# CHRONIC STRESS IMPAIRS LEARNING AND DECREASES CORTICAL FOS EXPRESSION IN ADULT MALE RATS[1]

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Formation of new behaviors during development determines growing complexity and differentiation of organism–environment relations. Accordingly, the structure of behavior and associated brain systems become more complex and differentiated as long as new experience is acquired. Our recent experiments demonstrated that acute stress induced short-term "*de*differentiation". In those studies we observed a decreased cortical and hippocampal Fos-activity (Bulava, Alexandrov, 2017; Bulava, Grinchenko, 2017). Phenomenologically this process is described as a "stress-induced return" to the previous (pre-learning) stages of development (Alexandrov et al., 2017). It can be regarded as an evolutionary mechanism of adaptation to stress and may be a necessary stage for learning. Short-term decrease in cortical activity may underline less complex behavior (less differentiated) which is necessary for performance in stressful environment. But long-term depression of cortical activity may contribute to stress-induced functional changes in brain and can have a particular strong association with progression of stress disorder. We have earlier identified the effects of daily stress on new experience-induced brain activity. In animals previously exposed to two-week period of intermittent electric foot-shock we found that Fos expression in the retrosplenial and motor cortices was significantly lower as compared to unstressed rats (Bulava et al., 2017). And finally, now we have continued our experiment with the main focus on acquiring a new skill after chronic stress. We have developed an experimental design (Fig. 1) consisting of two main stages: 1. formation of the state of "learned helplessness" (model of chronic intensive stress in animals); 2. formation of instrumental food-acquisition behavior. Adult male Long-Evans rats were used in this experiment. Transcription factor c-Fos was used as a cellular marker of learning-related neuronal activity changes, since it is known that c-fos expres-

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sion in the brain is related to the acquisition of new experience (Anokhin et al., 2001; Svarnik et al., 2005).

On the first day behavioral measures of all rats were assessed in open-field test. Then rats were either exposed with a single 5-min of inescapable electric footshock (15 trials x 20s: 10s - inescapable electric footshock, 10s - pause; AC, 50 Hz, 1 mA) daily for 2 weeks ("stressed group") or left unhandled except for weighing during this period ("unstressed group"). Both groups were placed in a new context for 5-min. And then some of these rats were decapitated, and the rest of the animals were trained in two phases of an instrumental learning (Task 1 and Task 2).

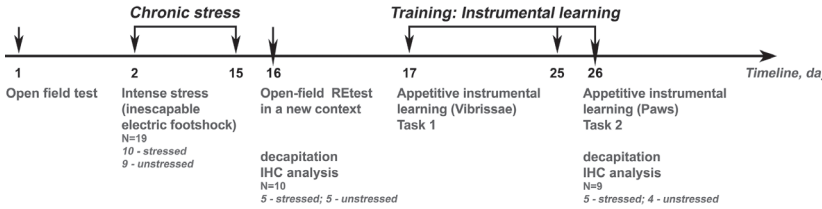


Fig. 1. *Timeline of stress manipulations and experiments.*

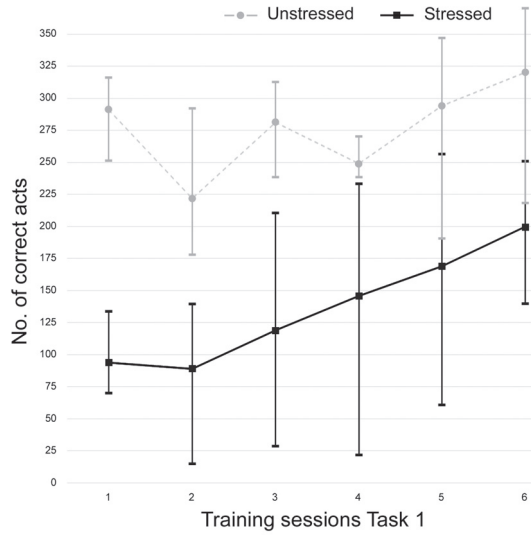


Fig. 2. *Learning curves Task 1. The number of correct acts in six trials, means, min/max. Impact of previous stress-experience on performance, Wilk's test p = 0.014.*

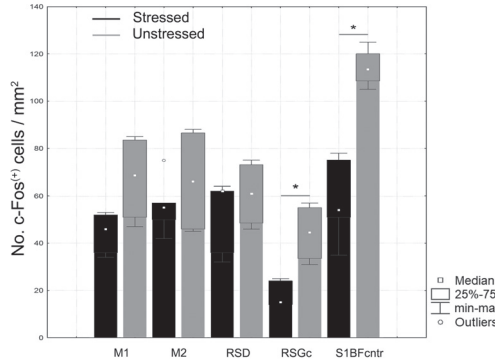


Fig. 3. *The number of c-Fos positive neurons in the primary (M1) and secondary (M2) motor cortices, the retrosplenial granular (RSGc) and dysgranular (RSD) cortices and in the primary somatosensory cortex, contralateral barrel field (S1BFcntr) after Task 2 acquisition in animals of the "unstressed group" and "stressed group", Mann-Whitney U Test *p < 0.02.*

In animals previously exposed to a 2-week period of intermittent electric footshock, we found that novelty-induced c-Fos expression in the cortex was significantly lower as compared to unstressed rats. There was a significant positive correlation between the locomotor activity on the last day of stress and the locomotor activity in the new context and we found the effect of chronic stress on success in learning (Fig. 2). Finally, we found that Fos expression in a cortices were significantly lower even after 10 days during instrumental re-learning of appetitive bar-pressing (long-term depression of cortical activity, Fig. 3).

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