Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning

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Reciprocal connections between the orbitofrontal cortex and the basolateral nucleus of the amygdala may provide a critical circuit for the learning that underlies goal-directed behavior. We examined neural activity in rat orbitofrontal cortex and basolateral amygdala during instrumental learning in an olfactory discrimination task. Neurons in both regions fired selectively during the anticipation of rewarding or aversive outcomes. This selective activity emerged early in training, before the rats had learned reliably to avoid the aversive outcome. The results support the concept that the basolateral amygdala and orbitofrontal cortex cooperate to encode information that may be used to guide goal-directed behavior.

The prefrontal cortex is important for the organization of goal-directed behavior[1–3]. Dysfunction of orbitofrontal cortex (OFC) is associated with disturbances in motivation and an inability to anticipate consequences, leading to poor judgment and maladaptive behavior[4,5]. For example, in the experimental setting of a gambling task in which choices were associated with contingencies of monetary rewards and penalties, normal subjects learned to optimize rewards whereas patients with damage to this region of prefrontal cortex performed poorly, unable to adjust their behavior appropriately to the contingencies of the task[6,7].

Functions that require the integrity of OFC are also dependent on information provided through interconnected structures, allowing access to information regarding the context of cues and associations formed during learning through inputs from other systems. One key region, with respect to goal-directed behavior, is likely to be the basolateral amygdala (ABL). The OFC is directly interconnected with ABL[8–11], a structure that is important for associative learning in primates and other species[12–17]. For example, rats with neurotoxic lesions of ABL have difficulty in learning to avoid an aversive outcome[13], and damage to this structure in both rats and monkeys is also associated with deficits in the ability to adjust behavior when the value of reinforcers is altered[14,15]. OFC and ABL may cooperate in a circuit that brings associative learning to bear on decision making. The current study examined neural activity in OFC and ABL during olfactory discrimination training, when rats were in the process of learning an adaptive behavioral strategy of responding on trials with a rewarding outcome and withholding responses on trials with an aversive outcome. Neurons in both regions fired selectively during a delay as the rat awaited the outcome of the trial. Moreover, this selective activity that encoded the impending outcome emerged early in training, before rats developed a reliable behavioral discrimination by avoiding the aversive outcome.

Results

We recorded neural activity in rats with electrodes positioned in either OFC or ABL (Fig. 1). The rats were trained on a series of discrimination problems in which the identity of an odor was informative about the consequence of making a response. The rat sampled the odor via a sampling port, and then placed its snout into a fluid well located several inches below the odor sampling port (see Fig. 2). Responses at the odor port and at the fluid well were registered by interruption of photobeams that detected the entry of the rat's snout into each port. The odor predicted whether the rat would receive a rewarding sucrose solution or an aversive quinine solution. To examine the effect of learning on neural activity, we used novel odors each day; thus rats had to learn the outcomes associated with a new set of odors in every session. In some sessions, a two-odor discrimination problem was presented in which one odor, designated the positive odor, predicted the delivery of a sucrose solution, and a second odor, designated the negative odor, indicated that the same response would result in delivery of a quinine solution. In other sessions, a four-odor discrimination problem was presented that had two positive odors and two negative odors. Rats were maintained on a restricted schedule of water consumption to motivate behavior in the task.

In the process of solving each new discrimination, rats initially responded by entering the fluid well after odor sampling on every trial (referred to as a 'go' response) but then gradually learned to withhold this response (referred to as a 'no-go') after sampling an odor that predicted the aversive outcome. These sequences of behavior are schematically illustrated in Fig. 2. It is important to note that a go response at the fluid well was not immediately followed by delivery of the fluid reinforcer, but rather resulted in a short variable delay period (300–800 ms) before fluid was delivered. During this short delay, the rat was required to maintain its snout in the fluid well. It was during this interval (see shaded region in Fig. 2), after the rat made a go response but before the outcome was presented, that we looked for changes in neural activity during learning.

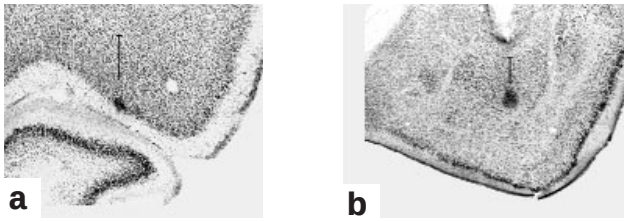

Fig. 1. Photomicrographs of histological sections showing the reconstruction of recording sites in representative subjects in **(a)** OFC and **(b)** ABL. The OFC encompasses the orbital regions and agranular insular cortex. In each photomicrograph, a vertical line represents the dorsoventral range along the electrode track from which neurons were recorded in the case shown. Recordings were localized to ventrolateral and lateral orbital regions and ventral agranular insular cortex in the four rats in the OFC group. Recordings were localized to the basolateral nucleus in the three rats in the ABL group.

Comparison of neural activity on positive go and negative go trials revealed that a substantial population of neurons in both OFC and ABL fired differentially depending on whether the subsequent outcome was to be the rewarding sucrose solution or the aversive quinine. This comparison of activity was statistically significant for 74 (or 22%) of 328 neurons sampled in OFC and 44 (or 36%) of 121 neurons sampled in ABL. The activity of these neurons, illustrated in Fig. 3, differed on positive and negative go trials as the rat awaited reinforcement in the fluid well. Note that negative go trials constitute errors, in which the rat makes a response after sampling the odor that predicts delivery of quinine. The development of differential neural activity is not, therefore, a function of a difference in behavior per se. Although the rat had not yet learned the adaptive behavioral discrimination of withholding responses on trials with the aversive outcome, these neurons nonetheless had acquired an ability to discriminate by anticipating the positive or negative consequences of making a response.

Consistent with this interpretation, further analyses indicated that selectivity developed as the rat learned the discrimination problem. These analyses examined activity during an early segment of training in each session, generally before the animal showed any behavioral learning (i.e. before it made any correct no-go responses; see methods). The relative selectivity of these neurons increased significantly between that early segment of training and the remaining trials before the behavioral criterion was reached (Fig. 4). These data show the contrast between neural activity on positive and negative go responses, calculated as the difference between the firing rates during positive and negative go responses divided by the sum of those rates. Indeed, comparison of activity on positive and negative go trials in individual cells for the early segment of training revealed that few neurons were selective at that point in training (only 17% or 6 of 35 in OFC and 15% or 5 of 34 in ABL). In contrast, for the great majority of such neurons, selectivity emerged as training progressed. These results provide strong evidence that the cells encode an expectancy for the consequences of the response, based on experience in the task.

If the observed selective activity during the delay represents anticipated outcomes, it should depend on whether the odor sampled on a trial predicted a rewarding or an aversive contingency. As expected, a number of neurons in the entire population that we recorded over the training trials considered in our analysis did fire differentially during odor sampling (66 of the 328 neurons in OFC and 40 of the 121 in ABL). Consideration of the cells with selective activity during the delay, however, revealed that relatively few of these cells (24% or 18 of 74 in OFC and 25% or 11 of 44 in ABL) had similar selectivity during odor sampling (see Fig. 2 for the interval of analysis). Thus several subsets of cells encode information in the task, but the majority of neurons that exhibited differential firing during the delay did not fire differentially earlier in the trial in response to the odor cues. Figure 5 illustrates a neuron that fired differentially during the delay after go responses but not when the rat was sampling the odors.

Table 1 shows additional features of the neurons that exhibited differential activity, and provides further indication of the strong influence of the expected outcome. The population of selective neurons is shown with reference to whether greater firing occurred on positive or negative go trials. In ABL, the great majority of these neurons had selective activity biased for negative go trials; 40 of 44 selective neurons fired more strongly preceding quinine delivery (Table 1). Such neurons, however, did not increase firing when the rat withheld its response (a no-go) after sampling the negative odor. This is consistent with the interpretation that elevated activity is related to the impending negative outcome, which is not delivered when a decision is made not to respond (Fig. 5). In addition, 36% of the OFC cells and 65% of the ABL cells that were selective in the four-odor task (Table 1) had activity that was elevated to a similar degree on trials involving either of two odors associated with the same outcome; these neurons clearly encoded the anticipated outcome independent of which odor had been sampled. Finally a substantial number of the selective neurons in ABL also responded differentially during subsequent reinforcement; 22 (or 50%) of the 44 neurons that were selectively active during the delay had similar selectivity during reinforcement. In OFC, the proportion of neurons that had parallel selectivity during the delay and reinforcement was considerably lower (28%). It is also evident from Table 1 that whereas a high proportion of ABL cells were biased for negative rather than positive contingencies, this was not the case for OFC.

Discussion

In the current study, neural activity was recorded as animals acquired new learning. During an early phase of training on novel odor discrimination problems, neurons acquired discriminative activity prior to overt changes in behavior. Specifically, a substantial proportion of cells sampled in OFC and ABL developed neural activity that differed reliably between trials with a negative outcome and trials with a positive outcome. This neural activity seemed to reflect an expectation about the impending consequences of making a response. Such activity could provide an important component in the learning process. Expectations about the occurrence of future events are useful in forming associations that represent accurate predictive information, and experience is required to determine whether anticipated outcomes are matched by actual outcomes. A subsequent adaptive change can then be made based on the established predictive value of information used to guide behavior. By this view, the differential

Table 1. Neural selectivity during the response delay in pre-criterion training

	2 odor		4 odor	
Trial Type	Positive Go	Negative Go	Positive Go	Negative Go
OFC (328)[1]	14	16	19	25
ABL (121)[1]	1	6	3	34

[1]The total number of neurons sampled in each region.

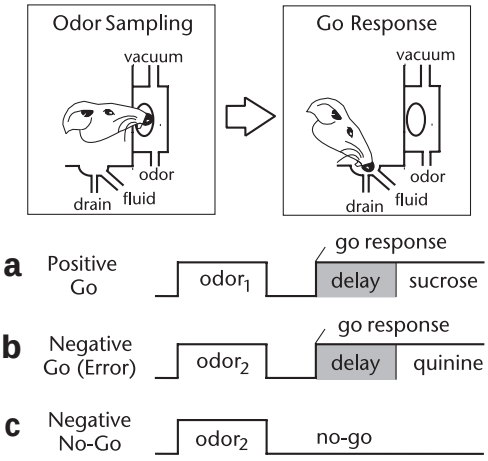

Fig. 2. Sequence of behaviors in **(a)** positive go, **(b)** negative go, and **(c)** negative no-go trials during acquisition of a go, no-go olfactory discrimination task. In this task, a water-deprived rat had to sample an odor presented at a port on each trial (odor sampling) and then respond (go response) to receive sucrose or withhold the same response (no-go) to avoid quinine. Responses at the odor port and at the fluid well were registered by interruption of photobeams that detected entry of the rat's snout into each port. When a go response was made, the rat had to remain in the fluid well for a brief delay before the reinforcer was delivered (shaded region). Because novel odors were presented in each session, the animal had to learn new associations each day. Learning was evident when the rat began to withhold responses after sampling the negative odor to avoid quinine delivery. Neural activity during the brief delay after a go response was compared on positive and negative go trials as the rats were learning the discrimination. During this part of the session, the rats made go responses and also withheld the response (no-go) on some negative trials but had not yet reached the behavioral criterion defined under behavioral methods. As illustrated, the positive go and negative go trials that were compared in our analysis involved identical responses and both involved a requirement that the rat remain in the well after the response; thus the analysis of neural activity during this time period controlled for motor behavior.

activity observed here would provide a neural substrate that supports subsequent behavioral change. Moreover, these correlates for anticipated outcomes developed early in the course of training in two interconnected structures that are widely viewed as serving important functions in adaptive behavior.

Clinical observations indicate that human patients with damage to the orbital region of prefrontal cortex are prone to poor judgment, making maladaptive decisions in complex social and naturalistic settings [4]. In such cases, it is commonly noted that the consequences of patients' actions fail to adequately influence their behavior. Maladaptive social behaviors are also characteristic of monkeys with surgical ablations of the amygdala[18], a phenomenon recognized in some of the earliest investigations of non-human primate behavior after brain lesions[19,20]. These observations, coupled with anatomical evidence that OFC and ABL are reciprocally connected[8–11], suggest that these regions function cooperatively in the regulation of adaptive goal-directed behavior. The neurophysiological findings reported here are compatible with such a cooperative relationship; neural correlates related to anticipated outcomes were found in each structure.

Evidence from clinical cases and laboratory animal research has also been taken to indicate that OFC and ABL are specialized for somewhat different functions. In this context, ABL is widely viewed as critical for associative learning[12–17], whereas OFC is implicated in the ability to integrate and organize information used in the selection of behavioral strategies[4,5,17,21]. Accordingly, OFC may function to guide adaptive behavior by accessing relevant information from afferent structures such as ABL. This view, distinguishing the functions of OFC and ABL, is consistent with certain features of our neurophysiological data.

In the present study, the neural correlates observed in ABL are consistent with encoding of the critical associative features of the task; the great majority (91%) of the selective neurons in ABL fired more strongly during errors (i.e. after responses that led to the aversive quinine solution), and a high proportion of those neurons had parallel selectivity when the fluid was subsequently delivered (i.e. they fired more strongly on exposure to quinine than sucrose). Notably this bias occurred in a go, no-go discrimination task that required an adjustment in behavior to avoid the aversive outcome.

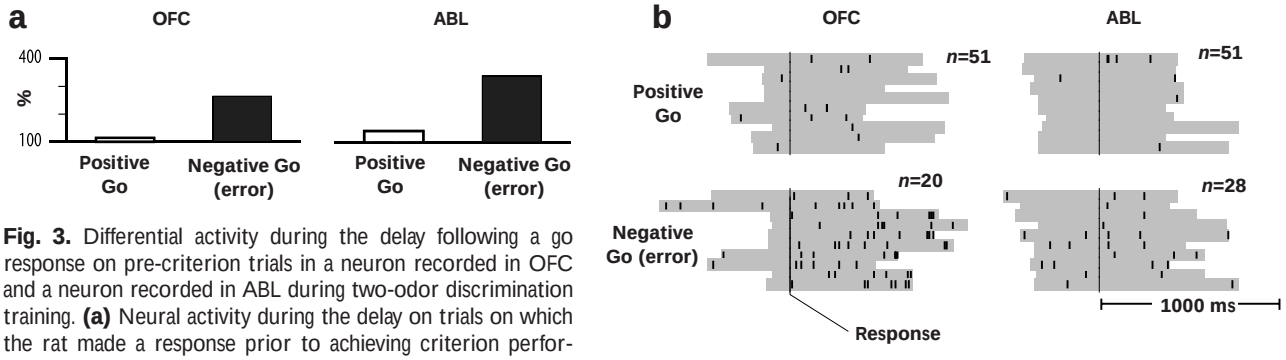

Fig. 3. Differential activity during the delay following a go response on pre-criterion trials in a neuron recorded in OFC and a neuron recorded in ABL during two-odor discrimination training. **(a)** Neural activity during the delay on trials on which the rat made a response prior to achieving criterion performance, represented as a percentage of the pre-trial baseline firing rates (baseline rate for OFC = 2.33 spikes/s; for ABL = 0.78 spikes/s). Neural activity during negative go responses (closed bars) was significantly higher than baseline in both cases and was elevated when compared to neural activity during positive go responses (open bars): OFC [$F(1,69) = 37.4$, $p<0.001$]; and ABL [$F(1,77) = 21.87$, $p<0.001$]. **(b)** Raster displays showing neural activity on ten representative trials from pre-criterion training for each of the neurons during positive go (upper rasters) and negative go responses (lower rasters). Neural activity, bounded by the shaded region in each trial, begins with odor offset corresponding to withdrawal from the odor port and is synchronized on the go response at the fluid well (thin vertical line). Activity is truncated at reinforcement delivery. In these displays, the activity is clearly greater for each neuron during the delay on negative go trials than during the delay on positive go trials.

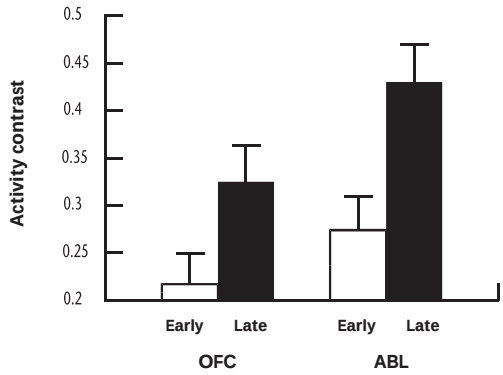

Fig. 4. Contrast in activity on positive and negative go trials during the early (open bars) and late (closed bars) segments of pre-criterion training for a population of neurons selective during the delay in OFC and ABL (see Methods for description of early and late segments and criteria for the analysis). The activity contrast was calculated as the absolute difference in the rates on positive and negative go trials divided by the sum of those rates, yielding values that ranged from 0 to 1. Note that these data include activity from the small subset of neurons that showed selectivity during the early segment of the pre-criterion phase. Nevertheless, the activity contrast increased significantly in both OFC [$t(34) = 2.32$, $p=0.026$] and ABL [$t(33) = 3.77$, $p=0.00065$] between the early and late segments of training, representing an increase in relative selectivity of these populations of neurons.

In contrast, OFC had similar proportions of neurons selective for positive and negative outcomes, a pattern consistent with a more general function of monitoring the expected consequences of ongoing behavior, irrespective of a need to change behavior. This interpretation agrees with prior recording studies using olfactory discrimination tasks in which learning was already well established; neural activity in both primate and rat OFC encoded the identity and behavioral significance of olfactory cues[22–24], as well as features of the context[22]. Those results and the current observations support the widely held view that prefrontal cortex serves an executive function, in part, by representing ongoing events and the expected consequences of actions[1–4,21].

Selective activity during delays is a well characterized feature of neurons in prefrontal cortex in non-human primates. Investigators have found such correlates in dorsolateral prefrontal cortex[25–28], and in some of those studies activity during the delay was clearly related to the anticipation of specific events[29,30]. Here we demonstrate selective activity during a delay that is also related to future events in a region of rat prefrontal cortex, the OFC, and in an interconnected subcortical region, the ABL. This delay activity seems particularly tied to the motivational significance of the expected outcome. Consistent with this concept, recent research with human patients has reported a deficit in autonomic responses that provide a marker for the motivational properties of anticipated outcomes[6]. In contrast to normal subjects, who exhibited an elevated skin conductance response when making choices that could result in a negative outcome, this response was lacking in patients with orbital damage. Interconnections between OFC and ABL may be critical for accessing information about the motivational properties of expected consequences when selecting a course of action. The current study offers a rodent model that can be used to study these and other ideas about the organization of systems that encode behavioral contingencies and govern the selection of adaptive behavior.

Methods

ELECTROPHYSIOLOGICAL METHODS. Extracellular activity was recorded in adult male Long-Evans rats using a driveable bundle of ten 25 μm diameter microwires described previously[22]. A single bundle was implanted in the left hemisphere in orbitofrontal cortex of four rats (3.0 mm anterior to bregma, 3.2 mm lateral, 4.0 mm ventral) and basolateral nucleus of amygdala of three rats (3.0 mm anterior to bregma, 5.0 mm lateral, 7.5 mm ventral). The rats were allowed two weeks to recover. Behavioral training began thereafter and was followed by recording once task procedures had been learned (see caption, Fig. 2). During recording, novel odors were utilized each day so that new learning could be examined repeatedly, and after each session the electrode bundle was advanced about 40 or 80 μm to acquire activity from new cells for the following day. Neural activity was passed through a high-impedance headstage and then activity on each microwire was amplified 5000×, bandpass filtered at 300–3000 Hz, and recorded on analog tape along with computer-generated TTL pulses to mark behavioral events. Later, signals were digitized at 25 kHz, and then individual units were discriminated using a template-matching algorithm (Cambridge Electronic Design) in concert with examination of the oscilloscope tracing. In this manner, data were collected in 43 sessions. Recording was stopped in a given rat when the estimated position of the electrode bundle was consistent with passage beyond the region of interest. The final electrode position was marked by passage of a 15 μA current through each microwire to create a small iron deposit, which was later visualized histologically using a 3% potassium ferrocyanide solution to produce a Prussian blue reaction. The electrode tracks were reconstructed to determine approximate recording sites using these marks.

BEHAVIORAL METHODS AND RESULTS. Behavioral testing was performed in an operant chamber employing a go, no-go olfactory discrimination task in which all behavioral events and data collection were controlled and monitored by computer as described[22]. Rats were water-deprived overnight prior to each recording session and, therefore, were strongly motivated to perform for fluid reward. On each trial, the rat poked its nose into an odor port to trigger odor presentation and then had 3 s after withdrawal from the port to respond by entering a nearby fluid well for reinforcement (go response). After a response was

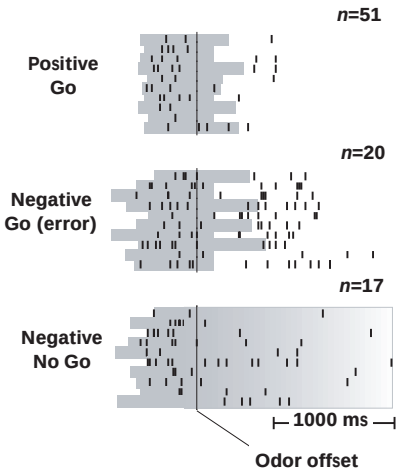

Fig. 5. Activity of the OFC neuron in Fig. 3 on positive go, negative go, and negative no-go trials. Each raster illustrates activity on ten representative trials from pre-criterion training. Activity during each trial in these rasters begins with odor onset and is synchronized on odor offset, indicated by the thin vertical line. A go response is indicated by abrupt termination of shading at the left of each raster, and activity is truncated at reinforcer delivery. When no response is made on negative no-go trials, activity is shown for a period of 1500 ms after odor offset. As illustrated previously, this neuron had higher activity during the delay after a negative go response, but examination of activity prior to odor offset reveals that this selectivity did not reflect activation during sampling of the negative odor. In addition, note that this neuron did not fire during an interval corresponding to the delay period on no-go trials.

made, delivery of fluid was delayed by a variable period of approximately 300–800 ms, providing a brief period in which neural activity could be examined independent of reinforcement. In the two-odor task, one odor signaled that a go response would produce approximately 0.05 ml of a palatable 10% sucrose solution, whereas the other odor signaled that a go response would produce approximately 0.05 ml of a distasteful 0.03 M quinine solution. In the four-odor task, two distinct odors were associated with sucrose and two distinct odors were associated with quinine. We examined neural activity during the acquisition phase of each session, defined as the trials before the rat reached a behavioral criterion of 90% accurate performance within a twenty-trial block. For the sessions analyzed in this study, this phase comprised, on average, 66 trials in the two-odor task and 82 trials in the four-odor task.

ANALYSIS. Neural activity was examined during go responses on trials before the rat reached the behavioral criterion within a time window extending from 50 ms prior to detection of a response at the fluid well until reinforcer delivery. Activity could be examined during this period independent of the outcome of the response because of the variable delay instituted between response and reinforcement (see caption, Fig. 2). Neural activity (spikes/s) on trials involving a positive go response was compared to that on trials involving a negative go response using analysis of variance. A statistically significant difference ($p<0.05$) was further evaluated if the session involved four-odors by post-hoc testing to compare activity on trials of each odor. Neurons with elevated activity on trials of a single odor or equally elevated activity on trials of either of the pair of odors associated with the same outcome were categorized similarly as either positive go- or negative go-selective.

Neurons with differential activity within the delay during pre-criterion training were further examined to determine whether selectivity was present initially or whether it developed as the rat learned the discrimination. To measure initial selectivity, we defined an early segment of the pre-criterion phase, including only those trials preceding the sixth negative go response (error), designed to include only trials before the rat began to withhold responses on negative trials. On average, this segment included 15 trials (10–18 trials). Only selective neurons from sessions ($n=31$ sessions) in which the rate of learning allowed an analysis of early activity were analyzed. Criteria for inclusion in the analysis were the presence of at least ten errors overall pre-criterion and five errors before the third no-go response. In addition, four neurons in OFC and two neurons in ABL were excluded due to a lack of activity in the early trials that were the focus of this analysis. Neural activity in this early segment of training was evaluated by analysis of variance ($p<0.05$) in cells that had exhibited selectivity in the earlier analysis. In addition, the response of the entire population of the selective neurons was evaluated by comparing the contrast in activity on positive and negative go trials between the early and late segments of pre-criterion training. The contrast was defined as the absolute difference between the rates on positive and negative go trials divided by the sum of those rates, and thus ranged from 0 to 1. The contrasts for the early and late segments of training were then compared within each region using a *t*-test for dependent samples ($p<0.05$).

All procedures and training was conducted in accordance with animal care guidelines and all protocols were approved by the institutional animal care and use committee.

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