European Journal of Neuroscience, Vol. 21, pp. 3447–3452, 2005

SHORT COMMUNICATION
Anterior cingulate error-related activity is modulated by predicted reward

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Keywords: frontal, learning, monkey, neuron, reward

Abstract

Learning abilities depend on detection and exploitation of errors. In primates, this function involves the anterior cingulate cortex. However, whether anterior cingulate error-related activity indicates occurrence of inappropriate responses or results from other computations is debated. Here we have tested whether reward-related parameters modulate error-related activity of anterior cingulate neurons. Recordings in monkeys performing stimulus–reward associations and preliminary data obtained with a problem-solving task revealed major properties of error-related unit activity: (i) their amplitude varies with the amount of predicted reward or the proximity to reward delivery; (ii) they appear both after execution and performance errors; (iii) they do not indicate which error occurred or which correction to make; and (iv), importantly, the activity of these neurons also increases following an external signal indicating the necessity to shift response. Hence, we conclude that anterior cingulate 'error' activity might represent a negative deviation from a predicted goal, and does not only reflect error detection but signals events interrupting potentially rewarded actions.

Introduction

Adaptations of movements, actions and complex behaviours are based on detection and calculation of errors used to minimize deviations from desired goals. Various error signals have been described in the brain (Schultz & Dickinson, 2000). One of them seems to represent a prediction error, i.e. the scalar difference between actual and predicted reward (magnitude × probability) and therefore is a potential key element of behavioural adaptation (Schultz, 2002). It reflects the unexpected presence (positive prediction error) or absence (negative prediction error) of rewards and is coded by mesencephalic dopaminergic cell activity (Schultz & Dickinson, 2000). Dopaminergic cells project directly to the frontal cortex, but the specific consequence of the prediction error signal on cortical information processing is unclear.

Important insight comes from event-related potential studies in humans, which describe a medial frontal error-related negativity (ERN), probably originating in the anterior cingulate cortex (ACC), subsequent to incorrect responses (also called Ne) and error feedback (medial frontal negativity, MFN) (Nieuwenhuis *et al*., 2004). The origin of the ERN is debated. One influential hypothesis is that it is generated when the consequences of an action are worse than expected (Holroyd & Coles, 2002). Referring to Schultz and colleague's work, Holroyd and Coles proposed that through the direct meso-cortical dopaminergic pathway a negative prediction error-signal disinhibits ACC neurons, which thereby produce the cortical error signal (Holroyd & Coles, 2002). Recent data in humans have been in favour of this model (Holroyd *et al*., 2003), which fits with the increasing consensus about a fundamental role for ACC in relating actions to their values and consequences (Rushworth *et al*., 2004).

Only a few experiments studied cortical error-related signals with non-human primate neurophysiology. Most have explored how ACC error-related activity is related to pure detection of missing rewards (Niki & Watanabe, 1976; Brooks, 1986; Watanabe, 1989; Ito *et al*., 2003). Here we investigate whether ACC error-related unit activity following feedback signalling errors contains information regarding predicted rewards, and thus supports the prediction error hypothesis. We describe monkey ACC unit activity recorded during a reward expectation task, and preliminary data obtained in one monkey during a trial and error task. These data are issued from two experiments devoted to behavioural adaptation in which error-related signals were not analysed (Procyk *et al*., 2000; Amiez *et al*., 2003).

Materials and methods

Surgical, electrophysiological and histological procedures were carried out according to the European Community Council Directive (1986) (Ministère de l'Agriculture et de la Forêt, Commission nationale de l'expérimentation animale) and Direction Départementale des Services Vétérinaires (Lyon, France). Briefly, the animals were surgically prepared using aseptic techniques and under general anaesthesia [chlorpromazine (Largactil® 1 mg/kg, i.m., Rhone Poulenc Rorer, France), Ketamine (Imalgene®, 10 mg/kg, i.m., Lab Rhone Merieux, France) and Propofol (Diprivan®, i.v., Zeneca Pharma)]. After surgery and over 7 days, antalgic (Paracetamol: Doliprane®, 125 mg, UPSA)

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Received 28 January 2005, revised 22 April 2005, accepted 25 April 2005

doi:10.1111/j.1460-9568.2005.04170.x

and antibiotics (Oxacilline: Bristopen® 0.2 g/ml, i.m., Lab. Bristol, France) were given to the animal. During the whole postsurgical period, implants were daily cleaned (Betadine scrub, Sarget) and treated with antibiotics (Staphylomycine®, Smith Kline & French). For final anatomical verification, the monkeys received an overdose of pentobarbital sodium and were perfused with saline followed by buffered formalin. Frozen coronal sections were taken and stained with cresyl violet. Individual recording sites that had been marked with electrolytic lesions (20uA, 20sec, tip negative) were identified and the locations of all electrode penetrations were reconstructed accordingly.

Experiment 1: effect of expected reward size on error-related activity

We studied ACC activity in situations devoid of difficult decision-making, using a stimulus–reward association task detailed elsewhere (Amiez *et al.*, 2003). Rhesus monkeys were seated in a primate chair in front of a touch-screen (Microtouch System) coupled to a TV monitor. Visual presentations, eye movements (scleral search coil) and behavioural controls were monitored by a devoted system (CORTEX; NIMH Laboratory of Neuropsychology, Bethesda, MD, USA).

When the monkey touched a starting item (located 10 cm below the rewarded targets), a central fixation point appeared. The animal was required to fixate this point. Then, two identical visual target stimuli simultaneously appeared to the right and to the left of the centre of the screen. Two stimuli were used for control purposes in a previous experiment (Amiez *et al.*, 2003). After a 2–3-s delay period and a 'GO' signal (targets extinguished for 100 ms and fixation point turned off) the monkey was allowed to look at the targets, to release the starting item and to touch one of the two targets. Touching either one extinguished the stimuli. The animal was then required to maintain contact so as to obtain the reward (fruit juice). If the monkey released the lever or broke central eye fixation (break of fixation) before the GO signal, all stimuli present on the screen were switched off and the trial was aborted. These were the only possible errors. The stimuli were fixed and identical throughout training and recordings: two blue rectangles were each associated with a reward of 1.2 mL, two green ellipses with 0.4 mL and two red disks with no-reward (0 mL). The quantity of reward delivered was thus predictable as soon as the stimuli appeared. Touching one of the two stimuli was mandatory for the experiment to proceed to other trials. The stimuli were randomly chosen trial by trial within the set of three couples.

Extracellular unit activity was recorded with single tungsten electrodes and analysed (MATOFF Software, NIMH, USA). Key recording sites were marked with electrolytic lesions (20 μA, 20 s, tip negative) and the locations of electrode penetrations were reconstructed accordingly. Recordings were from the dorsal bank of the anterior cingulate sulcus in or rostral to rostral cingulate motor area (CMAr), at levels anterior to the genu of the arcuate sulcus.

The activity of cells was label 'error-related' (ER) when significant change in firing rate was observed after errors (break of fixation or erroneous touch) compared with baseline activity (intertrial interval) and post-reward (within 1000 ms after reward delivery) activity. Error-related peak activity was measured in an epoch from 200 to 400 ms after the error event (touch or break of fixation) (Fig. 2). Starting and ending event codes defined each trial. Timings of errors were computed using the Start code as reference time 0.

Times of neuronal discharge (from the beginning of the first burst to the end of the last burst) were determined for each trial by a Poisson spike train analysis (see details in Procyk *et al.*, 2000). Significance level was set at $P < 0.01$. Relation of the burst to an event (saccade or touch) was determined by comparing the variances of bursts starting times relative to these events.

To compute average normalized error response, the mean activity for each cell in each error epoch was normalized to the maximum (max = 100) and minimum (min = 0) means across all error trials. Statistics were carried out with significance set at 0.05 (Statistica; Statsoft).

Experiment 2: effect of distance to reward delivery on error-related activity

The materials, recording sites (see Procyk *et al.*, 2000) and data analyses were identical to experiment 1. The monkey performed a problem-solving task (see previous publication for a detailed protocol: Procyk *et al.*, 2000) in which he had to search by trial and error the correct sequence for touching three visual targets displayed on a touch screen.

For each target of a sequence the animal had to make a saccade toward the target, fixate it and then touch it after a GO signal (illumination of all targets). If the touch was correct, all three targets reverted to standard illumination while the monkey maintained its hand position and saccaded to the next target. Each correct touch was associated with a brief sound and targets remained illuminated. If a touch was incorrect, all targets switched off at the time of touch, the trial was aborted and the animal had to start another trial in order to continue the search period. If a touch on the first target of the sequence was correct but the second was incorrect (incorrect second touch), in the following trial the animal could repeat his choice on the first target and change only the second. A correct trial was defined as three touches performed in the correct order and was rewarded at the end of that trial. Note that the first and second touches were never rewarded. The sequence was repeated until the animal had performed a total of four correct trials. When the repetition period was terminated, a visual signal (a central red circle) flashed three times, and a tone indicated a change in the correct sequence and the initiation of a new search. Breaking eye fixation induced trial interruption.

The design of the task made it possible to study two types of errors: selection errors (incorrect target touch) and execution (break of fixation) errors. The animal made both. The two types of errors were separated for analyses because although both are signalled by the same external event (stimuli switch off – blank screen), they are produced by different effectors and have different consequences in terms of behavioural adaptation.

Results

Experiment 1: effect of expected reward size on error-related activity

Out of 372 task-related ACC neurons from two monkeys, 44 (44) showed reward-related activity modulated by the amount of reward. Thirty-two (32) other cells showed strong activation after execution errors. Seventeen of these cells showed ER activities that varied according to the amount of expected reward (one-way ANOVA for each cell: factor: reward size, d.f. = 2; threshold: $P < 0.05$). The PSTH for one of these cells illustrates the change in average ER response as a function of the amount of expected reward (Fig. 1A). Out of 17, 12 cells showed higher activity in trial with larger expected reward size. The effect is evident for the population activity, i.e. large ER signals were produced if large rewards were expected (Fig. 1B).

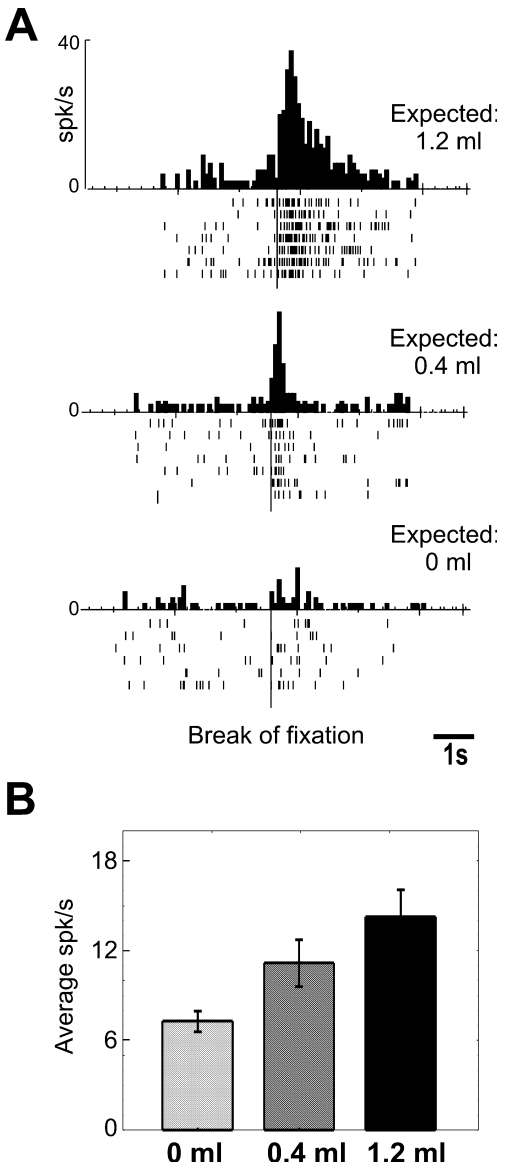

FIG. 1. Experiment 1. Error-related activity is modulated by expected reward size. (A) PSTHs, for one cell, aligned on detection of break fixation, for each amount of expected reward. (B) Average population ER activity measured at the peak epoch (12 cells). Main effect of expected reward size: ANOVA, $F_{2.290} = 8.66$; $P < 0.0002$.

Experiment 2: effect of distance to reward delivery on error-related activity

Only one monkey was recorded enough to find ER activity – see Discussion. Comparing activity in incorrect and correct trials revealed 15 ER cells (out of 149 task-related neurons) (see definition in Materials and methods, Experiment 1). This activity was not related to the absence of immediate reward as in correct trials no particular firing was observed after the first and second correct touches, although these were not rewarded (Fig. 2A). Moreover, firing rates did not change with reward delivery, or sensory event like target offset (see, e.g. correct third touch, which as for error touch is accompanied by the offset of all targets, Fig. 2A and D). The ER population activity had an onset latency of 100 ms and a peak between 200 and 300 ms after an erroneous touch or a break of fixation (Fig. 2C). Remarkably, ER cells also responded after the signal to change the sequence, although this signal did not indicate an error per se (Fig. 2A and D). Note that the signal to change sequence was never associated with reward delivery. This phenomenon is specifically discussed below.

While individual responses showed large variability, on average ER activity was lower for incorrect first than for incorrect second touches (*t*-test IC1 vs. IC2 average of all cells, dL = 28, $t = -2.26$, $P < 0.05$). The ER response was also weaker when break of fixation occurred at the beginning of trials rather than toward the end of trials. One hypothesis is that the error value changes during the course of a trial. A behavioural analysis revealed that there were more breaks of fixation at the beginning of trials than at the end of trials (Fig. 3A). We concluded that the closer to the end of a trial, the more the animal avoided execution errors. A similar behavioural phenomenon has previously been described during multi-trial serial schedules (Shidara & Richmond, 2002). Looking for relationships between behaviour and error signals, we measured the overall average population activity for break of fixation occurring at different times in trials, and found that the neural responses increased when approaching the end of trial (Fig. 3A). We normalized data to reduce potential biases from high firing rate cells and found again a strong correlation between ER activity and time of occurrence in the trial ($R^2 = 0.91$, $P < 0.02$ for average data – correlation on all normalized values: $P < 0.001$). A model with simulated random data was also used to test whether the heterogeneity of error numbers along the time scale for different cells or the normalization procedure would artificially create the effect observed on average activity. Random data, produced with the same proportions as real cases and normalized with the same procedure, revealed a continuous increasing activity with time in only 98 out of 10,000 runs of the model ($P < 0.01$). Thus, the effect observed with real data is significant. Hence, larger error activity occurred for errors committed when the animal was particularly trying to avoid errors. Finally, to appropriately compare ER activity for incorrect touches and breaks of fixation, we isolated those breaks that appeared late in trials, occurring later than 5.5 s after the beginning of a trial, i.e. at times similar to those measured for incorrect touches (on average 6.27 s and 8.56 s for incorrect first and second touches, respectively, see top of Fig. 3A for time dispersions). The average activity shows no difference between incorrect touches and late breaks of fixation (Fig. 2C). Indeed for individual cells, the activity measured for incorrect touches and for break of fixations form one single population correlated with the time from start of trial (Fig. 3B).

Higher ER activity might trigger higher control during subsequent behaviour and thus reduce the occurrence of another break of fixation immediately after. In other words, the next break of fixation should occur later in time. Contrary to this hypothesis, the average normalized ER activity recorded in Experiment 2 showed no relation to the time between two successive breaks of fixation (separated by less than 60 s).

Previous studies showed that ACC ER activity is not influenced by the direction of saccades inducing the errors (Ito *et al.*, 2003). Latencies between the start of ER bursts of activity and the onset of saccades produced around incorrect touches revealed very weak time relationships compared with the latencies with touch times (Analysis for 10 cells with clear bursts; Fig. 2B). We also tested whether ER activity following an incorrect first touch was modulated either by the location of the incorrect target touched or by the location of the target touched in the following trial (correction): one-way ANOVAs showed that for more than 80% of cells the ER activity did not code for target location. Only two cells showed an effect of 'target location' and one cell with an effect of 'next target location' (at $P < 0.05$).

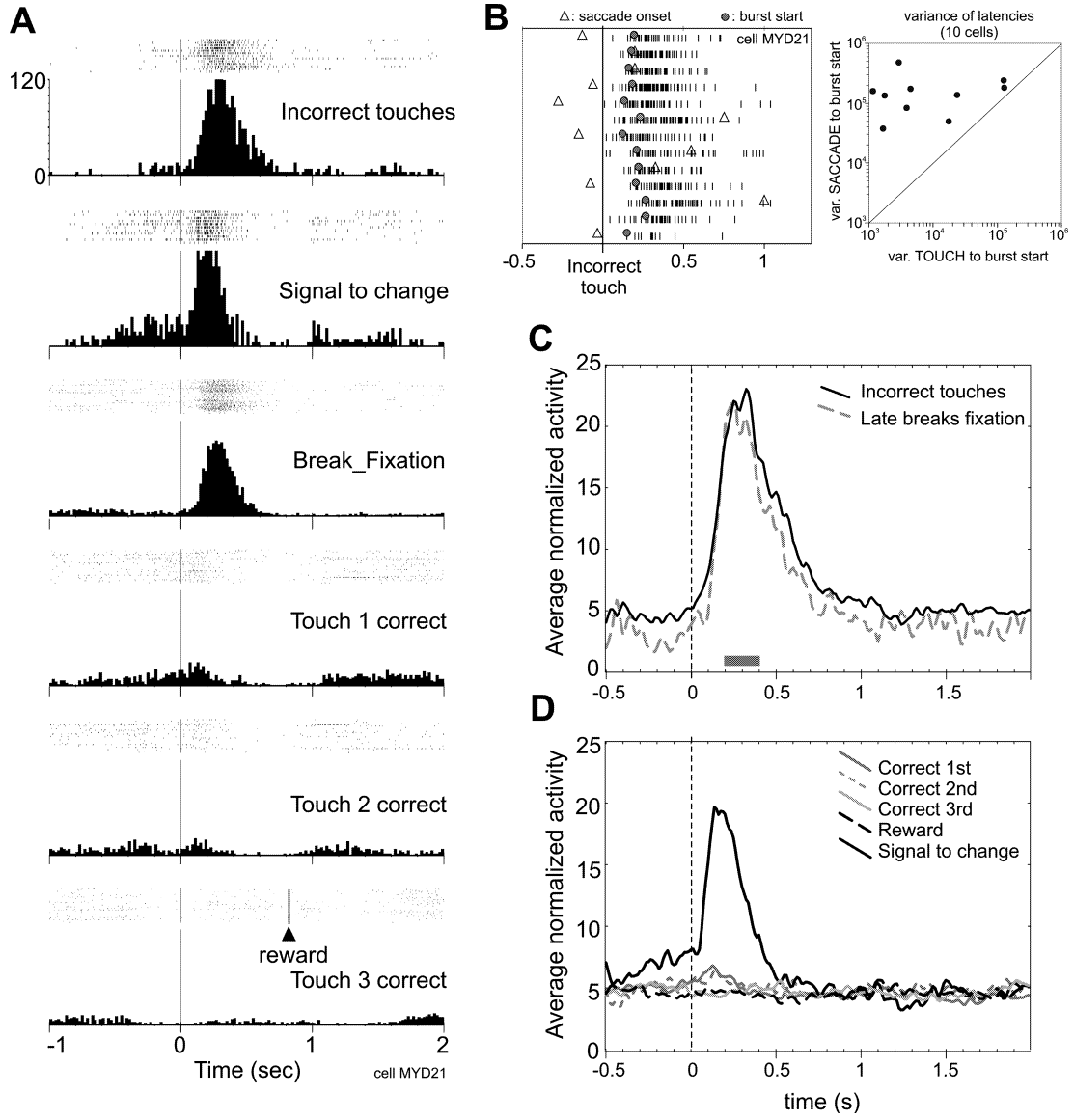

FIG. 2. Experiment 2. ER activity during the problem-solving task. (A) PSTHs for one ER cell, aligned on different events: all incorrect touches, signal to change sequence, break of fixation and correct touches. (B) Saccades and start of burst are presented for incorrect touch trials for the cell presented in (A). On the right, the plot shows higher variability for latencies between saccade (triangles on rasters) and the start of burst (circle) than for latencies calculated from touch times. *F*-test on variances revealed three cells with no significant differences (at $P < 0.05$). (C) Average normalized activity for the 15 ER cells. The graph shows error activity aligned on incorrect touches (first and second together – black) and on break of fixation occurring after 5.5 s from the beginning of a trial (dashed grey). (D) Activity aligned on reward, first, second and third correct touches in correct sequences, and on the signal of sequence change (smoothing of average curve: Lowess method). Average activity was measured at the peak epoch [bold grey line on *x* axis in (C)].

Discussion

Our experiments show that: (1) ACC error activity depends on reward prediction (size × probability); (2) ACC ER activity is not directly tied to a particular modality of error commission as it appears after execution errors (breaking eye-fixation) and selection errors (after incorrect choice), a characteristic feature of human ERN (Holroyd & Coles, 2002); (3) ER activity does not show clear variation with spatial parameters, which have been observed by previous experiments (Ito *et al*., 2003); and (4) ER activity is not uniquely linked to error per se or immediate absence of reward, as it also appears after the signal to change sequence. Hence, ACC 'error' activity might signal various events interrupting potentially rewarded actions.

Those preliminary results were obtained in separate experiments. Further experiments will be needed to confirm that ER activity of the same neurons can be influenced by *both* reward size and reward probability, and whether all cells do not discriminate between error types. No error cells were found during recordings in a second animal with the problem-solving task because fewer recordings were performed. Indeed, error cells are found in little proportions: about 10% (15/149) of task-related cells for the monkey in Experiment 2 and 8.5% (32/372) for the two monkeys in Experiment 1. Other authors have reported similar proportions (Ito *et al*., 2003).

Reward prediction errors should represent the difference in value between delivered and predicted rewards. Experiment 1 shows that, indeed, ACC ER activity codes for such difference in terms of magnitude. Experiment 2 shows how prediction errors evolve during time-extended and sequential goal-directed behaviour. In this experiment, ER activity is not related to the absence of immediate reward but

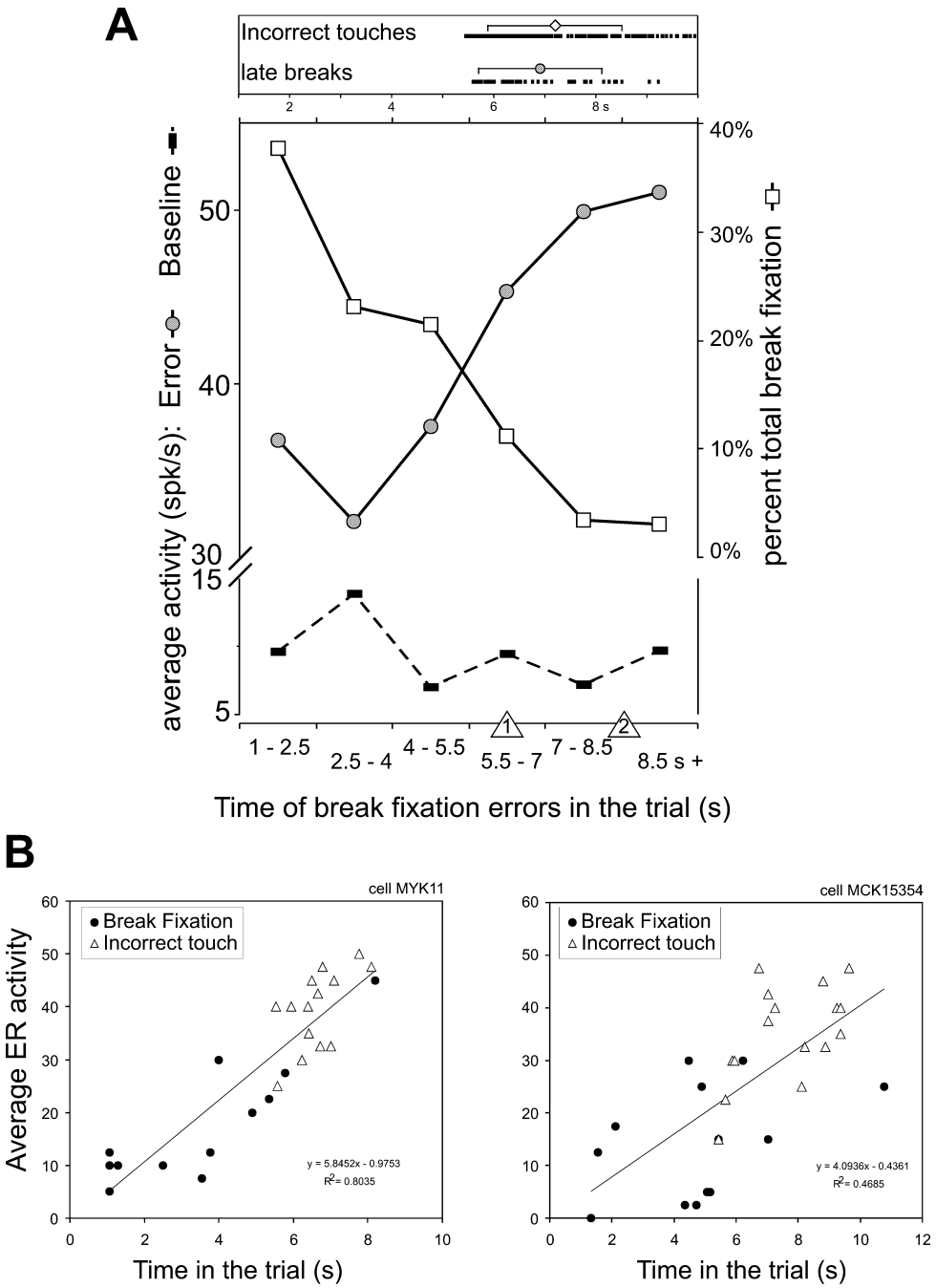

FIG. 3. Experiment 2. Effect of distance to reward on error-related (ER) activity. (A) Most break fixation errors occurred in the early phases of trials (open squares). Fewer occurred near the end of trials. The average normalized error response for the 15 cells followed the reverse evolution (grey discs). Average baseline (before the error) is represented (black rectangles). On top, the average times with standard errors are represented together with individual values (dots) for all incorrect touches (empty diamond -7.2 ± 1.3 s) and late break fixation errors (grey disc -6.9 ± 1.2 s). White numbered triangles represent the average time of touches during trials [on average 6.27 s and 8.56 s for incorrect first (1) and second (2) touches, respectively]. Time period effect: baseline: $F_{6;513} = 1.08$, $P = 0.3707$; error signal: $F_{6;513} = 5.45$, $P = 0.00002$. (B) Two cells in which activity measured at the time of either break of fixation or incorrect touches is plotted against the time of occurrence of the error in the trial. For both the correlation coefficient is statistically significant ($P < 0.001$).

rather to a 'distance' to the potential reward expected after three correct touches. These data are consistent with the fact that other ACC neurons encode the successive elements of motor sequences in terms of distance to the final reward delivery or in terms of degree of reward expectancy (Procyk *et al*., 2000; Procyk & Joseph, 2001; Shidara & Richmond, 2002). They are also consistent with feedback-related ERN data, although this evoked potential putatively originates from signals other than unit activity (Logothetis, 2003). The amplitude of the ERN increases when the probability of a positive outcome is high (Holroyd & Coles, 2002; Holroyd *et al*., 2003). Similarly, a MFN related to positive or negative outcomes was influenced by previous trials, and therefore presumably by the probabilities of success computed from previous outcomes (Gehring & Willoughby, 2002; Nieuwenhuis *et al*., 2004). Note that our data describe activity related to feedback signalling errors and not to internal error detection that would correspond to the ERN/Ne potential described in humans.

ER activity is generic and does not indicate which error was made or what action to perform after the error (Holroyd & Coles, 2002). It does not distinguish between different types of error (Fig. 2C). Strikingly, these activities also increase after the signal to change sequence, a cue that indicates the necessity to shift response and to enter a new search although the correct response had been discovered and the reward was highly expected. Similar activity has been found in humans (Williams *et al*., 2004). Thus, ACC ER activity is not specific to errors and can relate to events, other than erroneous behavioural responses. Unfortunately, our protocol did not vary the value or meaning of the signal to change sequence. Moreover, activity anticipating the signal to change (Fig. 2A and D) suggests that in a different context it could be self-triggered and that an external feedback might not be necessary.

The ER signal might serve to trigger subsequent processes like the updating of motor plans, the neural correlate of which is observed in the frontal lobe (Shima *et al*., 1996; Shima & Tanji, 1998). However, we failed to find a link between error signal and behaviour adjustments, and data on such a relation is still unclear (Gehring *et al*., 1993; Rodriguez-Fornells *et al*., 2002; Hajcak *et al*., 2003).

The present data and our previous report of ACC activity specific to search periods (Procyk *et al*., 2000) fit closely with the recent model involving error-signals and the ACC in associating error likelihood to behavioural situations (Brown & Braver, 2005). In this regard, activity related to the signal to change sequence could indicate the beginning of a period with high error likelihood by, as we evoked before, signalling the discrepancy between the low probabilities to be rewarded in the future search and the certainty to be rewarded in repetition.

Our results also support the idea of a link between anterior cingulate activity and midbrain dopaminergic activity that encodes 'reward prediction errors', and are modulated during trial and error and by expected values (Fiorillo *et al*., 2003; Satoh *et al*., 2003; Tobler *et al*., 2005). One important extension of our study will be to investigate whether unexpected rewards (leading to positive prediction error) inversely modulate anterior cingulate 'error'-related neurons as it does for mid-brain dopaminergic cells.

Acknowledgements

We thank H. Kennedy, H. Cooper and J. Sallet for their insightful comments. Authors are supported by Inserm, CNRS, ACI neurosciences intégratives and the FYSSEN foundation.

Abbreviations

ACC, anterior cingulate cortex; ER, error-related; ERN, error-related negativity; MFN, medial frontal negativity.

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