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PharmacoMRI and cognitive effects of the low-trapping NMDA channel blocker AZD6765 compared with ketamine in untreated major depressive disorder

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Introduction

- Subgenual cingulate (SGC) overactivity in depression is reversed by successful drug treatment[1]
- SGC activation induced by emotional faces is also diminished by antidepressants[2]
- Intravenous (IV) ketamine (NMDA antagonist) and IV AZD6765 (NMDA channel blocker) both show evidence of antidepressant efficacy in patients
- IV ketamine bolus caused immediate SGC deactivation in healthy volunteers[3]

Aim

- To investigate effects of AZD6765 and ketamine given by steady infusion on neural activity in the SGC and its relationship with subsequent change in depressive symptoms and emotion processing using pharmaco- and functional magnetic resonance imaging (phMRI, fMRI)

Methods

Subjects

- Sixty treatment-naïve males or females aged 18 to 45 years with major depressive disorder

Treatments

- On Day 1 subjects were assigned to 1 of 3 groups and received a single 40 mL (IV) infusion over 45 min of either:

  (i) Placebo (0.9% saline); (ii) Ketamine 0.5 mg/kg; (iii) AZD6765 100 mg (total dose)
- Day 1 phMRI scanning (75 min)

  (i) Structural brain scan (10 min); (ii) Arterial spin labelling (ASL) quantitative regional cerebral blood flow; (iii) IV drug/placebo-challenge phMRI scan (45 min); (iv) Infusions were started 15 min into the phMRI scan and second ASL scan followed the phMRI scan
- Day 2 emotion processing fMRI

  (i) Facial expression processing; (ii) Emotional counting Stroop; (iii) Emotional encoding: Resting state
- Day 2 emotion processing task performance

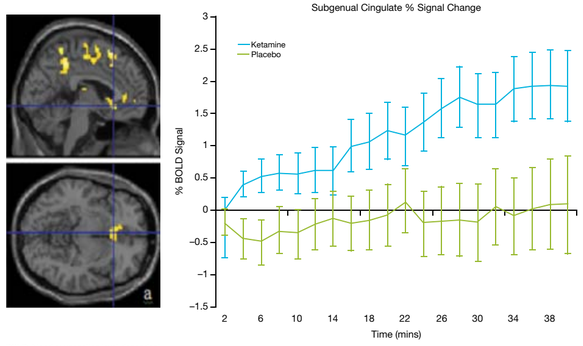
  (i) Emotional memory; (ii) Facial expression recognition; (iii) Dot probe
- Ratings Day 1 and Day 2

  (i) Montgomery-Åsberg Depression Rating Score (MADRS); (ii) Clinician Administered Dissociative Status Scale (CADSS); (iii) Bond-Lader Visual Analogue Scale (VAS); (iv) Beck Depression Inventory (BDI)

Results

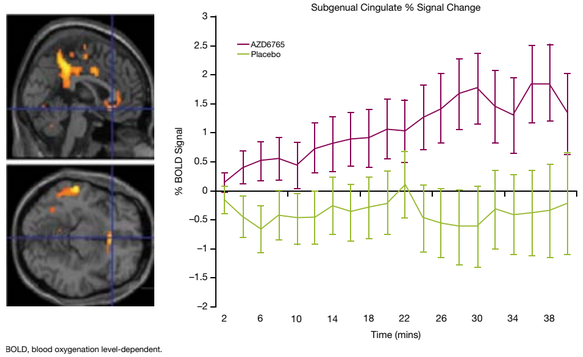
- Both AZD6765 and ketamine increased SGC BOLD signal responses; no decreases were seen in any brain region (**Figures 1** & **2**)
- The SGC responses correlated with improvement in MADRS scores 24 hours and 7 days post-infusion (**Figure 3**)
- Following administration of AZD6765, interviewer-rated psychotic and dissociative symptoms were minimal and not statistically significant
- By contrast ketamine induced a moderate statistically significant increase in dissociative symptoms that correlated with its effect on BOLD in the mid-cingulate and temporal cortex (**Table 1**)
- Both drugs reduced amygdala responses to fear and sadness in the emotional faces task 24 hours post-infusion (**Figure 4**)

Figure 1:
Ketamine minus placebo phMRI BOLD response in the SGC and percentage BOLD signal change over time in the SGC for ketamine and placebo.



BOLD, blood oxygenation level-dependent.

Figure 2:
AZD6765 minus placebo phMRI BOLD response in the SGC and percentage BOLD signal change over time in the SGC for AZD6765 and placebo.



BOLD, blood oxygenation level-dependent.

Figure 3:
Correlation between the % decrease in BDI scores and the % increase in phMRI BOLD response in the SGC following AZD6765 and ketamine compared to placebo after 1 week post-infusion (left). The location of the correlated cluster (right).

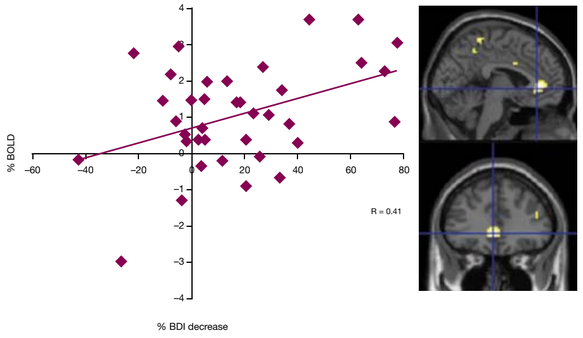


Figure 4:
AZD6765 significantly decreased activation of the right amygdala during covert presentations of fearful faces. The corresponding effect sizes are shown on the right.

Right Amygdala (24, −12, −12)

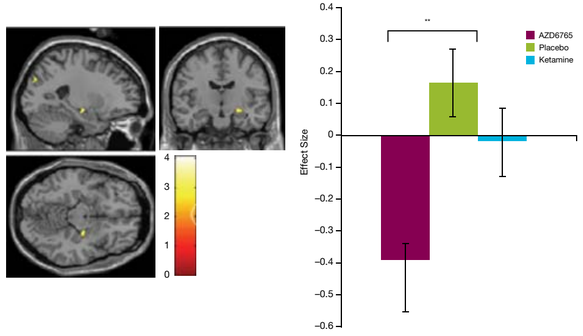


Table 1:
Ketamine-evoked dissociation correlated with phMRI activations

Brain regions	Brodmann Area	MNI Coordinates			Cluster Size (k)	Z Score	P unc whole brain
		X	Y	Z			
Mid-Cingulate Gyrus	BA24	12	14	37	27	4.13	$p<0.001$
Middle Temporal Gyrus	BA21	-57	8	7	74	4.01	$p<0.001$

CADSS scores after AZ6765 did not increase significantly or correlate with phMRI activations

Conclusions

- **Neither AZD6765 nor ketamine caused SGC deactivation in patients in this study**
- **These findings contrast with earlier findings in healthy volunteers in which ketamine induced deactivation of the SGC**
- **Activation of the SGC was seen following both drugs and this effect was associated with improvement in depressive symptoms 24 hours and 7 days post-infusion**
- **The results suggest that AZ6765 and ketamine both have antidepressant-like effects on emotion processing in the brain and that diminished NMDA glutamate neurotransmission in the SGC is a likely proximal mechanism**

References

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Disclosures

JFW Deakin, GM Goodwin, CA Harmer, CT Dourish, and GR Dawson are P1vital shareholders; DJ McCarthy and MA Smith are full-time employees of AstraZeneca

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