Executive function in socially-mature rats is significantly impaired by low (<20 cGy) doses of HZE particles with LETs of 51-180 keV/um.

*R.A. Britten[1,2], L. Davis[1], J. Jewell[1], V. Miller[1], G. Lonart[3]
1. Dept of Radiation Oncology, 2. Dept of Microbiology, 3. Dept of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA. 23507. Brittera@EVMS.Edu

INTRODUCTION. Astronauts on deep space missions will be exposed to ~25 cGy of Galactic cosmic radiation (GCR). The long-term consequence of exposure to such doses is largely unknown, but we have previously shown that exposure of juvenile rats to 20 cGy 1 GeV/µ ^{56}Fe resulted in pronounced deficits in hippocampus-dependent learning (Britten *et al*, 2012) and Attentional Set shifting (ATSET) (Lonart *et al*, 2012), a measure of executive function. ATSET can be simplistically thought of as the ability of an individual to relearn what the most important discriminating stimulus is (for a particular endpoint) in a changing environment. ATSET is thus one of the most advanced thought processes that enable humans to rapidly adapt and respond to a change in the environment, and to perceive what is important for survival or completion of a task, skills that are absolutely vital to deal with a sudden emergency. Aged rats have a reduced capacity to conduct various aspects of ATSET compared to younger rats, so it is possible that the effect of HZE exposure in rats of a comparable biological age to the Astronauts may result in further reductions in their ATSET capacity. We have thus assessed the impact that exposure of male Retired Breeder Wistar rats to 10, 15 or 20 cGy of the following ion beams: 600 Mev/µ ^{56}Fe , 1 GeV/µ ^{56}Fe, 1.1 GeV/µ ^{48}Ti or 600 Mev/µ ^{28}Si (with respective LET values of 180, 150, 106 and 51 keV/um) has on their ability to perform ATSET.

MATERIALS & METHODS. Retired breeder (6-9 months old) male Wistar rats were exposed to one of the four particle beams at BNL. At 3 months post exposure the ability of rats to conduct ATSET was established.

RESULTS. We now have data on at least two batches of retired breeder rats exposed to any of the four particle beams (dose range 10-20 cGy) with an average of 14, and a minimum of 8 rats at any given dose point.

There appears to be an age related decline in the ability, or the motivation of socially mature rats to conduct the first "Discrimination" (both Simple and Complex) stage of the testing, tasks believed to be regulated by the medial prefrontal cortex and perirhinal cortex respectively. Approximately 25% of the sham-irradiated rats were unable to complete the Discrimination step, as opposed to <10% in the juvenile rats. "Severe" aging has been shown to reduce ATSET performance, specifically an inability to conduct Extra-dimensional shifting which interestingly is also regulated by the medial prefrontal cortex.

Exposure to all particle beams resulted in a measurable decrease in the ability of the rats to perform the ATSET test, however there was considerable inter-ion (LET) variation in the dose response for the ATSET impairment. There was a high incidence of failure to habituate to the test (digging for food reward) amongst the irradiated rats, in some instances (e.g., 20 cGy 1 GeV/µ ^{56}Fe) ~30% of irradiated rats failed to habituate to the test (as compared to <5% of the controls). The majority of the rats that failed to habituate started to dig for the reward but quickly gave up, however, there were few instances where these rats were shown to have anhedonia (sucrose preference test).

Exposure to 600 Mev/µ ^{56}Fe, 1 GeV/µ ^{56}Fe and 600 Mev/ µ ^{28}Si resulted in further reductions in the ability of rats to perform the discrimination stages, with the Simple Discrimination step showing the largest degree of impairment. However, the dose response for these changes is highly ion (LET) specific, and paradoxically the largest impairment was seen at the 10 or 15 cGy dose point and not at the 20 cGy dose point. Similarly, the dose at which there was a "switch" from habituation failure to Discrimination failure being the primary cause of the decreased ATSET performance was very ion-specific, e.g. 10 cGy 600 Mev/µ ^{28}Si resulted in a high habituation failure rate, 15 cGy resulted in Simple discrimination failure and 20 cGy had no apparent effect. In contrast, when 1 GeV/µ ^{56}Fe was used, 10 cGy had not apparent effect, 15 cGy resulted in Simple Discrimination failure and 20 cGy resulted in habituation failure. These data are consistent with studies from other investigators who observe non-linear dose responses for impairment of other cognitive tasks.

SUMMARY. Mission-relevant doses (<20 cGy) of HZE particles with LETs of 50-180 KeV/u lead to significant impairment of ATSET performance in rats with a comparable biological age to the Astronauts cadre. However, the performance decrements can be manifested as an inability to complete the task (habituate), or through an inability to identify the discriminating (associative) clue. There appears to be little LET-dependency for ATSET impairment. The full extent of the radiation-induced impairment of ATSET performance is currently obscured by an age related decline in the rats' performance/motivation to complete the testing paradigm. Future studies will utilize rats that have been preselected for good performance in the behavioral assay prior to irradiation.

FUNDING: The authors gratefully acknowledge grant support from NASA (NNX11AC56G).