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The effect of orbitofrontal lesions on the error-related negativity

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ABSTRACT

Current theories of orbitofrontal cortex (OFC) function suggest that this region should participate in the generation of error-related signals associated with the outcomes of actions. We investigated the impact of lesions to OFC on the error-related negativity (ERN), an electrophysiological marker of performance monitoring. Four OFC patients and eight control subjects participated in a manual Stroop task while brain electrical activity was recorded. We found that the ERN was attenuated in the patient group. Three of the patients also had impaired error correction performance, but all showed normal post-error slowing. These findings suggest OFC involvement in monitoring and evaluation of ongoing performance.

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The orbitofrontal cortex (OFC) plays a critical role in the integration of cognitive and affective processes [1,5,6]. Linking decisions and actions with their consequences relies upon the integrity of this region [1,2]. While the role of OFC in high-level decision processes has been investigated extensively, it is unclear whether OFC's contribution to adaptive behavior extends to monitoring the successful performance of actions in elementary cognitive tasks.

Medial frontal cortex plays an important role in online monitoring of performance and evaluation of response outcomes [11,16,18,20,22,28]. In particular, dorsal anterior cingulate cortex (ACC) activity is closely associated with the error-related negativity (ERN or Ne), an electrophysiological marker for the detection and evaluation of errors in performance [8,11,12]. While integrity of ACC seems to be critical for performance monitoring in general and ERN generation in particular [27], there is evidence that lesions outside ACC can have a distal effect, possibly through alteration of modulatory influences. Lesions in lateral prefrontal cortex both attenuate the ERN and remove its specificity to errors [12], as do lesions in the basal ganglia [29]. Further, frontal lobe lesions restricted to white matter are sufficient to produce similar effects [14]. Thus, the generation of ERN and performance monitoring in general appear depend upon interactions among multiple frontal areas. Ventromedial regions of the OFC are interconnected with the dorsal ACC via the cingulum bundle [25], and the medial OFC includes the rostral cingulate areas involved in affective processes [4]. These considerations suggest that OFC may contribute to performance monitoring functions implemented by the dorsal ACC.

Published evidence for OFC involvement in performance monitoring and its electrophysiological correlates is still sparse, and inconclusive. Error-related intracranial signals that precede the ACC response by approximately 50 ms have indeed been recorded from multiple sites in the OFC [3]. However, frontopolar lesions extending to the anterior portion of the OFC, but sparing the perigenual ACC, do not appear to affect the ERN [30]. Therefore, testing patients with extensive OFC lesions that extend beyond frontopolar regions will be informative. We predicted that OFC patients would show performance monitoring deficits and abnormal electrophysiological responses to errors.

Four patients (all right-handed males, mean age 54.75 ± 6.60 years, mean education 12.0 years) with bilateral ventromedial PFC lesions (Fig. 1) were tested. Demographic information (age, education, years post-injury, and etiology) for individual patients is shown in Table 1. Lesions were transcribed onto corresponding axial templates in Montreal Neurological Institute (MNI) space using MRIcro [23]. The lesions in all four patients extended to perigenual ACC, and also covered a significant portion of ventral frontal lobe white matter. One patient's lesion extended to left anterior temporal pole. Estimated lesion volumes ranged from 108 to 156 cm^3. The patients were compared to eight healthy controls (all right-handed, mean age 54.25 ± 9.49 years, mean education 12.75 years, no history of neurological or psychiatric conditions). All participants signed informed consent statements approved by the Institutional Review Boards of the Veterans Affairs Northern

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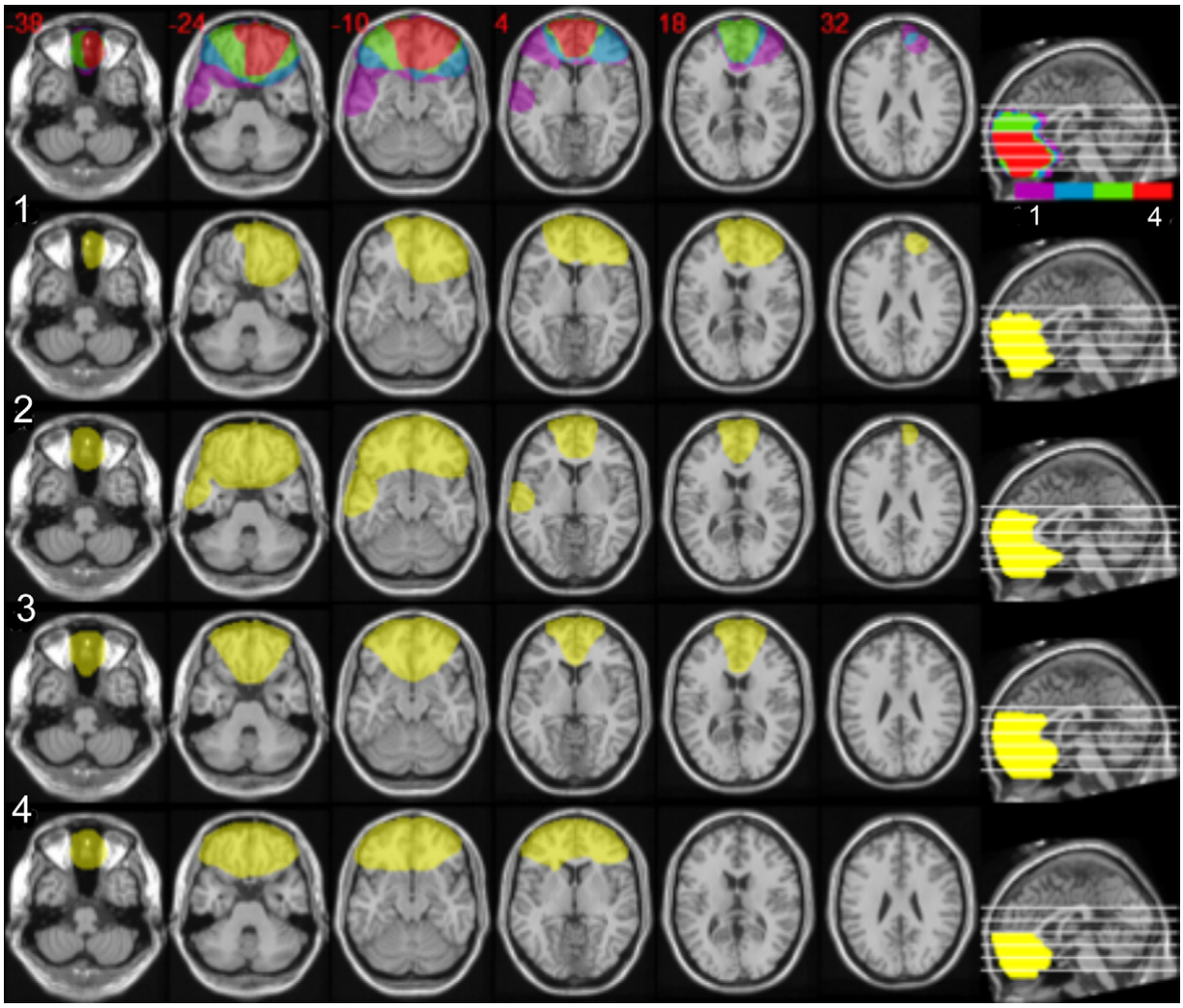

Fig. 1. Reconstructions of OFC lesions in Montreal Neurological Institute (MNI) space. The top row shows the extent of overlap across patients. Color coding indicates the number of patients with damage (from 1 in purple to 4 in red). The following rows show lesion reconstructions from individual patients.

California Health Care System and the University of California at Davis, and were paid for their participation.

Participants completed a variant of the Stroop task with manual responses [27]. On each trial, a word that read "LEFT" or "RIGHT" and an arrow pointing left or right were displayed above and below fixation for 350 ms. On half the trials, the word and arrow indicated the same direction (congruent trials), and on the other half, opposite directions (incongruent trials). Based on an instruction ("WORD" or "ARROW") appearing 1360 ms before stimulus onset, subjects indicated by a button press the direction associated with either the word or the arrow. The next trial started 3125 ms after stimulus onset. There were 12 blocks of 64 trials. Speed was emphasized over accuracy, and subjects were instructed to correct their errors with a second response.

Table 1
Demographic information for the individual OFC patients: age at testing, handedness, years of education, years post-injury, and etiology of injury

Patient	Age	Education	Years post-injury	Etiology
Patient 1	46	12	23	Head injury
Patient 2	55	12	25	Head injury
Patient 3	62	12	10	Head injury
Patient 4	56	12	2 ½	Meningioma

Mean reaction time (RT) and error rates across all conditions were calculated for each subject. Trials with response times three standard deviations from the mean were excluded from analyses. Error correction rate (percentage of errors corrected) and post-error slowing (mean RT difference between trials following errors and correct responses, expressed as a percentage of the latter) were used as the behavioral index for error processing performance.

EEG was recorded from 46 channels (42 scalp and two peri-ocular channels, and the right mastoid, all referenced to the left mastoid) using a sampling rate of 256 Hz, and an analog filter pass band of 0.1–80 Hz (SA Instrumentation, San Diego). Six midline electrodes were selected for analysis. Trials with gross artifacts were rejected automatically. Trials with "correctable" blinks (i.e., uncontaminated by other artifacts) were corrected with an adaptive filtering algorithm developed by Dale (Ph.D. Dissertation, University of California, San Diego, 1994) and included in the relevant average. Response-locked epochs were averaged for correct and error trials, and the mean ERP amplitudes over a 20–125-ms post-response interval, with respect to a −400 to −200 pre-response baseline, were submitted to a repeated-measures ANOVA with electrode (Fz, Fcz, Cz, CPz, Pz, POz) and response type (correct, error) as within-subject factors and group (OFC patients, controls) as the between-subject factor, using Greenhouse–Geisser correction

Table 2
Reaction times (RT), error rates, error correction rates, and post-error slowing for control and patient groups (top rows) and individual patients

Subject	Mean RT (ms)	Error rate (%)	Correction rate (%)	Post-error slowing (%)
Controls (mean)	479 ± 68	7.34 ± 2.59	84.15 ± 8.52	16.05 ± 20.43
Patients (mean)	802 ± 393*	6.96 ± 2.70	74.01 ± 15.68	19.47 ± 10.70
Patient 1	551	9.77*	76.92*	17.42
Patient 2	536	3.56	92.86	18.47
Patient 3	749*	8.32	71.43**	33.91
Patient 4	1373*	6.19	54.84**	8.08

Performance measures outside normal range are indicated by * and ** for the 95% and 99% confidence intervals, respectively.

for nonsphericity when appropriate. Within-subject ANOVAs were also run for control and patient groups separately.

The behavioral data showed that as a group, patients were slower than their controls [$t(10) = -2.37$, $P < 0.05$], but had comparable error rates [$t(10) = 0.23$, $P > 0.1$], error correction rates [($t(10) = 1.48$, $P > 0.1$], and post-error slowing [$t(10) = 0.31$, $P > 0.1$] (Table 2). When individual performance measures were considered for each patient, error correction performance was below the normal range for three patients, but all showed normal post-error slowing.

ERP data revealed significant differences between the two groups. In the control subjects, error trials were marked by a frontal-midline negativity which was largest at Cz when measured peak-to-peak (Fig. 2). Mean amplitude measures were entered in an ANOVA, revealing a main effect of condition [$F(1, 7) = 52.154$, $P < 0.001$] and a condition by electrode interaction [$F(5, 35) = 4.868$, $P < 0.05$]. For the patients, ERN amplitude did not distinguish between correct and error trials (Fig. 2). Neither the main effect of condition [$F(1, 3) = 3.313$, $P = 0.17$] nor the electrode by condition interaction [$F(5, 15) = 3.099$, $P = 0.16$] were significant. The between-subjects repeated-measures ANOVA revealed a significant group by condition interaction [$F(1, 10) = 16.146$, $P < 0.005$]. The three-way interaction between group, electrode and condition was not significant [$F(5, 50) = 0.43$, $P = 0.83$]. Hence, the ERN was not found for patients with OFC lesions.

The patients' ERPs were notable for a large Pe, or error positivity, component, which is often observed following the ERN [21]. However, ERP mean amplitude measures in the time window of the Pe (300–600 ms) did not differ at all between correct and error trials in controls [$F(1, 7) = 0.004$, $P = 0.95$] and only approached significance in the patients [$F(1, 3) = 5.557$, $P = 0.099$].

The present results demonstrate that the ERN component, an electrophysiological marker of performance monitoring, is eliminated in neurological patients with OFC lesions encompassing the ventromedial PFC. Three of the patients also had impaired error correction performance. These results are consistent with previous reports showing that damage within various sectors of the frontal lobes can affect the ERN [12,14,26,27,30], albeit in different ways. In accordance with current thinking on OFC function [1], the present findings raise the possibility of a significant OFC contribution to the monitoring and evaluation of ongoing performance.

A previous study found that the ERN was not affected in patients with frontopolar lesions sparing the ACC [30]. However, another study reported an almost complete absence of the ERN in patients with bilateral mesial frontal damage, including the medial aspect of the OFC, due to rupture of anterior communicating artery aneurysms [26]. The lesions reported here are not as extensive as the lesions in the latter investigation, but unlike the first, cover a large portion of the OFC. In addition to their extensive OFC lesions, the current patients have damage to the ACC as well. Functional neuroimaging studies have reported error-related activations in the perigenual ACC [15,16,20]. However, the "cognitive" subdivision of the ACC [4] is largely spared. This subdivision extends more dorsally and caudally with respect to the lesioned areas, and it is likely that the primary ACC generator of the ERN is located within this subdivision [3,7,13,17,27,28]. Further, the patients show normal post-error slowing, and the patients with lower than normal error correction rates still corrected a majority of their errors. These observations suggest that the performance monitoring system subserved by the dorsal ACC is functioning at some level, even though the ERN is completely missing.

The error positivity (Pe) can be seen following the ERN in some experiments, although its functional significance remains unclear [21]. The middle-aged control participants in the present study did not show a significant Pe on error trials. One possible explanation is that aging has been shown to decrease the amplitude of Pe, relative to that observed in young controls [19]. In addition, overt error

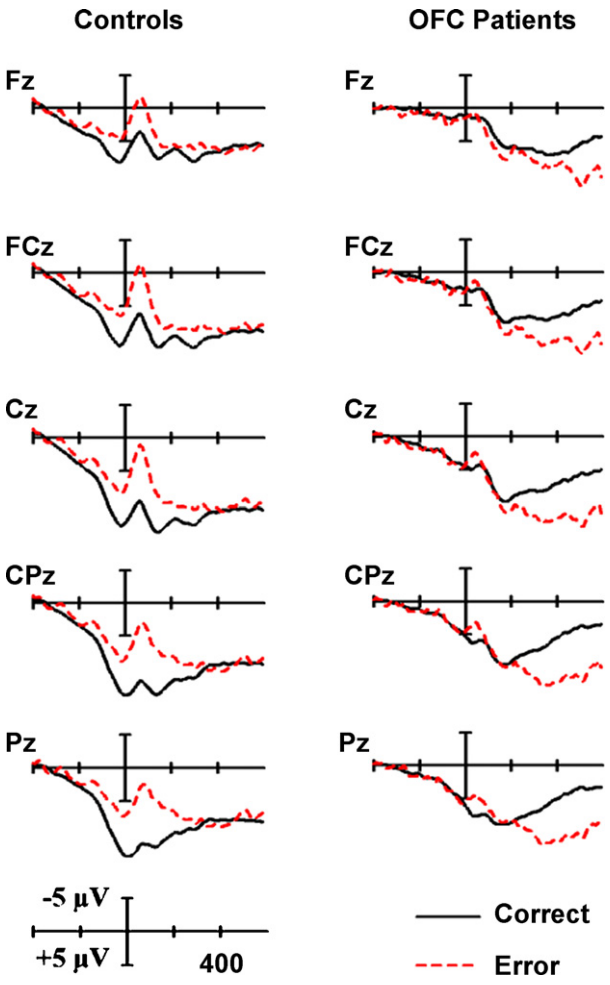

Fig. 2. Response-locked ERPs for control (left) and OFC patient (right) groups recorded at midline electrode sites arranged from frontal (Fz) to parietal (Pz). Response onset occurs at the vertical bar (time = 0 ms), tic marks are 200 ms, and negative is plotted upward.

corrections can produce a correction-related negativity (CoRN) that overlaps and obscures the Pe [10]. However, the Pe approached significance in the OFC patients, supporting the view that ERN and Pe are dissociable components [9,21,30]. This finding also suggests that error signals must have been processed at some level by the performance monitoring system, despite the OFC lesion. Hence, the ERN abnormality found in this investigation is not likely to be due to extensive damage to the dorsal ACC, which presumably mediates error monitoring [7], or due to a major dysfunction of the error processing system. Rather, error monitoring mechanisms might be functioning in a slow and variable manner.

The dorsal ACC might be relying upon a modulatory influence from the OFC, conveying the significance attached to errors, in order to function normally. This would be consistent with the observation that electrodermal activity associated with disadvantageous responses is missing in VMPFC patients [1,6], as well as the intracranial recording findings indicating that error-related activity in the OFC precedes the dorsal ACC activity by 50 ms [3]. The same patients who participated in the present investigation showed a disinhibition of the novelty P3a response and impaired habituation to emotional stimuli [24], which was interpreted to reflect an impairment of the modulatory influence of orbitofrontal cortex on distal brain regions. Similarly, OFC damage might disrupt the modulatory influence on the more dorso-caudally located ERN generator in the ACC, causing error processing to occur more slowly and in a variable manner. The result would be a "blurring" of the ERN on ERP averages due to high variance, and a failure to respond to errors in a timely or efficient manner.

In conclusion, we have found evidence suggesting that the orbitofrontal cortex contributes to the monitoring and evaluation of ongoing performance. The error-related negativity, an electrophysiological marker of performance monitoring, was attenuated in four patients with OFC damage. Further, three of the patients had below normal error correction rates.

Due to the broad extent of the OFC lesions, which encroach on but largely spare the dorsal ACC, further studies will be necessary to elucidate the precise nature of OFC involvement in performance monitoring.

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