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Reply to: Does High-Frequency Deep Brain Stimulation in Dorsal Regions of the Ventral Striatum Impair Extinction of Morphine-Induced Place Preference?

Freddyson J. Martínez-Rivera and Jennifer L. Barreto-Estrada

Department of Anatomy and Neurobiology, School of Medicine, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico

To the Editor

We recently published an article showing bidirectional modulation of extinction of drug-seeking behavior by high and low frequencies of deep brain stimulation (DBS) of the ventral striatum (VS) (1). Specifically, we reported that high-frequency DBS (HF-DBS) of the dorsal region of the VS (dorsal-VS) impaired the extinction of morphine-induced place preference. In contrast, HF-DBS of the ventral region of the VS (ventral-VS) had no effect. In that analysis, control (sham) rats that were implanted with electrodes into the dorsal ($n = 12$) and ventral ($n = 11$) regions of the VS showed no statistical differences across the 9 days of extinction ($F_{1,21} = 0.33$, $p = .56$) and therefore were combined into a single sham group. The combining of sham groups raises a question regarding the significance of the results because there was no comparison between DBS and specific sham groups (2). In our new analysis of the data, we compared rats receiving HF-DBS of the dorsal-VS with their original (dorsal) sham counterparts. Specifically, rats exposed to HF-DBS of the dorsal-VS were impaired in their extinction of the morphine-paired side across the 9 days of extinction training. This is compared with either the dorsal-VS sham group ($n = 12$; $F_{1,21} = 7.36$, $p = .013$) or, as previously reported, the dorsal-ventral VS sham combined group ($n = 23$; $F_{2,40} = 5.31$, $p = .008$) (1). Furthermore, the impairment of extinction in the dorsal-VS group persisted for 2 days following the cessation of DBS, as compared with the dorsal-VS sham group ($F_{1,21} = 8.93$, $p = .007$) or the combined dorsal-ventral VS sham group ($F_{2,40} = 5.24$, $p = .009$) (1).

In the same study, we reported that low-frequency DBS (LF-DBS) of the VS strengthened the memory for extinction of morphine-induced place preference. Because HF-DBS of the ventral-VS had no effect on extinction, we decided to focus on the dorsal-VS, the site where extinction was impaired by HF-DBS. To prevent floor effects caused by full extinction in this cohort of animals, rats received extinction training for 6 days together with LF-DBS of the dorsal-VS ($n = 14$) or sham stimulation ($n = 15$). In our initial analysis for LF-DBS, we combined sham groups from the dorsal-VS that included both HF-DBS ($n = 12$) and LF-

DBS ($n = 15$) experiments. In that analysis, there were no statistical differences between these groups during extinction sessions (days 1–8) ($F_{1,21} = 0.33, p = .56$). Therefore, we proceeded to report statistical analysis (1) between the LF-DBS group and its appropriate sham group ($n = 15$; LF-sham group) ($F_{1,27} = 5.013, p = .033$). In the current analysis, because the effect of LF-DBS was during DBS off days, we also analyzed days 7 and 8 for all dorsal-VS-implanted sham rats (HF- and LF-sham). Consistently, the strengthened extinction memory induced by LF-DBS was also observed when the analysis took into consideration the combined sham groups (HF- and LF-sham: $F_{1,39} = 5.36, p = .025$). This result was similar to our previous finding when the LF-DBS group was compared with uncombined dorsal-VS implanted sham rats (1). Likewise, the enhanced extinction memory was still observed 1 week later (extinction day 15; unpaired t test: $t_{12} = 2.27, p = .041$), when the uncombined analysis was done. Thus, our main findings survive analyses performed after either pooling or separating sham groups from different experiments, reinforcing our hypothesis of the bidirectional effects of DBS in the VS for the extinction of morphine-induced place preference.

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