Error detection and the Error-related ERP in patients with lesions involving the anterior cingulate and adjacent regions

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Running Title: ERN in anterior cingulate lesioned patients

Total number of words: 5434 (excluding tables, figures, references)

Keywords: error detection, error-related negativity, ERN, ERP, anterior cingulate, anterior communicating artery, dorsolateral prefrontal cortex, CNV

Abbreviations: AACA (aneurysm of the anterior communicating artery), CNV (contingent negative variation), DLPFC (dorsolateral prefrontal cortex), EEG (electroencephalography), EOG (electrooculogram), ERN (error-related negativity), ERP (event-related potential), fMRI (functional magnetic resonance imaging), PET (positron emission tomography)

Acknowledgment:
Preparation of this paper was supported by the Centre de Neurosciences de la Cognition, Université du Quebec à Montréal, Canada, in part by the German Federal Ministry for Education and Research (BMBF) grant 01GD9821/3, and in part by grant # 122222-98 from the Natural Sciences and Engineering Research Council of Canada.

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Abstract

Evidence indicates that the anterior cingulate region generates what appears to be a specific electrophysiological marker for the monitoring of error responses. When an auditory or visual stimulus is presented in such a way that the subject is likely to make an error, averaged encephalography (EEG) trials to erroneous responses consistently show a negative-going waveform which has been coined the error-related negativity (ERN). We examined ERNs in patients with a ruptured aneurysm of the anterior communicating artery (AACA), who are particularly prone to showing damage in the anterior cingulate and adjacent regions, and frequently display a variety of behavioral and cognitive disturbances such as disorientation, confabulation, apathy, unawareness of deficit, and problems of attention, control and monitoring. We found that these patients generally did not produce an ERN in comparison to healthy control participants suggesting that the anterior cingulate is essential for the ERN response. However, the patients' error rates were comparable to that of the controls and they showed a dissociation between overt error awareness and ERN production, suggesting that the ERN does not simply represent an error detection signal.

Introduction

Patients with an aneurysm of the anterior communicating artery (AACA) can show a variety of behavioral and cognitive disturbances such as apathy, unawareness of deficit, confabulation, disorientation and attention, memory, control and monitoring problems (Ptak & Schnider, 1999; Schnider & Ptak, 1999; Shallice, 1999; von Cramon & Müller, 1998). These impairments have been associated with lesions in the anterior cingulate region and dorsolateral prefrontal cortex (DLPFC), that is, with structures in the frontal lobe that sustain rich reciprocal anatomical circuits passing through the caudate nucleus, globus pallidus and thalamus, and connecting to limbic, other frontal and parietal structures (Burruss et al., 2000; Cummings, 1995; Mega & Cummings, 1994, Mega et al., 1997; Mesulam, 2000a; Roland, 1993; von Cramon & Müller, 1998). The functional significance of the anterior cingulate, which is the most likely structure to be lesioned in patients with a ruptured AACA, has been studied in behavioral, lesion and imaging studies.

Functional imaging studies using positron emission tomography (PET) and functional magnetic resonsance imaging (fMRI) have shown activation of the anterior cingulate in tasks that involve attention allocation or selection such as overcoming a pre-potent response tendency, situations that require divided attention, during novel versus practiced task performance, and when required to select arbitrarily from a range of possible responses (for a summary and discussion see Carter et al., 1999). Carter et al. (1999) hypothesize a role for the anterior cingulate in response-conflict resolution.

Mesulam (1999, 2000a, b) points out the complex organization of the architecture, connectivity, and function of the cingulate gyrus. The anterior cingulate has prominent limbic affiliations with major connections coming from the amygdala which plays a role in linking drive and emotion to extrapersonal events and mental states. Furthermore, he observes that the anterior cingulate is consistently active in effortful cognitive tasks and perhaps is critical in the sustaining of this attentional effort.

Support for a role of the anterior cingulate in attentional and executive control also comes from studies investigating patients after bilateral cingulotomy for chronic intractable pain (Janer & Pardo, 1991; Cohen et al., 1999). These patients have shown impaired focused and sustained attention, deficits in response intention and self-initiated behavior and reduced behavioral spontaneity following cingulotomy, but unaffected language, visual perception, motor control, and memory functions. Similar to Mesulam (1999), Cohen et al. (1999) interpret the functional role of the anterior cingulate within an attentional network as one of influencing the initiation of action, that is, altering attentional focus to match changes in motivation, incentive, and task demands. The anterior cingulate has vast interconnections with other cortical and subcortical areas, allowing it to bridge attention and emotional processing by modulating the intensity of affective and motivational signals in accordance with task demands and by integrating the salience of the momentary fluctuations of environmental information.

A related but somewhat different perspective has been suggested by Luu et al. (2000a) who ascribe an emotional evaluation function to the anterior cingulate that may modulate motivational processes related to the subjective monitoring of behavior - such as the monitoring of error responses - as one aspect of executive function that involves self-regulatory mechanisms. It is the monitoring of error responses that is pertinent for the present work.

Error detection using the event-related potential (ERP) technique. Research using this technique has identified what appears to be a specific electrophysiological marker for the monitoring of error responses. This electrophysiological marker occurs in response to an auditory or visual task where the subject has to react to a critical target stimulus which is presented in such a way that the subject is prone to making errors. Whenever such an error is made, the averaged EEG trials to such incorrect responses in comparison to correct responses consistently show a negative-going waveform which has been coined the error-related negativity, ERN (Falkenstein et al., 1991; Gehring et al., 1990, 1993). The ERN occurs when errors of choice (incorrect responses on go-trials), errors of action (uninhibited response on NoGo-trials) (Scheffers et al., 1996), and errors of

inaction (taking too long to respond) (Luu, 2000b) are made. The ERN peaks around 100-150 ms following EMG activity onset (approximately 50 to 70 ms post keypress response time), shows an amplitude in the range of 10μV or larger in individuals, and is most prominent over the front and middle of the scalp (Dehaene et al., 1994; Gehring et al., 1993). The ERN can be elicited under error feedback conditions, that is detection of the error can be internally driven or signaled by external cues (Badgaiyan & Posner, 1998; Miltner et al., 1997; Scheffers et al., 1996). These observations have led to the conclusion that for the ERN to occur conscious internal monitoring is necessary, that is, the subject needs to be aware of having committed an error (Dehaene et al., 1994; Gehring et al., 1993; Miltner et al., 1997). The ERN is not affected by stimulus (Bernstein, et al., 1995) nor modality differences (Miltner et al., 1997) and is output-independent (Holroyd et al., 1998). The ERN does not seem to be associated with motor or pre-motor events, nor is the ERN part of the stimulus-response pathway (Badgaiyan & Posner, 1998; Leuthold & Sommer, 1999). Finally, the ERN has been associated with individual differences in the general impulsivity of response style (Pailing et al., 1999; Gehring et al., 2000) and affective distress (Luu et al., 2000a).

Despite difficulties in determining the neural generator site of the ERN due to spatial localization difficulties of dipoles (Badgaiyan & Posner, 1998), evidence from human and animal studies points to the neural generator of the ERN to be distributed somewhere along the medial prefrontal cortex, most likely within the anterior cingulate, and possibly the supplementary motor area (Dehaene et al., 1994; Holroyd et al., 1998; Niki & Watanabe, 1979). Although most researchers have related the ERN to the anterior cingulate, error-related activity has also been found in the dorsolateral frontal cortex (as well as in the left premotor cortex) in functional magnetic resonance imaging (fMRI) (Carter et al., 1998), that is, in a structure in the prefrontal cortex that has - like the anterior cingulate - been related to monitoring of response tendencies and the control of attention (Kammer et al., 1997; for a summary see Davies et al., 1999), and - unlike the anterior cingulate - also to working memory (Ferreira et al., 1998; Kammer et al., 1997; Klingberg et al., 1997). Furthermore, different generator sites within the cingulate have been suggested for response selection tasks and error feedback tasks (Badgaiyan & Posner, 1998).

Interpretation of these findings in terms of the functional significance of the ERN has led to various suggestions. Some view the ERN as a general error processing mechanism (Gehring et al., 1993; Leuthold & Sommer, 1999) or as a means of tracking human self-monitoring in real time (Luu et al., 2000a), whereas for others the ERN indexes response conflict (Carter et al., 1998) or serves an evaluative rather than strictly strategic function in the service of executive control (Carter

et al., 1999). It has further been proposed that the ERN is implicated in the remediation of erroneous behavior, and in particular the reflection of inhibitory processes (Bernstein et al. 1995; Gehring et al. 1993; Falkenstein, et al. 1999).

Patients with a ruptured aneurysm of the anterior communicating artery (AACA). Patients with a ruptured AACA are particularly prone to showing damage in the anterior cingulate region (including Brodmann areas 24, 25, 32) due to pressure on the tissue in proximity to the lesion and an interrupted blood supply to the fornical columns, the septal nuclei (both regions in close proximity to the anterior cingulate), and to the part of the anterior cingulate that corresponds to Brodmann's region 25 (von Cramon & Müller, 1998). The detection of the ERN as a possibly specific electrophysiological marker for error processing and its relationship to the anterior cingulate raises the question of whether this marker can be elicited in patients who have suffered damage to the anterior cingulate region. Previous studies of the relationship of the ERN and the anterior cingulate are based exclusively on healthy individuals. Gehring and Knight (2000) investigated the elicitation of the ERN in stroke patients with damage to regions supplied by the middle cerebral artery, but not in patients with damage to the anterior cingulate area. Studying the ERN in patients with lesions in the anterior cingulate has not been reported.

The purpose of our study was to investigate whether patients with a ruptured AACA and thus damage in the anterior cingulate area show an ERN, and compare these patients with healthy control participants. We hypothesized that a lesion involving the anterior communicating artery and thus damaging circuits in the anterior cingulate would decrease the likelihood of occurrence for the ERN.

Method

Participants

Five patients with a ruptured AACA and ensuing neurosurgical intervention (clipping of the aneurysm) were investigated and compared with 9 healthy controls (see Tables 1 and 2 for demographic details). Figure 1 (a-e) shows the lesion reconstructions from the MRI scans (Damasio & Damasio, 1989). The site of the implanted clip produced a field artefact in the MRI scan. Although all patients showed bilateral involvement, the lesion was more pronounced on the left side in patient EM and on the right side in patients IE and MH. All patients demonstrated lesions in the anterior cingulate region (MH’s lesion being more ventrally located) and three patients (EM, IE, MH) in the posterior orbitofrontal areas. The anterior part of the corpus callosum was affected in

patients EM and RF, the left basal ganglia in patient EM, and the right thalamus, temporal pole and hippocampus in patient EZ. Patient MH also demonstrated a small lesion in Brodman's areas 9, 44, and 46 due to the surgical procedure.

At the time of examination, all patients were at an intensive rehabilitation ward (early rehabilitation) set up for patients with severe behavioral and cognitive impairment after brain-damage. All patients were right-handed with German as their native language.

All participants (or their legal guardians) were informed as to the aims and methods of the procedure and consent was obtained. The protocol was approved by the ethics committee.

Table 1. Summary of demographic data: AACA patients

AACA patients	Gender	School education in years and profession	Age at time of testing	Time span between lesion onset and testing
EM	F	13 yrs., industrial clerk	57 years	20 weeks
EZ	F	13 yrs., saleswoman	47 years	40 weeks
IE	F	16 yrs., teacher	51 years	8 weeks
MH	M	10 yrs., merchant	36 years	24 weeks
RF	F	12 yrs., lawyer's assistant	58 years	32 weeks

Table 2. Summary of demographic data: Control participants

Control participants	Gender	School education in years and profession	Age at time of testing
BG	F	16 yrs., mathematics	31 yrs.
CK	F	13 yrs., physiotherapist	37 yrs.
HG	M	16 yrs., psychologist	30 yrs.
KZ	F	14 yrs., student	25 yrs.
MT	F	16 yrs., social worker	25 yrs.
SA	F	16 yrs., psychologist	25 yrs.
SB	F	10 yrs., (highschool)	16 yrs.
SL	F	16 yrs., psychologist	30 yrs.
UV	F	16 yrs., psychologist	33 yrs.

Figure 1 (a-e). Lesion reconstruction in five patients with ruptured AACA. The shaded areas represent the lesion (including the clip artifact). The lines in the lateral and mesial views correspond to the level of the cuts in the transverse sections.

Figure 1 (a) Patient EM Figure 1 (b) Patient EZ Figure 1 (c) Patient IE

Figure 1 (d) Patient MH Figure 1 (e) Patient RF

Procedure and apparatus

ERN-paradigm. Two versions of the ERN-paradigm were constructed, that is, the Eriksen flanker task (Eriksen & Eriksen, 1974) with letter or geometric stimuli. In the letter flanker task, participants were required to press a button with the index finger of their left hand if the target letter S appeared in the centre of a 5-letter array on the computer screen and the right index finger if the target letter H appeared in the centre. Each target letter was flanked to the right and left by either congruent (HHHHH, SSSSS) or incongruent (HHSHH, SSHSS) letters. There was a total of 480 trials, 80 trials for each congruent array (HHHHH, SSSSS) and 160 trials for each incongruent array (HHSHH, SSHSS). For four control participants the total number of trials was 440. Each array remained on the screen for 250 ms followed by an inter-stimulus interval of 1000 ms.

In order to accommodate patients who may have reading problems after damage to the brain, we constructed a task in which the letters were replaced by geometrical forms (circles and squares) similar in size to the letters. The participants had to press the right button if the target was a circle and the left button if the target was a square. For patients with motor or mental slowing, for each condition (letter or form) a version with an inter-stimulus interval of 1750 ms was constructed. Of the patients reported here, the "slow" version was only presented to patient RF and only in the letter condition.

EEG recording and analyses. The EEG was recorded from 19 Ag/AgCl-cup electrodes according to the 10/20 system referenced to linked earlobes and using Fpz as ground. Signals were amplified using a 32-channel-DC-amplifier (MES) and the SCAN software packet (NeuroScan). Data were sampled at a rate of 256 points per second with a 70 Hz low pass filter and a time constant of 5 s. Horizontal and vertical eye movements were recorded from standard locations. Impedance for EEG and electrooculogram (EOG) electrodes was kept below 10 kOhms.

For each ERN trial, an EEG epoch beginning 800 ms before and ending 800 ms after response was selected. Eye-movement artifacts were corrected by regression analysis, waveforms with signals greater than +/- 100 μV in healthy controls and +/- 200 μV in patients were eliminated and a low pass filter of 20 Hz applied. The EEG epochs were time-locked to the response on each trial and averaged separately for correct and incorrect trials for each participant. The waveforms were examined at frontal (Fz), central (Cz) and parietal (Pz) midline sites.

Response times. Response times were calculated from stimulus onset to button press, with averages based on those greater than 100 ms.

Neuropsychological procedures. Patients were examined with regard to their attention,

memory, executive, language and gnostic functions using standard neuropsychological tests. A summary of the procedures used and results obtained are presented in the results section (see also Table 5).

Results

Error rate and response times. With regard to error rate, the overall task performance was similar in the two groups: Although the average error rate was lower in the control participants than in the AACA patients, the AACA patients did not differ significantly from controls ($t(12) < 1$, n.s., for both letter and form tasks) (Table 3). The controls produced significantly fewer no-responses than the AACA patients ($t(12)=3.7$ and 3.2 for letter and form tasks, respectively, $p < .01$), although these differences just failed to reach significance when adjusting for unequal variances in the samples ($t(4.1) = 2.7$ and $t(4.5)=2.5$, $p < .06$).

All participants showed faster response times to incorrect than to correct trials thus corroborating previous findings (Table 3) (Gehring et al., 1993; Pailing et al., 1999). The AACA patients were significantly slower than the controls in both form and letter condition and in correct and incorrect trials ($t(12)$ ranged from 3.1 to 10.2, $p<.01$ in all analyses).

Error awareness. The experimenter documented for each trial whether the participants behaviorally showed signs (exclamations, whispered swearing, mimics, gestures) of having noticed that they had made an error. Patients IE and RF clearly noticed when they had made an error. The other three patients' behavior was mixed: while some did not show overt error detection, others did, or did for half of the trials.

Table 3. Mean error rate, no-response rate and reaction times of Controls and AACA-patients in the form and letter paradigm

Response trial	Control Form	Control Letter	AACA Form	AACA Letter
Mean error rate	8.9%	8.8%	9.8%	9.7%
Error range	3.2% - 18.5%	3.8% - 11.8%	2.5% - 15.6%	6.0% - 14.4%
Rate of no-responses	4.1%	2.3%	29.7%	23.6%
Mean response time in ms				
correct trials	343	341	486	531
incorrect trials	300	291	377	439
Response time range in ms				
correct trials	292 - 426	295 - 395	442 - 529	495 - 564
incorrect trials	253 - 358	247 - 345	321 - 445	365 - 516

Post-error trials. Once a response has been made, one can ask whether the type of response produced (correct or incorrect) influences the following response trial. The mean time for correct responses following an erroneous trial (post-error response) was slower than the mean time for correct responses following a correct trial (post-correct response) (Table 4). However, post-error slowing was not highly consistent across individuals. Of the 9 controls, 5 slowed correct responses after making errors on the form task, while 3 of the 5 patients did (mean RT slowing for controls = 7 ms, for patients = 25 ms, $t < 1$, n.s.). There was somewhat more consistency for the letter task, with 6 of the 9 controls and all 5 patients showing post-error slowing, with 16 vs 49 ms slowing ($t(12) = 1.7$, n.s.), respectively.

Table 4 Mean reaction times in post-response trials of controls and AACA patients in the form and letter paradigm

Post-response trials	**Control Form** Mean response time in ms	**Control Letter** Mean response time in ms	**AACA Form** Mean response time in ms	**AACA Letter** Mean response ime in ms
Post-error response correct trial (PEc)	348	356	511	575
Post-correct response correct trial (PCc)	341	340	486	526
Diff. PEc minus PCc	+7	+16	+25	+49

Production of ERN. Control participants produced a clearly identifiable ERN in response to the letter and form paradigm, that is, a negative deflection maximal at Cz following incorrect but not correct trials (see Figure 2a and 2b). The negative deflection was followed by a sharp positive rise. In response to correct trials, a positive peak was produced followed by a negative deflection to or below baseline.

Patient EZ produced an ERN in response to the letter but not the form paradigm (see Figure 3a and 3b). Patient RF did not show an ERN in either of the two conditions. Patients IE and EM clearly did not produce an ERN in one of the paradigms while in the other paradigm they produced a waveform for error trials that differed from the waveform to correct responses but which did not resemble an ERN. This "deviant" waveform sometimes started off in the direction of an ERN but then trailed off. Patient MH produced waveforms possibly resembling an ERN in both letter and form conditions.

Figure 2a. Averaged waveforms for the 9 control subjects in the form condition.

Figure 2b. Averaged waveforms for the 9 control subjects in the letter condition.

Figure 3a. Waveforms for correct and error trials for each AACA patient in the form conditions. Some patients produced large EEG overall power in the averaged ERP, indicated by the µVolt indications at the ordinate. Waveforms have a 25-point (97 ms) moving window filter applied.

Figure 3b. Waveforms for correct and error trials for each AACA patient in the letter conditions. Some patients produced large EEG overall power in the averaged ERP, indicated by the µVolt indications at the ordinate. Waveforms have a 25-point (97 ms) moving window filter applied.

Results of neuropsychological examination

Patient IE performed within the average range on all tests (Table 5). Patient RF performed somewhat better than the other AACA patients, his WMS-R general memory score and the subtest attention being in the average range, although the delayed recall subtest of the WSM-R was well below average. All patients, except for IE, showed attention, memory, and executive function problems to various degrees in standardized testing procedures. MH, EZ, and RF's non-verbal IQ scores were well below average.

Table 5. **Neuropsychological Results**

Patient	WMS-R General Memory	Delayed recall	Attention	verbal fluency	d2 cancel-lation task	Trail Making A	Trail Making B	Wisconsin Card Sorting Test	Tower of Hanoi	Office organi-sation task	HAWIE (German version of WAIS) (non-verbal)
IE	n	n	n	n	-	n	n	-	-	-	-
EM	↓↓	↓↓	↓	↓↓	↓↓↓	↓	↓	↓	↓	↓	(↓) IQ = 88
MH	↓↓	↓↓	↓	↓↓↓	↓↓↓	↓	↓↓↓	↓↓	↓	(↓)	↓↓↓ IQ = 42
EZ	↓	↓↓	↓↓↓	↓	↓↓↓	↓↓	↓↓↓	↓↓	↓↓	↓↓	↓↓↓ IQ = 62
RF	n	↓↓	n	↓	↓	↓	↓↓	↓↓	↓	↓	↓↓ IQ = 70

n = within normal range
- = non-applicable/test not done with patient
(↓) = some subtests within normal range, some below
↓ = >1 SD below normal range
↓↓ = >2 SD below normal range
↓↓↓ = >3 SD below normal range or unable to complete test

Discussion

Our results showed a reliable and clear production of the ERN followed by a sharp positive rise ("second P3") in response to incorrect but not correct trials in the control participants. For the patients a different picture emerged. In general, four of the five AACA patients did not produce an ERN in one paradigm, or a deviant waveform in the other paradigm. Patient RF did not produce an ERN, either in response to the letter or the form paradigm. MH produced an ERN-like waveform in both paradigms.

As reported in previous studies, all participants were faster on error than correct trials with the patients being slower than the controls. However, general slowing of the response following an error trial (post-error slowing) was not consistently observed in our participants which is in contrast to Gehring & Knight's (2000) findings.

These results will be discussed in relation to issues of generator site, awareness of error, cognitive functioning, and functional significance of the ERN.

The generator question

Whereas EEG and fMRI studies have implicated the anterior cingulate as a major contributor to the generation of the ERN, the role of the dorsolateral prefrontal regions remains unclear. The results of our study suggest that the generators lie in the anterior cingulate and not in the dorsolateral prefrontal cortex (DLPFC). Evidence comes from various sources:

(1) The production of the ERN is hampered in patients with a lesion in the anterior cingulate region but not in patients with lesions in the DLPFC region. Our AACA patients with damage to the anterior cingulate but an intact DLPFC did not show an ERN or they produced a highly deviant waveform. Gehring and Knight (2000) have demonstrated that patients with lesions in the middle cerebral artery (involving the DLPFC but not the anterior cingulate) did produce an ERN.

Furthermore, our data demonstrate that damage in the anterior cingulate region either prevents the ERN from being produced or a deviant waveform is generated that clearly differs from the ERN waveform produced by the control subjects. We argue that this deviant waveform occurred despite impaired neural substrates because there was still sufficient intact substrate left to allow its initiation. It thus seems that the anterior cingulate is necessary to initiate the production of the ERN, and damage to this area leads to the occurrence of a deviant waveform or no ERN at all. This agrees with suggestions that assign an action-initiating role to the anterior cingulate which, in turn, influences attention and executive control (see introduction). It is also conceivable that - by

way of the anterior cingulate's connection to limbic structures - such action-initiating role is driven by motivational and/or emotional processes.

There is some indication that different parts of the cingulate subserve different functions (Roland, 1993). The fact that patients produced a deviant waveform in one paradigm and no ERN in another may be explained by different neural circuits being involved depending on the type of processing (verbal versus non-verbal). Patient MH, who produced an ERN-like waveform in both paradigms, may have had those circuits preserved that are crucial for the ERN to be generated. Compared to the other patients, his lesion was more ventrally located (particularly in the subcallosal area).

(2) It has been suggested that an interaction between the anterior cingulate and the dorsolateral areas may be necessary for a well-formed ERN to occur. Gehring and Knight (2000) discuss the possibility of a feedback mechanism between the anterior cingulate and the DLPFC. Their argument is based on the findings of an ERN in response not only to incorrect but also to correct trials in patients with a stroke in the middle cerebral artery, that is, in a patient group with an intact anterior cingulate but a damaged DLPFC. Our AACA patient data are non-conclusive in this regard as in general there was no ERN production, and the deviant waveform occurred in response to incorrect but not correct trials. However, in this context it is interesting to note that during a routine clinical work-up of a traumatic brain injured patient (JM) with a lesioned DLPFC and an intact anterior cingulate, we identified a well-formed ERN only to incorrect but not to correct trials.

In comparison to ours, Gehring and Knight's paradigm was more complex and the additional processes involved in their task may have been responsible for the results obtained from the DLPFC impaired patients. The authors used a flanker-like paradigm which required the subject to associate the letter S with one hand and the letter H with the other hand. In addition, the authors used the words "red" or "green" as precues indicating which letter would be the target, i.e., depending on whether the S or H was presented in red or green. The subjects thus had to remember which hand was associated with which letter plus identify the target letter according to the precue. It seems reasonable to assume that the task set-up made demands on working memory that exceed those made by a simple flanker task. The DLPFC has repeatedly been implicated in playing a role in working memory. It may thus be that patients with a lesion in the DLPFC responded differently to the complex task setup which ultimately may have had an effect on error detection or monitoring.

(3) The previous discussion was aimed at showing a dissociation between ERN production

and site of lesion. Another line of argument comes from the relationship between the ERN and the contingent negative variation (CNV) which has been associated with the DLPFC (Basile et al., 1997; DiPellegrino & Wise, 1991). In this context it is particularly noticeable that two AACA patients (IE and RF) who did not produce an ERN did, however, produce a CNV. (The CNV paradigm is performed routinely in the clinic with severely brain-damaged patients [visual stimuli, ISI=2.8 s, ITI= 4.8 s]). This dissociation supports the view that (a) ERN and CNV production does not rely on the same neural circuitry (Davies et al., 1999); (b) different functional mechanisms underlie ERN and CNV production, and (c) the DLPFC was intact in the AACA patients.

The error awareness question

It has been suggested that elicitation of the ERN is not dependent on whether the detection of the error is internally driven or signaled by external cues, as long as there is awareness that an error has occurred (see introduction). However, it is not quite clear what exactly "awareness" means in this context. Consider the behavioral and neuropsychological performance of patients IE and RF. Of the five AACA patients, these two patients were least impaired in terms of attention and memory functions. In fact, at the time of the ERN recording, patient IE had recovered from her previous severe orientation, attention and memory impairments to a point where the results of the neuropsychological tests were in the average range, and she was about to be discharged from the intensive rehabilitation ward. Patient RF's cognitive functioning was worse but generally better than that of the other patients. Thus, these two patients showed cognitive functioning that was relatively good compared to the other AACA patients. More important, however, during the ERN recording the experimenter documented for each error trial that both patients overtly noticed when they had made an error (as expressed by whispered swearing, comments or gestures). Nevertheless, RF did not produce an ERN nor did IE in the letter paradigm. The other patients' documented behavior was mixed: Some did not overtly recognize their errors, others did, or did for half of the trials. Patients like RF and IE clearly demonstrate that there need not be a strong relationship between occurrence of the ERN and overt error detection. In other words, awareness of errors as signaled by overt error detection did not predict production of an ERN if the neural substrates implicated in ERN production were impaired. If, however, "awareness of errors" is viewed within an attentional framework, then one could argue that (overt or covert) attention mechanisms should be impaired in these patients as it has been shown that the anterior cingulate is consistently activated in functional imaging studies involving tasks that require attentional engagement (Mesulam, 1999). However,

explicit awareness of errors is dissociated from ERN production in our patients.

Relationship of ERN to attention, memory and executive functions

Our findings suggest that the production of the ERN does not seem to depend *primarily* on intact attention and memory functions. Patient IE, who did not produce an ERN, performed in the average range in all neuropsychological tests tapping these functions whereas patients MH and EZ with clearly impaired attention, memory, and executive functions did produce ERN-like waveforms in at least one paradigm. However, standard neuropsychological testing may not tease apart facets of attention, memory, or executive functions implicated in ERN production. Furthermore, it cannot be ruled out that the production of the ERN is hampered - as one would expect - in patients with very severe impairments of these functions. This, however, is difficult to establish as patients with such severe functional deficits and AACA are usually not able to perform the task.

Functional significance of ERN

It has been proposed that the ERN is implicated in error detection and the remediation of erroneous behavior (see introduction). Our data demonstrate that while ERN production was hampered in patients with a lesioned anterior cingulate, the error response rate in patients and controls did not differ; that is, behaviorally the patients showed an ability to detect errors but still did not produce an ERN. This argues against the view that activity reflected in the ERN signals solely error detection, and that the anterior cingulate must be intact for the error detection function.

Furthermore, it has been suggested that the ERN represents an error detection signal which, in turn, triggers future compensatory behavior (Gehring et al. 1993; Pailing et al. 1999; Scheffers et al., 1996). It has been observed that after an error has been committed quick strategic adjustments occur in the form of a slower response. Our data are not in line with these findings; not all participants showed slower correct-response times after an error was made. There also does not seem to be a consistent relationship between error detection and future compensatory behavior in general, since such a view would also suggest that error compensation is intact in those patients who showed post-error slowing. This, however, seems difficult to reconcile with an impaired suppression mechanism in these patients, as will be argued in the next section.

Concerning remedial processes, several research groups have investigated the ERN as a reflection of inhibitory processes (see introduction). Although no clear-cut evidence for a close relationship between the ERN and mechanisms of inhibition has emerged, there are some behavioral observations that may support such a relationship. Damage to the ventral prefrontal cortex in

contrast to dorsolateral prefrontal cortex has been implicated in inhibitory control, in self-regulation of behavior, and impaired autonoetic ('self-knowing') consciousness (for a discussion see Levine et al., 1999). Although standard neuropsychological testing does not necessarily reveal such deficits, it has been observed that patients with a ruptured AACA frequently demonstrate spontaneous confabulatory behavior (Ptak & Schnider, 1999; Schnider & Ptak, 1999; Shallice 1999). Schnider and Ptak (1999) have shown that such patients were unable to suppress associations brought to mind by the situation they were involved in regardless of the particular memory task they were required to perform. In other words, spontaneous confabulators seem to have lost the mechanism that is required to suppress currently irrelevant mental models, such a mechanism presumably being part of an error correction process (Shallice, 1999). The AACA patients participating in our study demonstrated spontaneous confabulation to various degrees at the time of testing which makes it likely that some sort of suppression mechanism was impaired in these patients. Furthermore, as previously argued, the anterior cingulate seems implicated in attentional and action-initiating mechanisms. It would be difficult to explain how such mechanisms could function properly without the guidance of some sort of inhibitory (or excitatory) mechanisms. If viewed as part of a distributed network that subserves local as well as global functions, it may very well be that the anterior cingulate modulates specific attentional and affective functions in the service of suppression. Damage to the paralimbic sector (Brodmann areas 11-13, 24, 25, 32) can interfere with the interactions between emotions, visceral state, cognition and behavior leading to, for example, poor judgement and foresight, a disturbed ability to adequately decide in situations involving risk and conflict, or distort the experience of emotion (Damasio, 1996; Mesualm, 2000a). This view would be compatible with our patients being able to detect their errors but nevertheless missing a behavioral component leaving them at risk for confabulations. This is also in agreement with observations that relate the ERN to impulsive behavior and affective distress (Pailing et al., 1999, Gehring et al., 2000, Luu et al., 2000b).

Conclusions

The purpose of this study was to investigate whether patients with a lesion involving the anterior cingulate region produced an ERN. A ruptured AACA leads to damage of neural substrates in the anterior cingulate. We thus hypothesized that damage to neural circuits in this region would decrease the likelihood of occurrence for an ERN. We found that generally AACA patients did not

produce an ERN or only a highly deviant waveform. These results contrast with other findings showing that patients with damage involving the DLPFC do produce an ERN. We conclude that the anterior cingulate region is essential to initiate the ERN response.

ERN elicitation has been related to awareness that an error has occurred. However, all our patients demonstrated error rates comparable to those of the control participants. In addition, two patients without ERN production clearly showed error awareness during task performance suggesting that explicit awareness of errors is dissociated from ERN production. Thus, it seems that the ERN does not simply represent an error detection signal.

Finally, impaired ERN production in AACA patients conjointly with their confabulatory behavior and evidence in the literature relating such confabulatory behavior in AACA patients to a defective suppression mechanism leads us to suggest that inhibitory (and excitatory) mechanisms need to be intact for a normal ERN to occur but not for detection of or behavioral reactivity to errors. The anterior cingulate - as the generator site for the ERN - may subserve a gating function that relates specific attentional and affective functions by exerting inhibitory (and excitatory) control.

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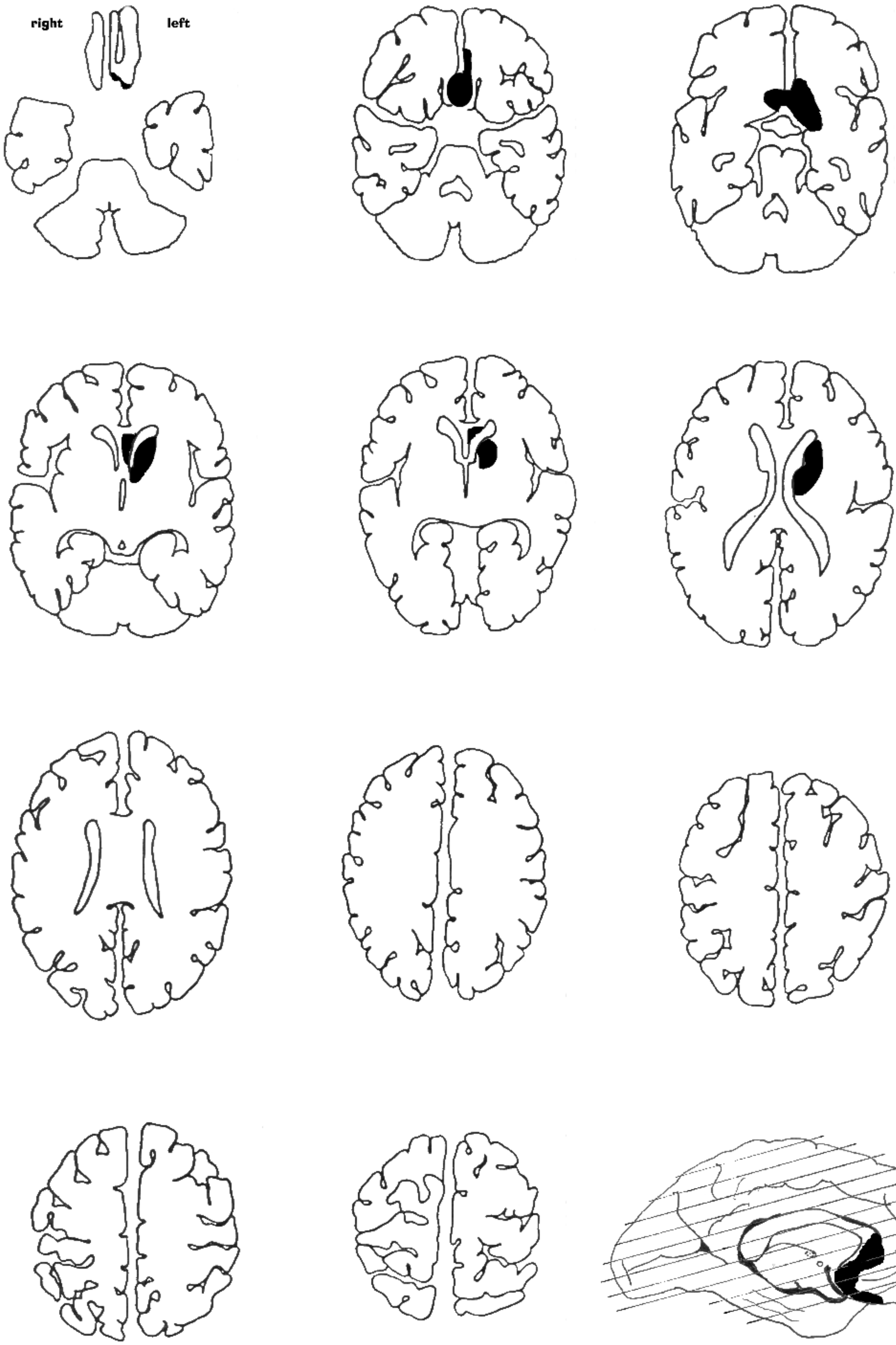

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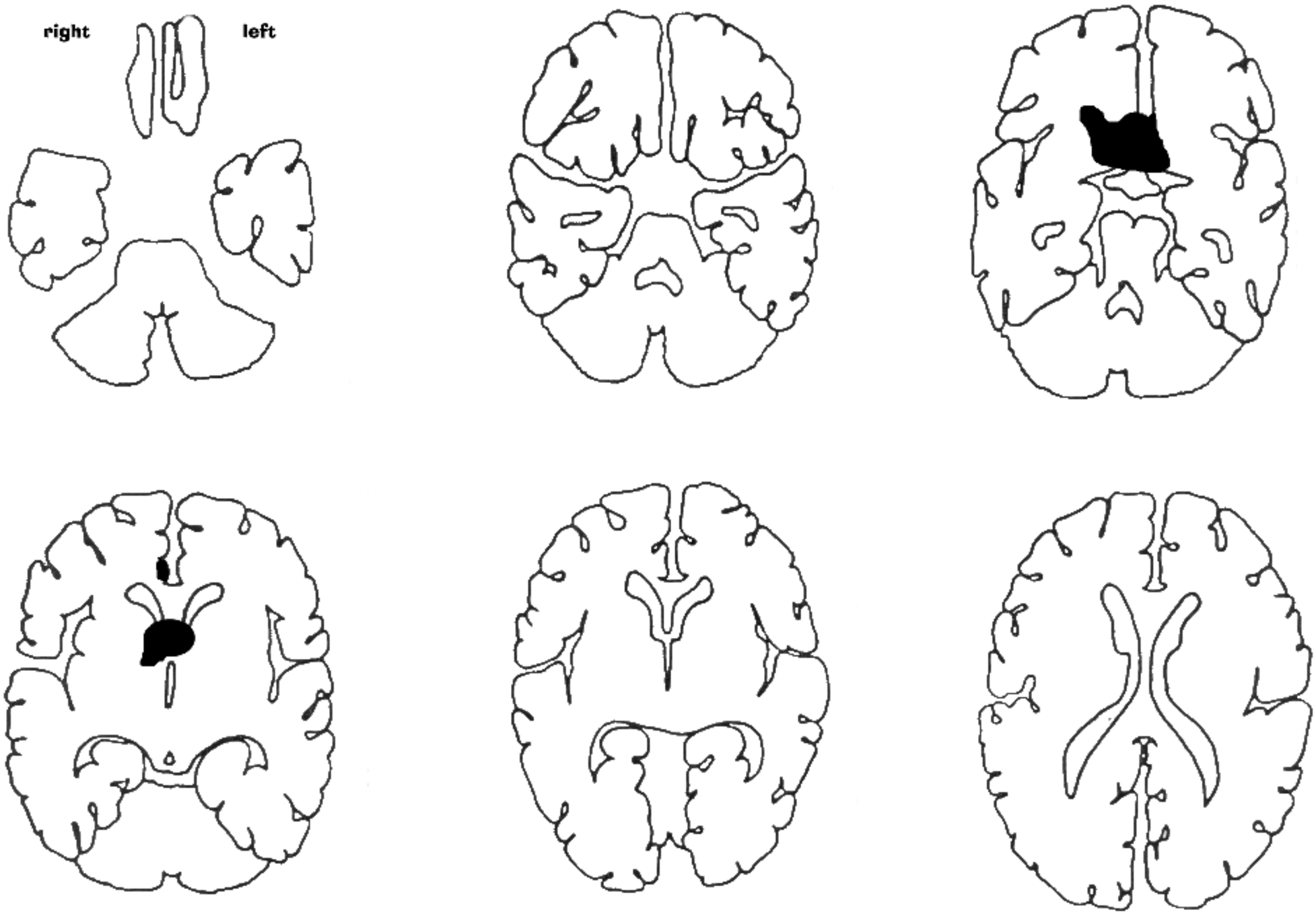

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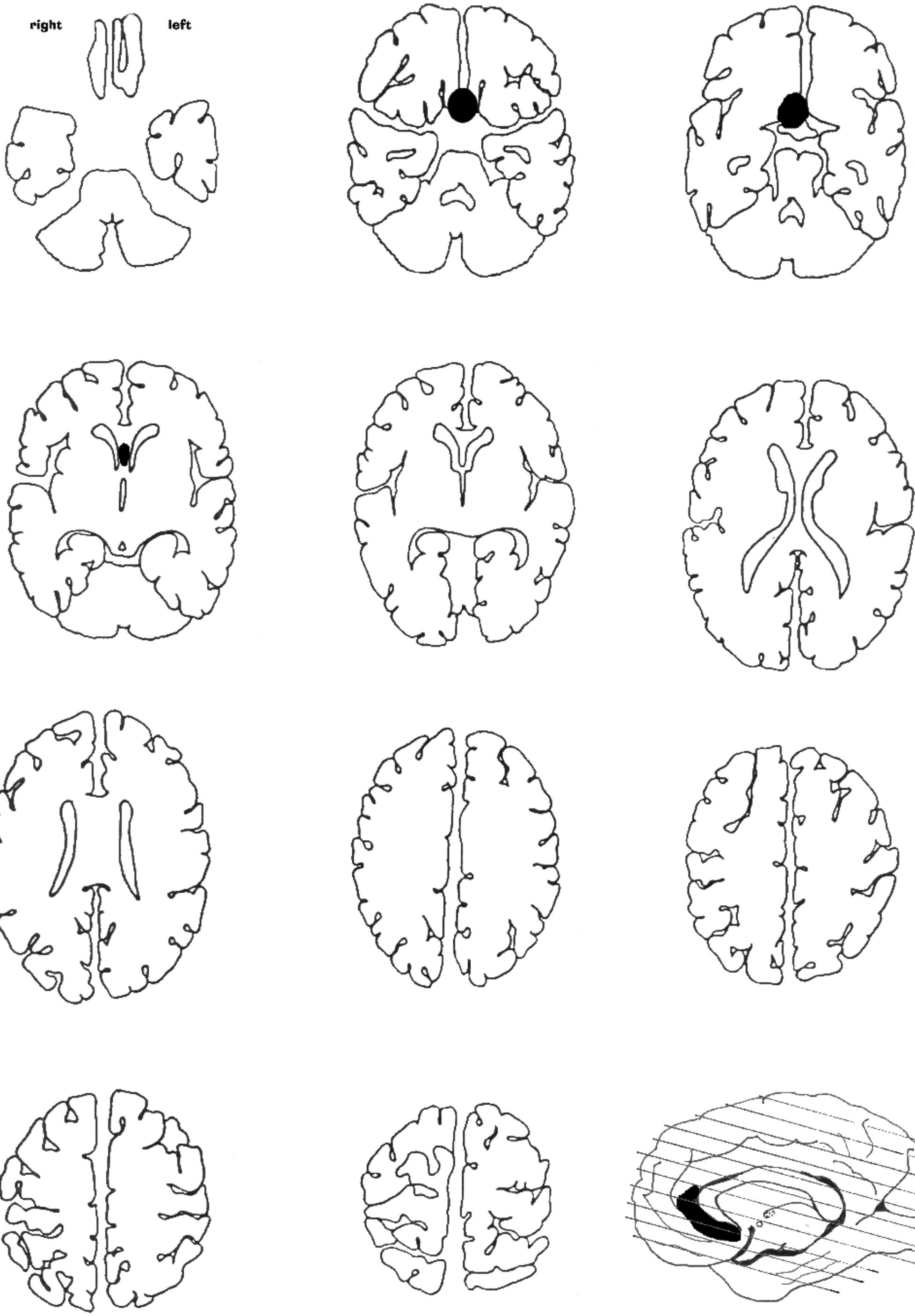

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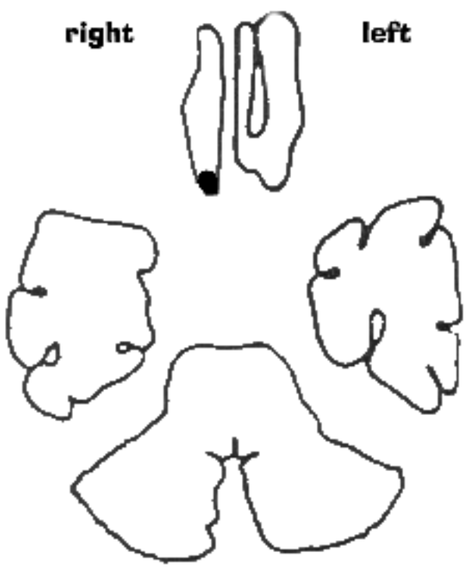

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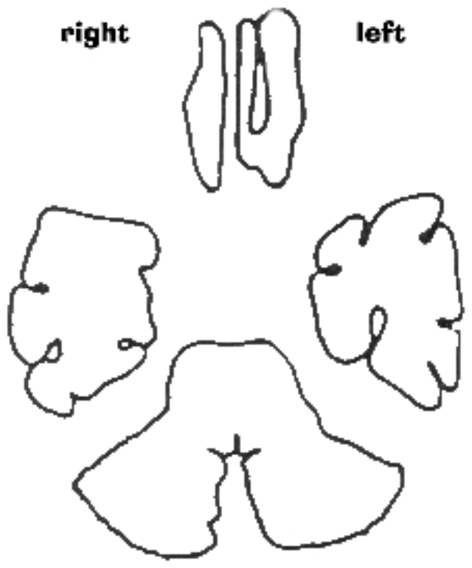

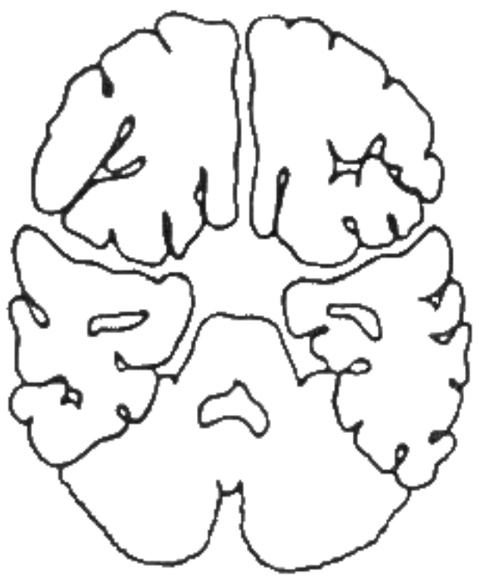
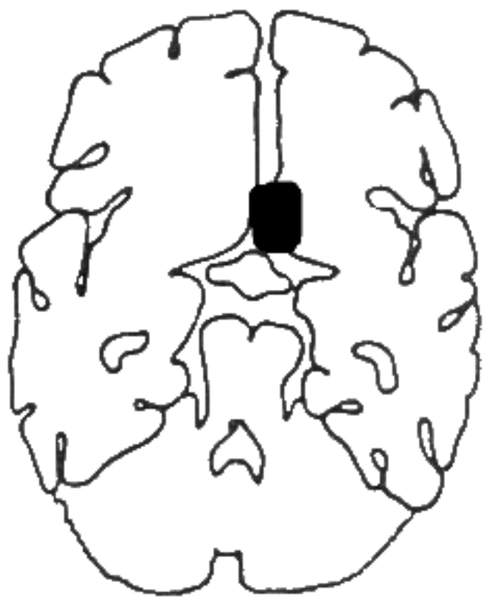
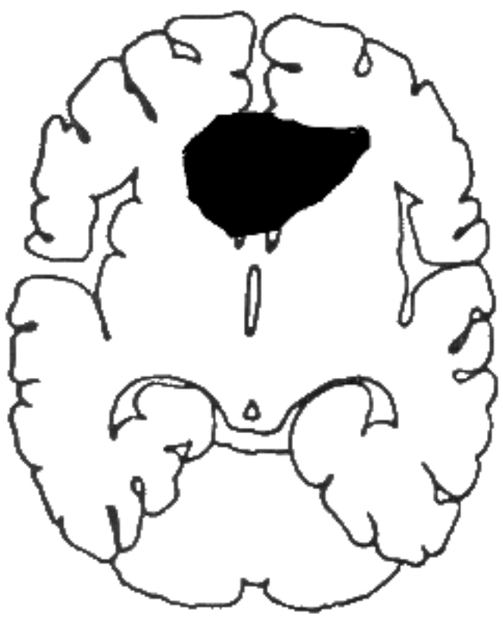
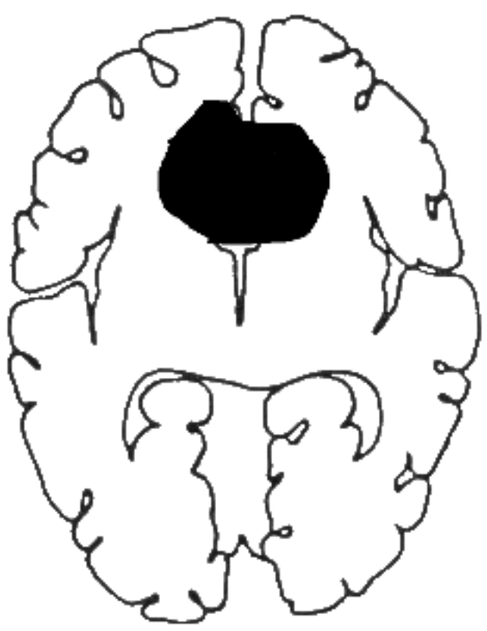
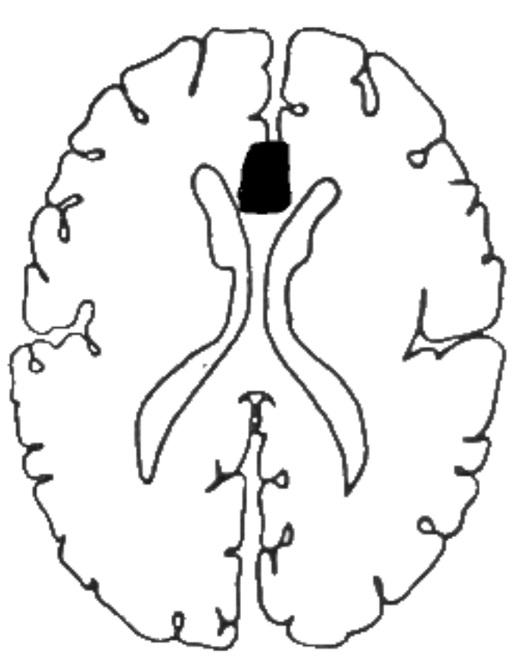
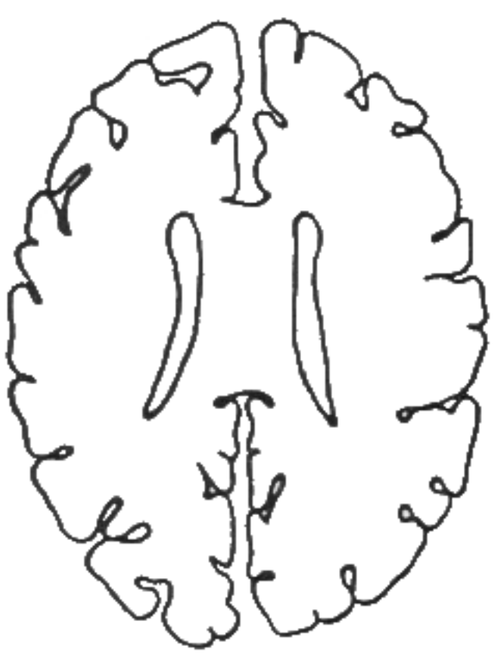
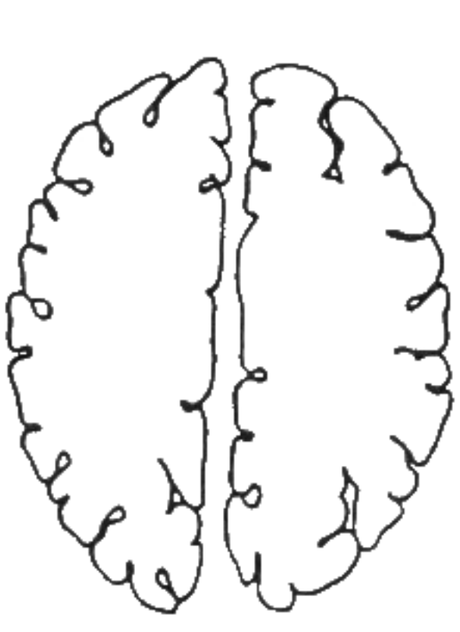
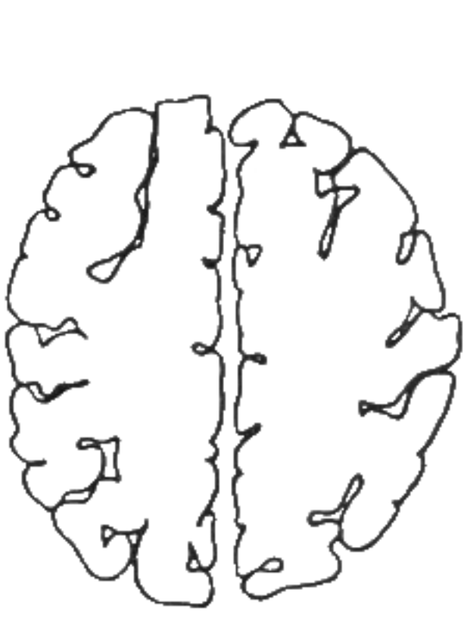
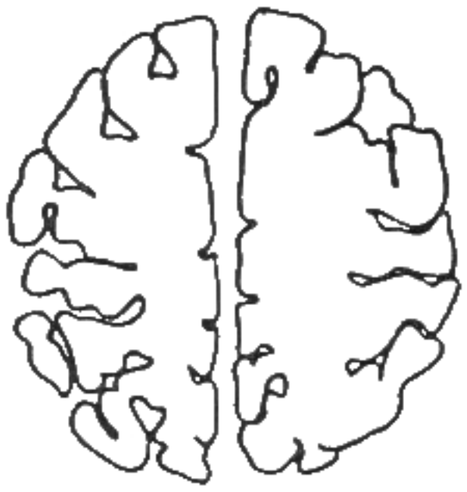
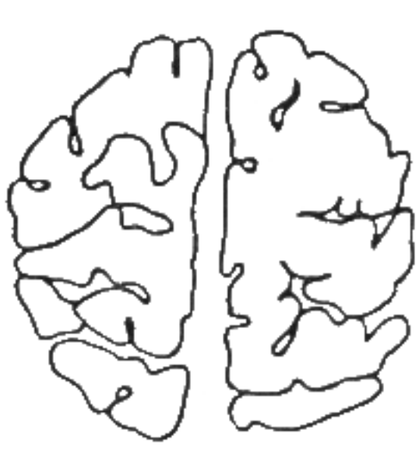
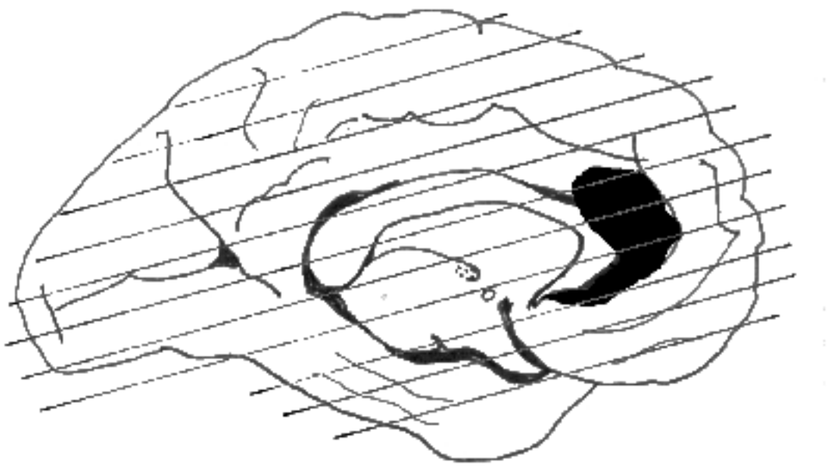

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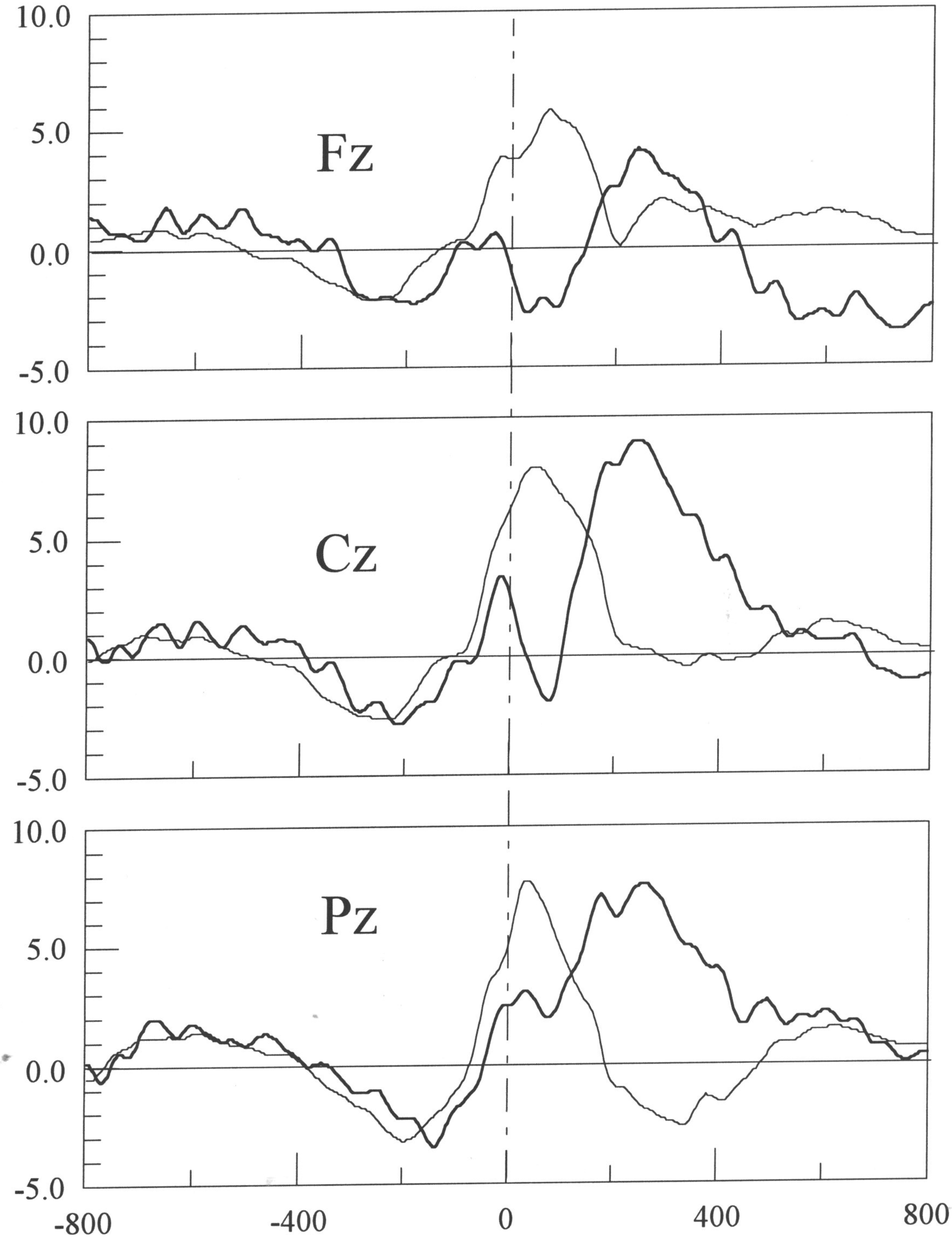

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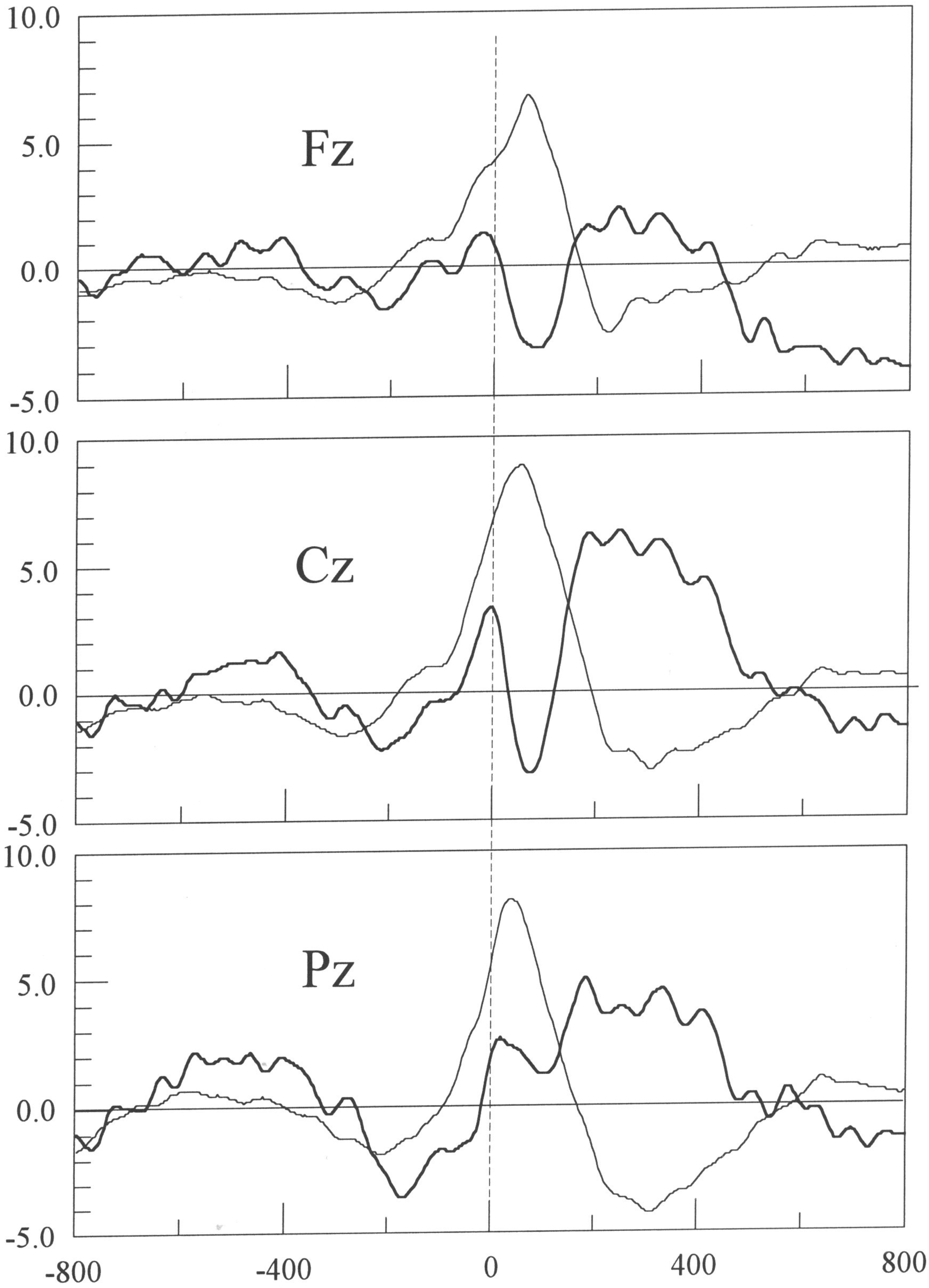

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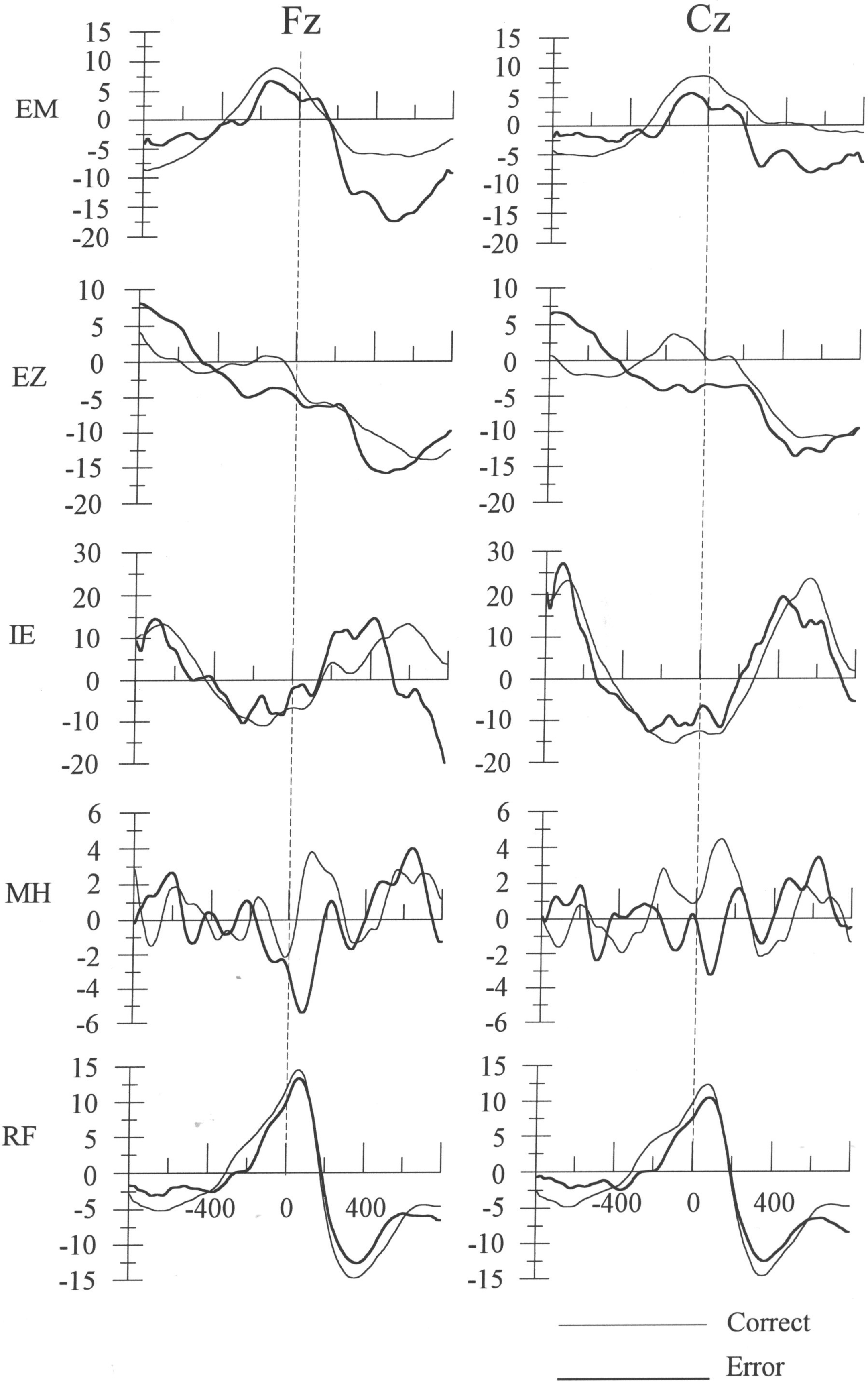

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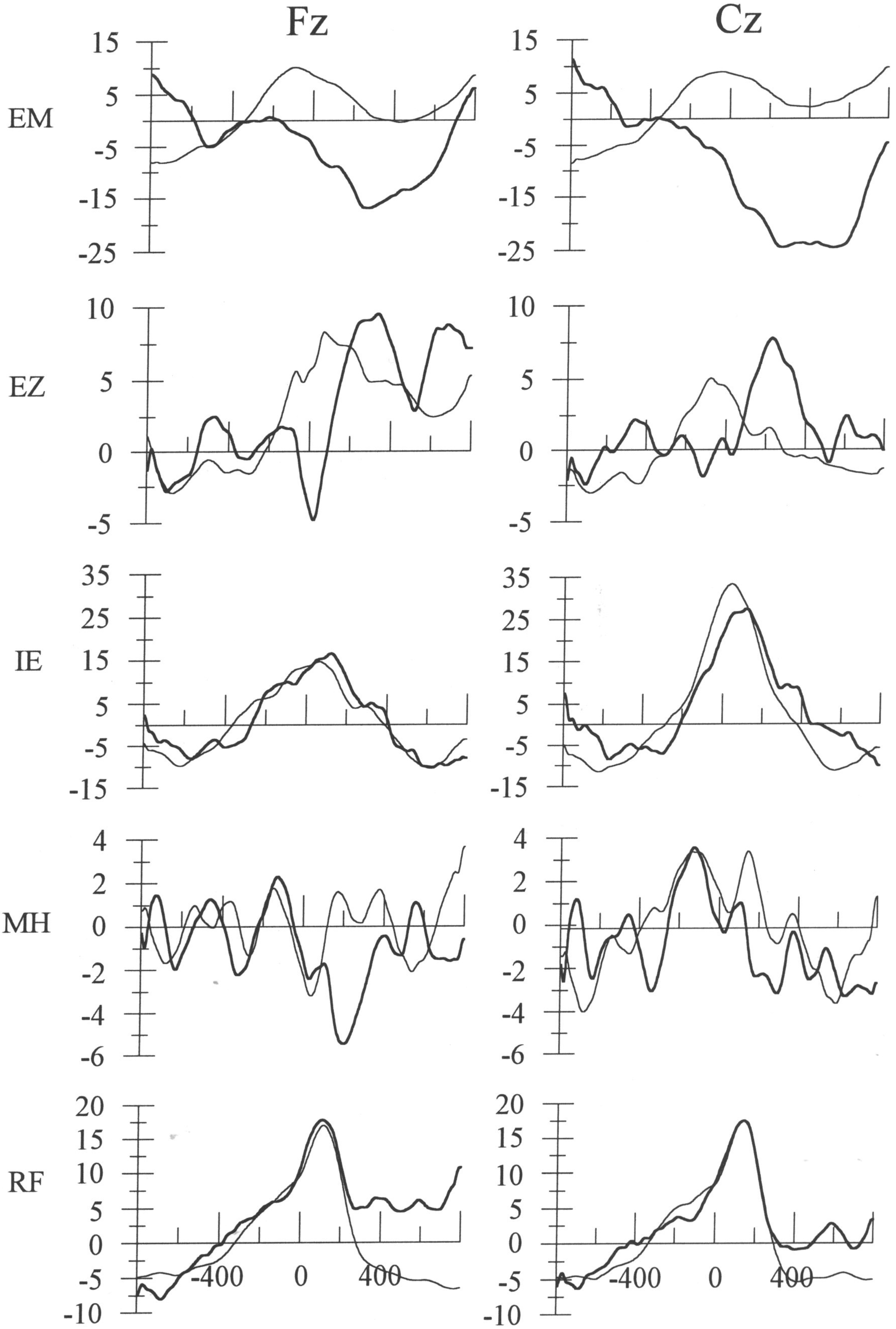

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