

Antipsychotic And Iron-Reducer Targeting Drug-Induced Psychosis

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Introduction

- Schizophrenia is a serious mental disorder that affects around 1% of the population, posing significant social and economic challenges.
- Despite ongoing efforts, there has been no major advancement in treatment over the past 40 years, and up to 30% of patients exhibit partial or complete resistance to available treatments.¹
- Schizophrenia in humans requires two or more of the following symptoms to be present for a significant portion of a one month period:²
 - Delusions
 - Hallucinations
 - Disorganized Speech
 - Grossly Disorganized or Catatonic behavior
 - Negative Symptoms
- The easiest of the 5 to simulate in mice is catatonic behavior through drug-induced psychosis
- Schizophrenic-like catatonic symptoms can be traced in mice through stereotypic behavior (a repeating behavior that doesn't seem to have any purpose).³
- A commonly observed stereotypy seen in mice is circling: where the mouse repeatedly walks in a circular path.⁴
- This experiment aimed to determine if an antipsychotic and an iron reducer, either used separately or in conjunction with one another, are capable of effectively reducing catatonic behavior in mice.
- This could provide insights into potential novel therapeutic approaches for treating schizophrenia in humans.

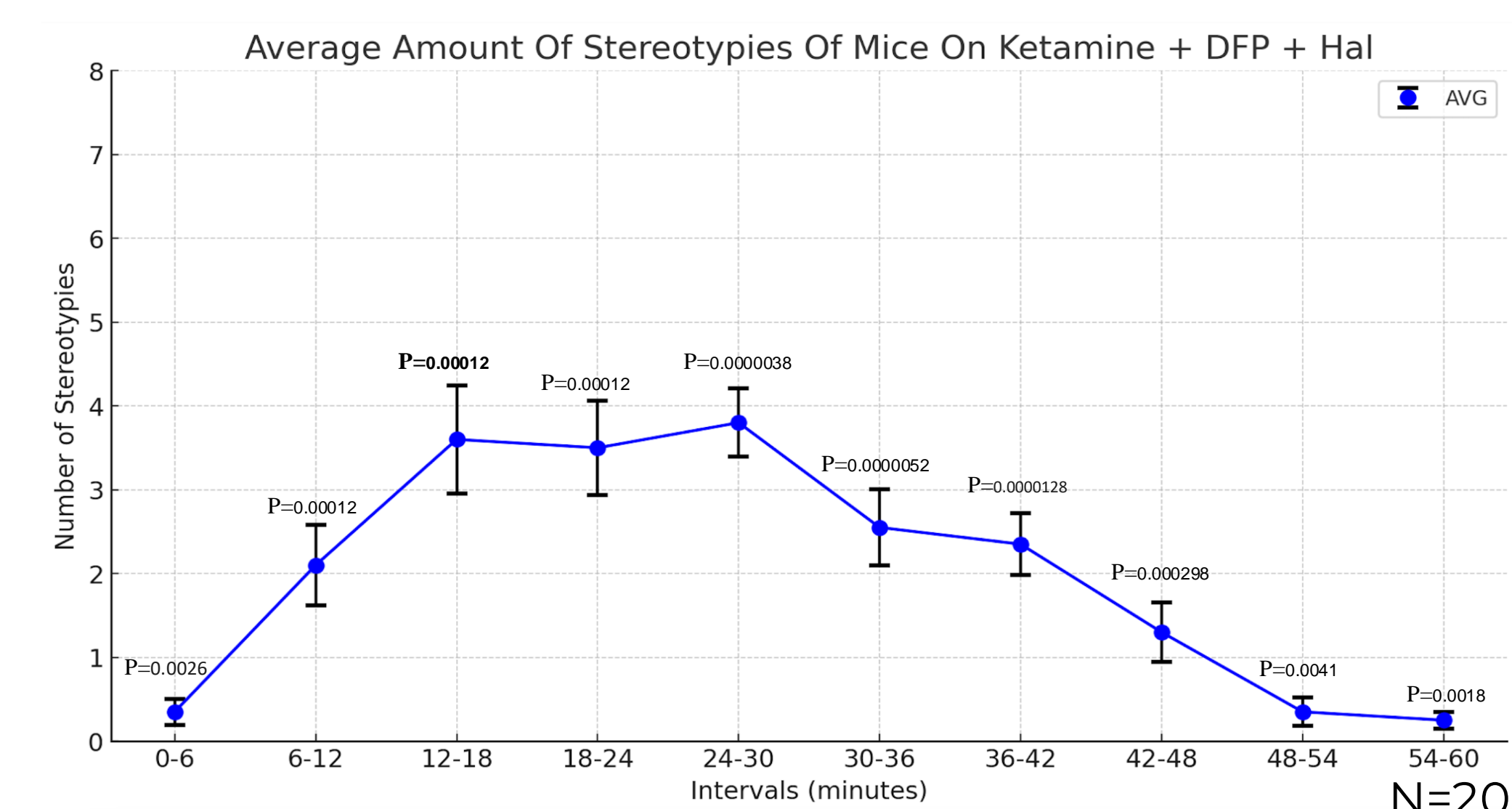
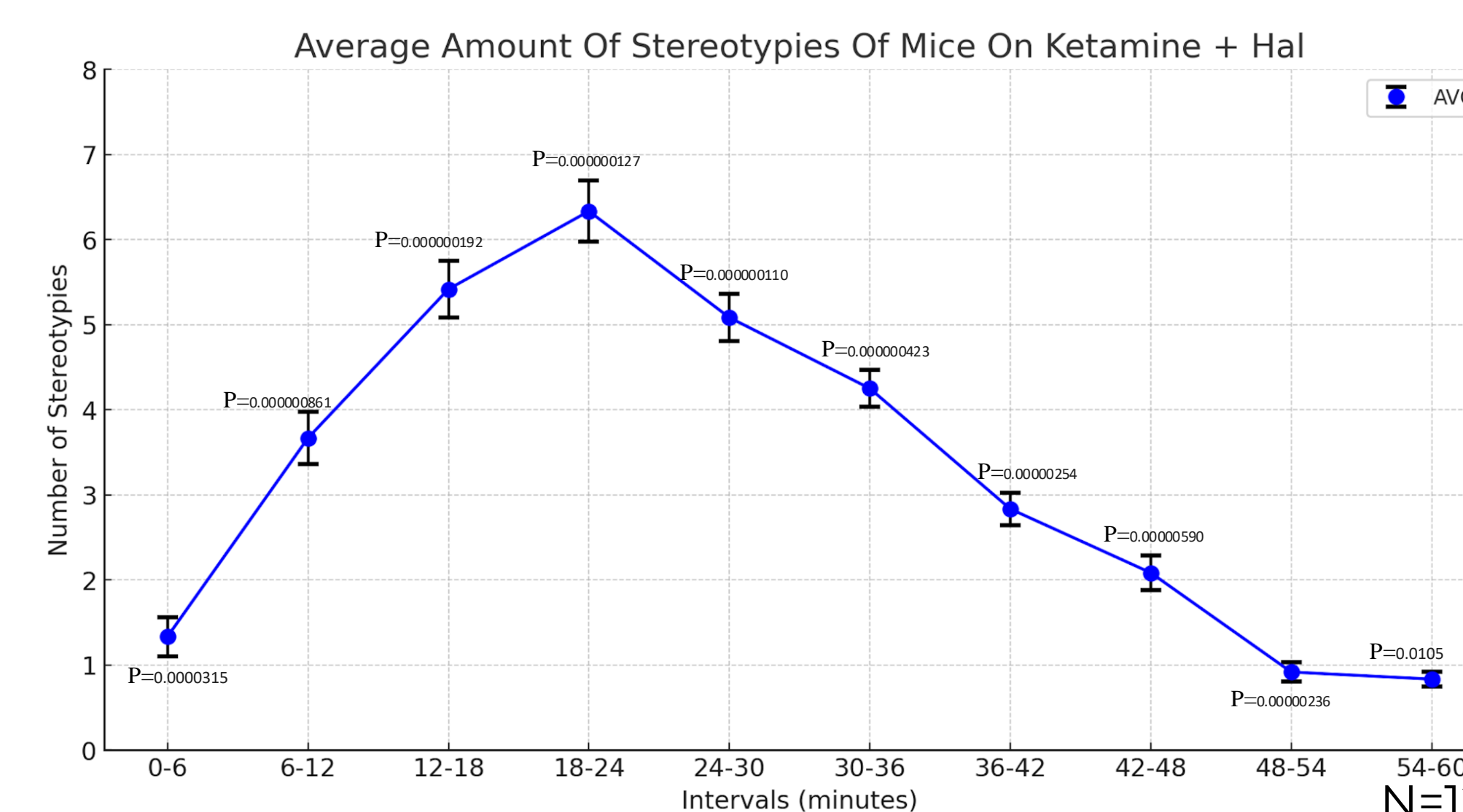
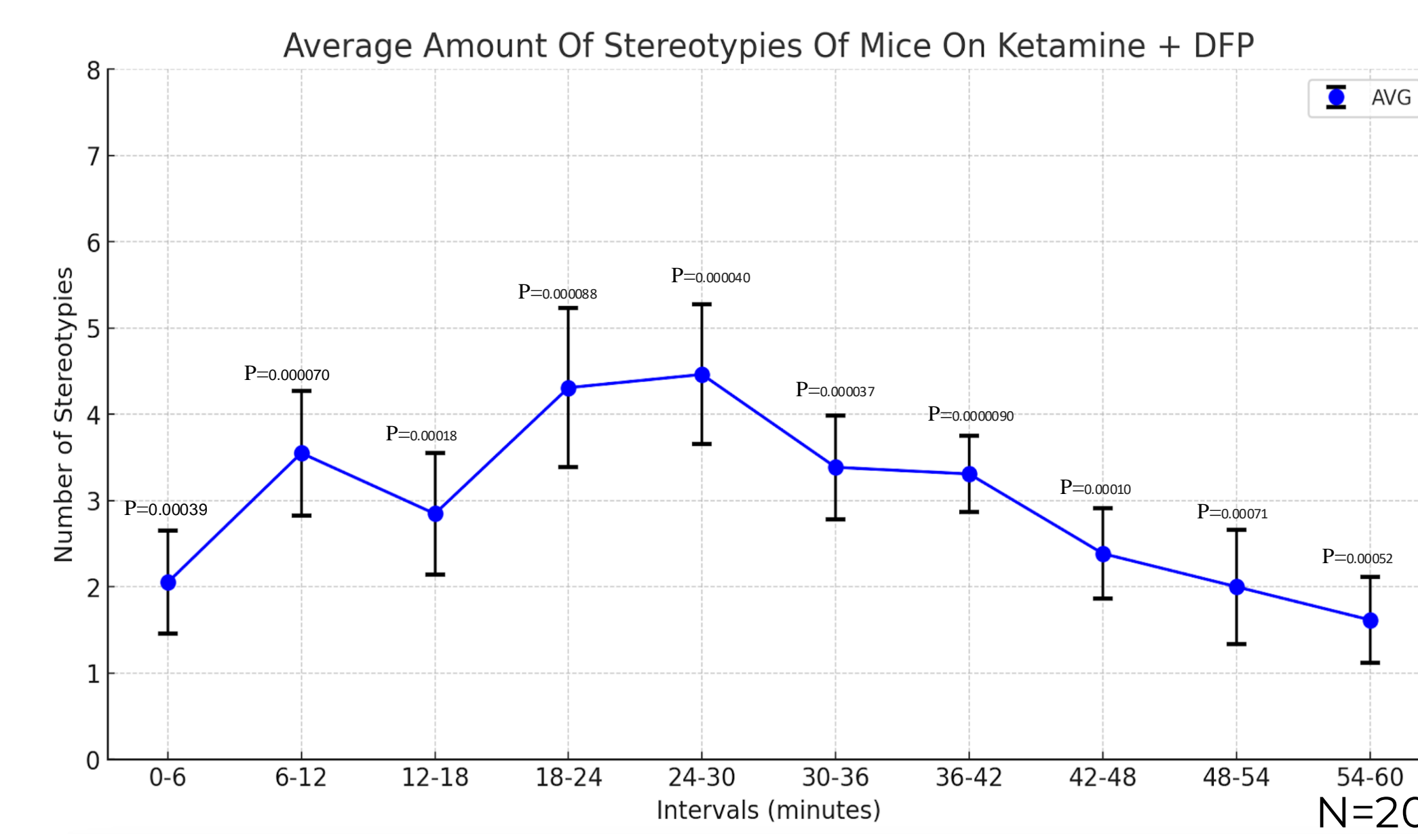
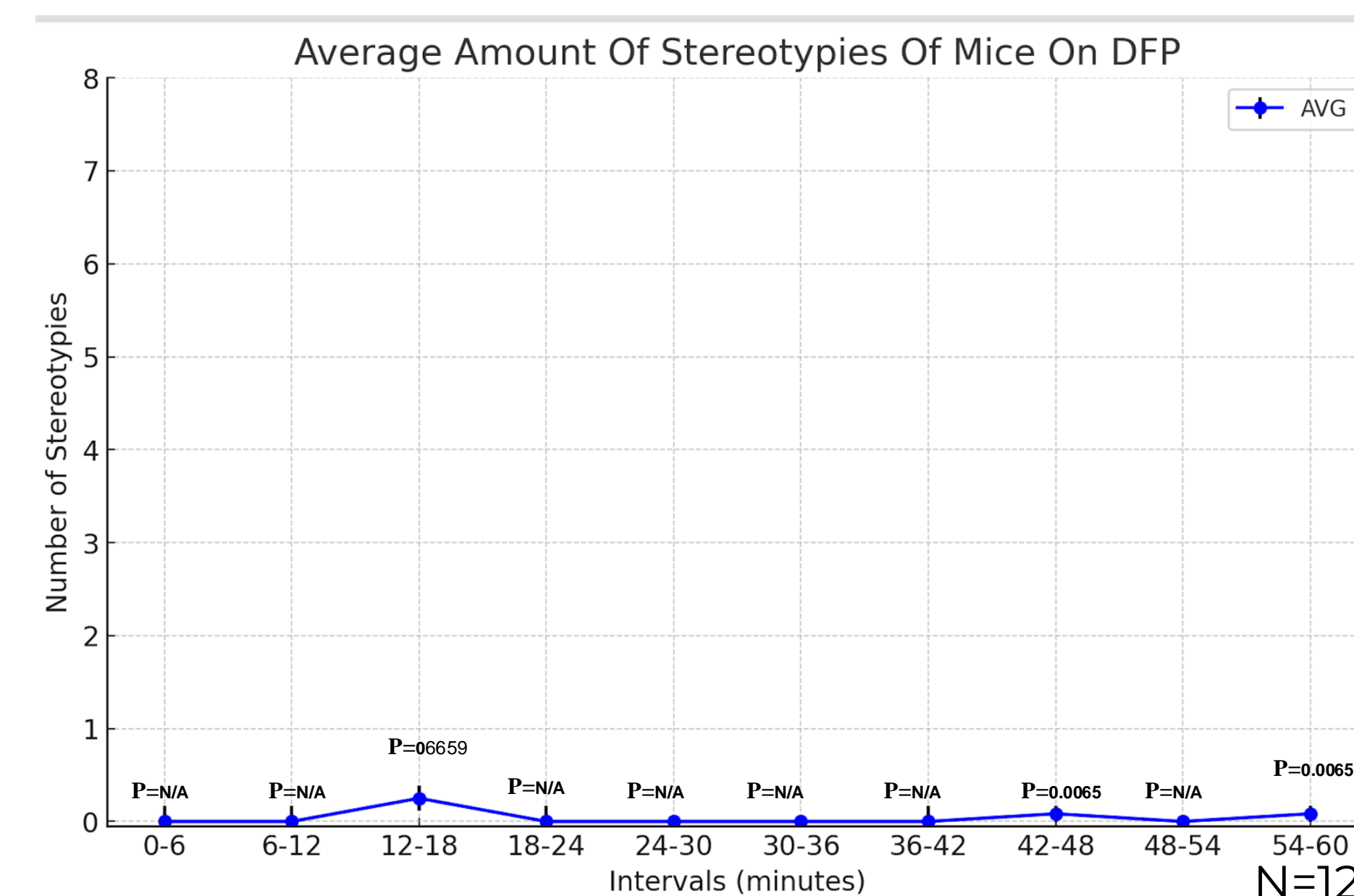
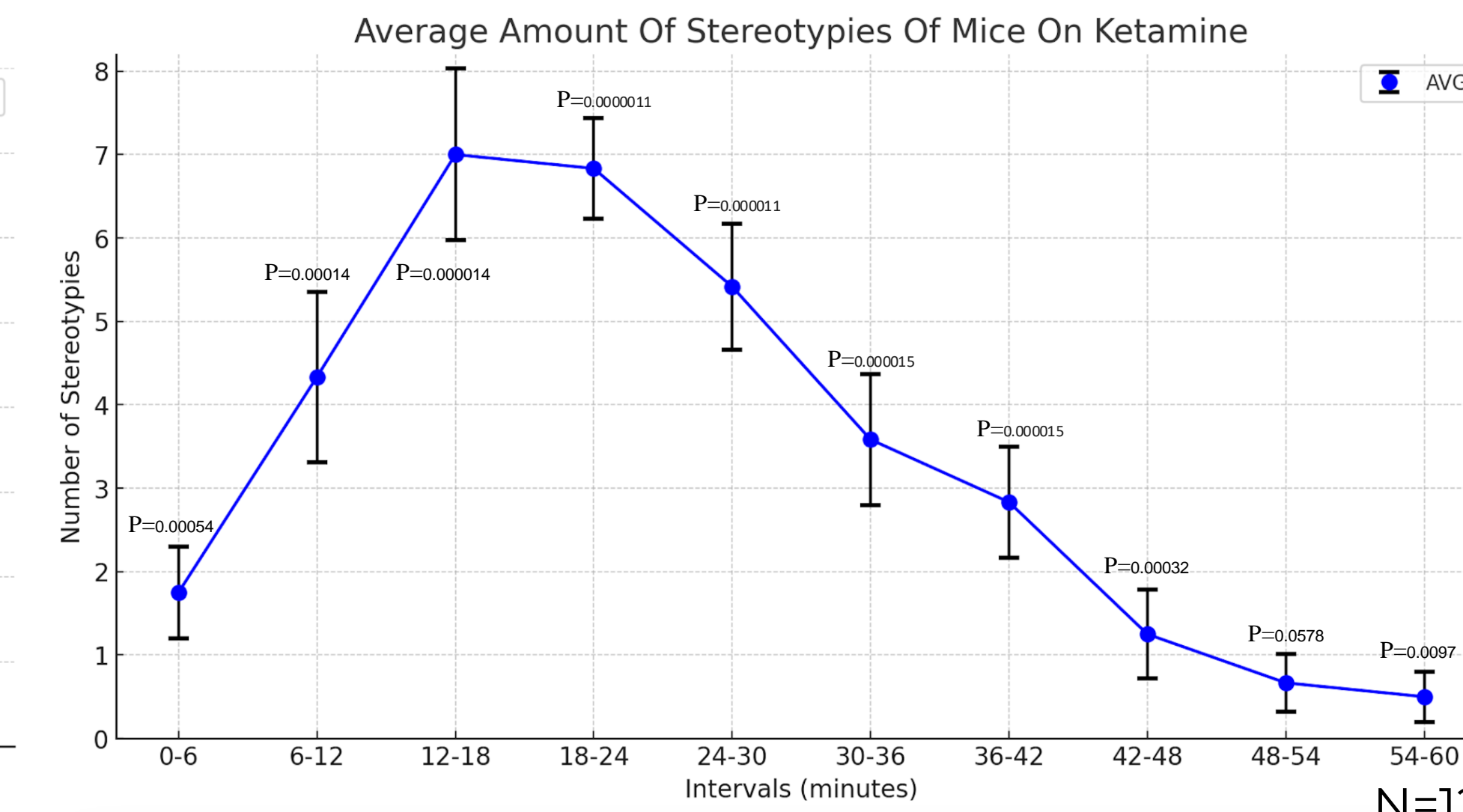
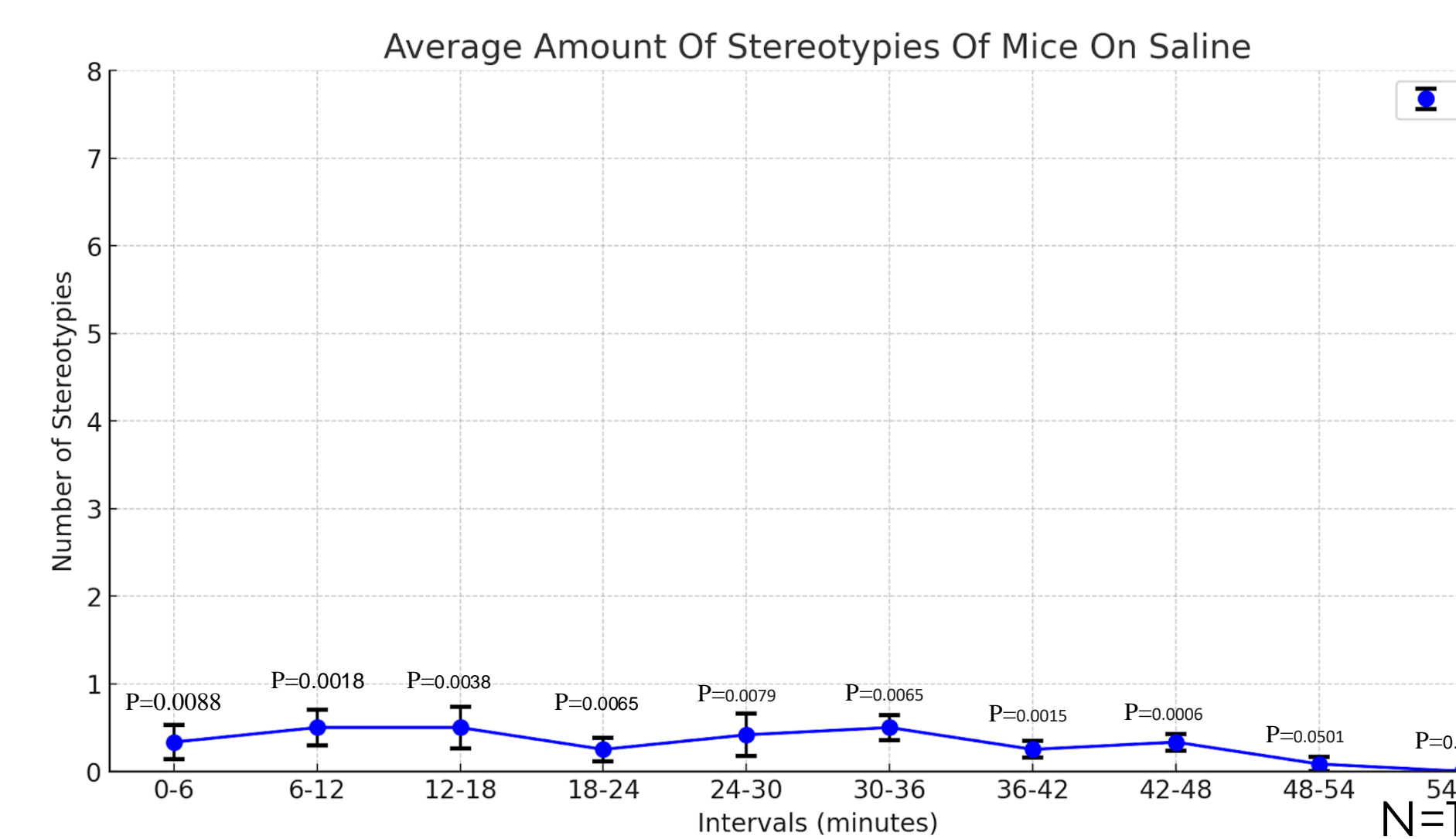
Methodology

- In this experiment, the following substances were used:
 - Saline(sodium chloride) - functions as control group
 - Ketamine (non combative NMDA antagonist, causes lower dopaminergic activity in frontal cognitive areas)
 - Deferiprone (DFP) (iron chelator, prevents accumulation of iron)
 - Haloperidol (Hal) (first generation antipsychotic, mostly D-2 antagonist)
- C57BL/6J OLA HSD (widely used as a standard inbred mouse strain in many fields of life science research) male mice aged 10-12 weeks were given standard diet and care under a reverse light cycle so the behavioral experiment could be performed during the mice's active phase.⁵
- The "active phase" refers to the time when mice are naturally most active, which usually happens during the dark part of their light cycle since they are nocturnal. By using a reverse light cycle, we ensure that the mice's active phase occurs during the daytime, making it easier to conduct behavioral experiments when the mice are most alert and active.⁶
- Mice were placed into the corner of a 50x50x30 cm (LxWxH) arena for a habituation period of 10 minutes.
- The mice were divided into 6 groups and injected with the following:

Acute Psychostimulant	Chelator	Antipsychotic
Vehicle (95% saline+5%DMSO)	saline	saline
Ketamine 50mg/kg	saline	saline
Vehicle (95% saline+5%DMSO)	DFP 100mg/kg	saline
Ketamine 50mg/kg	DFP 100mg/kg	saline
Ketamine 50mg/kg	saline	Hal 0.1 mg/kg
Ketamine 50mg/kg	DFP 100mg/kg	Hal 0.1 mg/kg

- The trial was recorded above with a digital camera for 60 minutes. In the videos, researchers were blinded and recorded circling in 6 minute increments..
- There were 2 researchers who recorded the data and analyzed the videos of the mice.
- For each interval in each case, the T-test was taken and the p-value was analyzed to determine the significance of the observed data.

Results



Conclusion

- Ketamine increases stereotypies more than tenfold
- Mice on Ketamine who were given DFP had a significant decrease in average number of stereotypies compared to those given just Ketamine
- Mice on Ketamine who were given Hal had a slight decrease in average number of stereotypies compared to those given just Ketamine
- The combination of Hal+DFP was slightly more effective than just DFP
- The combination of Hal+DFP showed the largest decrease in stereotypic behavior compared to just ketamine.
- Therefore, the two-hit model of Hal+DFP is the most effective at treating schizophrenic symptoms.
- Almost all of the data is considered to be significant as most data points had a p-value under 0.05
- The only data points that were not significant were within 0.01 of 0.05.

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Acknowledgements

Amit Lotan
Avigail Zucker
Atira Zeitchik (Summer in Jerusalem Internship Coordinator)