p<.001$.

Follow-up independent t-tests revealed that RT in MDD patients were not different from ND controls following the press trials, *t*s<1.42, *p*s>.17. MDD patients demonstrated, on the other hand, increased response latencies on the four other CECT trials (“opposite-sad”, “opposite-happy”, “actual-sad” and “actual-happy”), *t*s>4.18, *p*s<.001. However, as

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MNI152 template (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5% system (Jurcak, Tsuzuki, & Dan, 2007). The calculation of all reconstruction parameters was based on the computed common average reference. sLORETA units were scaled to ampere per square meter (A/m2).

hypothesized, within-group analysis revealed that MDD patients demonstrated greater RT to "opposite-sad" than "opposite-happy" trials, $t(18)=2.24$, $p=.04$, whereas the ND participants had balanced RT for both CECT trials, $t(18)=.78$, $p=.46$. Both groups had greater RT on "actual-sad" than "actual-happy" trials, $p$s<.001, but did not differ in RT to "press-sad" and "press-happy" trials, $p$s>.31

**ERP Data**

Figure 3 presents, for each group separately, the grand average ERP waveforms at electrode FCZ for either cue/word or target/face related activities.

**Topographical components**

**Target.** A spatio-temporal cluster analysis was performed on a large time-window (i.e. 2000 ms), encompassing the early (P1 and N170), mid-latency (P2) and late (N2 and P3) ERP components generated in response to the happy or sad faces. A solution with 10 dominant maps/topographies explained 93% of the variance. Remarkably, consistent with our prediction, this cluster analysis disclosed a dominant topography that was diagnostic of the condition "opposite-sad", for the MDD group selectively. This field configuration lasted ~400 ms, starting 650 ms following stimulus onset. This topography was characterized by a positive component over centro-parietal scalp leads, accompanied by a left-lateralized negative component over frontal/pre-frontal electrode locations (see Figure 4A). Following standard practice, a fitting of this dominant map back to the individual ERP data was performed to verify, at the statistical level, whether this topography was diagnostic of the "opposite-sad" condition, selectively for the MDD group. The dependent variable was the degree of similarity between the grand average topographical template (identified by the previous analysis) and the single-subject data. The duration values, obtained for this dominant map after fitting, were submitted to a 2 (*Group*) x 2 (*Emotion*) x 2 (*Cue*) mixed ANOVA. This analysis revealed a three-way interaction, $F(2, 35)=3.450$, $p=.04$. Whereas for the ND group,

the duration of this dominant topography did not vary depending on emotion and cue [interaction, $F<.7$, $p>.54$], it tended to do so in the MDD group [interaction, $F(2, 17)=2.96$, $p=.08$]. As can be seen from Figure 4B, in the MDD group only, this topography had a longer duration for the condition "opposite-sad" than for all other conditions. The direct comparisons between "opposite-sad" vs. "actual sad", $t(18)=2.56$, $p=.02$, and "opposite-sad" vs. "opposite-happy", $t(18)=3.19$, $p<.01$, confirmed a prolonged duration of this dominant topography selectively for the condition "opposite-sad".

**Cue.** A similar data-driven analysis was used to explore possible topographic changes across cues and between groups occurring prior to the onset of the imperative face stimuli, namely during the processing of the cue foreshadowing the type of visual categorization to be made by participants. The spatio-temporal cluster analysis was performed on a large time-window (i.e. 1500 ms), encompassing the early, mid-latency and late ERP components generated in response to the three possible cues ("press", "actual" or "opposite"). This analysis disclosed a solution with 8 dominant topographies accounting for 93% of the variance. A visual inspection of these maps (ND group) showed that early sensory processing of the cue (bilateral P1 and N1 occipital components) was later followed, after a transition phase where sustained mid-latency ERP components were generated, by a clear-cut CNV component (dominant topography), whose expression was most obvious starting 1000 ms following cue onset and showing a sustained effect until 1500 ms post-cue onset. Therefore, this prolonged time-interval (i.e. 1000-1500 ms post-cue onset) was used to assess whether the dominant CNV topography (characterized by a fronto-central negative activity, see Figure 5A) underwent change in strength depending on the task demands/conditions, as well as a function of the group (ND vs. MDD). Interestingly, during this time-interval, the amplitude of the CNV component appeared to be much reduced for the MDD patients, compared to the control participants. Moreover, for the ND participants only, the amplitude of this CNV

component varied according to the cue type, being the largest for the "press" instructions, but reduced alike for both the "opposite" and "actual" conditions. To corroborate these observations at the statistical level, the amplitude values, obtained for this dominant CNV map after fitting during this prolonged time-interval post-cue onset, were submitted to a 2 (*Group*) x 3 (*Cue*) mixed ANOVA. This analysis showed mains effects of *Group*, $F(1, 36)=33.68$, $p<.001$, and *Cue*, $F(2, 35)=6.58$, $p<.01$. Whereas the former effect confirmed that the strength of the CNV was substantially reduced for MDD patients compared to controls, the latter indicated a change in the amplitude of the CNV component depending on the cue type. Interestingly, as can be seen from Figure 5B, paired t-tests showed that for the ND participants, the CNV had the largest amplitude for the press condition than either the "actual", $t(18)=2.80$, $p=.01$, or "opposite" cue, $t(18)=2.31$, $p=.03$. These two latter cues ("actual" and "opposite") were not different with one another, $t(18)=1.64$, $p=.12$. In MDD patients, the CNV component was not different between cues "opposite" and "press", $t(18)=0.88$, $p=.39$, suggesting that the preparatory processes (reflected by the CNV component) were similar in these two different conditions. Moreover, the CNV component in MDD patients was less negative in amplitude for "actual" compared to "press", $t(18)=2.28$, $p=.04$, suggesting that their impairment during the cue period was not general (or generic), but mainly concerned the "opposite" cue condition (because no difference in amplitude between "press" and "opposite"). No difference for the amplitude of the CNV component was found between "actual" and "opposite" cue conditions, $t(18)=0.99$, $p=.34$.

**Inverse solutions**

**Target.** A source localization analysis based on sLoreta showed that the configuration of the intracranial generators associated with this dominant topography (ERPs for the target faces) mainly involved bilateral dorsal medial frontal cortex brain areas, with a maximum found in Brodmann area 6 (X= ±5, Y=-25, Z=54), with a notable spread of this broad

activation towards more ventral medial frontal sites, including the ACC-Brodmann area 24 (X=±4, Y=-17, Z=45; see Figure 4C). Next, a direct statistical comparison was performed in the inverse solution space to establish whether this enhanced medial frontal cortex activation was significant for the "opposite-sad" condition or not. For this purpose, we compared for the MDD patients the processing of the exact same face stimuli (namely sad faces) but when they were either associated with an opposite stimulus-response mapping ("opposite-sad") or the normal/intuitive one ("actual-sad"). A 100 ms interval was selected during which the dominant topography (see above) associated with the "opposite-sad" condition in the MDD group was found to be maximal (i.e. 800-900 ms time-interval post-stimulus onset). This contrast revealed a stronger bilateral dorsal ACC (BA 24) activation for "opposite-sad" than "actual-sad" (X=±5, Y=-15, Z=41; $t(18)=2.28$, $p<.025$), stimuli.

**Cue.** During the time interval corresponding to the dominant CNV topography (1000-1500 ms post-cue onset), the statistical comparison in the inverse solution space (sLoreta) was compared between the condition "opposite" vs. "actual", for the MDD patients selectively. Since the CNV in MDD patients during the "opposite" condition (where proactive control was required) showed an abnormal response profile (e.g. it was not numerically different compared to the CNV recorded during the baseline control condition "press"; see here above), this contrast enabled shedding light on possible impaired proactive or preparatory brain processes during the anticipation (foreperiod) for the "opposite" condition in the MDD group. This contrast revealed that "opposite" led to a larger activity than actual within a distributed network, involving mainly the right middle frontal gyrus (X=+21, Y=+22, Z=+44; $t(18)=2.41$, $p<.025$], and the precuneus on both sides (X= ±15, Y=-59, Z=+24; $t(18)=2.30$, $p<.025$] (see Figure 5C). This contrast revealed a stronger bilateral dorsal ACC (BA 24) activation for "opposite-sad" than "actual-sad" (X=±5, Y=-15, Z=41; $t(18)=2.28$, $p<.025$), stimuli.

## Discussion

The goal of the present study was to examine whether deficits to inhibit attention to negative information in MDD patients were related to anomalies in proactive and/or reactive cognitive control.

Behavioral results showed that, over all participants: 1) the processing of the actual emotion was faster for happy than sad faces; and 2) the difference between actual and opposite cues was greater for positive than negative faces. This pattern is consistent with a general positivity bias; i.e. participants are faster at categorizing stimuli as positive than categorizing stimuli as negative. Importantly, in MDD only, behavioural data showed a selective slowing of responses when actively inhibiting a dominant response to a sad face and being required to use the alternative (opposite) response mapping, i.e., to press the happy face response key. This emotion specific deficit in MDD is in accordance with prior research (e.g., Joormann & Gotlib, 2008), and indicates that these patients encounter selective difficulties in overriding habitual (dominant) responses to negative information and in turn select an alternative (and counter-intuitive) stimulus-response mapping in this condition.

For this “opposite-sad” condition, analyses of the ERP data - time-locked to the onset of the target faces - revealed a significant longer duration of a dominant topography than the other conditions in MDD patients. The reconstructed intracranial generators of this dominant topography involved bilateral dorsal medial frontal areas, with a spread towards ventral medial frontal sides, including the ACC. Crucially, this ACC area was significantly more active (800-900 msec post-stimulus onset) for MDD patients when they were required to process sad faces but had to categorize them as positive (happy), the condition eliciting the maximum interference (and hence conflict) at the behavioral level in these patients. The ACC

is known to be a critical hub for performance monitoring, and - following dominant models - conflict-related ACC activations usually reflect the need to exert additional top-down control in the face of conflict or error (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Possibly, the current ERP results suggest that MDD patients needed to spark enhanced conflict-related dorsal ACC activity following the onset of sad faces that had to be categorized as happy faces, in order to overcome this strong interference effect. Although the reason for the increased ACC activity in this 'opposite-sad' condition is unclear at the moment (i.e., it could reflect either compensatory processes or enhanced conflict detection), this result confirms the assumption of abnormal reactive control in major depression (Drevets, Price, & Furey, 2008), specifically when inhibiting attention to negative information.

Noteworthy, relative to ND participants, our results also showed proactive control abnormalities in MDD patients. In the ND group, the CNV component was found largest (i.e., more negative) when these healthy individuals anticipated a simple detection task ("press"), than the two other conditions requiring active maintenance of a complex task goal in working memory and hence, enhanced proactive control ("actual" and "opposite"). This association between CNV amplitudes and task demands or working memory load expressed by the cue is consistent with earlier ERP results in the literature (McEvoy, Smith, & Gevins, 1998; Gevins et al., 1996; tecce, 1972). Interestingly, the current ERP results showed that the cues "actual" and "opposite" had a comparable CNV amplitude change, which is in line with the DMC framework. This account states that "*Under proactive control conditions, prefrontal cortex activity should be present reliably across events, and not just on those in which it is most needed*" (Braver et al., 2007, pp. 89). In sum, these new electrophysiological findings suggest that healthy controls used, based on the specific instructional cue, a proactive strategy to actively maintain goal relevant information in working memory.

Strikingly, no such amplitude modulation of the CNV component (as was observed in the ND) was evidenced for MDD patients (i.e. only the cue "actual" led to a lower CNV amplitude than the cue "press", while the cue "opposite" was associated with a CNV that was equally large as for the cue "press"). Even though research is scarce on this topic, prior studies reported abnormal CNV amplitudes in individuals with MDD (Ashton et al., 1994; Ashton et al., 1988; Giedke & Bolz, 1980; Timsit-Berthier, 1993). The reasons as to why abnormal proactive control is "spontaneously" exerted by MDD patients during the foreperiod are not entirely clear yet at this stage. However, the possibility that this effect is simply caused by an overall breakdown in motivation or a cease in cognitive processing in MDD can be ruled out. This is because MDD patients showed a condition specific reactive effect, i.e. a differentiation between "opposite-sad" and "opposite-happy" trials at the behavioral and electrophysiological levels. Interestingly in the current study, CNV amplitudes in MDD patients were robustly decreased in general (i.e., more positive amplitudes for the three cue types). Such decreased CNV amplitudes have been related to problematic attentional resource allocation caused by mind wandering, daydreaming or active distraction by some other task (Rousseau, Bostem, & Dongier, 1968; Tecce, 1972; Travis & Tecce, 1998; Tecce & Cattanach, 1993; Travis, Tecce, Arenander, & Wallace, 2002; Travis, Tecce, & Guttman, 2000). Moreover, it is also assumed that CNV amplitudes reflect deficient ability to engage attention to the current task goal, and away from potentially depressogenic thinking or rumination (Bostanov et al., 2012). These assumptions are in line with our current research findings, for which – in the MDD only - the cue "opposite" led to a significantly larger activity than cue "actual" within a distributed network, involving mainly the right middle frontal gyrus and the precuneus on both sides. Interestingly, these two non-overlapping brain regions are typically related to the default mode network, being mostly responsive at rest and hypothesized to generate spontaneous thoughts or internally-guided (as opposed to external-

driven) mental processes, such as mind wandering (Raichle et al., 2001). Possibly, engaging in internal guided mental processing, such as mind wandering, might have distracted MDD patients from anticipating the upcoming imperative stimulus, leading to inefficient proactive control. Presumably, an exaggerated internal focus, which is known to consume important processing resources (Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010), prevented a sharpening of their cognitive resources during the foreperiod, although these patients never stopped processing during the anticipation period. Alternatively, as it is assumed that a more negative CNV amplitude corresponds to more cognitive efforts (McEvoy, Smith, & Gevins, 1998; Gevins et al., 1996; Tecce, 1972), this CNV pattern might reflect the fact that MDD patients, compared to ND, were perhaps exerting too much proactive control. Hence, in this scenario, MDD patients would show abnormal cognitive control because of an exaggerated or too high level of proactive control during conflict anticipation. In sum, these cue-locked findings suggest abnormal anticipation in MDD, i.e. abnormalities to maintain online, into short term memory, active goal relevant representations to adjust cognitive resources based on the specific instructional cue. Future studies are needed to establish whether this effect corresponds either to an abnormally low or high proactive control in these patients.

All together, our results provide evidence that the observed deficit to inhibit attention to negative information in MDD found at the behavioral level, might stem from a combination of abnormal proactive and reactive control mechanisms. The DMC framework posits that both modes of control are complementing, and the computational trade-off between both is dependent on individual differences. More specifically, based on this model, individuals scoring high on the Behavioral Approach System (BAS) show an increased tendency to use proactive cognitive control, whereas individuals scoring high on Behavioral Inhibition System (BIS) show an increased predisposition to use reactive control. It is well known that MDD patients are characterized by lowered BAS but overactive BIS activations (Kasch, Rottenberg,

Arnow, & Gotlib, 2002). In line with predictions of the DMC account, the present findings suggest that MDD patients are less able - than non-depressed individuals - to proactively use effective cognitive control resources during the foreperiod foreshadowing the onset of the imperative face stimulus. The DMC further suggests that affect-related traits influence the cost-benefit balance between proactive vs. reactive control during goal-directed performance monitoring (Braver, 2012). Although the present findings do not offer statistical evidence for a trade-off between both modes of cognitive control in MDD in the "opposite-sad" condition ($r19=.14$, $p=.55$ for the correlation between CNV topography and LPC topography), it might be that - based on predictions from the DMC - inefficient proactive control leads to an increased need of reactive control in order to overcome a strong interference at the behavioural level. In other words, MDD patients might be less able than non-depressed individuals to proactively employ cognitive control resources during the foreperiod foreshadowing the onset of the imperative face stimulus, which would result a greater conflict in the case this stimulus carries an interfering negative emotional expression. The non significant correlation between CNV and LPC (as observed here) does not contradict this latter prediction derived from the DMC framework, however. Indeed, neither the CVN, nor the LPC is uniquely related to cognitive control processes (proactive and reactive, respectively). Instead, each of these two ERP components/topographies appears to capture some variance related to cognitive control (besides other processes), but does not equate it. Accordingly, finding a significant correlation between these two distant neural events during cognitive control and conflict monitoring appears unlikely given that these two ERP components are not reflecting pure measures of these cognitive processes. Further research is needed to establish whether abnormal reactive control effects regarding the inhibition of attention to negative information in depression could be predicted by systematic and traceable

neurophysiological changes taking place earlier in time and corresponding to proactive control processes, as put forward in the DMC framework.

Some limitations of the present study should be mentioned. The majority of the MDD patients were on antidepressant medication (+/- 80%), which might have influenced cognitive functioning, even though medication alone cannot a priori account for interaction effects between cue type and emotional face content reported in our study. Moreover, only patients who had either serotonergic or noradrenargic antidepressants were included, for at least 2 weeks prior to testing, hence ruling out the possibility of acute effects of these specific drugs on the reported behavioral and/or electrophysiological results. Also, patients who had received anti-psychotics, monoamine oxidase inhibitors, tricyclic antidepressants and/or benzodiazepines, medications which are known to be associated with cognitive impairments, were excluded. Finally, it should be noted that although we are confident that these behavioral and ERP results cannot be explained easily by task-difficulty alone, it remains challenging nowadays to demonstrate modulatory effects of depression on cognitive control and conflict detection, which are eventually fully orthogonal to changes in task difficulty. Given that conflict typically arises in situations where interference is created and for which RT and error rate will by definition increase, it is important to ascertain that depression influences conflict detection processes specifically, rather than taxing difficult trials more generally.

In sum, our results showed that the observed inhibitory deficit for negative information in MDD found at the behavioral level might stem from inefficient proactive control (possibly due to excessive internally-focused processing that consumes important processing resources) and an abnormal reactive control.

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## Figures legend

Figure 1. Schematic overview of the Cued Emotional Conflict Task (CECT). First, a cue is presented in the centre of the screen ("actual", "opposite", or "press"), followed by a face with an emotional expression (either happy or sad), leading to six possible cue-face combinations/conditions. ISI=interstimulus interval; ITI=intertrial interval.

Figure 2. Median reaction time data (and standard deviations) (in ms) for correct CECT trials, both in the ND (n=19) and the MDD (n=19) sample. MDD patients demonstrated significantly greater RT to "opposite-sad" than "opposite-happy" trials, whereas the ND participants had balanced RT for both CECT trials. Both groups had significantly greater RT on "actual-sad" than "actual-happy" trials but did not differ in RT to "press-sad" and "press-happy" trials.

Figure 3. Grand average ERP waveforms at electrode FCZ, separately for the cue/word (upper panels) and the target/face (lower panels). (A) In the ND group, a clear modulation of the CNV component was evidenced at a late latency following cue onset, indicated by a larger amplitude for the "press" than both "actual" and "opposite". (B) In the MDD group, no similar amplitude variation of the CNV component was visible. (C) In the ND group, no systematic amplitude variation of the ERP signal was visible across the four main experimental conditions. (D) By contrast, in the MDD group, starting 650 msec post-stimulus onset, the opposite sad condition clearly elicited a differential ERP activity during a

prolonged time interval (indicated by the vertical red arrows), compared to the three other experimental conditions.

Figure 4. (A) Grand average ERP data (opposite sad, MDD patients) time-locked to the onset of the imperative (sad) face stimulus and shown using a standard butterfly plot (overlaid traces), including all 128 channels. The vertical dashed line indicates the onset of the imperative face stimulus. The topographical segmentation analysis showed that a dominant and diagnostic scalp configuration had a prolonged duration ~650-1050 msec post-face onset (highlighted by the shaded orange frame), in this condition, selectively for the MDD patients. This topography was characterized by a dipolar field including a left-lateralized lateral (pre)fontral negativity and a central posterior-parietal positivity. (B) The fitting of this dominant topography (see methods) revealed a condition and group specific effect. The duration of this topography was the longest in the opposite sad condition than the other experimental conditions in the MDD group, with no such variation seen across conditions for the ND group. *p<.05; **p<.01. (C) Source localization results for this dominant topography. A direct statistical comparison (MDD patients) in the inverse solution space (sLoreta) between opposite sad and actual sad (800-900 msec post-face stimulus onset) revealed a stronger dorsal ACC activity in the former than the latter condition. A sagital and coronal views are provided.

Figure 5. (A) Grand average ERP data (“press” condition, ND group) time-locked to the onset of the cue and shown using a standard butterfly plot (overlaid traces), including all 128 channels. The vertical dashed line indicates the onset of the (press) cue. The topographical segmentation analysis showed that a dominant and diagnostic scalp configuration had a larger amplitude (indexed by changes in the GFP) for the “press”, than either the “actual” or

“opposite” conditions in the ND group, ~1000-1500 msec post-cue onset (highlighted by the shaded purple frame). This topography was characterized by a central negativity sharing many similarities with a standard CNV component (latency, polarity and amplitude). (B) The fitting of this dominant CNV topography (see methods) revealed an increased amplitude (GFP) in the “press” compared to the two other experimental conditions (“actual” and “opposite”) in the ND group. However, in the MDD group, the CNV was substantially reduced compared to the ND group, and moreover, the CNV amplitude was not numerically lower for “opposite” than “press”, suggesting an abnormal proactive control effect. The CNV for “actual” was lower in amplitude than for “press”. *$p<.05$. (C) Source localization results for this dominant CNV topography. A direct statistical comparison (MDD patients) in the inverse solution space (sLoreta) between opposite sad and actual sad (1000-1500 msec post-cue stimulus onset) revealed a stronger middle frontal gyrus and precuneus (posterior parietal cortex) activity in the former than the latter condition. A sagital and two coronal views are provided (dashed lines: middle fontal gyrus; dotted lines: posterior parietal cortex/precuneus).

*Table 1. Demographical and clinical data.*

| | **ND n=19** | | **MDD n=19** | | **Statistics** |
|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | ***t*** |
| **Age** | 40.11 | 14.09 | 37.89 | 13.30 | 0.50 |
| **% Female** | 70% | N/A | 60% | N/A | 0.68 |
| **Number of depressive episodes** | N/A | N/A | 2.63 | 1.30 | N/A |
| **Age of onset depression (in years)** | N/A | N/A | 32.79 | 12.62 | N/A |
| **Duration present episode (in months)** | N/A | N/A | 6.95 | 5.51 | N/A |
| **BDI-II** | 1.53 | 3.79 | 34.21 | 10.84 | -12.41* |
| **HAM-D** | 0.21 | 0.54 | 28.26 | 5.04 | -24.11* |

*Note. BDI: Beck Depression Inventory-II; HAM-D: Hamilton Rating Scale for Depression*

**p*<.01.

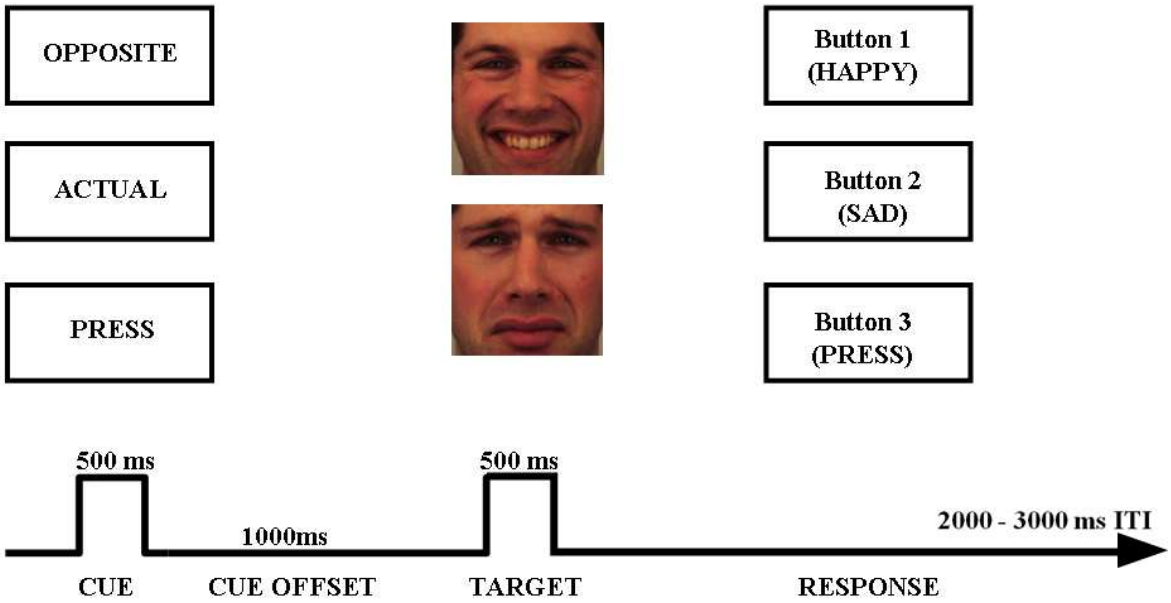
OPPOSITE
ACTUAL
PRESS
Button 1 (HAPPY)
Button 2 (SAD)
Button 3 (PRESS)
500 ms
1000ms
500 ms
2000 - 3000 ms ITI
CUE
CUE OFFSET
TARGET
RESPONSE

Figure1

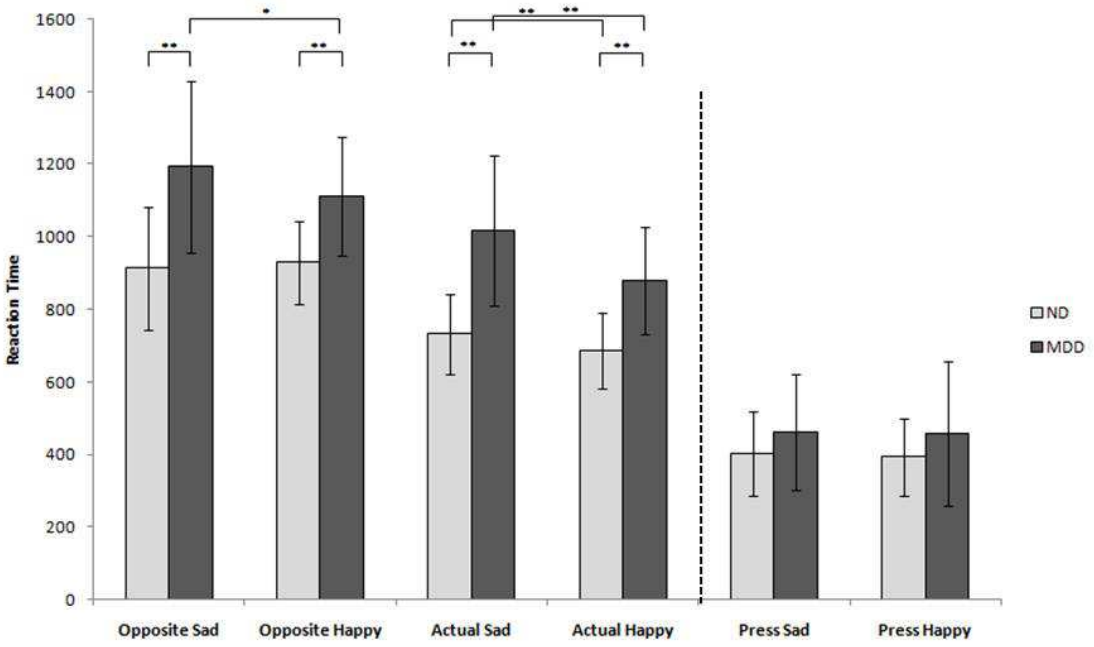
1600
1400
1200
1000
800
600
400
200
0
Reaction Time
*
**
**
**
**
**
**
Opposite Sad
Opposite Happy
Actual Sad
Actual Happy
Press Sad
Press Happy
ND
MDD

**Figure 2**

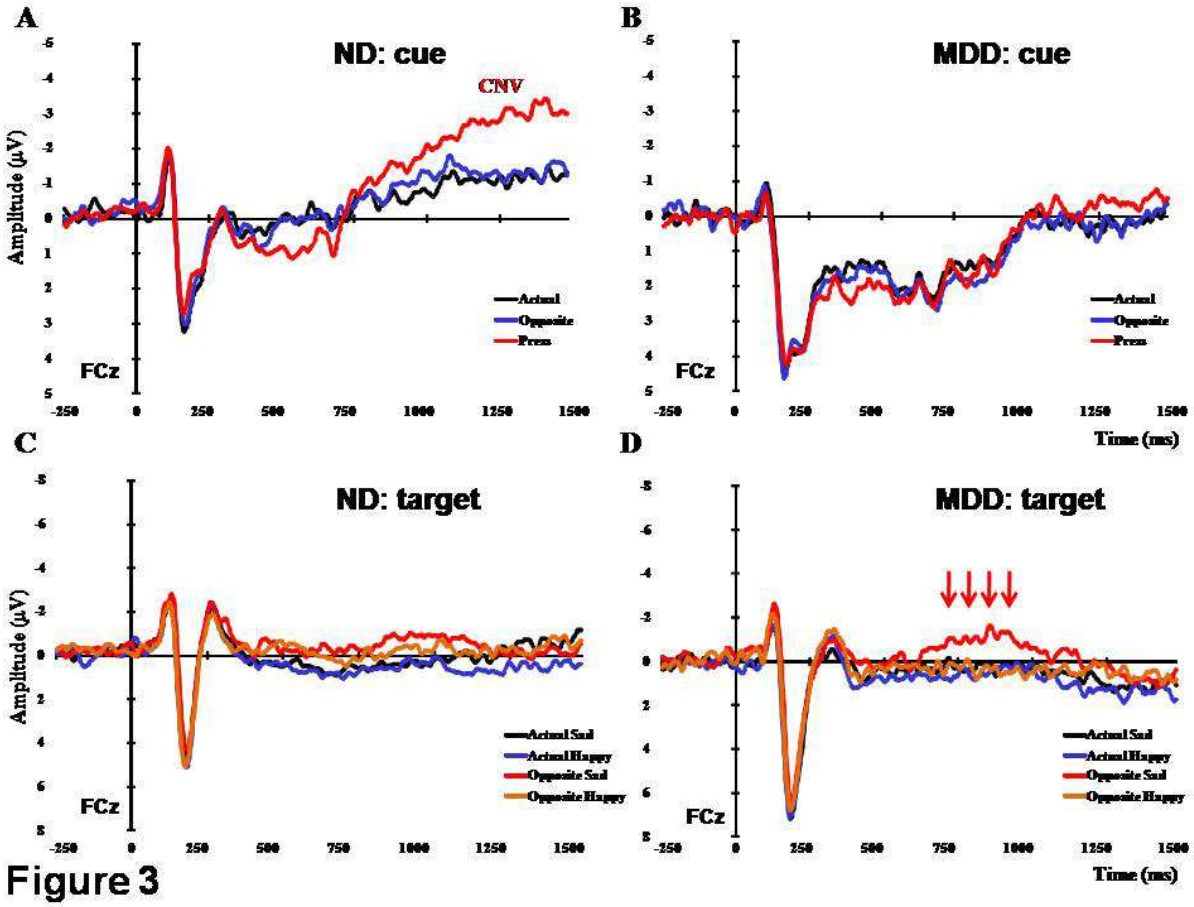
A
ND: cue
CNV
Amplitude (μV)
FCz
Actual
Opposite
Press
B
MDD: cue
FCz
Actual
Opposite
Press
Time (ms)
C
ND: target
Amplitude (μV)
FCz
Actual Sad
Actual Happy
Opposite Sad
Opposite Happy
D
MDD: target
FCz
Actual Sad
Actual Happy
Opposite Sad
Opposite Happy
Time (ms)

Figure 3

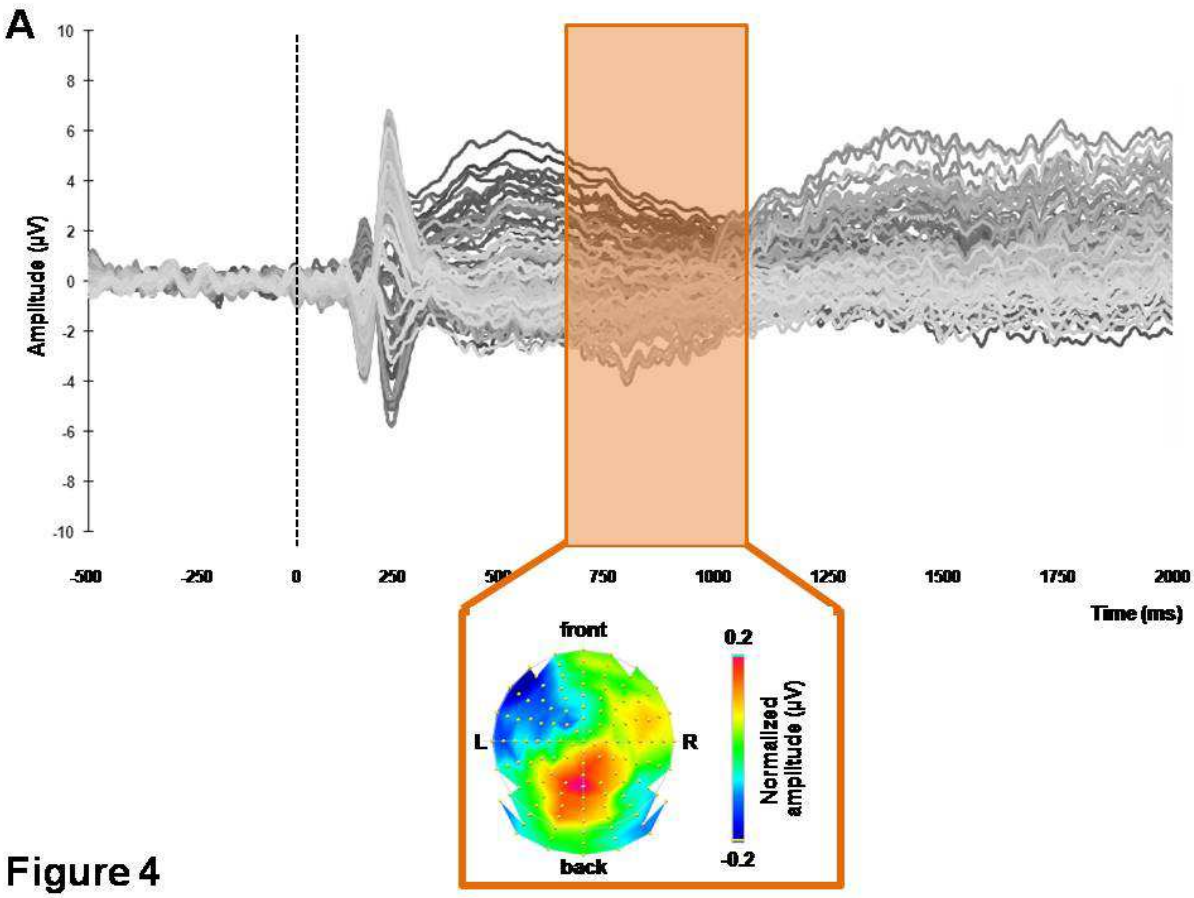
A
Amplitude (μV)
10
8
6
4
2
0
-2
-4
-6
-8
-10
-500
-250
0
250
500
750
1000
1250
1500
1750
2000
Time (ms)
front
back
L
R
0.2
-0.2
Normalized amplitude (μV)

Figure 4

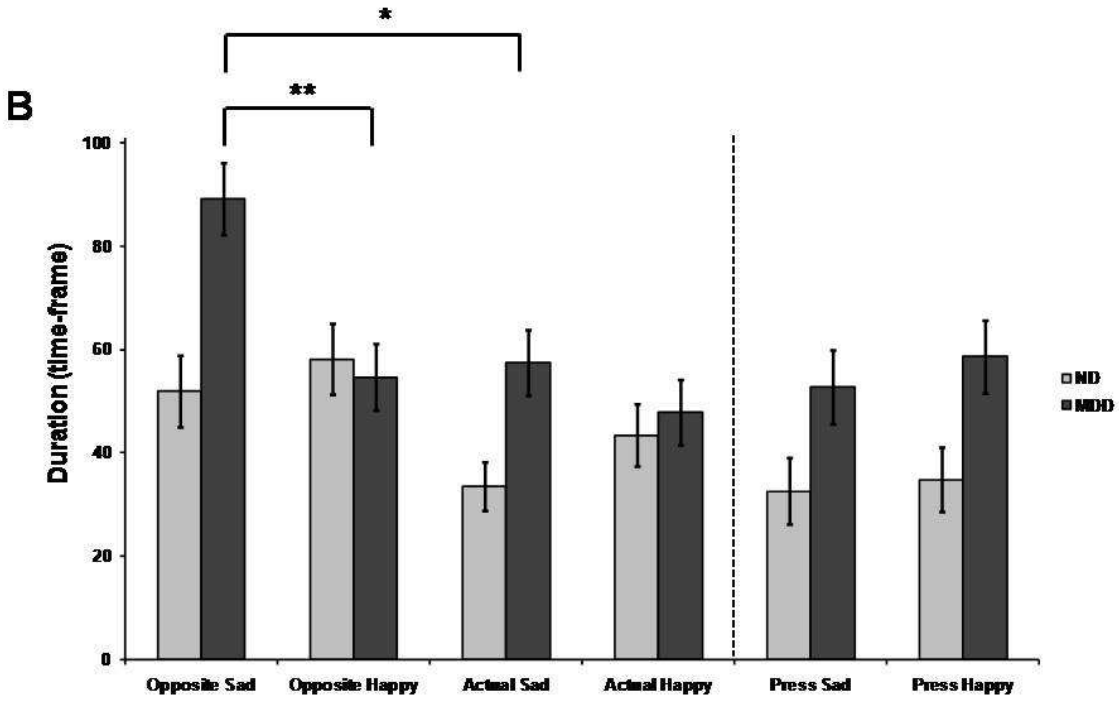
B
*
**
Duration (time-frame)
100
80
60
40
20
0
Opposite Sad
Opposite Happy
Actual Sad
Actual Happy
Press Sad
Press Happy
ND
MDD

Figure 4

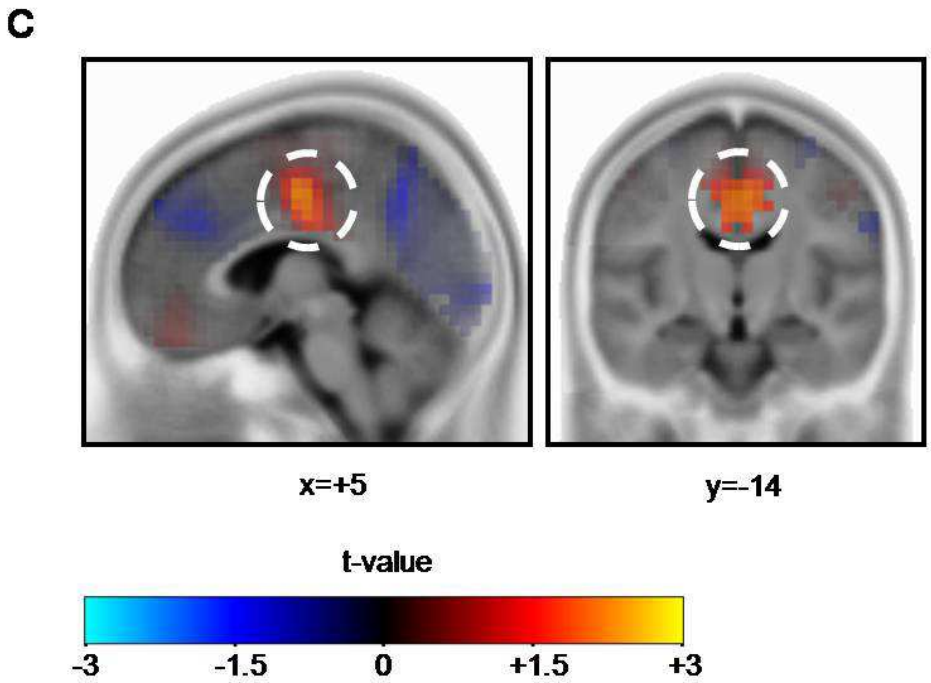


Figure 4

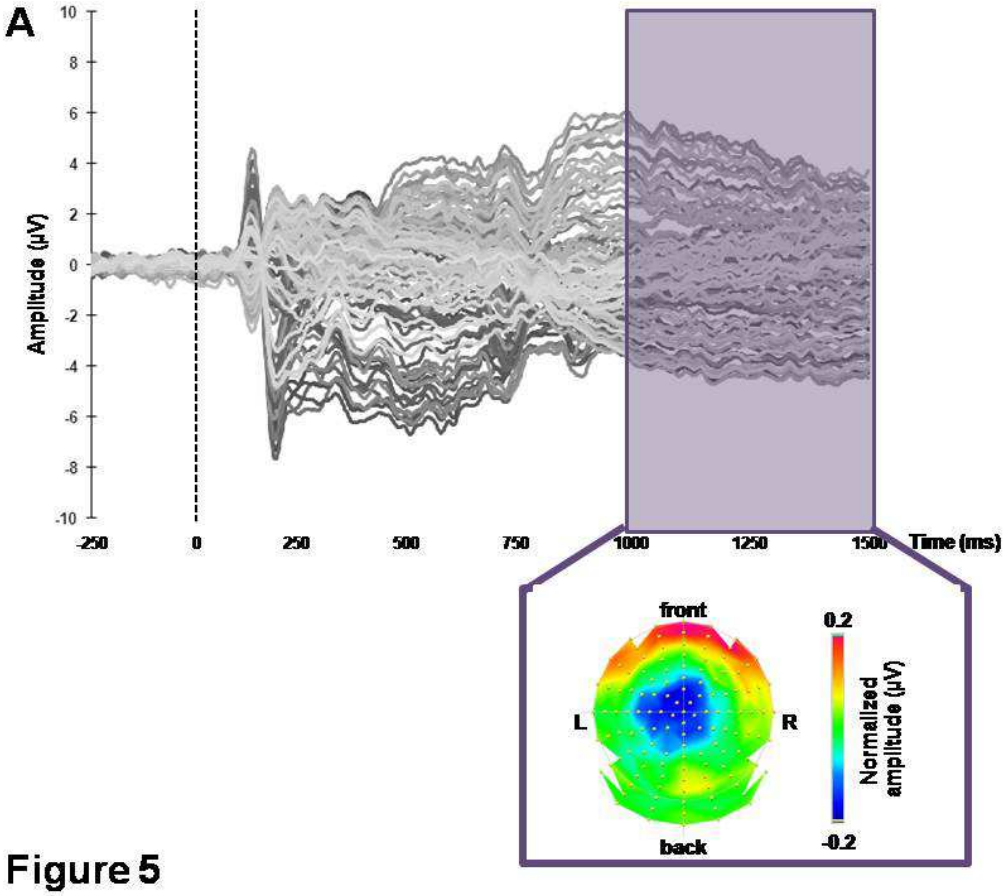
A
Amplitude (μV)
10
8
6
4
2
0
-2
-4
-6
-8
-10
-250
0
250
500
750
1000
1250
1500
Time (ms)
front
L
R
back
0.2
-0.2
Normalized amplitude (μV)

Figure 5

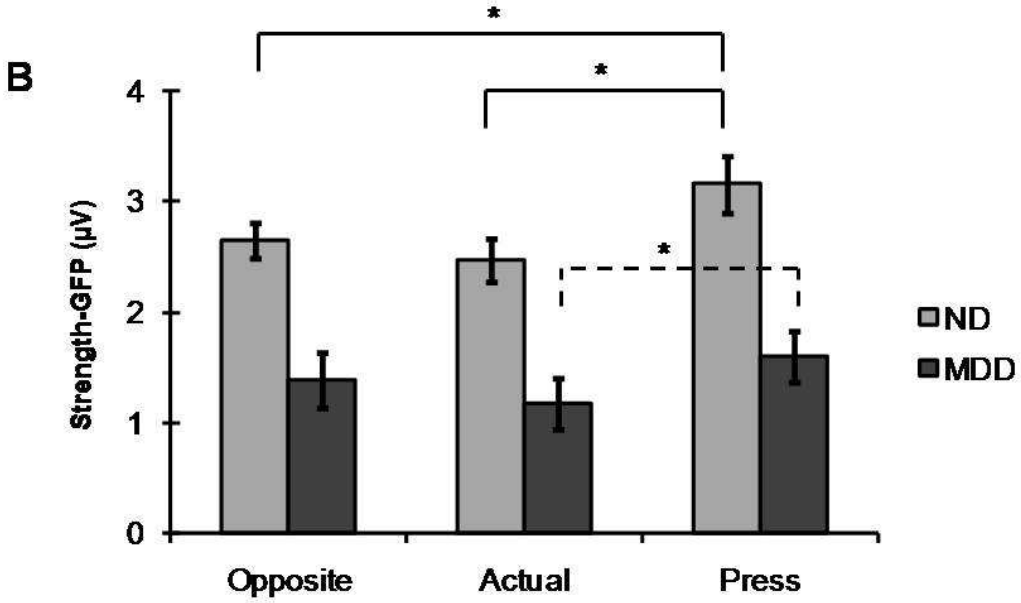


Figure 5

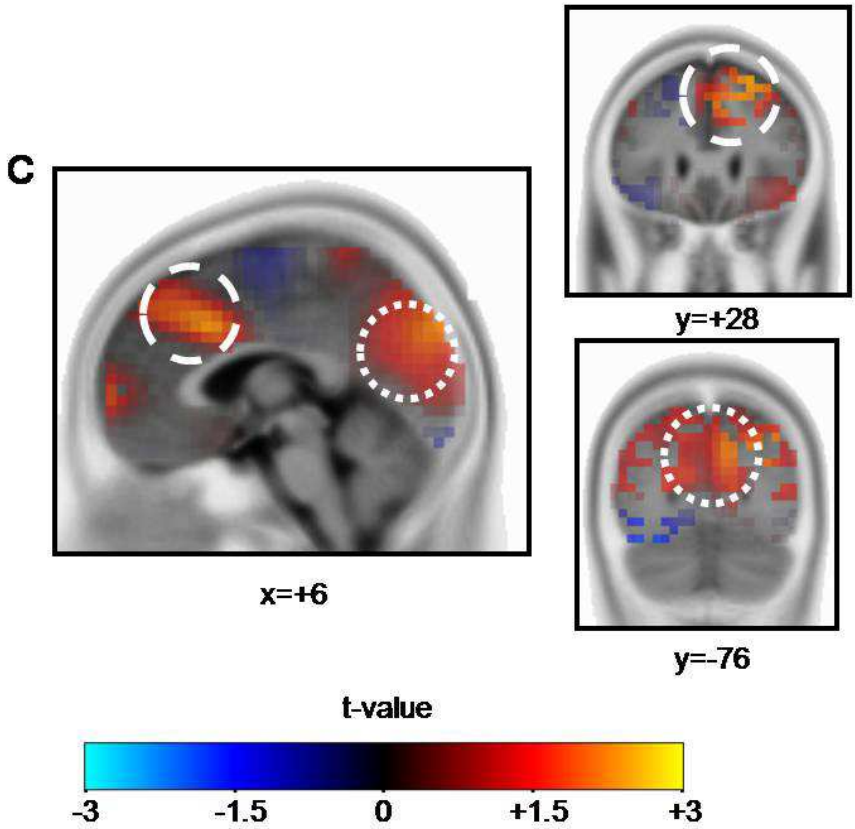


Figure 5