The Procognitive Effects of Ketamine – An analysis of the Ketamine for reduction of Alcoholic Relapse (KARE) trial memory data

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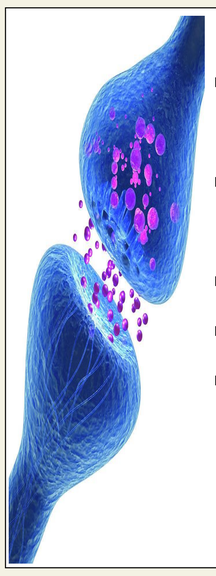


Introduction

- Ketamine is a non-competitive, high-affinity antagonist of the N-methyl-D-aspartate (NMDA) type glutamate receptor which for many years has been used for induction and maintenance of anaesthesia (Green & Li, 2000).
- This agent has been shown to have antidepressant effects in patients with major depressive disorder (MDD) by increasing synaptic connectivity in hippocampal and cortical neurons (Murrough et al., 2013) and also to reduce suicidality (Murrough et al., 2015).
- Studies of the effects of ketamine in MDD have observed a reversal of neuronal degeneration (Li et al., 2010).
- Ketamine also has acute effects on the maturation of new neurons and synaptogenesis (Soumier, Carter, Schoenfeld, & Cameron, 2016).
- Repeated doses of ketamine in a therapeutic context were found to be beneficial for attention, executive function, working and visual memory (Shiroma et al., 2014; Basso et al., 2020).

Hypothesis: *participants randomised to receive three weekly ketamine infusions would show improvements in memory performance, as measured by a mnemonic similarity and digit span task, relative to those in the placebo condition.*

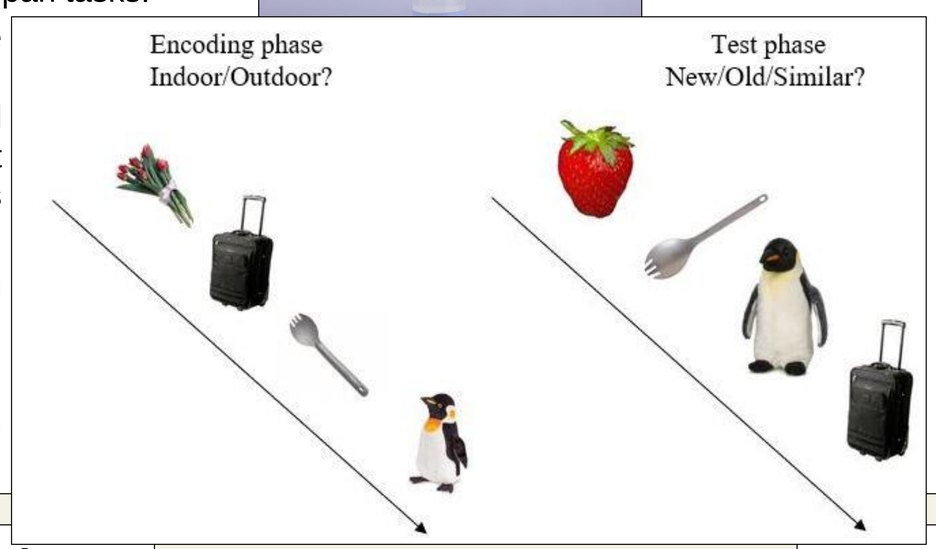
OUR RESEARCH

Method

Participants: 96 individuals with a diagnosis of moderate or severe alcohol disorder within the last 12 months (abstinent at the point of entering the trial).

Design and procedure: Mixed within and between-participants design.

- Ten testing sessions including the initial baseline visit.
- Two memory tasks: mnemonic similarity test (MST; Kirwan & Stark, 2007) and WAIS-IV forwards and backwards digit span tasks.
- Participants completed the MST twice every time they came to the lab for an infusion (**session 2, 4, and 6**), at **session 8**, which was the final hospital visit and did not include an infusion, as well as at the two follow-up sessions at three and six months (**sessions 9 and 10**).
- They completed the MST pre- and post-infusion (approximately four hours before and after), and once during each of the other sessions.
- The digit span tests were completed once during **sessions 2, 8, 9, and 10**.



Mnemonic Similarity Task Design

- **Phase 1 (encoding)**: participants were presented with a sequence of 128 pictures of common objects and had to decide whether each picture depicted an outdoor or indoor object.
- **Phase 2 (test)**: participants took a recognition test in which they categorised 192 items as “New” (64 items), “Old” (64 items), or “Similar” (64 items).

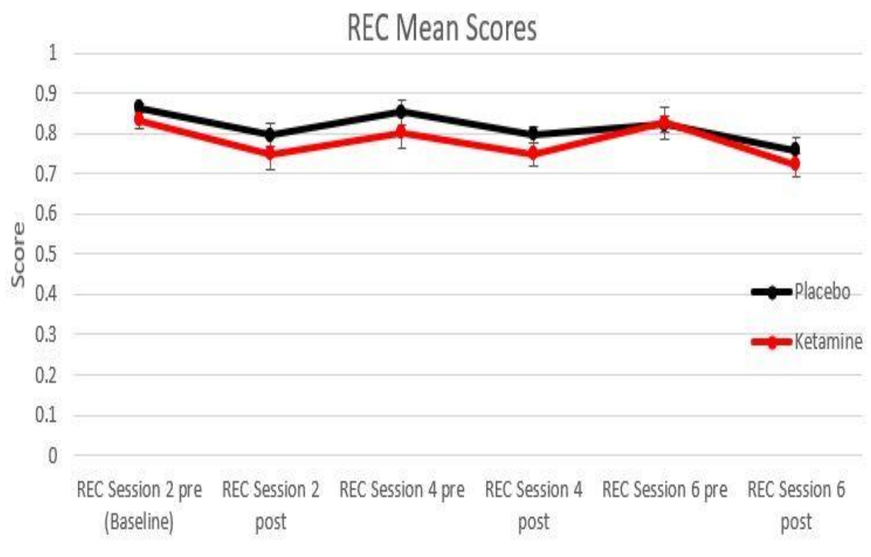
➡ 1/3 of the images in phase 2 were the same as those in phase 1, 1/3 were new images, and 1/3 were similar to the those seen during phase 1, but not identical.

- We computed two scores:
- Lure Discrimination Index (**LDI**) = the rate of “similar” responses given to foils - the rate of “similar” responses given to lures.
- Recognition Index (**REC**) = the rate of “old” responses given to foils - the rate of “old” responses given to targets.

Results - Infusion MST data analysis

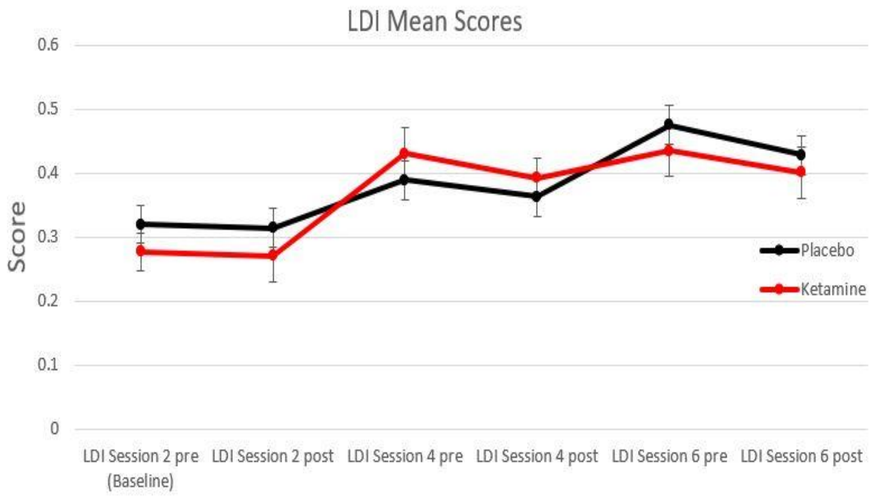
Recognition test

- Highly significant main effect of Time $F(1, 66) = 43.55$, $p < .001$, $\eta 2p = .398$.
- No other significant main effects or interactions.



Lure Index of Discriminability

- Highly significant main effect of Session $F(2,128) = 36.60$, $p < .001$, $\eta 2p = .364$, with it showing a significant linear contrast $F(1, 64) = 64.34$, $p < .001$, $\eta 2p = .501$.
- Session x Drug interaction approached significance, with $F(2,128) = 3.04$, $p = .053$, $\eta 2p = .045$.
- Main effect of Time approached significance $F(1,64) = 3.81$, $p = .055$, $\eta 2p = .056$.
- No other significant main effects or interactions.



DISCUSSION and CONCLUSION

- Our main hypothesis that ketamine infusions have a procognitive effect, as measured by the MST and digit span performance was not supported.
- We found no differences between the ketamine and placebo group, either acutely or at follow-up.
- While we did find that participants performed worse on the recognition component, and a trend towards a significant decrease in performance on the LDI component of the MST, we also found this effect for the participants who received placebo infusions suggesting that the impairment was not specific to ketamine.
- We did not find any deleterious effects associated with repeated ketamine infusions on cognition in contrast with other research findings (Morgan et al., 2004).

References

Basso, L., Bönke, L., Aust, S., Gärtner, M., Heuser-Collier, I., Otte, C., ... & Grimm, S. (2020). Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. Journal of Psychiatric Research.

Green, S. M., & Li, J. (2000). Ketamine in Adults What Emergency Physicians Need to Know about Patient Selection and Emergence Reactions. *Academic emergency medicine*, 7(3), 278-281.

Kirwan, C. B., & Stark, C. E. (2007). Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. Learning & Memory, 14(9), 625-633.

Li, N., Lee, B., Liu, R. J., Banasr, M., Dwyer, J. M., Iwata, M., ... & Duman, R. S. (2010). mTOR- dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, 329(5994), 959-964.

Morgan, C. J., Riccelli, M., Maitland, C. H., & Curran, H. V. (2004). Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug and alcohol dependence*, 75(3), 301-308.

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., ... & Charney, D. S. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *American Journal of Psychiatry*, 170(10), 1134-1142.

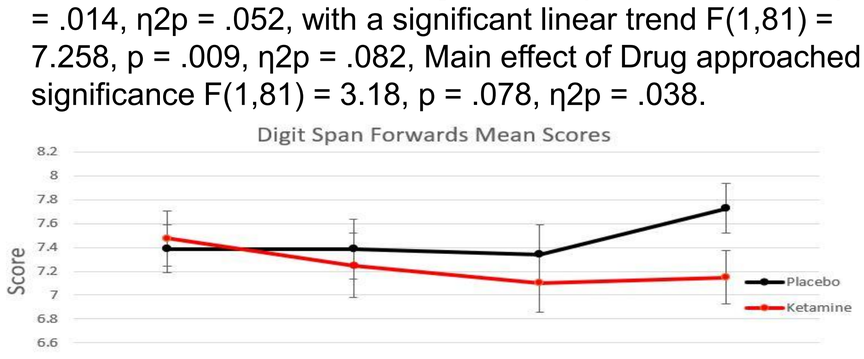
Murrough, J. W., Soleimani, L., DeWilde, K. E., Collins, K. A., Lapidus, K. A., Iacoviello, B. M., ... & Price, R. B. (2015). Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychological medicine*, 45(16), 3571-3580.

Soumier, A., Carter, R. M., Schoenfeld, T. J., & Cameron, H. A. (2016). New hippocampal neurons mature rapidly in response to ketamine but are not required for its acute antidepressant effects on neophagia in rats. *Eneuro*, 3(2).

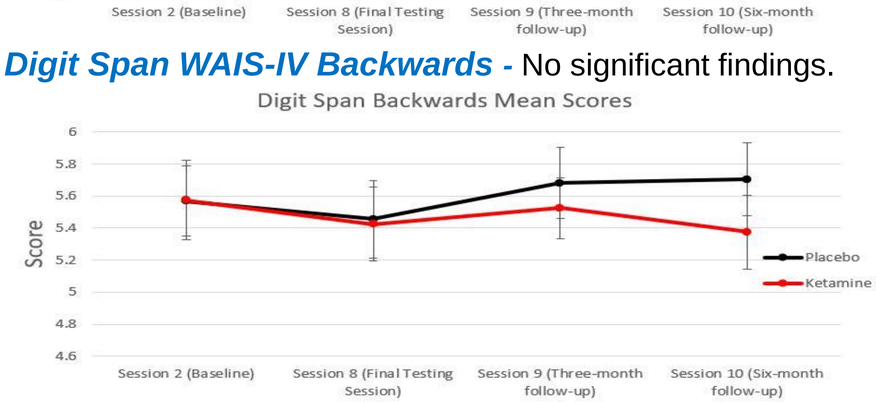
Shiroma, P. R., Albott, C. S., Johns, B., Thuras, P., Wels, J., & Lim, K. O. (2014). Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. *International Journal of Neuropsychopharmacology*, 17(11), 1805-1813.

Results - Follow-up data analysis

Recognition test - No significant findings.



Lure Index of Discriminability - No significant findings.



Digit Span WAIS-IV Forwards

- Main effect of Session was significant $F(1.96,162) = 4.41$, $p = .014$, $\eta 2p = .052$, with a significant linear trend $F(1,81) = 7.258$, $p = .009$, $\eta 2p = .082$, Main effect of Drug approached significance $F(1,81) = 3.18$, $p = .078$, $\eta 2p = .038$.

Digit Span WAIS-IV Backwards - No significant findings.