Ketamine modulates subgenual cingulate connectivity with the memory-related neural circuit – a mechanism of relevance to resistant depression?

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Background: Ketamine has been reported to have efficacy as an antidepressant in several studies of treatment-resistant depression. In this study, we investigate whether an acute administration of ketamine leads to reductions in the functional connectivity of subgenual anterior cingulate cortex (sgACC) with other brain regions. **Methods:** Thirteen right-handed healthy male subjects underwent a 15 minute resting state fMRI with an infusion of intravenous ketamine (target blood level=150ng/ml) starting at 5 minutes. We used a seed region centred on the sgACC and assessed functional connectivity before and during ketamine administration. **Results:** Before ketamine administration, positive coupling with the sgACC seed region was observed in a large cluster encompassing the anterior cingulate and negative coupling was observed with the anterior cerebellum. Following ketamine administration, sgACC activity became negatively correlated with the brainstem, hippocampus, parahippocampal gyrus, retrosplenial cortex, and thalamus. **Discussion:** Ketamine reduced functional connectivity of the sgACC with brain regions implicated in emotion, memory and mind wandering. It is possible the therapeutic effects of ketamine may be mediated via this mechanism, although further work is required to test this hypothesis.

1   **Ketamine modulates subgenual cingulate connectivity with the memory-related neural**

2   **circuit – a mechanism of relevance to resistant depression?**

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24 anterior cingulate cortex (sgACC) with other brain regions.

25 **Methods:** Thirteen right-handed healthy male subjects underwent a 15 minute resting state

26 fMRI with an infusion of intravenous ketamine (target blood level=150ng/ml) starting at 5

27 minutes. We used a seed region centred on the sgACC and assessed functional connectivity

28 before and during ketamine administration.

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30 observed in a large cluster encompassing the anterior cingulate and negative coupling was

31 observed with the anterior cerebellum. Following ketamine administration, sgACC activity

32 became negatively correlated with the brainstem, hippocampus, parahippocampal gyrus,

33 retrosplenial cortex, and thalamus.

34 **Discussion:** Ketamine reduced functional connectivity of the sgACC with brain regions

35 implicated in emotion, memory and mind wandering. It is possible the therapeutic effects of

36 ketamine may be mediated via this mechanism, although further work is required to test this

37 hypothesis.

39   **Introduction**

40   The subgenual anterior cingulate (sgACC), or Brodmann area 25, is a brain region that has been

41   implicated in the control and modulation of mood. Decreased mean sgACC gray matter volume

42   combined with metabolic hyperactivity and hyperconnectivity has been observed in patients with

43   major depressive disorder (MDD) (Davey et al. 2012; Drevets et al. 2008; Greicius et al. 2007;

44   Sundermann et al. 2014). With a growing number of studies demonstrating the association

45   between metabolic hyperactivity in this region and poor therapeutic response (Baeken et al.

46   2014; Konarski et al. 2009; Maletic & Raison 2009; Sheline et al. 2010; Taylor & Liberzon

47   2007), the activity of this region may prove important for attempts to predict treatment response

48   in patients (Siegle et al. 2012). Furthermore, given that connectivity between the sgACC and the

49   default mode network (particularly the ventromedial prefrontal cortex, and posterior cingulate

50   cortex) has been hypothesised to underlie depressive rumination (Hamilton et al. 2015),

51   therapeutic disruption of this connectivity might also be a potential target for novel

52   antidepressant action.

53

54   Treatment resistant depression (TRD) is common, with approximately 45% of patients failing to

55   respond to pharmacological treatment (Papakostas & Fava 2010). Currently available

56   antidepressants are characterised by a relatively slow onset of effect ranging from weeks to

57   months. There has been great interest in the potential of ketamine as a treatment for TRD

58   patients, given early reports of strong and rapid (within hours) antidepressant properties in

59   patients otherwise resistant to antidepressant treatment (Fond et al. 2014; Salvadore et al. 2009;

60   Zarate et al. 2012; Zarate et al. 2006). Ketamine has been reported to reduce sgACC activity in

61   healthy volunteers (De Simoni et al. 2013; Deakin et al. 2008; Doyle et al. 2013; Stone et al.

62   2015), and responders to ketamine with treatment resistant bipolar depression have been reported

63   to have increased glucose metabolism in this region (Nugent et al. 2014). However, the effect of

64   ketamine on subgenual connectivity, which might be hypothesised to underlie its antidepressant

65   effects, has not been fully investigated. To date there has only been one study on the effect of

66   ketamine on brain connectivity in relation to potential antidepressant mechanisms. Ketamine was

67   shown to disrupt connectivity between the sgACC and the dorsal nexus 24 hours following

68   administration in healthy volunteers, an effect that was hypothesised to be related to its

69   antidepressant properties (Scheidegger et al. 2012). We hypothesise that immediate effects of

70   ketamine might also play an important part in the therapeutic effects of ketamine in TRD, and

71   that the early modulation of circuits involved in maintenance of depressive cognitions may be

72   necessary for the emergence of objectively measureable clinical improvement.

73

74   In this study, which is an analysis of existing resting state data (Stone et al. 2015), we

75   investigated the effect of acute intravenous ketamine administration on functional connectivity of

76   the sgACC in healthy volunteers.

77

78   **Materials and Methods**

79   The study was approved by the East London Research Ethics Committee. Prior to screening for

80   the study, all participants gave written informed consent for inclusion. Inclusion criteria: healthy

81   right−handed male subjects (18-50 years old) with a total body weight 50−100 Kg. Exclusion

82   criteria: positive urine drug screen for drugs of abuse, the consumption of more than 5 cups of

83   coffee per day, smoking more than 5 cigarettes per day, taking prescription drugs, and any

84   history of mental illness, or serious medical condition that, in the opinion of the study doctors,

85   prevented their participation in the study.

86   Thirteen healthy, right handed, male volunteers (age 21-39, mean 27, standard deviation 6.90)

87   were selected for the study after screening. Each subject underwent medical, mental state,

88   physical, and psychiatric examination including electrocardiogram, urine drug screen, and taking

89   measurements of blood pressure, pulse rate, temperature, and weight. Each volunteer underwent

90   venous cannulation in the left antecubital fossa. We attached a 50ml syringe pump containing

91   4mg/ml racemic ketamine via an infusion line.

92

93   Image acquisition was conducted, as previously reported (Stone et al. 2015), at the Centre for

94   Neuroimaging Sciences on a General Electric (Milwaukee, Wisconsin) 3-Tesla HDx MRI

95   scanner. Pharmacological MRI (phMRI) blood-oxygen level dependent (BOLD) data were

96   acquired using gradient echo EPI (Echo-Planar Imaging) with parallel imaging accelerated by a

97   factor of 2. Each participant was scanned continuously for 15 minutes to yield a total of 450

98   functional image volumes of 37, continuous top down, 3 mm thick slices with a slice gap of 0.3

99   mm, repeat time (TR) of 2000 ms, echo time (TE) of 30 ms, flip angle of 75°, in-plane resolution

100   of 3.3 mm, 64 × 64 matrix, and 21.1 × 21.1 cm field of view. The ketamine infusion commenced

101   after 5 minutes of resting state acquisition and followed a dynamically modelled intravenous

102   infusion with a target plasma level of 150 ng/mL determined according to pharmacodynamic

103   properties of ketamine from the "Clements 250 model", with a rapid bolus over 20 seconds of

104   approximately 0.26mg/Kg, on average, followed by a slow infusion of approximately

105   0.42mg/Kg/Hr. Participants' peak ketamine-induced experience was rated by a trained

106 psychiatrist using the positive and negative syndrome scale (PANSS) immediately following

107 their exit from the scanning room.

108

109 Preprocessing and statistical analyses were performed using Statistical Parametric Mapping

110 software version 8 (SPM8; Wellcome Trust Centre for Neuroimaging, London, England).

111 Functional images were corrected for slice timing effects and subsequently realigned to correct

112 for the effects of volume-to-volume head motion. Data were examined to confirm that framewise

113 translational and rotational head movement did not exceed 2mm or 1 degree. Images were co-

114 registered to a high-resolution T1-weighted structural image, and normalised to Montreal

115 Neurological Institute (MNI) space via unified segmentation. The normalised images were

116 smoothed using an 8mm full width at half maximum (FWHM) Gaussian kernel. Additional

117 preprocessing was carried out using the REST toolbox for resting state fMRI analysis (Song et

118 al. 2011). Nuisance variables such as motion parameters (volume to volume translations in 3

119 axes and rotation around these axes), white matter and CSF signal were regressed from the data.

120 The residual time-series was then de-trended and band-pass filtered (frequency range 0.01-

121 0.08Hz) and a signal time-series was extracted from the sgACC seed (10mm sphere at [2, 28, -5]

122 based upon a previous publication (Scheidegger et al. 2012)). The 15-minute time series was

123 separated into three 5-minute time-series segments of pre-infusion, early-infusion and late-

124 infusion. The early-infusion portion of the time series was disregarded as any observed

125 connectivity would have been dominated by the phMRI response to the bolus. Finally,

126 connectivity maps between the sgACC seed and the whole brain were created using regression

127 within the REST toolbox, and the resultant r-maps underwent r-to-Z conversion again within

128 REST.

129

130 These Z-transformed maps were taken forward into a second level random effect analysis within

131 SPM8. A one sample t-test was used to characterise sgACC connectivity prior to ketamine

132 administration, and a paired t-test was employed (comparing pre- and post-ketamine

133 connectivity) to identify regional changes in sgACC coupling following ketamine administration.

134 We also directly investigated connectivity between the sgACC seed and the dorsal nexus region,

135 by use of two spherical masks of 10mm radius at $x = \pm36$, $y = 27$, $z = 29$ (Sheline et al. 2010).

136 Results were considered significant if they survived family wise error (FWE) correction on the

137 basis of cluster-extent ($p_{FWE}<0.05$). The PANSS general score was tested for normality using the

138 Shapiro-Wilk test prior to regression analysis against ketamine-induced change in sgACC

139 connectivity.

140

141 **Results**

142 Prior to ketamine administration, there was positive coupling ($p_{FWE}<0.05$) between sgACC and

143 multiple brain regions including anterior cingulate, ventral striatum, and thalamus. There was

144 negative coupling ($p_{FWE}<0.05$) between sgACC and regions including cerebellum, pons,

145 precentral gyrus, superior frontal gyrus, and parahippocampus (Table 1).

146

147 Following ketamine administration, there was significant reduction in sgACC coupling with a

148 large cluster including the hippocampus, retrosplenial cortex (RSC), and thalamus centred at [-2

149 -3 6] ($p_{FWE}=0.002$; $k_E=2885$; $Z_o=3.69$) (Figure 1). Plotting the contrast estimate from the cluster

150 peak, located in the retrosplenial cortex [-6 -55 3], revealed that the RSC was uncorrelated with

151 the sgACC before ketamine administration, but that it was negatively correlated with the sgACC

152   following ketamine administration (Figure 2). There was no significant change in connectivity

153   between sgACC and the dorsal nexus region following ketamine administration.

154

155   Ketamine administration was associated with a mean (SD) increase in PANSS positive, negative,

156   and general subscales to 10.7(2.89), 10.07(3.43), and 20.15(3.53) respectively (p<0.05). Multiple

157   regression analysis using cluster forming threshold of p<0.01 was performed to test for

158   correlations between changes in whole brain functional connectivity with sgACC following

159   ketamine administration and PANSS scores. No correlations with PANSS positive or negative

160   scores were found, but a negative correlation between the PANSS general score and sgACC

161   coupling was observed in the medial prefrontal cortex (mPFC) and subcallosal gyrus (SCG)

162   (p_{FWE}<0.05). In order to further investigate this correlation, we performed a post-hoc analysis of

163   the correlation between sgACC coupling and depression-related items using the 5 factor PANSS

164   (Lindenmayer et al. 1994). The level of the depression subscale (primarily anxiety and

165   preoccupation rather than the depression item) was significantly increased following ketamine

166   administration (p<0.05), and was found to be negatively associated with coupling between

167   sgACC and subcallosal gyrus and with right ventrolateral prefrontal cortex (p_{FWE}<0.05). The

168   depression subscale was positively associated with coupling between sgACC and right

169   ventromedial prefrontal cortex (p_{FWE}<0.05; Figure 3).

170

171   **Discussion**

172   In this study, we examined the acute effect of ketamine on functional connectivity between the

173   sgACC and other brain regions. Our primary aim was to investigate the effect of acute ketamine

174   administration in healthy volunteers on brain networks hypothesised to be involved in the

175 aetiopathology of depression. The most striking effect of acute ketamine administration in this

176 study is the disruption of connectivity between sgACC and a large cluster encompassing midline

177 thalamus, hippocampus, RSC. This may be of relevance to the antidepressant effect. Both

178 thalamus and hippocampus have been implicated in the pathology of MDD (Malykhin &

179 Coupland 2015; Yakovlev et al. 1960; Young et al. 2004). Furthermore, the network connectivity

180 between sgACC and the default mode network, including RSC is increased in patients with

181 MDD, and has been suggested to underlie depressive ruminations (Hamilton et al. 2015), a

182 process hypothesized to be of great significance in the maintenance of depressed mood (Disner et

183 al. 2011) . If ketamine is able to disrupt the tendency of the mind to return to depressive

184 ruminations through changing the functional connectivity within this network, this may be of

185 particular importance in its antidepressant action. Interestingly, two studies of ketamine effects

186 on functional connectivity revealed an increase rather than a decrease in connectivity between

187 hippocampus and prefrontal cortex following ketamine administration (Gass et al. 2014; Grimm

188 et al. 2015). In addition a graph theory analysis of whole brain connectivity showed a pattern of

189 reduced cortical and increased subcortical/cerebellar connectivity after ketamine in healthy

190 volunteers (Joules et al. 2015). It is worth noting, however, that none of these studies looked at

191 connectivity with sgACC, and it is possible that a decrease in connectivity may have been seen

192 between this region and the hippocampus.

193

194 Although ketamine acutely increased rather than decreased scores on the 5 factor PANSS

195 depression scale in this healthy volunteer sample (it would not have been possible to for

196 depressive scores to reduce as volunteers did not have any symptoms before ketamine

197 administration) it is notable that changes in functional connectivity between subgenual anterior

198   cingulate and other brain regions correlated only with the general and depressive scores on the

199   PANSS, and not with positive or negative subscales. Our finding of a correlation between

200   ketamine-induced increases on the depression subscale and reduced sgACC coupling with

201   surrounding regions of the SCG is of interest as the SCG is an important node in a neural

202   network comprising of cortical structures, the limbic system, thalamus, hypothalamus, and

203   brainstem nuclei. MDD patients generally show increased activity in SCG, which is normalised

204   by antidepressant treatment (Hamani et al. 2011). It is possible that this local reduction in

205   connectivity reflects a direct consequence of the reduced BOLD activity in this brain region seen

206   following ketamine administration (Stone et al. 2015).

207

208   It is interesting that we found a reduction in connectivity between sgACC and ventrolateral

209   prefrontal cortex associated with increases in ketamine-induced scores on the depression

210   subscale, whereas there was an associated increase in connectivity between sgACC and

211   ventromedial prefrontal cortex connectivity with the same scale. The reason for this is not

212   entirely clear, but both ventrolateral and ventromedial prefrontal cortices have been implicated in

213   depression (Ma et al. 2013; Miller et al. 2015). Ventromedial prefrontal cortex connectivity with

214   sgACC has been suggested to underlie depressive ruminations (Hamilton et al. 2015), so the fact

215   that ketamine acutely increased depression scores and increased this connectivity is in keeping

216   with this finding. In contrast, one study in patients with treatment resistant unipolar depression

217   found increases in connectivity between anterior cingulate cortex and a cluster including

218   ventrolateral prefrontal cortex associated with clinical response to transcranial magnetic

219   stimulation (Baeken et al. 2014), and thus decreases in connectivity between these two regions

220   might be predicted to increase depressive symptoms. However, it is not at all clear how

221 ketamine-induced increases in depression scores in healthy volunteers may be related to its effect

222 as an antidepressant in patients with existing clinical depression.

223

224 There are a number of limitations regarding the study design. The fact we were studying healthy

225 volunteers means that any effects we see in functional connectivity may not map directly onto

226 those that occur in patients with MDD. Ketamine modulation of brain circuits may vary

227 according to severity of depression and thus networks affected in healthy controls may be

228 different to those suffering from MDD. Related to this, we were not able to measure the

229 antidepressant effect of ketamine as the volunteers had no measureable depressive symptoms at

230 presentation, and so the current data cannot provide evidence that ketamine-induced changes in

231 connectivity are related to ketamine's antidepressant effect. Secondly, the effects investigated in

232 the present study occurred 5 minutes following ketamine administration, during the steady-state

233 infusion, whereas antidepressant effect in patients do not normally arise until 40 minutes to 2

234 hours after ketamine administration. We hypothesise that the changes reported in the current

235 study may be precursors to an antidepressant effect, but it is possible that changes in functional

236 connectivity relevant to antidepressant mechanism between other brain regions might arise at

237 later time points. Thirdly, we did not have a placebo arm. However, participants were not aware

238 when the ketamine was started, and our earlier placebo-controlled study using an identical

239 method of ketamine infusion did not show any effect of placebo on BOLD signal in any brain

240 region (Doyle et al. 2013). Lastly, because the volunteers in this study did not have any

241 depressive symptoms, the correlations of change in connectivity with mood symptoms are

242 difficult to interpret – participants had an increase rather than a decrease in depression-related

243 symptom following ketamine administration.

244

245 **Conclusion**

246 We found that ketamine alters the functional connectivity of the sgACC in healthy controls. The

247 networks affected suggest that these changes may be of importance in the therapeutic effects of

248 ketamine in patients with MDD. Further studies in patients are required to test the hypothesis that

249 ketamine may reduce depressive rumination via acute effects on sgACC- RSC connectivity.

250

251

252

253

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362

363

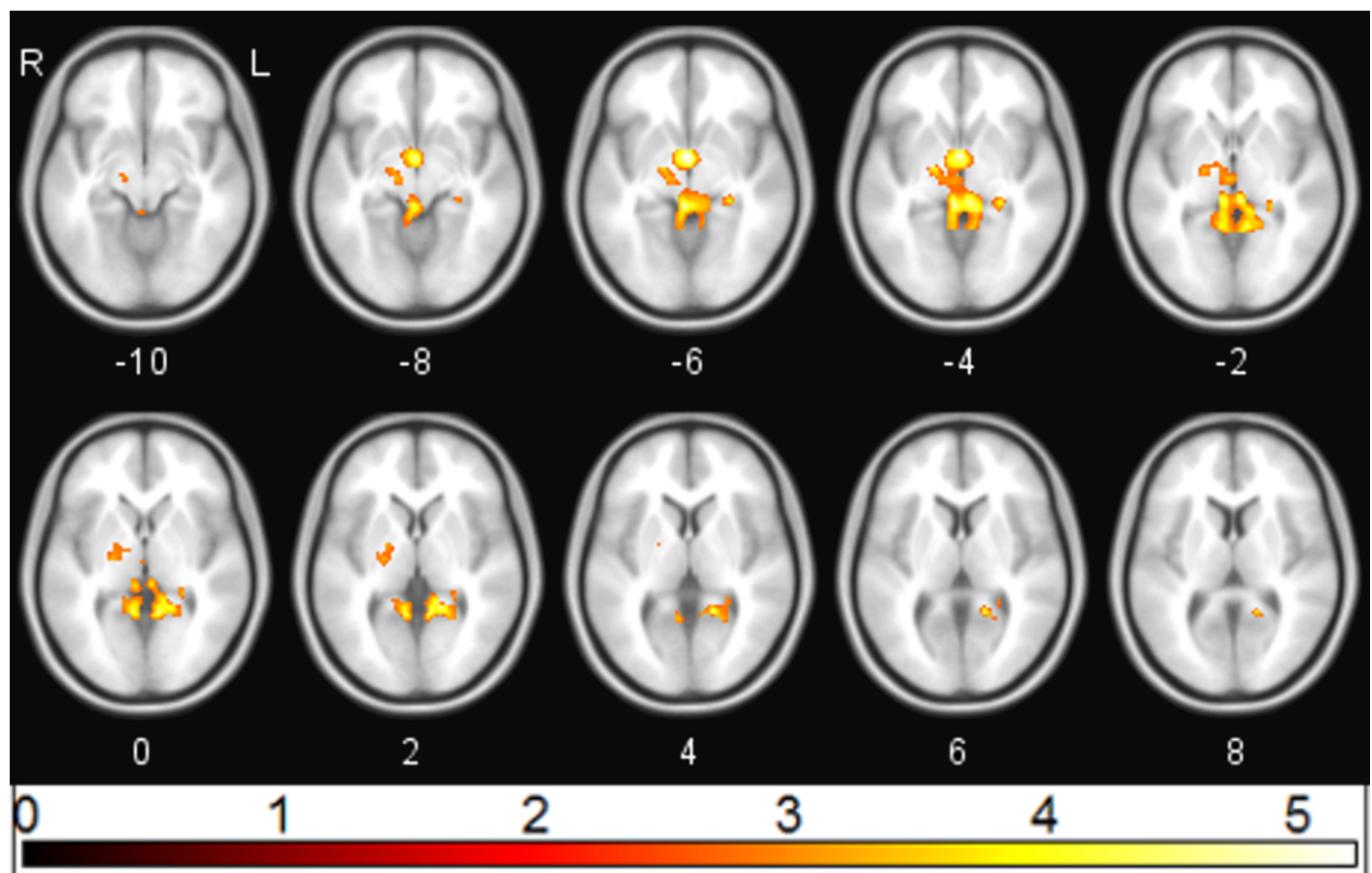
Resting state sgACC coupling prior to ketamine administration

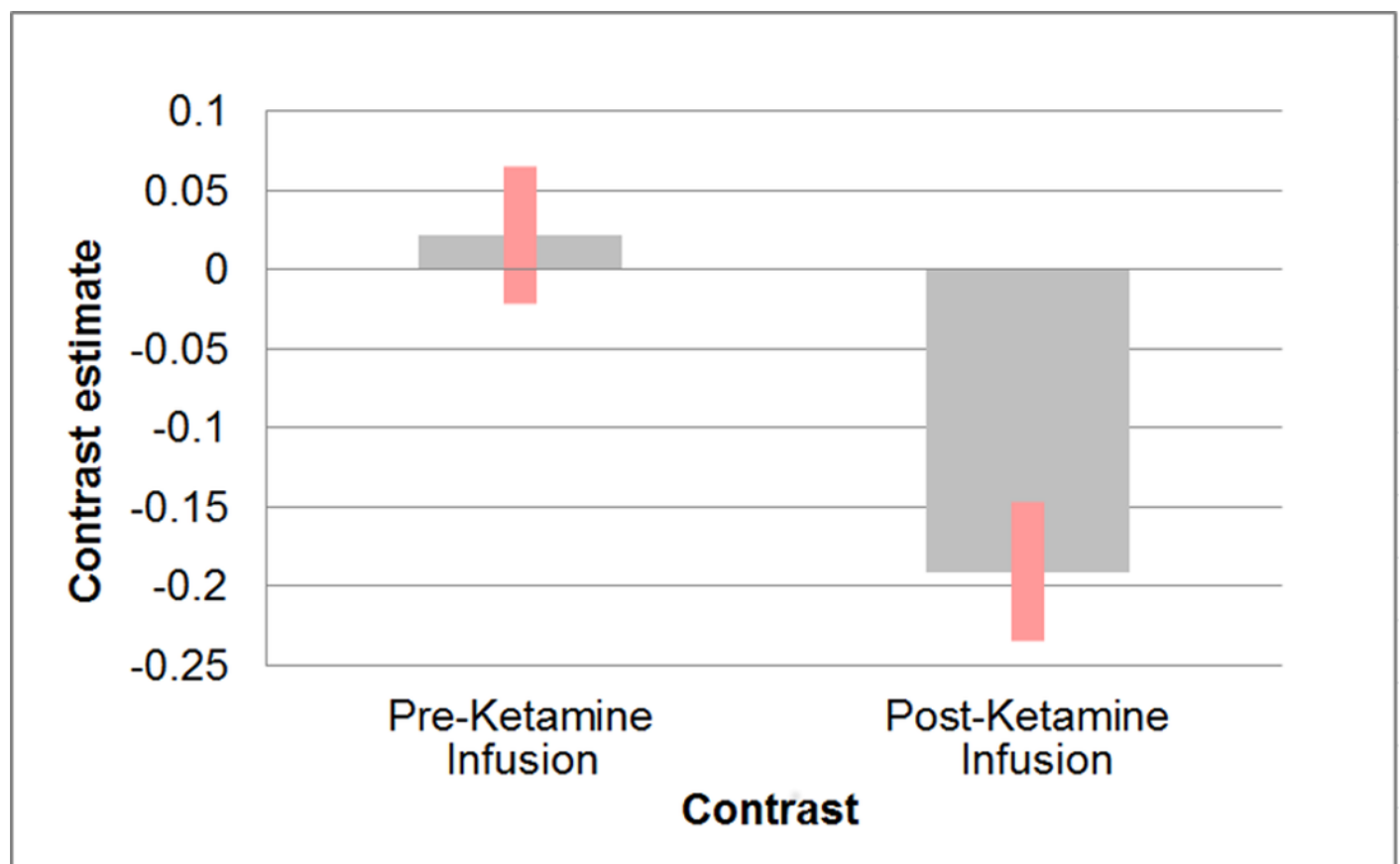
Regions showing significant coupling with sgACC prior to ketamine infusion (*pFWE*<0.05 corrected for multiple comparisons on the basis of cluster extent, using a cluster-forming threshold of z=3.1).

sgACC Coupling	Brain Region	Brodmann Area	Cluster-level		Peak-level	Coordinates		
			p_{FWE}	k_E	(Z_o)	x	y	z
Positive	Ventral Anterior Cingulate	24	<0.001	12610	6.69	4	27	-6
Positive	Dorsal Anterior Cingulate	32			6.23	-6	35	-3
Positive	Thalamus				5.79	-2	-3	-3
Negative	Anterior Cerebellum		<0.001	3705	4.69	-12	-37	-27
Negative	Pons				4.16	9	-22	-24
Negative	Anterior Cerebellum				3.96	10	-37	-26
Negative	Middle Frontal Gyrus	9	<0.001	1089	4.68	43	12	33
Negative	Middle Frontal Gyrus	9			4.50	42	3	39
Negative	Precentral Gyrus	6			4.03	51	0	40
Negative	Superior Frontal Gyrus	10	0.001	971	4.45	22	51	24
Negative	Middle Frontal Gyrus	9			4.12	34	29	28
Negative	Middle Frontal Gyrus	9			3.77	30	36	21
Negative	Inferior Parietal Lobule	40	0.007	649	4.17	66	-46	31
Negative	Inferior Parietal Lobule	40			3.46	70	-46	22
Negative	Postcentral Gyrus	2			3.44	61	-30	43

1

sgACC connectivity following ketamine administration.

Regions showing significant (pFWE<0.05) reduction in sgACC coupling following ketamine administration (red/yellow).

Effect of ketamine on connectivity between sgACC and retrosplenial cortex

Correlation between sgACC and retrosplenial cortex [-6 -55 3] before and after the start of ketamine administration.

3

Correlation between PANSS depression and sgACC coupling

Regions showing significant (pFWE<0.05) correlations between PANSS depression score and change in sgACC coupling following ketamine administration (blue – negative correlation, yellow – positive correlation).