

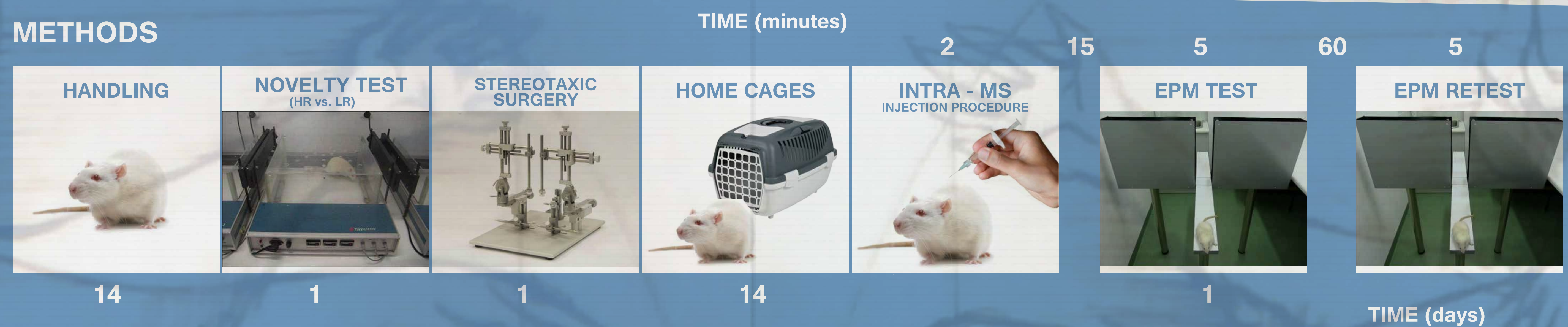
The medial septal glutamatergic receptor system involvement in modulation of learning is more pronounced in high responders to novelty

INTRODUCTION

The medial septum (MS) plays a significant role in learning, memory, anxiety and motivation while a high density of glutamatergic receptors in the MS, particularly the NMDA subtype, has been found. Learning and memory, especially in the context of stressful stimuli, such as fear and anxiety (emotional learning) vary among individuals, which may result from diverse behavioral characteristics and sensitivity to stress. One of the basic behavioral characteristics utilized to evaluate individual reactivity to stress is locomotor activity in the novelty test. In contrast to animals with low locomotor activity (LR), animals with high locomotor activity (HR) are considered to be more susceptible to stress as reflected by corticosterone response and reduced levels of fear and anxiety, along with increased novelty preference, which can be compared to sensation-seeking behavior in humans. The elevated plus maze test (EPM) is frequently used in rodents for the investigation of the behavioral activity related to memory processes and fear/anxiety, whereas the total time of moving from an open (unprotected) to a closed (protected) arm (transfer latency, TL) is one of the most valid measure of behavioral activity associated with emotional learning.

The purpose of the present study was to determine whether the MS NMDA receptor is involved in EPM-induced learning and anxiety-like behaviors in rats differing in behavioral characteristics, anxiety and stress susceptibility measured by their locomotor response to novelty: high (HR) or low (LR) responders. We used the test-retest paradigm which provides an index of trial-dependent changes in behavior (e.g. lower TL) occurring in process of learning.

METHODS



Male Wistar rats divided into HRs and LRs in the novelty test (2h) were exposed to EPM test (5 minutes) in the baseline and after drug or saline injections. Behavioral activity measured by TL was performed using the EPM test re-test paradigm: 15 minutes (1stEPM) and 60 minutes (2nd EPM, re-test) after injections of NMDA (N-methyl-D-aspartate receptor agonist, 0.25 µg/rat in 0.5 µl saline solution, n=14) or D-AP7 (DL-2-amino-7-phosphonoheptanoate, receptor antagonist, 0.1 µg/rat in 0.5 µl saline solution, n=15) or saline (0.5 µl/rat, n=12) via implanted cannulae into the MS (0.6 mm anterior to the bregma, 3.1 mm lateral to the midline and 7.6 mm below the skull surface).

NOVELTY TEST



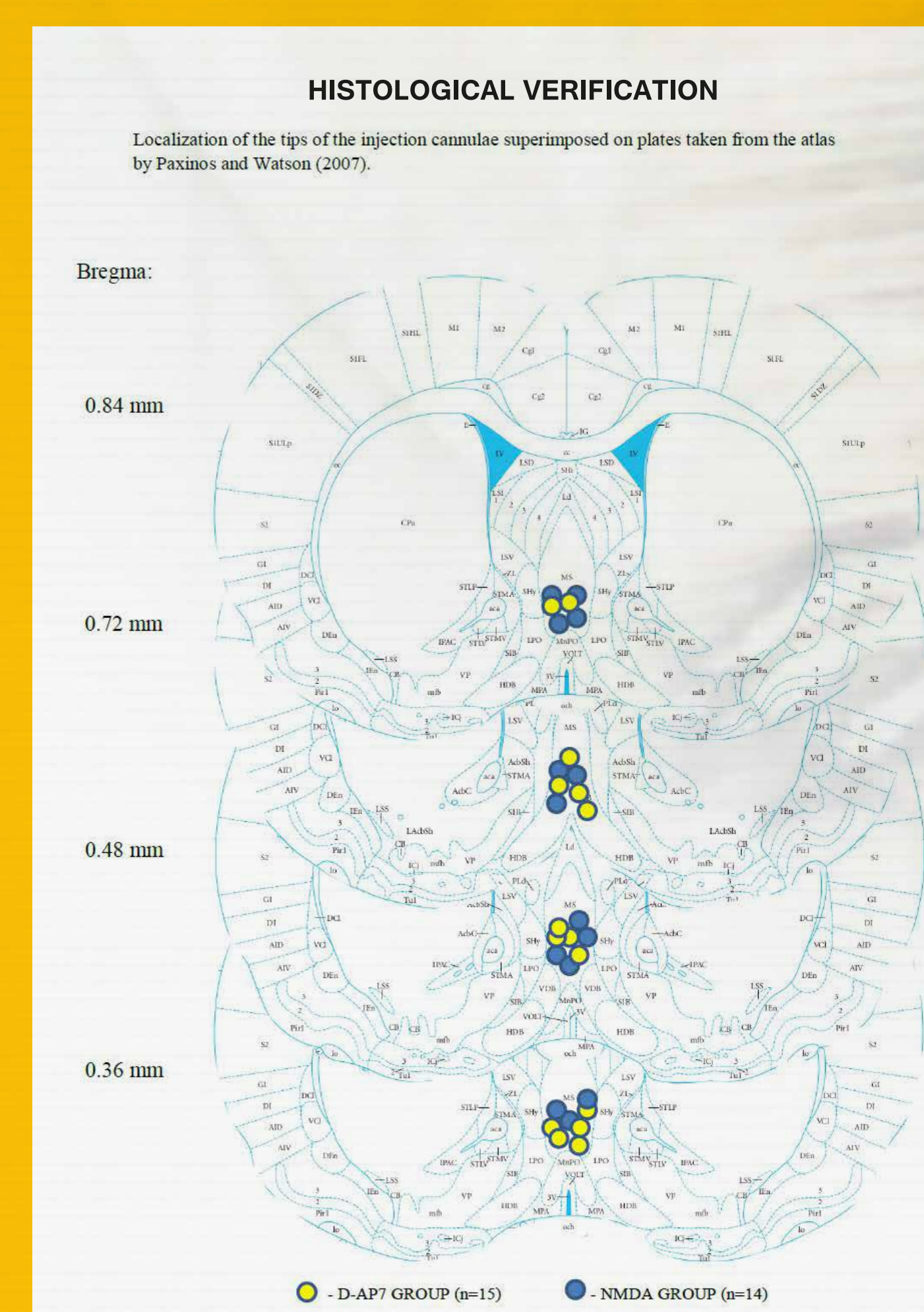
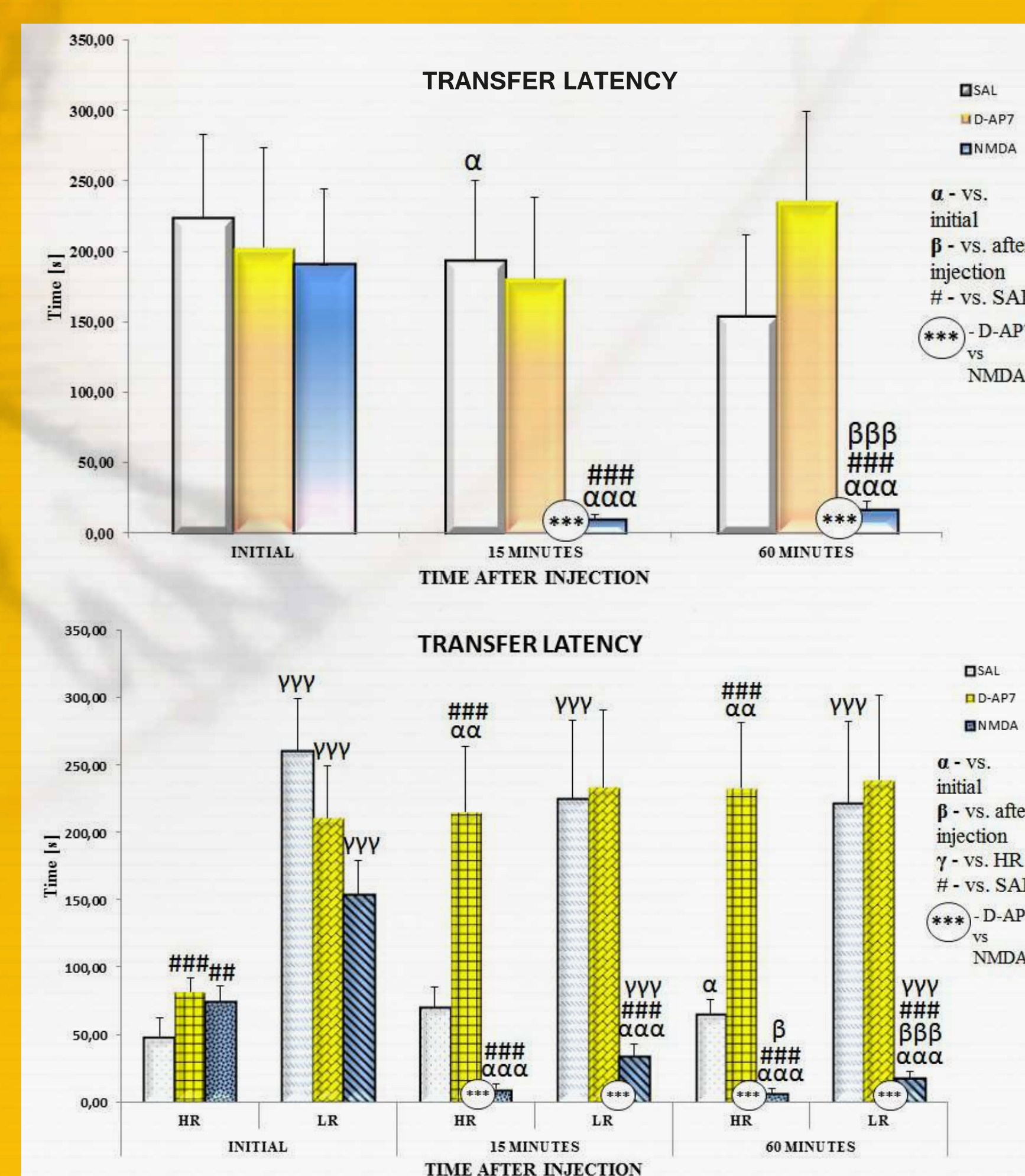
Rats were screened for locomotor response to novelty in plexiglass photocell cages between 4.00 and 6.00 p.m. Each of three apparatus (Opto Varimex Minor, Columbus, USA) was equipped with 15 photocells, that measured horizontal, vertical and ambulatory movements. Animals were placed in photocell cages for 2 h period. Based on the median determined for horizontal activity (number of times that beams located 25 mm above the floor are broken), animals were divided into high responders (HR) – rats with activity over the median value (>2638) and low responders (LR) – rats with activity below the median value (<2638).

The test was performed in a labyrinth composed of two white, open arms size 50 x 10 cm and two black (in order to increase fear and the difference between the open and enclosed arms) arms with closed ends, size 50 x 10 cm, forming a cross or a plus sign. The whole apparatus was elevated 50 cm above the floor. Experiment was realized at constant time between 8.00 and 12.00 a.m., at baseline and 15 minutes after drug injection. After the end of the test animals were returned to their cages and the same procedure was repeated after 1 hour (re-test). That allowed verification of memorized information and registration of behavioral changes associated with previous exploration of the maze.

EPM TEST RE-TEST



RESULTS



In comparison with the baseline and SAL groups, a significant decrease in TL in both HRs and LRs within the NMDA group, while a significant increase in TL in the HRs and no significant difference in TL in the LRs within the D-AP7 group, during the 1st and 2nd (re-test) exposition to EPM, was observed. There was a significantly lower TL in the HRs than in the LRs within the all groups of the animals in the baseline and within the SAL and NMDA group at the 1st and 2nd EPM. Moreover, a significantly lower TL in the HRs and LRs within the NMDA group in the re-test, as compared with the 1st EPM with a significant HR vs. LR difference, was noted. In contrast, there was no significant HRs vs. LR difference in TL following D-AP7 injection in the 1st and 2nd EPM exposition.

CONCLUSIONS

The study demonstrates an interaction between NMDA and medial septal glutamatergic receptor system on behavior measured by transfer latency in the elevated plus maze test in rats differing according to their locomotor response to novelty. It suggests that the MS NMDA receptor-dependent modulation of behavioral activity associated with emotional learning and memory process are more pronounced in rats with higher behavioral activity and decreased anxiety which are attributed to high responders to novelty.