

PUPIL RESPONSES DURING APPETITIVE PAVLOVIAN LEARNING IN MONKEYS WITH ORBITOFRONTAL CORTEX LESIONS

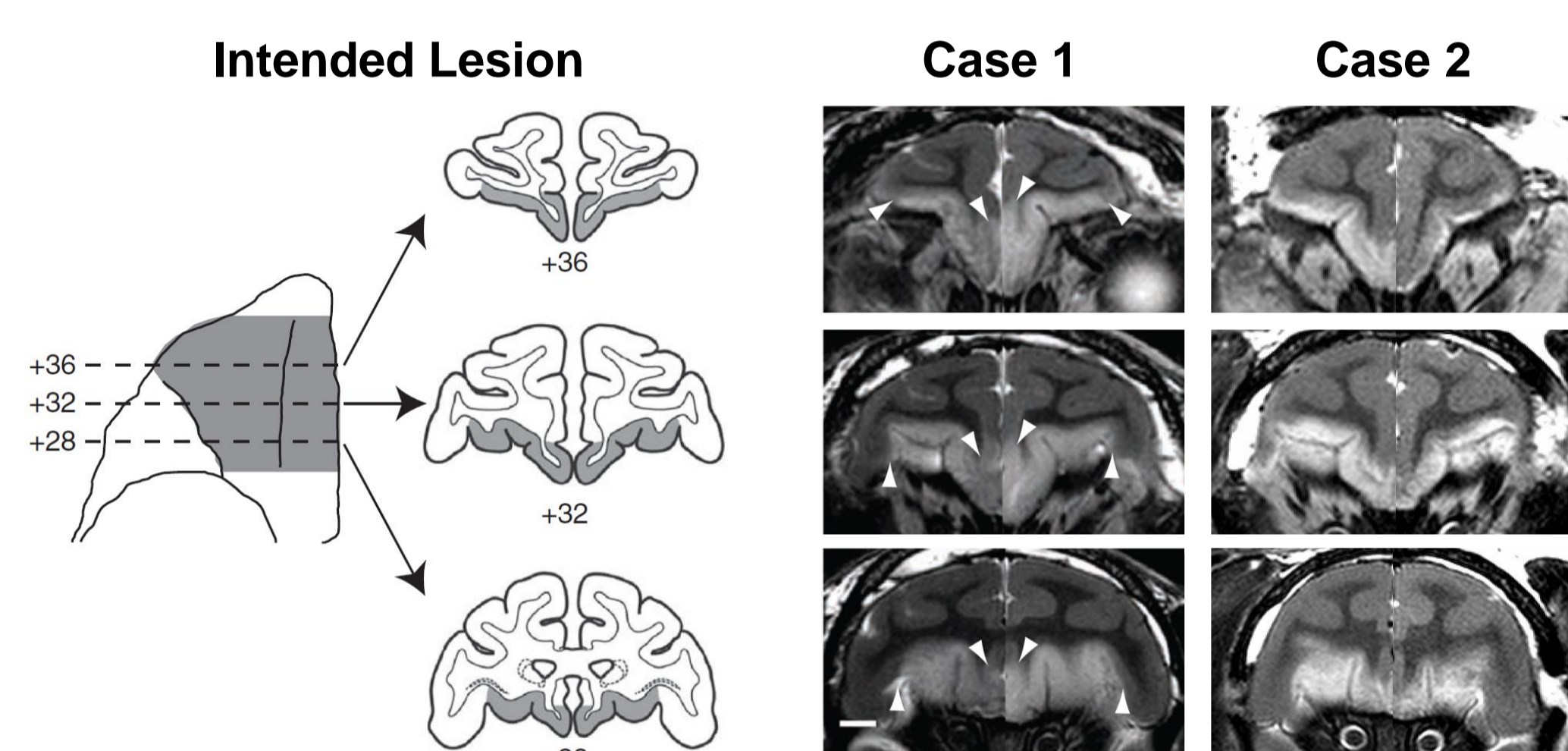
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INTRODUCTION

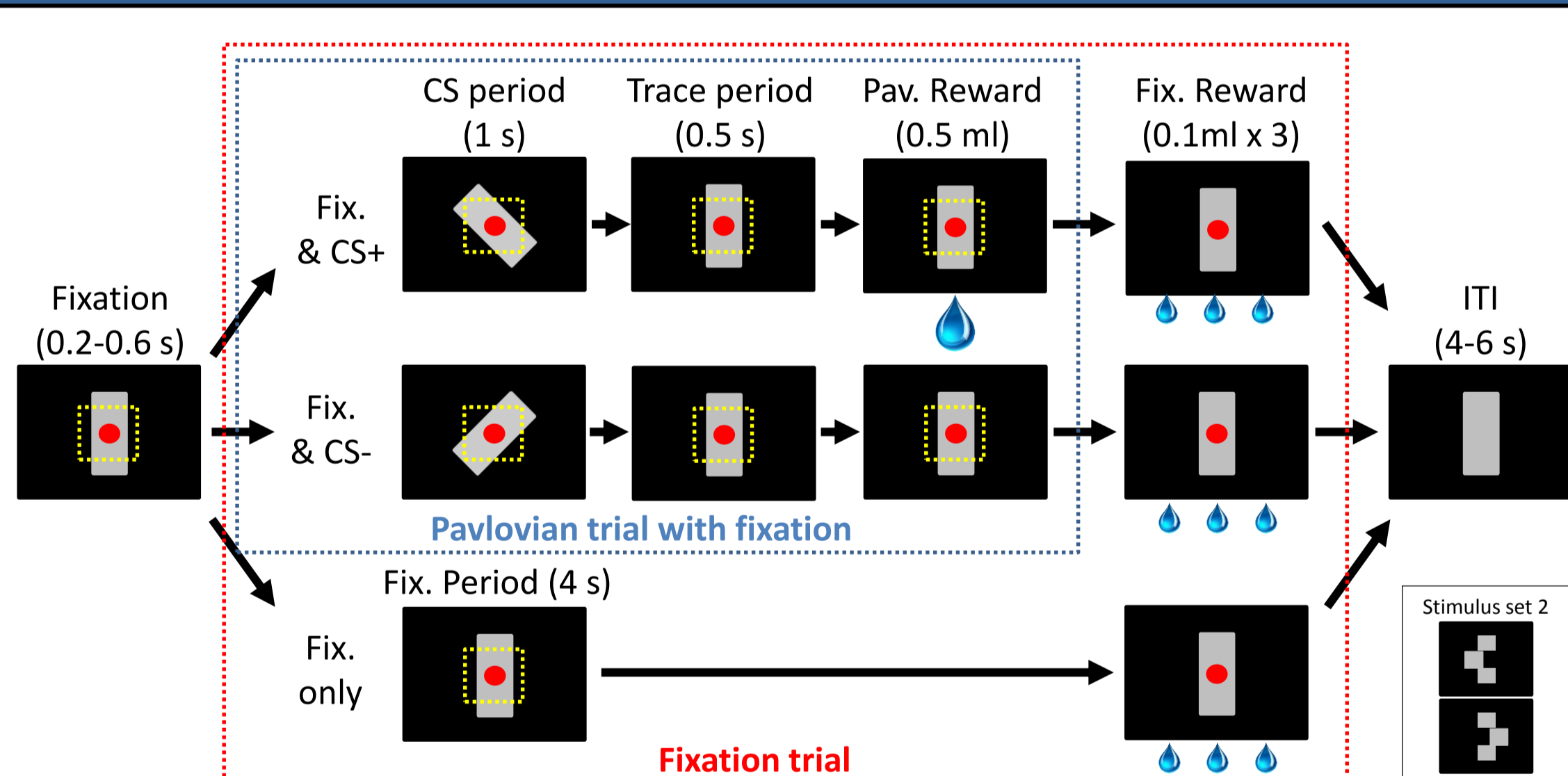
- Measures of stimulus-reward learning in macaques lean heavily on instrumental tasks. It is possible, however, that measures of Pavlovian learning might provide new insights into the neural substrates of stimulus-reward learning.
- The fast response of the pupil to external stimuli allows alterations in autonomic arousal to be correlated with behavioral events on a trial-by-trial basis with good temporal resolution (Mitz et al., 2017, *J Neurosci Methods*).
- To investigate whether the orbitofrontal cortex (OFC) contributes to Pavlovian learning of stimulus-reward associations, we compared monkeys with OFC lesions and unoperated controls on their rate of acquisition of changes in pupil diameter to a stimulus paired with reward delivery (CS+). If monkeys acquired changes in pupil diameter in response to a CS+, this would provide evidence they had learned the CS+ predicts a positive emotional event.

SUBJECTS AND SURGERY

- A total of 8 rhesus monkeys (*Macaca mulatta*) were used.
 - 4 unoperated controls
 - 4 subjects with bilateral OFC lesions (areas 11, 13 & 14)
- The lesions were made by ibotenic acid injection and assessed with postoperative T2-weighted MRI scans. White hypersignal on T2 scans is associated with edema and indicates the likely extent of damage.

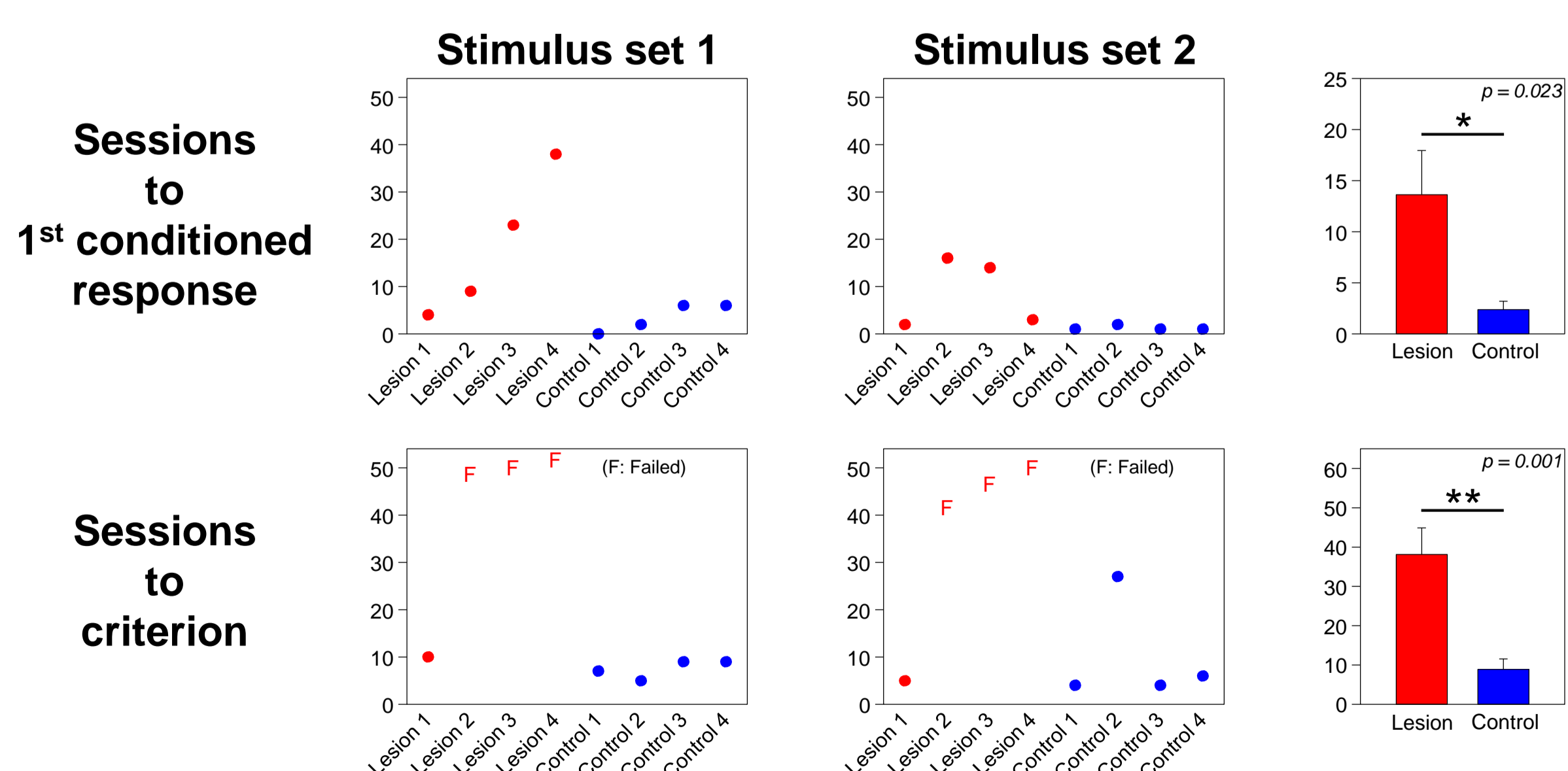


PAVLOVIAN CONDITIONING



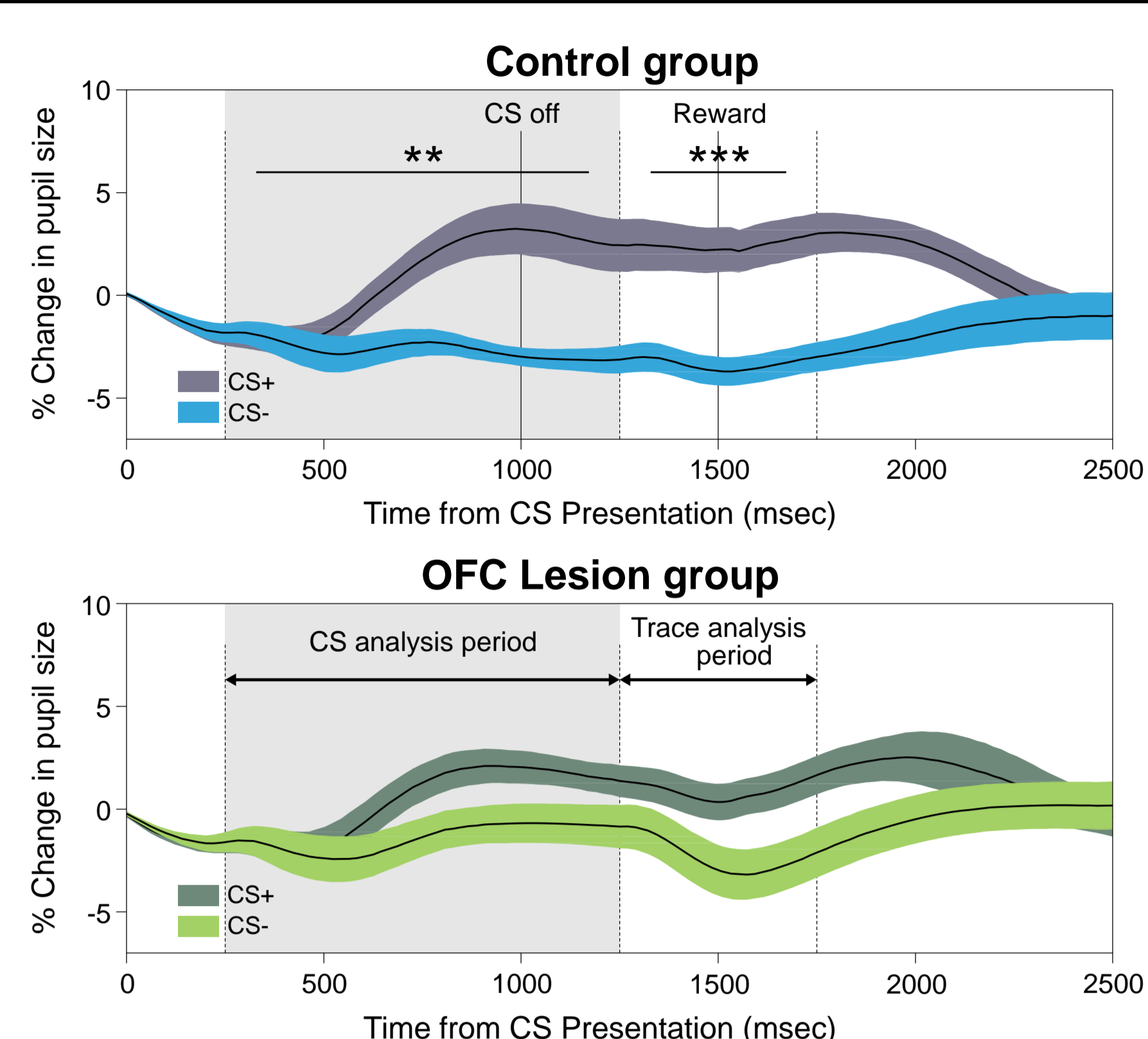
- We superimposed Pavlovian conditioning trials on fixation trials. Pavlovian conditioning proceeded independently of the fixation task.
- On a subset of trials (32%), one of two Pavlovian stimuli (CS+,CS-) was presented. Pupil size was recorded with an eye tracker as a measure of the autonomic response.

RESULT 1: DAYS TO CRITERION



- The control group acquired a conditioned pupil response to the CS+ within a few training sessions (2.4 ± 0.8) and continued to show it across at least 4 consecutive sessions.
- The lesion group required more sessions (13.6 ± 4.3) to acquire a conditioned autonomic response and three out of four subjects failed to sustain it for 4 consecutive sessions in training with both stimulus sets.

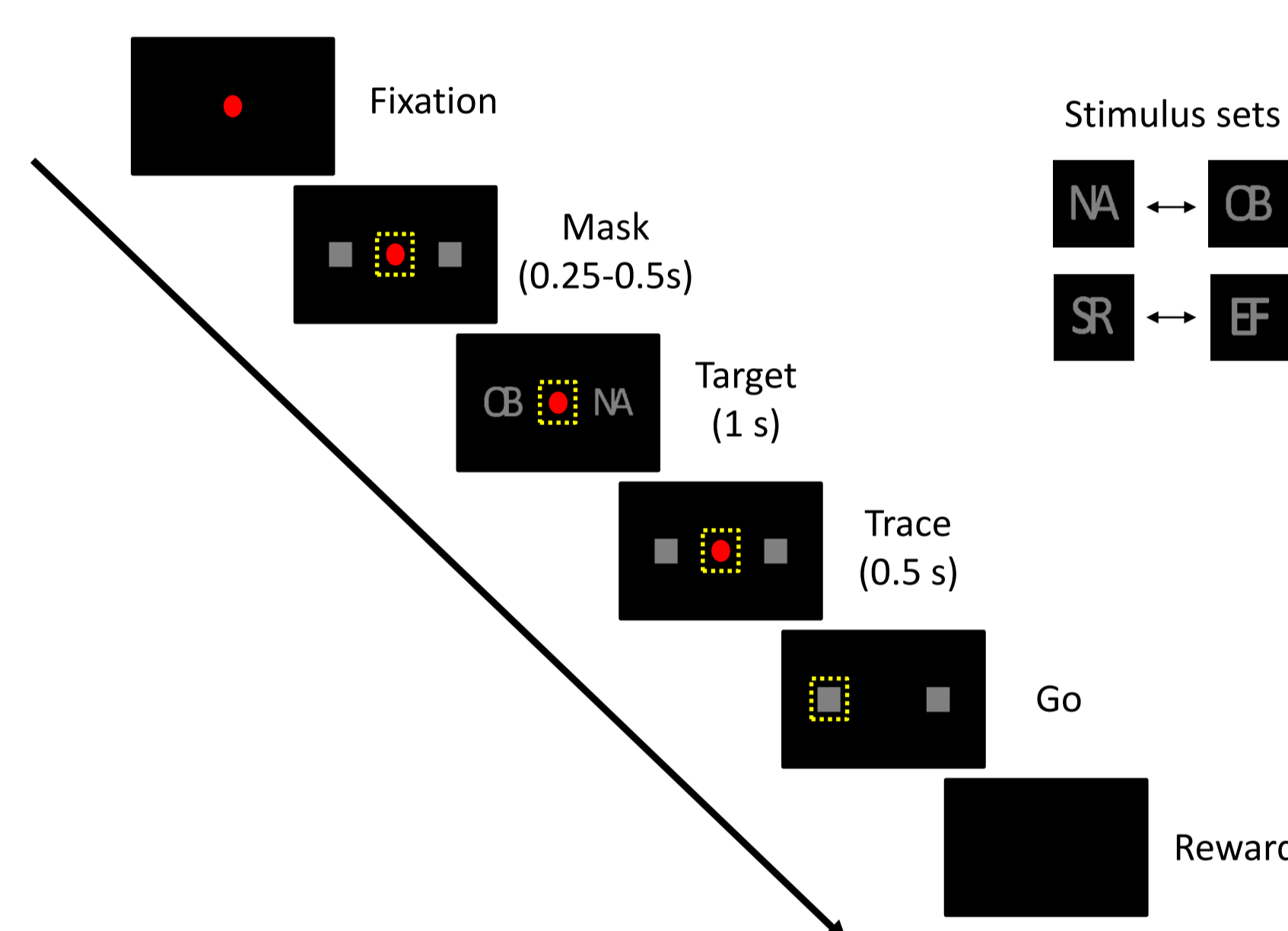
RESULT 2: PUPILLOMETRY



- Controls exhibited an increased pupil size to the CS+ during the CS analysis period, compared to the response to the CS-, and continued to show the conditioned pupil response in anticipation of reward during the trace analysis period.

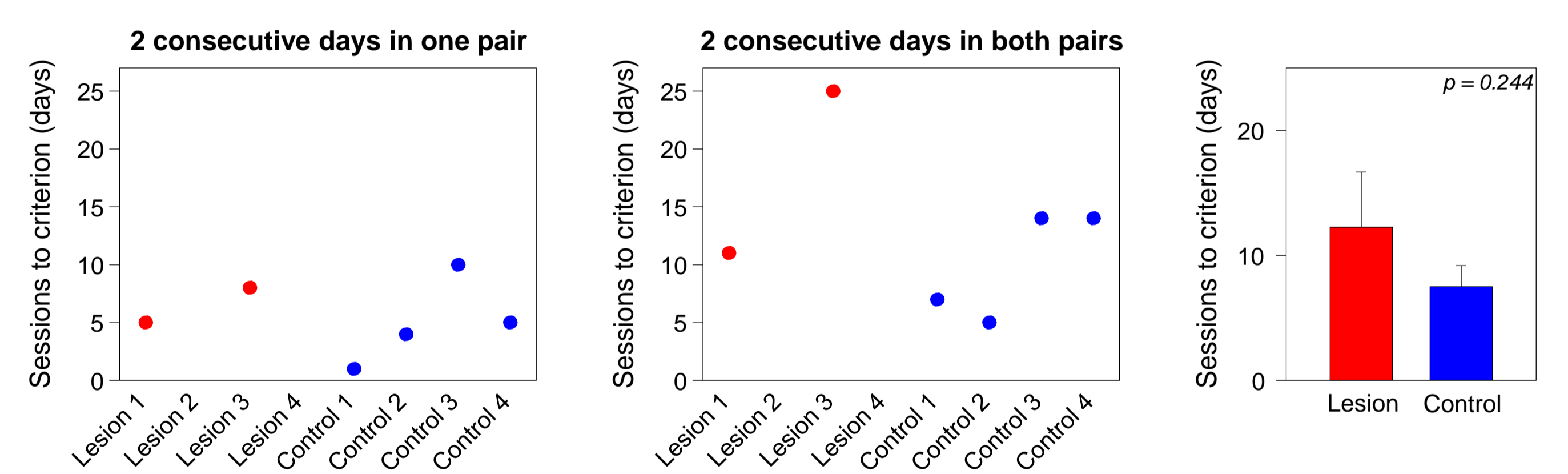
- By contrast, in monkeys with OFC lesions, the pupil response to the CS+ was not significantly different from that to the CS- in both CS and trace analysis periods.

INSTRUMENTAL CHOICE TASK



- To examine whether the differences in pupil responses between the control and lesion groups are due to a failure of cue discrimination, we tested the subjects additionally with an instrumental choice task in which only one choice cue (S+) was rewarded. Two pairs of stimuli were randomly interleaved.

- Both groups proved their ability to discriminate visual stimuli by choosing the S+ significantly more than the S-. There was no statistical difference found between the groups in the period required to exhibit successful discrimination in one or both stimulus pairs for two consecutive days.



CONCLUSIONS

- Macaque monkeys exhibit a reliable change in pupil diameter to visual stimuli that have been paired with reward in the context of Pavlovian learning.
- In macaques, OFC is necessary for acquiring Pavlovian autonomic responses to stimuli that predict reward, but not for learning an instrumental stimulus-reward association with similar perceptual and motor demands.
- Lesions of OFC yield a different impairment from that seen after lesions of the subgenual cingulate cortex (Rudebeck et al., 2014, *PNAS*).
- Using pupil responses as a measure of stimulus-reward learning in macaques may aid cross-species comparisons of the neural underpinnings of learning and decision making.

REFERENCES

- Mitz AR, Chacko RV, Putnam PT, Rudebeck PH, and Murray EA (2017) Pupil and heart rate metrics as tools for studying affective states in nonhuman primates. *J Neurosci Methods*, 279:1-12.
- Rudebeck PH, Putnam PT, Daniels TE, Yang T, Mitz AR, Rhodes SE, Murray EA (2014) A role for primate subgenual cingulate cortex in sustaining autonomic arousal. *Proc Natl Acad Sci U S A* 111:5391-5396.