Behavioral changes in a new substrain developed by selective breeding

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Introduction: Gene-environment interactions in psychiatric disorders can be modeled using selectively bred rats after receiving complex treatment, i.e. NMDA receptor antagonist administration and social isolation. The aim was to characterize behavioral profiles (sensory gating, pain sensitivity, memory function) in rats selectively bred through 15 generation after the complex treatment.

Figure 1.

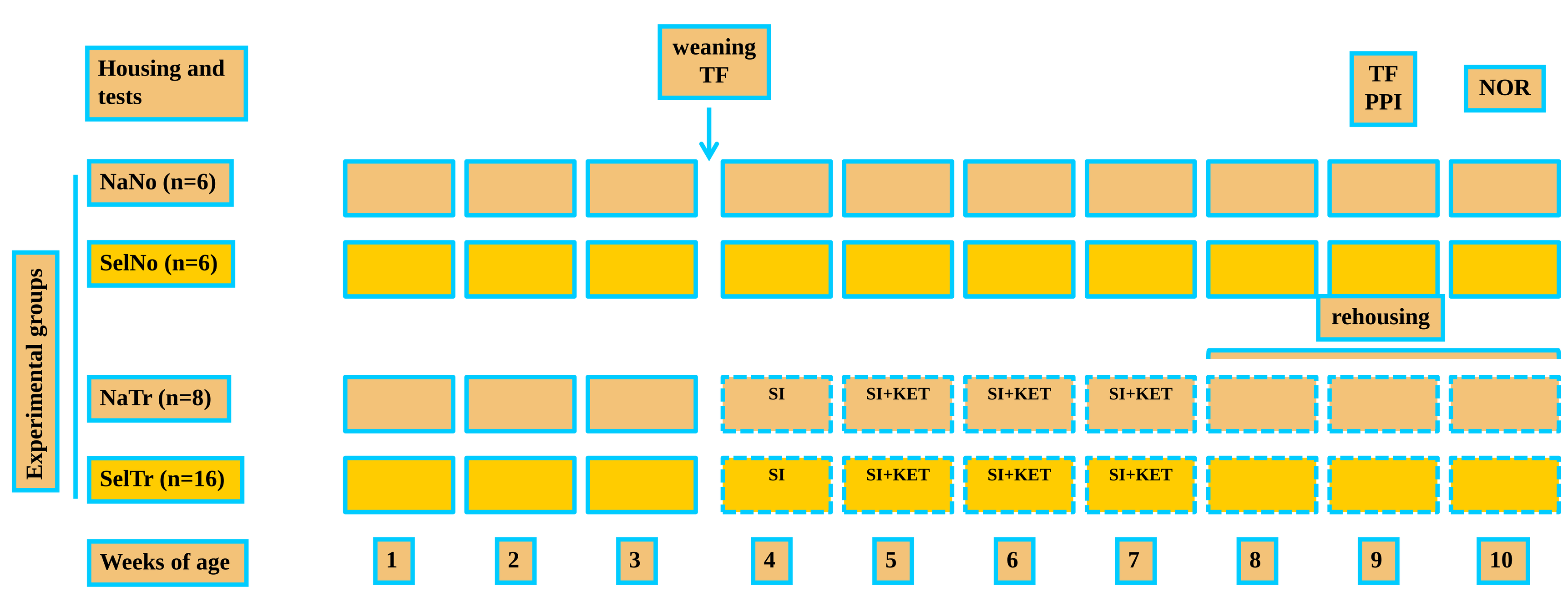


Figure 2.

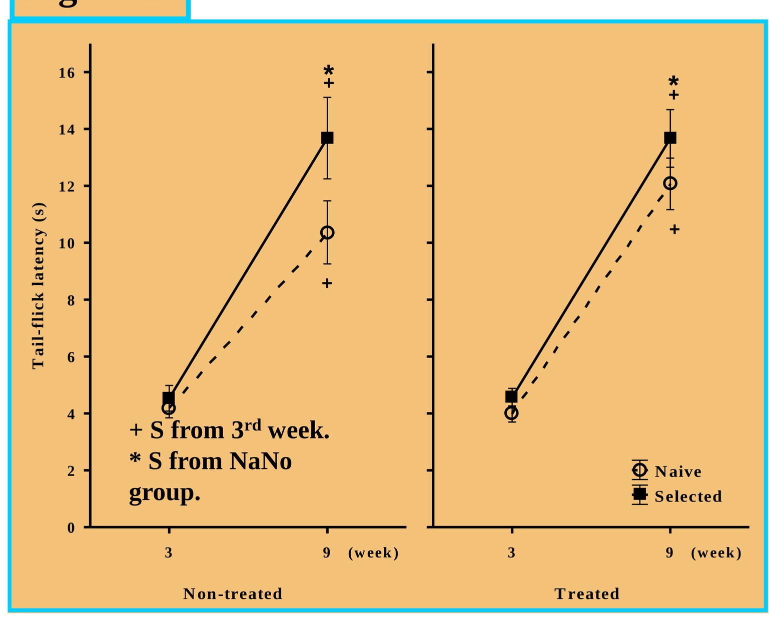


Figure 3.

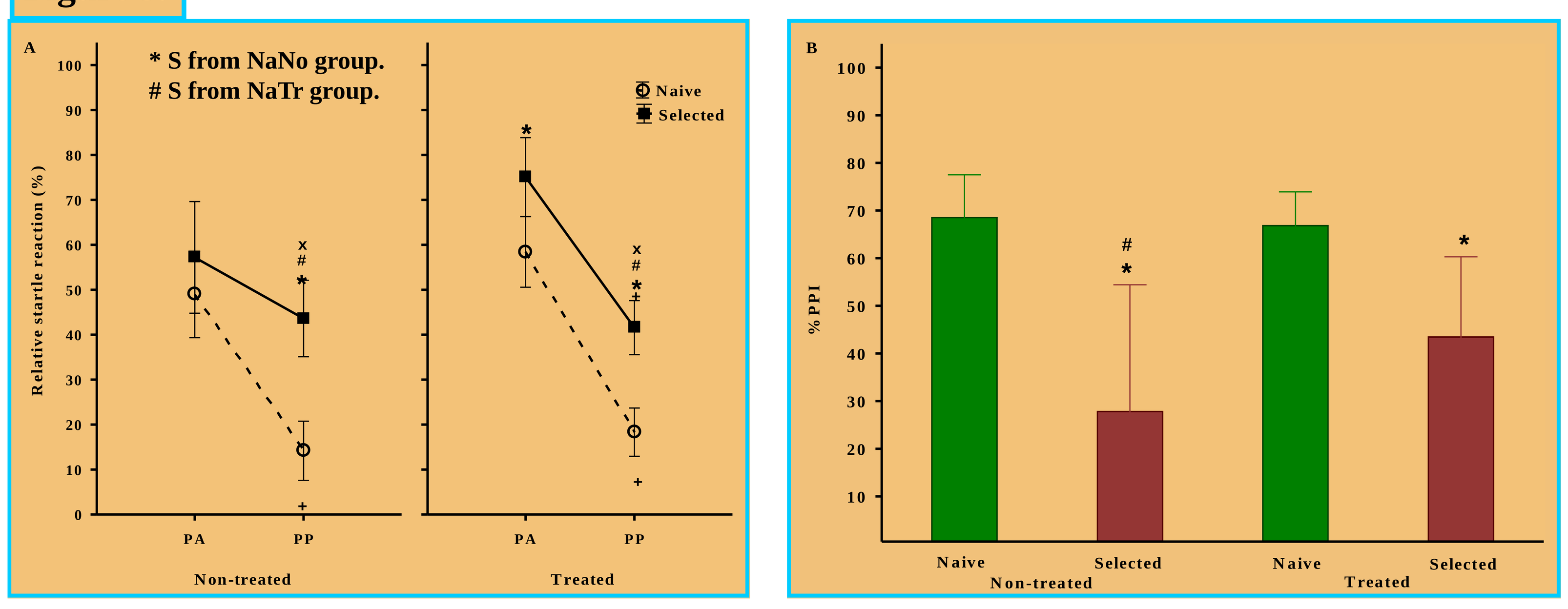
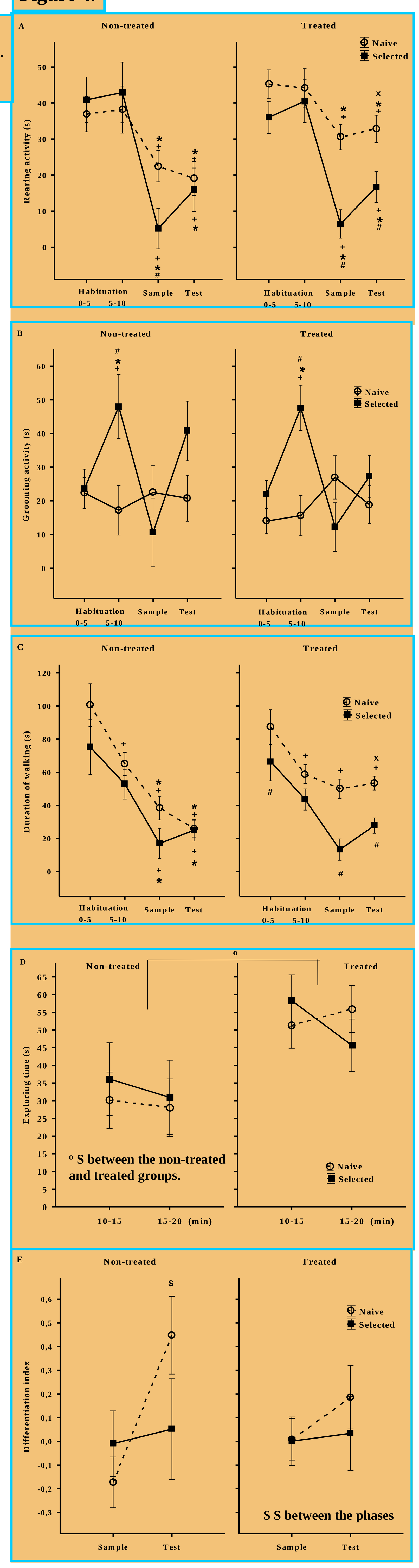


Figure 4.

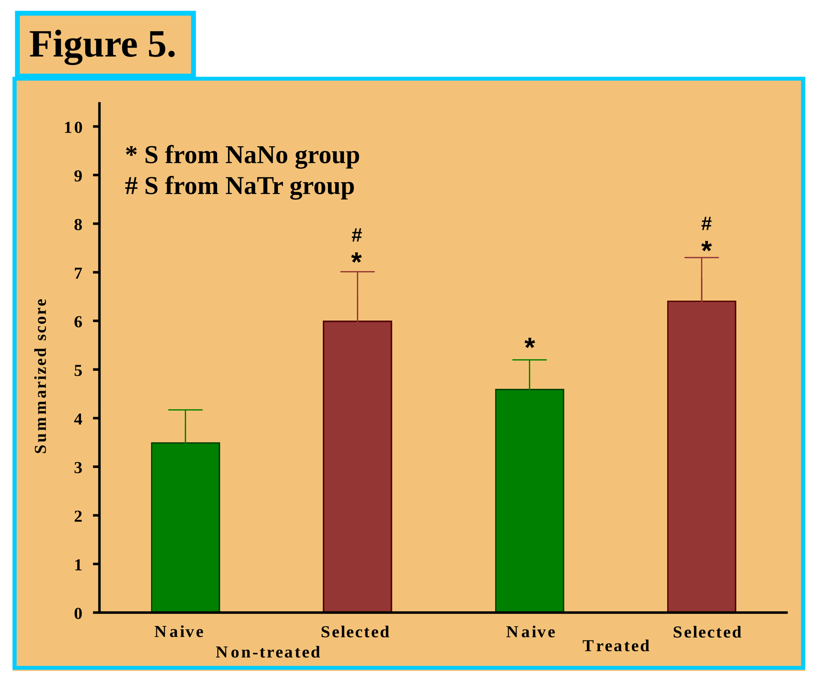
+ S from the first (0-5 min) habituation period.
* S from the second (5-10 min) habituation period.
X S difference with treatment.
S difference with strain.



Methods: Four experimental groups of male Wistar rats were studied (*n*=6-15 rats/group): naive rats without any treatment (NaNo); naive rats with postweaning social isolation and ketamine treatment (NaTr); 15th generation of selectively bred animals without any treatment (SelNo) or selectively bred rats with both isolation and ketamine treatment (SelTr) (Fig. 1.).
Groups were matched according to body weight and baseline tail-flick latencies obtained at the age of 3 weeks.
The startle reaction, tail-flick and novel object recognition tests were used for comparison of the different groups.

Results: As regards the tail-flick latencies, significant differences were observed at the age of 9 weeks between NaNo and both of the substrain groups (SelNo and SelTr), with these groups having the lowest pain sensitivity (Fig. 2.). The latency in the NaTr group did not differ from any other group. The 15th generation of the animals showed a higher degree of the startle reflex amplitude elicited with or without prepulse stimuli, and disturbed prepulse inhibition was also observed (Fig. 3. A-B). Altered motor activities in the novel object recogntiton test were observed in the new substrain (Fig. 4. A-D). Thus, rearing activity decreased with time (phase) in all groups, and the 15th generation showed lower rearing activity in the sample and/or testing phases (Fig. 4A.). The NaTr group showed enhanced rearing activity in the test phase compared to all the other groups. Strain differences were also found in the grooming behavior, i.e. the substrain showed increased grooming activity during the second part (5-10 min) of the habituation phase (Fig. 4B.). Analysis of walking duration revealed that walking activity decreased with time (phase), and was lower in the new substrain, while the NaTr group showed enhanced activity in the sample and test phases (Fig. 4C.). Both NaTr and SelTr groups showed an increased exploring time of the objects (Fig. 4D.). As regards the differentiation index (DI), the NaNo group showed high DI in the presence of the new object, while this enhancement could not be observed in any other groups (Fig. 4E.). Five functional indices (TF latency, startle reaction, prepulse inhibition, differentiation index, and grooming activity) were rated between 0 and 2, and the analysis of the summarized score revealed that the NaNo group had the lowest overall indication of schizophrenic-like signs, while the SelTr animals scored the highest (Fig. 5.).

Figure 5.



Conclusion:
These data suggest that both heritable and environmental factors were important in the generation of the behavioral alterations. We assume that further breeding after this complex treatment may lead to a valid and reliable animal model of schizophrenia.

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