Effects of Repeated Intravenous Esketamine Administration on Affective Biases

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Methodological Question

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INTRODUCTION

The current study aimed to investigate the effects of acute and repeated intravenous infusions of esketamine on several measures, including those related to emotional processing, in TRD patients.

An emerging efficacious and rapidly acting treatment option for TRD is esketamine. However, the mechanism of action (MOA) of esketamine that leads to improvements in mood is not well understood.

Experimental medicine approaches can help elucidate the MOA of esketamine and other rapidly acting antidepressants by providing objective measurements of changes in brain function induced by treatment.

METHODS

- 18 participants were recruited through in-patient visits at the University Hospital Frankfurt, and 11 of them received at least six infusions (see Table 1).
- Participants received infusions on an ad-hoc basis according to their individual needs and the clinicians' judgement.

Table 1: Participants

Participants	N	Age†	Sex (female)	No. of infusions†
All	18	44 (25 - 53)	9	7 (1 - 31)
Analysed§	11	45 (25 - 53)	6	13 (6 - 31)

§Data from participants with six or more infusions was analysed
†Median (min – max)

Assessments

- Data from the Facial Expression Recognition Task (FERT) and the FeelZoom and MoodZoom questionnaires were collected immediately pre-infusion and 4 hours post-infusion.
- In the FERT, participants were serially presented faces which express different emotions (happiness, sadness, anger, fear, disgust, surprise, neutral) at varying intensities and they responded by identifying the expressed emotion (see Figure 1).
- Additional data from FeelZoom and MoodZoom and from other assessments (DSST, short-FERT, QIDS-SR, GAD-7, WSAS, CGI-S, and CGI-I) were also collected at various time points.

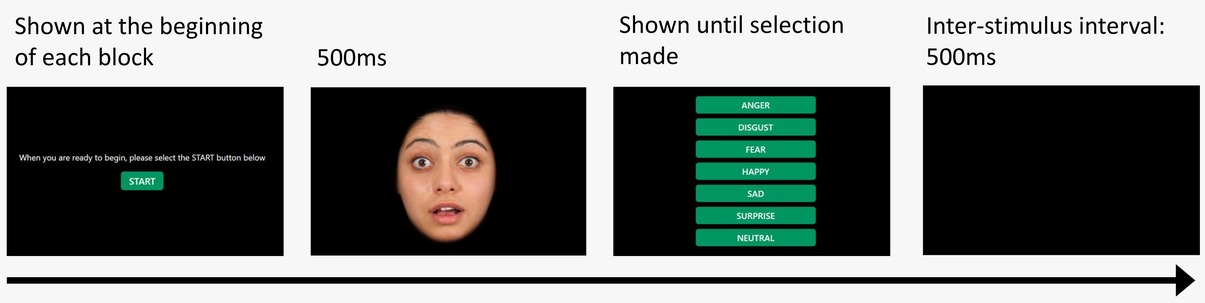

Figure 1. FERT block structure.
Participants performed 250 trials across 4 blocks.

Statistical analysis

- To test the effects of esketamine on the infusion-locked assessments (FERT, FeelZoom, MoodZoom, DSST, and short-FERT), paired t-tests were conducted between the scores at baseline (pre-infusion on the day of the first infusion) and after five infusions (pre-infusion on the day of the sixth infusion).
- Due to the exploratory nature of this study, no corrections for multiple comparisons were performed.

RESULTS

Response

- 8 out of 11 participants (72.7%) that received at least six infusions responded to treatment (indicated by CGI-I score of ≤2 measured on the day of the sixth infusion).

Modulation of affective biases

- Esketamine infusions were observed to significantly reduce FERT accuracy at recognising low intensity (≤ 30%) sad emotions ($t(9) = -3.46, p = .007$) and misclassifying other emotions at low intensities as sad ($t(9) = 2.48, p = .035$), suggesting a reduction in the bias towards sadness.
- Similarly, there were significant decreases in feelings of sadness ($t(10) = -2.95, p = .014$), assessed by FeelZoom, and irritability ($t(10) = -4.49, p = .001$), assessed by MoodZoom.

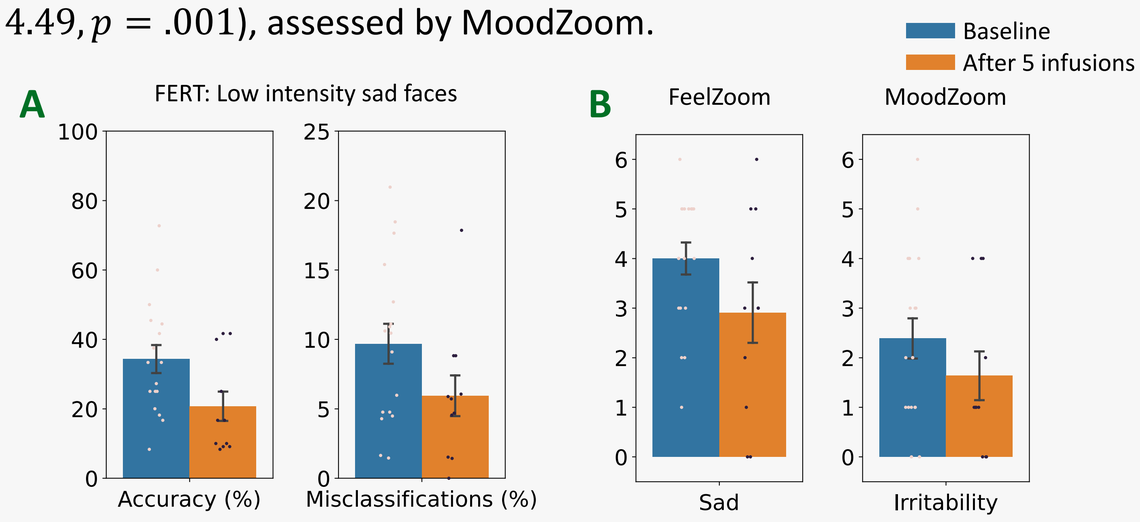

Figure 2. (A) Accuracies and misclassifications of FERT low intensity faces and (B) FeelZoom Sad and MoodZoom Irritability scores for assessments performed at baseline and after five infusions. Errors bars indicate standard error of the mean.

Pro-cognitive effects

- On the Digit Symbol Substitution Test (DSST), a significant increase in the number of correct responses was observed ($t(9) = 5.11, p < .001$).
- Across all emotions, an improvement in FERT accuracies ($t(9) = 4.58, p = .001$) and a reduction in the misclassification rates ($t(9) = -4.58, p = .001$) was observed.

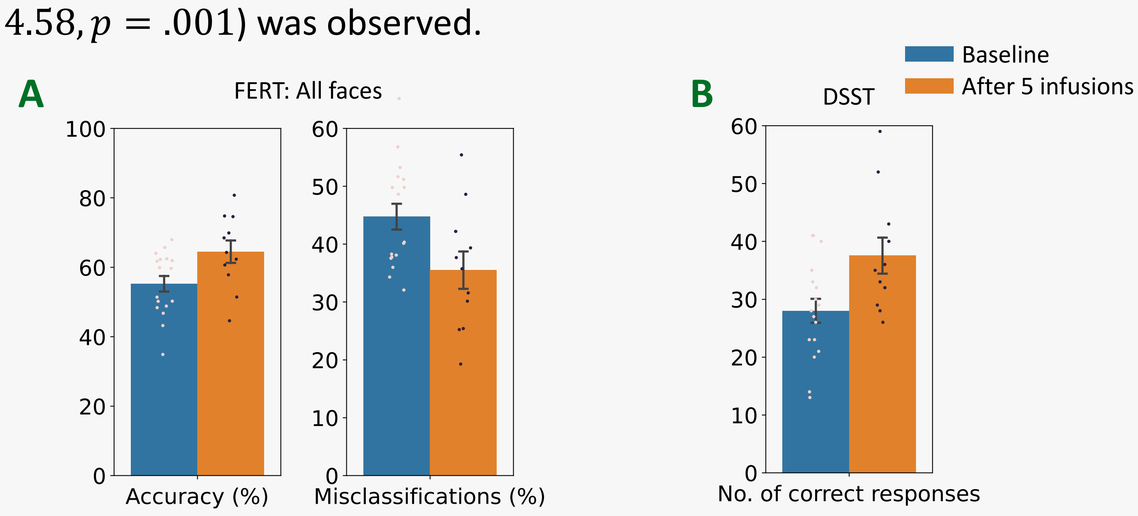

Figure 3. (A) Accuracies and misclassifications of all FERT faces and (B) number of correct DSST responses for assessments performed at baseline and after five infusions. Error bars indicate standard error of the mean.

CONCLUSIONS

- We have replicated previous findings that esketamine can improve subjective and objective measures of depressive symptoms.
- The decrease in both the accuracy of identifying the emotion in low intensity sad faces and the misclassification of other low intensity emotions as sad, along with the reduction in the FeelZoom and MoodZoom sub-scores, suggests that esketamine reduces the perception and subjective feelings of sadness.
- The increase in DSST performance as well as the increase in FERT accuracies and decrease in misclassification rates suggests that esketamine may have pro-cognitive effects.
- Overall, these results mirror findings in the wider literature that antidepressants elicit changes in cognitive processing which may underly the improvements in mood.

Disclosure statement: AM and GRD are full-time employees of P1vital Ltd, and AF was a full-time employee of P1vital Ltd. while working on this study. GRD is an owner and shareholder of P1vital Ltd. and P1vital Products Ltd. AR is on the speaker panel of Janssen, Medice, Servier, neuraxpharm and Shire/Takeda; also, he serves on Advisory boards for Janssen, SAGE, Medice, Cyclerion, Boehringer Ingelheim and Shire/Takeda. CRL received speaker honoraria from and serves on Advisory boards of Janssen and LivaNova. All other authors do not report conflicts of interest.