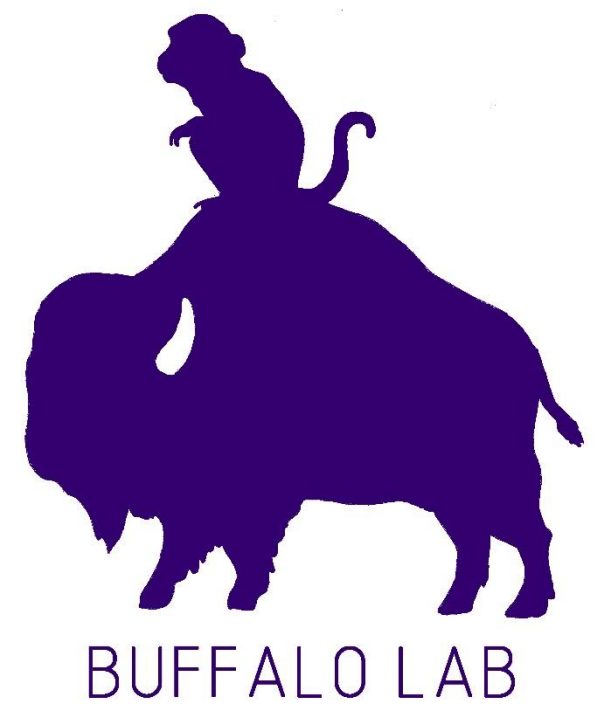


Mnemonic Discrimination and Image Viewing in Aged Rhesus Macaques



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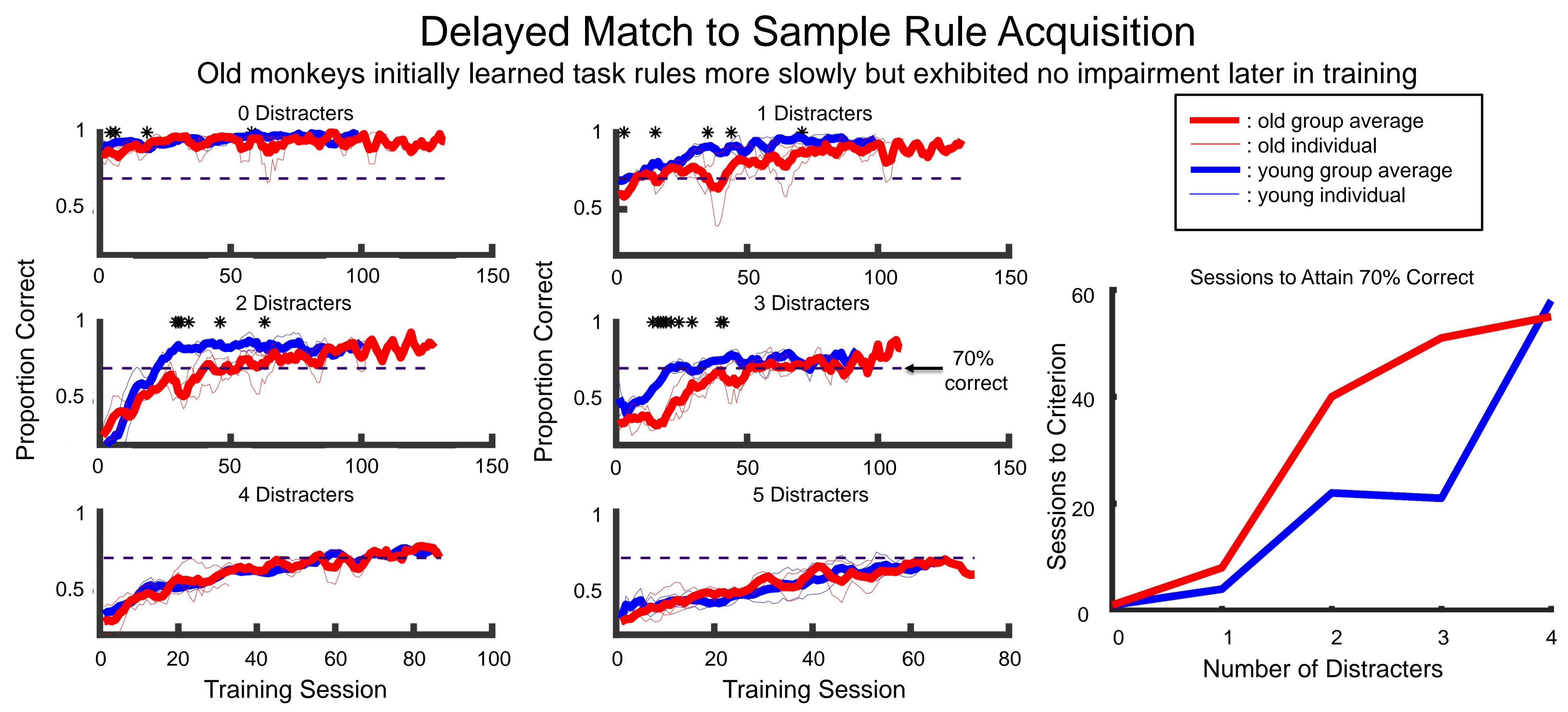


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Background

- Neuroimaging studies in humans have indicated that hippocampal subfields are differentially engaged when participants make memory decisions about perceptually similar items (Yassa et al., 2010).
- This ability has been called pattern separation, which is the process of orthogonalizing overlapping inputs into distinct memory representations.
- The mnemonic discrimination (MD) task is a standardized task of pattern separation which was developed for study in humans. Performance on this task has been shown to engage the DG/CA3 of the hippocampus, and MD performance is impaired in older adults.
- Here, we develop the MD task for use with nonhuman primates in order to study functional differences between hippocampal subfields across the lifespan using neurophysiological techniques.
- In addition, several measures of hippocampal activity have been shown to reflect memory in a free-viewing task (Jutras & Buffalo, 2010).
- In order to complement the highly-trained MD task, we also examined untrained free-viewing behavior in aged (21 to 24 years old) and young (5 to 15 years old) monkeys.

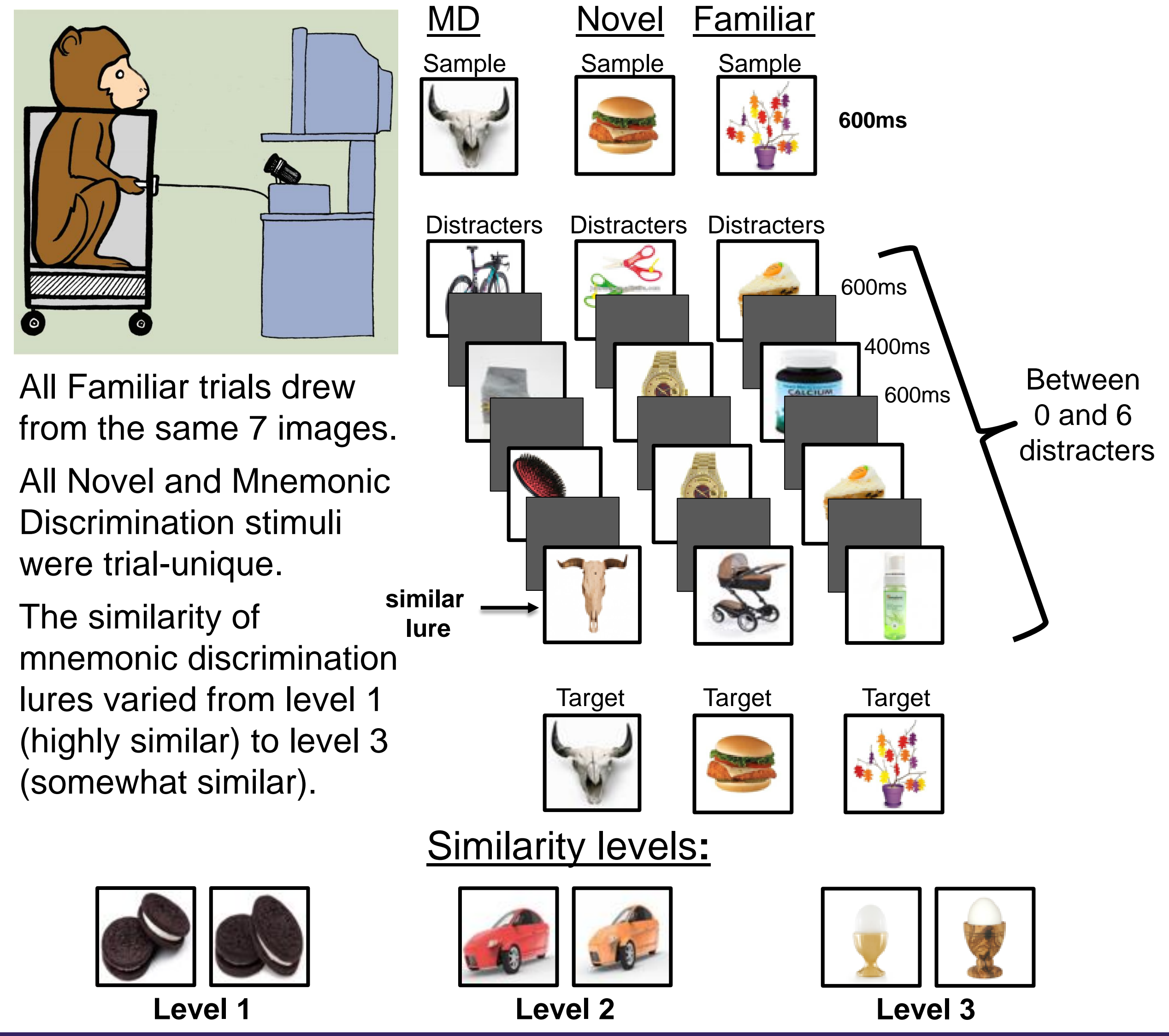
Results: Mnemonic Discrimination



Summary and Conclusions

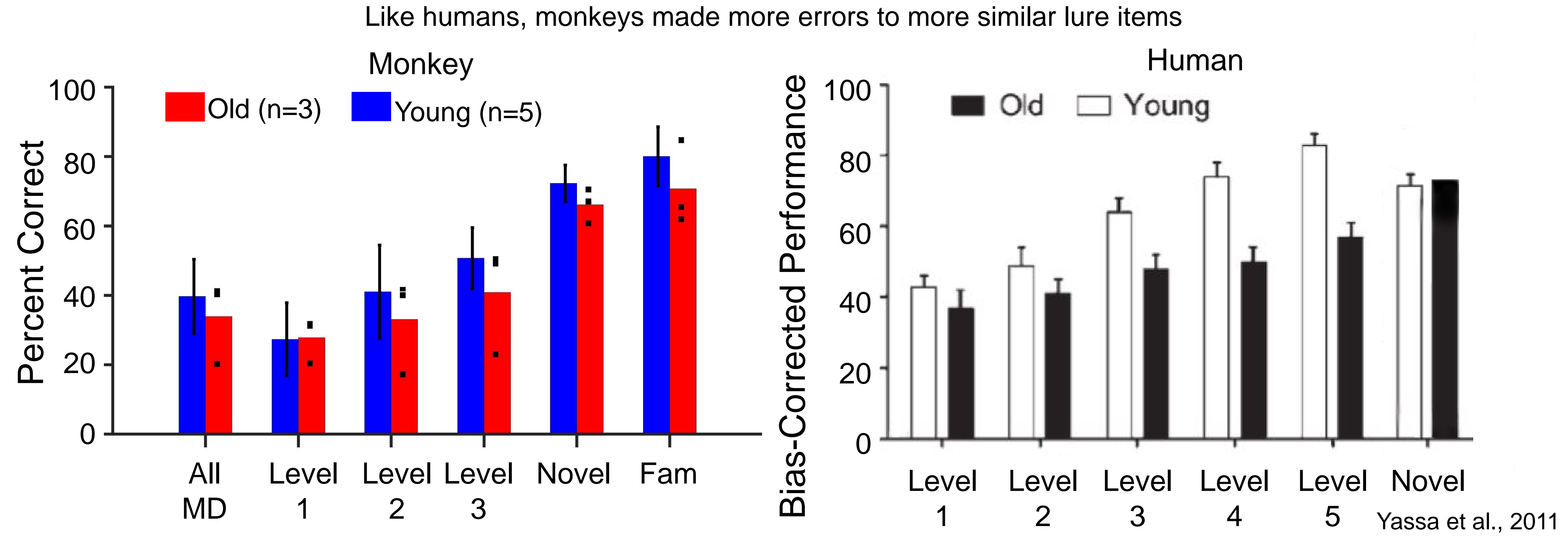
- The MD paradigm can be adapted for use with NHPs requiring only minor changes.
- NHPs perform at comparable levels to humans, making a high proportion of errors to similar lure items.
- Aged monkeys require more training to learn the rules of the DMS task when compared to young monkeys.
- Aged monkeys show a trend towards impairment on the MD task, similar to older humans.
- Work with human participants has suggested that the MD task involves differential engagement of hippocampal subfields. The ability to employ this task with NHPs presents a novel opportunity to perform cross species comparisons of hippocampal subfields.
- The repetition effect is somewhat weaker in aged as opposed to young monkeys.
- Aged monkeys tend to have longer fixation durations than young monkeys.
- Taken together, these results suggest a subtle impairment in hippocampal function across tasks in aged NHPs.
- Future experiments will examine the mechanisms underlying these deficits using pharmacological manipulations combined with neural recordings from the hippocampus.

Methods: Mnemonic Discrimination Task

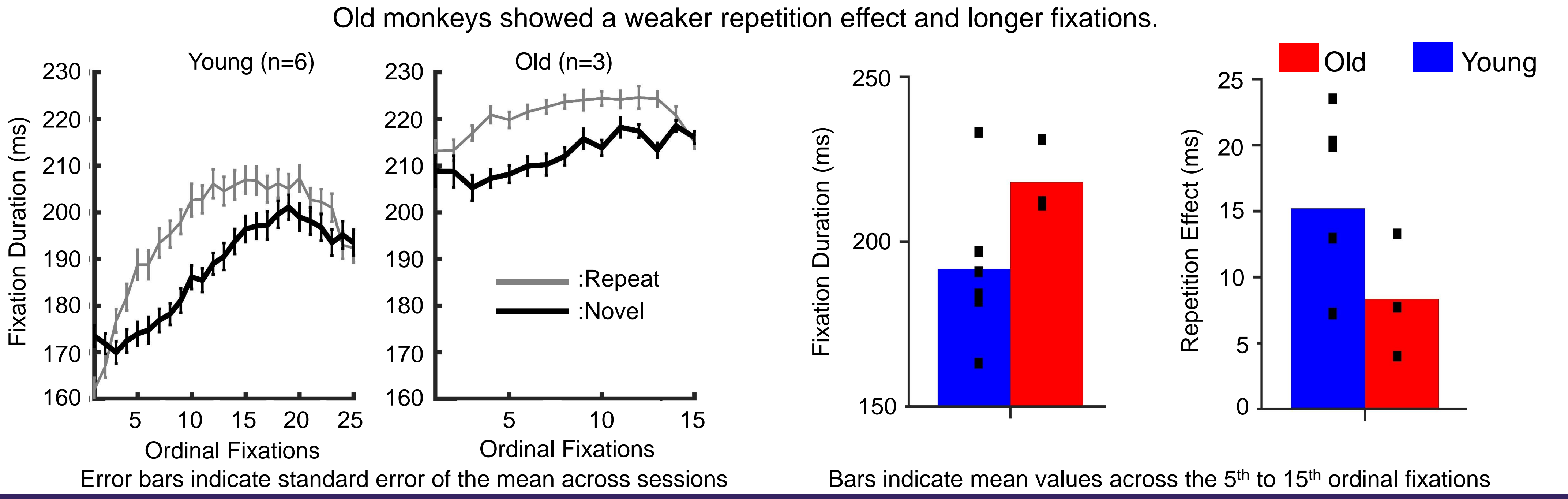


- All Familiar trials drew from the same 7 images.
- All Novel and Mnemonic Discrimination stimuli were trial-unique.
- The similarity of mnemonic discrimination lures varied from level 1 (highly similar) to level 3 (somewhat similar).

Mnemonic Discrimination Performance



Results: Image Viewing Task



Methods: Image Viewing Task

- Monkeys freely viewed full-screen images for 6s per presentation
- All images were viewed twice, with an average of 800 images/monkey
- The delay between novel and repeat viewing was 12 images
- Monkeys were given reward for interleaved eye calibration trials but were not rewarded for image viewing

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References

Jutras, M.J., Buffalo, E.A. (2010). Recognition memory signals in the macaque hippocampus. *PNAS: USA*.

Yassa, M.A., Lacy, J.W., Stark, S.M., Albert, M.S., Gallagher, M., Stark, C.E. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus*.

Yassa, M.A., Stark, S.M., Bakker, A., Albert, M.S., Gallagher, M., & Stark, C.E. (2010). High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnesic mild cognitive impairment. *Neuroimage*.