Voluntary Modulation of Anterior Cingulate Response to Negative Feedback

Matthew S. Shane1,2*, Christina R. Weywadt3

1 University of Ontario Institute of Technology, Oshawa, Ontario, Canada, 2 The Mind Research Network, Albuquerque, New Mexico, United States of America, 3 University of New Mexico, Albuquerque, New Mexico, United States of America

Abstract

Anterior cingulate and medial frontal cortex (dACC/mFC) response to negative feedback represents the actions of a generalized error-monitoring system critical for the management of goal-directed behavior. Magnitude of dACC/mFC response to negative feedback correlates with levels of post-feedback behavioral change, and with proficiency of operant learning processes. With this in mind, it follows that an ability to alter dACC/mFC response to negative feedback may lead to representative changes in operant learning proficiency. To this end, the present study investigated the extent to which healthy individuals would show modulation of their dACC/mFC response when instructed to try to either maximize or minimize their neural response to the presentation of contingent negative feedback. Participants performed multiple runs of a standard time-estimation task, during which they received feedback regarding their ability to accurately estimate a one-second duration. On Watch runs, participants were simply instructed to try to estimate as closely as possible the one second condition. Moreover, dACC activity correlated with post-feedback performance adjustments, and these adjustments were highest in the Increase condition. Potential implications for neuromodulation and facilitated learning are discussed.

Citation: Shane MS, Weywadt CR (2014) Voluntary Modulation of Anterior Cingulate Response to Negative Feedback. PLoS ONE 9(11): e107322. doi:10.1371/journal.pone.0107322

Editor: Emmanuel Andreas Stamatakis, University Of Cambridge, United Kingdom
Received December 23, 2013; Accepted August 15, 2014; Published November 6, 2014

Copyright: © 2014 Shane, Weywadt. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This project has been supported by an internal award by The Mind Research Network to MSS. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: matthew.shane@uoit.ca

Introduction

The ability to adaptively manage goal-directed behavior requires a consistent monitoring for, and adjustment to, indication of error in performed actions. To this end, electrophysiological and functional magnetic resonance imaging (fMRI) work have converged to demonstrate important neural signatures that appear sensitive to the receipt of feedback indicating goal-directed error [1–4]. This work originated with the identification of the feedback error-related negativity (fERN) – a unique electrophysiological signature that occurs reliably between 250–400 ms following the receipt of feedback indicating goal-directed error [1–2]. Source localization work has subsequently identified the likely source of this activity to the dorsal anterior cingulate cortex (dACC) and/or adjacent medial frontal cortex (mFC), and convergent fMRI work has confirmed a central role for dACC/mFC in the detection of negative feedback [3–4]. Contemporary models of reinforcement learning now stress that this dACC/mFC response likely reflects the generation of a critical neural reward-prediction error signal that indicates when outcomes do not occur as expected [5]. Indeed, several studies have reported that individuals with greater amplitude fERNs and/or increased dACC/mFC response to negative feedback show more adaptive post-feedback performance adjustment and/or greater operant learning proficiency [6–8]. This has led researchers to posit that dACC/mFC response to negative feedback represents not only a feedback detection system, but also a critical component for the adaptive selection and guidance of subsequent corrective behavior [9–10].

A burgeoning area of work has become interested in the extent to which brain activity may be responsive to adaptive modulation. Emerging technologies including transcranial direct current stimulation (TDCS) [11], transcranial magnetic stimulation (TMS) [12], and real-time functional magnetic resonance imaging (rt-fMRI) [13] have all shown potential for facilitating changes in specific neural firing patterns. More basic even, is complimentary work on “emotion regulation”, which has demonstrated that participants are capable of engendering changes in neural responses, simply through voluntarily-initiating up- or down-modulation of reactivity to presented stimuli [14–16]. In a standard emotion regulation paradigm, participants are shown a variety of emotionally-valet pictorial stimuli, and are simply asked to try to intentionally increase or decrease their responsiveness during stimulus processing. Evidence suggests that participants are quite capable of voluntarily modulating their neural responses in this fashion. Moreover, several studies have reported important relationships between voluntarily-induced modulation of neural responses, and subsequent changes in either behavior [17–18] or experience [19–20]. Thus, the ability to voluntarily modulate neural reactivity may be more than academic, and may offer a variety of useful real-world applications.
One such application could be the ability to foster improved sensitivity to information indicating error in goal-directed behavior. Increased sensitivity to error could promote improvements in cognitive control and/or operant learning proficiency. Decreased sensitivity to error could, in turn, prove adaptive for individuals with characteristic hypersensitivity to error (e.g., high-anxious populations) [21]. With this in mind, the present study sought to evaluate the extent to which participants could modulate their neural responses following the receipt of negative feedback within a standard time-estimation task (within which they received veridical positive or negative feedback indicating the accuracy of their attempts to estimate a one-second duration). Closely mirroring the technique employed in studies on emotion-regulation, each participant performed this task under three instructional conditions. In a Watch condition, participants performed the task normally, with standard instructions to estimate the one-second duration as accurately as possible. In Increase and Decrease conditions, participants were instructed to perform the same task, but to “try to increase [decrease] your brain’s response” as much as possible following the receipt of negative feedback. In this way, the study afforded a careful within-subject evaluation of the extent to which individuals could voluntarily modulate their neural responses to the presentation of contingent negative feedback. Of particular interest were changes in participants’ dACC/mFC response, given its well-established involvement in error-detection and action-monitoring. In addition, we sought to evaluate the relationship between dACC/mFC activity and post-feedback performance adjustments by evaluating changes in estimation attempts from trial n to trial n+1. We hypothesized that our sample of healthy individuals would show changes in dACC/mFC response following negative feedback in the direction instructed. Moreover, we hypothesized that these changes in neural response would be related to the magnitude of participants’ post-feedback performance adjustments.

Method
Participants
Eighteen healthy individuals (8 females) were recruited through advertisements posted on The University of New Mexico campus. Age ranged from 18 to 44 (M = 25.00, SD = 6.27).

Time Estimation Task
The time estimation task (depicted graphically in Figure 1) required that participants attempt to estimate as accurately as possible a one-second duration. Each participant performed 5 practice trials, followed by 60 experimental trials, all of which were similarly designed, and modeled after previous work [4]. Each trial began with a large asterisk presented on-screen for 1000 ms. Participants were informed that they should wait for the asterisk to disappear, and then try to press a button with their right index finger exactly 1000 ms after the asterisk’s offset. Following their button press was a randomly jittered interval (2000 ms, 3500 ms, or 5000 ms) to improve deconvolution from the standard hemodynamic response curve. Finally, participants received feedback regarding the accuracy of their estimate attempt. This feedback came in one of two varieties: on informative feedback trials, participants received either a plus sign (“+”) or a minus sign (“−”), which indicated whether their estimate was accurate or inaccurate on that trial. On uninformative feedback trials, participants received only a question mark (“?”), regardless of whether their estimate was accurate or inaccurate. These question mark trials were presented on exactly 50% of all accurate trials and 50% of all inaccurate trials. Thus four different trial types were possible (Informed-Accurate, Informed-Inaccurate, Uninformed-Accurate, Uninformed-Inaccurate), and each occurred with near-equal frequency. The uninformative trials may appear cumbersome, but constituted a critical component of the study design; because participants’ actual estimation accuracy could be matched across informative and uninformative trials, a direct comparison of these trials afforded a careful control for well-established effects of outcome anticipation on neural responses to feedback stimuli [5,22] (see Data Analytic Strategy section below for additional discussion within the present paper). Following a second jittered interval (2000 ms, 3300 ms, or 5000 ms) the next trial began.

Participants’ estimates were deemed accurate if they fell within a specified window surrounding 1000 ms. The initial window was set at ±250 ms; thus time estimates between 750 ms and 1250 ms received accurate feedback, and estimates that fell outside this window received inaccurate feedback. To ensure that participants received an equal number of accurate/inaccurate feedback trials, an adaptive algorithm was employed, such that the window of accuracy increased by 30 ms following each accurate estimate, and decreased by 30 ms following each inaccurate estimate. As in previous research, this algorithm allowed for the nearly equal presentation of positive (51.5% of all trials) and negative (48.5% of all trials) feedback trials in a manner that was undetectable by participants.

Procedure
After providing informed consent, participants completed 5 practice trials to familiarize themselves with the task. Following these practice trials, participants performed six separate 60-trial runs of the time-estimation task described above (two Watch runs, two Increase runs, two Decrease runs). Thus, participants completed 120 Watch trials, 120 Increase trials, and 120 Decrease trials of the task over the course of a single one-hour MRI session. All participants performed the two Watch runs first, to establish their baseline neural response to the positive and negative feedback, followed by the Increase and Decrease runs, which were presented in counter-balanced order. On Watch runs, participants were instructed to press a button as soon as they believed a one-second duration had expired following the offset of the presented asterisk. They were informed that they would receive accuracy/inaccuracy feedback, however no additional instructions were provided regarding how to process that feedback. On Increase and Decrease runs, participants were again instructed to estimate this one-second duration, but were explicitly instructed to “try to increase [decrease] your brain’s response every time you receive negative feedback”. Participants were not provided with instructions for how to accomplish this neuromodulation; rather, they were told that the intent of the study was to determine whether they could accomplish this by their own devices.

Ethics Statement
All procedures were approved by The University of New Mexico Internal Review Board, and were in accordance with the provisions of the World Medical Association Declaration of Helsinki. All participants provided written informed consent to participate in the study.

Data Acquisition
All fMRI data collection was performed using a Siemens TIM Trio 3 Tesla MRI system. Images were presented with a JVC DLA Multimedia projector (Model DLA-SX200-NLG) using E-Prime 2.0 software [25]. Thirty-two axial slices covering the whole
Trials were computed separately for each of the feedback under standard "passive-viewing" conditions, and compared against a contrast because we believe this contrast affords a more careful focus on the extent to which participants could follow the instruction to voluntarily increase or decrease their neural activity following receipt of the same Informed-Inaccurate feedback. Analyses thus evaluated Informed-Inaccurate > Uninformed-Inaccurate BOLD response within each of the three instruction conditions, and also evaluated the extent to which Informed-Inaccurate activity in the Increase and Decrease conditions differed from activity in the Watch condition.

For authenticity, we also report results for the Informed-Inaccurate > Informed-Accurate contrast; however, we primarily focus on the Informed-Inaccurate > Uninformed-Inaccurate contrast because we believe this contrast affords a more careful control for the participants' actual estimation accuracy. Increased control of this nature may generally be viewed as advantageous, but may be particularly important in the present context, given the well-established reciprocity of neural responses during the expectation and presentation phases of negative feedback processing [5,22]. Because of this reciprocity, neural responses during the presentation-phase of negative feedback processing have been shown to attenuate if participants have formed a previous expectation that such feedback is likely. In the Informed-Inaccurate > Informed-Accurate contrast the accuracy of participants' estimates (and, by proxy, their expectation of accurate or inaccurate feedback) is likely to vary. In contrast, the Informed-Inaccurate > Uninformed-Inaccurate contrast afforded a careful matching of participants' actual estimation accuracy, and thus minimized the likelihood that expectation-related effects would complicate the data.

All data were intensity-thresholded at \( p < .001 \), with a cluster-size correction undertaken via AlphaSim to equate to a family wise error (FWE) rate of \( p < .05 \) \( (k = 19) \). In addition, two 10 mm brain (3.5 mm) were collected using a gradient echo-planar pulse sequence (TR = 2000 ms, TE = 29 ms, FA = 65, FOV: 24×24 cm, 64×64 matrix, 3.44 mm×3.44 mm in plane resolution, flip angle: 75°). All preprocessing and GLM-based statistical analyses of data were carried out using Statistical Parametric Mapping 5 (SPM5) as described below.

Functional images were reconstructed offline and reoriented to approximately the anterior commissure/posterior commissure (AC/PC) plane. Functional image runs were motion corrected using an algorithm unbiased by local signal changes (INRIAlign) [24] as implemented in SPM5. No participants showed head movements in excess of 5 mm, and thus all 18 participants were retained for the analyses reported below. A mean functional image volume was constructed for each run from the realigned image volumes. The mean EPI image was normalized to the EPI template. The spatial transformation into standard MNI space was determined using a tailored algorithm with both linear and nonlinear components [25]. The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each participant. The normalized functional images were smoothed with a 9 mm full width at half-maximum (FWHM) Gaussian filter. A latency variation amplitude-correction method was used to provide a more accurate estimate of hemodynamic response for each condition [26].

Data Analysis

Individual participant data was analyzed using a mixed-effects event-related model in SPM5. The asterisk cue, the participant's response (accurate, inaccurate), and the feedback presentation (Informed-Accurate, Uninformed-Accurate, Informed-Inaccurate, Uninformed-Inaccurate) were each modeled as separate events. The primary event of interest, feedback presentation, was modeled with a standard hemodynamic response function with 2 s duration. Contrast images corresponding to Informed-Accurate, Informed-Inaccurate, Uninformative-Accurate and Uninformative-Inaccurate trials were computed separately for each of the Watch, Increase and Decrease conditions, and compared against each condition's implicit baseline using the general linear model.

Group analyses utilized a random effects ‘flexible factorial’ approach in SPM5 to create a 3 (Instruction: Watch, Increase, Decrease) × 4 (Feedback: Informed-Accurate, Informed-Inaccurate, Uninformed-Accurate, Uninformed-Inaccurate) within-group ANOVA at the second level. Evaluation of higher-order main effects and interactions were followed by t-contrasts, guided by a priori hypotheses, which focused on comparing the Informed-Inaccurate > Uninformed-Inaccurate contrast across each of the Watch, Increase and Decrease conditions. Activity in the Watch condition was used as a representation of participants’ neural responses upon receipt of Informative-Inaccurate feedback under standard “passive-viewing” conditions. Activity in the Increase and Decrease conditions, in turn, was used as a representation of the extent to which participants could follow the instruction to voluntarily increase or decrease their neural activity following receipt of the same Informed-Inaccurate feedback. Analyses thus evaluated Informed-Inaccurate > Uninformed-Inaccurate BOLD response within each of the three instruction conditions, and also evaluated the extent to which Informed-Inaccurate activity in the Increase and Decrease conditions differed from activity in the Watch condition.
regions of interest (ROIs) spheres were constructed, within dACC (central coordinate: x = 9, y = 30, z = 27) and mFC (central coordinate: x = 6, y = 15, z = 57), to allow for optimal evaluation of activity within regions with primary involvement in error-monitoring. Coordinates for these ROIs were arrived at by averaging coordinates obtained through an instructed sampling of the relevant literature on error-monitoring responses to negative feedback [27,29], and were thresholded at p < .05, FWE-svc.

**Voluntarily-induced modulation and post-feedback performance adjustments.** To evaluate the extent to which voluntarily-induced changes in neural response to negative feedback would influence performance adjustments on the following trial, we calculated ‘estimation change scores’ for each participant on a trial-by-trial basis, by calculating the absolute value of (participants’ estimation time on trial n) - (participant’s estimation time on trial n+1). For instance, if a participant’s time estimates on successive trials were: 1250 ms, 950 ms, and 1400 ms, then two change scores could be calculated as follows:

- **Trial 2 change score:**
  \[\text{1250} - \text{950} = 300\]
  \[-450\]
  \[\text{450}\]

- **Trial 3 change score:**
  \[\text{950} - \text{1400}\]

Note that by using absolute values, change scores were not sensitive to the direction of change. This was deemed appropriate given that the negative feedback did not provide participants with directional information.

Three mean change scores were calculated, representing the extent to which participants adjusted their estimation attempt on trials following Informed-Inaccurate feedback in each of the Watch, Increase and Decrease instruction conditions. These estimation change scores were then interrogated in two complimentary ways. First, change scores were entered into SPSS and evaluated via one-way ANOVA to identify behavioral differences in adjustment magnitude across the three instruction conditions. Second, estimation change scores were entered as a first-level parametric modulator (tied to the feedback presentation) in SPM5, and then interrogated via a 3 (Instructions: Watch, Increase, Decrease) x 4 (Feedback: Informed-Accurate, Informed-Inaccurate, Uninformed-Accurate, Uninformed-Inaccurate) “flexible-factorial” ANOVA, to afford whole-brain \(p < .05\), FWE, cluster-corrected via AlphaSim \(k = 19\) and ROI \(p < .05\), FWE-svc) evaluations of neural activity that varied with estimation change scores on a trial-by-trial basis. As before, higher-level main effect and interaction analyses were followed by planned comparisons capable of targeting instruction-related differences across each of the Informed-Inaccurate > Uninformed-Inaccurate contrast images.

**Results**

**Behavioral Results**

After evaluation with box and whisper plots, trials during which estimation attempts were greater than 3654 ms (3 standard deviations above the mean; 1.7% of all trials) were removed from the dataset. One participant showed particularly high inaccuracy (16.7% of their estimates fell above the exclusion threshold); thus their data was excluded from the analyses reported below. For the remaining 17 participants, the adaptive algorithm was highly successful in balancing the presentation of accurate/inaccurate feedback. Across all participants, 51.5% of all trials (62 trials/participant) were scored as accurate, and 48.5% (58 trials/participant) of all trials were scored as inaccurate.

Mean estimation time across all trials was 1125 ms (SD = 144 ms; range = 901–1354 ms). These estimation times were analyzed within a 3 (Instruction: Watch, Increase, Decrease) x 4 (Feedback: Informed-Accurate, Informed-Inaccurate, Uninformed-Accurate, Uninformed-Inaccurate) repeated-measures ANOVA, which revealed a main effect of Feedback, \(F = 19.8, \eta^2 = .533, p < .001\), but no Instruction, \(F = 1.65, p > .10\), or Feedback x Instruction, \(F = 1.18, p > .10\), effects. The main effect of Feedback followed anticipated patterns: estimation attempts were shorter and less variable on accurate (Informed-Accurate: \(M = 1043\) ms; SD = 80 ms; range = 901–1178 ms; Uninformed-Accurate: \(M = 1043\) ms; SD = 76 ms; range = 922–1159 ms) than on inaccurate (Informed-Inaccurate: \(M = 1215\) ms; SD = 208 ms; range = 896–1524 ms; Uninformed-Inaccurate: \(M = 1199\) ms; SD = 223 ms; range = 851–1575 ms) trials (mean difference: \(t(16) = 4.78, p < .001\); variance difference: \(t(16) = 6.67, p < .05\)).

**Neuroimaging Results**

**Analysis of variance brain activation maps.** Evaluation of the 3 (Feedback: Watch, Increase, Decrease) x 4 (Instruction: Informed-Accurate, Informed-Inaccurate, Uninformed-Accurate, Uninformed-Inaccurate) ANOVA revealed a significant main effect of Feedback within various regions including dACC/mFC, bilateral insula, bilateral orbitofrontal cortex, and bilateral inferior parietal cortex (see Figure S1). Subsequent paired t-tests indicated that this main effect was carried by the Informed-Inaccurate condition, which showed increased dACC/mFC activity compared to the other three feedback types (all \(ts > 7.68\)) in clusters that included bilateral putamen and bilateral dorsal/ventral attentional streams (see Figure S2). These main effects were modulated by a significant Feedback x Instruction interaction which occurred within eight clusters including dACC/mFC as well as bilateral insula/orbitofrontal and bilateral inferior parietal cortices (see Figure 2 and Table 1).

**Figure 2. Clusters showing significant changes in the 4 (Feedback) x 3 (Instruction) Interaction.**

doi:10.1371/journal.pone.0107322.g002
Dissection of this interaction followed *a priori* hypotheses, and thus separately evaluated activity following Informed-Inaccurate feedback in each of the Watch, Increase and Decrease conditions.

Baseline neural response to presented feedback

Participants’ baseline responses to error feedback were investigated by evaluating activity following Informed-Inaccurate feedback in the Watch condition. A preliminary one-way ANOVA with Feedback as a within-subject variable revealed no significant clusters; however, a planned comparison of the Informed-Inaccurate vs. Uninformed-Inaccurate contrast revealed significant peaks of activity within both dACC and mFC ROIs, as well as within left insula (see Figure 3a and Table 2). A similar comparison of the Informed-Inaccurate vs. Informed-Accurate contrast revealed no significant effects.

**Efficacy of voluntarily-initiated increases in neural response to error feedback.** Initial evaluation of participants’ neural responses in the Increase condition were evaluated via one-way ANOVA, with Feedback as a within-subject variable. This analysis identified significant differences within several clusters, including a large cluster spanning across both dACC and mFC regions ($F = 20.85$, $k = 8751$). Subsequent planned comparisons indicated that this dACC/mFC cluster was enhanced following Informed-Inaccurate feedback compared to both Uninformed-Inaccurate (see Figure 3b and Table S1) and Informed-Accurate (see Figure S3a) feedback. To directly test for evidence of significant up-modulation, we compared neural activity following Informed-Inaccurate feedback in both the Increase and Watch conditions. This analysis indicated that participants showed significantly greater dACC/mFC response in the Increase condition, indicative of a successfully upregulated error-related response (see Figures 3d and 3e, which display percent signal change graphs for the dACC and mFC ROIs, respectively). Additional regions showing increased response in the Increase condition included supplementary motor area, bilateral insula, and bilateral inferior frontal cortex (see Table 3 for complete listing of all activated regions).

**Efficacy of voluntarily-initiated decreases in neural response to error feedback.** Evaluation of neural responses in the Decrease condition followed a similar course. Initial one-way

### Table 1. Regions showing significant differences in the 4 (Feedback) × 3 (Instruction) Interaction.

| Region                  | Coordinates | F-score |
|-------------------------|-------------|---------|
| dACC/mFC                | 1037 9 9 60 | 22.75   |
| Insula/OFC              | 508 42 15 36 | 19.79   |
| Insula/OFC              | 537 −39 12 0 | 16.21   |
| Inferior Parietal Cortex| 189 −57 −42 36 | 13.50   |
| Inferior Parietal Cortex| 152 60 −39 33 | 11.12   |
| Inferior Frontal Cortex | 109 48 0 45 | 10.31   |
| Inferior Frontal Cortex | 36 −36 −78 36 | 7.64    |

Note: All clusters met cluster-corrected thresholding of $p < .05$, FWE. dACC/mFC cluster spanned across both study ROIs.

Figure 3. dACC/mFC activity in response to Informative-Inaccurate feedback in each of the Watch (Figure 3a), Increase (Figure 3b), and Decrease (Figure 3c) conditions. Note that dACC activity increased in the Increase condition, and decreased in the Decrease condition, compared to the Watch condition (Figure 3d), while mFC activity increased in both Increase (significantly) and Decrease (nonsignificantly) conditions (Figure 3e). doi:10.1371/journal.pone.0107322.g003
ANOVA, with Feedback as a within-subject variable, revealed significant differences within several clusters, including a large cluster within mFC that extended somewhat into dACC ($F = 8.18, k = 247, p < .05, \text{FWE}$). Subsequent planned comparisons indicated that the dACC/mFC cluster was enhanced following Informed-Inaccurate feedback compared to both Uninformed-Inaccurate (see Figure 3c and Table S2) and Informed-Accurate (see Figure S3b) feedback. To directly test for evidence of significant down-modulation, we compared neural activity following Informed-Inaccurate feedback in both the Decrease and Watch conditions. Activity within the dACC, but not the mFC, trended towards a significant decrease in the Decrease condition (see Figure 3d and 3e for percent signal change estimates), suggesting that participants held a similar (albeit less robust) capacity to voluntarily down-regulate error-related neural responses following receipt of negative feedback.

Consideration of Neural Responses Underlying the Initiation of Effortful Control. It is unlikely that neural changes observed in the Increase and Decrease conditions represented only participants’ modulated responses. Rather, we may anticipate that attempts to voluntarily modulate this response would necessarily also invoke neural resources underlying the utilization of effortful control strategies. Dissection of neural activity underlying the generation versus modulation of error-

Table 2. Regions showing increased activity to Informed Inaccurate versus Uninformed Inaccurate feedback during Watch instructions.

| Region                              | Coordinates | t-score |
|-------------------------------------|-------------|---------|
| Dorsal Anterior Cingulate Cortex    | 6 9 30 27   | 2.72*   |
| Middle Frontal Cortex               | 17 −33 33 42 | 2.88*   |
| Insula                              | 106 −39 15 6 | 3.34    |

Note: Whole-brain activity met cluster-corrected thresholding of $p < .05, \text{FWE}$. Activity in a priori ROIs denoted with a * thresholded at $p < .05, \text{FWE-svc}$. doi:10.1371/journal.pone.0107322.t002

Table 3. Regions showing differential activity to Informed-Inaccurate feedback in the Increase and Decrease conditions compared to the Watch condition.

| Region                              | Coordinates | t-score |
|-------------------------------------|-------------|---------|
| Increase > Watch                    |             |         |
| Activity spans: dACC/mFC/SMA        | 733 6 0 66  | 5.56*   |
| Activity spans: Insula/IFC/Putamen  | 338 42 9 −3 | 4.98    |
| Activity spans: Insula/IFC/sTC/Putamen | 345 −39 6 0 | 4.44    |
| Activity spans: mTC/smC             | 217 45 −45 6 | 4.25    |
| Precentral Cortex                   | 143 42 −6 45 | 4.57    |
| Precentral Cortex                   | 75 −48 −3 39 | 3.49    |
| Supr marginalized Cortex            | 123 −63 −39 27 | 3.77    |
| Increase < Watch                    |             |         |
| Activity spans: IPC/IPC             | 206 48 −69 42 | 4.72    |
| Superior Frontal Cortex             | 176 24 24 57 | 4.29    |
| Decrease < Watch                    |             |         |
| Insula                              | 37 45 15 −9 30 | 3.16    |
| dACC                                | - 12 39 30  | 2.62*   |
| Decrease > Watch                    |             |         |
| Mid Frontal Cortex                  | 145 −27 24 48 | 4.78    |
| Activity spans Pre-/Post-central Cortex | 446 −36 −18 57 | 5.22    |
| Activity spans Anterior Insula/sTC | 577 −36 −24 21 | 4.69    |
| Angular Gyrus                       | 165 45 −72 42 | 4.53    |
| Lingual/Vermis/ Precuneus           | 251 6 −54 3 | 4.12     |

Note: dACC = dorsal anterior cingulate cortex, mFC = medial frontal cortex, SMA = supplementary motor region, IFC = inferior frontal cortex, sTC = superior temporal cortex, IPC = inferior parietal cortex, smC = supramarginal cortex, sPC = superior parietal cortex. Whole-brain activity met cluster-corrected thresholding of $p < .05, \text{FWE}$. Activity in a priori ROIs denoted with a * thresholded at $p < .05, \text{FWE-svc}$. doi:10.1371/journal.pone.0107322.t003
related responses is difficult, as the neural systems underlying generation versus modulation are likely to show considerable overlap [29]. However, while regions involved in the generation of error-related responses were expected to vary in the direction of the instructed modulation (as participants’ dACC response did), we may expect regions underlying effortful control processes to show increased activity in both Increase and Decrease conditions. Consistent with this hypothesis, we identified several regions including middle frontal cortex, as well as left insular cortex, which showed enhanced responses in both Increase and Decrease conditions compared to the Watch condition. Moreover, a conjunction analysis of Increase > Watch and Decrease > Watch contrasts identified several clusters within mFC, insula and inferior frontal corticies that reached family-wise significance thresholds (see Figure 4). Importantly, however, directly contrasting the Increase and Decrease contrasts indicated that both dACC and mFC activity were greater in the Increase condition compared to the Decrease condition (see Table 4). Thus, we see evidence of successful modulation of dACC/mFC response, even under the backdrop of top-down resource recruitment.

Voluntarily-induced modulation and post-feedback performance adjustments. Figure 5a displays participants’ estimation change scores following Informed-Inaccurate feedback in each of the Watch, Increase and Decrease conditions. Confirming hypotheses, participants showed higher change scores following Informed-Inaccurate feedback in the Increase condition compared to each of the Watch (t = 3.65, p < .05) and Decrease (t = 3.53, p < .05) conditions, which did not differ from each other (p > .10). Thus, participants showed greater post-feedback performance adjustment following inaccurate feedback when they were instructed to increase their neural response to that feedback, but did not show reduced post-feedback performance adjustments when instructed to decrease that neural response.

We also conducted a parametric modulation analysis in SPM5, whereby participants’ trial-by-trial estimation change scores (see method section for relevant calculations) were entered as a parametric modulator locked to the presentation of the feedback stimulus. This analysis thus afforded a consideration of neural activity that correlated with the extent to which participants altered their estimation on the trial following receipt of inaccurate feedback. As hypothesized, this analysis identified a dACC cluster (peak coordinate: x = 9, y = 18, z = 21) that extended into our dACC ROI, which significantly predicted participants’ change scores across both Watch and Increase conditions (but not in the Decrease condition; see Figure 4b).

Discussion

The present study was designed to evaluate the extent to which participants could undertake voluntary up- and/or down-modulation of error-related neural activity in response to the presentation of negative feedback. To this end, participants were asked to perform a simple time-estimation task under a standard Watch condition, and under Increase and Decrease conditions during which they were asked to intentionally enhance or reduce their brain’s response following the presentation of the negative feedback. Despite being given no guidance as to how to accomplish this neuromodulation, participants showed considerable capacity for altering their neural responses in the instructed direction. Activity within a large cluster that spanned across hypothesized regions increased in the Increase condition; and a more specific sub-cluster within dACC trended towards a significant reduction in the Decrease condition. To our knowledge, this is the first study to demonstrate that neural activity underlying the processing of error-related information may be modulated through such voluntary efforts (but see [30] for evidence that one’s emotional response to error can be regulated).

This finding may be interpreted within the context of a growing literature suggesting that humans may have the capacity to invoke substantive influence over the nature of their neural responses to specific stimulus types, including emotionally-valent pictures [15,31], pain [32], stimuli that evoke craving [33], and during the processing of happy memories [34]. The ability to modulate neural activity to negative feedback may have particularly practical implications, however. The magnitude of this dACC response is believed to index the activity of a generalized error-monitoring system important for the adaptive selection and guidance of subsequent corrective behavior [6–8]. If this is true, then up-regulation of this dACC response could facilitate one’s ability to learn through trial-and-error, and to manage goal-directed behavior in the face of changing environmental demands. The results of the present study support this hypothesis: magnitude of dACC response following negative feedback correlated with the extent to which participants adjusted their estimation attempts on the following trial (in the Increase and Watch conditions, at least). Moreover, estimation change scores correlated with dACC response across the Watch and Increase conditions, and were higher in the Increase condition compared to the Watch and Decrease conditions. While these results did not translate to the Decrease condition, they nonetheless suggest that participants’ voluntary modulation of their neural response to the negative feedback also influenced the extent to which they adjusted their post-feedback behavior. The possibility that more prolonged neuromodulatory training could serve to facilitate operant learning proficiency is an intriguing possibility that future research could further consider (see [35]).

It is also relevant to note that differential responsivity to error has been shown characteristic of a variety of personality characteristics related to clinical and subclinical states. Individuals with low levels of inhibitory control, including those with substance abuse disorders and attention hyperactivity deficit disorder (ADHD) have, for instance, been characterized with a hypoactive dACC response to error-related information [36,37]. Individuals characterized by heightened levels of anxiety have, in
turn, been characterized with increased dACC response to error-related information [21,38]. The extent to which these individual differences would themselves influence the capacity to successfully undertake dACC neuromodulation to error remains an open question, but one that future research may do well to consider. It should also be noted, however, that participants in the present study showed dACC reductions in the Decrease condition that only reached trend levels of significance – while this may be the result of the small sample size of the present study, it also may deem consideration of therapeutic benefits of dACC down-regulation somewhat premature.

It is important to note that our two primary regions of interest showed somewhat different patterns of activity across the three instruction conditions. Activity in dACC showed the hypothesized pattern: activity increased in the Increase condition, and decreased in the Decrease condition, compared to the Watch condition. However, activity in mFC, as well as in insular and inferior frontal regions, showed significant increases in both the Increase and Decrease conditions. A simple interpretation of this data could be that participants were capable of modulating their dACC response to the presentation of negative feedback, but that this capacity did not extend to adjacent mFC regions. However, such interpretation would ignore the extent to which participants’ modulation attempts themselves required the recruitment of frontoparietal resources towards the initiation of top-down effortful control [39,40]. Indeed, we may anticipate increased control-related recruitment in both the Increase and Decrease conditions, as participants attempt to modulate their neural reactivity in the instructed direction. In this context, the increased mFC activity seen across Increase and Decrease conditions may not imply

Table 4. Regions showing differential activity to Informed-Inaccurate feedback in the Increase compared to the Decrease condition.

| Region                                | Coordinates | k   | x    | y    | z    | t-score |
|---------------------------------------|-------------|-----|------|------|------|---------|
| Increase > Decrease                   |             |     |      |      |      |         |
| Activity spans: dACC/mFC/SFC          |             | 665 | 21   | -30  | 66   | 5.51    |
|                                       |             | 0   | -6   | 48   | 4.89 |
|                                       |             | 0   | -9   | 66   | 5.22 |
| Superior Frontal Cortex               |             | 105 | -18  | -30  | 60   | 4.60    |
| Superior Frontal Cortex               |             | 169 | 39   | -33  | 15   | 4.67    |
| Superior Temporal Cortex              |             | 211 | -48  | -27  | 12   | 4.57    |
| Superior Temporal Cortex              |             | 25  | -60  | -12  | 9    | 4.08    |
| Pre/Post Central Cortex               |             | 152 | -42  | -15  | 45   | 5.04    |
| Precentral Cortex                     |             | 44  | 45   | -12  | 42   | 4.27    |
| Calcarine                             |             | 179 | -24  | -63  | 9    | 4.25    |
| Calcarine                             |             | 28  | 27   | -57  | 3    | 4.17    |
| Insula                                |             | 19  | -33  | 6    | 3    | 4.07    |

| Increase < Decrease                   | None        |

Note: dACC = dorsal anterior cingulate cortex, mFC = medial frontal cortex, sFC = superior frontal cortex. Whole-brain activity met cluster-corrected thresholding of $p < .05$, FWE. Activity in a priori ROIs denoted with a * thresholded at $p < .05$, FWE-svc.

doi:10.1371/journal.pone.0107322.t004

Figure 5. a) The degree to which participants altered their inaccurate time estimates following Informed-Inaccurate feedback in each of the Watch, Increase and Decrease modulation conditions. b) Region of dACC that correlated positively with magnitude of post-feedback change in time estimation in the Watch and Increase, but not the Decrease, modulation condition.

doi:10.1371/journal.pone.0107322.g005
increased modulation capacity, but rather increased recruitment of regulatory resources. To separate activity associated with each process, we undertook a direct comparison of post-error feedback in the Increase and Decrease conditions (both of which should have required similar recruitment of effortful control processes). This contrast identified increased activity in both dACC and mFC in the Increase condition. We interpret this as evidence of successful modulation of dACC/mFC response, even after parsing activity associated with the initiation of resource-intensive top-down control processes.

This study is not without its limitations. First, our sample size is relatively modest, which may have challenged our ability to identify small- or medium-sized effects. This may be particularly relevant when interpreting the results from the Decrease condition, where dACC reductions only reached trend significance levels. Future research would do well to replicate this effect within a larger sample, at which point more conclusive evidence for the capacity to down-modulate error-related responses may be acquired. Second, we once again acknowledge the challenges associated with trying to distinguish between generative versus regulatory processes. This is an oft-acknowledged challenge [17] that characterizes the majority of emotion-regulation work, and the present study is no exception. The time-estimation paradigm was not designed to explicitly leverage the ability to distinguish generative versus regulatory processing; however, direct contrast of the Increase and Decrease conditions provided some useful insights. Future work specifically designed to isolate the heavily overlapping processes would greatly benefit the field.

To summarize, our results expand on work undertaken within the "emotion regulation" literature, and demonstrate that individuals have the capacity for voluntary modulation of neural activity underlying a more cognitively-mediated error-monitoring process. This synthesizes well with growing work indicating the plasticity of neural structure and function, and highlights the fact that such plasticity is not necessarily reliant on emerging high-tech methodologies such as TMS, TDCS or rt-fMRI. It is frequently assumed that both automatic and controlled emotion regulation strategies serve adaptive (and/or maladaptive) self-regulatory functions; the extent to which cognitive regulation strategies also serve such functions has received less, and perhaps less-than-warranted, attention.

Supporting Information

Figure S1 Main effect of feedback. (TIF)
Figure S2 Main effect of instruction. (TIF)
Figure S3 a) Significant clusters within the Informed-Inaccurate > Informed-Accurate contrast in the Increase condition; b) Significant clusters within the Informed-Inaccurate > Informed-Accurate in the Decrease condition. (TIF)

Table S1 Regions showing increased activity to Informed-Inaccurate compared to Uninformed-Inaccurate feedback in the Increase instruction condition. (DOCX)
Table S2 Regions showing increased activity to Informed-Inaccurate compared to Uninformed-Inaccurate feedback in the Decrease instruction condition. (DOCX)

Author Contributions
Conceived and designed the experiments: MSS. Performed the experiments: CRW MSS. Analyzed the data: MSS CRW. Contributed reagents/materials/analysis tools: MSS CRW. Wrote the paper: MSS CRW.

References
1. Milner WHR, Beaus CH, Coles MGH (1997) Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a “generic” neural system for error detection. J Cog Neuro 9: 788–798. doi:10.1162/ jocn.1997.9.6.788
2. Holroyd CB, Hajcak G, Larsen JT (2006) The good, the bad and the neutral: Electrophysiological responses to feedback stimuli. Brain Res 1105: 93–101. doi:10.1016/j.brainsc.2005.12.015
3. Gehring WJ, Willoughby AR (2002) Medial prefrontal cortex and error processing: Science 296: 597–600. doi:10.1126/science.296.5573.1611
4. Nieuwenhuis S, Yeung N, Holroyd CB, Schurger A, Cohen JD (2004) Sensitivity of Electrophysiological Activity from Medial Frontal Cortex to Utilitarian and Performance Feedback. Cereb Cortex 14: 741–747. doi:10.1093/ercor/ bh403
5. Holroyd CB, Coles MH (2002) The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. Psychol Rev 109: 679–709. doi:10.1037/0033-295X.109.4.679
6. Lau P, Tucker DM, Derryberry D, Reed M, Poulsen C (2003) Electrophysiological responses to errors and feedback in the process of action regulation. Psychol Sci 14: 47–53. doi:10.1111/j.1467-9280.2003.01417
7. van Duijvenvoorde AK, Zanolie K, Rombouts SB, Raijmakers MJ, Crone EA (2003) Real-time fMRI of temporo-limbic regions detects amygdala activation during single-trial self-induced sadness. NeuroImage 18: 760–768. doi:10.1016/S1053-8119(03)00004-1
8. Ochsner KN, Bunge SA, Gross J, Gabrieli JD (2002) Rethinking feelings: an fMRI study of the neural regulation of emotion. J Cog Neuro 14: 1213–1229. doi:10.1016/S0898929X(02)00721-2
9. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, et al. (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23: 483–499. doi:10.1016/j.neuroimage.2004.06.030
10. Davidson RJ, Jackson DG, Kalin NH (2000) Emotion, plasticity, context and regulation: perspective for affective neuroscience. Psychol Bull 126: 890–906. doi:10.1037/0033-295X.126.6.890
11. Gross JJ (2001) Individual differences in two emotion regulation processes: implications for affect, relationships and well-being. J Pers Soc Psych 80: 348–362. doi:10.1037/0022-3514.80.2.348
12. Lewis MD, Granic I, Lamm C, Zelazo PD, Steinberg L, et al. (2008) Changes in the neural bases of emotion regulation associated with improvement in children with behavior problems. Develop Psychopathol 20: 913–939. doi:10.1017/S0954579408000448
13. Posse S, Gareau G, Habel U, Rosenfeld D, et al. (2003) Real-time fMRI of temporo-limbic regions detects amygdala activation during single-trial self-induced sadness. NeuroImage 18: 760–768. doi:10.1016/S1053-8119(03)00004-1
14. Ochsner KN, Bunge SA, Gross J, Gabrieli JD (2002) Rethinking feelings: an fMRI study of the neural regulation of emotion. J Cog Neuro 14: 1213–1229. doi:10.1016/S0898929X(02)00721-2
15. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, et al. (2004) For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23: 483–499. doi:10.1016/j.neuroimage.2004.06.030
16. Davidson RJ, Jackson DG, Kalin NH (2000) Emotion, plasticity, context and regulation: perspective for affective neuroscience. Psychol Bull 126: 890–906. doi:10.1037/0033-295X.126.6.890
17. Gross JJ (2001) Individual differences in two emotion regulation processes: implications for affect, relationships and well-being. J Pers Soc Psych 80: 348–362. doi:10.1037/0022-3514.80.2.348
18. Lewis MD, Granic I, Lamm C, Zelazo PD, Steinberg L, et al. (2008) Changes in the neural bases of emotion regulation associated with improvement in children with behavior problems. Develop Psychopathol 20: 913–939. doi:10.1017/S0954579408000448
19. Ekblad E, Måksel M, Stier S, Siaramadaro A, Gapp V, et al. (2010) Acute and sustained effects of cognitive emotion regulation in major depression. J Neurosci 30: 14726–14734. doi:10.1523/jneurosci.18356.1010
20. Gross JJ (1998) Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. J Pers Soc Psych 74: 224–237. doi:10.1037/0022-3514.74.1.224
21. Hajcak G, McDonald N, Simons RF (2003) Anxiety and error-related brain activity. Bio Psych 64: 77–90. doi:10.1016/S0306-425X(03)00103-0
22. Wrase J, Kahnt T, Schlagenhauf F, Beck A, Cohen XM, et al. (2007) Different mechanisms contribute to feedback processing in a rule-learning task. NeuroImage 36: 1253–1262. doi:10.1016/j.neuroimage.2007.04.001
Voluntary Modulation of ACC to Negative Feedback

PLOS ONE | www.plosone.org 10 November 2014 | Volume 9 | Issue 11 | e107322

23. Schneider W, Eschman A, Zuccolotto A (2002) E-Prime User’s Guide. Pittsburgh: Psychology Software Tools Inc.
24. Freire L, Mangin JF (2001) Motion correction algorithms may create spurious brain activations in the absence of subject motion. NeuroImage 14: 709–722. doi:10.1006/nimg.2001.0669
25. Friston KJ, Frith CD, Frackowiak RS, Turner R (1995) Characterizing dynamic brain responses with fMRI: a multivariate approach. NeuroImage 2: 166–172. doi:10.1006/nimg.1995.1019
26. Calhoun VD, Stevens MC, Pearlson GD, Kiehl KA (2004) fMRI analysis with the general linear model: removal of latency-induced amplitude bias by incorporation of hemodynamic derivative terms. NeuroImage 22: 252–257. doi:10.1016/j.neuroimage.2003.12.029
27. Holroyd CB, Larsen JT, Cohen JD (2004) Context dependence of the event-related brain potential associated with reward and punishment. Psychophys 41: 245–253. doi:10.1111/j.1469-8986.2004.00152.x
28. Ullsperger M, von Cramon DY (2001) Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. NeuroImage 14: 1387–1401. doi:10.1006/nimg.2001.09351
29. Gross JJ, Barrett LF (2013) Emotion generation and emotion regulation: One or two depends on your point of view. Emot Rev 5:8–16. doi:10.1177/1754073910380974
30. Ichikawa N, Siqueira GJ, Jones NP, Kamishima K, Thompson WK, et al. (2011) Feeling bad about screwing up: emotion regulation and action monitoring in the anterior cingulate cortex. Cogn Affect Behav Neurosci 11: 354–371. doi:10.3758/s13415-011-0026-z
31. Dan-Glauser ES, Gross J (2013) Emotion regulation and emotion coherence: evidence for strategy-specific effects. Emotion 13: 832–842. doi:10.1037/a0032672
32. deCharms CR, Macchi F, Glover GH, Ludlow D, Pauly JM, et al (2005) Control over brain activation and pain learned by using real-time functional MRI. Proc Nat Acad Sci 102: 10626–10631. doi:10.1073/pnas.0505210102
33. Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, et al (2010) Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. NeuroImage 49: 2536–2543. doi:10.1016/j.neuroimage.2009.10.088
34. Zotev V, Phillips R, Yuan H, Miski M, Bodurka J (2014) Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. NeuroImage 85: 985–995. doi:10.1016/j.neuroimage.2013.04.126
35. Williams NR, Taylor JJ, Snipes JM, Short EB, Kantor EM, et al. (2014) Interventions for psychiatry. How should psychiatric educators incorporate neuroimaging into training? Acad Psy 38: 166–176. doi:10.1007/s40596-014-0030-x
36. Hall JR, Bernat EM, Patrick CJ (2007) Externalizing psychopathology and the error-related negativity. Psy Sci 18: 326–333. doi:10.1111/j.1467-9280.2007.01899.x
37. Groom MJ, Liddle EB, Searf G, Liddle PF, Baty MJ, et al. (2013) Motivational incentives and methylphenidate enhance electrophysiological correlates of error monitoring in children with attention deficit/hyperactivity disorder. J Child Psy & Psy 54: 836–845. doi:10.1111/jcpp.12069
38. Mower JS, Durbin CE, Patrick CJ, Schmidt NB (2013) Combining neural and behavioral indicators in the assessment of internalizing psychopathology in children and adolescents. J Clin Child & Adol Psych: 0–12. doi:10.1080/15374416.2013.863191
39. Silvers JA, Buhle JT, Ochser KN (2013) The neuroscience of emotion regulation: Basic mechanisms and their role in development, aging and psychopathology. In: The Oxford handbook of cognitive neuroscience, Volume 2: The cutting edges. KN. Ochser &SM. Kosslyn (Eds.) Oxford University Press:NY.
40. Wessing I, Rehbein MA, Postert C, Fumian T, Junghofer M (2013) The neural basis of cognitive change: Reappraisal of emotional faces modulates neural source activity in a frontoparietal attention network. NeuroImage 81: 15–25. doi:10.1016/j.neuroimage.2013.04.117