

Chronic Behavioral Changes in a Ferret Model of Combined Under-Vehicle Blast and Controlled Cortical Impact-Induced Traumatic Brain Injury

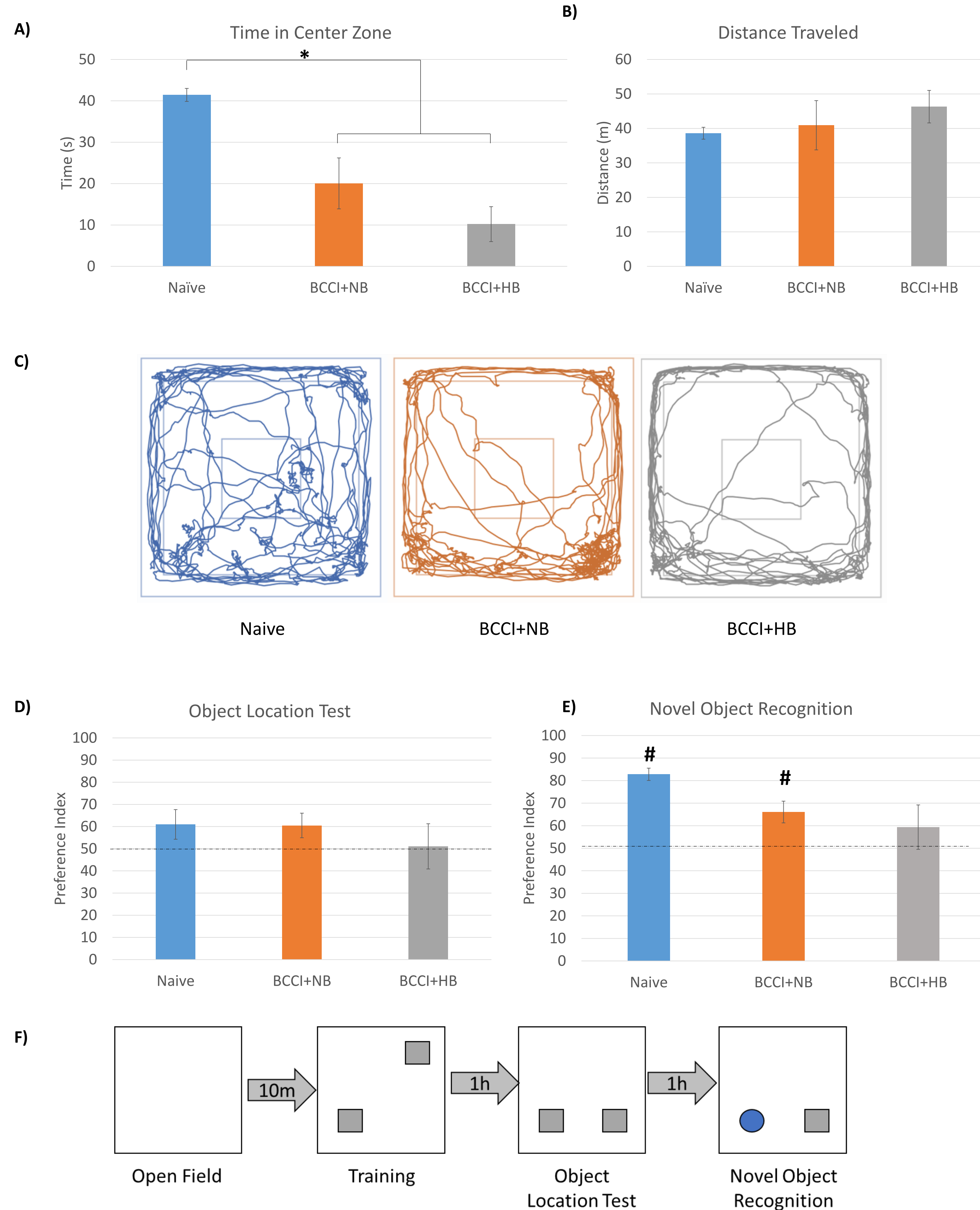
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Under-vehicle blast (UVB) causes a unique traumatic brain injury (TBI) in warfighters targeted by improvised explosive devices. UVB hyper-acceleration can produce a TBI independent of impact, however, an impact injury can also occur. Previous studies in rats have shown that aeromedical evacuation-relevant hypobaric exposure within 72 hours of exposure to TBI exacerbates neurologic injury [2,3]. While rodent studies investigating TBI are useful, translating findings to improved patient outcomes is challenging, perhaps due to the rodent lissencephalic brain. Thus, a model of UVB + impact TBI was developed in ferrets, who possess human-like gyrencephalic brains [4].

Methods: The protocol was reviewed and approved by the University of Maryland, Baltimore Institutional Animal Care and Use Committee (0620009) and the U.S. Air Force Surgeon General's Office of Research Oversight and Compliance as protocol number FWR-2020-0015A. Animal activities were conducted in compliance with all federal regulations governing the protection of animals and research. In this study, male ferrets were sedated, secured to a metal plate "vehicle," and exposed to UVB via detonation of pentaerythritol tetranitrate and then anesthetized and given a controlled cortical impact (BCCI). 24 hours post-injury animals underwent a 6-hour simulated aeromedical evacuation (hypobaric; HB) or remained at sea level (normobaric; NB). Mood (play behavior) and motor function (ladder walk) were assessed monthly in BCCI and age-matched naïve animals. Additional tests examining mood & motor function (Open Field) and memory (Novel Object Recognition and Object Location) were employed only once six months post-injury (MPI).

Open Field and Object Recognition: Anxiety, Locomotion, Memory



Behavior Observation: Anxiety and Mood

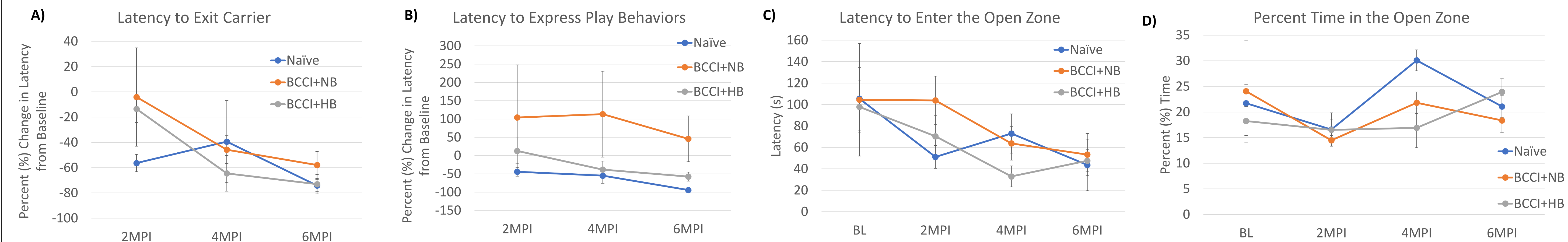


Figure 3. (A) Latency to exit the carrier. Animals appear to habituate by 6MPI. (B) Latency to express play behaviors. There is a trend toward naïve animals having a shorter latency and injured animals having a longer latency, particularly NB-exposed animals. (C) Latency to enter the open zone of the room. Animals appear to have a shorter latency with repeated exposures but no group differences are apparent. (D) No trends are apparent in time spent in the open zone of the room. $n = 3-7$ per group.

Ladder Walk: Motor Function

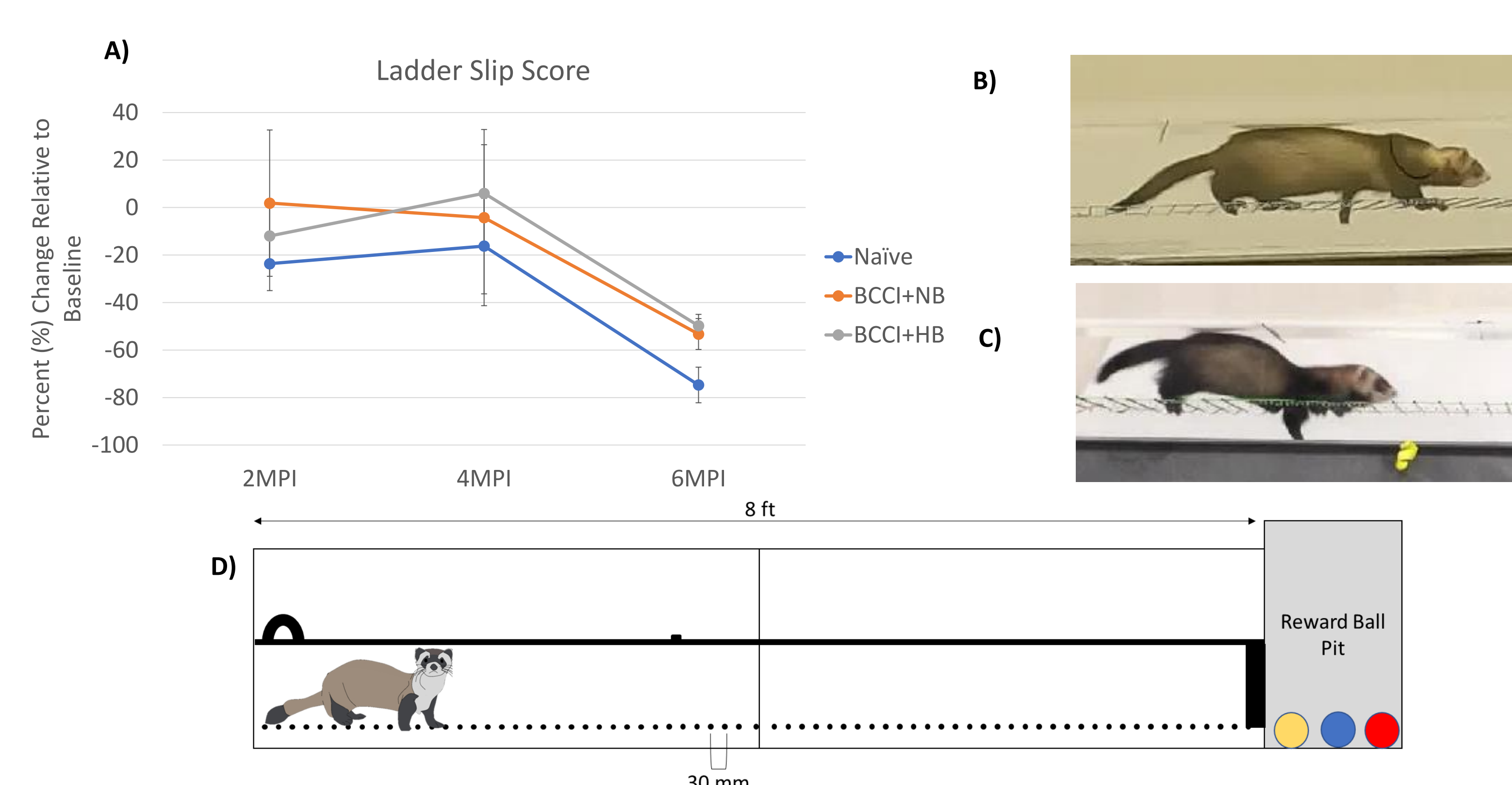


Figure 4. Animals were trained to walk across a horizontal ladder. Crossings were filmed and a frame-by-frame analysis [1] revealed the number and severity of slips to determine a slip score. (A) The change in slip score normalized to baseline. By 6 months post-injury, all groups show improvement in their slip score relative to baseline. At all timepoints, naïve animals trend toward the greatest improvement relative to their own baseline, particularly at 6 months post-injury. (B) A photo depicting a slight slip of the front paw. (C) A photo depicting a deep slip of the front paw. (D) Ladder apparatus schematic. $n = 3-7$ per group.

Conclusions

- Decreased time spent in the center zone of the open field apparatus suggests increased anxiety-like behavior in BCCI ferrets at 6 months post-injury, particularly in those exposed to hypobaric.
- Perirhinal cortex-dependent and, perhaps, hippocampus-dependent learning and memory may be impaired 6 months following BCCI+HB.
- Repeated exposures of ferrets to assays of mood may decrease the sensitivity of the tests.
- Impairments in gross motor function/learning may persist for at least six months. However, even injured animals do show improvement over time
- Ferrets have great potential as a gyrencephalic model for brain injury, allowing for the collection of rich neurobehavioral data [2,4].

References

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