Research Report

Medial frontal cortex and response conflict: Evidence from human intracranial EEG and medial frontal cortex lesion

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ABSTRACT

The medial frontal cortex (MFC) has been implicated in the monitoring and selection of actions in the face of competing alternatives, but much remains unknown about its functional properties, including electrophysiological oscillations, during response conflict tasks. Here, we recorded intracranial EEG during a modified Flanker task from the MFC of two patients undergoing pre-surgical evaluation for the treatment of epilepsy. Performance on the task was associated with a suppression of beta (15–30 Hz) frequency oscillation power prior to and just following the response and an enhancement of theta (4–8 Hz) frequency power following the response. Beta (theta) power was anatomically distributed towards more dorsal/caudal (rostral/ventral) electrode sites along the cortex, suggesting an anatomical/functional specialization along the medial frontal wall for pre-response versus post-response action monitoring. Inter-site phase coherence analyses demonstrated that the ventral/rostral MFC theta oscillations were coupled with theta oscillations observed at scalp electrodes Fz and Cz. One patient was tested before and after having epileptogenic tissue in the MFC surgically removed; task performance increased from chance levels to near-perfect, and an ERP conflict effect was observed only following surgery. These findings provide novel evidence for the role of MFC oscillations and their relation to surface EEG-recorded potentials during action monitoring.

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1. Introduction

Adaptive and flexible behavior requires the ability to choose among multiple response options, often in the face of conflict or uncertainty. Although target monitoring and response selection engaged electrophysiological activity in several cortical and subcortical brain regions (Brazdil et al., 2005, 2002; Clarke et al., 1999; Rector et al., 2003, 2007; Roman et al., 2005), response conflict appears to engage specifically the dorsal cingulate and surrounding medial frontal cortex (MFC).

This has been shown with functional MRI and EEG event-related potentials (Botvinick et al., 1999; Gehring and Fencsik, 2001; Lau et al., 2006; Nieuwenhuis et al., 2003; Ullsperger and von Cramon, 2001; van Veen and Carter, 2006; West et al., 2004). The precise neurocognitive mechanisms that these activations reflect remain debated. In brief, different theoretical accounts have proposed a role of the dorsal cingulate and surrounding MFC in terms of conflict monitoring, outcome evaluation [suggesting that MFC receives negative reinforcement signals to avoid actions that yield poor outcomes, Cohen
Several studies have demonstrated that enhancements in medial frontal theta (4–8 Hz) power follow incorrect, compared to correct, responses (Gevins et al., 1997; Luu and Tucker, 2001; Luu et al., 2004; Trujillo and Allen, 2007; Yordanova et al., 2004), and one recent study found that ERPs following response conflict occur in theta and lower frequency bands, which increased in older and Parkinson’s patients compared to controls (Schmiedt-Fehr et al., 2007). Whether this theta enhancement and activity in other frequency bands generalizes to situations of response conflict (e.g., prior to the response) has not, to our knowledge, been investigated.

A second issue that remains unknown is the relation between surface EEG potentials and local activity in the MFC. Surface EEG records activity from large swaths of cortex, and although mathematical point-source generator models have suggested that, consistent with functional MRI work, action monitoring effects might be generated by tissue in the dorsal cingulate cortex or surrounding MFC (Alain et al., 2002; Holroyd et al., 1998; Wills et al., 2007), these are indirect evaluations and not direct measurements of deep brain activity. Further, the intracranial sources of medial frontal theta have been speculated to originate in the dorsal cingulate cortex and surrounding MFC (Cohen et al., 2007; Luu et al., 2004), although this has not been verified in humans. Although functional MRI has better spatial resolution than surface EEG, it has neither the temporal resolution nor capability to measure neural oscillations and neurocognitive processes that change rapidly over time. Further, results from functional MRI do not always match those of intracranial EEG (Brazdil et al., 2005). Thus, recording electrophysiological activity directly from the MFC in the human may shed light onto the neural generators of surface-recorded ERP conflict-related potentials.

The third issue addressed here relates to anatomical/functional dissociations of regions within the MFC. Activity in many cortical regions dissociates correct from incorrect responses (Brazdil et al., 2002), although the medial frontal wall appears to play a prominent role (Carter and van Veen, 2007; van Veen and Carter, 2006). Within the medial frontal wall, meta-analyses of the literature suggest an anatomical division of labor, such that more dorsal/caudal regions (e.g., Brodmann area [BA] 8 and pre-SMA) are sensitive to pre-response conflict or uncertainty, whereas more rostral regions are sensitive to errors and post-response monitoring (e.g., BA 24) (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2001). Both intracranial EEG and functional MRI could provide insight into possible anatomical/functional dissociations, but only intracranial EEG can uncover the electrophysiological oscillatory processes—and differences in oscillatory characteristics—in different regions.

Finally, we tested whether and how a lesion in part of the MFC would affect task performance and associated ERPs. Previous studies have demonstrated that lesions in the anterior cingulate lead to an attenuated error-related negativity (Swick and Turken, 2002), and impaired ability to adjust behavioral control following high conflict (di Pellegrino et al., 2007). Further, lesions of the lateral prefrontal cortex lead to reduced error-related negativities (Gehring and Knight, 2000). Here we examined whether performance in a conflict task and associated ERPs would be affected by the resection of epileptic tissue in MFC. Note that lesion studies of humans with epileptogenic foci are not necessarily comparable to lesion studies in animals or in humans with damage to healthy tissue (e.g., injury from an accident). This is because in animals and humans with natural injuries, lesioned tissue was previously healthy, and thus making appropriate functional contributions to cognition. In contrast, epileptogenic tissue is more or less dysfunctional, and thus may contribute aberrant activity that can impair cognition. Indeed, focal resection of epileptic tissue can sometimes improve cognitive performance (Leijten et al., 2005; Lendt et al., 2002; Sanyal et al., 2005), perhaps due to neural functional reorganization or a reactivation of functions previously suppressed by influence of epileptogenic areas (Elger et al., 2004).

Intracranially recorded EEG provides a rare opportunity to understand the functions of the human cortex with better spatial precision than surface EEG, and with better temporal resolution than functional MRI. Further, the increased signal-to-noise ratio compared to surface EEG allows for reliable results from a small number of patients. Thus, to investigate the issues delineated above, we conducted a variant of the Flanker task with two patients who had electrodes implanted in the MFC, including dorsal and caudal, as well as more ventral/rostral, portions of the anterior cingulate cortex and superior frontal gyrus (spanning BA 6, 8, 24, and 32), as part of pre-surgical evaluation for the treatment of epilepsy (Fig. 1). One patient subsequently had part of the MFC surgically resected, providing the opportunity to examine changes in behavioral performance and surface electrophysiology pre- and post-surgical removal of part of the medial frontal wall. We focus our analyses on task-induced oscillations and how neural processes recorded at focal sources relate to activity recorded over the scalp. With respect to the three aspects of the neurocognitive functions of the MFC, considered above, we expect (1) to observe enhancements of oscillatory power in theta and perhaps other frequency bands during action monitoring; (2) to confirm that ERP and oscillatory patterns recorded from surface EEG correspond (functionally and
Fig. 1 – Localization of electrode placement and lesion. (A) Sagittal MRI of patient AP prior to (left; taken on a 1.5 T scanner) and thirteen weeks following (middle; taken on a 3T scanner) surgery. The small black circles on the left MRI are caused by signal drop-out artifacts from the electrode contacts, and do not reflect missing or damaged brain tissue. At right is the planning scheme of the electrode location. (B) Pre-surgical planning map in patient RK. A post-implantation MRI for this patient was not available.

Fig. 2 – Overview of the task and behavioral performance. (A) Two example trials, separated by an inter-trial-interval. The numbers below each box corresponds to the length of time the stimulus was on screen. (B) Behavioral performance for patient RK. (C, D) Behavioral performance for patient AP prior to (C) and 13 weeks following (D) surgical removal of part of the medial frontal cortex.
temporally) to those recorded directly from intracranial sources in the MFC; and (3) to establish whether pre- versus post-response conflict is represented by electrophysiological oscillations in different frequency bands and anatomical locations. These findings provide novel insights into the neural mechanisms of action monitoring, and increase our understanding of the neurocognitive functions of the MFC during flexible, goal-directed behavior (Fig. 1).

2. Results

2.1. Behavioral performance

RK performed quite well at the task (Fig. 2b). Accuracy was 97% for congruent trials and 98% for incongruent trials. RTs increased for incongruent compared to congruent trials, from 726 to 852 ms (std: 154/157; p < 0.001), obtained by boot-strapping; see Experimental procedures). We did not analyze reaction times for incorrect trials because there were so few errors (these trials were not included in the behavior or EEG analyses). We also analyzed whether these effects were dependent on whether the previous trial was congruent or incongruent (di Pellegrino et al., 2007), but we found no significant effects or interactions for either patient, and thus combined the data for these analyses.

Patient AP performed poorly during her first testing session (Fig. 2c), with accuracy during congruent and incongruent trials at 53% and 51%, respectively. AP used the correct hand on 99% of trials; thus, most of her errors were driven by using the incorrect response (upper or lower) within the appropriate hand. However, there were no differences between RTs during correct and incorrect trials (p = 0.44), so we combined these for subsequent analyses. RTs increased for incongruent compared to congruent trials, from 837 to 974 ms (std: 174/248; p < 0.001).

AP’s performance increased markedly at the second testing session (13 weeks after a piece of her MFC was removed; see Fig. 2). Here, performance was comparable to RK’s. Accuracy was 97% for congruent trials and 97% for incongruent trials (Fig. 2d). RTs increased for incongruent compared to congruent trials, from 707 to 826 ms (std: 161/166; p < 0.001). As with RK, we did not analyze reaction times for incorrect trials during this session because there were so few errors.

2.2. Oscillatory activity in medial frontal cortex

In Fig. 3 we display the time-frequency plots, separately for each patient, electrode strip, and condition (incongruent versus congruent). Note that because RTs differed on each trial, we separated the plots into peri-cue and peri-response plots. Several findings were consistently observed. First, pre-response suppression of beta (~15–30 Hz) increased in intensity with more posterior electrodes. This beta suppression began around 300 ms following the cue, and lasted until around 200 ms or longer after the response was made. In patient RK, we also observed increase in post-response theta (4–8 Hz) from the response until around 400 ms following the response. The post-response theta, as well as post-cue alpha (~8–12 Hz) enhancement was accompanied by increases in inter-trial phase coherence, but the pre-response beta suppression was not associated with a change in the ongoing phases of the oscillations (Supplemental Fig. 1). As seen in Fig. 4, oscillation power differences between incongruent and congruent trials were statistically significant in several time-frequency clusters, particularly in the peri-response/theta range, when using a map-wise threshold in each patient (see Experimental procedures for statistical analysis procedures).

As seen in Figs. 3b, c, f–h, the post-response theta power enhancement was more pronounced in more anterior electrodes, whereas the pre-response beta suppression was more pronounced in posterior electrodes. Strong post-response theta enhancements were not observed in patient AP, and she did not have electrodes that went as far anterior as RKs, consistent with the anatomical localization of these effects. AP did exhibit an increase in pre-response beta suppression in more posterior electrodes. To examine this anatomical gradient of power distributions more closely, we correlated pre-response beta power with post-response theta power across electrodes. We observed a highly significant positive correlation within each patient (Figs. 3d, i), such that electrodes that exhibited larger pre-response beta suppression had smaller post-response theta enhancements, and vice-versa.

We next examined whether there were significant differences in oscillation power across incongruent and congruent conditions. The most prominent difference was in theta/alpha in anterior electrodes, where post-response power from the time of the response until around 300 ms thereafter was greater for incongruent compared to congruent trials (Fig. 4). Following the cue, we found that incongruent trials (compared to congruent trials) were associated with enhanced beta suppression in more posterior electrodes. These post-cue differences were statistically robust in patient RK, and also observable in patient AP. Statistical comparisons were conducted on each time-frequency pixel, using stringent within- and across-electrode thresholding (see Experimental procedures).

2.3. Surface ERPs

In addition to intracranial EEG electrodes, both patients had some surface electrodes. Patient RK had electrode Cz but not Fz, whereas patient AP had electrode Fz but not Cz during the first visit, and both Cz and Fz during the post-surgery visit.

Fig. 3 – Changes in task-related spectral power, plotted separately for each patient and electrode strip. Time-frequency plots in A and E are averaged over all electrodes in specified strip. (B, C, F, H) Results from a pre-response beta window (15–30 Hz, ~200 to 0 ms prior to onset of response) and post-response theta window (4–8 Hz, 100 to 300 ms after the response) for each electrode. (D, I) Correlation of pre-response beta (y-axis) and post-response theta (x-axis) across electrodes. Each dot represents a single electrode. Note that because RTs were different on each trial, we separated the peri-cue and peri-response plots. The labels “IHLa,” etc. refer to electrode strip labels: IH is inter-hemispheric; L (R) is left (right); and the small letters correspond to which strip (see electrode schemas in B, C, F, and H for localization).
(choice of electrodes is at the discretion of doctors, and varies patient-to-patient). As seen in Fig. 5, both patients exhibited a P300-like response following the cue. At the time of response, both patients exhibited a negative peak at around 50 ms following the response, which resembles the correct-related negativity (CRN). Patient RK exhibited a large P300-like
potential following the response, which was absent in AP, both at Fz and at Cz, pre- and post-surgery.

It has been previously demonstrated that a medial frontal lesion leads to a reduced neural differentiation between errors and correct responses (Swick and Turken, 2002). We therefore investigated whether a similar effect occurred in our patients, particularly in patient AP, for whom we obtained EEG recordings prior to and following surgical removal of pathological tissue within the MFC. We tested for conflict effects both following the onset of the cue, and following the response (van Veen and Carter, 2002). For the cue-locked EEG, we used a time window of 50 ms surrounding the most negative peak at around 200 ms following the cue (perhaps corresponding to the N2). For patient RK, we found a significant ERP conflict effect for the negative peak (peak time: 230 ms; $p=0.03$; Fig. 5a). For patient AP's pre-surgery session, the N2 occurred slightly later than in patient RK and was not significant different between congruent and incongruent trials (peak time: 308 ms; $p=0.51$; Fig. 5b). During the post-surgery visit, the post-cue conflict effect was significant at Fz at two selected analysis windows (peak time: 362 ms; $p=0.01$; and peak time: 376 ms; $p=0.016$; Fig. 5c); at Cz there were two negative peaks; the first showed a significant difference (peak time: 248 ms; $p=0.05$; Fig. 5d), and the second did not (peak time: 310 ms; $p=0.35$).

Next, we examined conflict effects following the response, here using a 50-ms window surrounding the most negative peak following the response (possibly corresponding to the CRN). For patient RK, we found that ERPs following responses during incongruent trials were significantly more negative than were ERPs following responses during congruent trials (peak time: 50 ms; $p=0.05$; Fig. 5a). For patient AP, during the pre-surgery session, ERPs were marginally significantly more negative during congruent compared to incongruent trials (i.e., the opposite of what was observed in RK and post-surgery; peak time: 40 ms; $p=0.06$; Fig. 5b). However, this ERP peak was relatively more extended compared to that in RK and in post-surgery tests; thus it is unclear whether this ERP reflects the same CRN process. We next re-examined the congruent-incongruent difference separately for errors and correct responses. The previous effect was significant when taking only correct responses into consideration (peak time: 36 ms; $p=0.02$), and was not significant, though numerically in the same direction, for error responses (peak time: 40 ms; $p=0.33$). Finally, we examined whether there were differences between error and correct responses during congruent and incongruent trials, but there were none (peak time: 48 ms; $p=0.23$ and peak time: 28; $p=0.27$, respectively). During her post-surgery visit, post-response ERPs were significantly more negative during incongruent compared to congruent trials at Fz (peak time: 32 ms; $p=0.04$; Fig. 5c) and at Cz (peak time: 36 ms; $p<0.001$; Fig. 5d).

### 2.4. Intracranial ERPs

Examining the ERPs recorded from intracranial sites provides insight into the possible contributing intracranial generators of the surface-recorded ERPs. To do this, we plot the topographical effects of the conflict effect at the peak time points identified from the surface data (see previous section). This provides a snapshot of the electrophysiological activity in intracortical foci at the peak time of the surface ERP components. All ERPs plotted continuously over time are displayed in the Supplemental Information section (Supplemental Figs. 2–

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**Fig. 4** – Differences in oscillation power between incongruent and congruent trials. Red colors indicate more power for incongruent trials, and blue colors indicate more power for congruent trials. Pixel clusters that were significant at $p<0.05$ at each electrode in that electrode strip, and at a false discovery rate-corrected value across electrodes of $p<0.05$ are outlined in black. (A) Shows results from patient RK; (B) shows results from patient AP. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
As seen in Figs. 5e, f, the direction of the intracranial ERPs effects largely paralleled those on the surface. The post-cue intracranial effects were present throughout, although stronger in more rostral sites, whereas the post-response effects were generally stronger in more posterior sites. In a complementary analysis, we correlated the magnitude of the EEG in these time windows (see above) across trials for each intracranial site with the surface EEG electrode, separately for the post-cue and post-response ERP components. We observed positive correlations throughout the MFC (see Supplemental Fig. 4), which were generally on the order of 0.1 to 0.25 (Pearson’s correlation coefficient), and, in most cases, were not statistically significant.

2.5. Phase coupling between intracranial and surface electrodes

In our final set of analyses, we examined dynamic spectral phase coupling between intracranial and surface electrodes. We transformed phase coherence values into percent change from baseline levels of phase coherence, which allowed us to examine how the task induced increases or decreases in cross-site coherence [e.g., Fell et al., 2001, 2003]. As seen in Fig. 6, both increases and decreases in phase coherence between depth electrodes and Cz were observed throughout the trial. The most prominent changes in patient RK were a pronounced decrease in coupling with surface electrodes prior to

Fig. 5 - (A–D) ERPs recorded over the scalp for incongruent (blue) and congruent (red) trials for each patient, experiment session, and electrode (see labels). Gray boxes illustrate the time windows used for statistical analyses. We used two windows for patient AP’s post-surgery session because an unambiguous N2-like component was difficult to identify. Asterisks indicate that the conditions differ in those windows at $p < 0.05$; plus sign indicates the difference is $p < 0.10$. In E and F, we illustrate the magnitude of the intracranial ERP difference between incongruent and congruent trials at each electrode during the peak of the selected surface ERPs. This provides a visual window into the activities of deep sources during surface potential differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Fig. 6 – Inter-channel oscillation phase coherence (ICPC) between intracranial electrodes and surface electrodes (Cz for patient RK and Fz for patient AP).
the response in the alpha and lower beta range (8–15 Hz), and an increase in coupling following the response in the theta and alpha range. These changes in coupling were generally stronger in more anterior and ventral intracranial contacts (Fig. 6b). There were no significant differences in ICPC values between congruent and incongruent conditions, although there were trends towards relatively increased coupling during incongruent compared to congruent trials in the beta frequency range, and increases in coupling during congruent compared to incongruent trials in the alpha frequency range (see Supplemental Fig. 5).

3. Discussion

Here we examined the behavioral performance, intracranial and surface electrophysiology of two patients who had electrodes implanted along the inner wall of MFC. The modified Flanker task was successful at inducing response conflict, evidenced by the increased RTs for incongruent conditions. Patient RK performed quite well at the task. Interestingly, patient AP performed better following surgery compared to before surgery, although RTs suggested that she was sensitive to the conflict manipulation in both sessions. In general, RTs in both patients were longer than is typically observed in young healthy subjects. However, epilepsy patients typically are slower than healthy controls. This phenomenon seems not to systematically depend on the age of onset of epilepsy, EEG abnormalities, or treatment (Bruhn and Parsons, 1977; Mitchell et al., 1992). Additionally, we did not stress speeded reactions. Despite the longer RTs, however, the expected conflict effects on RTs were observed and were significant. Because conflict effects were observed in absence of errors, these findings add to a growing literature supporting the role of the MFC in response conflict monitoring/action selection, rather than response error monitoring (Bartholow et al., 2005; Botvinick et al., 1999; Gehring and Fencsik, 2001; Swick and Turken, 2002; Ullsperger and von Cramon, 2001). In the present study, it is difficult to disentangle conflict monitoring from outcome evaluation, risk prediction, action selection, or regulative action control, because each and any of these processes may engage increased activation during incongruent compared to congruent trials. Thus, the pre-response activity we observed may reflect each or any of these action monitoring processes. Indeed, outside laboratory settings, some of these processes might not be neurocognitively distinct. Also, with regard to differentiating neural responses to conflict from neural responses to errors, we unfortunately had too few error trials to make a reliable dissociation, because the small number of error trials would lead to a small signal-to-noise ratio for this condition. Although patient AP showed no ERP difference between error and correct trials (i.e., no ERN) during the pre-surgery session, it is possible that errors were not perceived due to the low accuracy. Note that most of AP’s pre-surgery errors were from selecting the incorrect response within the correct hand; given that she was able to verbally repeat the instructions, it is possible that her deficit was related to the fine motor control necessary to alternate rapidly between closely spaced response options.

3.1. Oscillatory correlates of pre- and post-response conflict

Task-induced electrophysiological oscillations are prominent in the medial frontal cortex, particularly in the theta frequency range. In the present study, power in beta (15–30 Hz) and theta (4–8 Hz) frequency bands were significantly modulated by the task. Increases in oscillatory power are driven in large part by increased coherent and rhythmic activation of local inhibitory neurons, which help to entrain networks of pyramidal cells into coherent, rhythmic oscillations (Bartos et al., 2007; Mann and Paulsen, 2005; Mitzdorf, 1987; Wilson and Kawaguchi, 1996). The phase reset of ongoing oscillations (Supplemental Fig. 1) might reflect the realignment of these neural networks into a common and cohesive processing unit.

We found that beta power was suppressed from before until shortly after the response was made, and theta power increased following the cue and response. Beta oscillation suppressions around motor and supplementary motor regions have been linked to motor preparatory processes (Miller et al., 2007; Neuper et al., 2006; Pfruntschler et al., 2003) and are thought to reflect decreased global neural coherence during the processing and planning of movements. Following the response we also observed enhancements in theta power. The pre-response beta and post-response theta changes are related to each other, as seen in their strong correlations in Fig. 3. Indeed, the anatomical distribution of beta and theta suggests a functional/anatomical double distinction between processes engaged by more dorsal versus rostral regions of the MFC: dorsal regions, which exhibited significant pre-response beta suppression and little post-response theta enhancement, may be preferentially involved in signaling or resolving pre-response conflict, whereas rostral regions, which exhibited significant post-response theta enhancement and little pre-response beta suppression, may be preferentially involved in post-response monitoring, and perhaps signaling the need for other structures, such as the lateral or dorsolateral–prefrontal cortex, to adjust control or decision processes on the following trial (MacDonald et al., 2000).
More generally, our findings highlight the importance of examining event-related oscillations in addition to ERPs. For example, the beta suppression effect had no observable correlate in the ERPs. Indeed, the pre-response ERPs suggest no changes in activity. This was likely because changes in beta power were not accompanied by increases in phase coherence (indeed, phase coherence values were close to zero; see Supplemental Information). This means that when averaging over many trials, the non-phase-locked oscillations will cancel out, resulting in an ERP hovering about 0. In contrast, theta (as well as lower frequencies) power increases following the response were associated with increases in phase coherence, and thus may have contributed to the observed ERPs. Indeed, the error-related negativity comprises significant phase-locked and non-phase-locked theta power increases (Luu et al., 2004; Trujillo and Allen, 2007), although it has been questioned how well this can be measured (Yeung et al., 2004, 2007). Another advantage of the current method is that functional MRI might not be able to differentiate among activities in different frequency bands, or between increases versus decreases in event-related oscillatory power. For example, Ullsperger and Von Cramon (Ullsperger and von Cramon, 2001) demonstrated, using functional MRI, that activity in different frequency bands, or between increases versus decreases in event-related oscillatory power. For example, Ullsperger and Von Cramon (Ullsperger and von Cramon, 2001) demonstrated, using functional MRI, that separate subregions in the MFC are involved in conflict versus error processing. It is possible that the neural networks underlying these activations had different oscillatory characteristics, in a similar way as what we observed.

3.2. Surface ERPs and pre- vs. post-surgery results

During the pre-surgery session, AP exhibited no ERP differences between correct and error trials. This is consistent with a finding from Swick and Turken (Swick and Turken, 2002), in which they reported that a patient with an anterior cingulate lesion showed a reduced error-related negativity. However, Swick also reported an intact conflict effect in the patient. During the pre-surgery session, AP showed no cue-locked conflict effect and a marginally significant response-related conflict effect that, but AP did show a significant cue- and response-response conflict effect at both Fz and Cz following the surgery. However, this pre-surgery cue-locked conflict effect was in the opposite direction as would be expected from previous conflict studies, despite the fact that RTs did demonstrate expected conflict effects. Thus, our ERP results appear to buttress this aspect of Swick and colleagues’ conclusion that this region of the MFC may not be critically involved in signaling conflict. It seems that action monitoring is not confined to the dorsal region of MFC lesioned in AP, but rather is a more widely distributed neural process. Conflict effects in absence of errors have previously been observed in surface ERP studies (Bartholow et al., 2003).

One striking difference between the ERPs recorded from RK and AP is that RK exhibited a strong pre-response P300-like component, which was completely absent from AP both pre- and post-surgery. However, the early post-response peak, which resembles the CRN, was similar for RK and AP following surgery. It is tempting to speculate that the MFC that was resected in AP was related to this ERP differences. It is possible that the resected area of tissue were likely not healthy prior to the surgery. However, Swick and Turken’s (Swick and Turken’s (2002) cingulate lesion patient RN displayed a P300-like component. It is possible that individual differences factors unrelated to AP’s MFC drove this difference.

There were also striking differences in accuracy performance in patient AP prior to, compared to following, surgery. However, AP’s RT results were consistent across sessions and with RK’s RTs, suggesting that the high error rate may have been due to the tissue that was removed. One interesting, though speculative, possibility is that dysfunctional activity in this medial frontal region, which may have caused the patient’s seizures, disrupted activity in other regions of the brain, such as dorsolateral prefrontal cortex and premotor cortex. Thus, resecting the tissue may have removed the “aberrant node” in this neural network, thus restoring normal function on a global level. Consistent with this possibility, in some cases performance on several cognitive tasks including memory and intelligence tests may improve following surgical removal of epileptic tissue (Leijten et al., 2005; Lendt et al., 2002; Sanyal et al., 2005).

3.3. Oscillation and ERP coupling between medial frontal cortex and surface electrodes

We found dynamic modulations in the extent to which oscillatory activity in the intracranial electrodes and scalp electrodes were coupled. The overall pattern of results from this coherence analysis was similar to the effects observed when examining the intracranial electrodes alone (e.g., compare Figs. 2 and 4). This demonstrates that EEG recordings from scalp electrodes are similar to activity that can be directly measured from intracranial sources. Some researchers also refer to ~10-20 Hz oscillations in sensory-motor cortices as “mu” rhythms (Miller et al., 2007; Pfurtscheller et al., 2003; Ulloa and Pineda, 2007). It is possible that the alpha synchronizations observed here are functionally similar to these mu rhythms, although mu activity typically refers to more primary sensory-motor regions, whereas our alpha coupling was relatively ventral and anterior. Regardless of nomenclature, these findings provide important insight into the functioning of the MFC, and its relation to activity observed over the scalp, during action monitoring. The pre-response desynchronization relative to baseline mirrored the pre-response beta suppression in the intracranial contacts, although the frequency range of the desynchronization was slightly lower than the overall beta suppression effect. In contrast, post-response coherence was robust in the theta and alpha ranges, increasing 20% or more relative to baseline levels of coherence. This is interesting in light of the suggestion that response-locked ERPs, including the error-related negativity, comprise largely enhanced theta activity (Luu et al., 2004; Trujillo and Allen, 2007; Yordanova et al., 2004), as discussed above. Our findings support this idea, and link surface theta enhancements to theta activity in the anterior cingulate and surrounding MFC.

Phase coupling in the theta-alpha range was enhanced for incongruent compared to congruent trials just following the response, especially in more anterior electrodes. This finding complements the enhanced response-locked ERP for incongruent compared to congruent trials. Thus, it appears that action monitoring is accompanied by enhanced long-range
neural synchronization. Unfortunately, we did not have enough surface electrodes to compute source generator estimates and compare these estimates with the intracranial data. However, such analyses have been conducted for epileptic activity, and the results suggest a reasonable correspondence between source estimates and intracranial potentials (Benar et al., 2006), at least during epileptic spikes.

Aside from coupling in the frequency domain, we also observed correspondences between intracranial and surface ERPs (i.e., in the time domain). This was noteworthy in the post-response ERP in patient AP, in which there was a trend towards an inverse-conflict effect, and although this was not statistically significant, the direction of the effect was mirrored in the intracranial sites. There were also moderately robust positive correlations between all intracranial contacts and surface EEG (Supplemental Information). On the one hand, these findings (both the time- and frequency-domain couplings) support the large ERP literature that focuses on medial frontal-generated conflict- and error-related surface ERPs. On the other hand, the correspondences between intracranial and surface EEG were not overwhelmingly strong, either in the time or frequency domain. Indeed, trial-by-trial EEG magnitude correlations were in the range of 0.1 to 0.25, and the percent change in ISPC was also in the range of 10–20%. This is an important finding because it demonstrates that the surface ERPs observed in such studies cannot be fully explained by focal sources that lie along the midline of the MFC: Rather, these conflict-related (and perhaps other cognitive- and perceptual) surface ERP components must reflect activity integrated over larger cortical areas, for example including dorsal and lateral frontal cortical sites, and perhaps parietal cortex as well (Brazdil et al., 2002). Future studies could further shed light on this issue by examining the relations among intracranial and surface potentials during other tasks and in other brain regions (O’Connor and Starr, 1985; Poepel et al., 2007).

3.4. Functions of the medial frontal cortex during response conflict

Although the anterior cingulate and surrounding medial frontal cortex is one of the most commonly activated regions in functional neuroimaging (Duncan and Owen, 2000), growing evidence highlights a specific role of the medial frontal cortex in action selection/monitoring, particularly in the face of conflict or difficult decisions (Ridderinkhof et al., 2007, 2004a, 2004b). Together, our and previous findings demonstrates that the medial frontal cortex’s role goes beyond error monitoring/correction to more general response conflict monitoring. For example, Bartholow and colleagues (Bartholow et al., 2005) provided evidence that the conflict effect reflects a disparity between the response strategy used and the internal representation of the appropriate response strategy. This might also be the case in reinforcement learning, in which a “conflict effect” can be observed when subjects select a suboptimal, though not strictly incorrect, response (Frank et al., 2005).

Given the involvement of the medial frontal cortex in several kinds of processes including response conflict, reinforcement learning, pain perception, emotion, memory, it is possible that spatially overlapping populations of neurons within the medial frontal wall are responsible for different cognitive/emotional processes, or that similar neural networks are recruited to serve different functions in different circumstances. A related possibility is that different functions are represented at different frequency bands in partially spatially overlapping networks. For example, in our study, theta was prominent following the response in more anterior electrodes whereas beta suppression was prominent prior to the response in more posterior sites. This suggests that pre- and post-response conflict is represented by different neural mechanisms in space and frequency range. Other experiments provide additional evidence that different dimensions of information may be processed preferentially in different frequency bands. For example, several related studies suggest that relatively global versus local features of language may be processed in theta and gamma frequencies, respectively (Giraud et al., 2007). Additionally, Marcos-Pallares and colleagues (Marco-Pallares et al., 2008) recently suggested that an increase in beta oscillations reflects enhanced cognitive control on correct trials that follows error responses; this beta power effect correlated with the degree of post-error slowing. Interestingly, this effect appears to be driven by relatively less beta suppression during correct trials following errors compared to correct trials following other correct trials. Based on our findings, it is possible that their beta effects were generated in posterior cingulate cortex. In the present study, there were no significant trial-to-trial RT effects, so we did not test for similar effects.

3.5. Limitations and conclusions

We acknowledge several limitations to the current study. First, these patients suffer from epilepsy that was acute enough to warrant pre-surgical electrode implantation. For AP, this resulted in the surgical removal of parts of MFC, and histology confirmed that this tissue was not entirely healthy. However, some of the oscillation results were similar to RKs, suggesting that the contacts recorded from functioning tissue. Note that because these contacts were placed mid-sagittally, it is possible that tissue in the contralateral hemisphere (which was not identified as being unhealthy in patient AP) contributed to the results via volume conduction, which is on the order of up to a few centimeters for intracranial depth contacts (Goff et al., 1978). Another limitation is that there is a small number of patients included in this study; such patients are rare. However, despite these limitations, many patterns of effects were similar across the two patients, and some features of the surface EEG data resemble previous ERN studies, suggesting that our findings are generalizable to healthy brains. This rare opportunity to examine both intracranial sources, and their relations to surface electrodes, provides some advances over previous studies, and provides a novel link for the underlying neural generation of the response-related conflict effects.

4. Experimental procedures

4.1. Patients

Two patients with pharmacoresistant epilepsy (both women; aged 17 [AP] and 53 [RK]) participated in the study. Recordings
were performed at the Department of Epileptology, University of Bonn, Germany. No seizure occurred in either of the patients during the 24 h preceding the experiment. The location of electrode placement was made entirely on clinical grounds (see Fig. 1). Patient RK suffered from a cryptogenic epilepsy with single-focal seizures and hypomorphic complex-focal seizures. The MRI showed no typical epileptogenic lesion. Surgery was not performed because an ictal onset area could not be defined during invasive pre-surgical evaluation. Patient AP suffered from a symptomatic epilepsy with complex-partial and secondary generalized tonic-clonic seizures, due to a focal cortical dysplasy of type IIb (i.e., a dysplasia with cellular abnormalities including balloon cells) according to the scale proposed by Palmini and Lüders (Palmini and Lüders, 2002). After invasive pre-surgical evaluation, an extended right frontal paramedian lesionectomy was performed including cortical areas beneath the contacts IHRa 1–4, IHRb2–4 und IHRc4 while protecting the motor cortex. AP remained seizure-free at the time of this writing (approximately 16 months after surgery). Fig. 1 displays the pre- and post-surgery MRI for patient AP. To localize the lesion anatomically, we normalized this MRI, drew a mask that covered the lesion, and calculated the percentage of the lesion that was in each Brodmann area. We found that 65.5%/22.3%/12.2% of the lesion was in Brodmann areas 6, 8, and 32, respectively. Therefore, the lesion affected mostly pre-SMA, although surrounding areas of the medial frontal and anterior cingulate cortices were resected as well.

During the time of the experiments, both patients received antiepileptic medication with plasma levels within the therapeutic range (RK: Carbamazepine; AP: Clonazepam, Lamotrigine, Oxcarbazepine). With regard to background EEG, antiepileptic drugs may lead to a slowing of the dominant rhythm and increased slow activity [e.g., Duncan, 1987]. But there are hardly any studies on the effects of antiepileptic drugs on cognitive EEG and ERPs. Carbamazepine has been shown to produce an increase of beta activity during mental arithmetic tasks (Marciani et al., 1992) and a decrease of the contingent negative variation (Rockstroh et al., 1987). There is no evidence that antiepileptic medication impacts the difference between response conflict conditions.

4.2. Task

Patients sat comfortably in a chair in an EEG testing room designed to monitor EEG and other biophysical signs. The experiment was run on a laptop computer using Presentation software, and was placed on a movable table approximately 2 ft in front of the patients. The laptop was equipped with a parallel trigger cable, which delivers square wave pulses to the EEG recording device, and provides millisecond precision information about when stimuli came on-screen, and when responses were made.

To examine neural processes during response conflict, we used a modified version of the Flanker task (Eriksen and Eriksen, 1974). An outline of the task is displayed in Fig. 2a. On each trial, patients saw five vertically aligned arrowheads on either the right or left side of a fixation dot. Their task was to ignore the upper and lower two arrowheads, and to respond as quickly as possible according to the direction (up vs. down) of the middle arrowhead and using the hand corresponding to the side of presentation (left hand response for stimuli presented on the left side; right hand response for stimuli presented on the right side). Although the term “response conflict” generally refers to situations in which one of several possible responses must be selected, the term has been operationalized in different ways, and therefore may be difficult to disentangle from other terms such as “action selection” or “decision-making.” We refer to trials in which all five arrowheads pointed in the same direction as “congruent” and to trials in which the middle and outer arrowheads pointed in opposite directions as “incongruent.” For convenience, we use the term “conflict effect” to refer to differences between these conditions, without implying that other processes such as action selection or uncertainty resolution did not occur or are not relevant. The stimulus remained on screen for 1500 ms, or until a response was made. To increase difficulty, a randomly selected vertical offset ranging from –30 to +30 pixels (approximately two cm from the patients’ viewing distance) was applied to the stimulus. This prevented patients from simply focusing on the center of the screen while ignoring stimuli under and above the horizontal midline of the screen. All conditions (side of presentation, congruent versus incongruent arrowheads, up versus down) were equally likely to occur, and were presented in a pseudo-random order, defined by an m-sequence previously shown to maximize statistical power (Buracas and Boynton, 2002). To indicate their responses, patients used a USB video game controller, which had top and bottom buttons on the left and right back side. These buttons were accessible with the pointer fingers of each hand; patients were instructed to use only their pointer fingers. A 1500-ms inter-trial-interval separated each trial. Because behavioral performance and EEG results were similar for left- and right-side trials, we combined these to increase statistical power. There were 600 trials in total, broken into two blocks of 300 trials each, and self-paced rest breaks were provided every 30 trials. Prior to the start of the experiment, patients went through at least 10 practice trials, or until they indicated that they understood the task. Before we began testing, patients repeated the instructions of the task to us; this was how we confirmed that they understood the instructions.

Because performance was so high (97.5% and 97% accuracy for patients RK and AP post-surgery, respectively), there were only 10–15 error trials to analyze. Although this may be sufficient if there were many patients to average over, this is insufficient for within-patient analyses, and would make condition differences would be difficult to interpret. Therefore, we did not include error trials in our analyses, and the present findings focus more on response conflict than on error detection. However, error-related activity is plotted in the Supplemental Information section (Supplemental Figs. 6 and 7).

4.3. Behavior analyses

The dependent variables were reaction time (RT), defined as the latency from the onset of the visual stimulus until the button press in milliseconds (ms), and accuracy, defined as the proportion of trials in which a correct response was made. To
test for differences between conditions, we did not use parametric statistics (e.g., ANOVA) because we wished to conduct statistics within each patient, and the within-patient data fail to meet assumptions of ANOVA, such as independence of observations. Therefore, we used the following data-based boot-strapping procedure. First, we calculated the difference in mean RT between conditions (e.g., congruent vs. incongruent). Next, we randomly re-assigned the RT for each trial to condition, such that the RT for each trial was randomly assigned to, e.g., congruent or incongruent condition. The mean RT difference between conditions was again calculated. This procedure was repeated 1000 times, creating a distribution of RT condition differences under the null hypothesis that there are no differences between conditions. Finally, the number of boot-strapped RT differences that exceeded the observed RT difference, scaled by the number of iterations (1000), was taken as the p-value. Visual inspection confirmed that the shape of the RT distribution (Gaussian with a positive skew) was similar for both real and boot-strapped RTs. We also used the median instead of the mean (because of the positive skew), and the results were the same.

4.4. EEG recording and analyses

Depth EEG recordings were referenced to linked mastoids, recorded at a sampling rate of 1000 Hz, and band-pass filtered (0.01 Hz (6 dB/octave) to 300 Hz (12 dB/octave)). All analyses and illustrations were conducted in Matlab 6.5, utilizing custom-written software. Time-frequency decomposition was conducted via wavelet analysis, in which the EEG time series was convolved with a set of complex Morlet wavelets, defined as a Gaussian-windowed complex sine wave: \( \hat{Z}(t) = \frac{\hat{e}^{2i\pi f t}}{\sqrt{2\pi} \sigma} \). \( f \) is frequency, which increased from 3 to 100 Hz in 70 logarithmically spaced steps. \( \sigma \) defines the width of each frequency band, and is set according to 4.7/(2\( f \)). 4.7 is a common value used in other studies (e.g., Trujillo and Allen, 2007). We also explored other values, ranging from 3 to 10; the resulting time-frequency maps were similar for values in this range. After convolution of the wavelet with the EEG, power was defined as the modulus of the resulting complex signal \( Z(t) \) (power time series: \( P(t) = real[Z(t)]^2 + \text{imag}[Z(t)]^2 \)). Oscillation power decreases in a 1/f fashion; this makes it difficult to compare and visualize effects across multiple frequency bands. DB scaling provides a useful method for converting data from different frequency bands into the same scale, thus allowing direct visual and numeric comparison of effects across different frequencies. Converting task-induced power time courses to a decibel (dB) scale is done with the following equation: \( 10 \log_{10}(\text{power/baseline}) \). The baseline was defined as average frequency power from \(-300\) to \(-200\) ms prior to the onset of the cue, similar to previous studies (Luu et al., 2004; Trujillo and Allen, 2007). We used the pre-cue baseline period for both cue- and response-locked data. This was done because temporally extended, pre-response oscillatory activity would not be observable if it were included in the pre-response baseline. This choice of baseline thus allowed us to examine changes in oscillatory power compared to a pre-task baseline, rather than power relative to other task-related events.

Inter-trial phase coherence measures the consistency of phase values at each point in time over trials. Phase coherence values vary from 0 to 1, with 0 indicating that phase values at a particular frequency are random across trials at that point in time, and with 1 indicating that phase values are exactly the same across trials at the point in time. To calculate inter-trial phase coherence (displayed in the Supplemental Information section), the EEG data were convolved with Morlet wavelets, as described above. However, instead of extracting power values from the result of the convolution, phase angle values were extracted: \( \phi_j = \arctan(\text{imag}[Z(t)]/\text{real}[Z(t)]) \). Phase coherence is defined as: \( \text{ICPC} = \frac{1}{n} \sum_{t=1}^{n} e^{i(\phi_j - \phi_k)} \), where \( n \) is the number of trials. This produces a phase coherence value for each time \( t \) and each frequency band, and reflects the extent to which oscillation phase values are consistent across trials at that point in time-frequency space.

Inter-channel phase coupling (ICPC) measures the extent to which oscillation phases are similar across different electrodes. Mathematically, it is performed using a similar statistical measure as phase coherence, described in the previous paragraph. Here, phase values are extracted from two electrodes, and their phase values are subtracted: If the phase values from the two electrodes fluctuate in synchrony over a period of time, their difference will be constant, leading to ICPC values close to 1. The equation is similar to that for inter-trial phase coherence: \( \text{ICPC} = \frac{1}{n} \sum_{t=1}^{n} e^{i(\phi_j - \phi_k)} \), where \( n \) is the number of points, \( \phi_j \) and \( \phi_k \) are the phase angles of electrode \( j \) and \( k \).

To visualize the effects over electrode positions, we first digitized the electrode schemes, identified the X- and Y-coordinates of each electrode, mapped EEG measures onto these positions taken from specified windows in time-frequency, smoothed the resulting image by convolution with a \( \times 25 \) pixel 2-D Gaussian filter (the size of the kernel is related to the image resolution, and does not affect the results), and color-coded the results overlay. Smoothing was done to improve visibility (otherwise the topographical maps would have single colored points); the time-frequency maps were not smoothed. In Fig 1, one can see the exact location of the electrodes in the post-implantation MRI for patient AP. Post-implantation MRIs were not obtained for patient RK. The electrode scheme is used for surgical pre-planning; the actual position of electrodes is similar, but not necessarily identical to, what is displayed in the planning scheme.

To assess whether there were differences in oscillation power across conditions, we used a boot-strapping procedure similar to what was described for RTS, above. Here, for each pixel in time-frequency space, the assignment of power to condition across trials was randomized, and the difference between conditions was calculated. This procedure was repeated 200 times, which resulted in a distribution, at each time-frequency pixel, of condition differences under the null hypothesis of no differences. We selected 200 iterations to reduce computation time; we observed negligible changes in the data distributions with increasing iterations. Next, a standardized \( z \)-value was created at each pixel, which was the distance of the observed difference from the mean of the distribution of the boot-strapped differences, scaled by the standard deviation of the bootstrapped distribution. This \( z \)-value therefore is an unbiased and un-scaled metric of the
distance of the observed difference away from the distribution under the null hypothesis. To identify pixels with statistically significant condition differences, we used a multi-pronged thresholding approach: First, each electrode in a strip had to exhibit the effect with an uncorrected significance of at least $p < 0.05$. Second, we calculated a one-sample $t$-test across electrodes within each electrode strip for each pixel in time-frequency space. The resulting map of $p$-values assesses the extent to which the effect is consistent across electrodes. If the $p$-value from the $t$-test was less than a false discovery rate corrected level of $p < 0.05$ [FDR, 28], it was considered statistically significant. The uncorrected pixel-level $p$-value for these maps that corresponded to the FDR corrected level ranged from 0.04 to 0.001, depending on electrode strip. Significant pixel clusters are outlined in black in the figures.

4.5. ERP analyses

ERPs were low-pass filtered at 20 Hz and baseline-corrected using a −200 to 0 ms baseline. This baseline period was subtracted from the ERP time series. Here, we used separate pre-cue and pre-response baselines, as is typically done. For statistical analyses, we used a boot-strapping procedure that was identical to that described above, except that as the dependent measure we used the average voltage potential from a window of 50 ms surrounding the most negative peak around 200 ms following the cue (possibly the N2), and a 50 ms window surrounding the most negative peak following the response (possibly the correct-related negativity, or CRN). We used a window instead of, for example, peak voltage, because single trial EEG traces from surface electrodes can be noisy, and a window approach is less susceptible to inadvertently identifying noise spikes as signal peaks. Because the putative N2 was difficult to identify in patient AP’s post-surgery session (Figs. 5c, d), we report results from two time windows.

Appendix A. Supplementary data


REFERENCES


