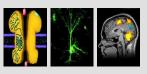


## IGSN/RDN CONFERENCE



## CHARACTERIZATION AND RESCUE OF NEURONAL DYSFUNCTION

**April 25<sup>th</sup> - 26<sup>th</sup>, 2023** 

Session 2 Mechanistic insights into psychiatric and affective disorders

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## Ketamine exerts its sustained antidepressant effects via cell-type specific regulation of Kcnq2

A single sub-anesthetic dose of ketamine can produce a rapid and sustained antidepressant response, yet the molecular mechanisms responsible for these effects remain unclear. Here, we identified cell-type-specific transcriptional signatures associated with a sustained ketamine response in mice. Most interestingly, we identified the Kcnq2 gene as an important downstream regulator of ketamine action in glutamatergic neurons of the ventral hippocampus. We validated these findings through a series of complementary molecular, electrophysiological, cellular, pharmacological, behavioural and functional experiments. We demonstrate that the adjunctive treatment of ketamine with retigabine, a KCNQ activator, augments antidepressant-like effects in mice. Intriguingly, these effects are ketamine-specific, as they do not modulate a response to classical antidepressants, such as escitalopram. These findings constitute a significant advancement to our understanding of the mechanisms underlying the sustained antidepressant effects of ketamine, with important clinical implications.



