Behavioural and neurobiological evidence for low-dose ketamine as a treatment for chronic suicidality

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Background

- Suicide is an urgent public health concern, estimated as the cause of more than 1 million deaths per year, globally
- Ketamine, a non-competitive NMDA receptor antagonist, has been shown to exert rapid anti-suicidal action by enhancing excitatory neurotransmission and increasing protein synthesis
- Behavioural and neuroimaging data provide evidence for transient (minutes – hours) and sustained (days – weeks) effects in chronically suicidal patients
- Few studies have examined low-dose ketamine's efficacy a) across a sustained treatment period, b) using a combination of clinical scales and neurobiological/neurophysiological measures

The Oral Ketamine Trial for Suicidality (OKTOS)

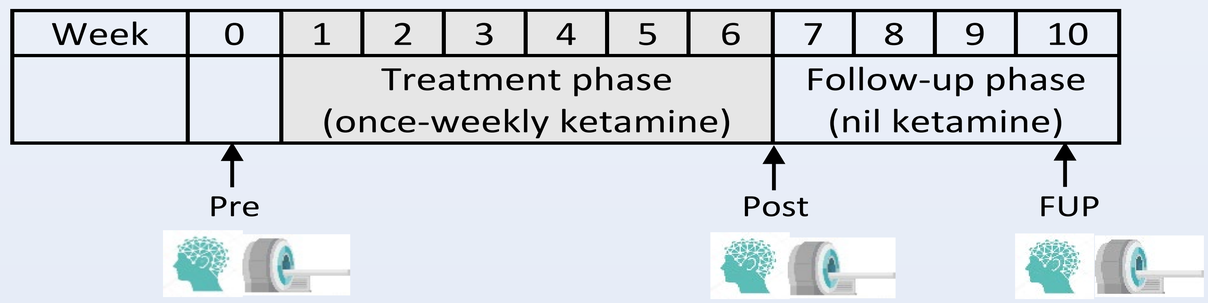
An open label, dose ranging, clinical trial exploring ketamine as a treatment for chronic suicidality

Participants: 32 adults (aged 22–72 years; 53% female) with chronic suicidality

Intervention: once-weekly doses of low-dose oral ketamine titrated up (0.5 mg/kg - 3.0 mg/kg) across 6 weeks

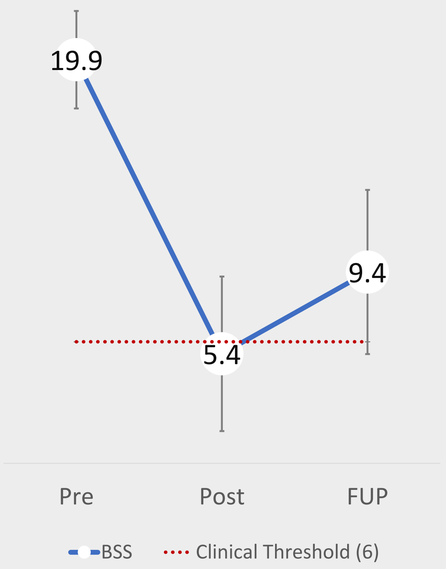
Primary outcome: Beck Scale for Suicide Ideation (BSS). Secondary measures investigated change in depression, wellbeing, social-occupational functioning

Exploratory neurobiological measures: MRI and EEG



Key Clinical Results

- Mean BSS scores significantly reduced from a high level of suicidal ideation at the pre-ketamine timepoint (week 0) to below the clinical threshold at the post-ketamine (week 6) timepoint.
- 69% of participants achieved significant clinical improvement from pre-ketamine (week 0) to post-ketamine (week 6) timepoint.
- 50% of participants maintained a significant clinical improvement from post-ketamine timepoint (week 6) to follow-up (week 10).

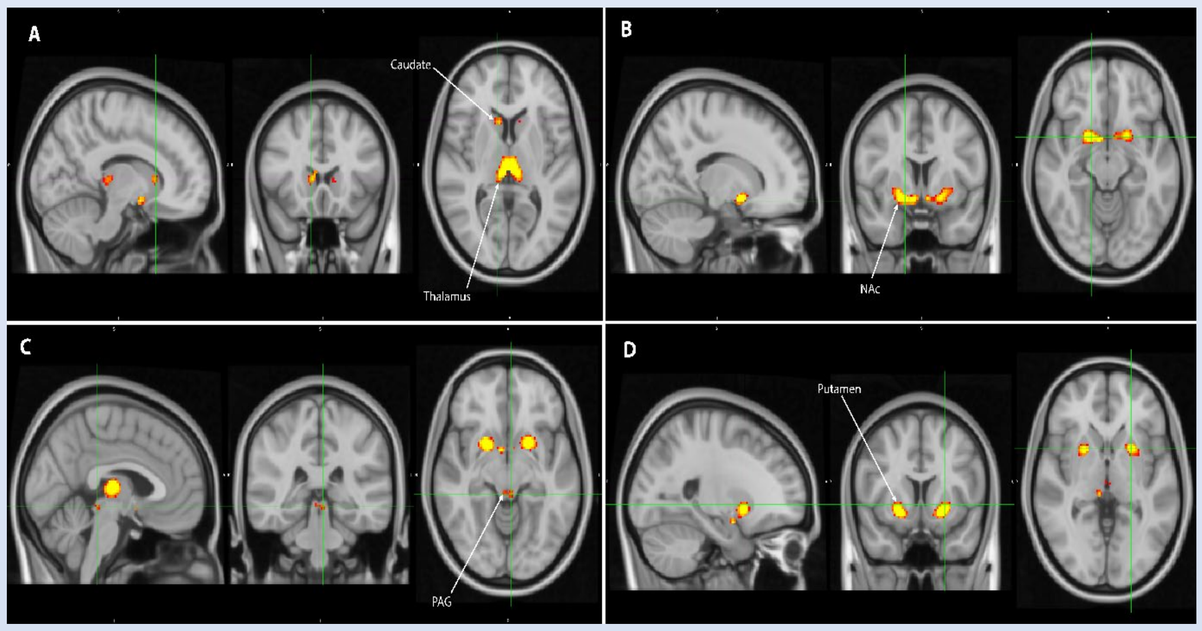


Mean scores (± SD) for Secondary Outcomes: Depression, Wellbeing, Social-occupational Function

	Pre-Ketamine (n=30)	Follow-up (n=30)	Sig.test (*p*), Effect size (*d*)
MADRS total	38.6 ± 7.7	15.9 ± 11.8	*F*(1,29)=84 [0.000], *d*=1.67
SOFAS	57.3 ± 9.1	69.3 ± 19.3	*F*(1,29)=12.9 [0.001], *d*=-0.62
WHO-5	17.6 ± 17.2	33.6 ± 29.4	*F*(1,29)=11.6 [0.002], *d*=-0.66

MADRS: Montgomery-Åsberg Depression Rating Scale, *SOFAS:* Social and Occupational Functioning Assessment Scale, *WHO-5:* World Health Organisation-Five Well-Being Index.

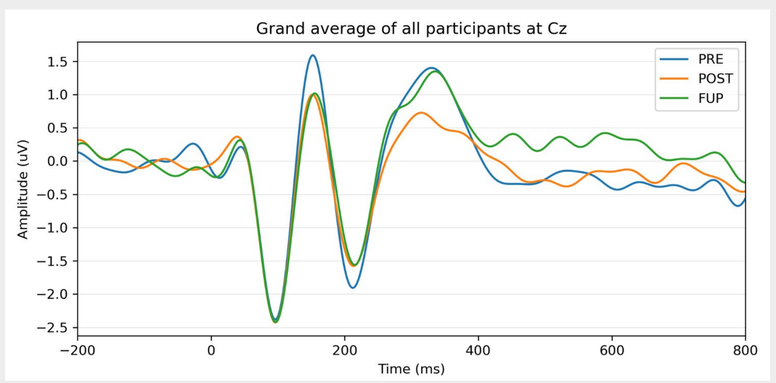
Key Neurobiological & Physiological Results

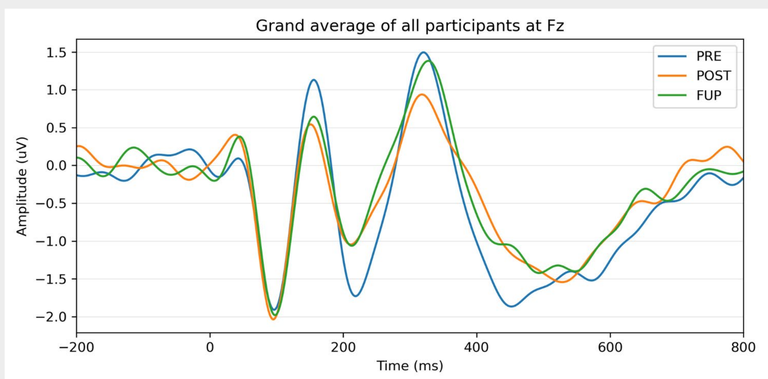


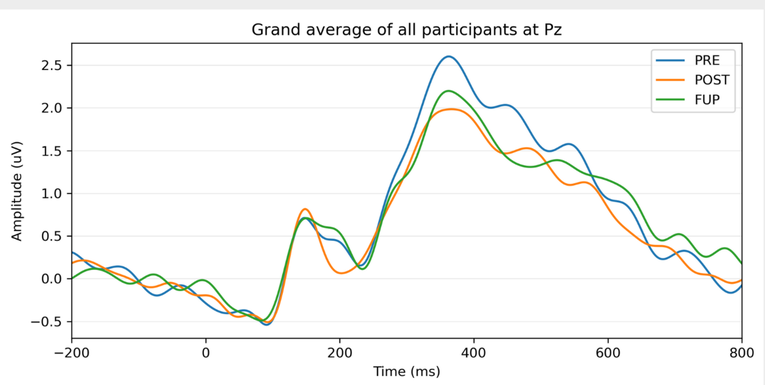
Voxel-Based Morphometry (VBM)

- VBM was used to investigate grey matter changes in chronically suicidal participants (N = 30, 16 female) from pre-ketamine (week 0) timepoint to post-treatment (week 6) timepoint
- Results found significantly increased grey matter in striato-limbic structures following 6 weeks ketamine administration.
- Specifically, the putamen, thalamus, caudate, nucleus accumbens, and the periaqueductal grey (PAG) all showed bilateral increases in grey matter following ketamine treatment
- Notably, no grey matter changes were found in cortical areas, including the prefrontal cortex or the anterior cingulate cortex – regions associated with suicide and suicidality

Preliminary ERP findings: P300 Auditory Oddball Task







We are currently conducting an analysis of ERP grand averages in an auditory oddball task (n = 30) to investigate changes in latency across pre-treatment (week 0), post-treatment (week 6) and follow-up (week 10) timepoints. We plan to run a bivariate correlation and hierarchical regression analysis. We hypothesise that a correlation will exist between ERP latency and clinical outcome measures of suicidality and depression.

Conclusion, Limitations, Future Directions

- 6 weeks of oral ketamine treatment in participants with chronic suicidality led to significant reduction in suicidal ideation.
- Significant increases in whole brain grey matter volume in key areas associated with suicidality were observed from pre-treatment to-post treatment
- As the OKTOS trial was open label and with small participant numbers, further studies are required in order to tease out the neurobiological mechanisms of clinical change.

Acknowledgments

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