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# ALCOHOL WITHDRAWAL RESULTS IN DEPRESSIVE-LIKE BEHAVIOR IN RATS

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## INTRODUCTION

Many epidemiological studies report significant co-morbid expression of alcoholism and depression (Haver and Dahlgren, 1995). It has been suggested (Hasin & Grant, 2002; Kessler et al., 1997; Schuckit et al., 1997) that alcoholism may induce depression; however, a causal relationship between these two conditions is yet to be established.

During alcohol withdrawal (AW) autonomic hyperactivity (De Witte, et al., 2003) and/or altered psychological states can facilitate the relapse (Glenn and Parsons, 1991). In fact, depression appears to be particularly common during and following detoxification (Beck et al., 1993; Behar et al., 1984; Turnbull and Gomberg, 1988). Therefore, occurrence of depression during AW is an important determinant of treatment seeking but worsens the prognosis in detoxifying alcoholics (Kendall and Clarkin 1992). Moreover, depression in alcoholics is underestimated diagnosed and undertreated.

The major aim of this study was to determine whether withdrawal from chronic alcohol administration might lead to depressive-like behavior in a rat model. Moreover, because of known strain-dependent responses to alcohol, the studies were carried out in two strains of rats: the Wistar and Wistar-Kyoto (WKY). WKY rats, derived from the Wistar stock are considered an animal model of depression as they exhibit exaggerated immobility in the forced swim test (FST) compared to the Wistar rats.

## METHODS

### Animals

Age matched adult female WKY and Wistar rats (Charles Rivers) were kept in a temperature-controlled room (24-26°C) on a 12:12 hour reversed light/dark cycle (lights on at 19:00). The animals had ad libitum access to food and water, except during experiments.

### Ethanol Vapor Exposure

Animals were exposed daily 95% ethanol via inhalation chamber (La Jolla Alcohol Research Inc. La Jolla, CA) for 7 or 14 days. To minimize problems of ethanol vapor condensation, the following parameters were used: air pressure = 5 psi, airflow rate = 10-15 liter/min and alcohol flow rate = 10-75 ml/hr.

Every 3 days blood Alcohol Level (BAL) was determined.

Note: Mean BALS were equivalent in both groups during the alcohol exposure (approximately \*150 mg/dl, at various time points).

### Behavioral Testing

**Locomotor Activity Test (LCA):** On the day of behavioral testing i.e., day 8 and 15 (14-18 hr after last ethanol exposure) automated analysis of LCA in an open field was performed prior to the FST.

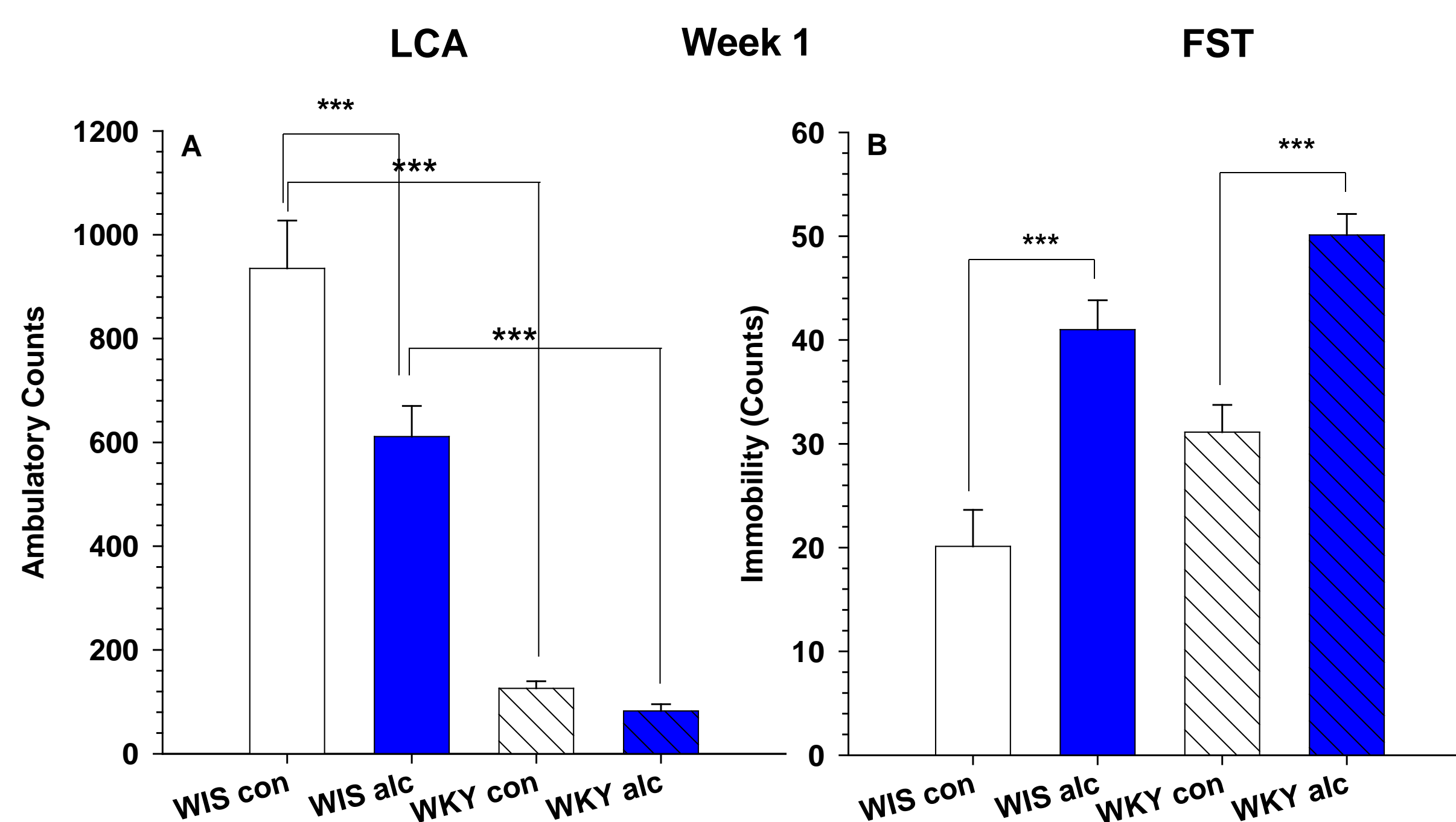
### Forced Swim Test

A modification of the method of (Porsolt et al., 1977) was used. The FST measures immobility of animals in an inescapable cylinder of water. The total amount of time the animal demonstrates this behavior reflects the animal's state of behavioral despair. The animals were placed in the water cylinders for 5 minutes, videotaped and their swimming and immobility was scored at every 5 second interval according to Detke, et al., 1995.

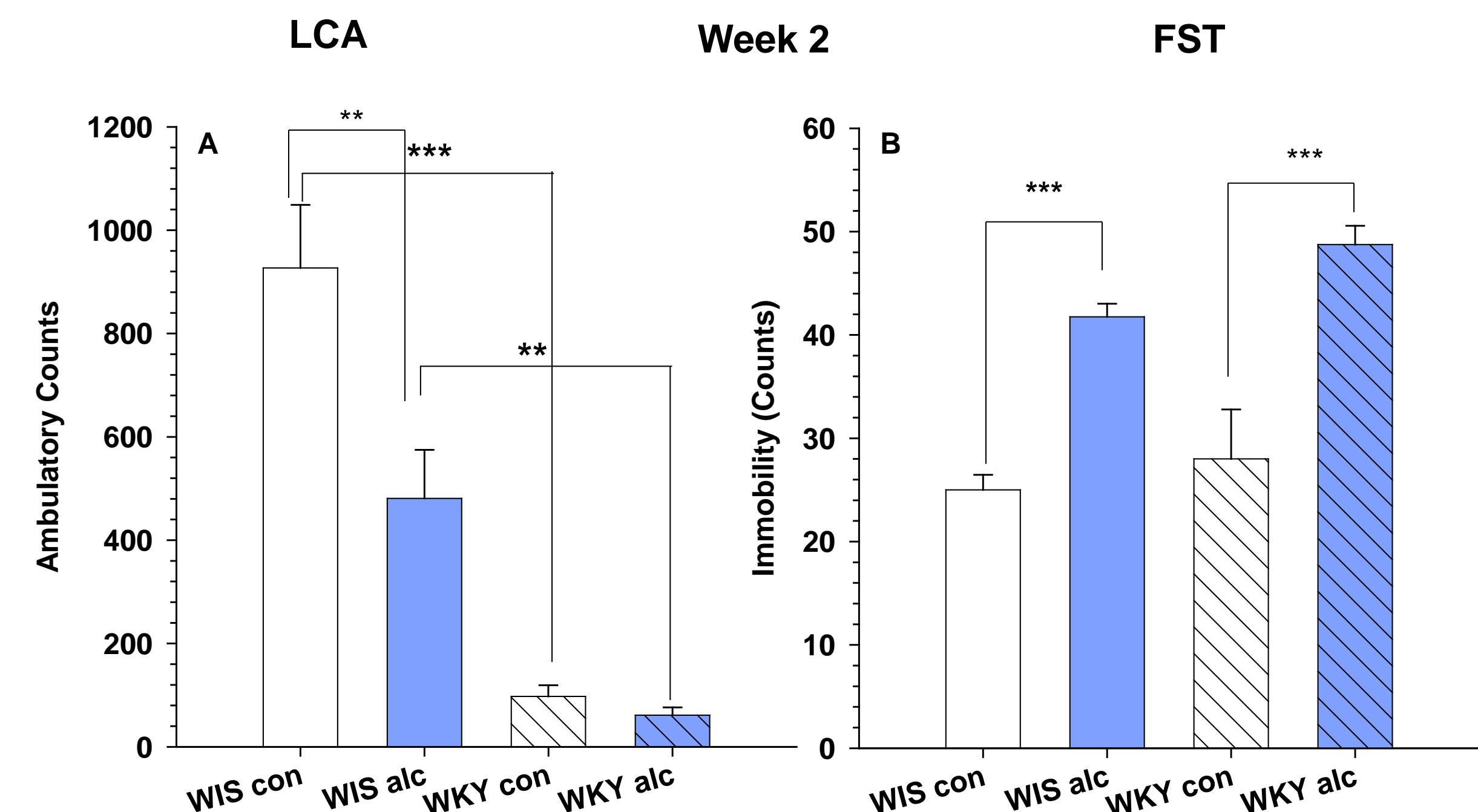
### Statistical Analysis

All data were expressed as the mean  $\pm$  S.E.M. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test when significant main effects were indicated. All analyses were two-tailed and  $P < 0.05$  was considered significant.

## Results



**Figure 1a and b.** Effects of 14-16 hour withdrawal from 1 week daily ethanol exposure on LCA and FST immobility counts of WKY and Wistar rats. Values are mean  $\pm$  SEM. \* $P < 0.05$ . N=7-8.



**Figure 2A and B.** Effects of 14-16 hour withdrawal from 2 weeks daily ethanol exposure on LCA and FST immobility of WKY and Wistar rats. Values are mean  $\pm$  SEM. \* $P < 0.05$ . N=7-8.

## Summary of Results

- WKY rats show lower baseline LCA compared to Wistar rats.
- Withdrawal from 1 or 2 weeks daily ethanol resulted in significant LCA reduction in Wistar rats only.
- Withdrawal from 1 or 2 weeks daily ethanol exposure resulted in increased FST immobility in both WKYs and Wistars.

## Concluding Statement

Alcohol Withdrawal may lead to depressive-like characteristics in at least two strains of rats. This model may be used to investigate the neurobiological bases of affective disorder following alcohol withdrawal.

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