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The Effects of Traumatic Experience on the Behavior, c-Fos Expression and Functional Connections in the Mouse Brain Resting State Networks

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Abstract

It is known that the brains of animals and humans is active at resting state. In this paper we investigate how past experience affects characteristics of such resting state networks in animals. To do this we subjected mice to single traumatic experience that induced posttraumatic stress disorder (PTSD) and then analyzed activity of their brain (including cortex; hippocampus; amygdala; basal ganglia; thalamus; hypothalamus and midbrain) by c-Fos cellular mapping during traumatic memory retrieval and at rest in comparison with non-stressed animals.

PTSD development led to global changes in brain activity: number of c-Fos-active neurons was significantly increased in different areas during traumatic memory retrieval. Similarly, at rest PTSD animals showed increased activity in 11 brain regions participating in fear memory.

We identified resting state functional connections in PTSD and controls and compared them with model networks: random, scale-free and small-world. In both groups of mice clusterization exceeded random level. At the same time, these clusters did not interact well with each other: global efficiency of experimental networks was at the level of random network. Resting state networks of PTSD and control mice differed (Fig. 1): PTSD network was less clustered and longer paths linked the clusters. Induction of PTSD led to global changes in the structure of resting state networks. In naive animals, cortical regions had the most connections, whereas in PTSD thalamus, striatum and amygdala had. PTSD destroyed virtually all functional connections present in naive mice; only fully connected cluster of auditory and visual cortices remained. In addition, if in naive animals the main hubs were cingulate and retrosplenial cortices in PTSD animals paraventricular

thalamic nucleus became the hub. In contrast, amygdala functional connectivity was virtually zero in naive animals, whereas in PTSD significant number of connections between amygdala, associative cortices, and striatum were observed.

In addition, we have shown that PTSD induction changes spontaneous behavior, causing elevated anxiety and decreased research activity in safe conditions of home cages. Behavior in conditioned fear, EPM and sensitization tests also changed, and these changes could be disrupted by protein synthesis inhibition during traumatic experience, which also returned brain activity and structure of resting networks to normal in PTSD animals.

Our findings show that stressful experiences can alter spontaneous behavior, induced and spontaneous brain activity and patterns of functional connections in resting state neuronal networks long after traumatic episode. We assume that these changes reflect replay of neuronal ensembles of the animal's past subjective experience. This assumption was tested by disrupting the development of PTSD.

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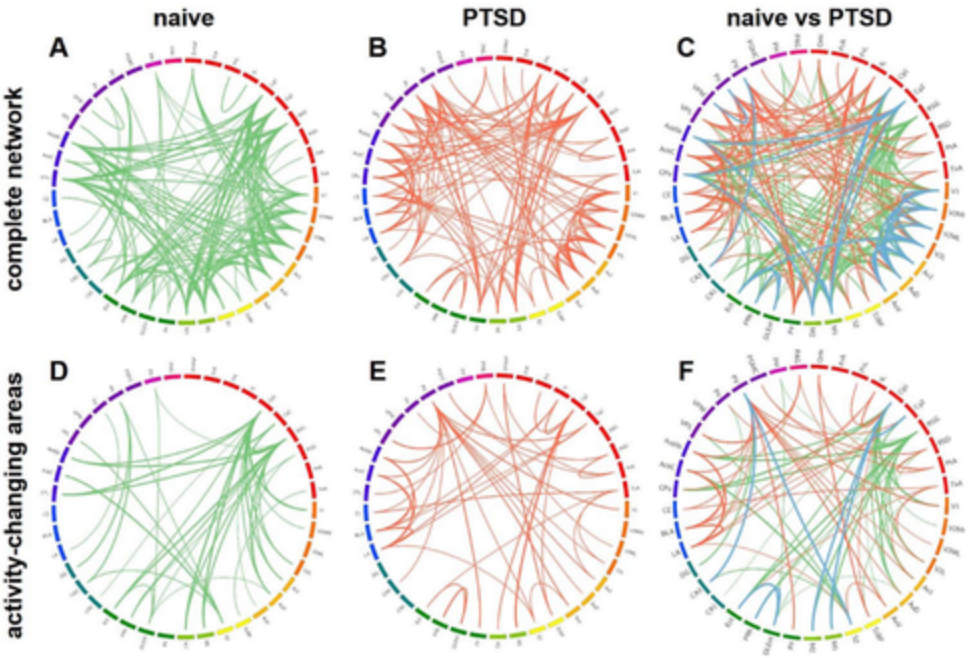

Figure 1

Open in figure viewer | PowerPoint

Resting state networks of naive mice (A, D) and PTSD animals (B, E), and their interception (C, F). A, B and C are for complete resting state networks, and D, E and À represents only connections of 11 brain areas that significantly change their activity in PTSD compared to naïve mice. Lines are Pearson's correlations with R>0.5, p<0.05; green

> lines – naive resting state network; red lines – PTSD resting state network; blue lines – correlations that are present in naive and PTSD mice.