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Research Report

Effort-Based Reward (EBR) training enhances neurobiological efficiency in a problem-solving task: Insights for depression therapies

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ABSTRACT

Effort-Based Reward (EBR) training strengthens associations between effort and rewards, leading to increased persistence in an unsolvable task when compared to control animals. EBR training involves placing animals in a test apparatus in which they are trained to dig in mounds to retrieve froot loop rewards (contingent group); these animals are compared to control animals that are given the same number of rewards, regardless of expended effort (noncontingent group). In the current study, the effect of EBR training on performance in a spatial task (Dry Land Maze) was explored to determine cognitive resilience during behavioral testing. Additionally, animals received BrdU injections during training to assess the role of neurogenesis on subsequent behavioral performance. Following the probe test, animals were perfused so that fos-immunoreactive (ir) cells in the hippocampus and cortical areas could be assessed. Behavioral results indicated that contingent rats were approximately 50% more efficient in locating and interacting with the previous baited well during the probe test than noncontingent animals, recruiting approximately 20% less c-fos ir-cells in the insular cortex, retrosplenial cortex, and dentate gyrus. A multidimensional scaling analysis grouped noncontingent animals together in a quadrant characterized by high latencies to find the previous baited well and higher ir-cell activation in the aforementioned areas. Thus, our data support the hypothesis that the EBR training enhances both cognitive functioning and emotional regulation during challenging events. Considering the ongoing controversy about the efficacy of pharmacological interventions in treating depression, the EBR model provides a valuable alternative for the investigation of the neurobiology of mood disorders.

Abbreviations: EBR, Effort-Based Reward; DLM, dry land maze; PRT, probe trial; BrdU, bromodeoxyuridin; DG, dentate gyrus; RSC, retrosplenial cortex; PFC, prefrontal cortex; ir, immunoreactive; VTA, ventral tegmental area; NAc, nucleus accumbens; DCX, doublecortin; PBS, phosphate-buffered saline; MANOVA, multivariate analysis of variance; MDS, multidimensional scaling

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1. Introduction

Behavioral activation is a form of psychotherapy that attempts to help individuals affected by depression symptoms by reengaging them in adaptive daily responses using focused activation strategies (Dimidjian et al., 2011). This empirically supported therapy emphasizing techniques such as activity monitoring, skills training, and contingency management successfully in the treatment of depression (Kanter et al., 2010,2012). A challenge with this therapy, however, has been the lack of animal models to examine critical neurobiological changes accompanying symptom improvement.

Recently, our laboratory has investigated animal models elucidating neurobiological changes accompanying symptom improvement or enhanced resilience in the presence of challenging and stressful tasks. For example, the Effort-Based Reward (EBR) semi-naturalistic behavioral training paradigm requiring the animal to adjust foraging strategies daily to maximize rewards, has been proposed as a training technique that enhances resilience against the onset of depressive symptoms (Lambert, 2006,2008). This model requires rats to exert physical effort to obtain rewards each day, potentially activating brain areas typically implicated in depression such as the prefrontal cortex (PFC), nucleus accumbens, and striatum (Dichter et al., 2010). Past research has indicated that, when faced with a challenge task, EBR contingently trained animals persisted longer than control, non-contingent animals (Lambert, 2006). We also found that, regardless of a rat's predisposed coping strategy, EBR rats persisted longer than noncontingent rats in an appetitive problem-solving task (Bardi et al., 2012). Furthermore, training and coping styles interacted to yield the seemingly most adaptive response to a forced swim task, thus showing a direct link between EBR training and emotional regulation during a challenging event (Salamone et al., 2007; Treadway et al., 2009; Bardi et al., 2012). In the current study we extended our investigation to include more cortical and hippocampal brain areas to determine the potential effectiveness of the EBR model against cognitive symptoms of depression.

Evidence from animal models indicates that contingency training, resulting in increased associations between effort and consequences, enhances prefrontal executive and cognitive functions, likely influenced by dopaminergic activity (Neill et al., 2002; Dalley et al., 2004; Ishiwari et al., 2004; Salamone et al., 2009). Although many brain areas are involved, past research has emphasized the roles of the retrosplenial cortex (RSC) and insula in emotional tasks with cognitive demands (Bush et al., 2000; Damasio et al., 2000; Vann et al., 2009). Specifically, difficulties regulating emotions during a cognitive challenge are associated with reduced activity in cortical dorsal systems, including the RSC and the insular cortex (Mériau et al., 2006; Vann et al., 2009). Additionally, the insular cortex and adjacent areas appear to play a crucial role in evidence accumulation and decision signaling in decision-making tasks (Rebola et al., 2012), making these areas a priority target of investigation in the current study. Moreover, it has been shown that the RSC is consistently compromised in several neurological disorders involving memory impairment, including mood disorders and post-traumatic stress disorders (Vann et al., 2009). Accordingly, the aim of the current study was to investigate the effect of EBR training on relevant behavioral and neural responses to a challenging cognitive task. Specifically, following either EBR contingent training or non-contingent training, rats were exposed to the Dry Land Maze (DLM), culminating with a probe trial (PRT), which marked the final day of testing. No wells were baited during the PRT, so problem solving strategies could be assessed when the expected food reward was not found in the expected location. It was hypothesized that contingent EBR training would be more efficient in their solving strategies and critical structures in the dorsal system of the cerebral cortex would be more active during the same task.

c-Fos immunoreactivity was used to quantify immediate-early gene expression in the targeted brain areas. The c-fos gene defines a multigene family encoding several transcription factors, including the protein c-fos (Chinenov and Kerppola, 2001). Evidence of a role of c-fos during memory formation emerged from expression studies in which c-fos induction was observed during behavioral training and learning tasks (Guzowski, 2002). However, because c-fos is induced by many different stimuli, the functional relevance of these results have been questioned (Herdegen and Leah, 1998). Recent studies, however, have demonstrated the involvement of c-fos in hippocampus dependent learning and memory as well as in NMDA receptor-dependent LTP formation (Fleischmann et al., 2003). Since c-fos is an unstable protein, histological assessments must be conducted at appropriate times following behavioral assessments (Gass et al., 1992; Herdegen et al., 1993).

A secondary aim of the current study was to investigate the effect of EBR training on neural plasticity. Plasticity of the hippocampus, a structure known to be involved in spatial ability and cognitive functions, has demonstrated sensitivity to physical exercise (Clark et al., 2012). Although EBR training emphasizes the connections between effort and rewards more than intense physical exertion, contingent-based physical effort is a component of the model, potentially contributing to enhanced cognitive function by increasing hippocampal plasticity. Accordingly, rats were injected with bromodeoxyuridine (BrdU), a synthetic nucleotide commonly used to detect cellular proliferation in living tissues, to detect neurons generated during training for the cognitive task known as the dry land maze. We also assessed c-fos immunoreactivity (ir) in the dentate gyrus of the hippocampus as an additional measure of hippocampal involvement to further assess the role of the hippocampus in adaptive performance in the final probe trial of the cognitive task when the expected reward was removed from the previously baited well.

2. Results

2.1. Behavioral responses

Both contingent and noncontingent animals significantly decreased the latency to approach the well during the DLM training ($F_{6,90}=40.42$, $p<0.001$). Latency decreased exponentially from an average of about 140 s in the first day of training to little more than 13 s in the last day of training (Figs. 1 and 2). No significant differences were found in both