NeuroImage **17,** 851–858 (2002)
doi:10.1006/nimg.2002.1232

Volition to Action—An Event-Related fMRI Study

Georg Winterer,*,† Charles M. Adams,† Douglas W. Jones, and Brian Knutson†

**Clinical Brain Disorders Branch, National Institute of Mental Health, and †National Institute on Alcohol Abuse and Addiction, National Institutes of Health, Bethesda, Maryland 20892*

Received February 7, 2002

Current concepts of the anterior cingulate cortex (ACC) increasingly emphasize its role as an interface between limbic and neocortical functions. It has been pointed out that ACC activation reflects the intentional amount of effort (volition) that a subject uses in a task. In previous electrophysiological source localization investigations during a choice reaction task, we described a strong early activation in the ACC region approximately 120–150 ms after stimulus presentation. The degree of midline ACC activation correlated negatively with reaction time. This observation together with the finding that ACC activation precedes information processing in cortical association areas provided preliminary support to the notion that the extent of ACC activation is related to a subject's task engagement. However, due to the inverse problem and the relatively low spatial resolution of the electrophysiological measurements, we were not able to make inferences about the validity and the exact localization of the observed midline activation maximum. We addressed this question and performed an event-related fMRI study in six healthy volunteers during a visual choice reaction task. Two checkerboard stimuli were presented either in the left or right visual hemifield in randomized order and with an interstimulus interval requiring an appropriate motor response (left–right button press). A bilateral BOLD maximum was observed in the region of the supplementary motor area confluent with the neighboring motor area of the dorsal ACC. The degree of ACC activation correlated significantly with reaction time. These results are in line with our previous electrophysiological findings and provide further evidence that early ACC activation during a choice reaction task reflects the intentional effort of a subject to carry out a task.

INTRODUCTION

Anterior cingulate cortex (ACC) activation has been considered to reflect the degree of intentional effort, motivation, or volition that is needed to carry out a task (e.g., Paus, 2001). This notion originates in clinical observations of patients with medial frontal and ACC lesions (Kleist, 1934; Laplane *et al.,* 1981; Nemeth *et al.,* 1988) and was recently supported by a large meta-analysis of PET studies (Paus *et al.,* 1998) showing that the amount of effort which has to be engaged in a task is the common denominator of ACC activation across task conditions. This functional characterization of the ACC is also compatible with its role as a neuroanatomic interface between the limbic system and neocortical regions and its functional segregation, with different portions of the ACC being activated depending on particular task requirements (Devinsky *et al.,* 1995; Allman *et al.,* 2001; Paus, 2001). However, it is still a matter of debate exactly how ACC activation relates to particular functions in the behavioral and cognitive domain. Thus, it has been proposed that ACC activation may be critical for attention (Bench *et al.,* 1993; Carter *et al.,* 1997), conflict monitoring (Carter *et al.,* 1998, 1999, 2000; MacDonald *et al.,* 2000; Cohen *et al.,* 2000; Banich *et al.,* 2000), and motor response behavior (Paus *et al.,* 1993; Naito *et al.,* 2000). In particular, the conflict monitoring theory has recently received much interest. The theory is an extension of the earlier error-detection theory that postulated on the basis of electrophysiological findings (error-related negativity, ERN) in conjunction with functional neuroimaging data that the ACC is activated time-locked to the onset of an incorrect response, with a peak activation around 100 ms after movement onset (Falkenstein *et al.,* 1991; Gehring *et al.,* 1993; Dehaene *et al.,* 1994). However, subsequent investigations suggested that the original concept of the error-detection theory with regard to the role of the ACC might be too narrow. For instance, it was found that an ERN—albeit of smaller amplitude—is also seen in response to correct trials (Vidal *et al.,* 2000). Also, it turned out that the presence of a conflict situation may be more relevant than the error itself, leading to an even stronger ACC activation—particularly when the conflict is unpredictable (Carter *et al.,* 1998, 2000). So far, however, these latter studies have not yet convincingly clarified whether the observed ACC activation is indeed related to a particular neurocognitive operation or rather reflects the

1053-8119/02

amount of effort that a subject uses in a particular task.

A potential approach to solving the question of whether ACC activation reflects a subject's general effort during a task or whether it is related to a particular cognitive process is to take the timing of ACC activation into account. For instance, it is currently undecided whether the ACC becomes active before or after conflict perception or decision making. In a series of previous investigations of scalp-recorded event-related potentials during a two-stimulus auditory choice reaction task, we addressed the question of the timing of ACC activation (Winterer *et al.,* 1999, 2000a, 2001; Mulert *et al.,* 2001; 2002; Gallinat *et al.,* 2002). Because these studies involved current density and equivalent dipole source analyses in realistic head models with a time resolution of 6 ms, we were able to track cortical activation continuously between stimulus onset and movement response. We reported strong, anterior midline activation in the region of the ACC approximately 120–150 ms after stimulus presentation. During subsequent stimulus processing, only a few and very transient ACC activations were observed up to the time of the motor response. According to these electrophysiological studies, the ACC activation around 120–150 ms came immediately after activation in the primary auditory cortex but prior to subsequent stimulus evaluation in the auditory association area. At the same time, it was found that this activation in the ACC area was reduced in subjects with poor reaction times, including schizophrenic patients. Of note, an additional, extensive psychopathological evaluation of schizophrenic patients revealed that it is the syndrome "apathy/avolition" which shows the strongest negative correlation with early frontal midline activation (Winterer *et al.,* 2000b). From these observations, it was deduced that early ACC activation reflects the amount of effort or volition that a subject is willing or able to engage in the task. This effort-related ACC activation may constitute a part of the attentional network supporting the allocation of attention to a stimulus (Posner and Rothbart, 1998). The reason for this conclusion is that observed ACC activation occurs at a very early stage of information processing, i.e., at a time before the subject has likely started to process the "conflict" and has made any decision about the appropriate movement response. The other two reasons are that ACC activation correlated negatively with reaction time and with apathy/avolition in schizophrenic patients.

In our previous electrophysiological studies, we also tried to validate our electrophysiological source analytical model because of the inverse problem by comparisons with intracortical electrophysiological studies as reported in the literature. However, before more definite conclusions can be drawn, electromagnetic sources ideally should be validated in a more direct way with functional neuroimaging tools, which was the main purpose of the present study. The question that needed to be answered was whether the previously observed electromagnetic source in the ACC area is actually located in the ACC. The second issue that had to be addressed was exactly where in the ACC the activation maximum is located, since the ACC shows a neuroanatomic, functionally relevant segregation (Devinsky *et al.,* 1995; Paus, 2001). If the electrophysiologically observed ACC midline activation were primarily related to the motor response effort, one might expect a maximum physiological response in the motor portion of the ACC adjacent to the supplementary motor area. Conversely, if the electrical source activity were a physiological equivalent of conflict-monitoring effort, the response should be strongest in more ventrally located areas that are possibly more closely related to cognitive processes in the ACC. Again, this question can be better clarified with functional neuroimaging techniques since the spatial resolution of electromagnetic source analysis is relatively low. In any case, ACC activation should negatively correlate with reaction time—as was observed in previous electrophysiological studies, if the notion is correct that early ACC activation facilitates subsequent information processing.

METHODS

The study was approved by the Institutional Review Boards of the National Institute of Mental Health and the National Institute of Alcohol Abuse and Alcoholism. Participants were recruited through the NIH Normal Volunteer office. Written informed consent was obtained from each participant. Participants were included only if there was no evidence for any medical, neurological, or psychiatric disorder, including current or recent drug or alcohol abuse, as assessed by a Structured Clinical Interview (First *et al.,* 1995), a formal neurological and medical exam, and a full battery of neuropsychological screening tests. Of originally nine subjects, three subjects were excluded because of movement artifacts. Of the remaining six healthy subjects, one was male and five were females (mean age, 36.7 $\pm$ 6.7 years). All subjects were right-handed.

Task conditions were kept as similar as possible with respect to the previous electrophysiological source localization studies (Mulert *et al.,* 2001; Winterer *et al.,* 2001; Gallinat *et al.,* 2002). The main difference was that visual stimuli rather than auditory stimuli were used because of the difficulty of using auditory stimulation in the MRI scanner and because the main interest of this study was related to brain regions that are considered supramodal (Downar *et al.,* 2000). Two subsequent blocks (sessions) of 80 visual stimuli (i.e., checkerboards) that could be easily distinguished were presented on the left or right side of the visual field on a screen. While fixating a crosshair in the center of the screen, subjects were required to respond as fast as

possible to each stimulus by pressing either a left or right button with the left or right thumb, depending on the side of appearance of the stimuli. Stimuli were presented in counterbalanced and pseudorandom order at interstimulus intervals (ISIs) of 2–6 s between stimulus onsets and a stimulus duration of 400 ms. The relatively short ISIs were chosen because a similar stochastic design was used in the previous electrophysiological studies.

FMRI Acquisition

Imaging was performed using a 3T General Electric MRI scanner (General Electric, Milwaukee, WI) and a standard quadrature head coil. Structural scans were acquired using a T1-weighted spoiled grass pulse sequence (TR, 100 ms; TE, 7 ms; flip, 90°; 0.9375 * 0.9375 * 2-mm^2 voxels), which facilitated localization and coregistration of functional data. Interleaved multislice BOLD T2*-weighted gradient echo functional MRI images were acquired in the saggital plane (FOV, 24 cm; TR, 2 s, TE, 30 ms; 24 slices; no gap; 3.75 $mm^2 \times$ 5 mm (0.7 cc). Stimulus presentation was continuously synchronized to slice acquisition of functional images since FMRI volume acquisitions were time-locked to the onset of each visual stimulus (SOA). However, in order to reduce the possibility of a sampling bias (Price *et al.*, 1999), one half of randomly selected SOAs were placed at the beginning of slice acquisition and the other half in the middle of slice acquisition within a TR.

FMRI Analysis

FMRI analysis was performed using Analysis of Functional Neural Images software *AFNI* (Cox, 1996). For preprocessing, two-dimensional motion correction was performed within each slice (using the third volume of the first session as reference). Voxel time series were then interpolated to correct for nonsimultaneous slice acquisition within each volume (using sinc interpolation and the rightmost slice as reference), concatenated across both task sessions, and then corrected for three-dimensional motion (again using the third volume of the first session as reference). Visual inspection of motion-correction estimates confirmed that no participant's head moved >1.5 mm in any dimension from one volume acquisition to the next. Preprocessed data for each individual were analyzed by multiple regression (Neter *et al.*, 1996). The regression model consisted of one regressor of interest, six motion regressors (three angles, three offsets), and four regressors modeling baseline differences and linear trends for each of the two experimental sessions. The regressor of interest was modeled with a delta function representing the stimulus time course that was convolved with a gamma-variate function that modeled a prototypical hemodynamic response before inclusion in the regression model (Cohen *et al.*, 1997). A comparative analysis with exclusion and inclusion of stimuli with a very short preceding ISI of 2 s did not change the overall result. Therefore, the regressor of interest was modeled under inclusion of all stimuli.

Voxelwise regression analysis contrasting stimulus presentation versus 2-s prestimulus baseline produced statistical maps for each individual. Group maps of t statistics representing the regressor of interest were transformed into Z scores, coregistered with structural maps, spatially normalized by warping to Talairach space, spatially smoothed (FWHM, 8 mm), and combined into a group map using a meta-analytic formula (average Z * sqrt(n)) (Knutson *et al.*, 2000). Using the *AFNI 3dmerge* voxel-cluster threshold technique ($r = 2$ mm; minvol, 1000 μl), group maps were thresholded at an omnibus voxel value of $P < 0.0001$. This threshold was based on a prior convention for multiple test correction in cortical gray matter (i.e., orbitofrontal cortex, anterior cingulate, supplementary motor area, and primary motor cortex) and subcortical areas (i.e., nucleus accumbens, putamen, caudate, thalamus) in a representative brain (~500 voxels; $P = 0.05$, corrected) (Knutson *et al.*, 2000). For comparison, a less conservative threshold ($P = 0.001$) was also applied.

RESULTS

The group mean reaction time for both blocks of stimuli was 468.82 ms (SD, 84.40). Significant main effects of event-related BOLD responses across the entire brain are presented in Table 1. As seen in Table 1, when using the combined left–right stimulus vector for analysis, BOLD responses were generally stronger (i.e., higher Z values) on the left than on the right side, with the exception of the cerebellum. A separate analysis of the right and left button press conditions did not significantly affect the overall result. A region of the ACC showed a significant BOLD response in the vicinity of and confluent with the supplementary motor area (Fig. 1). The degree of activation in the ACC region (each subject's maximum voxel Z value) correlated significantly with reaction time (Spearman $\rho = -0.83$, $t = -3.0$, $P = 0.0416$). For comparison, maximum BOLD responses in the other brain areas (depicted in Table 1) did not show significant correlations with reaction time ($P > 0.05$). Only the BOLD response in left thalamus was negatively correlated with reaction time (Spearman $\rho = -0.98$, $t = -7.6$, $P = 0.0048$, uncorrected) and a weak, negative trend correlation was observed with the BOLD response in the left motor cortex (Spearman $\rho = -0.70$, $t = -1.70$, $P = 0.1881$, uncorrected).

Upon lowering the significance threshold by 1 order of magnitude, it became obvious that the BOLD response may also involve a larger and more anterior portion of the anterior cingulate cortex than the impression obtained from Figure 1. No clusters of in-

TABLE 1

Talairach Coordinates of Z_{Max} Scores

Brain (Brodmann's) areas	*x*	*y*	*z*	Z_{Max} scores[a]	*P* values
Left thalamus	−12,	−24,	3	5.01	<0.0001
Right thalamus	14,	−17,	7	3.77	<0.001
Left calcarine fissure BA 17	−5,	−83,	11	5.01	<0.0001
Right calcarine fissure BA 17	1,	−83,	14	5.38	<0.0001
Left secondary visual cortex BA 19	−38,	−69,	4	6.86	<0.0001
Right secondary visual cortex BA 19	38,	−68,	4	5.23	<0.0001
Left anterior cingulate gyrus BA 24	**−6,**	**−3,**	**41**	**4.13**	**<0.0001**
Right anterior cingulate gyrus BA 24	**2,**	**−12,**	**48**	**5.12**	**<0.0001**
Left dorsolateral prefrontal cortex				No significant maximum	
Right dorsolateral prefrontal cortex				No significant maximum	
Left supramarginal gyrus BA 43	−21,	−24,	21	5.93	<0.0001
Right planum temporale BA 46	55,	−39,	21	4.74	<0.0001
Left lateral temporal cortex				No significant maximum	
Right lateral temporal cortex				No significant maximum	
Left medial temporal lobe	−36,	−10,	−9	4.10	<0.0001
Right medial temporal lobe	36,	−14,	−3	3.61	<0.001
Broca's Area BA 45	−52,	3,	7	4.74	<0.0001
Left striatum	−23,	−1,	7	4.74	<0.0001
Right striatum	29,	4,	7	3.90	<0.0001
Left cerebellum	−18,	−62,	−15	4.65	<0.0001
Right cerebellum	9,	−59,	−12	7.41	<0.0001
Left supplementary motor cortex BA 6	**−4,**	**−9,**	**56**	**6.44**	**<0.0001**
Right supplementary motor cortex BA 6	**1,**	**9,**	**53**	**5.87**	**<0.0001**
Left motor cortex BA 4	−35,	−26,	50	8.12	<0.0001
Right motor cortex BA 4	33,	−31,	50	4.89	<0.0001

[a] Regression analysis contrasting stimulus presentation versus prestimulus baseline (Z_{Max} scores, uncorrected *P* values) (spatial filter, FWHM, 8 mm).

creased BOLD responses could be identified in the rest of the prefrontal cortex—even after further lowering the significance threshold ($P < 0.001$) and varying the parameters (e.g., delay) of the gamma-variate function.

DISCUSSION

This study is a continuation of a series of prior electrophysiological studies that have shown an early activation approximately 120–150 ms after stimulus presentation in the area of the ACC during a choice reaction task. Using event-related fMRI, we tried to validate and pinpoint the location of the electromagnetic source, which may have been mislocalized because of the inverse problem and relatively low spatial resolution.

The results from the present study suggest that the overall activation pattern throughout the brain is essentially in agreement with general neurophysiologically based expectations. BOLD responses were observed in the visual and motor cortex, in the striatum, thalamus, and cerebellum. Interestingly, a significant negative correlation was observed between the left thalamic BOLD response and reaction times, which is in accordance with previous studies showing a relation between cognitive speed and arousal (e.g., Paus *et al.*, 1997). Also a BOLD maximum was detected at the temporoparietal junction that may represent the BOLD response equivalent of the event-related potential P300 (McCarthy *et al.*, 1997; Linden *et al.*, 1999), which is typically seen during choice reaction tasks. The generally observed left-sided dominance of the BOLD responses might be related to our particular slice acquisition procedure. With regard to the question of ACC activation, the subsequent observations were made. The finding from the present fMRI study first of all confirms our prior electrophysiological source localization study that an activation maximum is seen in the ACC confluent with the supplementary motor area during choice reaction. Notably, no additional frontal BOLD response was seen. At this point, it is again important to mention that we have previously explored electromagnetic sources with high time resolution in the time window 50–420 ms after the stimulus (i.e., beyond the initiation of the motor response) (Winterer *et al.*, 2001; Mulert *et al.*, 2001; Gallinat *et al.*, 2002). In these studies, we did not find any evidence of other frontal electromagnetic sources except a few very transient and weak frontal activations between 240 and 420 ms that are unlikely to elicit a comparable BOLD response. Thus, the statement seems to be justified that the measured ACC BOLD response is actually the hemodynamic equivalent of the early electromagnetic source in the ACC. The results of the present investi-

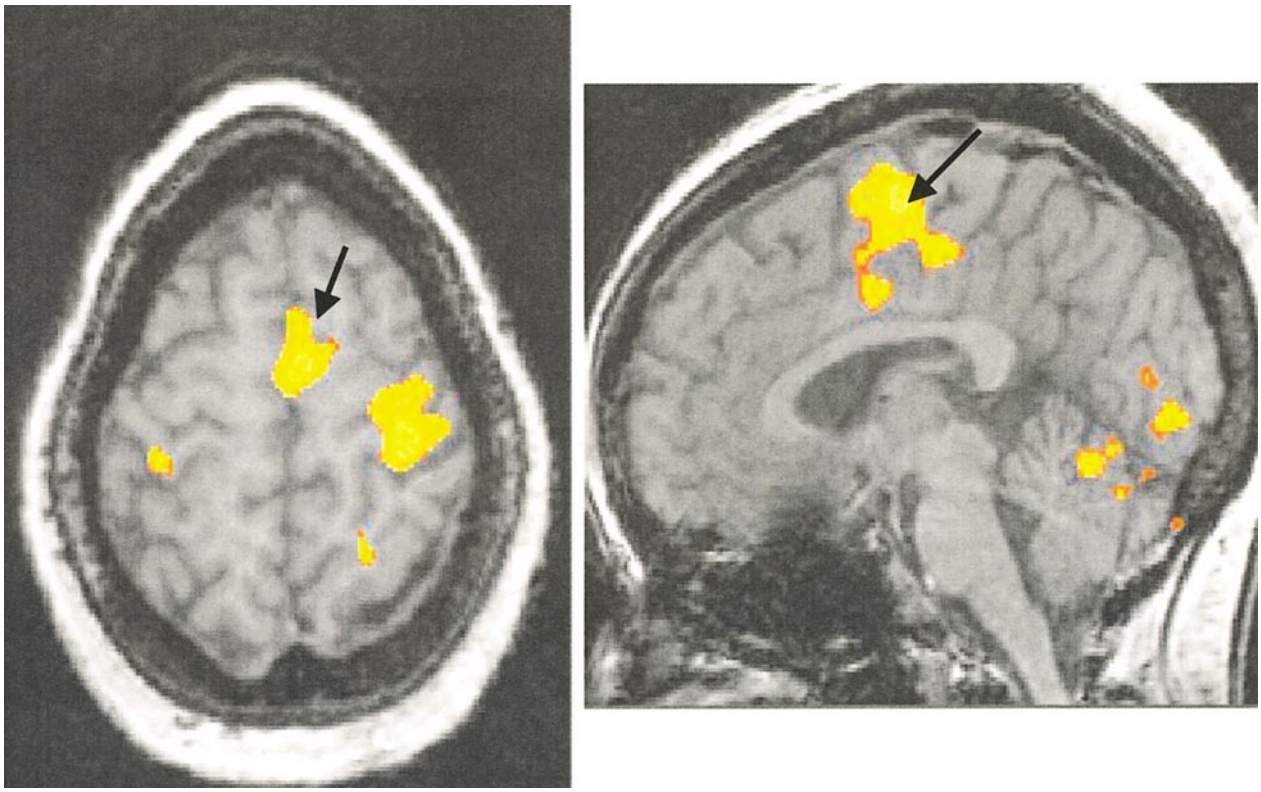

FIG. 1. BOLD activation in supplementary motor cortex BA 6 (arrow) with ventrocaudal extension into anterior cingulate gyrus BA 32. Activation also in both motor areas BA 4 in cerebellum and calcarine fissure BA 17 (spatial filter, FWHM, 6 mm).

gation further suggest that it is primarily the motor portion of the ACC that is activated together with the supplementary motor area during the choice reaction task. Only when lowering the significance threshold by 1 order of magnitude did the BOLD response encompass a more widespread, ventral ACC area. This result seems to be plausible because the task design requires primarily a fast motor response, and the decision-making process is not particularly challenging, as reflected by the low error rate (Winterer *et al.*, 2000). Accordingly, the results are similar to those reported by Naito *et al.* (2000) for a simple reaction task that did not require any kind of decision making. However, it has to be taken into account that the sensitivity of event-related fMRI may not be sufficient to detect neural activity maxima elsewhere in the ACC (Logothetis *et al.*, 2001; Bandettini and Ungerleider, 2001). Alternatively, it is also conceivable that the applied gamma-variate function was not optimally chosen to capture event-related BOLD responses in other parts of the ACC, although in pilot work we systematically varied the slope and delay of the gamma-variate function without producing different results. Finally, the actual focus of neural activity may be offset by some 5–10 mm because of spatial normalization and because of the larger spatial scale of the perfusion increase relative to electric activity (Jezzard and Clare, 2001). However, the continuous spread of ACC activation that encompasses the supplementary motor area suggests otherwise and rather favors the notion that the maximum BOLD response does indeed lie in the motor division of the ACC. Nevertheless, it is quite possible that the ACC activation extends to some degree into more ventrally located portions of the ACC that are likely more involved in cognitive processes.

The results of the present fMRI study are particularly meaningful in conjunction with our prior electrophysiological studies. This is because the fMRI findings validate the previously described electrophysiological source solution and by extension also help to validate the electrophysiological model about the organization of information processing in the time domain during a choice reaction task. According to these previous electrophysiological studies, ACC activation immediately follows stimulus processing in the primary sensory cortex and precedes the evaluation of stimulus properties in the association cortex. Therefore, ACC activation likely occurs before conflict detection, decision making, and the initiation of the motor response because one would expect that these functions would also involve associative brain areas to evaluate the stimulus. This is not to say that the ACC is generally not activated at a later stage during information processing, again. Thus, it is conceivable that tasks with a

higher error probability or a stronger conflict, as in the present study, lead to a later ACC activation—possibly in more ventral parts of the ACC. For instance, error detection seems to be generated in the ACC and typically peaks about 100 ms *after* "wrong" movement initiation (Gehring *et al.*, 1993; Gehring and Knight, 2000). On the other hand, Gehring and Willoughby (2002) recently concluded from the results of a variant of their earlier task that medial frontal activation may result from the "assessment of the motivational impact of an event" rather than from detecting an error. In order to clarify this issue, future studies should try to separate the early ACC activation and ACC activation that might be more directly related to error detection or conflict processing. One possible way this could be achieved might be to take into account the time information.

Although it is unlikely that early ACC activation is directly related to error detection or conflict monitoring, early midline ACC activation seems to predict reaction time according to our previous electrophysiological studies and the present fMRI investigation. The negative correlation with reaction time together with the observation that early ACC activation occurred before any other cortical information processing in association cortices suggests that this early ACC activation constitutes a particular aspect of attention which is related to the effort or volition of a subject. The notion that this early ACC activation is related to effort and volition facilitating subsequent information processing is supported by our previous finding of a strong negative correlation between early frontal midline activation and apathy/avolition in schizophrenic patients (Winterer *et al.*, 2000b). It is also supported in an analogous way by studies that measured the readiness potential (Bereitschaftspotential). The readiness potential is elicited by self-initiated, voluntary movements before the initiation of the motor response. It is generated in the ACC and supplementary motor area and is also thought to facilitate subsequent information processing (Kornhuber and Deecke, 1964; Kristeva *et al.*, 1991; Boecker *et al.*, 1994; Cui *et al.*, 1999). The readiness potential has been closely linked to the concept of effort and volition, although it seems likely that other potentially relevant aspects, i.e., anticipation or decision making, also play a role. Nevertheless, both our findings and the readiness potential studies are in agreement with the concept that early ACC activation may facilitate subsequent information processing in that the ACC subserves the function of an interface between the limbic system and neocortex that translates volition and drive into action. The possible neurophysiological properties of this facilitating mechanism were reported and discussed elsewhere in more detail (Winterer *et al.*, 1999). According to this previous study, an increase in coherence (EEG synchronization), which can be considered an electrophysiological index of functional connectivity, was observed both within the prefrontal cortex and between the prefrontal cortex and other parts of the brain. This coherence increase correlated with the extent of frontal midline (ACC) activation. The question that arises here is whether ACC activation also facilitates subsequent attentional processes in sensory association cortices, which have recently been described as being accompanied by an increase in EEG synchronization in the gamma-frequency band (Fries *et al.*, 2001). Addressing this issue would be of particular interest with regard to the possible role of the ACC as part of the brain's attentional control network (Posner and Rothbart, 1998).

In summary, the present study of event-related BOLD responses confirms prior electrical source localization studies since an activation maximum could be demonstrated in the anterior cingulate cortex which is negatively correlated with reaction time. The findings further suggest that it is primarily the motor portion of the anterior cingulate cortex that is activated during a relatively simple choice reaction task. These results are particularly meaningful in the context of previous electrophysiological studies. Together, the electrophysiological and fMRI findings suggest that early ACC activation around 120–150 ms after stimulus presentation might be an index of task engagement or volition. The results provide further evidence for the particular role of the anterior cingulate cortex as an interface between limbic and cortical systems.

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