

# Experiences of Awe Mediate Ketamine's Antidepressant Effects: A Randomized Controlled Trial in Treatment-Resistant Depression

Julia Aepfelbacher, Ben Panny, Rebecca Price  
University of Pittsburgh, Department of Psychiatry and Psychology

## BACKGROUND

- Depression is a leading cause of morbidity and mortality worldwide
- NMDA-receptor antagonist Ketamine provides rapid and short-lived anti-depressant effects
- It is important to consider psychological mechanisms that may contribute to its therapeutic efficacy, including mystical or psychedelic experiences
- Understanding ketamine's psychedelic properties may help to inform development of novel approaches that prolong and/or heighten its effects

## METHODS

- 116 participants were randomized in a 2:1 ratio to receive ketamine (0.5mg/kg over 40 minutes, n= 77) while matched controls (n=39) received saline placebo
- All participants completed a validated measure of awe (the AWE-scale) at 40 minutes post-infusion

### 6 Subdomains:

Check the one response to each item that best describes your experience SINCE THE INFUSION.

	Strongly Disagree	Moderately Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Moderately Agree	Strongly Agree
Physical, connectedness, vastness, self-loss, accommodation, time distortion	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I've sensed things momentarily slow down.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I've felt that my sense of self has been diminished.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I've had the sense of being connected to everything.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I've felt that I've been in the presence of something grand.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I've felt my jaw drop.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

- Mean AWE-scores (total and sub-domains) were tested as potential mediators of clinical depression outcomes, measured by % improvement in Montgomery-Asberg Depression Rating Scale (MADRS) at five time points post-infusion (24 hour, 5 days, 12 days, 21 days, 30 days)
- General dissociative side effects (Clinician-Administered Dissociative Symptoms Scale; CADSS scores) were tested in parallel mediation models

## RESULTS

Figure 1: 40 min AWE by Group

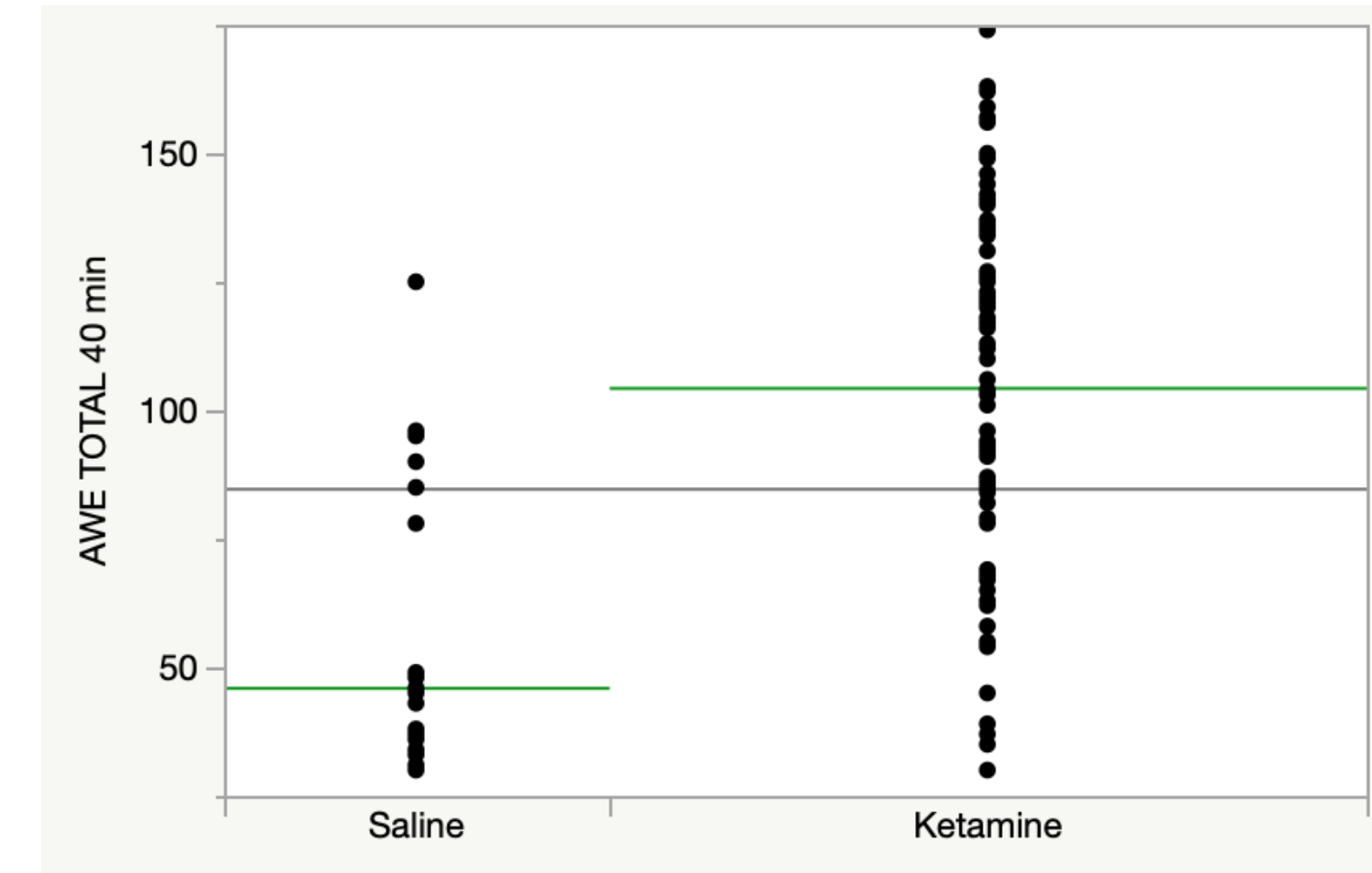
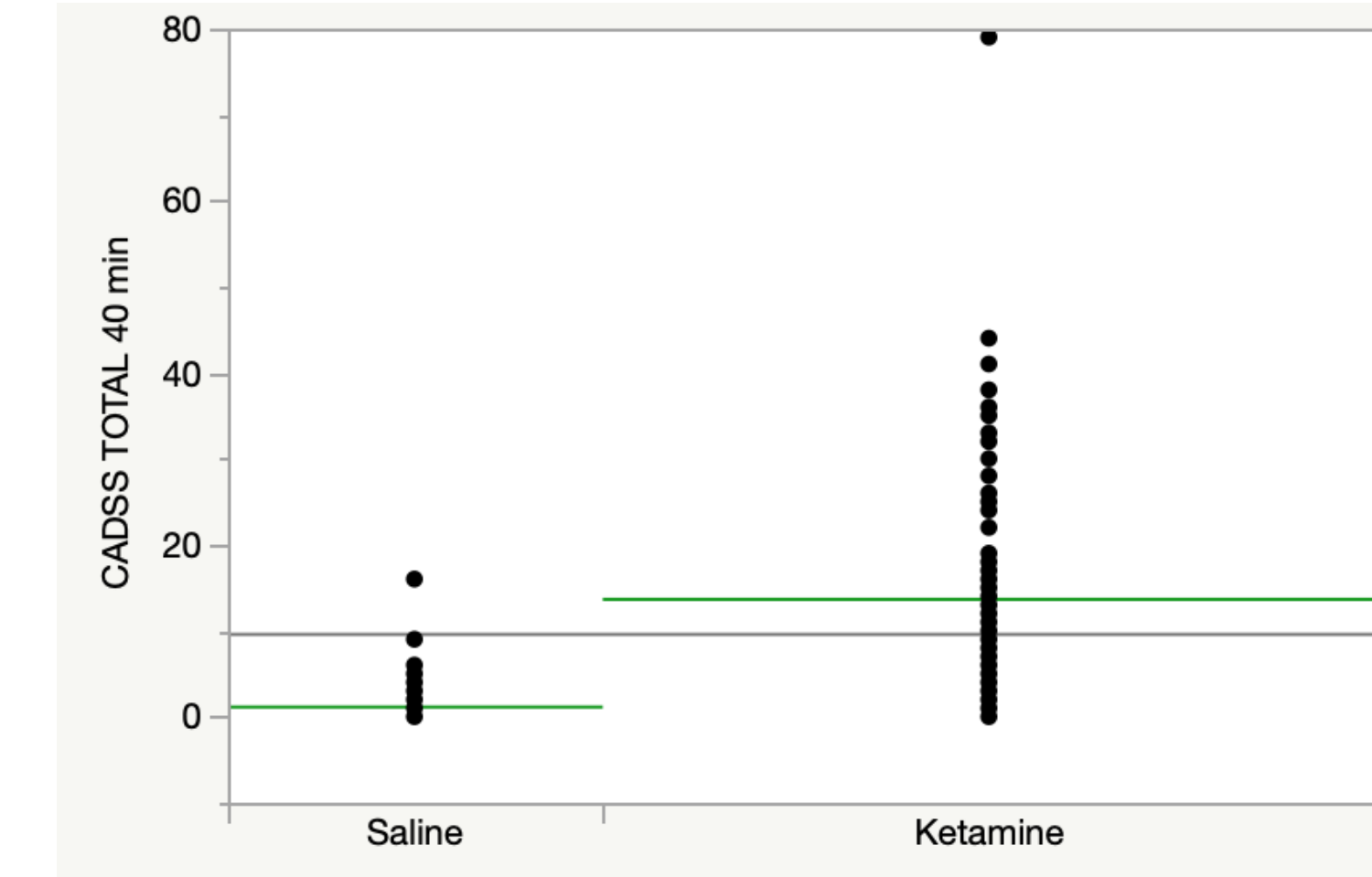
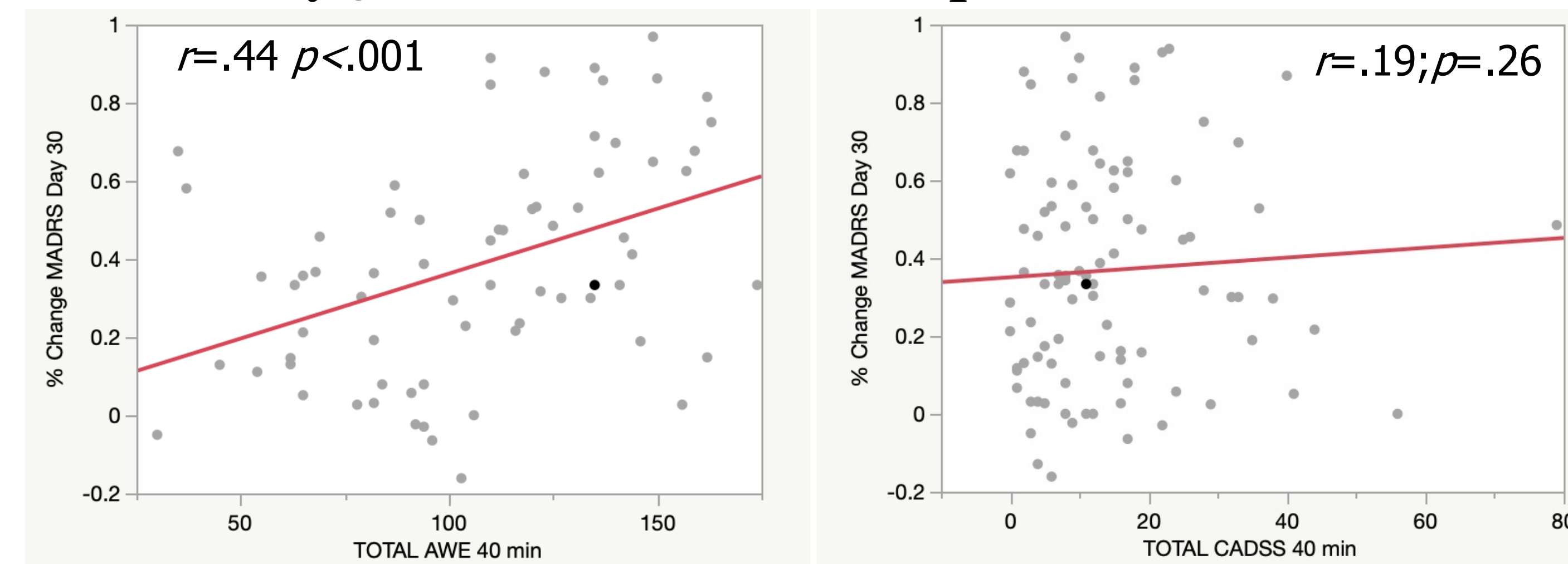


Figure 2: 40 min CADSS by Group



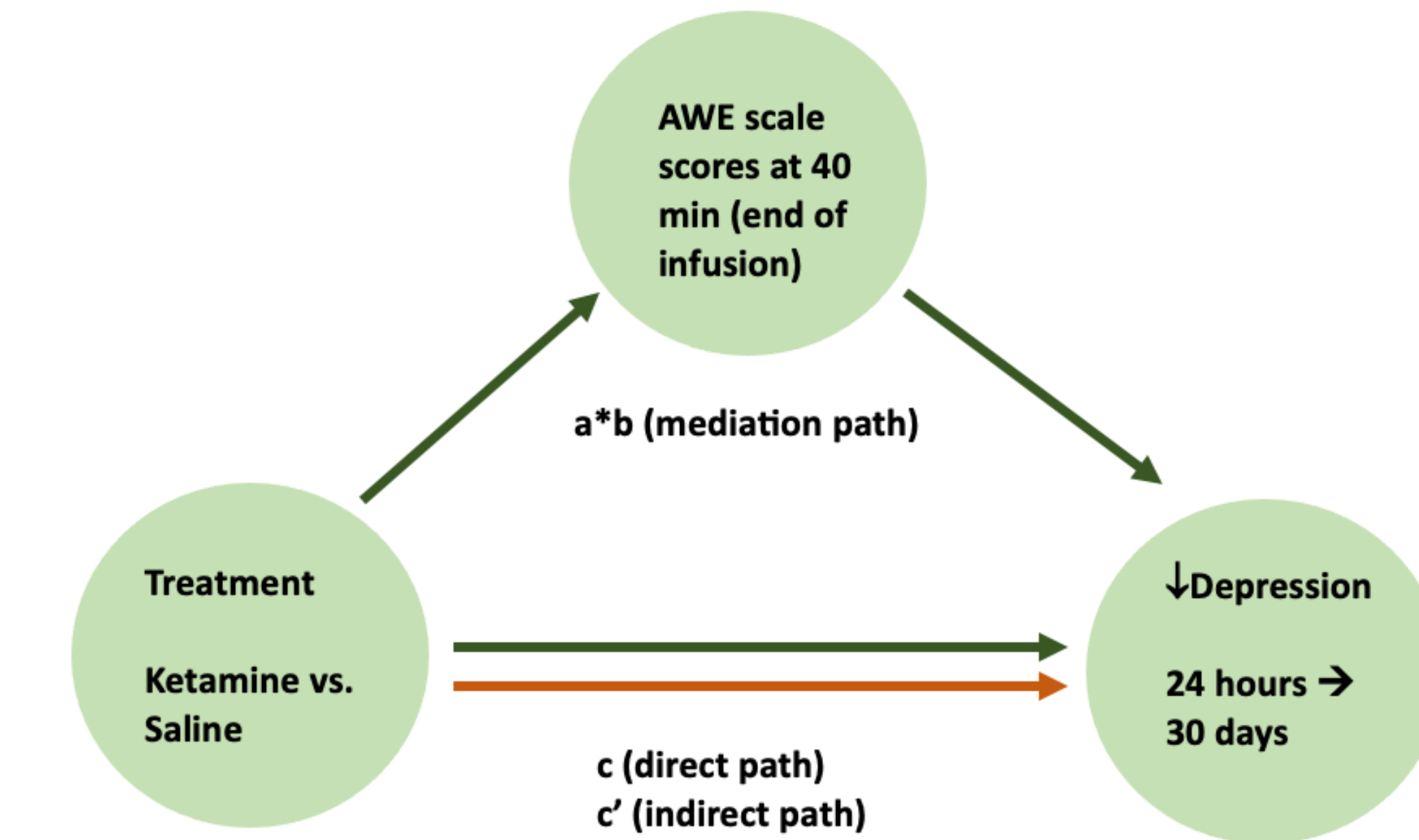
- Total AWE score (and each sub-component) & total CADSS differed significantly by treatment group ( $p < 0.0001$ ) at 40 minutes
- In accordance with previous studies, there was a significant improvement in MADRS % change in the treatment group compared to controls at 24 hours ( $p = 0.0001$ ) and 5 days ( $p = 0.0001$ ) post infusion

Figure 4. Comparison of AWE and CADSS in % improvement in MADRS day 30 in the Ketamine Group



- Significant relationship between AWE and % improvement in MADRS day 30
- No association between general dissociative-perceptual side effects and antidepressant effects

Figure 4: Mediation Pathway



- At all 5 timepoints the total AWE-scores significantly mediated the relationship between ketamine and MADRS (a\*b mediation effect:  $p = 0.0028$ ,  $p = 0.0154$ ,  $p = 0.0027$ ,  $p = 0.0018$ ,  $p = 0.0052$ , respectively).
- By contrast, CADSS scores did not mediate outcomes at any timepoint

## CONCLUSIONS

- Ketamine infusion strongly induced heightened feelings of awe
- These experiences significantly mediated depression outcomes until at least 30 days post-infusion while general dissociative side effects did not
- The specific awe-inspiring properties of ketamine may contribute to its anti-depressant effects
- Further research is needed to elucidate the role of mindfulness and other practices that support an experience of 'awe' in the setting of ketamine infusion

Reference to Primary Paper:

