The effect of concurrent reward on aversive information processing in the brain

Andy J. Kim[a] & Brian A. Anderson[a]

[a]*Texas A&M University*
Department of Psychological & Brain Sciences
Texas A&M Institute for Neuroscience
4235 TAMU College Station, TX, USA 77843-4235
Emails: jskim628@tamu.edu, brian.anderson@tamu.edu

To whom correspondence should be addressed:

Andy Jeesu Kim
Texas A&M University
Department of Psychological & Brain Sciences
Texas A&M Institute for Neuroscience
4235 TAMU College Station, TX 77843-4235
E-mail: jskim628@tamu.edu
Phone: (408) 387-3808

Abstract

Neural networks for the processing of appetitive and aversive information, in isolation, have been well characterized. However, how the brain integrates competing signals associated with simultaneous appetitive and aversive information is less clear. In particular, it is unknown how the presence of concurrent reward modulates the processing of an aversive event throughout the brain. Here, we propose utilizing a four-armed bandit task in an fMRI study to measure the representation of an aversive electric shock with and without the simultaneous receipt of monetary reward. Using an ROI approach, we will first identify regions activated by the experience of aversive electric shock, and then measure how this shock-related activation is modulated by concurrent reward using independent data. Informed by prior literature and our own preliminary data, analyses will focus on the dorsolateral prefrontal cortex, anterior and posterior insula, anterior cingulate cortex, and the thalamus and somatosensory cortex. Of interest will be the extent to which responses to the aversive electric shock are attenuated due to the presence of concurrent reward, consistent with either the integration of valence signals or competition between punishment and reward.

Keywords**:** reward; punishment; fMRI; decision-making

Introduction

Decision-making involves the evaluation of the potential costs and benefits of different possible actions one can take, based on prior experience, that ultimately results in choice behavior (O'Doherty et al., 2017). Effective decision-makers seek to maximize rewards while minimizing aversive outcomes and thereby maximize overall utility. In experimental paradigms, decision-making tasks commonly consider the role of reward or punishment in isolation, in which the explicit goal of the task is either to maximize reward or minimize punishment (Burnett et al., 2010; Figner et al., 2009; Ilango et al., 2012; Navalpakkam et al., 2010; Paulsen et al., 2011; Singh & Khan, 2012; Stark et al., 2004; Stevens et al., 2014; Worthy et al., 2011). Even tasks that incorporate both reward and punishment, such as the Iowa Gambling Task, often utilize a design in which a given choice is either rewarded (monetary gain) or punished (monetary loss), and the goal of the task is to maximize overall rewards across multiple decisions (Bechara et al., 1994; Toplak et al., 2010). Under such conditions, a given outcome is either distinctly positive or distinctly negative, and these individual outcomes must be integrated over time in order to arrive at a representation of overall utility.

What about situations in which a given decision can have multiple consequences, some of which are positive and some of which are negative? In this sort of situation, it is necessary to balance the weight of these positive and negative outcomes in order to arrive at an integrated representation of the overall utility of a single decision. A given reward is not as desirable in situations in which it is accompanied by an aversive outcome, and a given punishment is not as strong of a deterrent in situations in which it is accompanied by a rewarding outcome. How does the brain perform the computations necessary to arrive at an understanding of such tradeoff?

One possibility is that the brain represents reward and punishment independently via distinct neural systems specialized for detecting the respective outcome, and these punishment- and reward-specific representations are only integrated into something akin to a common utility currency at a later stage of value integration (Yacubian et al., 2006). By this account, the brain network activated by punishment will be largely unaffected by reward considerations. On the other hand, the receipt of reward may affect the representation of the punishment itself and vice versa, with one outcome suppressing the representation of the other. By this second account, reward and punishment share a competitive relationship in how they are represented in the brain. Such competition could extend all the way to the sensory-discriminative aspects of aversive information processing, or be restricted to the affective and/or cognitive-evaluative aspects.

A distributed neural network involved in the processing of the sensory-discriminative, affective, and cognitive-evaluative components of aversive outcomes has been identified that includes the thalamus and somatosensory cortex (DaSilva et al., 2002; Davis et al., 1998; Wager et al., 2013), dorsolateral prefrontal cortex (dlPFC, see Seminowicz & Moayedi, 2017, for an extensive review), anterior insula (AI, Davis et al., 1998; Starr et al., 2009; Wager et al., 2013), posterior insula (PI, Davis et al., 1998; Kross et al., 2011; Wager et al., 2013), and anterior cingulate cortex (ACC, Fuchs et al., 2014; Price, 2000; Wager et al., 2013). The thalamus, somatosensory cortex, and PI have been implicated in the sensory-discriminative dimension of aversive information processing (e.g., DaSilva et al., 2002; Davis et al., 1998; Wager et al., 2013), the AI and ACC in the affective dimension (e.g., Davis et al., 1998; Fuchs et al., 2014; Price, 2000), and the dlPFC in the cognitive-evaluative dimension, endogenously mitigating the experience of pain (Seminowicz & Moayedi, 2017). The extent to which these different

components of punishment processing are integrated with the representation of other outcomes (and in particular, reward) is unclear.

Some studies have utilized the approach-avoidance conflict (AAC) paradigm to identify brain regions specifically recruited during conflict (Amemori & Graybiel, 2012; Aupperle et al., 2015). Others have examined interactions between reward and punishment in neuroeconomical models of valuation (Park et al., 2011) and in the anticipation of possible outcomes (Choi et al., 2014), suggesting widespread representations of expected value that integrate reward and punishment information. Talmi et al. identified the modulation of reward anticipation in the ventral striatum and rostral anterior cingulate cortex (rACC) by anticipated punishment: reward predictions were reduced when a painful compared to a neutral stimulus would accompany the reward (Talmi et al., 2009). However, to our knowledge, the effect of concurrent reward on the processing of punishment outcomes (i.e., the experience of the punishment itself) remains unexplored. In an effort to address this gap in knowledge, our focus in the present study is explicitly on the role of reward in modulating the neural representation of punishment.

In the present fMRI study, we will use monetary reward and punishment in the form of electric shock to examine the modulation of punishment processing due to simultaneous presentation of reward. Monetary gains and electric shock are frequently manipulated to study reward and punishment processing in the brain, including in studies assessing the relationship between them (e.g., Choi et al., 2014; Talmi et al., 2009). Although they differ in that money is a secondary reinforcer and shock is a primary punisher, the manipulation of monetary reward still permits an opportunity to assess whether concurrent reward influences the representation of punishment more broadly. In light of prior precedent, we chose to use money as a reward and electric shock as a punishment outcome.

More specifically, to address our research question, we will utilize a functional localizer approach (Poldrack, 2007) to identify regions of interest (ROIs) involved in representing punishment and probe the nature of these representations during situations of conflicting reward and punishment (presented simultaneously), punishment only, and no feedback. ROIs sensitive to the experience of punishment without concurrent reward will be identified through a localizer scan. Our ROIs will encompass brain areas previously identified in punishment processing including the dorsolateral prefrontal cortex (dlPFC), anterior and posterior insula (AI/PI), anterior cingulate cortex (ACC), and the thalamus and somatosensory cortex (SSC). During the main portion of the experiment, participants will perform a four-armed bandit task with pseudo-random outcome probabilities, where reward alone, punishment alone, reward and punishment simultaneously, or no outcome are equiprobable. In this sense, our behavioral paradigm amounts to a gambling task, although we included a choice element in an effort to help maintain participant engagement and render the outcomes behaviorally relevant. By equating the frequency of different outcomes, we will be able to measure outcome-specific processing uncontaminated by differences in prediction errors brought about by differences in learning or behavioral strategies. We therefore limit our research question to decision-making contexts in which outcomes follow actions that participants take, which has similarly been the focus of related work in this area (Choi et al., 2014; Talmi et al., 2009).

Of interest in the present study is whether and where punishment-sensitive responses in brain will be reduced by the receipt of concurrent reward, with the experience of reward attenuating the representation of the aversive outcome. Based on the work by Talmi et al. (2009) in the context of reward prediction and work by Choi et al. (2014) in the context of outcome anticipation, we hypothesize that at least some of the aforementioned ROIs will demonstrate an

attenuated response to punishment in the presence of concurrent reward. We do not have specific hypotheses concerning which regions will show this attenuated response and therefore endeavored to include a wide variety of punishment-sensitive regions in our analyses to provide a comprehensive account of the nature of reward-dependent modulation.

Hypotheses

Our overarching hypothesis is that the neural response to punishment will be attenuated by concurrent reward. Specifically, concerning the hemodynamic response to feedback: punishment alone > simultaneous punishment and reward. This hypothesis will be tested in the following ROIs that were both determined a priori and supported by pilot data (see Methods), being examined independently for each ROI given that we have no a priori hypotheses concerning which regions are more or less likely to demonstrate the predicted relationship:

H1a: right dlPFC

H1b: left dlPFC

H1c: mid ACC

H1d: thalamus (bilateral)

H1e: contralateral (right) somatosensory cortex

H1f: left AI

H1g: right AI

H1h: left PI

H1i: right PI

Methods

Participants

At least 29 but no more than 40 participants will be recruited from the Texas A&M University community (see **Preliminary Data and Power Analysis** below). All participants will have reported normal or corrected-to-normal visual acuity and normal color vision. All procedures have been approved by the Texas A&M University Institutional Review Board and are consistent with the principles expressed in the Declaration of Helsinki. Written informed consent will be obtained for each participant.

Experiment Procedure

Participants will be scheduled for an initial in-lab visit for 1 hr and a scan-center visit on the following day. During their initial appointment, participants will come into the lab for consenting, MRI safety screening, and to practice the decision-making tasks to acquire familiarity with the different possible outcomes as well as the stimulus-response mapping. Each eligible participant will undergo fMRI in a single 1 hr session that will take place the following day. During the fMRI session, participants will first complete 4 runs of the (main) conflict task, an anatomical scan, and a punishment functional localizer scan. Data from a functional localizer scan for regions sensitive to reward feedback will also be acquired for a pilot study examining the effect of reward feedback on stimulus-specific reactivation in the visual cortex that is unrelated to the questions posed in the present study. The functional localizer scans will be performed after the main task in order to avoid potentially biasing participants towards reward-seeking or punishment-avoidance; this order allows us to assess how reward modulates punishment responses when the two outcomes were only ever equiprobable in the task.

Apparatus

During the initial in-lab visit, all tasks will be completed on a Dell OptiPlex 7040 computer (Dell, Round Rock, TX, USA) equipped with Matlab software (Mathworks, Natick, MA, USA), and Psychophysics Toolbox extensions (Brainard, 1997). Stimuli will be presented on a Dell P2717H monitor. The participants will view the monitor from a distance of approximately 70 cm in a dimly lit room. Paired electrodes (BioPac Systems, Inc., Goleta, CA, USA) will be attached to the left forearm of each participant, and electric shocks will be delivered through an isolated linear stimulator under the constant current setting (STMISOLA, BioPac Systems), which will be controlled by custom Matlab scripts.

For the fMRI portion of the experiment, stimulus presentation will be controlled by an Invivo SensaVue display system. The eye-to-screen distance will be approximately 125 cm. Key responses were entered using two Cedrus Lumina two-button response pads. MRI-compatible electrodes (BioPac Systems) will be attached to the left ankle of each participant, and electric shocks will be delivered through an STM100C controlled by an MP160 system (BioPac Systems) triggered by custom Matlab scripts via parallel port interface.

Procedure

For all tasks, each trial will consist of a fixation display, choice array, an inter-stimulus-interval (ISI), a feedback display, and an inter-trial-interval (ITI). The fixation display will consist of a white fixation cross (0.8° x 0.8° visual angle) for 1200 ms (see Fig. 1). The choice array will consist of the fixation cross flanked by two boxes to the left and right (each box 3.7° x 4.8°). The two inner boxes will be 4.9° center-to-center from the fixation cross and the two outer

boxes will be 7.4° center-to-center from the neighboring box. The color of each box will be drawn from the following set without replacement {red (RGB: 255 0 0), green (RGB: 0 255 0), blue (RGB: 0 0 255), yellow (RGB: 255 255 0)}.

Prior to completing the decision tasks, participants will undergo a shock calibration procedure to achieve a level of shock that is "unpleasant, but not painful" (Murty et al., 2012; Schmidt et al., 2015, 2017). In the task, participants will be instructed to choose a colored box, but if a decision is not made fast enough a random box will be chosen for them. During the in-lab portion, box choices will be made using the keyboard via the "Z", "X", "N", and "M" keys corresponding to location from left-to-right. During the fMRI portion, box choices will be made using two dual-button response pads (middle and index finger of each hand), again corresponding to the location of the boxes from left-to-right. The choice array will remain on screen for 2400 ms. Whether or not a response was logged within this 2400 ms, all four boxes will disappear and only the fixation cross will remain visible during the ISI. The ISI will last for 600, 1200, or 1800 ms (equally distributed). The feedback display will then be presented for 1500 ms, which will consist of the fixation cross, the amount of monetary reward earned on the current trial (+15¢ or +00¢), and the total reward accumulated across all trials. In this way, the reward and no reward feedback differ only in the magnitude of the monetary increment indicated (+15¢ or +00¢), being equated for reading demand and number of characters (physical salience). Electric shock, if administered on that trial, will be delivered simultaneously with the onset of the feedback display. Lastly, the ITI will last for 1200, 3000, or 4800 ms (exponentially distributed, with 1200 ms occurring most frequently). The fixation cross will disappear for the last 200 ms of the ITI to indicate to the participant that the next trial is about to begin.

Design

The punishment localizer task will consist of one run of 64 trials while each of 4 runs of the conflict task will consist of 32 trials. During the punishment localizer task, there will never be any money earned (every trial is +00¢). To determine the ROIs, the localizer task will be designed to yield punishment or no punishment an equal number of times regardless of the choices participants make. Similarly, for the conflict task, the four outcomes of reward only, punishment only, simultaneous reward and punishment, or no outcome will be equiprobable regardless of the choices participants make, such that all possible outcomes are experienced with equal frequency for every participant. It is important to note that punishment only feedback is still accompanied by text indicating the (lack of) monetary increment and total earnings, such that the receipt of reward is not accompanied by increased information processing demands. The location of each color will be determined randomly on each trial, and the order of outcomes will be pseudorandomly determined with the constraint that each type of outcome occur equally-often in each run of the task.

MRI Data Acquisition

Images will be acquired using a Siemens 3-Tesla MAGNETOM Verio scanner with a 32-channel head coil at the Texas A&M Institute for Preclinical Studies (TIPS), College Station, TX. High-resolution whole-brain anatomical images will be acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) pulse sequence [150 coronal slices, voxel size = 1 mm isotropic, repetition time (TR) = 7.9 ms, echo time (TE) = 3.65 ms, flip angle = 8°]. Whole-brain functional images will be acquired using a multiband $T2^*$-weighted echo planar imaging (EPI) pulse sequence [56 axial slices, TR = 600 ms, TE = 29 ms, flip angle = 52°,

image matrix = 96 x 96, field of view = 240 mm, slice thickness = 2.5mm with no gap]. Each EPI pulse sequence will begin with dummy pulses to allow the MR signal to reach steady state and conclude with an additional 6 sec blank epoch to allow for measurement of the unfolding of the blood oxygenation level dependent (BOLD) response.

Proposed Analyses

Preprocessing

All preprocessing will be conducted using the AFNI software package (Cox, 1996). Each EPI run for each participant will be motion corrected using the image following the anatomical scan as a reference. EPI images will then be coregistered to the corresponding anatomical image for each participant. These images will then be non-linearly warped to the Talairach brain (Talairach & Tournoux, 1988) using 3dNwarpApply to aid in identification of the ROIs. Finally, the EPI images will be converted to percent signal change normalized to the mean of each run, and then spatially smoothed to a resulting 5 mm full-width half-maximum using 3dBlurToFWHM.

Statistical Analysis

All statistical analyses will be performed using the AFNI software package. For the localizer task, the data will be subjected to a general linear model (GLM) with regressors for (1) the presentation of the choice array and corresponding button press, (2) feedback with shock, and (3) feedback without shock, in addition to standard nuisance regressors for six degrees of head motion and drift in the scanner signal. Furthermore, images during which head motion exceeds one-half the width of a voxel, along with the image preceding and following such motion spikes,

will be censored from analysis. Each of the three task-related regressors will be modeled using 16 finite impulse response functions (FIRs), beginning at event onset. The mean beta value for each regressor from 3-6 sec post stimulus presentation, corresponding to the approximate peak of the response, will be extracted. Analysis of the data from the main task will follow this same approach, only with four different feedback regressors corresponding to the four different types of possible outcomes (punishment alone, reward alone, punishment and reward simultaneously, no reward or punishment).

To define the targeted ROIs, we will contrast the peak of the hemodynamic response (averaged over the 3-6 sec time period) for feedback with and without punishment separately for each participant. Up to the 50 most significant voxels in each region (plus ties) will be identified, provided that each voxelwise $p < 0.01$. To maintain consistency in ROI definition across participants, particularly for larger regions such as the dlPFC, each cluster for each ROI must share some overlap with the corresponding clusters identified in Fig. 2, with the exception of the thalamus given its small size and well-defined anatomical structure. For the main task, the peak of the response to punishment, reward + punishment, and neither outcomes will be extracted from these ROIs (i.e., the mean of the beta values 3-6 sec post stimulus presentation, computed separately for each voxel and then averaged over all voxels in an ROI to arrive at a mean level of activation of that ROI) and compared, with particular emphasis on the comparison of punishment with and without concurrent reward (punishment versus neither outcome will serve as a positive control, see below). We will test our main hypothesis separately and independently for each ROI as outlined in the Introduction, applying Bonferroni correction for multiple comparisons.

Positive Control

The appropriateness of each ROI will be confirmed by contrasting punishment alone with feedback consisting of no punishment or reward, which should provide a replication of the contrast used to define the region using independent data. To be included in the primary analysis (comparing punishment vs. punishment + reward), for a given ROI this contrast of punishment vs. no reward or punishment must be significant at $p < 0.005$. ROIs not meeting this criterion will be deemed to have potentially insufficient sensitivity to detect a modulation of the punishment response by reward and excluded from the main analysis.

Criteria for Data Exclusion

Data for a given participant will be discarded and replaced if (a) more than 10% of all time points would be censored due to motion spikes, (b) motion artifact in the anatomical image produces noticeable banding that obscures structure, (c) the participant does not make a behavioral response on at least 85% of trials, which would suggest low task engagement, and/or (d) no a priori ROIs are identified in the localizer scan. In the event of scanner failure or crashing of the presentation software, the run affected will be repeated if available scanner time allows; participants failing to complete at least 80% of trials in each of the localizer and main tasks will be replaced.

Timeline for Completion of the Study

We anticipate completion of the study, including submission of a Stage 2 manuscript, within 12 months of notification of acceptance of this Stage 1 manuscript.

Preliminary Data and Power Analysis

We collected data from five participants using the above-described protocol. We were able to identify bilateral AI, bilateral PI, bilateral dlPFC, thalamus, contralateral SSC, and ACC, in all five participants from the functional localizer scan, which will serve as the a priori ROIs to be used for the present study (Fig. 2) and are reflected in the a priori hypotheses (see Introduction).

To obtain a measure of effect size for the potentially suppressing influence of concurrent reward on the representation of punishment, we computed the primary contrast of interest (punishment alone vs. simultaneous reward and punishment) for each ROI and then collapsed across ROI for each participant to arrive at an overall average influence of concurrent reward in reducing punishment-evoked activity. The resulting effect size for this collapsed comparison was $d_z = 0.863$. A similar analysis using the average of the computed effect sizes for each individual region (without collapsing) yielded a slightly larger effect size estimate.

Although there are no published studies to our knowledge that have examined the role of reward in modulating the neural response to punishment, there is one study that examined a different modulator (concurrent cognitive processing) in attenuating the neural response to punishment (pain) using an ROI approach with regions that overlap with the present study (Seminowicz et al., 2004). In that study, the effect size of the attenuation effect was $d_z = 0.675$ or greater in each of the significant regions identified. As the lowest of all estimates obtained, we chose $d_z = 0.675$ for the purpose of power analysis.

A power analysis using G*Power 3 (Faul et al., 2007) with effect size $d_z = 0.675$, desired power $\beta = 0.8$ and $\alpha = 0.05/9$ (one-tailed, experiment-wise $\alpha = 0.05$, Bonferroni corrected for 9 ROIs) yielded a sample size of 29, which is the minimum sample size we propose to collect. We will collect data until (a) each a priori ROI is represented in 29 participants, yielding the desired

minimum power in each ROI, or (b) data from 40 retained participants is collected, at which point study resources will have been exhausted. In the event that an ROI has fewer than 29 participants represented in the final sample, this ROI will be dropped from the main analysis along with its corresponding hypothesis, although the results of the contrast will still be reported as an exploratory/secondary analysis for transparency.

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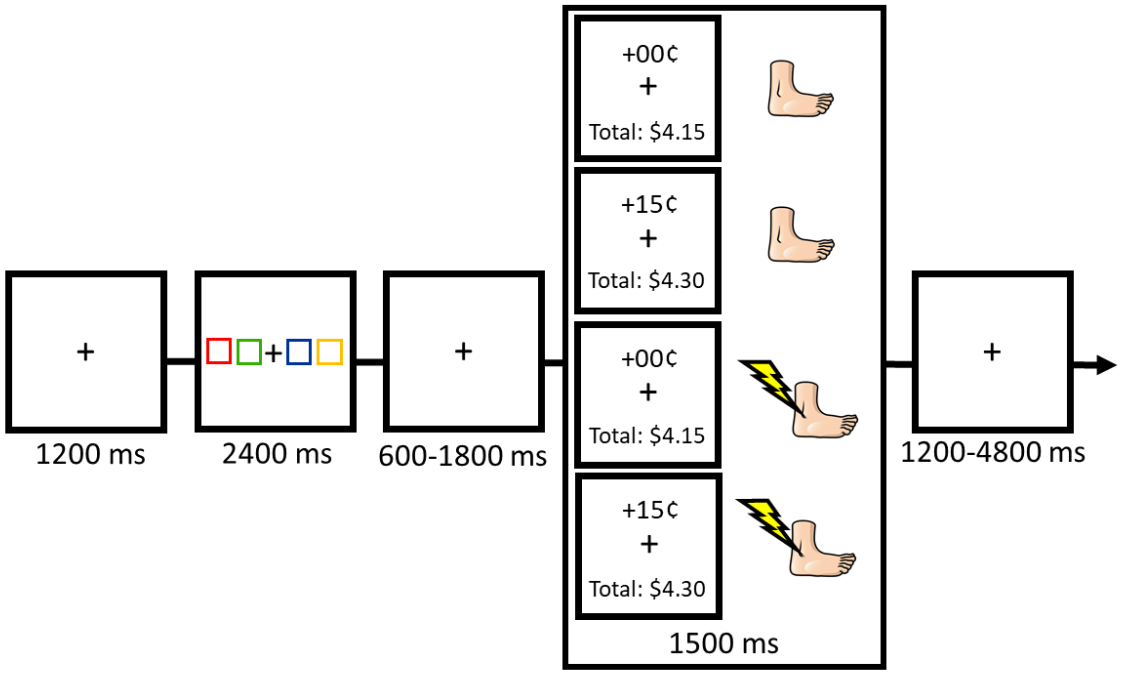

Fig 1. Sequence of events for a trial in the main task of the experiment. Each of the four possible outcome pairings occur equally-often in each run of the task. For the punishment localizer task, no monetary rewards are ever received, and half of all trials result in a shock outcome.

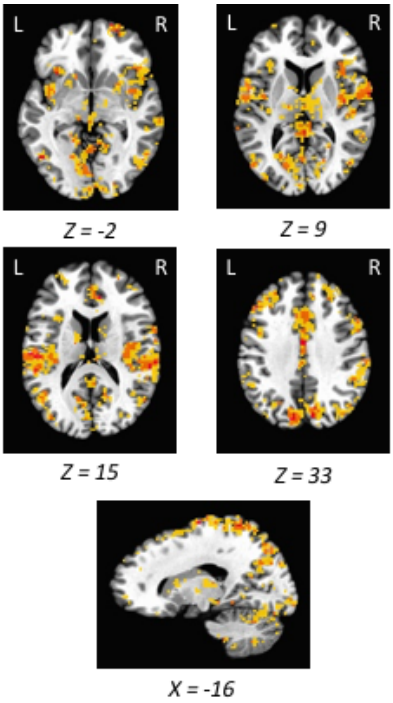

Fig 2. Overlapping regions of activation from the punishment localizer task used in ROI definition (n = 5). Activations are overlaid on an image of the Talairach brain. Red indicates overlapping activation from all 5 participants, orange from 4 participants, and yellow from 3 participants.

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