

The effect of NMDA receptor antagonists and antidepressants on resting state in major depressive disorder

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Table of contents

Table of contents.....	3
Abstract	11
Declaration	12
Copyright statement.....	12
Acknowledgements	13
List of tables	14
List of figures	15
Table of abbreviations.....	16
About the author.....	23
Contribution	24
List of publications.....	25
List of posters presented.....	25
Chapter One: An overview of major depressive disorder	26
1.1. Historical background	27
1.2. Epidemiology.....	28
1.3. Diagnostic criteria	30
1.3.1. ICD-10 Diagnostic criteria for depressive disorders	30
1.3.2. DSM-IV-TR Diagnostic criteria for depressive disorders	31
1.3.3. DSM-5	33
1.4. Neurobiological aetiology	34
1.4.1. Serotonin ((5-hydroxytryptamine (5-HT))	34
Table 1 Evidence of 5-HT dysfunction in MDD	35
1.4.2. Noradrenaline.....	36
Table 2 Evidence of noradrenaline dysfunction in MDD	37
1.4.3. Dopamine	38
Table 3 Evidence of dopamine dysfunction in MDD	39
1.4.4. GABA	40
Table 4 Evidence of GABA dysfunction in MDD	41
1.4.5. Acetylcholine	42
1.4.6. Corticotrophin releasing factor and hypothalamic-pituitary-adrenal axis	42

Table 5 Evidence of HPA axis dysfunction in MDD	43
1.4.7. Glutamate.....	44
1.5. Imaging studies in MDD	44
1.5.1. Structural brain imaging	44
Table 6 MRI structural brain changes in MDD	47
1.5.2. Functional imaging	48
1.5.2.1. <i>Positron emission tomography - cerebral blood flow (CBF)/glucose metabolism</i>	48
1.5.2.2. <i>Single photon emission tomography (SPET)</i>	50
1.5.2.3. <i>Magnetic resonance imaging (MRI) – Arterial spin labelling (ASL)</i>	50
1.5.2.4. <i>fMRI – Blood oxygen level dependent response (BOLD)</i>	51
1.6. Conclusions.....	56
Chapter Two: Resting state networks in major depressive disorder	58
2.1. Resting state networks.....	59
2.2. Default mode and salience networks.....	61
2.3. Other resting state networks in MDD.....	62
2.4. Resting state fMRI studies in MDD.....	63
Table 7 Resting state network fMRI studies in MDD sorted by methodology.....	67
2.5. Effect of antidepressant drugs on the default mode network.....	78
2.6. Using an NMDA receptor antagonist to probe resting state networks	79
2.7. Conclusions.....	80
Chapter Three: The role of the NMDA receptor in major depressive disorder and antidepressant effects	82
3.1. Introduction	83
3.2. The glutamate synapse	83
Figure 1 Diagram of the Glutamate Synapse.....	85
3.3. Normal NMDA receptor function	86
Figure 2 Diagram of the NMDA receptor with sites of drug action.....	87
3.4. Glutamate neurotransmission in MDD.....	88
3.4.1. Cerebrospinal fluid evidence.....	88
3.4.2. Proton magnetic resonance spectroscopy evidence	88
Table 8 Recent proton magnetic resonance spectroscopy studies of neurotransmitters in patients with MDD	91

3.4.3.	Glial pathology in MDD	93
3.4.4.	Changes in glutamate receptors in MDD	94
	Table 9 Post mortem changes in glutamate receptor subunits.....	95
3.4.5.	Knockout/Knock in mice.....	96
3.5.	Effects of standard antidepressants on glutamate function in humans/animals	97
3.6.	Efficacy of ketamine in MDD	98
3.6.1.	Mechanisms of action of ketamine.....	98
3.6.2.	Methodology of clinical studies	101
3.6.3.	Response to ketamine infusion	103
3.6.4.	Biomarkers of response to ketamine	104
3.6.5.	Trials to identify mechanisms of ketamine effects	105
	Table 10 Clinical studies of ketamine in MDD	108
3.7.	Effects of other glutamate drugs on depression (Clinical studies)	116
3.7.1.	Modulators of glutamate release.....	116
3.7.1.1.	Lamotrigine.....	116
3.7.1.2.	Riluzole.....	116
3.7.2.	Drugs acting at NMDA receptors.....	117
3.7.2.1.	Memantine.....	117
3.7.2.2.	Amantadine	117
3.7.2.3.	Traxoprodil (CP-101,606).....	117
3.7.2.4.	GLYX-13.....	118
3.7.2.5.	MK-0657	118
3.7.2.6.	AZD6765 (Lanicemine)	118
3.7.3.	Drugs acting at AMPA receptors	119
3.7.3.1.	RO4917523/AZD2066/Coluracetam	119
3.8.	Conclusions and need for future studies	119
	Table 11 NMDA antagonists as antidepressants: summary of evidence	122
3.9.	Thesis hypotheses	123
	Chapter Four: Effects of AZD6765 on resting state networks in major depressive disorder	
	124
4.1.	Introduction	125
4.2.	Aims.....	126

4.3. Hypotheses	126
4.4. Methods and materials	126
4.4.1. Ethics	126
4.4.2. Study design and recruitment	126
4.4.3. Study recruitment	127
4.4.4. Screening and randomisation	127
4.4.5. Study procedures	127
4.4.6. Image preprocessing	128
4.4.7. Independent Component Analysis	128
Figure 3 AZ study mean component maps	131
4.5. Results	132
4.5.1. Demographics and mood rating scales	132
Table 12 Demographics and mood rating scales	133
4.5.2. Effects of drug in regions expressing significant ACC RS activity - SPM voxel-wise analysis	134
Table 13 SPM voxel-wise analysis	134
Figure 4 SPM voxel-wise analysis contrast map – positive (red/yellow) and negative (blue) effect	134
4.5.3. Effects of drug in regions expressing significant ACC RS activity - regional MarsBaR analysis	135
4.5.3.1. Drug modulation of day 1 positive ACC RS component	135
4.5.3.2. Drug modulation of day 1 negative ACC RS component	135
Table 14 Component 10 positive ACC RS component regions that show differences between treatment groups on day 1	136
Figure 5 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 1: * $p < 0.05$ uncorrected	136
Table 15 Component 10 negative ACC RS component regions that show differences between treatment groups on day 1	138
Figure 6 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 1: * $p < 0.05$ uncorrected	138
4.5.3.3. Drug modulation of day 2 positive ACC RS component	139
4.5.3.4. Drug modulation of day 2 negative ACC RS component	139

Table 16 Component 10 positive ACC RS component regions that show differences between treatment groups on day 2	141
Figure 7 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 2: * $p < 0.05$ uncorrected.....	142
Table 17 Component 10 negative ACC RS component regions that show differences between treatment groups on day 2	146
Figure 8 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 2: * $p < 0.05$ uncorrected.....	146
4.5.3.5. Drug effects on positive day 1-day 2 differences (day1>day2) in ACC RS component	147
4.5.3.6. Drug effects on negative day 1-day 2 differences (day1>day2) in ACC RS component	147
Table 18 Component 10 positive ACC RS component (day 1 > day 2) regions that show a day x treatment group interaction	148
Figure 9 Overlays & line graphs for regions of positive ACC RS component that show a significant day x treatment group interaction: * $p < 0.05$ uncorrected.....	148
Table 19 Component 10 negative ACC RS component (day 2 > day 1) regions that show a day x treatment group interaction	149
Figure 10 Overlays & line graphs for regions of negative ACC RS component that show a significant day x treatment group interaction: * $p < 0.05$ uncorrected.....	149
4.5.4. Drug effects on ACC RS and MADRS mood rating scales.....	152
Table 20 Regions in which component 10 correlated with MADRS improvement	153
Figure 11 Significant MADRS mood rating scales correlations with component 10	153
4.6. Discussion	154
4.6.1. Effects of drug in regions expressing significant ACC RS activity	154
4.6.1.1. SPM voxel-wise analysis.....	154
4.6.1.2. Regional MarsBaR analysis	155
4.6.2. Drug effects on ACC RS and MADRS mood rating scales.....	158
4.7. Limitations and future studies.....	159
4.8. Conclusions.....	160
Chapter Five: Effects of citalopram on resting state networks in major depressive disorder	162
5.1. Introduction	163

Citalopram Study 1 - Healthy controls vs current MDD vs remitted MDD after citalopram	164
5.2. Aims	164
5.3. Hypotheses	164
5.4. Methods and materials	164
5.4.1. Ethics	164
5.4.2. Study design and recruitment	164
5.4.3. Study recruitment	164
5.4.4. Screening and randomisation	165
5.4.5. Image acquisition	165
5.4.6. Study procedures	165
5.4.7. Independent Component Analysis	165
Figure 12 Citalopram study 1 & 2 mean component maps	166
5.5. Results	168
5.5.1. Demographics	168
Table 21 Demographics and mood rating scales	168
5.5.2. Effects of group in regions expressing significant ACC RS activity - SPM voxel-wise analysis	168
Table 22 SPM voxel-wise analysis	169
Figure 13 SPM voxel-wise analysis contrast maps	169
5.5.3. State vs trait effects on positive ACC RS component – regional MarsBaR analysis..	170
5.5.4. State vs trait effects on negative ACC RS component – regional MarsBaR analysis	170
5.5.5. State vs trait effects on ACC RS and MADRS mood rating scales	171
Table 23 Component 5 positive ACC RS component regions that show differences between groups	172
Figure 14 Overlays & histograms for regions of positive ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected	173
Table 24 Component 5 negative ACC RS component regions that show differences between groups	176
Figure 15 Overlays & histograms for regions of negative ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected	177
5.6. Discussion	178
5.6.1. State vs trait effects on positive ACC RS component after acute citalopram	178

5.6.2.	State vs trait effects on negative ACC RS component	180
5.7.	Conclusions	181
5.8.	Limitations and future studies	182
Citalopram Study 2 - Healthy controls vs current MDD after citalopram or placebo infusion		183
5.9.	Aims	183
5.10.	Hypotheses	183
5.11.	Results	183
5.11.1.	Demographics	183
Table 25 Demographics and mood rating scales		184
5.11.2.	SPM voxel-wise analysis	184
Table 26 SPM voxel-wise analysis		185
Figure 16 SPM voxel-wise analysis contrast maps – positive (yellow) and negative (blue) effects are plotted at peak-level threshold of $p=0.001$ and extent threshold of $p_{FDRc}<0.05$		185
5.11.3.	Drug modulation of positive ACC RS component – regional MarsBaR analysis	186
5.11.4.	Drug modulation of negative ACC RS component – regional MarsBaR analysis	186
5.11.5.	Drug effects on ACC RS component and MADRS mood rating scales	187
Table 27 Component 5 Positive ACC RS component regions that show drug, group, and drug x group interactions		188
Figure 17 Overlays & line graphs for regions of positive ACC RS component that show a significant difference of drug, group or drug x group interaction		189
5.12.	Discussion	193
5.12.1.	Drug modulation of positive ACC RS component	193
5.13.	Conclusions	196
5.14.	Limitations and future studies	197
Chapter Six: General discussion		198
6.1.	Overview	199
6.2.	Summary of findings	201
6.3.	Possible abnormal resting state networks in MDD	204
6.3.1.	Frontal cortical network – Medial and superior frontal gyri	204
6.3.2.	Posterior DMN – Precuneus and inferior parietal lobule	205
Figure 18 Summary MarsBaR analysis results of possible abnormal RSNs in MDD		206

6.3.3.	Saliency Network - Insula	207
6.3.4.	Basal ganglia network – caudate and lentiform nuclei.....	208
6.4.	Conclusions on the effect of antidepressants on resting state networks	209
	References	211
	Appendix	245

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Abstract

The effect of NMDA receptor antagonists and antidepressants on resting state in major depressive disorder: a thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Medical and Human Sciences by Arpan Dutta (17th December 2014)

Introduction: The aim of the project was to investigate the effects of antidepressants on brain networks whilst at rest. My hypothesis was that antidepressants work by reversing persistent activity in the brain's default mode network (DMN). The DMN is implicated in self-reflection and rumination in MDD. The methodologies and results of studies of resting state networks in MDD and the effects of antidepressants are reviewed in the thesis. Increasing evidence implicates glutamate in the action of antidepressant drugs. Whether there are illness related changes in glutamate function is unresolved, largely because of the lack of techniques for assessing it. Ketamine and other NMDA antagonists have improved MDD symptoms within 24 hours though the effects are short lasting. The molecular neural networks involved in ketamine's putative antidepressant effects are unclear. The thesis reviews the evidence. Much evidence implicates ACC as a site of action of antidepressant effects but whether this is through its regulation of the DMN or other networks is not known. This thesis compares the effect of ketamine and citalopram on ACC-related systems.

Method: The thesis combines two systematic reviews of the effects of MDD and antidepressant drugs on i) resting state networks (53 studies) and ii) glutamate neurotransmission (45 studies of clinical efficacy of ketamine). There are two experimental chapters. The first describes investigation into two rapid acting antidepressant drugs acting via glutamate mechanisms. 54 unmedicated cMDD were scanned across two centres on 3T MRI scanners while being infused with placebo (0.5% saline), 0.5mg/kg ketamine or 100mg AZD6765 over 1 hour. fMRI resting state data between drug treatments was compared for the final 25 minutes of the drug infusion and for a 25 minute resting state scan a day later. The second experimental chapter examines whether these effects were shared by citalopram, a standard antidepressant. 67 unmedicated cMDD, rMDD and HC were administered citalopram 7.5mg i.v. and scanned on a 1.5T MRI scanner. In a second study 63 cMDD and HC were administered i.v. citalopram 7.5mg or placebo (0.5% saline). fMRI resting state data for the final 12 ½ minutes following drug infusion was compared. Independent Component Analysis was performed using the Group ICA for fMRI toolbox. The resting component with the highest spatial correlation to the ACC was used. Brain maps of the intensity of the selected component were constructed for each individual. Group averages were calculated and compared using SPM. Regional analysis was performed using Marseille Boite a Regions d'interet.

Results: On day 1 AZD6765 significantly increased mean intensity of ACC resting component in the right insula, right IPL and left cingulate gyrus greater than ketamine or placebo. Ketamine increased mean intensity of ACC resting component greater than placebo in the right lentiform nucleus and left MFG. Significantly decreased mean intensity of ACC resting component in the left insula in the AZD6765 group compared to placebo was noted. On day 2 AZD6765 increased mean intensity of ACC resting component greater than ketamine and placebo in the left and right lentiform nuclei. AZD6765 reduced mean intensity of the ACC resting component in the left and right MFG. The first citalopram study revealed reduced mean intensity of ACC resting component in cMDD compared to rMDD and HC in PCC. rMDD had reduced mean intensity of ACC resting component in the precuneus compared to HC. In the second study, citalopram had no effect in HC but normalised precuneus activity in cMDD producing a significant drug x group interaction.

Conclusions: The acute antidepressant effects of citalopram are modulated by changes in the bilateral precuneus. The precuneus is central to connectivity with other regions in MDD. It has a prominent role in the DMN and is linked to rumination. The mechanism of the antidepressant effects of AZD6765 is different from those of ketamine and citalopram. The insula, IPL, MFG, cingulate gyrus and lentiform nuclei are all regions implicated in MDD suggesting antidepressant effects. The rapid antidepressant effects of AZD6765 are possibly due to a resetting of the interface between DMN and salience networks.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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List of tables

Table 1 Evidence of 5-HT dysfunction in MDD	35
Table 2 Evidence of noradrenaline dysfunction in MDD	37
Table 3 Evidence of dopamine dysfunction in MDD	39
Table 4 Evidence of GABA dysfunction in MDD	41
Table 5 Evidence of HPA axis dysfunction in MDD	43
Table 6 MRI structural brain changes in MDD	47
Table 7 Resting state network fMRI studies in MDD sorted by methodology.....	67
Table 8 Recent proton magnetic resonance spectroscopy studies of neurotransmitters in patients with MDD	91
Table 9 Post mortem changes in glutamate receptor subunits.....	95
Table 10 Clinical studies of ketamine in MDD	108
Table 11 NMDA antagonists as antidepressants: summary of evidence	122
Table 12 Demographics and mood rating scales	133
Table 13 SPM voxel-wise analysis	134
Table 14 Component 10 positive ACC RS component regions that show differences between treatment groups on day 1	136
Table 15 Component 10 negative ACC RS component regions that show differences between treatment groups on day 1	138
Table 16 Component 10 positive ACC RS component regions that show differences between treatment groups on day 2	141
Table 17 Component 10 negative ACC RS component regions that show differences between treatment groups on day 2	146
Table 18 Component 10 positive ACC RS component (day 1 > day 2) regions that show a day x treatment group interaction	148
Table 19 Component 10 negative ACC RS component (day 2 > day 1) regions that show a day x treatment group interaction	149
Table 20 Regions in which component 10 correlated with MADRS improvement	153
Table 21 Demographics and mood rating scales	168
Table 22 SPM voxel-wise analysis	169
Table 23 Component 5 positive ACC RS component regions that show differences between groups	172
Table 24 Component 5 negative ACC RS component regions that show differences between groups	176
Table 25 Demographics and mood rating scales	184
Table 26 SPM voxel-wise analysis	185
Table 27 Component 5 Positive ACC RS component regions that show drug, group, and drug x group interactions.....	188

List of figures

Figure 1 Diagram of the Glutamate Synapse.....	85
Figure 2 Diagram of the NMDA receptor with sites of drug action.....	87
Figure 3 AZ study mean component maps.....	131
Figure 4 SPM voxel-wise analysis contrast map – positive (red/yellow) and negative (blue) effect	134
Figure 5 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 1: * $p < 0.05$ uncorrected.....	136
Figure 6 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 1: * $p < 0.05$ uncorrected.....	138
Figure 7 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 2: * $p < 0.05$ uncorrected.....	142
Figure 8 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 2: * $p < 0.05$ uncorrected.....	146
Figure 9 Overlays & line graphs for regions of positive ACC RS component that show a significant day x treatment group interaction: * $p < 0.05$ uncorrected.....	148
Figure 10 Overlays & line graphs for regions of negative ACC RS component that show a significant day x treatment group interaction: * $p < 0.05$ uncorrected.....	149
Figure 11 Significant MADRS mood rating scales correlations with component 10.....	153
Figure 12 Citalopram study 1 & 2 mean component maps.....	166
Figure 13 SPM voxel-wise analysis contrast maps	169
Figure 14 Overlays & histograms for regions of positive ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected.....	173
Figure 15 Overlays & histograms for regions of negative ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected.....	177
Figure 16 SPM voxel-wise analysis contrast maps – positive (yellow) and negative (blue) effects are plotted at peak-level threshold of $p = 0.001$ and extent threshold of $p_{FDRc} < 0.05$	185
Figure 17 Overlays & line graphs for regions of positive ACC RS component that show a significant difference of drug, group or drug x group interaction.....	189
Figure 18 Summary MarsBaR analysis results of possible abnormal RSNs in MDD.....	206

Table of abbreviations

[¹ H] MRS	Proton magnetic resonance spectroscopy
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
ACC	Anterior cingulate cortex
ACTH	Adrenocorticotrophic hormone
AKT	Protein kinase B
ALFF	Amplitude of low frequency fluctuations
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPT	A-methylparatyrosine
AMYG	Amygdala
AN	Affective network
ANOVA	Analysis of variance
ant	Anterior
ASL	Arterial Spin Labelling
b/l	Bilateral
BA	Brodmann area
BD	Bipolar disorder
BDI	Beck Depression Inventory
BDV	Borna Disease Virus
BOLD	Blood Oxygen Level Dependent
BPD	Bipolar disorder, depressed
BPM	Bipolar disorder, manic
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CBF	Cerebral blood flow

CBT	Cognitive Behavioural Therapy
CEN	Central executive network
CES-D	Center for Epidemiologic Studies Depression Scale
CGI-S	Clinical Global Impression- Severity Scale
cMDD	Current major depressive disorder
Cohe-ReHo	Coherence based regional homogeneity
Cr	Creatinine
CRF	Corticotrophin releasing factor
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CX546	2,3-dihydro-1,4-benzodioxin-7-yl-(1-piperidyl)methanone
D	Dopamine receptor
dACC	Dorsal anterior cingulate cortex
DAG	Diacylglycerol
dalPFC	Dorsal anterolateral prefrontal cortex
DAT	Dopamine transporter
dIPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
dmPFC	Dorsomedial prefrontal cortex
dmTHAL	Dorsomedial thalamus
DSM	Diagnostic and Statistical Manual
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition
EAAT	Excitatory amino acid transporter
ECA	Epidemiological Catchment Area Study
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
ERK	Extracellular-signal-related-kinases

fALFF	Fractional amplitude of low frequency fluctuations
FC	Functional connectivity
FDR	False discovery rate
FDRc	False discovery rate corrected
FG	Fusiform gyrus
fMRI	Functional Magnetic Resonance Imaging
FnC	Functional connectivity
FWE	Family wise error
FWEc	Family wise error corrected
GABA	γ -aminobutyric acid
GAD	Glutamic acid decarboxylase
GFAP	Glial fibrillary acidic protein
GIFT	Group ICA of fMRI Toolbox
Glu	Glutamate
GluR	AMPA receptor
Glx	Glutamate + Glutamine
GS	Glutamine synthetase
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Depression Rating Scale
HC	Healthy controls
HCN	Heads of caudate nuclei
HV	Healthy volunteers
HVA	Homovanillic Acid
hx	History
I	Iodine
i.m.	Intramuscular

i.v.	Intravenous
ICA	Independent Component Analysis
ICD-10	International Classification of Diseases 10 th Edition
IFG	Inferior frontal gyrus
INS	Insula
i.p.	Intraperitoneal
IP ₃	inositol-1,4,5- triphosphate
IPL	Inferior parietal lobule
ITG	Inferior temporal gyrus
KA	Kainate
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MaRSBaR	Marseille Boite a Regions d'interet
mCPP	m-chlorphenylpiperzine
MDD	Major depressive disorder
MF	Medication free
MFG	Middle frontal gyrus
mFG	Medial frontal gyrus
mg	Milligrams
Mg ²⁺	Magnesium
mGlu	Metabotropic glutamate receptor
MHPG	3-methoxy-4-hydroxyphenylglycol
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
mOFC	Medial orbitofrontal cortex
mPFC	Medial prefrontal cortex
MR	Magnetic resonance

mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MTG	Middle temporal gyrus
Na ⁺	Sodium
NAA	N-acetyl aspartate
NAcc	Nucleus accumbens
NaSSA	Noradrenergic and specific serotonergic antidepressants
NBQX	2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f)-quinoxaline
NCS	National Co-morbidity Survey
NCS-R	National Co-morbidity Survey Replication
NDRI	Noradrenaline and dopamine reuptake inhibitor
NMDA	N-methyl-D-aspartate
OCC	Occipital cortex
OFC	Orbitofrontal cortex
OR	Odds ratio
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
pgACC	Pregenual anterior cingulate cortex
PHG	parahippocampal gyrus
PI3k	Phosphatidylinositol 3-kinase
PLC	Phospholipase C
PM	Post mortem
PO	Oral
post	posterior
rCBF	Regional cerebral blood flow
RCT	Randomised controlled trial

ReHo	Regional homogeneity
rFIC	Right fronto-insular cortex
rMDD	remitted major depressive disorder
ROI	Region of Interest
RS	Resting state
RSC	Retrosplenial cortex
RSN	Resting state network
rTMS	Repetitive Transcranial Magnetic Stimulation
SFG	superior frontal gyrus
sgACC	Subgenual anterior cingulate cortex
sibsMDD	Healthy siblings of MDD patients
SNRI	Serotonin and noradrenaline reuptake inhibitor
SPET	Single photon emission tomography
SPL	Superior parietal lobule
SPM	Statistical parametric mapping
SSI	Scale for Suicide Ideation
SSRI	Selective serotonin reuptake inhibitors
STG	Superior temporal gyrus
T	Tesla
TCA	Tricyclic antidepressant
TE	Echo time
THAL	Thalamus
TIA	Transient ischaemic attack
TPN	Task positive network
TR	Time to repetition
tr MDD	Treatment resistant major depressive disorder
vACC	Ventral anterior cingulate cortex

VAS	Bond-Lader visual analogue scale
VGLUT	Vesicular glutamate transporter
VLPFC	Ventrolateral prefrontal cortex
VMHC	Voxel-mirrored homotopic connectivity
vmPFC	Ventromedial prefrontal cortex
vPFC	Ventral prefrontal cortex
VST	Ventral striatum
VTA	Ventral tegmental area

About the author

Arpan Dutta completed his undergraduate medical training from the University of Liverpool, England in 2004 passing with honours. He did his core psychiatry training in Mersey Deanery. He gained membership of Royal College of Psychiatrists in 2009. He then went on to higher specialist training in general adult psychiatry in Mersey Deanery. In 2010 the author pursued a part time Doctor of Medicine degree at the University of Manchester and was privileged to be supervised by Professor Bill Deakin and Dr Shane McKie. The author's desire to complete the Doctor of Medicine degree came from his curiosity into the mechanisms of psychiatric illness and more specifically depression.

During this time he was involved in a number of trials of novel antidepressant compounds in depressed patients and healthy controls at the Neuroscience and Psychiatry Unit, University of Manchester. Alongside this he continued his clinical training and received his certificate of completion of training in 2012 in general psychiatry with sub-specialty endorsement in rehabilitation psychiatry. He also completed the Master of Laws in Mental Health Law from the University of Northumbria in 2013. He currently works as a Consultant Psychiatrist in Rehabilitation Psychiatry in Mersey Care NHS Trust. After completing his Doctor of Medicine degree the author plans to continue combining clinical practice with further research at the University of Manchester.

Contribution

My involvement in fMRI research came from the opportunity to work on a study investigating a novel glutamate based antidepressant, AZD6765 (lanicemine), in comparison to ketamine. Working on this study led to my interest in discovering common features of the antidepressant response. The thesis is my own work and I wrote all of the chapters.

In Chapter 1 I performed the literature search to provide an overview of the neuropsychopharmacology of MDD.

Chapter 2 of the thesis examined resting state networks that are relevant to MDD, the effect of antidepressant drugs on resting state networks and whether a NMDA antagonist could be used to alter resting state networks. I performed the literature search, extracted and reviewed the evidence.

Chapter 3 reviewed the evidence for NMDA receptor dysfunction in MDD including evidence from proton MRS, glial pathology, changes in glutamate receptors, effects of standard antidepressants on glutamate and clinical use of ketamine. I performed the literature search, extracted and reviewed the evidence.

Chapter 4 described the general methods that were common to both experimental chapters performed using SPM voxel-wise analysis, regional MarsBaR techniques and mood rating scales.

Chapter 5 presented the analyses of i.v. AZD6765 (lanicemine), ketamine and placebo fMRI resting state data in MDD. I assisted in the initial design of the experiment alongside guidance from Dr Shane McKie and Professor Bill Deakin. I performed the recruitment, screening, gaining consent, supervision of fMRI scanning, drug administration, dissociative and mood rating scales. I was assisted in recruitment and fMRI scanning by Dr Darragh Downey, Research Associate. I was guided through fMRI analysis using SPM, GIFT and MarsBaR by Dr Shane McKie. The data presented were the analyses of i.v. AZD6765 (lanicemine), ketamine and placebo fMRI resting state data in MDD across day 1 and day 2.

In Chapter 6 to understand whether common effects existed between glutamate based antidepressants and conventional SSRIs I was provided access to already collected data of i.v. citalopram fMRI resting state data from NewMood and REMEDi studies. The first experiment investigated cMDD, rMDD and HC as a cross sectional design and the second experiment investigated cMDD and HC as placebo controlled design. I analysed the data available from the two studies using identical methodology to the AZD6765 study.

In Chapter 7 I drew conclusions from thesis as a whole and considered regions that could be further examined as biomarkers of MDD. I also suggest possible future experimental work.

List of publications

Dutta A., McKie S., Deakin J.F.W. 2014. Resting state networks in major depressive disorder. *Psychiatry Research: Neuroimaging*, 224, 139-51

Dutta A., McKie S., Deakin J.F.W. 2014. Ketamine and other potential glutamate antidepressants. *Psychiatry Research*, 225, 1-13

Downey D., Dutta A., McKie S., Dawson G.R., Dourish C.T., Craig K., Smith M.A., McCarthy D.J., Harmer C.J., Goodwin G.M., Williams S., Deakin J.F.W. Comparative antidepressant mechanisms of lanicemine and ketamine: (i) key role of anterior cingulate activation. *Submitted for publication to Biological Psychiatry, December 2014*

List of posters presented

Dutta A., McKie S., Deakin J.F.W. 2014. Are the acute effects of citalopram mediated by the dopamine system? *European Neuropsychopharmacology*, 24(Suppl 2), S308
Presented at 27th European College of Neuropsychopharmacology Congress 2014

Dutta A., McKie S., Deakin J.F.W. 2014. Acute intravenous citalopram normalises reduced mean amplitude of low frequency fluctuations in the bilateral precuneus in major depressive disorder. *Journal of Psychopharmacology*, 28(Suppl 8), A94
Presented at British Association for Psychopharmacology Summer Meeting 2014

Dutta A., McKie S., Downey D., Dourish C.T., Dawson G.R., McCarthy D.J., Deakin J.F.W. 2014. Rapid antidepressant effects of lanicemine (AZD6765) may be related to effects on regions of the default mode and salience networks. *Journal of Psychopharmacology*, 28(Suppl 8), A94
Presented at British Association for Psychopharmacology Summer Meeting 2014

Chapter One: An overview of major depressive disorder

1.1. Historical background

Major depressive disorder (MDD) is not a new illness. The concept of melancholia reaches as far back as the writings of Hippocrates and Galen, but until the late 20th century there have been few successful treatments (Hindmarch, 2001). Hippocrates described the first historical case of melancholia as a state of “*aversion to food, despondency, sleeplessness, irritability and restlessness*” (Hippocrates et al., 1923). Later Greco-Roman medicine recognised the contributions of alcohol, seasons and disturbed sleep cycles (Sadock et al., 2004). The actual term depression came much later from the Latin verb *deprimere* meaning “to press down” (Fowler et al., 2011).

It was not until 1621 that the first published English language description of affective disorders appeared in Robert Burton’s “*Anatomy of Melancholy*”. He described a broader concept of affective disorders and their causes (Burton R, 1621). In the early 1800s came the first description of primary mood disturbance separate from any other form of “insanity” by the French psychiatrist Jean-Etienne Esquirol (Sadock et al., 2004, Esquirol and Hunt, 1965). Throughout the late 19th and early 20th century biological theories of affective disorders were put forward including endocrine dysfunction and the revival of ancient views of about the role of the liver in melancholia (Lewis, 1934).

Treatments prior to the 1950s had included insulin coma therapy, malarial induced fever and electroconvulsive therapy (Sadock and Sadock, 2004). The discovery of antidepressant drugs was serendipitous and came before a mechanistic theory was proposed. Following the discovery that antidepressants inhibit the degradation or reuptake of monoamines, it was proposed in the 1960s that antidepressant drugs act by reversing an impairment of monoamine function in depression; the monoamine deficiency theory (Carlsson et al., 1968, Schildkraut, 1965, Owens, 2004). Variants of the theory proposed that depression originated from a deficit of serotonin and noradrenaline function. Despite the many limitations of the theory, monoamine mechanisms of depression and drug action remain a central focus of research (Hirschfield, 2000, Stone, 2008).

Since the introduction of selective serotonin reuptake inhibitors (SSRIs) in the 1980s several other types of drugs, with mechanisms of antidepressant action revolving around monoamine theory, have been brought to market: serotonin and noradrenaline reuptake inhibitors (SNRIs); noradrenaline and dopamine reuptake inhibitors (NDRIs); and noradrenergic and specific serotonergic antidepressants (NaSSAs). Whilst these agents have offered alternative treatment options they have done little to change the incidence and prevalence of MDD.

In summary, MDD is not a new disorder and has been recognised for thousands of years. Despite this our understanding of the pathophysiology remains poor. The majority of theories still revolve around the monoamine hypothesis which has limited the development of novel antidepressants.

1.2. Epidemiology

Savitz and Drevets have suggested that MDD is the “*epidemic of our times*” (Savitz and Drevets, 2009). The National Comorbidity Survey Replication (NCS-R) found lifetime prevalence of MDD was 16.2% with a 12-month prevalence of 6.6% across a US based population. These prevalence results were between those of the initial National Comorbidity Survey (NCS) and previous Epidemiological Catchment Area Study (ECA). The mean episode duration was approximately 16 weeks which lengthened with symptom severity. The figures, however, need to be interpreted with caution given that almost three-quarters had other co-morbid psychiatric disorders (Kessler et al., 2003).

Course and prognosis

Depressive episodes on average last approximately 6 months but in approximately 25% can last longer than 12 months (Keller et al., 1992). Approximately 85% of those recovered will experience further episodes of MDD with a median of four episodes (Mueller et al., 1999). About 50% do not achieve full remission of symptoms between episodes (Yeh et al., 2014).

Age/Sex/Marital Status

MDD occurs approximately twice as frequently in women than men (Kessler et al., 2010, Weissman et al., 1996). The average age of onset is 25 to 35 years old with more frequent occurrence in those who are separated, widowed or divorced. Furthermore prevalence varies across countries but age of onset does not which may be due to poor identification of cases (Weissman et al., 1996).

Urbanisation/Employment

Depression is more common in rural, compared to urban, populations in the United States which may be attributed to health and social characteristics (Probst et al., 2006). These studies do not always delineate clearly between communities close to urban centres, leading to contrasting results from other researchers which showed rural areas had lower prevalence of MDD in Canada (Wang, 2004).

Higher rates of MDD are seen in the unemployed. A recent study in pregnant women demonstrated that those who continued to work had lower proportions of major depressive symptoms compared to housewives, those who had stopped working and students. Confounding this, however, working women who were pregnant tended to be older, better educated and of a higher socioeconomic class. Even so the significant differences remained after adjusting for these variables (Fall et al., 2013).

Disability

MDD is the leading cause of moderate and severe disability in those under 60 worldwide. In 2004 it was estimated that there were approximately 151 million people worldwide with MDD. By 2030 it is projected to become the leading cause of disease burden worldwide, outstripping ischaemic heart disease (World Health Organization, 2008). Co-morbid psychiatric disorders are also increased in MDD. In the European Study of the Epidemiology of Mental Disorders (ESEMeD) a higher rate of 12 month co-morbidity was observed with alcohol abuse (Odds Ratio (OR) 2.6) and alcohol dependence (OR 6.7), dysthymia (OR >99.9) and anxiety disorders including: generalised anxiety disorder (OR 33.7), panic disorder (OR 29.4), agoraphobia (OR 25.8) and post-traumatic stress disorder (OR 20.7). Whilst reliable, these data must be interpreted with the limitations of using lay interviewers to establish diagnosis and its retrospective nature (Alonso et al., 2004).

Treatment resistance

Treatment resistance is a significant issue in MDD. Response rates remain approximately 30% despite the introduction of new antidepressants (Mulrow et al., 2000). Naturalistic studies have observed remission of major depressive disorder (MDD) in only 28% of patients after first line treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Trivedi et al., 2006). Second and third line treatments demonstrated declining rates of remission in spite of various augmentation strategies (Nierenberg et al., 2006, Trivedi et al., 2008). A number of risk factors for treatment resistance have been suggested (Bennabi et al., 2014). These include co-morbid anxiety disorder, suicidality, non-response to first antidepressant, early onset and lack of full remission from a previous episode.

Suicide

Suicide is a cause of death in approximately 15% of individuals with MDD (Manji et al., 2001). The most important risk factor for lifetime suicide risk is MDD with a population attributable risk of approximately 28% (Bernal et al., 2007). Better treatment, or even prevention, could therefore reduce mortality and morbidity.

Economic impact

MDD has a huge financial impact too. The cost of MDD in the United States in 2000 was \$83.1 billion of which \$26.1 billion were direct medical costs (Greenberg et al., 2003). In the UK in 2000 the total cost was £9 billion with £370 million in direct treatment costs (Thomas and Morris, 2003). These costs are probably underestimates given that people with less severe depressive symptoms may continue to work but with reduced productivity. The other difficulty is the higher rates of physical and mental comorbid illness. Early and effective treatment of depression would hopefully reduce the economic burden of MDD.

Conclusions

MDD is a common, debilitating illness. It is more common in females and is linked to social and cultural isolation with further correlations with employment and marital status. Treatment efficacy is poor and relapse occurs in a considerable proportion of MDD patients. Suicide is a cause of death in a significant number of MDD patients. The financial burden of MDD is massive, both to the health system and the wider economy. Development of novel therapies, or prevention, should therefore be of prime importance. Alongside this an understanding of MDD pathophysiology is essential.

1.3. Diagnostic criteria

There are two sets of diagnostic criteria for MDD. The International Classification of Diseases (ICD) produced by the World Health Organization (1993) and the Diagnostic and Statistical Manual (DSM) of Mental Disorders produced by the American Psychiatric Association (2000). The criteria are as follows:

1.3.1. ICD-10 Diagnostic criteria for depressive disorders

Depressive Episode

1. The depressive episode should last for at least 2 weeks.
2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode at any time in the individual's life.
3. The episode is not attributable to psychoactive substance use or to any organic mental disorder.

A. Core symptoms

1. depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks
2. loss of interest or pleasure in activities that are normally pleasurable
3. decreased energy or increased fatigability

B. Additional symptoms

1. loss of confidence or self-esteem
2. unreasonable feelings of self-reproach or excessive and inappropriate guilt
3. recurrent thoughts of death or suicide, or any suicidal behaviour
4. complaints or evidence of diminished ability to think or concentrate
5. change in psychomotor activity, with agitation or retardation (either subjective or objective)

6. sleep disturbance of any type
7. change in appetite (decrease or increase) with corresponding weight change

Mild depressive episode requires 2 A criteria and 2 B criteria.

Moderate depressive episode requires at least 2 of criteria A and 4 of criteria B to give a total of at least 6 symptoms.

Somatic syndrome specifies additional biological features such as anhedonia, lack of emotional reactivity, early morning waking, diurnal mood variation, weight or libido loss and decreased appetite. Any 4 symptoms must be present to qualify but it can only be specified in either mild or moderate depressive episodes.

Severe depressive episode without psychotic symptoms requires 3 of criteria A and at least 5 of criteria B to give a total of at least 8 symptoms. In *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*, the presence or absence of the somatic syndrome is not specified for severe depressive episode, since it is presumed to be present in most cases.

Severe depressive episode with psychotic symptoms requires the same criteria as above for severe depressive episode but with the addition of delusions or hallucinations, other than those listed as typically schizophrenic. The commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content or depressive stupor.

Recurrent depressive disorder requires at least one previous episode of mild, moderate, or severe nature, lasting a minimum of 2 weeks and separated from the current episode by at least 2 months free from any significant mood symptoms.

1.3.2. DSM-IV-TR Diagnostic criteria for depressive disorders

Major Depressive Disorder

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Where at least 2 of the symptoms below are present but less than five this is diagnosed as **Minor Depressive Disorder**
- B. The symptoms do not meet criteria for a mixed episode
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)
- E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

The symptoms are:

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Additional exclusion criteria are schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder and other schizophrenia spectrum disorders, mania or hypomania that is not substance induced or related to a medical condition. As with ICD-10 MDD can be classified as mild (with limited functional and social impairment), moderate or severe (with or without psychotic features). In severe MDD there is interference in occupational and social functioning. Psychotic symptoms can be further classified as either mood congruent around themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or mood incongruent such as persecutory delusions, thought insertion, thought broadcasting, and delusions of control. MDD can either be classified as single episode or recurrent, along with specifiers such as severity, seasonal affective disorder and atypical features.

1.3.3. DSM-5

A new revision to the Diagnostic and Statistical Manual for Mental Disorders was published in 2013 (American Psychiatric Association, 2013). DSM-5 removes the bereavement exclusion for MDD and further clarifies the differentiation between bereavement and major depressive disorder. "With anxious distress" can be now specified to identify the presence of cognitive symptoms of anxiety. In addition, mixed features can now be specified where at least three manic or hypomanic symptoms are present nearly every day. These symptoms include: elevated or expansive mood, inflated self-esteem or grandiosity, more talkative than usual or pressure to keep talking, flight of ideas or racing thoughts, increased energy or goal-directed activity, increased or excess involvement in activities with high potential for painful consequences (such as spending sprees) and decreased need for sleep.

Overall the diagnostic criteria in both ICD and DSM classifications are similar. The DSM criteria are more explicit in ruling out medical and psychiatric co-morbidities. Both systems offer descriptions of severity, recurrence and the presence of psychotic symptoms. The DSM criteria are more suited to research due to their simplicity since severity does not produce a heterogeneous sample.

1.4. Neurobiological aetiology

Neurobiological studies have focussed on monoamine neurotransmitter systems (Manji et al., 2001). The monoamine hypothesis of depression postulates a deficit in serotonin and noradrenaline in key areas of the brain. Antidepressants were thought to act by blocking the action of the monoamine transporter leading to increased availability of neurotransmitter in the synaptic cleft (Hindmarch, 2002). There is evidence to suggest that each neurotransmitter has a role in MDD but most is inconclusive. This section will briefly outline the evidence to support the role of each neurotransmitter.

1.4.1. Serotonin ((5-hydroxytryptamine (5-HT))

Table 1 summarises the evidence to support 5-HT dysfunction in MDD. Unfortunately the evidence of reduced serotonin, or CSF 5-hydroxyindoleacetic acid (5-HIAA), in depressives is inconsistent (Gelder et al., 2006, Cowen, 2008). Savitz and Drevets review of PET studies of 5-HT_{1A}, 2A and serotonin transporter binding showed a varied picture that is complicated by the use of different radioligands and heterogeneous patient samples. In the PET studies of 5-HT_{2A} binding a number of patients were also noted to be medicated with benzodiazepines (Savitz and Drevets, 2013). Blunted neuroendocrine challenge responses have been observed in MDD but may only account for effects of 5-HT function in the hypothalamus (Cowen, 2001). Furthermore whilst plasma tryptophan is reduced in unmedicated MDD patients, acute tryptophan depletion does not lower mood in healthy controls (Cowen et al., 1989, Ruhe et al., 2007). This suggests lower brain 5-HT alone is not sufficient to produce MDD symptoms, yet in rMDD patients who have discontinued medication, tryptophan depletion produces a return of depressive symptoms (Smith et al., 1997).

The evidence suggests a varying increases and reduction in a number of measures of 5-HT system which have been associated with current and remitted MDD. However the relationship between these findings and MDD are unclear.

Table 1 Evidence of 5-HT dysfunction in MDD

5-HT measure	Reference	Effect in MDD	Comments
Platelet 5-HT uptake	(Coppen et al., 1978)	Reduced	
Platelet imipramine binding	(Suranyi-Cadotte et al., 1984)	Reduced	
Platelet 5-HT_{2A} binding	(Mendelson, 2000)	Increased	
Postmortem 5-HT_{1A} receptors	(Stockmeier, 2003)	Increased/normal	Hippocampus and PFC reviewed. Varying causes of death
Postmortem 5-HT_{2A} receptors	(Stockmeier, 2003)	Increased/normal	Forebrain regions/hippocampus/OFC reviewed
Plasma tryptophan	(Cowen et al., 1989)	Reduced	
CSF 5-HIAA	(Asberg et al., 1976)	Reduced	Likely to predict increased suicide risk. Bimodal distribution of results.
Neuroendocrine response to SSRI	(Bhagwagar et al., 2002, Attenburrow et al., 2001)	Reduced	Prolactin and cortisol response reduced. Not necessarily reflective of brain 5-HT changes.
5-HT_{1A} PET receptor binding	(Savitz and Drevets, 2013, Drevets et al., 2007)	Reduced/normal	Presynaptic - Raphe Postsynaptic - ACC, lateral OFC, insula, amygdala, hippocampus, mesiotemporal cortices. Review noted some studies reported elevated pre and postsynaptic 5-HT _{1A} binding.
5-HT_{1B} PET receptor binding	(Murrough et al., 2011)	Reduced	Ventral striatum and globus pallidus.
5-HT_{2A} PET receptor binding	(Savitz and Drevets, 2013)	Reduced/normal/increased	Reduced in ACC, OCC, orbitoinsular, frontal, temporal cortices Radioligands used also bind to D ₂ receptors. Other studies have reported no change or increased in frontal, parietal and OCC binding.
5-HT transporter PET binding	(Selvaraj et al., 2011, Savitz and Drevets, 2013)	Increased/normal/reduced	Increased in thalamus, left frontal cortex, insula, mPFC, periaqueductal gray matter. No change noted in some studies in addition to decreases in brainstem, thalamus, ACC, hippocampus, amygdala, caudate, putamen.
Tryptophan depletion	(Delgado et al., 1990, Reilly et al., 1997)	Increased relapse	Remitted MDD receiving antidepressant treatment and low tryptophan diet + acute tryptophan free amino acid drink. Associated with increased glucose utilization on PET for rMDD in OFC, medial thalamus, ACC, PCC and VST (Neumeister et al., 2004).

1.4.2. Noradrenaline

Noradrenaline function was hypothesised to be reduced in MDD because of the dual action of many of the early tricyclic antidepressants. Table 2 summarises the evidence to support noradrenaline dysfunction in MDD. There is no conclusive evidence of changes in CSF, plasma or noradrenaline metabolite changes in MDD (Anand and Charney, 2000). Neuroendocrine tests using desipramine and clonidine demonstrate blunted response and reduced hypothalamic postsynaptic α_2 receptor sensitivity. Catecholamine synthesis can be reduced by inhibition of tyrosine hydroxylase preventing conversion of tyrosine to L-DOPA using AMPT. Catecholamine depletion with AMPT results in depressive symptoms in rMDD patients treated with noradrenaline reuptake inhibitor antidepressants (Delgado et al., 1993). No lowering of mood is seen, however in healthy controls or medication free depressed patients (Salomon et al., 1997, Miller et al., 1996) .

Overall there is no consistent evidence for the mechanism of noradrenaline in MDD but there are trait markers of abnormalities following recovery. Despite this there is no simple increase or decrease in noradrenaline that is likely to be the primary pathophysiology in depression (Ressler and Nemeroff, 1999).

Table 2 Evidence of noradrenaline dysfunction in MDD

Noradrenaline measure	Reference	Effect in MDD	Comments
CSF noradrenaline	(Post et al., 1973, Potter et al., 1993)	Increased/ normal/ reduced	
Plasma noradrenaline	(Roy et al., 1985)	Increased	
Urinary MHPG	(Maas et al., 1972, Davis et al., 1988)	Reduced/ increased	Likely inaccurate measure of central noradrenaline metabolism due to conversion to vanillylmandelic acid (Blombery et al., 1980).
α_1 receptor binding	(Arango et al., 1993)	Increased	Postmortem sample. Difference noted in temporal cortex. No difference in α_2 receptor binding between controls and suicide victims in prefrontal cortex.
α_{2A} receptor binding	(Escriba et al., 2004)	Increased	Postmortem sample. Frontal cortex. Various methods of suicide.
Postsynaptic β receptor binding	(De Paermentier et al., 1990)	Reduced	Postmortem suicide victims but more brain regions sampled. Previous studies have shown increases in the superior frontal and cingulate gyrus and frontal cortex (Biegon and Israeli, 1988, Mann et al., 1986).
α_2 receptor platelet sensitivity	(Charney et al., 1981)	Increased	Charney and colleagues demonstrated that chronic desipramine reduced the sensitivity of presynaptic α_2 receptor to cause release of noradrenaline when stimulated by clonidine.
α_2 receptor platelet binding	(Theodorou et al., 1986, Piletz and Halaris, 1988, Takeda et al., 1989, Karege et al., 1992, Maes et al., 1999)	Increased/ normal/ reduced	
Depletion Studies	(Freis, 1954, Delgado et al., 1993, Miller et al., 1996)	Increased/ no change in depressive symptoms	Alpha-methyl-paratyrosine (AMPT) depletes catecholamines leading to return of depressive symptoms in remitted MDD on noradrenaline reuptake inhibitor antidepressants. . Return of symptoms correlated to dlPFC, OFC, MFG and thalamus metabolism (Bremner et al., 2003).

1.4.3. Dopamine

There is also evidence that dopamine dysfunction is important in MDD pathology. Dopamine neurons are well known to play a key role in the experience and effects of pleasurable experiences and reward (Dunlop and Nemeroff, 2007). Table 3 summarises the evidence for dopamine dysfunction in MDD. There is reduced in plasma and CSF HVA. There is reduced D₁ but not D₂ binding on PET studies. However evidence from SPET is less conclusive.

Whilst there is evidence of changes in metabolites and effects on D₂ receptor and DAT binding in the striatum, the effects are inconclusive. This could be due to confounding use of medication as noted by the increased D₁/D₂ receptors found in post-mortem studies.

Table 3 Evidence of dopamine dysfunction in MDD

Dopamine measure	Reference	Effect in MDD	Comments
CSF HVA	(Banki, 1977, Mendels et al., 1972, Vestergaard et al., 1978)	Reduced/ increased	Especially with psychomotor retardation. Doesn't predict treatment response (Maas et al., 1984). Elevated in psychotic depression
Plasma HVA	(Lambert et al., 2000)	Reduced	Internal jugular venoarterial levels
Lymphocyte D₄ mRNA expression	(Rocc et al., 2002)	Reduced	Increased following paroxetine treatment
Postmortem D₁/D₂ receptor binding	(Bowden et al., 1997)	Normal	Examined caudate, putamen and nucleus accumbens. Increased D ₁ / D ₂ receptors in those treated with antidepressants
PET D₁ binding	(Cannon et al., 2009)	Reduced	
PET D₂ binding	(Hirvonen et al., 2008)	Normal	Medication free. Examined caudate, putamen, thalamus and ventral striatum
SPECT D₂ binding	(Ebert et al., 1996, Klimke et al., 1999)	Normal/ Increased	Other studies noted increased striatal D ₂ binding using 123I-iodobenzamide but patients had no drug washout (D'Haenen H and Bossuyt, 1994, Shah et al., 1997). Lower D ₂ binding correlates with treatment response (Klimke et al., 1999)
DAT binding	(Meyer et al., 2001, Amsterdam et al., 2012)	Increased/ reduced	Seen in putamen and caudate. DAT density using SPET can be affected by age, sex, previous psychotropic use, length of illness and severity
Depletion Studies	(Freis, 1954, Lemieux et al., 1956, Hasler et al., 2009) (Delgado et al., 1993, Miller et al., 1996)	Increased/ no change in depressive symptoms	Alpha-methyl-paratyrosine (AMPT) depletes catecholamines leading to return of depressive symptoms in remitted MDD treated with mazindol . Return of symptoms correlated to dlPFC, OFC, MFG and thalamus metabolism (Bremner et al., 2003)

1.4.4. GABA

Despite GABA being the central inhibitory neurotransmitter in the brain, with clear links to anxiety, the role in MDD is less well validated than other neurotransmitters (Mohler, 2012). Table 4 summarises the evidence for GABA dysfunction. One difficulty with measuring GABA in the brain is that it varies with menstrual cycle (Harada et al., 2011) and therefore studies need to control for this. In MDD there are consistent reductions in GABA levels in the ACC and OCC on [¹H] MRS which is increased by treatment. Reduction in GABA in the OCC has been negatively correlated to selective attention and cognitive failures (Sandberg et al., 2014). GABA_B antagonists have been trialled for mild cognitive impairment which may provide a link to the clinical presentation in MDD where cognitive dysfunction is present (Bullock, 2005).

The studies presented in the table lead to the hypothesis that low plasma GABA may be a state marker of MDD that increases with treatment. Treatment tends to increase the levels of GABA in the OCC. GABA agonists are reported to be effective antidepressants.

Table 4 Evidence of GABA dysfunction in MDD

GABA measure	Reference	Effect in MDD	Comments
CSF GABA	(Kasa et al., 1982, Gerner and Hare, 1981)	Reduced	
Plasma GABA	(Petty and Schlessner, 1981, Petty and Sherman, 1984)	Reduced	
Post mortem GABA neurons	(Rajkowska et al., 2007)	Reduced	
[¹H] MRS GABA - Unmedicated	(Hasler et al., 2007)	Reduced	PFC in unmedicated MDD. Low spatial resolution - increased voxel size to provide sufficient signal to noise ratio. Normalisation of GABA by creatine levels differences may have been due to creatine rather than GABA.
	(Price et al., 2009, Sanacora et al., 1999)	Reduced	OCC
[¹H] MRS GABA - Remitted	(Bhagwagar et al., 2008)	Reduced	ACC and OCC.
[¹H] MRS GABA - First episode	(Song et al., 2012)	Reduced	
PET - GABA_A binding	(Klumpers et al., 2010)	Reduced	Parahippocampal and superior temporal gyrus.
Treatment - SSRI	(Sanacora et al., 2002)	Increased	[¹ H] MRS GABA in OCC. No control group. Direct effects of serotonin axons on cortical GABA interneurons may explain effects.
Treatment - ECT	(Sanacora et al., 2003)	Increased	OCC. No control group.
GABA_A agonist - alprazolam	(Petty et al., 1995)	Antidepressant	Meta-analysis effect size similar to low dose TCA. Not noted with diazepam or chlordiazepoxide
GABA_B agonist - baclofen	(Post et al., 1991)	Depressant	Small sample of 5 patients. Suggests GABA _B antagonism may be antidepressant. Effect may be through 5-HT release (Cryan and Slattery, 2010).

1.4.5. Acetylcholine

Evidence for the role of acetylcholine in MDD comes from the use of anticholinergic drugs. There are reports of acetylcholinesterase inhibitors causing depression and having antimanic effects (Janowsky et al., 1974). The effects on MDD may come from modulation of dopamine and GABA on the dopamine neuron, as well as presynaptic terminals of corticotrophin releasing factor (CRF) neurons (Philip et al., 2010). Recent crossover trials of scopolamine, an anti-emetic, anaesthetic and muscarinic acetylcholine receptor antagonist, have demonstrated improvement in depressive symptoms compared to placebo at high doses (Drevets and Furey, 2010). A paradox arises, however, as nicotinic acetylcholine receptor agonists, such as nicotine, and antagonists, such as mecamylamine, also have antidepressant actions (Philip et al., 2010).

Interest has focussed on nicotinic acetylcholine receptors especially $\alpha 4\beta 2$ subtype which is distributed in areas implicated in MDD. The areas include the basal ganglia, thalamus, hypothalamus, VTA, locus coeruleus and dorsal raphe nucleus. PET studies have demonstrated patients with mild depressive symptoms and Parkinson's disease have reduced $\alpha 4\beta 2$ binding in the midbrain, pons, ACC and frontoparietal cortex and cerebellum (Meyer et al., 2009). However, this PET study's evidence was confounded by the use of psychotropic medication in a large number of the patient sample.

The evidence for a role of acetylcholine in depression is far from convincing for either muscarinic or nicotinic receptors. Recent trials of scopolamine have only been replicated by the same research group. There was a significant crossover effect (Furey and Drevets, 2006, Drevets and Furey, 2010). Whilst there are associations between action at acetylcholine receptor and antidepressant response, these are likely to be mediated through other receptors/neurotransmitter systems.

1.4.6. Corticotrophin releasing factor and hypothalamic-pituitary-adrenal axis

Evidence suggests depressed patients have overactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Holsboer, 1999). Table 5 summarises the evidence for HPA axis dysfunction in MDD. Corticotrophin-releasing factor (CRF) is an important factor in the stress response (Vale et al., 1981). Biological stress causes the parvocellular neurons of the paraventricular nucleus of the hypothalamus to produce increased CRF which then activates release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary through CRF receptor type 1. ACTH released into the circulation then causes cortisol secretion from the adrenal cortex (Holsboer, 1999). There are currently a number of CRF₁ antagonists undergoing Phase 2 clinical trials (Grady and Stahl, 2013).

The evidence in Table 5 suggests that cortisol is increased secondary to stress. The negative feedback mechanisms, however, are not clearly affected. Despite reports of raised urinary,

plasma and salivary cortisol, features of Cushing's disease are not found in MDD patients. This could be due to downregulation of corticosteroid receptors (Rupprecht et al., 1991). Dexamethasone suppression test results are also inconsistent (Carroll et al., 1981, Vreeburg et al., 2009). Furthermore attenuated CRF response was not replicated when cortisol synthesis was blocked by metyrapone (Holsboer et al., 1986, von Bardeleben et al., 1988).

There are abnormalities in the HPA axis which occur in MDD but the nature of these is unclear and inconsistent. There is an underlying problem with the control of HPA axis feedback.

Table 5 Evidence of HPA axis dysfunction in MDD

HPA axis measure	Reference	Effect in MDD	Comments
CSF cortisol	(Carroll et al., 1976b, Geraciotti et al., 1997)	Increased/normal	Decreased after antidepressants. Lumbar puncture can cause increases (Mitchell, 1998). Low CRF and cortisol levels with continual CSF sampling (Geraciotti et al., 1997).
Salivary cortisol	(Bhagwagar et al., 2003, Young et al., 2002, Vreeburg et al., 2009)	Increased	
Urinary cortisol	(Carroll et al., 1976a)	Increased	
Plasma cortisol	(Linkowski et al., 1985)	Increased	Noted to have normal ACTH.
CSF CRF-like immunoreactivity	(Nemeroff et al., 1984, Banki et al., 1987)	Increased	
CRF response	(Holsboer et al., 1986)	Reduced ACTH response	No effect on cortisol response.
CRF receptors – post mortem	(Nemeroff et al., 1988)	Reduced	Frontal cortex of suicide victims.
Pituitary and adrenal volume	(Krishnan et al., 1991, Nemeroff et al., 1992)	Increased	Pituitary MRI / Adrenal CT.
Hippocampal volume	(Videbech and Ravnkilde, 2004)	Reduced	Meta-analysis of MRI studies. Heterogeneous studies. Age & sex may be confounders. Hippocampus has central role in regulating HPA axis function.
Dexamethasone suppression test	(Carroll et al., 1981, Vreeburg et al., 2009)	Normal/increased cortisol	
Pre-treatment - metyrapone	(von Bardeleben et al., 1988)	Normal ACTH response	Metyrapone pre-treatment followed by i.v. infusion of human CRF.

1.4.7. Glutamate

There is growing evidence for a role of glutamate in MDD. There is limited evidence for changes in glutamate, glutamine or glycine in CSF (Garakani et al., 2013). Proton MRS studies have reported decreased glutamate, glutamine in the ACC, dlPFC and amygdala (Yildiz-Yesiloglu and Ankerst, 2006). There have been significant increases in glutamate reported following ECT and antidepressants in some but not all studies (Taylor et al., 2010, Taylor et al., 2012, Zhang et al., 2013a). Glutamate receptor subunits post mortem have also been reported as both increased and decreased in patients that had a diagnosis of MDD (Beneyto et al., 2007, Karolewicz et al., 2009b). More recently numerous studies have reported a rapid antidepressant effect of the NMDA antagonist ketamine in MDD patients (see Chapter 3) (Dutta et al., 2015). The evidence will be discussed further in Chapter 3, but suggests that further clinical and preclinical studies are required in MDD to provide better demonstration of the role of glutamate in MDD pathophysiology.

Neurobiological aetiology conclusions

The neurotransmitters with the strongest evidence base are 5-HT and GABA, although glutamate has not been fully discussed as yet. Reductions were noted in platelet 5-HT uptake, plasma tryptophan and CSF metabolites. PET studies have reported reductions in ligand binding across a range of 5-HT receptors and transporters. Acute tryptophan depletion in rMDD suggests a potential psychological sensitivity to 5-HT following clinical recovery. GABA levels are consistently reduced even in first episode MDD increasing in the OCC following treatment. The evidence for noradrenaline is less convincing with conflicting studies. Results of AMPT and reserpine depletion studies are probably due to presynaptic depletion of dopamine and may explain the symptoms seen in retarded MDD. Finally the effects of the HPA axis and cortisol are likely to be a state rather than trait effect but remain unclear. The effect of MDD pathology on neurotransmitter systems and the effect of drugs on these systems remains inconclusive.

1.5. Imaging studies in MDD

1.5.1. Structural brain imaging

There are a number of key brain regions that seem to demonstrate changes in MDD which are summarised in Table 6. Reduced volume is noted in the frontal cortex, hippocampus, ACC, dlPFC and dmPFC, OFC and caudate.

State vs trait effects

There are significant decreases in overall brain volume which appears to be a state effect as it increases following sustained remission (Phillips et al., 2012). Other state effects include volume

reductions in the dlPFC and hippocampus (Zeng et al., 2012a, Arnone et al., 2013). The dmPFC and ACC gray matter loss is a more noticeable feature of recurrent depressive episodes. There are notable reductions in the OFC, thalamus, and caudate but the results are not consistent (Nugent et al., 2013, Arnone et al., 2012a).

Chronic or recurrent depressives have lower gray matter density compared to remitted depressives in the left middle, right superior and inferior temporal gyri and cuneus bilaterally (Salvadore et al., 2011). Remitted depressives showed greater gray matter volume in the rACC and right ACC compared to healthy controls. Absence of gray matter abnormalities in the dlPFC may prove prognostic significance since these patients show less treatment resistance (Li et al., 2010a). There is therefore an improvement in gray matter volume following recovery from MDD. Changes in ventricular volumes are not consistently associated with clinical characteristics such as age of onset, number or duration of episodes (Konarski et al., 2008). This may be due to the lack of regional specificity of the ventricular volume loss.

Predictors of response to antidepressants and cognitive behavioural therapy

Chen and colleagues (2007) have suggested that faster recovery from MDD is predicted by ACC, left PFC, OFC and caudate nucleus volumes and right inferior parietal, temporal and occipital cortices, insula, brainstem and cerebellum following 8 weeks treatment with fluoxetine. There was no placebo control group. Costafreda and colleagues (2009a) have suggested that structural neuroanatomy of acutely depressed patients is able to predict recovery with fluoxetine but not CBT. Remission was predicted by increased gray matter density in the right rACC (BA 32), left PCC (BA 31), left MFG (BA 6) and right OCC (BA19). Residual symptoms were predicted by OFC (BA11) on both sides, right superior frontal cortex (BA10) and left hippocampus. There was decreased gray matter in the right vACC (BA25), mFG (BA11), superior temporal cortex (BA22), precuneus (BA7), hippocampus, thalamus, inferior parietal cortex (BA40), OCC (BA19) and cerebellum. Predicted improvements with fluoxetine were not tested on novel data. A recent meta-analysis reported reduced caudate, left dlPFC and right hippocampal volume was predictive of reduced likelihood of antidepressant response (Fu et al., 2013).

Brain regions that have predicted improvement of depressive symptoms following CBT include the ACC, superior and middle frontal cortices, paracentral and superior parietal cortex, precuneus and cerebellum (Costafreda et al., 2009a, Costafreda et al., 2009b). The effects on non-pharmacological interventions affect similar brain regions to antidepressants. The brain region common to both modalities of treatment is the ACC.

Effects of antidepressant treatment

Increased amygdala and hippocampal sizes have been reported following antidepressant treatment (Frodl et al., 2008, Bellani et al., 2011). Earlier studies, however, reported no changes secondary to SSRI/SNRI treatment (Vythilingam et al., 2004). The dlPFC increased in an

uncontrolled study following sertraline (Smith et al., 2013) and with SSRI/SNRIs (Zeng et al., 2012a).

Conclusions

There are some consistent structural changes as a result of MDD. The ACC is found to be reduced in volume along with the dlPFC and hippocampus. In several studies reduced volume in all three areas predicted residual symptoms and poor recovery from MDD. Regions of interest that have predicted treatment response include the rACC, insula and precuneus in studies. The ACC, insula, and precuneus are components of the default mode and salience networks and therefore are likely to form dysfunctional networks in MDD. That volume changes in these regions can predict response provides the opportunity to investigate them whilst administering antidepressant medication.

Table 6 MRI structural brain changes in MDD

Brain Region	Reference	Volume change	Comments
Whole brain/ Gray/White Matter	(Arnone et al., 2012a)	No change	Meta-analysis
Frontal cortex (total)	(Arnone et al., 2012a)	Reduced	Meta-analysis
Ventricles	(Savitz and Drevets, 2009)	Increased	Mostly 3 rd /lateral ventricle in elderly or chronic MDD. Not seen in younger samples. May be due to tissue loss/cerebrovascular disease
Anterior Cingulate Cortex	(Lai, 2013, Bora et al., 2012)	Reduced	Meta-analyses. Most consistent finding but significant heterogeneity
dIPFC & dmPFC	(Grieve et al., 2013)	Reduced	
Ventral ACC	(Arnone et al., 2012a)	No change	Meta-analysis
Orbitofrontal cortex	(Grieve et al., 2013, Nakano et al., 2014, Arnone et al., 2012a)	Reduced	
Hippocampus	(Videbech and Ravnkilde, 2004)	Reduced	Meta-analysis. Seen from first episode (Cole et al., 2011) Some evidence of normalising with ECT (Tendolkar et al., 2013). Only in current depressives not recovered (Arnone et al., 2013)
Amygdala	(Arnone et al., 2012a)	No change	Reduced in recurrent MDD (Sheline et al., 1998)
Thalamus	(Arnone et al., 2012a, Nugent et al., 2013)	Reduced/ no change	
Caudate	(Arnone et al., 2012a)	Reduced	Meta-analysis
Putamen	(Arnone et al., 2012a)	No change	Meta-analysis
Cerebellum	(Escalona PR et al., 1993, Shah et al., 1992, Zeng et al., 2012a, Pillay et al., 1997)	Reduced/ no change	

1.5.2. Functional imaging

1.5.2.1. Positron emission tomography - cerebral blood flow (CBF)/glucose metabolism

PET detects gamma rays emitted from a positron emitting biologically active radionuclide introduced into the body (Ter-Pogossian et al., 1975). One of the difficulties of PET, unfortunately, is the spatial resolution of structures of interest relative to their physical size which limits sensitivity and specificity.

Abnormalities in MDD

PET studies have demonstrated elevated CBF and metabolism in the ACC, amygdala, thalamus and anterior insula and decreases in the dlPFC, dmPFC/dlPFC and caudate in primary unmedicated MDD (Drevets, 2000). Other reviewers report decreased CBF and glucose metabolism in the dlPFC, ACC and increased CBF and glucose metabolism in the PCC in MDD (Videbech, 2000). Prior to symptom onset there is reported decreased metabolism in the right mFG (BA6) and increased metabolism in the right PCC (BA29), right ACC (BA25 - also described as the subgenual cingulate) as well as left subcallosal gyrus (BA25), and left caudate compared to controls (Kumano et al., 2007). Prodromal cases of MDD could be screened if consistent metabolic changes were noted in the anterior brain structures.

A more recent PET study of 42 ROIs in a sample of MDD patients reported negative correlation between psychomotor retardation and increased blood flow to the hippocampus, cerebellum, ACC and left amygdala and putamen, dlPFC, BA11 and BA47. HAM-D scores were correlated with hippocampal blood flow (Videbech et al., 2002). In this study, unfortunately, some patients were medicated with antidepressants and there was no statistical correction for the large number of ROIs tested.

Abnormalities in rMDD

Remission from MDD has also been investigated. Regions that demonstrate reductions in CBF included left PFC, anterior temporal cortex, left ACC, bilateral thalamus, putamen and cerebellum following treatment. The difficulties in this trial were the limited number of males, and variety of antidepressants utilised (Holthoff et al., 2004).

Predictors of treatment response

MDD patients responsive to antidepressants have higher pre-treatment rACC metabolism (Mayberg et al., 1997, Pizzagalli et al., 2001). Treatment response has been linked to reductions in metabolism in the left amygdala and vACC (Drevets et al., 2002). Amygdala, hippocampus and ACC changes may be related to motor changes in cMDD. Venlafaxine was compared to cognitive behavioural therapy in a PET study looking at neural correlates after 16 weeks of either treatment (Konarski et al., 2009). There was no control group in this study. What they did note was increased metabolism in the interface between the rACC and vACC in non-responders to either

treatment. A similar previous non-randomised study by the same research group comparing venlafaxine and CBT reported reduced metabolism in non-responders in the left lateral OFC, dlPFC, ACC and globus pallidus. Positive drug effects were linked to reductions in metabolism in the vACC and the right NAcc. Positive CBT effects were associated with decreased metabolism in the vACC and ventromedial frontal cortex (Kennedy et al., 2007). More recently escitalopram and CBT have been studied. Right anterior insula hypermetabolism was associated with response to CBT while the hypometabolism was associated with response to escitalopram. Whole brain voxel-wise analysis did not reflect a significant main effect for any brain region across treatments (McGrath et al., 2013).

Effects of antidepressant treatment

Previous results have provided differing results when examining the effects of paroxetine in MDD. Increases in CBF and metabolism in the dlPFC, vlPFC, mPFC, parietal cortex and rACC have been noted, but only a single PET scan post treatment was studied (Kennedy et al., 2001). The differences were observed after 6 weeks of treatment but there was no way of discovering any dysfunction present in individuals prior to treatment due to the lack of a pre-treatment scan. To compensate for this a healthy control group was used. This would suggest initially metabolism/CBF is decreased in a variety of areas prior to treatment. Mayberg et al. (1999) reported that a ventral limbic (vACC, insula) increase in rCBF and a dorsal cortical (dACC, dlPFC, IPL, PCC) decrease was observed with induced sadness in healthy volunteers. This pattern was reversed by antidepressants following recovery. These findings suggest a reciprocal relationship between the ventral and dorsal structures as mood changes occur.

Further open label studies using ketamine and PET have not provided any robust whole brain results. Using an ROI method, Carlson et al. (2013) discovered reductions in metabolism in the right habenula and amygdala. Areas of increase in metabolism on voxel-wise analysis included bilateral OCC, left inferior parietal and right postcentral gyri with decreases in the right dlPFC, vlPFC and bilateral vACC. The lack of a control group limits interpretation of the results. Interestingly the rate of response to ketamine was only 30% which was much less than the 52% previously reported (Zarate et al., 2006a).

Conclusions

There are a number of regions with altered CBF and metabolism in MDD including the ACC, amygdala, thalamus, insula, dlPFC, dmPFC, caudate and ventral striatum. There appear to be increases in metabolism as a result of MDD which are reduced after treatment but these remain inconsistent. CBF and metabolism of ACC appears to be predictive of response from PET studies. This further supports the hypothesis of a number of abnormal circuits that are involved in MDD. These circuits include the DMN, SN and CEN.

1.5.2.2. Single photon emission tomography (SPET)

SPET uses the effects of gamma ray emitting radionuclide but offers lower spatial and temporal resolution with reduced sensitivity. SPET uses stable radionuclides which have a longer half-life than those used in PET and is therefore cheaper (Rahmim and Zaidi, 2008).

Abnormalities in MDD

Investigators have reported global brain hypoperfusion in MDD (Fountoulakis et al., 2004). Symptom clusters have been further studied using PET and the HAM-D scale. Perico et al. (2005) reported that depressed mood was negatively correlated with rCBF in the left lentiform nucleus, amygdala and PHG and positively correlated with the posterolateral parietal cortex. Insomnia was negatively correlated with rACC, vACC, left insula and claustrum. In one trial hypoperfusion was reported in bilateral ACC, precentral and left postcentral cortices, IPL, insula, superior temporal cortex in MDD (Richieri et al., 2011). There was also bilateral hypoperfusion in the inferior, middle, medial and left superior frontal cortices. Richieri et al. (2011) suggested that rCBF differences between responders and non-responders were predictive of treatment resistance. This has also been suggested by other authors (Brockmann et al., 2009).

Effects of treatment

Early case control studies using SPET demonstrated bilateral increased rCBF to the bilateral basal ganglia, vACC, right thalamus and PCC following antidepressant treatment (Goodwin et al., 1993). Other trials have investigated the changes in rCBF as a result of rTMS (Kito et al., 2008). Decreases in rCBF in male MDD patients were reported bilaterally in the premotor area, dlPFC, mPFC, OFC, anterior insula, left ACC, somatosensory and inferior parietal regions and right vACC following right sided low frequency rTMS. There was no control group in this study, due to this and the continuation of medication during this study it was difficult to separate the drug effects from those of rTMS.

Overall results are inconsistent across treated and untreated MDD studies. Areas of hypoperfusion have been reported in the ACC, basal ganglia, amygdala, IPL and frontal cortex.

1.5.2.3. Magnetic resonance imaging (MRI) – Arterial spin labelling (ASL)

ASL is a non-invasive MRI technique utilised for the measurement of cerebral perfusion by magnetically labelling blood water and tracking it through the brain. It does not require any form of contrast agent and provides quantitative changes in local blood flow (Detre et al., 1992).

Abnormalities in MDD

Duhameau and colleagues (2010) observed significant hyperperfusion bilaterally in the vACC and left dmPFC, ACC, putamen, globus pallidus and amygdala in medicated tr MDD compared to

controls. A further study examined the effect of MDD and controls in later life with the only difference reported being increased white matter cerebral blood flow (Colloby et al., 2012). All patients in this study were currently taking antidepressants and one third had had a previous episode, therefore no sufficient control was present.

Abnormalities in tr MDD and rMDD

Lui and colleagues (2009) reported that rMDD had significantly increased cerebral blood flow to the hippocampi bilaterally and the right lentiform nucleus. The study compared rMDD with tr MDD and controls using both ROI and voxel based analyses. Reduced left MFG perfusion on voxel based analysis appeared to be a trait marker of MDD. rMDD were differentiated from tr MDD by greater perfusion bilaterally in the occipital lobe, paracentral lobule, lentiform nuclei, ACC and right hippocampus using a voxel based analysis.

In summary there have been limited ASL studies in MDD although findings support those of other imaging modalities reporting changes in metabolism in the hippocampus and ACC.

1.5.2.4. fMRI – Blood oxygen level dependent response (BOLD)

An alternative method of mapping neural responses in the brain is by using functional MRI (fMRI). The blood oxygen level dependent (BOLD) contrast is exploited in fMRI studies. BOLD is based on the MR signal change as a result of increased localised neuronal activity when the subject is engaged in a cognitive task. This is because the magnetic properties of deoxyhaemoglobin are different to those of oxyhaemoglobin (Pauling and Coryell, 1936). Deoxyhaemoglobin is restricted to the intracellular space of red blood cells which are confined to the blood vessels. Changes in deoxyhaemoglobin levels create changes in MR signal. During task engagement the local BOLD signal is paradoxically increased due to increases in cerebral blood flow and glucose usage and no change in oxygen consumption which results in a decreased oxygen extraction fraction and lower deoxyhaemoglobin content per volume unit of brain tissue (Logothetis, 2002, Fox and Raichle, 1986).

Limitations of BOLD fMRI

Limitations with BOLD fMRI include the low signal to noise ratio, image distortion (in addition to movement artefacts caused by respiration and heart beat) and temporal delay from neuronal activation to the BOLD response. The BOLD response is also non-quantitative and so the response can only be related as a response to some form of challenge. The BOLD response is dependent on local CBF, blood volume and oxygen metabolism. Signal dropout in orbitofrontal and anterior medial temporal regions also occurs. There are also difficulties around spatial resolution of signal from veins downstream from the capillaries supplying active neurones due to the differential oxygen saturation between veins, capillaries and arteries. This is more problematic at higher field strengths such as 3T (Brown and Eyler, 2006). Caffeine intake can

increase the BOLD response whereas cigarette smoking may cause decreases or increases (Davis et al., 1998, Domino et al., 2004, Liu et al., 2004).

Pharmacological MRI

Pharmacological MRI (phMRI) is a specific technique of administering a drug and measuring the drug's effects in the BOLD signal. Trials either utilise "modulatory phMRI" (drug pre-treatment is followed by a neuropsychological task) or "challenge phMRI" (the effects on the BOLD signal by the drug alone) (Anderson et al., 2008). Anderson and colleagues (2008) comprehensively reviewed the effect of 5-HT manipulation using phMRI techniques in healthy volunteers and patients with MDD. They noted that current drug treatment studies had a number of problems including baseline similarities in emotional processing between MDD and healthy controls or lack of appropriate control group (Anderson et al., 2008, Davidson et al., 2003, Schaefer et al., 2006, Fu et al., 2007). Other studies whilst using face emotion recognition had no neutral face in the paradigm (Fu et al., 2004). As a result there were few reliable conclusions which could be drawn from the studies. The modulatory phMRI evidence is discussed further with neuropsychological correlates in the following sections.

Facial emotion processing

There is consistent evidence of altered BOLD responses in varying brain regions in MDD in response to negative emotional stimuli (Samson et al., 2011). Impaired processing of positive facial emotion has also been reported, with increased amygdala, PHG, insula, thalamus, putamen and caudate response and decreased hippocampus in response to sad facial expressions. There is less agreement around how activity changes in the PFC, ACC and PCC. More consistent increases in BOLD have been observed in the motor cortex, fusiform and temporal gyri in MDD (Stuhrmann et al., 2011). There is additional evidence of increased vigilance towards sad expressions in MDD and a reduction in the accuracy of recognition of happy and sad facial expressions. The problem with this evidence is the heterogeneous samples, paradigms and drug treatments (Bourke et al., 2010).

As part of an emotional interference task, MDD patients had greater bilateral amygdala BOLD compared to controls when attending to happy faces (Liao et al., 2012). There was no difference when they ignored happy faces or responded to neutral faces. Responses were also correlated with mood rating scales. When an emotional and non-emotional Stroop test was utilised MDD patients had increased response in bilateral anterior insula. Interestingly there was no difference in BOLD in patients when using the two forms of Stroop test but this must be counterbalanced by potential gender effects, as there were more females, and also different medications patients were being treated with (Chechko et al., 2013). More recent emotion processing task studies

have demonstrated reduced response in the right dlPFC with explicit viewing of negative emotions and dorsal ACC with positive emotions (Korgaonkar et al., 2013).

Increasing left amygdala BOLD response to all faces, particularly fearful faces has been demonstrated using affective facial stimuli tasks in MDD before and after 8 weeks treatment with sertraline (Sheline et al., 2001). Others have reported no difference in the recognition of fear between MDD and controls (Kan et al., 2004). Changes in the amygdala appear to be the most reliable result when MDD patients are exposed to sad or fearful facial expression.

Effects of antidepressants on facial emotion processing

Increased amygdala response to masked facial emotions has been reversed following treatment with sertraline in MDD patients (Sheline et al., 2001). Citalopram has been shown to increase bilateral hippocampus response to happy faces and right anterior insula to sad faces in controls compared to rMDD patients. Comparison with neutral faces was not able to explain the BOLD response changes (Anderson et al., 2011). More recently, treatment with citalopram abolished increased BOLD response in the bilateral amygdala to sad but not fearful facial emotion in currently depressed patients who achieved remission (Arnone et al., 2012b). This contrasts with the earlier findings of reduced response in the right amygdala and increased response in the left amygdala following sertraline treatment, in currently depressed patients when masked sad faces were presented compared to neutral faces (Victor et al., 2010).

Impaired facial emotion processing has been linked to changes in response of the PFC, amygdala, ACC and PCC. Treatment with antidepressants can reduce or increase abnormal responses in the amygdala.

Reward

There is a growing body of literature suggesting structural and functional alterations in the brain's reward system in MDD. The primary reward deficit in MDD is anhedonia. A key reward 'circuit' includes dopamine neurons in the VTA which project to the NAcc. The VTA neurons also have projections to the PFC, amygdala and hippocampus (Russo and Nestler, 2013, Savitz and Drevets, 2009). These secondary regions appear to also be hyporesponsive in MDD (Kumar et al., 2008). When oral dextroamphetamine has been used as a dopamine probe to stimulate the reward system fMRI BOLD response was decreased in the right vlPFC, PCC and mFG, bilateral caudate, putamen and left OFC (Tremblay et al., 2005). Antidepressant response has been linked to improving reward experience in MDD (Wichers et al., 2009) and reduced reward learning signalling as well as salience toward rewarding events (Kumar et al., 2008). Antianhedonic effects of stimulating the NAcc have been reported by Bewernick and colleagues (2010) in an uncontrolled study using deep brain stimulation of the region. Linked to this they also found decreased metabolism on PET imaging in the PFC, OFC, vACC, PCC, thalamus and caudate (Bewernick et al., 2010).

Increased BOLD response in the PCC, vlPFC and ventral striatum are related to reward system abnormalities in MDD.

Rumination

There is strong evidence for a role of rumination and increased self-focus in MDD. Rumination is a form of self-referential processing which is likely a trait marker of MDD (Nolen-Hoeksema, 2000). Rumination and self-focus has been strongly associated with negative affect (Mor and Winquist, 2002). Self-referential processing is associated with increased activity of structures that constitute the default mode network (DMN), a network of several brain regions that show high levels of functional connectivity in the resting brain. The DMN includes the posterior cingulate/precuneus, mPFC, vACC and bilateral lateral and inferior parietal cortex (Bluhm et al., 2008).

Verbal items (e.g. judging statements about one's own abilities, traits or attitudes) are associated with increased response of vmPFC, dmPFC, PCC and retrosplenial cortex (RSC) (Johnson et al., 2002). Spatial tests (e.g. counting balls taking either own or avatar's perspective) appear to recruit PCC, dmPFC, vACC, rACC, insula and temporal cortex (Vogeley et al., 2004). Similar effects were reported on emotional and autobiographical recall tests (Northoff et al., 2006, Nejad et al., 2013, Fossati et al., 2003, Gilboa, 2004). Brain structures appear to be recruited differentially when self-referential processing occurs. Increased response of the mFG and ACC has been linked to aspirational thinking in MDD compared to precuneus/PCC response linked to thinking about duties and obligations (Johnson et al., 2009). In addition the amygdala BOLD response modulates mood congruent memory biases during transient sad mood (Ramel et al., 2007).

The cortical midline structures are part of the DMN and are centrally involved in rumination but are also associated with regions of the salience network. Drugs targeting attenuating self-referential processing in these cortical midline structures could be used to test as biomarkers of treatment response.

Cognition

There are a number of areas where cognitive deficits occur in MDD. These worsen with increasing severity of symptoms, co-morbid psychiatric disorders and number of hospital admissions (Austin et al., 2001). The cognitive deficits include reduced attention, concentration, working memory (Marquand et al., 2008), psychomotor speed, learning, and executive functioning (Elliott et al., 1996). The cognitive deficits in attention, memory, executive function and global cognitive function are noted to remain present even when in remission (Hasselbalch et al., 2011). It has been hypothesized that the reasons for cognitive impairment may include a

tendency toward intrinsic processing, rumination and filtering negative material from working memory (Joormann and Gotlib, 2008) .

Cognition – executive function and working memory

MDD patients when performing complex planning tasks, using an adapted Tower of London task, had increased response in the vIPFC, dIPFC and angular gyrus/cuneus in an fMRI study (Fitzgerald et al., 2008b, Thomas and Elliott, 2009). There was poorer accuracy and higher response times in the MDD group. An n-back working memory task was also used in Fitzgerald et al. (2008b) with increased activation in the MFG, mFG, inferior frontal gyri, ACC, precentral gyrus, IPL, middle temporal gyrus, precuneus and thalamus. Other investigators have reported reduced response in the thalamus, right precentral gyrus and right parietal cortex to word and face n-back tasks (Barch et al., 2003). The working memory and executive function abnormalities correlate with a number of structures but there are no conclusive findings.

Cognition - memory

When memory encoding in medicated MDD was investigated, increased left PHG, bilateral fusiform gyri, lingual gyri, right mFG and left superior frontal gyrus response was observed (Werner et al., 2009). There was no difference in task accuracy reported. Reduced response was noted in the mFG, ACC, PCC, cingulate gyrus and middle temporal gyrus during encoding. There are no clear conclusions of the regions involved in memory deficits due to the varying paradigms used to test.

Cognition - emotional processing

There are emotional processing biases in MDD. Increased and sustained amygdala response to negative words has been reported in MDD compared to controls (Siegle et al., 2002). Increased amygdala response to encoding negative emotional pictures has been reported in MDD compared to controls (Hamilton and Gotlib, 2008). In another study, where paired pictures and sentences were used, decreased rACC, left PCC, left insula/striatum and right cerebellum response was noted in MDD compared to controls, when positive and negative stimuli were presented (Kumari et al., 2003). There is a noted affective bias in the interpretation of sad faces and words which has been linked to differential neural responses in the hippocampus and vACC (Elliott et al., 2000b, Chamberlain and Sahakian, 2006). Using an emotional Stroop task, with sad and neutral words presented in varying colours, increased response of the left rACC and right precuneus has been reported (Mitterschiffthaler et al., 2008). The ACC appears to have a central role in abnormal emotional processing and is likely to be important in salience of appropriate stimuli. It could therefore have an important role in the switching between different resting state networks.

There are a number of cognitive deficits in MDD across several domains. There are a number of structures involved. The most consistent are dIPFC for executive function and ACC and

amygdala for emotional processing biases. The nature of the response, however, has not been consistent due to the varying paradigms used.

1.6. Conclusions

There are a number of changes noted in imaging studies of MDD. Structural brain imaging suggests reduced volume in the ACC, dlPFC, dmPFC, OFC, caudate and hippocampus in MDD. Overall brain volume loss and volume reductions of the dlPFC and hippocampus may be state effects, while increased rACC volume may be a trait marker. The volume reductions in some of these structures have been suggested to predict response to treatment including the ACC, PCC, MFG precuneus, insula and OCC. Increased amygdalar, hippocampal and dlPFC sizes have been reported following antidepressant treatments.

A number of changes in regional brain function have been reported using PET including the ACC, amygdala, thalamus, insula, dlPFC, dmPFC, caudate and ventral striatum. In the rACC, CBF and metabolism has been reported to be predictive of response. There were reductions in CBF in the ACC, thalamus, putamen and cerebellum despite remission. Following antidepressant treatment increases in metabolism/CBF occur in the PFC and rACC. Mayberg et al. (1999) reported ventral limbic increases in CBF and dorsal cortical reduction in CBF on PET which was reversed by antidepressants following recovery, suggesting interplay between collective networks of structures proposed to be modulated by the ACC in MDD.

Functional imaging, using ASL, further extends the structural findings with noted elevated CBF and glucose metabolism in the ACC, amygdala, thalamus and insula. It is difficult, however, to draw definite conclusions regarding the effects of treatment and it is likely that there are differential effects on structures as a result of drug treatment.

SPET imaging findings are inconclusive but suggest hypoperfusion in the ACC, basal ganglia, amygdala, IPL and frontal cortex. Evidence from challenge phMRI also does not add any further conclusions.

The largest amount of evidence from imaging studies in MDD comes from fMRI particularly the use of neuropsychological tasks linked to fMRI BOLD response. Impaired facial processing of positive faces has been linked to changes in BOLD response in the amygdala, PHG, insula, thalamus, putamen and caudate. Antidepressants alter amygdala response to facial emotion.

The roles of reward, rumination and cognition in MDD allow further investigation of dysfunctional brain networks. Reward tends to be modulated by dopamine and may provide further opportunity to understand the links between the structural correlates and neurotransmitter systems. Increased BOLD response in the PCC, vlPFC, mFG, caudate, putamen and OFC are reported following dextroamphetamine. Rumination appears to be linked to structures that form part of the default mode network and may provide a future biomarker for antidepressant treatment response. Self-

focus tasks have been associated with increased response in the PFC, PCC, ACC and insula. The cortical midline structures are part of the DMN and are centrally involved in rumination but are also associated with regions of the salience network.

Cognitive impairments in attention, concentration, memory, learning and executive function have been well demonstrated and are likely linked in part to the effects of MDD on rumination. Problems with executive function and working memory have been associated with increased response in the PFC, ACC, frontal gyri, IPL, precuneus and thalamus. Several of these regions including the ACC and amygdala have been linked to emotional processing biases.

The structural and functional imaging findings point to the collective dysfunction of brain networks in MDD. These include the default mode network (PCC/precuneus, mPFC, vACC), salience network (ACC and insula) and central executive network (ACC, dlPFC and portions of the parietal lobe). The latter two have collectively been known as the task positive network (TPN). Mayberg et al. (1997) proposed the role of the ACC as a switching area between these resting state networks linking dorsal neocortical and ventral paralimbic structures. Investigating the interplay between the DMN, SN and CEN networks, focussing on the ACC and the effects of pharmacological probes, will therefore be the focus of the thesis.

Chapter Two: Resting state networks in major depressive disorder

An abbreviated version of this chapter has been published:

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2.1. Resting state networks

The resting state refers to regional neural activity of the brain when humans or animals are awake and alert but not actively involved in any activity that requires attention or a goal-directed activity (Raichle et al., 2001, Broyd et al., 2009). Resting state fMRI studies of major depressive disorder (MDD) have focused on several distinct networks containing brain regions that have been shown to have correlated oscillating blood oxygenation level dependant (BOLD) signal. Veer et al. (2010) identified a total of 13 functionally relevant resting state networks (RSNs) from a study of 19 recovered depressives and 19 HC. The 13 functionally relevant RSN were: 1) Primary visual; 2) Lateral visual; 3) Medial visual; 4) Sensory-motor; 5) Right lateral; 6) Left lateral; 7) Precuneus; 8) Ventral stream; 9) Medial temporal; 10) Salience; 11) Task positive; 12) Auditory; and 13) Default Mode (Veer et al., 2010); all of which have previously been demonstrated in healthy volunteers (Damoiseaux et al., 2006).

Methods of analysing resting state networks

Resting state networks are most frequently assessed first by identifying regions that show correlated activity over time against a region of interest (ROI; seed-based correlation) or that emerge from independent components analysis (ICA). ICA is able to extract the BOLD time series from a number of spatially independent components which can be interpreted as a network showing similar BOLD activity (Rosazza and Minati, 2011). The degree to which the component is present is expressed as a power function. Direct comparisons of the different analysis methodologies have identified similar networks (Bluhm et al., 2008). An alternative method of regional homogeneity (ReHo) analyses the differences in neural activity between one voxel and its nearest neighbours. It assumes that the haemodynamic characteristics of the neighbouring voxels are similar and also that a cluster of voxels will demonstrate synchronised activity (Liang et al., 2013). Abnormal ReHo is therefore likely to be related to temporal changes in BOLD signal (Zang et al., 2004). Other measures include Uddin and colleagues' "network homogeneity", where voxels are compared with all other voxels in the brain network (Uddin et al., 2008), "integrated local correlation" (Deshpande et al., 2009) and Greicius et al. (2004) "goodness of fit" model (Greicius et al., 2004). More recently newer techniques for the analysis of resting state have emerged. These include analysis of the fractional amplitude of low frequency fluctuations (fALFF) or the amplitude of low frequency fluctuations (ALFF) and voxel-mirrored homotopic connectivity. Fractional ALFF is the fractional component of the low frequency range of the ALFF which is closer to the spontaneous resting neural activity (Zou et al., 2008). Voxel-mirrored homotopic connectivity measures the functional connectivity (FnC) between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere (Wang et al., 2013).

Strengths vs weaknesses of different analysis methods

There are strengths and weaknesses with each of these methods. ICA is a model-free data driven approach. The number of components generated in ICA during the analysis, however, will

affect the number of spatially distinct networks detected. Components can be functional networks or physiologically linked regions but may also be imaging artefacts. It is also difficult to compare components between groups and participants (Uddin et al., 2008). In the ROI based method, seed placement can be arbitrary affecting the patterns of FnC observed (Uddin et al., 2008). Furthermore, the ROI based method is more susceptible to contamination from other non-neural low frequency fluctuations when compared to the ICA based approach (Greicius et al., 2007). Kuhn has also commented that seed-voxel-based analysis approach is highly dependent on the positioning of the seed voxel and may therefore produce inconsistent results (Kuhn and Gallinat, 2013).

The newer method of network homogeneity is better suited to examining long range connectivity and group differences in pathology, since it allows comparison of one voxel with all the other voxels in a particular network. However, the network of interest needs to be identified and well characterised prior to analysis, making network homogeneity less useful in paediatric populations, as there is potential to miss differences between networks which would otherwise be demonstrated (Uddin et al., 2008). The “goodness of fit” model developed by Greicius et al. (2004) also suffers from similar problems because the data are matched to a spatial template which is decided upon prior to analysis. Attempts to alleviate this by examining the four “best-fit” components have been incorporated. These components are then matched using an automated process followed by the examination of the differences between them (Greicius et al., 2004).

The advantage of regional homogeneity (ReHo) is the model free nature of the method which allows discovery of unpredicted BOLD response. However, regional homogeneity can be affected by the level of spatial smoothing, cluster size and volume examined (Zang et al., 2004). This method was reported to be insensitive to phase variability, such as random noise across the time series, leading to an improvement in sensitivity to detect differences in spontaneous neural activity (Guo et al., 2012a). Integrated local correlation was introduced to alleviate the problems of ReHo. ReHo uses only the neighbouring voxels whereas in integrated local correlation the integration of the spatial correlation function for each voxel is used. Integrated local correlation is also reported to be unaffected by fluctuations from cardiac and respiratory cycles except around large blood vessels (Deshpande et al., 2009).

Functional connectivity (FnC) provides information regarding the correlation between a set of pre-specified brain regions. As FnC is not data driven it does not demonstrate changes in specific brain regions and will not identify the part of the network that is dysfunctional (Zang et al., 2007, Zou et al., 2008). ALFF allows detection of spontaneous BOLD signal changes without these challenges. Greater regional ALFF is especially prevalent, however, around large blood vessels and cisternal areas due to physiological noise (Zang et al., 2007, Zou et al., 2008). To improve the approach Zou et al. (2008) utilised the ratio of the power of the low frequency range (0.01-0.08Hz) to the whole frequency range (0-0.25Hz), termed fractional ALFF (fALFF).

Conclusions

There are a number of resting state networks which can be analysed by several different methods which each have their own advantages and disadvantages. The methods include ROI, ICA, network homogeneity, integrated local correlation, goodness of fit, ReHo, FnC, ALFF and fALFF.

2.2. Default mode and salience networks

Default mode network

Raichle first coined the phrase “default mode” to describe correlated brain activity in its resting state (Raichle et al., 2001). The default mode network (DMN), one of several resting state networks of brain regions that show high levels of FnC in the resting brain, includes the posterior cingulate cortex (PCC)/precuneus, medial prefrontal cortex (mPFC) ventral anterior cingulate cortex (vACC) and lateral and inferior parietal cortex. As it is most active at rest, the DMN has been associated with self-referential processing (Bluhm et al., 2008). Different components have been emphasised by other authors. For example, Franco et al. (2009) emphasise the ACC (BA 11/32), dorsolateral and superior frontal gyrus (BA 8/9/10), inferior frontal cortex (BA47), PCC (BA 23/31), posterior parietal lobule (BA 7/39/40), inferior temporal gyrus (BA19/37) and PHG (BA 30/36) (Franco et al., 2009). The most consistently defined parts of the DMN are the precuneus/PCC and mPFC. The PCC is believed to be related to monitoring of internal and external environments (Raichle et al., 2001), whilst the mPFC is thought to be involved in social cognition and observing self and others psychological state. The DMN therefore interfaces task performance and emotion (Simpson et al., 2001). Self-referential tasks have demonstrated increased response in the dorsomedial prefrontal cortex (dmPFC) whilst reduced response was observed in the ventral mPFC when affective stimuli were used (Gusnard et al., 2001).

Task positive and task negative networks

The DMN is suppressed by external task requirements and it has been termed the task negative network (TNN), inversely correlated with task positive networks (TPN). The task positive network is now described as the central executive and salience networks. The TPN typically involves the dlPFC, medial temporal cortex, parietal lobe, insula bilaterally and supplementary motor area and is related to task performance activation (Biswal et al., 1995, Fox et al., 2005, Broyd et al., 2009). Hamilton and colleagues compared DMN dominance over TPN utilising fMRI data in 17 depressed and 17 HC. DMN dominance has been shown to have significant positive correlation with Ruminative Responses Scale depression subscale scores and negative correlation with self-reflection subscale scores (Hamilton et al., 2011). However, in this study participants were not questioned about their symptoms at the time of scanning. They also noted that the right fronto-insular cortex (r-FIC) activated at DMN peaks whereas in controls it activated at TPN peaks. The r-FIC is therefore thought to control switching between the DMN and TPN. DMN response is

attenuated when task related activations are seen (Raichle et al., 2001, Broyd et al., 2009). More complex and demanding tasks cause greater suppression of the task negative DMN (McKiernan et al., 2006) and the DMN may remain intact when performing simple sensory tasks, during conscious sedation and the early stages of sleep (Greicius et al., 2003). Abnormalities of the DMN have been reported in depression, anxiety, dementia, schizophrenia, epilepsy, autism and attention deficit/hyperactivity disorder (Broyd et al., 2009). The specificity of such changes has not so far been investigated. It is possible some may relate to transdiagnostic neurobiological processes.

FnC is the temporal correlation between fluctuations in the BOLD signal that is measured using fMRI at different anatomical sites (Fox and Raichle, 2007). Bluhm et al. (2008) reported that there are gender differences in the DMN with women having increased PCC/precuneus and bilateral medial frontal connectivity in a ROI analysis, and greater activity in bilateral superior frontal gyrus and right angular gyrus (Bluhm et al., 2008). Age has also been demonstrated to alter the DMN and FnC. Task negative attenuations in the DMN are less sensitive to cognitive demand in older adults, whilst there is reduced FnC between regions of the DMN in older adults (Bluhm et al., 2008, Esposito et al., 2008).

Salience network

The salience network, another RSN, is involved in filtering information to support behaviour choice. It is structurally correlated to the ACC and insula. (Seeley et al., 2007, Elton and Gao, 2014). The insula is thought to be important in the early evaluation of the significance of sensory and affective stimuli presented. This involves perception of the body's physiological responses (Craig, 2002, Lovero et al., 2009).

Rostral ACC (rACC) is classically engaged by errors in task performance (error-related brain activation) along with mPFC, insula, precuneus and PCC (Menon et al., 2001). These regions form parts of both the salience network and DMN. Some of the structures are related to self-referential thinking (mPFC) and monitoring of eye movements and spatial memory (PCC) (Vogt et al., 1992, Ridderinkhof et al., 2004). It is hypothesized that in MDD there would be increased activation of the DMN and reduced activity of the salience network.

Conclusions

The DMN consists of the PCC/precuneus, mPFC and vACC while the salience network consists of the ACC and insula. The DMN is associated with rumination but abnormalities in the DMN are not unique to MDD.

2.3. Other resting state networks in MDD

Other networks of importance in MDD include the affective network and central executive network. The central executive network (CEN) is involved in complex cognitive tasks, working

memory, decision making and conflict resolution (Corbetta and Shulman, 2002, Sheline et al., 2010). The CEN contains the rACC, dPFC and portions of the parietal lobe; overlapping with regions of the DMN (Alexopoulos et al., 2012). The affective network includes the amygdala, temporal poles, pallidum, insula and superior temporal gyrus. The role of this network is emotional regulation and processing (Zeng et al., 2012b). Abnormalities have previously been noted in the affective network between the amygdala and hippocampus/PHG, OFC and temporal poles in MDD but there was no control for physiological effects (Zeng et al., 2012b, Zhang et al., 2014b). Overall there are fewer studies that have examined the central executive and affective network abnormalities in MDD when compared to those investigating the DM and salience networks. The populations used in previous resting state studies are complicated by age related or diagnostic issues which affect the findings and limit reliability (Alexopoulos et al., 2012). To my knowledge, there are no published studies that examine the effects of antidepressants on the CEN or affective network.

Other networks of importance include the CEN which includes the rACC, dPFC and portions of the parietal lobe and the affective network which include the amygdala, insula and temporal regions. There are few studies that have examined these networks.

2.4. Resting state fMRI studies in MDD

Analysis methods

Table 7 shows fMRI studies of resting state networks in MDD. Studies of adolescents were excluded due to difficulty with emerging MDD diagnoses, as were those studies without a control group. Whilst most studies examined the DMN others examined the resting state activity and connectivity of specific structures using the various methods highlighted above. No studies investigated changes in the salience network. Two studies examined the affective network (Sheline et al., 2010, Zhang et al., 2014b). Patients in most studies were unmedicated either prior to, or as part of, the study. The scanner's magnetic field strength varied between 1.5 to 4 Tesla. Six studies incorporated a tr MDD group (Lui et al., 2011, Wu et al., 2011, Guo et al., 2011b, Guo et al., 2012b, Guo et al., 2012a, Guo et al., 2013b). In these studies there are varying effects on the cerebellum, lingual, fusiform and temporal gyri, although the pattern was inconsistent. First episode patients were incorporated in 17 studies. (Zhou et al., 2010, Guo et al., 2011a, Peng et al., 2011, Cao et al., 2012, Wang et al., 2012a, Guo et al., 2012a, Peng et al., 2012, Ye et al., 2012, Zhu et al., 2012, Wang et al., 2013, Guo et al., 2013a, Liu et al., 2013b, Guo et al., 2013c, Guo et al., 2014b, Li et al., 2014, Wang et al., 2014b, Zhang et al., 2014b). A few studies report consistent changes in reduced ALFF, fALFF and ReHo in the left PHG (Guo et al., 2011a, Guo et al., 2013c, Liu et al., 2013b). Findings from "late life" depression were reported in five studies (Kenny et al., 2010, Bohr et al., 2012, Liu et al., 2012a, Yue et al., 2013, Andreescu et al., 2013).

18 studies used a seed region of interest FnC method (Anand et al., 2005a, Anand et al., 2007, Anand et al., 2009, Bluhm et al., 2009, Horn et al., 2010, Kenny et al., 2010, Sheline et al., 2010, Zhou et al., 2010, Lui et al., 2011, Bohr et al., 2012, Cao et al., 2012, Liu et al., 2012b, Peng et al., 2012, Ye et al., 2012, Andreescu et al., 2013, Guo et al., 2013b, Tang et al., 2013, Avery et al., 2014). No studies corrected for cardiac or respiratory cycles when using seed region analyses. 14 studies used ReHo to show differences in connectivity (Yuan et al., 2008, Yao et al., 2009, Liu et al., 2010, Guo et al., 2011a, Guo et al., 2011b, Peng et al., 2011, Wu et al., 2011, Guo et al., 2012a, Liu et al., 2012a, Liang et al., 2013, Ma et al., 2013, Yue et al., 2013, Li et al., 2014, Wang et al., 2014b). Two of these studies also used coherence based ReHo (Guo et al., 2012a, Liu et al., 2012a). One study examined surface based ReHo which takes account of cortical folding patterns (Li et al., 2014). One study used network homogeneity within the DMN (Guo et al., 2014b).

Independent component analysis

Spatial ICA was utilised in seven studies (Greicius et al., 2007, Zhu et al., 2012, Li et al., 2013a, Guo et al., 2013c, Manoliu et al., 2013, Sambataro et al., 2013, Buchanan et al., 2014). Each of the studies reported increased FnC of the DMN in MDD with other structures such as the vACC, OFC, hippocampus and thalamus. This suggests these structures form interconnecting circuits as has been suggested in the limbic-cortical dysregulation model of MDD (Mayberg, 2003). Manoliu et al. (2013) reported aberrant FnC between the DMN, SN and CEN. Right anterior insula FnC within the SN was associated with dysfunction in DMN-CEN interaction and symptom severity. Li et al. (2013a) reported that increases in FnC of the DMN normalised following treatment with antidepressants (Li et al., 2013a).

Amplitude of low frequency fluctuations/fractional amplitude of low frequency fluctuations

ALFF/fALFF was utilised in the methodology of 9 studies (Guo et al., 2012b, Wang et al., 2012a, Jing et al., 2013, Liu et al., 2013a, Guo et al., 2013a, Liu et al., 2013b, Guo et al., 2014a, Liu et al., 2014, Zhang et al., 2014b). ICA was combined with fALFF in two studies (Guo et al., 2013c, Sambataro et al., 2013). Three studies examined whole brain FnC (Veer et al., 2010, Zeng et al., 2012b, Wang et al., 2014a).

ALFF/fALFF has been used to examine treatment resistant, remitted and first episode MDD. The results highlight similar themes which include increased ALFF in the cerebellum and increased FnC between the cerebellum and hippocampus (Guo et al., 2012b, Guo et al., 2013a). The cerebellum has connections to a number of frontal and limbic regions (such as the amygdala and hippocampus) that are important in emotional and cognitive processing (Schmahmann and Caplan, 2006). ALFF changes were less consistent between anterior and posterior lobes of the cerebellum; Wang et al. (2012a) reported increased ALFF in both the anterior and posterior lobes whilst Guo et al. (2012b) reported increased ALFF in the posterior lobe only. Additionally reduced

ReHo in first episode MDD in the posterior cerebellum is reported in two studies (Guo et al., 2011a, Peng et al., 2011).

The lingual gyrus was consistently reported to have reduced ALFF even in siblings of patients with MDD (Guo et al., 2012b, Jing et al., 2013, Liu et al., 2013a). This finding was also reported in 1st episode MDD (Wang et al., 2012a). The lingual gyrus is reported to be within the visual recognition network and is believed to have a role in the perception of emotions when facial stimuli are presented (Jing et al., 2013, Tao et al., 2013). The other interesting finding was the changes in ALFF in the mFG/ACC were reported as both increased (Guo et al., 2012b, Liu et al., 2013a) and decreased (Liu et al., 2013b). The finding of increased fALFF in the mFG/ACC in siblings suggests neural response in these regions could be investigated as a biomarker for MDD. Liu et al. (2013a) suggested this abnormality may relate to the insula since it has reciprocal connections to the inferior frontal gyrus, ACC and mFG.

Regional homogeneity

ReHo studies report abnormalities in a number of areas. The studies considered treatment resistant, sub threshold and later onset MDD. Decreased ReHo has been reported in the posterior cerebellum in two studies. Several studies reported decreased ReHo in the insula (Yao et al., 2009, Guo et al., 2011b, Li et al., 2014), ACC (Yao et al., 2009, Liu et al., 2012a) and dorsolateral prefrontal cortex (dlPFC) (Liu et al., 2012a, Ma et al., 2013). It is known that the ACC plays a central part in cognition, emotional regulation and attention functions (Elliott et al., 1997). The left and right dlPFC has been suggested to manage emotional judgement and anticipation of emotional judgement (Nitschke and Mackiewicz, 2005). The insula is associated with emotional response to interoceptive sensory stimuli (Reiman et al., 1997).

Functional connectivity

The ROI FnC studies examined a number of different brain areas and populations including both first episode and later onset MDD. Anand et al. (2005a) reported consistent findings of decreased FnC between the ACC, amygdala and thalamus (Anand et al., 2005a, Anand et al., 2007, Anand et al., 2009). Liu et al. (2012b) reported decreased FnC between the PCC/precuneus, ventromedial prefrontal cortex (vmPFC), hippocampus, OFC and superior frontal gyrus. These findings were further extended by Guo et al. (2013b) who reported decreased cerebellar FnC with the right precuneus, IPL and angular gyrus. First episode MDD appears to have decreased vACC and PFC/IPL connectivity (Zhou et al., 2010). These regions seems to have decreased FnC with the ACC, hippocampus, insula, amygdala and thalamus (Lui et al., 2011) There is also some agreement regarding increased FnC of the caudate, cingulate and precentral gyrus. The problem comparing these studies is that the population sample and seed regions used are generally not the same between studies. Overall, in the future large studies are needed using a standardised methodology.

The whole brain FnC studies present some further curious findings. Wang et al. (2014a) reported on patients with MDD with or without a history of neglect. It is interesting to note that the findings of decreased connectivity in the ACC, hippocampus, PHG and insula were present both Wang et al. (2014a) and Zeng et al. (2012b) whether or not there was a history of neglect. This would suggest a history of neglect produces the same effects on FnC in MDD, potentially through a common pathway.

Increased ALFF, fALFF and FnC of the ACC and insula is reported in medicated and first episode MDD with reductions noted in unmedicated MDD samples (Anand et al., 2005a, Anand et al., 2007, Greicius et al., 2007, Yao et al., 2009, Anand et al., 2009, Horn et al., 2010, Zhou et al., 2010, Lui et al., 2011, Wu et al., 2011, Peng et al., 2012, Liu et al., 2012a, Ye et al., 2012, Zeng et al., 2012b, Zhu et al., 2012, Liu et al., 2013a, Sambataro et al., 2013, Wang et al., 2014a). Findings in the dlPFC and mPFC were not consistent (Ye et al., 2012, Ma et al., 2013). There were reductions in ALFF, fALFF and FnC of the precuneus, caudate and IPL in medicated MDD and increased effects in unmedicated samples (Greicius et al., 2007, Yuan et al., 2008, Bluhm et al., 2009, Kenny et al., 2010, Zhou et al., 2010, Lui et al., 2011, Wu et al., 2011, Bohr et al., 2012, Guo et al., 2012b, Liu et al., 2012b, Liu et al., 2012a, Peng et al., 2012, Wang et al., 2012a, Zhu et al., 2012, Andreescu et al., 2013, Guo et al., 2013a, Guo et al., 2013b, Jing et al., 2013, Li et al., 2013a, Wang et al., 2014a). Decreased FnC was reported in the thalamus in unmedicated MDD (Anand et al., 2005a, Anand et al., 2007, Anand et al., 2009, Peng et al., 2011). It is important to note that markers of intensity such as ALFF, fALFF and ReHo are different from those of FnC as a reduced intensity does not automatically imply a reduction in connectivity. On balance, the evidence suggests overactivity of the DMN and underactivity of the SN which could be corrected by antidepressant treatment. This is most supported by the evidence from measures of intensity such as ALFF and fALFF. These measures represent spontaneous brain activity which correlates with regional blood flow, BOLD and neural response.

Table 7 Resting state network fMRI studies in MDD sorted by methodology

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Studies using amplitude of low frequency fluctuations (ALFF)					
Guo et al. (2012b)	18 trMDD (med) 17 cMDD (med) 17 HC	cMDD mFG, ACC, post CER , MTG, inferior occipital gyrus, FG, putamen, caudate, IFG trMDD mFG, ant CER , LG, middle occipital gyrus, cuneus	cMDD ITG, ant CER trMDD ACC/mFG, post CER	Varying medication profiles. trMDD had longer episode duration.	trMDD higher ALFF in DMN and lower ALFF in visual recognition network compared to treatment responsive
Guo et al. (2014a)	44 cMDD 44 HC	I-MTG, r-STG, I-culmen		First episode had decreased ALFF in I-MTG and culmen whereas recurrent MDD had decreased ALFF in culmen only	Decreased ALFF in temporal regions. No correlation with gray matter volume
Jing et al. (2013)	19 cMDD (med) 19 rMDD 19 HC	cMDD & rMDD r-precuneus, I-LG cMDD r-precuneus, I-LG	rMDD r-putamen cMDD r-mFG, r-putamen	All female population. Varying medication profile. No correction for multiple comparisons. ALFF positive correlation with number of episodes, fALFF positively correlated with disease duration.	r-mFG could be biomarker for MDD. DMN nodes still affected even when medicated.
Zhang et al. (2014b)	32 cMDD 1 st episode 35 HC	b/l OFC	b/l INS, b/l temporal lobe, I-fusiform cortices and mid occipital gyrus decreased I-OFC-AMYG FnC.	Due to young age could not guarantee diagnosis of MDD and not BD.	Decreased ALFF in OFC suggests hypofunctioning of emotional regulation in AN
Studies using fractional amplitude of low frequency fluctuations (fALFF)					
Guo et al. (2013a)	24 cMDD 1 st episode 24 HC	FnC IPL and b/l ITG positive correlation with severity	I-Crus I and I-cerebellar lobule VI FnC right hippocampus negative correlation with severity	Abnormal fALFF regions as seeds.	Increase CER ALFF may be disease state phenomenon.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Liu et al. (2013a)	22 cMDD (19 med) 22 sibsMDD 26 HC	cMDD l-precuneus, r-precentral, b/l postcentral gyri, l-mid occipital gyrus, b/l LG, l-superior and l-inferior occipital gyri sibsMDD r-mFG/ACC, r-precuneus	cMDD r-mFG/ACC, l-MFG, r-IPL, r-precuneus, l-precentral gyrus, l-angular gyrus, r-ventrolateral IFG, sibsMDD b/l LG, l-MFG, r-MTG	Varying medication profiles.	l-MFG endophenotype for MDD. r-dorsal mFG may be state marker for MDD. DMN/CEN abnormalities seen in siblings.
Liu et al. (2013b)	22 cMDD 1 st episode 19 HC	r-post CER, l-PHG, r-MFG,	l-superior occipital gyrus/cuneus	Control group from previous study.	Abnormal regions part of cortical-limbic dysregulation model of MDD.
Liu et al. (2014)	30 cMDD 30 HC	b/l OCC, cerebellum, r-STG	b/l vACC, rACC, OFC, premotor cortex, vPFC, dlPFC, l-SFG, r-putamen, l-caudate, l-INS, r-ant entorhinal cortex, l-inferior parietal cortex	No correlations with severity.	Findings may be related to DMN/CEN dysfunction
Wang et al. (2012a)	18 cMDD 1 st episode 18 HC	l-ITG, bilateral IPL and r-LG, left dlPFC, bilateral mOFC, MTG and r-IPL.	r-fusiform gyrus, ant and post CER, r-precentral gyrus, ITG, bilateral FG,	No correlations with severity.	May be related to disturbances of multiple emotion and cognition networks
Studies using ALFF, fALFF or FnC within Independent component analysis (ICA) defined networks					
Buchanan et al. (2014)	20 cMDD 26 HC	r + l-frontoparietal network and language network		All female sample. Applied ICA to produce 70 independent components	May be linked to abnormalities in cognitive control DMN and other networks
Guo et al. (2013c)	24 cMDD 1 st episode 24 HC	l-PHG	l-dmPFC	Mood rating scales not completed in controls.	dmPFC may be a marker of severity. No network effects noted

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Greicius et al. (2007)	28 cMDD (med) 20 HC		precuneus, vACC, OFC and THAL	Varying medication profile. 25 ICA components used. length of MDD episode positively correlated with FnC in vACC. vACC FnC may indicate treatment response.	vACC dysfunction may be related to CEN or salience network.
Li et al. (2013a)	24 cMDD 29 HC		post DMN/precuneus	Normalised following treatment.	Abnormal FnC of ant DMN may be biomarker
Manoliu et al. (2013)	25 cMDD recurrent 25 HC	Sup post DMN + precuneus, SN + b/l INS, l-ventral CEN + l-precuneus/MTG	Ant DMN + b/l ACC, inf/sup post DMN + b/l precuneus, SN + b/l ACC, l-ventral CEN + angular gyrus, dorsal CEN + r-postcentral gyrus	Most had co-morbid anxiety disorders. Varying medication profile. 75 independent components used.	r-ant INS correlated with symptom severity and altered DMN-CEN interaction. Aberrant connectivity between DMN + SN + CEN
Sambataro et al. (2013)	20 cMDD (14 med) 20 HC		DMN + vACC, r-lateral temporo-parietal cortex and PCC, rACC, r-hippocampus	Varying medication profile. Mood rating scales not completed in controls.	MDD characterised by widespread increases in DMN connectivity.
Zhu et al. (2012)	35 cMDD 1 st episode 35 HC	b/l PCC/precuneus and angular gyrus – associated with overgeneral memory	dmPFC/vACC, vmPFC, medial orbital PFC – associated with rumination.	MDD reported to be 'mild'. 30 ICA components used.	Dissociation of ant and post DMN is MDD trait.
Studies using Regional Homogeneity (ReHo)					
Guo et al. (2011a)	17 cMDD 1 st episode 17 HC	l-post CER and PHG, r-post central gyri and FG	r-ITG	Mood rating scales not completed in HC. Short illness episode duration.	Limbic-cortical network dysregulation.
Peng et al. (2011)	16 cMDD 1 st episode 16 HC	l-THAL, temporal lobe, post CER and bilateral occipital lobe		Longer TR (3s)	Limbic-cortical network dysregulation.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Guo et al. (2011b)	24 trMDD 19 HC	l-INS, STG, IFG, LG, culmen	l-STG, tuber, culmen, r-cerebellar tonsil and b/l FG	Short medication washout. Mood rating scales not completed in controls.	Abnormality of prefrontal–amygdalar–pallidostratial–mediothalamic mood circuit.
Wu et al. (2011)	22 trMDD (med) 22 cMDD (med) 26 HC	trMDD + cMDD – l-inferior mPFC, l-post FG, l-inferior frontal area, l-IPL, l-caudate, trMDD – l-precuneus/SPL, l-IFG, l-post FG, b/l IPL cMDD – l-prefrontal gyrus	trMDD + cMDD – b/l ACC and mFG, r-insula, r-PHG trMDD – l-mid cingulate, b/l ACC and mFG, r-MTG, r-INS, r-STG cMDD – l-mPFC, r-PHG	Mood rating scales not completed in controls.	Limbic-cortical network dysregulation suggested. DMN/salience network and CEN regions affected more in trMDD.
Li et al. (2014)	33 cMDD 1 st episode 32 HC	l-INS		Surface-based ReHo used which takes account of cortical folding patterns	Abnormal cortico-limbic regulation of emotional and cognitive information
Liang et al. (2013)	16 cMDD 17 BPD 16 HC	l-PHG, r-precentral gyrus, l-postcentral, precentral and cingulate gyri	r-IPL, r-precuneus, l-middle occipital lobe	Longer TR (3s).	DM/Salience network may be affected.
Liu et al. (2010)	15 MDD 15 1 st degree relatives 15 HC	cMDD – r-INS, r-MFG, r-lentiform nucleus, l-ant CER, l- STG, l-precentral gyrus, l-postcentral gyrus. relatives – r-INS and l-CER	cMDD – b/l IPL, l-IFG, l-post CER relatives – l-precentral gyrus	Relatives 9 years older on average.	Regions of salience network and CEN affected.
Ma et al. (2013)	19 MDD sub-threshold (Elderly) 18 HC	l-dIPFC, r-OFC, l-postcentral gyrus, l-MFG and l-ITG	b/l INS and r-dIPFC	Concomitant medical conditions and medication. Longer TR (3s) No correlation with CES-D.	Regions of CEN affected.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Yue et al. (2013)	22 MDD 'late onset' (1 st episode) 30 HC	r-MFG, l-SFG, l-AMYG + r-occipital and r-parietal lobe, r-AMYG + l-parietal lobe	l-AMYG + b/l putamen/frontal lobe, r-AMYG + frontal lobe	Not properly corrected for multiple comparisons. MDD patients significantly less educated.	Findings may be markers of cognitive dysfunction in this group.
Yao et al. (2009)	22 MDD 22 HC	r-PCC, r-INS, r-vACC, l-dACC, r-OFC, r-FG, l-lentiform nucleus r-OFC correlated with cognitive disturbance, r-post cingulate gyrus and r-INS with retardation, r-vACC and r-INS with hopelessness		More severe on HAM-D scoring. Long duration of illness (mean 5 years) Longer TR (3s). No correction for multiple comparisons.	Dysfunctional limbic–cortical–striatal–pallidal–thalamic circuit. Regions of DM/Salience Network have decreased ReHo.
Yuan et al. (2008)	18 rMDD 14 HC	l-MFG, b/l precuneus, b/l SFG, r-STG, r-MTG, r-FG, r-postcentral gyrus	r-SFG, b/l putamen, l-postcentral gyrus		Decreased ReHo in DMN regions even after remission. Trait marker.
Studies using coherence based Regional Homogeneity (ReHo)					
Guo et al. (2012a)	23 trMDD 22 cMDD 1 st episode 19 HC	trMDD l-CER (b/l CER when compared to cMDD) cMDD b/l SFG	trMDD l-FG	Treatment resistant group not clearly established. Mood rating scales not completed in controls.	CER involved in mood regulation. No effects on any network noted.
Liu et al. (2012a)	15 cMDD 'late life' (1 st episode) 15 HC	r-ACC, l-dIPFC, b/l mPFC, r-precuneus, r-angular gyrus, l-caudate	l-post CER, STG, r-postcentral gyrus, b/l supplementary motor area	Significant difference in MMSE scores. Mood rating scales not completed in controls. No correlation with HAM-D.	Decreased Cohe-ReHo in CEN/DMN regions.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Wang et al. (2014b)	14 cMDD 1 st episode 14 HC	r-SFG, l-MTG and r-ITG, r-precuneus, l-superior OCC, r-cuneus	l-dmPFC, l-cerebellum.	Baseline differences only reported in this table.	No inference
Studies using Network Homogeneity (NeHo)					
Guo et al. (2014b)	24 cMDD 1 st episode 24 HC	r-ITG	l-dmPFC	DMN mask produced from HC. Only examined effects within DMN.	dmPFC may prevent coordination of dorsal cognitive system and ventral emotional system
Studies using Region of Interest (ROI) methodology and functional connectivity (FnC)					
Anand et al (2007)	12 MDD 11 HC	ACC + AMYG/striatum/THAL		Mood rating scales not completed in controls. No correction for multiple comparisons. FnC increased, ALFF reduced following treatment.	No inference.
Anand et al (2009)	11 BD (5 BPD) 15 MDD 15 HC	rACC + dorsomedial THAL / r-AMYG		No correction for multiple comparisons. More severe decreases in BPD than MDD.	State dependent decreased FnC.
Anand et al. (2005a)	15 MDD 15 HC	b/l ACC + l-medial THAL, ACC and r-medial THAL, ACC + l-pallidostriatum.		Mood rating scales not completed in controls. Long duration of illness (mean 6 years). No correction for multiple comparisons.	Decreased cortical regulation of limbic activation. Regions of CEN/salience network affected.
Andreescu et al. (2013)	47 cMDD (elderly) (med) 46 HC	b/l MFG. Treatment responsive – l-dACC, r-dlPFC, r-cuneus	r-precuneus Treatment responsive – r-mPFC, l-precuneus, l-striatum	Participants gathered from several other trials. Controls significantly older and higher MMSE score.	Increased DMN FnC. ant DMN FnC increased after treatment.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Avery et al. (2014)	20 cMDD 20 HC		Dorsal mid insula cortex + AMYG, mOFC, right mid OCC and right MTG	Incorporated interceptive task.	No inference
Bluhm et al. (2009)	14 cMDD (1 med) 15 HC	Precuneus/PCC + b/l caudate		Longer TR (3s) but 4T MR scanner.	Decreased DMN FnC may be early marker.
Cao et al. (2012)	42 cMDD 1 st episode 32 HC	l-hippocampus + b/l MFG	r-hippocampus + r-IPL	Mood rating scales not completed in controls.	Limbic-cortical network dysregulation suggested.
Guo et al. (2013b)	23 trMDD (med) 22 cMDD (med) 19 HC	cMDD l-MFG, b/l IPL connections with various cerebellar lobules trMDD l-MFG, b/l ITG, r-IPL, l-IFG connections with various cerebellar regions trMDD v MDD r-precuneus, l-IPL, r-angular gyrus connections with various cerebellar regions	cMDD r-precuneus, r-mFG, l-PHG, l-calcarine, l-LG, r-IFG, r-IFG, l-middle occipital gyrus, b/l middle temporal gyrus, l-calcarine, r-FG connections with various cerebellar lobules trMDD b/l PHG, b/l LG, r-SFG, r-IFG, l-MTG, r-STG connections with various cerebellar regions	Patients from previous study.	Decreased DMN FnC in trMDD and cMDD. Increased FnC in both groups in visual recognition network
Horn et al. (2010)	18 MDD 22 HC	Glx/Cr ratio in rACC negatively correlated with FnC between rACC + ant INS cortex	FnC between rACC + ant INS cortex positively correlated to HAM-D	Varying severity of MDD. No correction for multiple comparisons.	Salience network/DMN linked to reduced glutamate function

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Kenny et al. (2010)	16 MDD 'late life' (12 med) 17 HC		b/l precuneus, l-caudate + l- precentral, r-sub-gyral, b/l paracentral lobule, b/l THAL, l- postcentral gyrus, r-caudate + b/l cingulate, r-INS, l-precentral gyrus, l- MFG, l-paracentral lobule, r- postcentral gyrus, r-IPL, r- supramarginal gyrus, r-STG	Varying medication profiles. Mood rating scales not completed on controls.	Increased DMN FnC.
Liu et al. (2012b)	20 MDD 20 HC	various PCC, precuneus, mPFC, FG, LG, OFC, STG, SFG connections with various cerebellar lobules	temporal cortical connections with various cerebellar regions		Reduced DMN FnC with CER.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Lui et al. (2011)	28 trMDD 32 cMDD 48 HC	cMDD ACC + l-MTG, l-parietal cortex, r-IFG, l-AMYG + l- cingulate cortex, l-frontal + r- INS, b/l cingulate cortex, l- hippocampus + cingulate cortex, l-putamen, l-parietal cortex, l-INS + l-precuneus, r-parietal cortex, l-MTG, r- OCC, r-cingulate cortex, l- THAL + r-IFG, r-AMYG + l- cingulate cortex, r-INS + r- hippocampus, l-INS, r-OCC, l- precuneus, r-MTG, r-putamen + l-precuneus, r-THAL + cingulate cortex, r- hippocampus + r-IFG, r-INS, l- cingulate cortex trMDD l-frontal + precuneus, r- parietal cortex, l-THAL + r- INS, r-putamen, r-cingulate cortex, l-MFG, l-hippocampus + l-MTG, r-INS + r-precuneus, r-cingulate cortex, r-putamen + l-MFG and r-IFG, r-THAL + r-IFG, l-MFG, l-putamen, r-INS	trMDD>MDD l-AMYG + cingulate cortex, r-INS + cingulate cortex, r-precuneus	Mood rating scales not completed on controls.	Decreased DMN FnC. More widespread decreases in cMDD.
Peng et al. (2012)	16 cMDD 1 st episode 16 HC	THAL + b/l parietal lobe, r- cingulate gyrus, r-precuneus	rACC + PHG/l- parietal lobe/l-frontal lobe	Longer TR (3s). No correction for multiple comparisons.	Multiple networks may be affected.
Ye et al. (2012)	22 cMDD 1 st episode 30 HC	r-dIPFC + r-parietal lobe	r-dIPFC + l-dACC, l-PHG, l-THAL, l- precentral gyrus	Varying medication profiles.	No inference.

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Zhou et al (2010)	18 cMDD 1 st episode 20 HC	PCC + l-mPFC, l-lateral parietal cortex + l-INS/IFG, r-ant temporal cortex + l-inferior parietal gyrus, l-ant temporal cortex + l-inferior parietal gyrus, l-PHG + l-inferior parietal gyrus, r-CER + left inferior parietal gyrus/postcentral gyrus, l-CER + l-MFG	mPFC + r-PCC/precuneus, l-medial SFG + mPFC/OFC, l-lateral parietal cortex + mPFC/OFC, precuneus, r-ant temporal cortex + mOFC/rectal gyrus, b/l PCC/precuneus, l-ant temporal cortex + r-precuneus, mOFC/rectal gyrus, l-PHG + r-precuneus		Multiple changes in DMN FnC
Sheline et al. (2010)	18 cMDD 17 HC		b/l dmPFC.	FnC positively correlated with HAM-D scores	dmPFC interconnects DMN, CEN & AN
Tang et al. (2013)	28 cMDD 30 HC	b/l AMYG + vPFC		More severe MDD	Limbic-cortical network dysregulation
Bohr et al. (2012)	14 cMDD 'late life' (8 med) 16 HC		caudate + r-precuneus, b/l paracingulate, b/l supramarginal gyrus, b/l cingulate gyrus, b/l lateral OCC, l-central operculum, l-precentral gyrus, b/l parietal operculum, r-angular gyrus	Varied age of onset and number of episodes. Mixed medicated and unmedicated patients.	Increased DMN FnC
Wang et al. (2013)	17 cMDD 1 st episode 17 HC	mOFC, PHG, FG, middle occipital gyri and cuneus.		FG negative correlation to illness duration, MFG, IFG, CER, crus II negative correlation to cognition	No inference
Studies using whole brain functional connectivity (FnC)					
Veer et al. (2010)	19 cMDD 19 HC	b/l AMYG + l-INS, left frontal pole, b/l LG, r-STG	r-IFG	Significant difference in educational level between groups. Some patients in remission according to MADRS score. Mixed 1 st episode and recurrent MDD.	Abnormal FnC in AN, visual recognition network

Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Wang et al. (2014a)	18 cMDD w/o neglect hx (17 med) 20 cMDD with neglect hx (18 med) 20 HC	without neglect hx b/l vmPFC/vACC with neglect hx b/l vmPFC/vACC, dlPFC, dmPFC, vlPFC, INS, caudate, THAL, PHG, hippocampus, AMYG, CER		Varying medication profiles. Mood rating scales not completed in controls. Higher education and longer duration of illness in those without childhood neglect history. Recall bias.	Childhood neglect leads to widespread FnC reductions in MDD greater than those without.
Zeng et al. (2012b)	24 cMDD 29 HC	ACC, mPFC, AMYG, PCC, INS, PHG, hippocampus, THAL, ITG, temporal poles, globus pallidus, STG, LG, FG, inferior occipital and calcarine gyrus			DMN, AN and visual recognition network all affected in cMDD.

All populations were unmedicated unless otherwise stated. Those medicated indicated by (med)

Abbreviations: AMYG = amygdala; AN = affective network; ant = anterior; ACC = anterior cingulate cortex; BD = bipolar disorder; BPD = bipolar depression; b/l = bilateral; CES-D = Center for Epidemiologic Studies Depression Scale; Cohe-ReHo = coherence based regional homogeneity; cMDD = current major depressive disorder; Cr = creatinine; FnC = functional connectivity; fALFF = fractional amplitude of low frequency fluctuations; ALFF = amplitude of low frequency fluctuations; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; FG = fusiform gyrus; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; Glx = glutamate + glutamine; HAM-D = Hamilton Depression Rating Scale; HC = healthy controls; hx = history; inf = inferior; INS = insula; IPL = inferior parietal lobule; LG = lingual gyrus; MDD = major depressive disorder; MFG = middle frontal gyrus; mFG = medial frontal gyrus; MMSE = mini mental state examination; mOFC = medial orbitofrontal cortex; MR = magnetic resonance; MRS = magnetic resonance spectroscopy; MTG = middle temporal gyrus; PCC = post cingulate cortex; PHG = parahippocampal gyrus; post = posterior; OCC = occipital cortex; rMDD = remitted major depressive disorder; ROI = region of interest; ReHo = regional homogeneity; sibsMDD = healthy siblings of MDD patients; SFG = superior frontal gyrus; SPL = superior parietal lobule; STG = superior temporal gyrus; sup = superior; T = Tesla; THAL = thalamus; trMDD = treatment resistant major depressive disorder; TR = Repetition time; tx = treatment; vlPFC = ventrolateral prefrontal cortex; VMHC = Voxel-mirrored homotopic connectivity; vmPFC = ventromedial prefrontal cortex; vACC = ventral anterior cingulate cortex; vPFC = ventral prefrontal cortex

2.5. Effect of antidepressant drugs on the default mode network

There are limited studies investigating the effects of antidepressants on RSNs. van Wingen *et al.* (2013) demonstrated that two weeks of oral duloxetine reduced the connectivity between the mPFC, lateral parietal cortex and dlPFC regions of the DMN in healthy volunteers. Reduced connectivity between the left dmPFC and left hippocampus was observed after 7 days of oral citalopram administered to healthy volunteers (McCabe *et al.*, 2011). Whilst McCabe and Mishor (2011) discovered reduced FnC in the amygdala and vmPFC following citalopram, these differences were not observed with the norepinephrine reuptake inhibitor antidepressant, reboxetine (McCabe and Mishor, 2011). Interestingly there is considerable doubt as to the clinical efficacy of reboxetine which may explain this (Eyding *et al.*, 2010).

More recently Wang *et al.* (2014b) investigated the effects of 8 weeks escitalopram therapy on ReHo in first episode MDD patients. Compared to HC, MDD patients had reduced ReHo in the right SFG, left MTG and right ITG, right precuneus, left superior occipital gyrus and right cuneus. Increased ReHo was reported in the left dmPFC and cerebellum. Following treatment reduced ReHo was reported in the left dmPFC, right insula, bilateral thalamus and right SFG. Significantly decreased ReHo was reported when MDD patients post treatment were compared to controls. This suggests ReHo decreases in regions of the DMN and SN following escitalopram. Whole brain FnC in the same sample revealed increased connectivity in the bilateral dmPFC which reduced following escitalopram. In the bilateral hippocampi reduced connectivity was reported which increased following escitalopram (Wang *et al.*, 2014c).

In MDD, antidepressant treatment appears to normalize abnormalities in the DMN but the effects are inconsistent due to limited studies. In a study investigating the effect of 6 weeks oral sertraline on MDD patients Anand *et al.* (2005b) discovered that connectivity between ACC, medial thalamus and pallidostriatum normalized following treatment at rest and also when exposed to positive and neutral pictures (Anand *et al.*, 2005b). Andreescu *et al.* (2013) explored the effects of antidepressants in 'late-life' MDD in a sample of 47 MDD patients and 46 HC. Patients received either SSRI or SNRI medications following the first MR session. After 12 weeks treatment there was greater FnC between the mFG and dACC, which disappeared when white matter hyperintensity was adjusted for (Andreescu *et al.*, 2013). However, several participants were lost to follow up before the post treatment scan. Posner *et al.* (2013) also examined the effects of duloxetine but in dysthymia. Using the PCC as a seed region they observed DMN connectivity following a 10 week course of oral duloxetine. DMN connectivity was normalized between the PCC and right lateral parietal cortex in the treatment arm (Posner *et al.*, 2013). A similar methodology was used by Li *et al.* (2013a) but patients were prescribed a variety of SSRI or SNRI medications after the first MR session. They also observed the effects on the anterior and posterior subnetworks of the DMN. Antidepressant treatment normalized the increased connectivity observed in the precuneus before treatment (Li *et al.*, 2013a).

Although there is a significant reduction in ReHo and FnC of the DMN following antidepressant treatment the importance of the effects clinically are unclear. No studies are available on the effects of antidepressants on the AN, CEN or SN. Few resting state studies are available to draw reliable conclusions on the role of the AN and CEN in MDD. There is also no evidence of any correlations of the DMN changes with improvements in clinical mood rating scales. There are variations between drug treatment and seed ROIs used in analysis. Furthermore there is also no clear evidence of the effects in first episode and remitted MDD.

2.6. Using an NMDA receptor antagonist to probe resting state networks

There is increasing evidence of rapid antidepressant actions of antagonists of N-methyl D-aspartate glutamate receptor function such as ketamine and lanicemine (AZD6765) (Berman et al., 2000, Zarate et al., 2006a, Zarate et al., 2013a). Ketamine has also shown effects on the DMN in healthy volunteers. DMN connectivity of dmPFC, rACC, mPFC and PCC was reduced 24 hours after *i.v.* infusion of S-ketamine. S-ketamine was also shown to reduce FnC between the rACC and dmPFC although no related change in mood was noted. (Scheidegger et al., 2012). An earlier ketamine pharmacological challenge fMRI (phMRI) study also found increases in the BOLD signal in the PCC, precuneus and cerebellum in healthy volunteers following acute *i.v.* administration of racemic ketamine (Deakin et al., 2008).

In view of the reduced connectivity between the rACC and dmPFC due to ketamine reported by Scheidegger *et al.* (2012) in healthy volunteers it would be expected that NMDA antagonists would normalise DMN abnormalities in MDD, as this effect has been observed with accepted antidepressants in MDD (Anand et al., 2005b, Li et al., 2013a). The ACC has been proposed as one of the 'central hubs' of the DMN because of its role in self-referential processing including rumination (Pizzagalli, 2011). Furthermore it has previously been suggested that normalisation of vACC hyperactivity is essential for symptom remission (Mayberg, 2003).

There is a growing body of evidence to suggest that pretreatment activity of the rACC is predictive of response to antidepressants and ketamine (Salvadore et al., 2009). Decreased BOLD signals have been correlated with reduced glutamate in the rACC (Walter et al., 2009). The rACC also has higher densities of AMPA, Kainate and GABA_B receptors than the vACC (Palomero-Gallagher et al., 2009). Several studies have established that NMDA antagonists disable normal inhibitory controls from GABA interneurons on cortical pyramidal neurons increasing release of glutamate onto non-NMDA receptors. (Bustos et al., 1992, Liu and Moghaddam, 1995). Animal studies have revealed that blockade of AMPA receptor prevents the emergence of the antidepressant effect in forced swim and learned helplessness tests (Maeng et al., 2008). Magnetic resonance spectroscopy (MRS) studies suggest in humans that ketamine disinhibits glutamate release in ACC (Rowland et al., 2005) although this may be depend on the rate of infusion (Taylor et al., 2012). Experimental drug-challenge studies on RSNs combined with neurochemical measures using MRS in patients and volunteers holds great promise for neuropsychopharmacological insights in MDD.

Overall, ketamine reduced DMN connectivity in the same fashion as conventional antidepressants. Given that rACC response has been correlated with treatment response, network effects linked to the ACC would be important to investigate given its role in switching between different brain networks in MDD.

2.7. Conclusions

A number of resting state networks have been inferred from spontaneous low frequency neural activity that is correlated across brain regions. These include the DMN, SN, CEN and affective network. The resting state networks can be analysed using a number of methods each with their own limitations. The methods include ROI, ICA, network homogeneity, integrated local correlation, goodness of fit, ReHo, FnC, ALFF and fALFF. MDD research has largely focussed on the DMN rather than resting state networks such as the SN. There is an increasing volume of literature examining the resting state in MDD which have reported interesting findings in the cerebellum, lingual gyrus, ACC, MFG, dlPFC, amygdala and insula. There is decreased ALFF, fALFF and FnC of the ACC, insula but increased activity in precuneus, caudate and IPL. This suggests overactivity of the DMN and underactivity of the SN. Both ketamine and conventional antidepressants normalise the effects in the DMN by reducing connectivity.

The ACC forms part of the DMN and SN. The ACC has been proposed as one of the 'central hubs' of the DMN because of its role in self-referential processing including rumination (Pizzagalli, 2011). Furthermore it has previously been suggested that normalisation of vACC hyperactivity is essential for symptom remission (Mayberg, 2003). Several studies report increased ALFF, fALFF and FnC of the ACC and insula is reported in medicated and first episode MDD with reductions noted in unmedicated MDD samples. Finally, pretreatment response of the rACC predicts response to ketamine (Salvadore et al., 2009) and reductions in FnC between the ACC and other structures have been reported in healthy volunteers following ketamine infusion (Scheidegger et al., 2012).

Examining the individual methods ALFF studies report decreased intensity in DMN structures in medicated MDD. With fALFF methods the DMN in unmedicated MDD intensity appears both decreased/increased, while for SN/CEN there is increased intensity. Independent component analysis methods suggest increased intensity of DMN structures in unmedicated MDD. ReHo methods suggest decreased intensity of DMN structures in medicated MDD with SN structures having increased intensity in unmedicated MDD. ROI and FnC methods suggested decreased FnC in medicated MDD in the DMN, increased FnC of regions of the SN and both increases and decreases in the CEN structures.

The DMN findings following antidepressant treatment in MDD suggest it would be beneficial to investigate resting state networks using NMDA receptor antagonists with comparisons made to traditional antidepressants. It is hypothesized that resting state fMRI following *i.v.* administration

of an NMDA antagonist such as ketamine would demonstrate the functional neural correlates of the rapid antidepressant response.

Chapter Three: The role of the NMDA receptor in major depressive disorder and antidepressant effects

An abbreviated version of this chapter has been published:

Dutta A., McKie S., Deakin J.F.W. 2014. Ketamine and other potential glutamate antidepressants. *Psychiatry Research*, 225, 1-13

3.1. Introduction

The need for rapid acting antidepressants is widely recognised. Despite the introduction of selective serotonin reuptake inhibitors (SSRIs), and several other mechanisms of antidepressant action revolving around monoamine theory in the 1980s, response rates have not improved beyond approximately 60% (Mulrow et al., 2000). Naturalistic studies have observed remission of major depressive disorder (MDD) in only 28% of patients after first line treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Trivedi et al., 2006). Furthermore, second and third line treatments demonstrated declining rates of remission in spite of various augmentation strategies (Nierenberg et al., 2006, Trivedi et al., 2008). This has led to interest in new targets for antidepressant action over recent years including neurokinin, corticotrophin releasing factor, intracellular signalling cascades and modulation of glucocorticoid, cytokine, opioid and cannabinoid receptors (Pacher and Kecskemeti, 2004).

Interest in the role of glutamate in depression and antidepressant effects goes back to pharmacological studies in the late 1980s. Reynolds and Miller (1988) reported that tricyclic antidepressants had zinc-like functional effects on the NMDA receptor – they occluded the ion channel associated with the NMDA glutamate receptor. Trullas and Skolnick (1990), on the basis of stress and antidepressant effects on long-term potentiation in the hippocampus, proposed and demonstrated that functional antagonists at the NMDA receptor had antidepressant-like behavioural effects in animals. Berman et al. (2000) made the seminal human observation that a single intravenous infusion of ketamine (a NMDA receptor antagonist anaesthetic agent) alleviated depressive symptoms in patients within hours of administration and peaking some days later (Berman et al., 2000, Zarate et al., 2006a). These effects were replicated by Zarate et al. (2006a) and in bipolar depressive disorder by Diazgranados et al. (2010a). These findings stimulate a number of questions about the role of glutamate in MDD; what is the effectiveness of different glutamate drugs, what is their mechanism of action and how do they affect the glutamate system in MDD?

3.2. The glutamate synapse

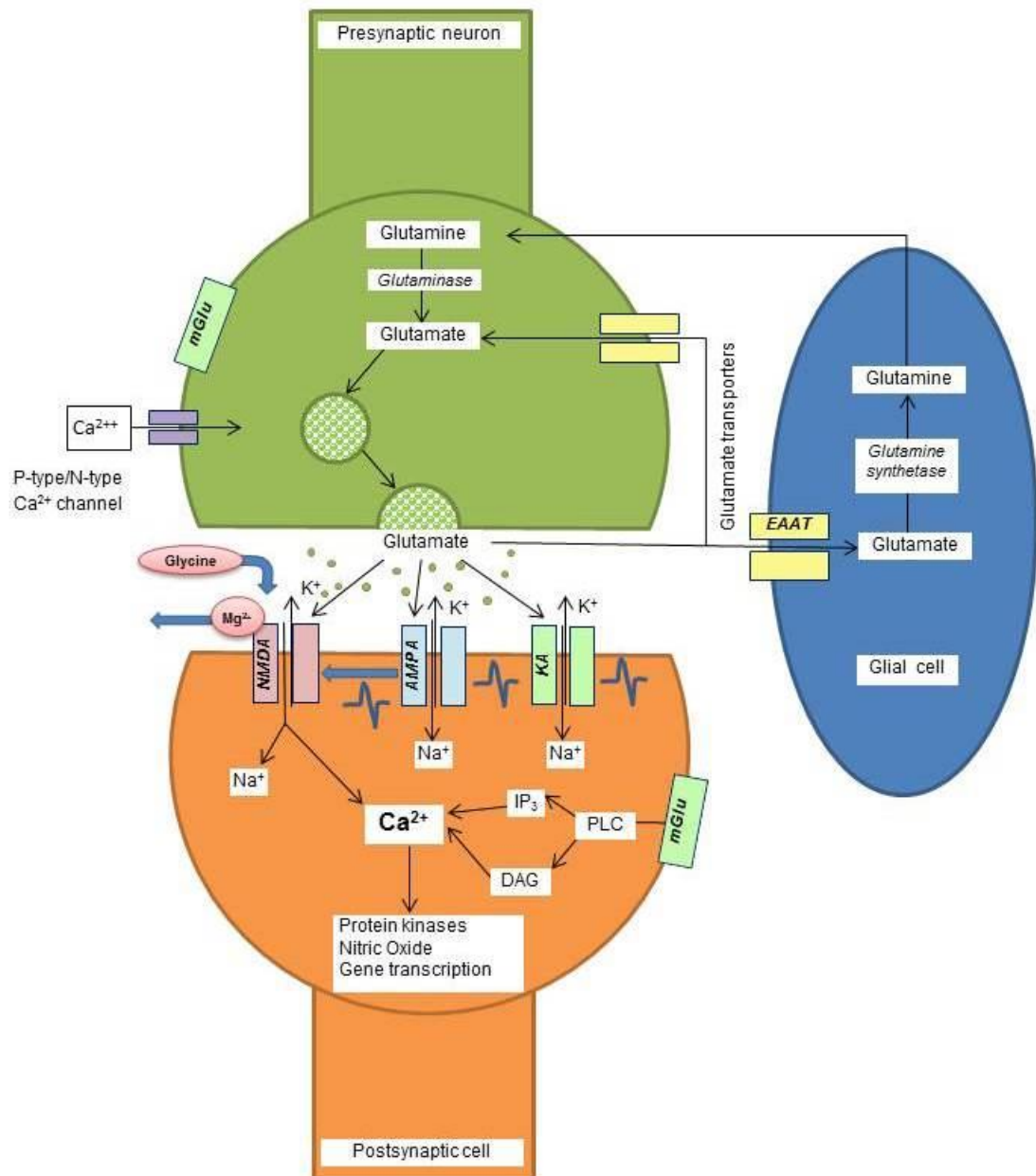
The role of the amino acid glutamate as an excitatory neurotransmitter has been well known since the 1950s (Curtis DR and Watkins JC, 1960). Glutamate is found abundantly in the pyramidal cells of the cortex, cerebellum, striatum and corticostriatal projections. There are two classes of glutamate receptors – ionotropic and metabotropic. The ionotropic receptors are classified according to their specific agonists α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate (KA) and N-methyl-D-aspartate (NMDA) (Watkins JC and Evans RH, 1981). There are 4 AMPA receptor subunits (GluA1-4), 5 KA subunits (GluK1-5) and 7 NMDA subunits (GluN1, GluN2A-D, GluN3A-B). The metabotropic receptors are G protein linked and function by second messenger systems or by influencing ion channels through release of G protein subunits (Meldrum BS, 2000). There are 8 reported types of metabotropic receptors (mGlu₁₋₈) which have

been classified into three groups: Group 1 mGlu (mGlu₁ and ₅) which increase activity of PLC and regulate postsynaptic excitability; Group 2 (mGlu₂ and ₃); and Group 3 (mGlu₄₋₈) which decrease the activity of adenylate cyclase. Group 1 receptors are postsynaptic while Group 2 and 3 are both pre and postsynaptic. The presynaptic receptors limit the release of glutamate. Their function appears to be related to synaptic plasticity particularly in the cerebellum and hippocampus (Krystal et al., 2010).

Glutamate is synthesised from glutamine in presynaptic neuron terminals or via the tricarboxylic acid cycle. Glutamate is then stored in synaptic vesicles prior to release into the synaptic cleft to act on receptors (Hudspith, 1997, Belsham B, 2000). The function of the normal glutamate synapse is shown in Figure 1.

Figure 1 Diagram of the Glutamate Synapse

adapted from Hashimoto (2011) and Barrett and Ganong (2012)



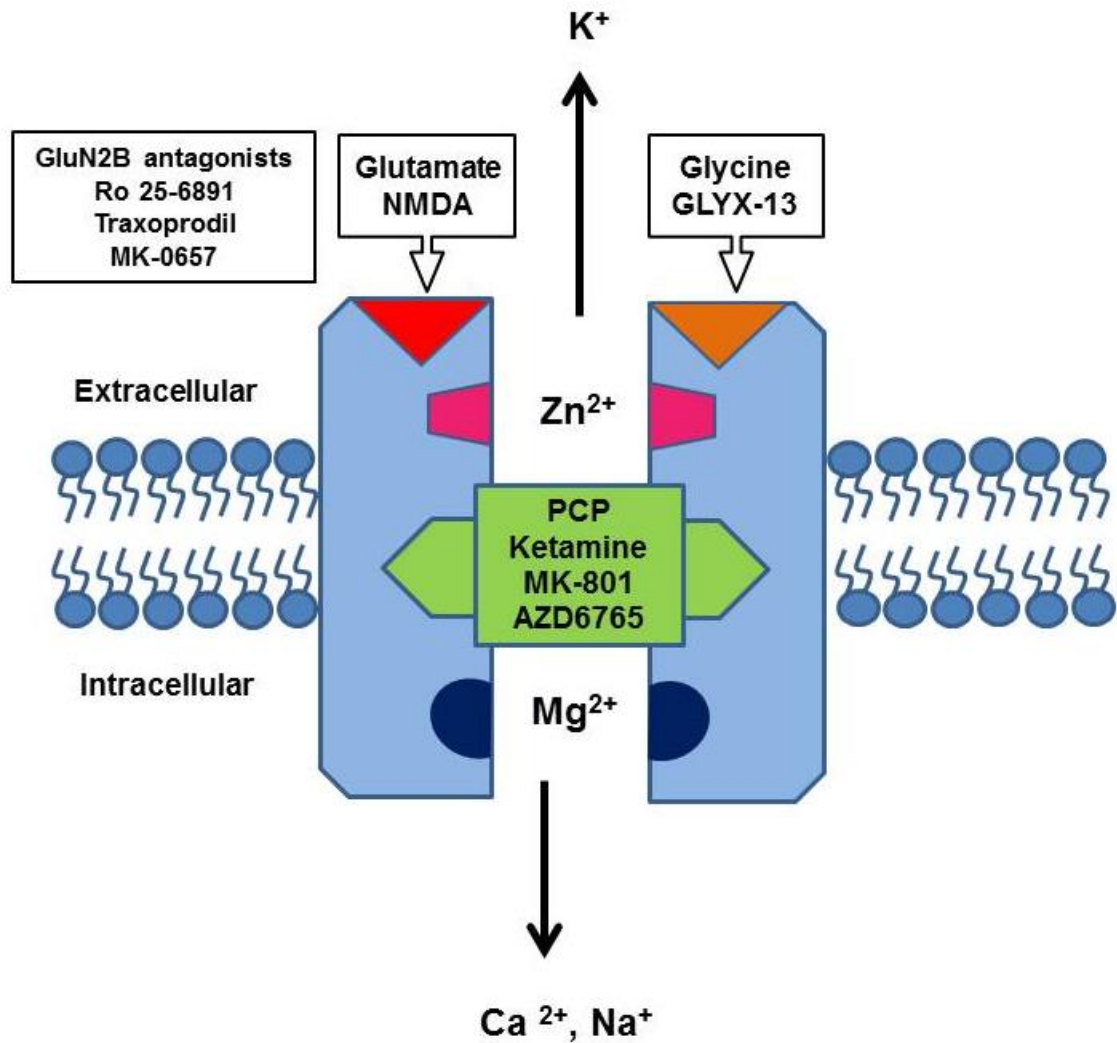
Abbreviations: AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; KA = kainate; NMDA = N-methyl-D-aspartate; mGlu = metabotropic glutamate receptor; Na^+ = sodium; Ca^{2+} = calcium; Mg^{2+} = magnesium; K^+ = potassium; PLC = phospholipase C; IP_3 = inositol-1,4,5-triphosphate; DAG = diacylglycerol; EAAT = excitatory amino acid transporter

3.3. Normal NMDA receptor function

NMDA receptors are tetrameric combinations of subunits; glycine binding GluN1, glutamate binding GluN2(A-D) and glycine binding GluN3(A,B) (Ishii et al., 1993, Dingledine et al., 1999, Beneyto et al., 2007). Responses at the NMDA receptor are gated by both voltage and ligands. The voltage dependence is due to Mg^{2+} blockade within the NMDA receptor ion channel. The NMDA ion channel is also highly permeable to Ca^{2+} , in contrast to AMPA and kainate receptors (Mayer et al., 1984, Nowak et al., 1984, Mori and Mishina, 1995). When the NMDA receptor is activated by neuronal depolarization there is relieving of the Mg^{2+} blockade with an influx of Na^+ and Ca^{2+} ions and an efflux of K^+ ions. Full activation of the NMDA receptor channel requires glycine as a co-agonist (Johnson and Ascher, 1987). When glutamate is released it binds to AMPA or kainate receptors allowing influx of sodium and efflux of potassium. These are ligand gated cationic channels that mediate the fast excitatory response (Pin and Duvoisin, 1995). Glutamate also binds to the NMDA receptor at normal membrane potentials but the ion channel remains closed because it is blocked by extracellular magnesium. The magnesium blockade is only removed when the receptor is depolarised by the activation of AMPA and KA receptors. Reuptake of glutamate occurs via surrounding excitatory amino acid transporters (EAAT1 and EAAT2) present predominantly on glial cells. It is then converted to glutamine by glutamine synthetase in glial cells and transported to the presynaptic neurons followed by reversion to glutamate and repackaging into presynaptic vesicles by the vesicular glutamate transporters (VGLUT)(Hashimoto, 2011, Gao S.F. and Bao A.M., 2011). Figure 2 shows the NMDA receptor with sites of drug action.

Figure 2 Diagram of the NMDA receptor with sites of drug action

adapted from Hashimoto et al. (2013) and Szewczyk et al. (2012)



Abbreviations: NMDA = N-methyl-D-aspartate; Na⁺ = sodium; Ca²⁺ = calcium; Mg²⁺ = magnesium; K⁺ = potassium; PCP = Phencyclidine

3.4. Glutamate neurotransmission in MDD

3.4.1. Cerebrospinal fluid evidence

CSF glutamate and glycine were significantly reduced in a group with refractory affective disorders including 8 with MDD (Frye et al., 2007). The group was heterogeneous and medication effects were not excluded. Increased levels of glutamine in MDD compared to controls have been reported, which may be due to increased glutamate uptake by glial cells (Levine et al., 2000). In Levine et al. (2000) there was a very short medication washout period used and lumbar punctures were also completed at different times. A recent comparison of CSF glutamate and glutamine in 18 MDD patients and 25 HC noted no difference in glutamate or glutamine at baseline (Garakani et al., 2013). There was, however, age discordance between patients and controls.

The evidence for CSF glutamine or glycine in MDD changes is poor. It is probable that there are not sufficient changes in the CSF to note gross alterations in glutamate levels.

3.4.2. Proton magnetic resonance spectroscopy evidence

Recent proton magnetic resonance spectroscopy ($[^1\text{H}]$ MRS) studies in MDD are presented in Table 8. Studies prior to 2007 including those encompassing ECT have been reviewed by Yildiz-Yesiloglu and Ankerst (2006) highlighting a number of interesting findings. Lower values of N-acetylaspartate (NAA) were noted. NAA has a role in lipid synthesis, as an acetyl donor for acetyl co-enzyme A, and is associated with neuronal loss or dysfunction. Studies of NAA in the basal ganglia, dlPFC, ACC, thalamus, hippocampus and parietal lobe have shown no significant changes (Yildiz-Yesiloglu and Ankerst, 2006).

NAA was significantly reduced in recovered MDD and bipolar disorder (BD) patients compared to HC in the OCC (Bhagwagar et al., 2007) and in the thalamus of patients with current tr MDD (Mu et al., 2007). There were no changes reported in NAA in cMDD in the dmPFC, dlPFC, vmPFC (Hasler et al., 2007), left dlPFC (Kaymak et al., 2009, Nery et al., 2009) hippocampus (Milne et al., 2009, Block et al., 2009), mPFC (Taylor et al., 2009) or ACC in rMDD (Bhagwagar et al., 2008, Taylor et al., 2009). No changes are demonstrated between recovered, first episode or tr MDD in the frontal brain structures. GABA appears more uniformly reduced (see Table 8) in the ACC, dmPFC/dlPFC and OCC (Bhagwagar et al., 2007, Bhagwagar et al., 2008, Hasler et al., 2007).

Significantly lower Glx (glutamine and glutamate) has been reported in the ACC, dlPFC and amygdala in MDD patients compared to HC. Occipital cortex GABA has also been found to be significantly lower in patients, which increased with antidepressant or electroconvulsive therapy. In paediatric MDD patients increased Glx has been reported in the left caudate (Yildiz-Yesiloglu

and Ankerst, 2006). More recent findings have also demonstrated lower Glx in the dmPFC, dlPFC, vmPFC and hippocampus in unmedicated MDD (Hasler et al., 2007, Block et al., 2009).

Bhagwagar et al. (2007) have found increased Glx in the OCC in recovered MDD patients yet others have reported normal levels of Glx in tr MDD and non-tr MDD patients in the ACC and OCC suggesting an increase beyond normal levels following recovery in the OCC (Bhagwagar et al., 2007, Price et al., 2009). In the hippocampus, Block et al. (2009) reported lower Glx which is at odds with Milne et al. (2009) finding of normal levels of Glx in MDD compared to HC. This may be explained by 11 of the 28 MDD patients tested taking antidepressants during the Milne et al. (2009) study (Milne et al., 2009, Block et al., 2009).

Valentine et al. (2011) found no significant correlation between improvement in mood on HAM-D and glutamate, glutamine or GABA levels in the OCC using a 4T scanner performing [¹H] MRS following single i.v. infusion of ketamine. The trial consisted of a crossover method in 10 patients with MDD and MRS scans were undertaken at baseline, 3 and 48 hours post infusion. Patients had a long duration of illness (mean 21 years). Seven patients had a history of anxiety disorder. There was a high level of patient dropout. Despite this a rapid antidepressant effect was observed from 60 minutes post infusion. In another study, no difference in Glx or glutamate was noted in healthy volunteers in the ACC following administration of i.v. ketamine or in the frontal cortex following 7 days oral citalopram (Taylor et al., 2010, Taylor et al., 2012). Salvatore et al. (2012) reported that the pretreatment Glx/glutamate ratio in the dmPFC and dlPFC was negatively correlated to treatment response to ketamine although GABA and glutamate concentrations were not correlated. This equates to lower intracellular glial glutamine levels correlating with improved ketamine response. The study examined 14 MDD patients, but there was no control group and patients were not scanned after ketamine administration.

High anhedonia has previously been associated with reduced functional rACC response, lower glutamine but normal glutamate and GABA (Walter et al., 2009). Although this correlation disappeared with lower anhedonia scores.

Significant increases in glutamate in the ACC following treatment of MDD patients with ECT have recently been reported although patients had lower glutamate levels at baseline (Zhang et al., 2013a). Increases were associated with increases in NAA and choline and were positively correlated with improvements in HAM-D and MADRS scores. Treatment was not randomised. Normalisation of decreased Glx has been replicated more recently following treatment with SSRIs (Chen et al., 2014).

In summary, the proton MRS evidence suggests no change or decreased Glx, no changes in glutamate and decreased GABA mainly toward the frontal brain structures in MDD. NAA changes are more consistent and largely show no change in similar brain regions. Treatment with NMDA antagonist medications potentially increases the levels of glutamine but not glutamate in the rACC. ECT may potentially increase levels of glutamate in the ACC. These are not definite findings and further evidence to support these hypotheses is required. Furthermore if

antidepressant treatments affect glutamate in the ACC this should be able to be correlated with changes in the DMN and SN.

Table 8 Recent proton magnetic resonance spectroscopy studies of neurotransmitters in patients with MDD

Reference	Year	Brain Region	Patients/controls	Field Strength (Tesla)	Glx	Glu	Gln	GABA	NAA	Comment
Chen et al.	(2014)	ACC	15 MDD/15	1.5	↓	–	–	–	↓	Differences in ACC resolved after treatment with SSRI
Price et al.	(2009)	ACC	18 MDD +15 tr MDD/24	3	↔	–	–	↓(ns)	–	High anxiety co-morbidity.
Bhagwagar et al.	(2008)	ACC	12MF rMDD/11	3	↓(ns)	–	–	↓	↔	Patients were older than controls
Taylor et al.	(2009)	mPFC & ACC	14 MF rMDD/16	3	↔	↔	–	–	↔	Higher levels of trait anxiety were reported in patients compared to controls
Portella et al.	(2011)	vmPFC	10 1 st episode MDD + 16 rMDD + 19 chronic MDD/15	3	↓	–	–	–	↓	Effect more significant in remitted-recurrent and chronic MDD. Cannot rule out effects of medication
Mu et al.	(2007)	vmPFC	20 tr MDD/20		↓	–	–	↔	↔	Short medication washout and patients allowed to continue psychotherapy treatment
Chen et al.	(2014)	dIPFC	15 MDD/15	1.5	↔	–	–	–	↔	
Sozeri-Varma et al.	(2013)	PFC	181 st episode MDD/16	1.5	–	–	–	–	↔	Glx/Glu/Gln/GABA not measured. Decreased NAA/Cr ratio
Nery et al.	(2009)	Left dIPFC	37 MF/ 40	1.5	↔	↔	–	–	↔	Only examined left dIPFC (due to prior evidence of left side MDD pathology post stroke). Mixed remitted and current MDD
Kaymak et al.	(2009)	Left dIPFC	17 MF female only /13	3	–	–	–	–	↔	All female sample
Hasler et al.	(2007)	dmPFC/dalPFC	20 MF MDD/20	3	↓	–	–	↓	↔	
de Diego-Adeliño et al.	(2013)	Hippocampus	14 1 st episode MDD + 18 rMDD +20 trMDD/16	3	↓	–	–	–	↓	

Reference	Year	Brain Region	Patients/controls	Field Strength (Tesla)	Glx	Glu	Gln	GABA	NAA	Comment
Milne et al.	(2009)	Hippocampus	14 1 st episode + 14 tr MDD/ 27	3	↔	-	-	-	↔	tr MDD patients were medication. Differences across age, sex and mood rating scores. No correction for multiple comparisons
Block et al	(2009)	Hippocampus	18 MDD/10	3	↓	-	↓	-	↔	
Godlewska	(2015)	OCC	39 MDD/31		-	↔	↔	↔	-	No additional changes noted after 6 weeks citalopram
Bhagwagar et al.	(2007)	OCC	15 MF rMDD + 16 BD / 18	3	↑	-	-	↓	↓	Females scanned in 1 st half of menstrual cycle.
Mu et al.	(2007)	Thalamus	20 tr MDD/20	1.5	↔	-	-	-	↓	Short medication washout and patients allowed to continue psychotherapy treatment

Abbreviations: ACC= anterior cingulate cortex; BD = bipolar disorder; dlPFC = dorsolateral prefrontal cortex; GABA = γ-aminobutyric acid; Glu = glutamate; Gln = glutamine; Glx = glutamate + glutamine; MDD = major depressive disorder; MF = medication free; mPFC = medial prefrontal cortex; NAA = N-acetyl aspartate; rMDD = remitted major depressive disorder; tr MDD = treatment resistant major depressive disorder; vmPFC = ventromedial prefrontal cortex; ↔ = no change; ↓ = decrease; ↑ = increase; ns = not significant

3.4.3. Glial pathology in MDD

Glial cells are classified into three major groups; astrocytes, oligodendrocytes and microglia. Glial pathology in depression has been previously reviewed in Sanacora and Banasr (2013). Their evidence suggests a loss of glial cells in the amygdala, vACC, rACC, dlPFC and OFC in MDD. Conversely increases in glial cell numbers in the hippocampal CA subfields and dentate gyrus are reported in patients with MDD (Rajkowska and Miguel-Hidalgo, 2007). There are also reports of microgliosis in the dlPFC, ACC and thalamus of suicide patients (Steiner et al., 2008). Part of the difficulty is that these abnormalities are not unique to mood disorders.

Astrocyte markers have been examined in MDD. Glutamine synthetase (GS) catalyses the conversion of glutamate to glutamine exclusively in the glial cells. Glial fibrillary acidic protein (GFAP) is a cytoskeleton marker for astrocytes. Levels of GS and GFAP in the OFC and PFC were not significantly different in a post mortem MDD sample compared to controls. There were potential confounding effects of increased post mortem interval which could have reduced brain expression of proteins (Toro et al., 2006). Reviewing the evidence, Sanacora and Banasr (2013) reported reduced GFAP in the hippocampus, PFC, ACC, amygdala and cerebellum. Reductions in immunoreactive markers for oligodendrocytes (such as myelin basic protein) in the anterior frontal cortex and reduced density of oligodendrocytes in the amygdala have also been discovered (Rajkowska and Miguel-Hidalgo, 2007). Reduction in astrocytes will be present where GFAP and GS are reduced.

EAAT1 (Excitatory Amino Acid Transporter-1) and EAAT2 are found on astroglia, whereas EAAT3 and 4 are found on neurons where they are involved in glutamate uptake from the synapse. Reductions in gene expression of SLC1A2 (EAAT1 gene) and SLC1A3 (EAAT2 gene) and down regulation of GLUL (glutamine synthetase gene) was demonstrated in the ACC and dlPFC using GeneChip arrays in MDD compared to controls (Choudhary et al., 2005). In ACC and dlPFC reduced glutamate uptake would be expected. There was upregulation in GluA1 and GluK5 in the ACC and GluA3, GluK1 and GluK5 in the DLPFC. More recently, significantly lower levels of EAAT1, EAAT2 and GFAP have been found in MDD using immunohistochemistry and western blotting techniques in the post mortem PFC (Miguel-Hidalgo et al., 2010). In this study, however, several patients were taking antidepressants before death which may have led to marked variability in protein levels. Increased upregulation of receptors would fit with the theory of reduced glutamate uptake.

In summary, there seems to be a trend toward reduced glial cell numbers and density in a number of areas. The majority of evidence points towards astrocyte dysfunction in the fronto-limbic brain regions (Rajkowska and Stockmeier, 2013). EAAT dysfunction in the ACC and dlPFC appear significant in MDD producing decreased glutamate removal from the synapse with potential to create excitotoxic damage. There is no evidence to clarify whether these are state or trait abnormalities.

3.4.4. Changes in glutamate receptors in MDD

Table 9 summarises the key subunit and structural protein changes observed. Studies of GluN1 subunit changes have been conflicting due to the different regions studied. Whereas, an earlier study had reported reductions in the hippocampus (Law and Deakin, 2001). Toro and Deakin (2005) later examined the OFC and anterior hippocampus post mortem in 15 MDD patients and 15 controls reporting no change in GluN1. Controls were, however, significantly older. Reductions in GluN1 in the superior temporal cortex (BA22) have been reported (Nudmamud-Thanoi and Reynolds, 2004). Reduced GluN2A and GluN2B has been reported in the medial temporal lobe and right anterior frontal cortex, hypothesised to result in compromised long term potentiation which would decrease fast trafficking of the AMPA receptor to the postsynaptic membrane (Beneyto et al., 2007, Feyissa et al., 2009). Beneyto et al. (2007) did not report any changes in kainate receptor numbers or binding, however, the evidence indicates a reduction in NMDA and AMPA receptor subunits in post-mortem brains in MDD in the hippocampus and surrounding area.

Changes are noted in the metabotropic glutamate receptors. Increases in mGlu_{2/3} (by 67%) have been noted as have reduction in mGlu₅ in the PFC in human post mortem brain samples (Feyissa et al., 2010, Karolewicz et al., 2009a). Part of the difficulty in interpreting these data is Feyissa et al. (2010) used cortical tissue homogenates which combined both mGlu₂ and mGlu₃ immunoreactivity. Patients also had varying usage of antidepressants in this study. Comparison to treatment with fluoxetine in rhesus monkeys did not yield significant post-mortem changes in mGlu₂ or mGlu₃ levels. PET studies of the PFC in MDD have revealed reduced binding of mGlu₅ (Hasler, 2009). Reductions in mGlu₂ and mGlu₃ occur in MDD and are therefore unchanged by SSRI antidepressants.

Reductions in GluN2A and GluN2B in have been reported in a human post-mortem MDD sample of perirhinal cortex (Beneyto et al., 2007). There was also reduced GluA1 and GluA3. NMDA receptor density is lower in MDD patients when studied using radioligand binding to the glycine site of the GluN1 subunit in the superior temporal cortex (Nudmamud-Thanoi and Reynolds, 2004). There was no difference in [³H]MK-801 binding to NMDA receptors between suicide victims with a retrospective MDD diagnosis and controls in the motor cortex (BA11), OCC (BA17/18) temporal cortex (BA21/22), hippocampus, thalamus, putamen, caudate nucleus and cerebellum (Holemans et al., 1993). Post mortem results of the temporal regions therefore suggest reductions in NMDA and AMPA receptors.

In summary, there are few consistent repeated studies highlighting the same brain regions. MDD patients often had diagnoses made retrospectively. Some were taking antidepressants or other psychotropic medication. The mode of death was difficult to keep consistent and may be confounded by the use of violent methods.

Table 9 Post mortem changes in glutamate receptor subunits

Reference	Year	Brain region	Discovery method	Receptor subunit							
				GluN1	GluN2A	GluN2B	GluN2C	PSD-95	GluA1	GluA3	GluK1
Law & Deakin	(2001)	Dentate gyrus/hippocampus (CA3)	In situ hybridisation histochemistry	↓							
Toro & Deakin	(2005)	OFC/anterior hippocampus	Immunautoradiography	↔				↔			
Nudmamud-Thanoi & Reynolds	(2004)	Superior temporal cortex	Western Blot	↓							
Beneyeto et al.	(2007)	Medial temporal lobe (perirhinal cortex) / hippocampus	In situ hybridisation histochemistry and autoradiography		↓	↓			↓	↓	↓
Feyissa et al.	(2009)	Right anterior PFC	Western Blot	↔	↓	↓		↓			
Karolewicz et al.	(2009b)	Lateral nucleus amygdala	Western Blot	↔	↑			↑			
Karolewicz et al.	(2005)	Locus coeruleus	Western Blot	↔			↑				
Karolewicz et al.	(2009a)	PFC	Western Blot		↓	↓					
		Locus coeruleus & amygdala	Western Blot		↑		↑				

Abbreviations: ↔ = no change; ↓ = decrease; ↑ = increase; ns = not significant; OFC = orbitofrontal cortex; PFC = prefrontal cortex;

3.4.5. Knockout/Knock in mice

There is little known about the specific roles of the different glutamate receptor subunits. To this end animal models using glutamate receptor subunit knock in/knockout have been investigated. Complete GluN1 knockout mice do not tend to survive after birth and hence there are no studies investigating these types of mice in models of MDD (Inta et al., 2010). Homozygous mice with GluN2A inactivated (GluN2A^{-/-}) were compared with heterozygous and wild type mice using forced swim test and tail suspension tests, as models of MDD, and novel open field test, elevated plus maze and light/dark exploration test, as models of anxiety. In antidepressant tests GluN2A^{-/-} homozygous mice show reduced immobility in the forced swim test and tail suspension tests (Boyce-Rustay and Holmes, 2006). Animals were tested in cohorts rather than repeated testing on the same animals. In addition the animal models of MDD are poor replications of the human illness. These results, however, suggest that GluN2A subunit antagonism is a potential antidepressant mechanism for investigation.

Taniguchi et al. (2009) examined tyrosine 1325 phosphorylation in GluN2A mutant mice where tyrosine 1325 was mutated to phenylalanine. Homozygous GluN2A mutant mice showed reduced immobility compared to homozygous wild type mice in the forced swim and tail suspension tests. This suggests mice with phenylalanine 1325 substitution might be less susceptible to MDD (Taniguchi et al., 2009). There was no control group in this study. Mice with GluN2B deleted (GluN2B^{-/-}) in the principal cortical neurons and hippocampus were tested using the sucrose preference, novelty induced hypophagia and forced swim models of MDD. No differences were noted between GluN2B^{-/-} and normal mice. When the forced swim paradigm was repeated, however, GluN2B^{-/-} mice demonstrated less immobility (Kiselycznyk et al., 2011). This suggests GluN2A is linked to the initial antidepressant response.

GluA1 knockout mice demonstrate increased learned helplessness by significantly more escape failures and increased escape latencies compared to wild type controls (Chourbaji et al., 2008). Increased levels of glutamate and the GluN1 subunit, by up to 30%, were also detected in the hippocampus. This evidence suggests that medications that increase AMPA signalling or reduced NMDA function should therefore have antidepressant effects (Chourbaji et al., 2008).

Several metabotropic glutamate receptor knockout mice have also shown antidepressant-like effects including mGlu₅ and mGlu₇ in the forced swim and tail suspension tests when compared to wild type mice (Li et al., 2006, Cryan et al., 2003). Animal models of depressive symptoms differed.

It is important to note that animal models are poor representations of human MDD. Blocking the function of GluN2A subunits and increasing GluA1 receptor subunits may have an antidepressant effect. There may also be a role for mGlu₅ and mGlu₇. GluN2B knockout mice did not differentiate in animal models of MDD.

3.5. Effects of standard antidepressants on glutamate function in humans/animals

The SSRI fluoxetine has effects on 5-HT_{2A} and 5-HT_{2C} receptors, noradrenaline and dopamine transporters (Koch et al., 2002). Chronic treatment in rats for 4 weeks with fluoxetine demonstrated an upregulation of the GluN1, GluN2A, GluA1 and GluA2 subunit levels in forebrain homogenates whilst reducing immobility in tail suspension and forced swim tests (Ampuero et al., 2010). No changes were noted in PSD-95, a synaptic anchoring protein. Chronic treatment with an SSRI has indirect effects on upregulating NMDA and AMPA receptors and reducing glutamate neurotransmission.

Citalopram is one of the most 5-HT selective of the SSRIs, however it may also have effects at H₁ histamine receptors (Owens et al., 2001). Citalopram given once daily for 14 days to mice reduced binding to glutamate recognition sites of the NMDA receptor in the cortex, but not in the hippocampus. Citalopram treatment has also been reported to reduce the potency of glycine to bind to the glycine recognition site of the NMDA receptor in the cortex but not the hippocampus (Nowak et al., 1996). Citalopram increased aspartate concentrations in the hippocampus and cortex. Similar findings were noted when repeated with chronic fluoxetine and citalopram over 21 days in mice (Nowak et al., 1998). The findings from citalopram and fluoxetine in animals suggest that chronic SSRI treatment decreases functional NMDA neurotransmission by reducing receptor number and by downregulating the positive allosteric glycine regulatory site. Ketamine would achieve the same effect immediately through its affinity for the NMDA-associated ion-channel. Significantly increased glutamate synthesis from labelled glucose in the midbrain and increased glutamine in the frontal and mid-brain of rats following acute administration of citalopram 20mg/kg has also been reported (Williams et al., 2007). The acute effects of SSRIs may also be linked to increased glutamate cycling.

Both fluoxetine and desipramine reduced NMDA induced currents when tested using whole-cell patch-clamp recording in rat cortical cell cultures (Szasz et al., 2007). This effect increased with time and was more pronounced with desipramine. Desipramine was voltage dependent in its effects whereas, fluoxetine was not. Response to NMDA was blocked by MK-801 and GluN2B antagonist ifenprodil using a “fast drug application system” where the agent was applied between NMDA applications. Given the similar kinetics to ifenprodil the authors proposed that both drugs were acting in part acting as GluN2B selective NMDA receptor antagonists.

Proton MRS studies have revealed short term treatment with citalopram in healthy volunteers increased Glx: Cr ratio (Taylor et al., 2008). This effect was not seen in this study when the healthy volunteers were administered reboxetine. That reboxetine does not affect glutamate has been suggested by Taylor et al. (2008) to be due to β -adrenoceptor mediated activation of astrocytes causing increased glutamate-glutamine cycling masking the effect. However, a recent study where MDD patients were treated with escitalopram for 6 weeks yielded no change in glutamate or glutamine despite improvement in HAM-D scores (Godlewska et al., 2014). In both Taylor et al. (2008) and Godlewska et al. (2014) the OCC was investigated and not the anterior brain structures where changes would be expected in MDD.

The evidence for conventional antidepressants to function through effects on the glutamate system are not clear. Chronic SSRI treatment indirectly upregulated NMDA and AMPA receptor subunits in animals. Although increased Glx has been reported in healthy volunteers, this has not been replicated with other antidepressants or indeed in MDD patients.

3.6. Efficacy of ketamine in MDD

3.6.1. Mechanisms of action of ketamine

Ketamine works by “trapping block” channel closure and slow open-channel blocking/unblocking kinetics of the NMDA receptor (MacDonald et al., 1991, Machado-Vieira et al., 2009a). Non-competitive NMDA receptor antagonists, like ketamine, produce a block only when the NMDA channel is in its open state after activation, therefore they are use-dependent (Huettnner and Bean, 1988). This means that the drug will act selectively at the site of excess NMDA activation (Mealing et al., 1999). One consequence of the blockade of the NMDA receptor-associated ion-channel is that glutamate release is increased (Moghaddam et al., 1997) and is thus available to act on non-NMDA glutamate receptors. The increase in glutamate release is known to have behavioural effects in animals because the effects of ketamine-like drugs are blocked by glutamate antagonists that act on AMPA receptors (Maeng et al., 2008). A number of animal and human studies have attempted to determine whether increased glutamate release (possibly acting on AMPA receptors) or the primary NMDA block is the mechanism of antidepressant effect of ketamine.

NMDA receptor subunits

The NMDA receptor is a combination of four subunits GluN1, GluN2 (A-D) and GluN3 (A,B). AMPA receptors are similarly tetrameric with combinations of GluA1-4 subunits (Machado-Vieira et al., 2009a). Ketamine subunit selectivity for GluN1/GluN2A (Narita et al., 2001) and GluN2B (De Vry and Jentsch, 2003) has been discovered in an animal drug discrimination model utilising compounds to mimic the behavioural effects of ketamine. The response to ketamine in rats was mimicked by PCP and dizocilpine (antagonists at GluN1/GluN2A/GluN2B) but was only partly reproduced by the GluN2B receptor antagonist ifenprodil (Narita et al., 2001). This would suggest the psychotomimetic effects of ketamine are produced by GluN1/GluN2A subunits rather than GluN1/GluN2B. An in-vitro receptor binding study found evidence that ketamine binds to the high affinity D2 receptor, 5-HT_{1A} (Fukumoto et al., 2014), and 5-HT₂ receptors (Kapur and Seeman, 2002). Ketamine increases extra-cellular dopamine and serotonin levels in the mPFC in rats when given acutely (Lindfors et al., 1997, Hirota and Lambert, 1996) but i.v. ketamine in humans failed to displace raclopride binding (Kegeles et al., 2002). An interaction with μ - and κ -opioid has also been suggested (Wong et al., 1996, Hirota et al., 1999).

Ketamine in animal models of MDD

Ketamine is antidepressant-like in animal models of MDD. The effects of a single dose of ketamine on behavioural despair in rats, utilising two forced swim tests 24 hours apart, showed a significantly shorter duration of immobility compared to saline controls 24 hours after administration (Yilmaz et al., 2002). Ketamine prevented the onset of behavioural despair for up to 10 days after single intraperitoneal (i.p.) administration. Single intraperitoneal infusion of ketamine in rats after chronic unpredictable stress produced a reduction in anhedonic behaviour (measured by sucrose consumption) (Li et al., 2011). The doses used in both these trials are markedly higher than those used in humans.

Several lines of evidence suggest that ketamine may exert some of its behavioural effects through its paradoxical ability to increase glutamate release on non-NMDA receptors as demonstrated in experimental animal models where there were increases in extracellular dopamine in the PFC (Moghaddam et al., 1997). Maeng et al. (2008) compared ketamine with two NMDA antagonists, Ro25-6981 and MK-801, and imipramine in a learned helplessness paradigm using footshocks, forced swim test and passive avoidance conditioning in mice. Ketamine and imipramine reduced immobility times in the forced swim test but ketamine maintained this effect 2 weeks later. The AMPA receptor antagonist, NBQX, did affect reduction in ketamine-induced but not imipramine-induced immobility times suggesting the effect in animal models was related to AMPA receptor antagonism. Both Ro25-6981 and MK-801 demonstrated significant dose dependent reductions in immobility times, but neither sustained this effect as long as ketamine and the effects were blocked by NBQX. Acute ketamine reduced escape failures and latency to escape in the learned helplessness paradigm but did not affect fear memory tested with passive avoidance conditioning (Maeng et al., 2008). This suggests that whilst the acute effects of ketamine are related to glutamate release on non-NMDA receptors, effects of tricyclic antidepressants are not.

The mammalian target of rapamycin (mTOR) has been linked to local protein synthesis in synapses. Li et al. (2010b) presented evidence that the rapid action of ketamine could be mediated by activation of the mTOR signalling cascade in the PFC seen in rats. The authors demonstrated transient increases in rat brain preparations of mTOR, 4E binding protein (4E-BP1), P70S6 kinase (p70S6K) phosphorylation, extracellular regulated kinase (ERK) and protein kinase B following administration of low dose ketamine to rats. These increases were associated with antidepressant behavioural actions of ketamine which was not observed with conventional antidepressants such as imipramine or fluoxetine. Pre-treatment with an AMPA receptor antagonist, NBQX, blocked these molecular effects completely supporting the theory of increased glutamate release onto AMPA receptors. Ketamine additionally increased levels of PSD-95 and GluA1 in the PFC. Rapamycin, an mTOR inhibitor, blocked this increase as did inhibitors of ERK and PI3k/Akt which mediate ketamine induction of mTOR. Similar increases in phosphorylation of 4E-BP1, p70S6K and mTOR were discovered with the selective GluN2B antagonist Ro25-6891 which was also blocked by rapamycin (Li et al., 2010b). This experiment

has been replicated with a chronic unpredictable stress animal model of MDD where blocking the mTOR pathway abolished the effects of ketamine (Li et al., 2011). Zhou et al. (2014) reported increases in mTOR and BDNF following i.p. ketamine which were blocked by the AMPA antagonist NBQX and enhanced by the AMPA agonist CX546 in both the PFC and hippocampus. There were also reductions in immobility in the forced swim test following ketamine administration. This further supports the theory that ketamine's antidepressant effects are mediated by increased release of glutamate onto non-NMDA receptors. Such findings have encouraged interest in drugs which enhance AMPA receptor function, the AMPAkinases or positive allosteric modulators.

Ketamine in humans

That ketamine increases glutamate release in humans was confirmed using [¹H] MRS by Rowland et al. (2005), although Taylor et al. (2012) did not corroborate this. Two studies, however, reported effects of ketamine in healthy volunteers which were blocked by pre-treatment with lamotrigine. The rationale was that lamotrigine, an anticonvulsant, decreases glutamate release by acting on sodium channels in the nerve terminals. In a human pharmacological-challenge MRI (phMRI) study, Deakin et al. (2008) found that i.v. ketamine in healthy volunteers evoked increases in blood oxygen level dependent (BOLD) signal in a variety of cortical and subcortical brain regions, notably positive responses in mid-posterior cingulate, thalamus, and temporal cortical regions. Furthermore these effects were prevented by pre-treatment with lamotrigine. Both Deakin et al. (2008) and Anand et al. (2000) reported that lamotrigine blocked most of the dissociative and mild psychotomimetic effects of ketamine. However, in both studies the only subjective effect that was not attenuated by lamotrigine was euphoria which was actually augmented in the Anand et al. (2000) study. This suggests that ketamine's immediate effects on mood may be mediated directly by NMDA blockade and not by the secondary effect of increased glutamate release. This delayed antidepressant effect seen in patients might, however, involve a different mechanism from the acute effect on mood in volunteers.

Ketamine infusion in healthy volunteers has produced increased BOLD signal in the precuneus, PCC, motor cortex, superior frontal gyrus, inferior temporal gyrus, hippocampus and superior temporal gyrus. Decreases were noted in the bilateral mOFC and temporal pole (Deakin et al., 2008). A phMRI study of acute intravenous citalopram 7.5mg in healthy male volunteers have revealed activations in common with ketamine in the superior frontal gyrus (BA6 + BA8), mFG (BA6), superior temporal gyrus (BA38), middle temporal gyrus (BA21) and thalamus (McKie et al., 2005). A decrease in BOLD from baseline in the case of ketamine and increase for citalopram has been noted in the vACC in healthy volunteers following drug infusion (Deakin et al., 2008, McKie et al., 2005). mCPP, a partial 5HT_{2C} receptor agonist, also shows a decreased phMRI effect in the same region (McKie et al., 2011).

Repeated ketamine infusion in animal models of MDD

Repeated ketamine infusion has also produced a response in the chronic mild stress animal model of MDD. Garcia et al. (2009) found that 40 days of chronic mild stress produced anhedonia (measured by sweet food consumption), adrenal hypertrophy, body weight loss, increased corticosterone and adrenocorticotrophic hormone (ACTH) in rats. Rats treated once daily for 7 days with ketamine i.p. reduced anhedonic behaviour in this study. Additional studies investigating acute and chronic ketamine i.p. reported that both administrations reverted adrenal gland hypertrophy, body weight loss and changes in corticosterone and ACTH (Garcia et al., 2009). However the authors could not rule out direct effects of ketamine on the satiety centre as an explanation for body weight gain and there was no use of forced swim paradigms to further support results. This could be explained by ketamine's hypothesized effects on 5-HT_{2C} receptors as highlighted by an increase in BOLD in the human hypothalamus due to the 5-HT_{2C} agonist mCPP (McKie et al., 2011). Ketamine at 10mg/kg also significantly reduced immobility in the forced swim test comparably to imipramine 20 and 30mg/kg (Garcia et al., 2008). Higher doses of ketamine (50mg/kg) in rats have shown similar results in the forced swim test (Engin et al., 2009).

There is an inherent difficulty in the animal models. Whether animal models truly replicate MDD and whether the numbers of different paradigms used as models of MDD allow real comparison of the results of such studies. Animal models tend to replicate one aspect of MDD such as anhedonia. Whilst the human data does support hypotheses derived using animal models there are a number of other factors that need to be taken into account. These include the effects of i.p. administration and cannulation, use of rats compared to mice and the living conditions of the animals.

Conclusions

Ketamine works through both blockade of NMDA receptors and increase in glutamate release onto non-NMDA receptors; as demonstrated in animal models. Other proposed mechanisms have included the mTOR pathway. Ketamine may also have effects on D₂ receptor, 5-HT_{1A}, and 5-HT₂ receptors and its effects may be related to the GluN2A receptor subunit. pHMRI studies in healthy volunteers have demonstrated that lamotrigine can block the dissociative and psychotomimetic effects of ketamine and that ketamine affects similar brain regions to citalopram.

3.6.2. Methodology of clinical studies

Study methods and populations

The clinical studies of ketamine are summarised in Table 10. Five of the studies were double-blind crossover randomised controlled trials (RCTs) (Berman et al., 2000, Zarate et al., 2006a,

Diazgranados et al., 2010a, Zarate et al., 2012b, Sos et al., 2013), one trial was a double blind RCT (Murrough et al., 2013a) and the remaining RCTs were not double blinded. Of the remaining trials, a single blind study observed the effect of ketamine when used as part of an anaesthetic in patients with MDD undergoing orthopaedic surgery (Kudoh et al., 2002). The remaining studies were open label (aan het Rot et al., 2010, Paslakis et al., 2010, Correll and Futter, 2006, Salvatore et al., 2009, Okamoto et al., 2010, Carlson et al., 2013, Duncan et al., 2013a, Ibrahim et al., 2011, Ibrahim et al., 2012b, Machado-Vieira et al., 2009b, Murrough et al., 2013b, Phelps et al., 2009, Rasmussen et al., 2013, Salvatore et al., 2010, Salvatore et al., 2012) or crossover studies (Paul et al., 2009, Valentine et al., 2011). Mathew et al. (2010b) used open label i.v. ketamine examining the effects of lamotrigine pre-treatment and riluzole maintenance treatment. Two studies, which were open label, compared drug effects in MDD patients and healthy volunteers (Okamoto et al., 2010, Salvatore et al., 2009). Although the majority of studies included only patients with MDD, two studies were carried out in bipolar depression and another included one bipolar depressive into the trial group (Diazgranados et al., 2010a, Berman et al., 2000, Zarate et al., 2012b). A number of studies had MDD patients with comorbid anxiety disorders (Salvatore et al., 2009, Salvatore et al., 2010, Valentine et al., 2011).

The main problems with the studies are that they employed small sample sizes – most less than 20 participants in the active treatment groups. The samples in seven of the studies had statistically significant differences in patient characteristics. They included differences in baseline MADRS scores, age, number and severity of episodes (Mathew et al., 2010b, Diazgranados et al., 2010a, Sos et al., 2013, Valentine et al., 2011, Salvatore et al., 2009, Phelps et al., 2009). Additionally, datum was read from graphs in the published papers which may have led to errors.

Dosing and administration

Most studies used ketamine 0.5mg/kg by intravenous infusion over 40 minutes but some used lower dosages (Correll and Futter, 2006, Sos et al., 2013). Higher doses of 1.0mg/kg and 1.5mg/kg have been used as anaesthetic during ECT and preoperatively prior to orthopaedic surgery (Kudoh et al., 2002, Goforth and Holsinger, 2007). A problem common to all studies is that the immediate subjective effects of ketamine reveal the treatment condition so the use of saline placebo infusions does not maintain the blind. One study used midazolam as an active placebo with no saline control group (Murrough et al., 2013a). A number of trials allowed the use of concomitant medications including other antidepressants (Kudoh et al., 2002, Stefanczyk-Sapieha et al., 2008, Diazgranados et al., 2010a, Irwin and Iglewicz, 2010, Rasmussen et al., 2013).

Mood and dissociative symptom rating scales

The majority of studies used reduction in the Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D) as primary outcome measures except

Messer et al. (2010) which used Beck Depression Inventory (BDI) and Rasmussen et al. (2014) which used Hospital Anxiety and Depression Scale (HADS). However these scales may have limited validity when used more frequently than weekly. The time points at which MADRS was measured limited the understanding the time of the peak effect. Some studies included measures of psychotomimetic effects using Clinician Administered Dissociative States Scale (CADSS) (Phelps et al., 2009, DiazGranados et al., 2010b, Ibrahim et al., 2011, Ibrahim et al., 2012b, Zarate et al., 2012b, Carlson et al., 2013, Murrough et al., 2013a, Murrough et al., 2013b, Lapidus et al., 2014).

3.6.3. Response to ketamine infusion

Single ketamine infusion

All the studies agree that the antidepressant effect of ketamine begins within 24 hours of a single intravenous infusion and can last up to 14 days. However, there is some variability in the response. The peak reductions on HAM-D scores varied from 15% (Abdallah et al., 2012) to 86% (Denk et al., 2011). Similar changes have been reported in BDI and MADRS scores. The response rates following ketamine infusion range from 20% (Rasmussen et al., 2013) to 90% (aan het Rot et al., 2010). In bipolar depression peak reduction in mood rating scales was noted as early as 40 minutes after start of infusion (Diazgranados et al., 2010a, Zarate et al., 2012b). The antidepressant effect noted in the bipolar depression study (Diazgranados et al., 2010a) occurred earlier but was less sustained than noted by Zarate and colleagues (2006a) in MDD. Furthermore, lower response rates were noted in bipolar depression than in MDD at the end of day 1 (42% in bipolar depression vs. 71% in MDD) in the ketamine group (Diazgranados et al., 2010a, Zarate et al., 2006a).

Repeated ketamine infusion

Eight studies examined whether repeated doses of ketamine cause a more sustained effect than single dosage (aan het Rot et al., 2010, Murrough et al., 2013b, Rasmussen et al., 2013, Messer et al., 2010, Szymkowicz et al., 2013, Liebreinz et al., 2009, Stefanczyk-Sapieha et al., 2008, Correll and Futter, 2006). aan het Rot et al. (2010) demonstrated relapses in depressive symptoms could be delayed by up to 19 days after the final i.v. ketamine infusion when repeated infusions of ketamine were used. The patients studied, however, had previously shown response to ketamine in the riluzole and ketamine trials by the same group. Repeated i.v. ketamine dosing demonstrated improved mean reductions in MADRS scores compared to single i.v. ketamine infusion (85% after 6th infusion vs. 67% after 1st infusion) (aan het Rot et al., 2010). Murrough et al. (2013b) administered a regime of open label ketamine three times a week over 12 days. Whilst there were a number of methodological problems with this those who responded had a median time to relapse of 18 days. Rasmussen et al. (2013) further demonstrated that repeated infusions improved response rates to ketamine utilising a slower infusion rate of

0.5mg/kg i.v. over 100 minutes. Correll and Futter (2006) observed the benefits of 5 days continuous i.v. ketamine infusion. Although onset of efficacy appeared no better than with single or repeated i.v. infusions, remission was maintained for at least 12 months from discontinuing i.v. ketamine.

3.6.4. Biomarkers of response to ketamine

Ketamine treatment response correlates

A number of biomarkers of ketamine response have been suggested (Zarate et al., 2013b). These include pre-treatment predictor effects of ketamine and the effect of ketamine as a correlates or predictors. Response to i.v. ketamine was associated with increases in circulating brain derived neurotrophic factor (BDNF) and slow wave EEG sleep activity on the night of ketamine infusion (Duncan et al., 2013b). Baseline delta sleep ratio has also correlated with MADRS score reductions following ketamine infusion (Duncan et al., 2013a). Plasma BDNF levels were also shown to negatively correlate with MADRS scores following ketamine infusion but not midazolam, an active control, in another sample of tr MDD (Haile et al., 2014). Increased BDNF has previously been observed in MDD patients on standard antidepressants (Kurita et al., 2012) but another ketamine study did not report changes in BDNF (Machado-Vieira et al., 2009b). Increased BDNF function may be explained by the results of a recent study which demonstrated that MDD patients with Val/Val BDNF allele at rs6265 (Val66Met single nucleotide polymorphism) exhibited increased antidepressant response to ketamine (Laje et al., 2012).

Ketamine responders, at 230 minutes according to MADRS, have significantly lower D- and L-serine plasma concentrations compared to non-responders (Moaddel et al., 2014). Baseline D-Serine levels in ketamine responders were also associated with higher Clinician Administered Dissociative States Scale (CADSS) scores. This is opposite to the findings of a previous study of standard antidepressants which revealed non-response corresponded to lower D- and L-serine levels (Maes et al., 1998). Luckenbaugh et al. (2014) recently suggested that the dissociative, but not psychotomimetic, effects of ketamine are a biomarker of final response, in a meta-analysis of ketamine effects in bipolar disorder and MDD patients. The prolonged antidepressant effects of ketamine may also be related to the half-life of active metabolites such as dehydronorketamine and hydroxynorketamine which have been reported to be present up to 3 days later following dosing (Zarate et al., 2012a, Zhao et al., 2012).

Pre-treatment predictors

Pre-treatment predictor effects are also observed. Increased pre-treatment rACC activity measured by magnetoencephalographic recordings (MEG), has predicted response to ketamine infusion following exposure to fearful faces (Salvadore et al., 2009). There was no control group or follow up MEG recording following ketamine. Cornwell et al. (2012) reported increased cortical excitability on MEG within the period of antidepressant response, with responders to ketamine having increased γ -band responses in the somatosensory cortex. In another study

MDD patients with the least engagement of the rACC during a working memory task (N-back) had the greatest improvement in mood within 4 hours of ketamine infusion (Salvadore et al., 2010). Patients, however, had a high frequency of co-morbid anxiety disorders. Effects after 230 minutes were not examined. Effects were only examined in this study to 230 minutes to remain comparable to one of the initial trials of ketamine in MDD by Zarate et al. (2006a).

Pre-treatment neurotransmitter and metabolic abnormalities have been reported. Salvadore et al. (2012) discovered pre-treatment Glx/glutamate ratio in the dorsomedial/dorsal anterolateral prefrontal cortex negatively correlated with improvement in depressive symptoms in MDD following ketamine. A preliminary PET study demonstrated decreased metabolism in the right habenula, insula, ventrolateral and dorsolateral prefrontal cortices following ketamine infusion (Carlson et al., 2013). The effects in the ACC, neurotransmitter and metabolic abnormalities suggest it may be possible to identify ketamine responders by the effects in the ACC and PFC.

Several studies have found biological predictors of, or association with, the effects of ketamine but so far there are no replicated findings and their clinical utility and relevance to the mechanism of action of ketamine remain uncertain. They include: a family history of alcohol dependence (Phelps et al., 2009) and, in bipolar depression, increased peripheral vitamin B₁₂ levels (Permoda-Osip et al., 2013). Across both MDD and BPD clinical improvement was correlated with higher body mass index and fewer previous suicide attempts (Niciu et al., 2014). The current biomarkers, however, are not currently practical for clinical usage.

Conclusions

Pre-treatment predictors of ketamine response include rACC activity, Glx/glutamate ratio in the dmPFC and dlPFC and decreased metabolism on PET imaging in the insula, habenula, vlPFC and dlPFC. Effects of ketamine that have correlated with treatment response include BDNF levels, D- and L-serine plasma concentrations and dissociative effects.

3.6.5. Trials to identify mechanisms of ketamine effects

Eight mechanistic trials using i.v. ketamine have been carried out (Mathew et al., 2010b, Paslakis et al., 2010, Paul et al., 2009, Sos et al., 2013, Duncan et al., 2013a, Ibrahim et al., 2012b, Machado-Vieira et al., 2009b, Segmiller et al., 2013, Denk et al., 2011). One study investigated the effect of lamotrigine on ketamine response in tr MDD. Mathew et al. (2010b) randomised patients to receive lamotrigine pre-treatment followed by open label i.v. ketamine as well as riluzole maintenance treatment in an attempt to prolong the duration of the effects of ketamine. Lamotrigine acts by inhibiting glutamate release. Riluzole modulates glutamate release but also enhances synaptic AMPA receptor expression (Du et al., 2007) and blocks NMDA receptor activation (Kalia et al., 2008). Mathew et al. (2010b) hypothesised that lamotrigine would block the enhanced glutamate release produced by administration of ketamine and riluzole would prolong the effects of ketamine. Lamotrigine failed to attenuate psychotomimetic symptoms produced by ketamine or enhance its antidepressant effects.

Furthermore riluzole did not sustain response in those patients that had responded to i.v. ketamine infusion and the same negative result was reported by Ibrahim et al. (2012b). Both lamotrigine and riluzole reduce glutamate release and their lack of effect on ketamine's efficacy in the Mathew et al. (2010a) study suggests that antidepressant effects were not dependent on a secondary increase in glutamate release. Serum levels of lamotrigine were not measured.

Isomers of ketamine

Two open-label case studies investigated the S-isomer of ketamine which has a higher affinity than the R-isomer for phencyclidine site of the NMDA receptor site (Paul et al., 2009, Paslakis et al., 2010). S-ketamine has a 4 fold greater anaesthetic potency and higher frequency of psychotomimetic side effects in humans (Kohrs and Durieux, 1998). One study compared single infusions of the two isomers 7 days apart in two patients (Paul et al., 2009). They found one patient did not improve. The second patient had a 58% reduction after initial racemic ketamine infusion and 46% reduction following the second infusion of S-ketamine 7 days later. The other S-ketamine study exploited the use of oral S-ketamine preparation as add-on therapy (Paslakis et al., 2010). Four patients showed a mean improvement in HAM-D of 43% after 14 days treatment. Others have examined the adjunctive effects of S-ketamine with propofol and ECT but no difference was found with the addition of S-ketamine compared to treatment as usual (Jarventausta et al., 2013).

There are no trials of R-ketamine reported, however, in an animal model, R-ketamine immobility times were significantly reduced in the forced swim and tail suspension tests 7 days following ketamine infusion compared to S-ketamine (Zhang et al., 2014a). There were no changes in sucrose preference, a model of anhedonia, in animals. These studies suggest S-ketamine does not have the same efficacy as racemic ketamine and that R-ketamine in animal models is more potent and long acting than S-ketamine. This is paradoxical given the evidence of S-ketamine being more potent in humans.

Alternative routes of ketamine administration

Alternative routes of administration have recently been examined. Lapidus et al. (2014) reported comparable improvement in mood with intranasal ketamine in a randomised, double-blind placebo controlled trial although there was no group that received i.v. ketamine as a comparator. Chilukuri et al. (2014) observed that 0.25mg/kg intramuscular (i.m.) ketamine produced the similar reductions in HAM-D to i.v. ketamine in MDD.

One difficulty in evaluating ketamine studies is that patients, because of the dissociative effects of the ketamine, are not blind to treatment therefore making an appropriate sham/placebo treatment is hard to envisage. The psychotomimetic effects of ketamine also make its use problematic in clinical practice. Slow infusion of low dose ketamine is not associated with serious psychotomimetic side-effects but a drawback to clinical use is that the benefits are short-lasting.

Conclusions

One mechanistic trial has questioned whether ketamine acts through increased glutamate release. Alternative routes of ketamine administration are as effective as i.v. administration. R-ketamine may be more potent than S-ketamine as an antidepressant agent.

Table 10 Clinical studies of ketamine in MDD

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Berman et al. (2000)	Double blind placebo controlled crossover RCT	7 MDD	0.5mg/kg i.v. /40min	HAM-D	-42%*	-7%*	3 days	50%	Patients aware of placebo
Diazgranados et al. (2010a)	Double blind placebo controlled crossover RCT	18 BPD TR	0.5mg/kg i.v. /40min + lithium / valproate	MADRS	-48%*	-18%*	40min	56%	Earlier peak reduction at 40mins. Concurrent use of lithium/valproate. Differing sample characteristics (some rapid cycling BD). Patients aware of placebo
Mathew et al. (2010b)	Double blind RCT lamotrigine pretreatment + riluzole for maintenance	13 MDD (placebo + ketamine) 13 MDD (lamotrigine + ketamine)	0.5mg/kg i.v./ 40min + lamotrigine/ placebo	MADRS	-60% ^f	No placebo	1 day	65%	No saline control. Higher BMI than in other studies. Ketamine administered open label. Pre-treatment effects.
Sos et al. (2013)	Double blind placebo controlled crossover RCT	27 MDD	0.27mg/kg i.v. / 10min then 0.27mg/kg i.v. / 20min + current antidepressant	MADRS	-28%	-2%*	1 day	37%	Mixed patient group differed in number of episodes and baseline MADRS score between those who had placebo and ketamine first.
Zarate et al. (2006a)	Double blind placebo controlled crossover RCT	18 MDD TR	0.5mg/kg i.v. /40min	HAM-D	-56%	-9.8%	1 day	71%	Inpatient sample. Some had history of substance misuse. Patients aware of placebo

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Zarate et al. (2012b)	Double blind placebo controlled crossover RCT	15 BPD TR	0.5mg/kg i.v./ 40min + lithium / valproate	MADRS	-50%*	-6%*	40min	79%	Patients aware of placebo
Murrough et al. (2013a)	Double blind placebo controlled RCT	47 MDD (ket) 25 MDD (midazolam)	0.5mg/kg i.v./ 40min	MADRS	-55%	-27% midazolam	1 day	64%	Longer duration of illness and current episode in patients receiving ketamine. Active comparator but no saline control.
Abdallah et al. (2012)	Single blind placebo controlled RCT	8 MDD (thiopental) 8 MDD (thiopental + ketamine)	0.5mg/kg i.v. as anaesthesia for ECT	HAM-D	-15% ^j	-16% ^j	Not reported		No significant difference after first or subsequent ECT sessions. Concurrent use of antidepressants and other medications. Differences between groups in medication used. Longer seizure duration in ketamine group.
Yoosefi et al. (2014)	Double blind placebo controlled RCT	15 MDD (thiopental) 14 MDD (ketamine)	1-2mg/kg i.v. as anaesthesia for ECT	HAM-D	-32%	-13%	2 days		Significant difference in HAM-D favouring ketamine. Longer seizure duration with ketamine and increased electrical dose for ECT.
Lapidus et al. (2014)	Double blind placebo controlled crossover RCT	18 MDD TR	50mg intranasal	MADRS	-43%*	-17%*	1 day	44%	Patients aware of placebo. Concurrent use of psychotropic medications

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Kudoh et al. (2002)	Single blind, parallel group RCT ketamine anaesthesia prior to orthopaedic surgery	35 MDD (ket) 35 MDD (no ket) 25 CON (ket)	1.5mg/kg propofol + 2µg/kg fentanyl i.v. +/- 1.0mg/kg ketamine i.v. anaesthetic	HAM-D	-22%	-17%	1 day		Concurrent use of antidepressants and other medications. Higher dosages of ketamine than in other trials. No detail of length of infusion or whether bolus dosing occurred.
Loo et al. (2012)	Single blind RCT	17 MDD/ 5 BPD (ket) 17 MDD/ 7 BPD (saline)	0.5mg/kg i.v. following anaesthesia for ECT	MADRS	-51%	-56%	Not reported		No significant differences in MADRS score reduction. High rate of dropout. Significantly higher thiopentone dose in placebo group. Variation between unilateral and bilateral ECT and dosage reported.
Rasmussen et al. (2014)	Single blind RCT	21 MDD (ket) 17 MDD (methohexital)	1.0mg/kg i.v. as anaesthetic prior to ECT	HADS	Baseline scores not present	Baseline scores not present	Not reported		No significant differences in HADS score reduction. No baseline scores reported. Variation between unilateral and bilateral ECT. Differences in confusion, visual disturbance and seizure motor effects.
Wang et al. (2012b)	Single blind RCT	12 MDD (propofol) 12 MDD (ketamine) 16 MDD (ketamine + propofol)	0.8mg/kg i.v. as part of anaesthetic for ECT	HAM-D	-79%*	-60%*	1 day		No significant differences in HAM-D score reduction. Variation between unilateral and bilateral ECT and dosage reported. Concurrent use of antidepressant drugs.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Paul et al. (2009)	Open label crossover trial	2 Recurrent MDD	0.5mg/kg i.v. / 50min + 0.25mg/kg S-ketamine / 50min 7 days apart	HAM-D	-58%	No placebo	1 day	50%	Too small a sample to draw proper conclusions. Response not measured before 1 day. Older mean age. One patient showed no change. No saline control group.
Valentine et al. (2011)	Open label crossover trial	10 MDD	0.5mg/kg i.v. / 40min	HAM-D	-29%*	-10%*	3 days*		Older mean age of patients. Co-morbid anxiety disorders. Heterogeneous sample with regard to number of MDD episodes and severity of MDD.
Salvadore et al. (2009)	Open label case control	11 MDD TR 11 CON	0.5mg/kg i.v. / 40min	MADRS	-36%	No placebo	230 min		No saline control of ketamine infusion. Older mean age of patients. High levels of co-morbid anxiety
Kranaster et al. (2011)	Open label case control	16 MDD (ket) 26 MDD (thiopenthal)	S-ketamine (mean dose 46.7mg) as anaesthesia prior to ECT	HAM-D	-76%	-73%	Not reported		No significant differences in HAM-D score reduction. Mixed group. Some were psychotic. Retrospective study. Variable number of ECT sessions
Okamoto et al. (2010)	Open label case control	11 MDD TR (ket) 20 MDD TR (propofol)	0.86 mg/kg i.v. bolus or 0.94 mg/kg propofol (mean dose) ketamine anaesthesia prior to ECT	HAM-D	-78%	-76% (propofol)	28 days ^h		Continued current antidepressant after ECT. No true control group.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
aan het Rot et al. (2010)	Open label trial	10 MDD TR	0.5mg/kg i.v./ 40min x6	MADRS	-67% ^j	No placebo	240 min ^j	90% ^j	Older mean age of patients. Repeat infusions given as outpatients and had reducing efficacy. No saline control group.
Carlson et al. (2013)	Open label trial	20 MDD	0.5mg/kg i.v. / 40min	MADRS	-44%	No placebo	40 min	30%	No saline control group.
DiazGranados et al. (2010b)	Open label trial	33 MDD TR	0.5mg/kg i.v. / 40min	MADRS	-44%* ^f	No placebo	40 min		No saline control group. Mood rating scale score differences in those with suicidal ideation.
Duncan et al. (2013a)	Open label trial	30 MDD TR	0.5mg/kg i.v. / 40min	MADRS	-46%	No placebo	240 min	40%	No saline control group. Positive correlation between baseline delta sleep ratio and response to ketamine
Ibrahim et al. (2011)	Open label trial	40 MDD TR	0.5mg/kg i.v. / 40min	MADRS	-44%* ^f	No placebo	40 min		No saline control group. Response to treatment whether previously responded to ECT or not.
Ibrahim et al. (2012b)	Open label trial	42 MDD TR	0.5mg/kg i.v. / 40min +/- riluzole/ placebo	MADRS	-39%* ^f	No placebo	1 day	62%	Hospital inpatients. No saline control group.
Machado-Vieira et al. (2009b)	Open label trial	23 MDD TR	0.5mg/kg i.v. / 40min	MADRS	-42%* ^f	No placebo	40 min	48%	Most patients obese. Very high number of episodes of MDD (Mean 32). No saline control group.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Murrough et al. (2013b)	Open label trial	24 MDD TR	0.5mg/kg i.v. / 40min – x6 infusions	MADRS	-59%* ^j	No placebo	2 hours	71%	No saline control. Part of previous study. Protocol change removed patient exclusion if non-response halfway through. Not all received multiple dosing.
Phelps et al. (2009)	Open label trial	26 MDD TR	0.5mg/kg i.v. / 40min	MADRS	-42%* ^f	No placebo	40 min	43%	No saline control group. Significant baseline differences in mood rating scale scores.
Rasmussen et al. (2013)	Open label trial	10 MDD	0.5mg/kg i.v. / 100min x4	MADRS	-34%* ^j	No placebo	Post infusion	20% ^j	No saline control group. Variable number of completed infusions. Concurrent use of other medications.
Salvadore et al. (2010)	Open label trial	15 MDD	0.5mg/kg i.v. / 40min	MADRS	-37%	No placebo	230 min		Older mean age of patients. Large number with co-morbid anxiety disorder. No saline control group.
Salvadore et al. (2012)	Open label trial	14 MDD	0.5mg/kg i.v. / 40min	MADRS	-25%	No placebo	230 min		No saline control group. Some participants from previous trials. Older mean age of patients.
Chilukuri et al. (2014)	Open label trial	27 MDD	0.5mg/kg i.v. / 40min or 0.5mg/kg i.m. or 0.25mg/kg i.m.	HAM-D	59% - i.v. 60% - i.m.	No placebo	120 min		0.25mg/kg i.m. dose produced reduction in HAM-D of 57%. No saline control group.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Ghasemi et al. (2014)	Single blind RCT	9 MDD (ket) 9 MDD (ket + ECT)	0.5mg/kg i.v. / 45min x3	HAM-D	-42%	-14% ECT	1 day	77%	No saline control group. Continued use of other psychotropic medication
Messer et al. (2010)	Open label case series	2 MDD TR	0.5mg/kg i.v. / 40min x2 – x6	BDI	-35%*	No placebo	Not reported		No saline control group. Both patients markedly overweight and had medical comorbidities.
Jarventausta et al. (2013)	Single blind RCT	16 MDD TR (S-ket + propofol) 16 MDD TR (propofol)	0.4mg/kg S-ketamine bolus prior to anaesthetic for ECT	MADRS	-73% ^{k*}	-73% ^{k*} (propofol)	Not reported		No additional benefit of S-ketamine. Concurrent use of antidepressants. No active comparator.
Paslakis et al. (2010)	Open label case series	4 MDD	1.25mg/kg oral S-ketamine for 14 days + current antidepressant	HAM-D	-43%	No placebo	14 days ^g	50%	No saline control group. Potential augmentation effect of current antidepressants.
Segmiller et al. (2013)	Open label case series	6 MDD TR	0.25mg/kg S-ketamine i.v. / 40min x6 + current antidepressant	HAM-D	-55%	No placebo	120 min	50%	No saline control group. Older mean age and long illness duration. Potential augmentation effect of current antidepressants.
Szymkowicz et al. (2013)	Open label case series	3 MDD TR	0.5mg/kg i.v. / 40min x6	MADRS	Data unclear	No placebo	Data unclear		No saline control group. Patients taking other medications. All patients responded after repeated infusions.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Correll and Futter (2006)	Case reports	2 MDD	0.1-0.3mg/kg/h i.v. for 5 days	HAM-D	-73%	No placebo	4 days		Open label. No saline control group. Patients markedly overweight.
Denk et al. (2011)	Case report	1 MDD TR	0.25mg/kg i.v. S-ketamine / 40min	MADRS	-86%	No placebo	Post infusion		Open label. No saline control group.
Glue et al. (2011)	Case report	2 MDD	0.5/ 0.7 /1.0 mg/kg i.v./ 40min	MADRS	-34%*	No placebo	Not reported		Open label. No saline control group. Ascending dosages. Peak effect seen after 0.7mg/kg
Goforth and Holsinger (2007)	Case report	1 Severe MDD with psychotic features	100mg i.m. anaesthesia prior to ECT	MADRS	-60%	No placebo	3 days		Open label. No control group.
Irwin and Iglewicz (2010)	Case reports	2 MDD	0.5mg/kg PO	HAM-D	-41%	No placebo	60 min		Open label. No control group. Several concurrent psychotropic medications. Comorbid anxiety disorders also present.
Liebrenz et al. (2009)	Case report	1 MDD TR	0.5mg/kg i.v./ 50min x2	HAM-D	-57% ^j	No placebo	1 day		Open label. No saline control group. Polysubstance dependence.
Stefanczyk-Sapieha et al. (2008)	Case report	1 MDD TR	0.5mg/kg i.v. / 60min x2	HAM-D	-43% ^j	No placebo	60 min		Open label. No saline control group. Diagnosis of metastatic prostate cancer. Several concurrent medications.

Abbreviations: BDI= Beck Depression Inventory; BPD= Bipolar Depression; CON= Controls; HADS= Hospital Anxiety and Depression Scale; HAM-D= Hamilton Depression Rating Scale; i.m.= Intramuscular; i.v.= Intravenous; ket= Ketamine; MADRS= Montgomery-Asberg Depression Rating Scale; MDD= Major Depressive Disorder; PO= oral; RCT= Randomised Controlled Trial; Response= 50% reduction in scores; TR=Treatment resistant; *= calculated from graphical data presented in paper ^f = only ketamine data presented here ^g= in two cases ^h= maximal reduction after 8th ECT session ⁱ= after 1st infusion ^k= after final session of ECT

3.7. Effects of other glutamate drugs on depression (Clinical studies)

3.7.1. Modulators of glutamate release

3.7.1.1. Lamotrigine

Lamotrigine is an anticonvulsant that stabilizes neuronal membranes and prevents glutamate release via inhibition of sodium channels (Leach et al., 1991, Grunze et al., 1998, Pisani et al., 2004). Lamotrigine is also thought to affect 5-HT, noradrenaline and dopamine uptake (Southam et al., 1998).

In bipolar depression, a multicentre double-blind randomized controlled trial of lamotrigine (50mg daily or 100mg twice daily for 7 weeks) in 192 outpatients demonstrated significant improvement in the Clinical Global Impression (CGI), HAM-D and MADRS (Calabrese et al., 1999). Rashes, headaches and a small proportion of manic or hypomanic episodes were noted. A recent meta-analysis reported lamotrigine was effective in bipolar depression (Geddes et al., 2009). Unfortunately these positive results have not translated to studies in humans in MDD comparing lamotrigine to placebo (Amann et al., 2011, Reid et al., 2013).

3.7.1.2. Riluzole

Another inhibitor of glutamate release originally used in the treatment of amyotrophic lateral sclerosis is riluzole. It acts to inhibit glutamate release through inactivation of sodium channels with a similar mechanism to lamotrigine (Benoit and Escande, 1991, Wang et al., 2004). Riluzole also enhances synaptic AMPA receptor expression (Du et al., 2007) and blocks NMDA receptor activation (Kalia et al., 2008). There were significant improvements in the MADRS with response rate of 32% overall in an open labelled trial of riluzole alone over 6 weeks in 19 patients with tr MDD (Zarate et al., 2004b). As with lamotrigine headaches were a significant proportion of the adverse side effects, as were gastrointestinal side effects and restlessness. There was a short drug washout period prior to commencement and varying length of medication (Zarate et al., 2004b). A similar positive result was found in an open label study of 14 patients with bipolar depression of riluzole up to 200mg/day in combination with lithium. Improvements in the MADRS and CGI during the 8 week trial period were reported. There was no control group (Zarate et al., 2005). Concomitant use of lithium may have also affected the results given its reported effects on NMDA receptors (Nonaka et al., 1998).

However, as noted previously, riluzole did not maintain the acute antidepressant effects of ketamine in Mathew et al. (2010a) leading to early trial termination. Brennan et al. (2010) reported riluzole 100-200mg significantly decreased HAM-D, MADRS and CGI-S scores in bipolar disorder depression in an open label trial. Follow up was very frequent which may have also improved scores. In addition some patients were also continuing to use antidepressants and antipsychotics. Open label augmentation of current antidepressant therapy using riluzole by Sanacora et al. (2007) reported significant improvements in both anxiety and depressive

symptoms. Overall, there is good evidence to support the antidepressant effect of riluzole in MDD (Sanacora and Banasr, 2013).

3.7.2. Drugs acting at NMDA receptors

3.7.2.1. Memantine

Memantine is derivative of amantadine and an NMDA receptor antagonist used in the treatment of moderate to severe Alzheimer's dementia (Hashimoto, 2009). It may have agonist activity at dopamine D₂ receptors (Seeman et al., 2008). Zarate and colleagues reported on 32 patients with MDD in a double-blind placebo controlled trial of memantine versus placebo for 8 weeks (Zarate et al., 2006b). No difference was noted between the treatment groups in MADRS scores at the end of the trial. Differences between this and previous ketamine studies in humans were explained by lower NMDA receptor affinity, faster open channel blocking/unblocking kinetics and partial trapping channel closure of memantine (Zarate et al., 2006b). A 12 week open label trial of memantine in 8 patients however found MADRS scores improved within 1 week of treatment, continued till week 8 and were maintained till the end of the trial. At 12 weeks mean improvement was 16.7 points. There was no washout period or control group and patients were not excluded from taking other medications (Ferguson and Shingleton, 2007). Somnolence, headaches, dizziness and anxiety were all noted as side effects in this trial (Ferguson and Shingleton, 2007). The evidence for memantine's antidepressant effect is not clear and the mechanism is not consistent with the rapid actions reported with ketamine.

3.7.2.2. Amantadine

Amantadine is an NMDA antagonist commonly prescribed for the treatment of Parkinson's disease and has been used as an antiviral. It is thought to inhibit NMDA responses through stabilization of the ion channel and a more rapid rate of closure (Blanpied et al., 2005). Amantadine has been shown to improve mood in humans with "chronic depressive syndrome" when given up to 200mg/day for 4 weeks (Vale et al., 1971). Use as an adjunctive therapy in major and bipolar depression has been trialled open label in 25 patients with 68% having >50% reduction on the HAM-D (Dietrich et al., 2000). However there is no RCT evidence to support its efficacy in depression and as such the evidence is limited and unreliable. The mechanism of action is somewhat different to ketamine that might explain this.

3.7.2.3. Traxoprodil (CP-101,606)

CP-101,606 is an GluN2B subunit selective NMDA receptor antagonist which has been studied as adjunctive therapy to paroxetine (Preskorn et al., 2008b). Patients initially had 6 weeks of open-label treatment with paroxetine 40mg/day. Non-responders (30 patients) were then randomized to CP-101,606 intravenous infusion or placebo. Non-response was defined as

improvement of 20% or less on the HAM-D. They continued on paroxetine 40mg/day for another 4 weeks till the end of the study. The addition of CP-101,606 produced a 60% response rate versus 20% for placebo on the HAM-D with 33% meeting criteria for remission by day 5. Response was maintained in 42% of patients till 15 days after. The dosing of CP101,606 was reduced to 0.5mg/kg for 1.5 hours for half the patients. This was done for safety reasons due to the high number of dissociative effects caused by CP-101,606 at higher doses but would have led to methodological bias (Preskorn et al., 2008b).

3.7.2.4. GLYX-13

GLYX-13 is a novel NMDA receptor glycine site functional partial agonist. It recently completed phase II trials and was reported to have antidepressant effects within 24 hours which lasted up to 7 days in MDD patients who had failed one or more antidepressant medications. There were no dissociative effects (Burch, 2012).

3.7.2.5. MK-0657

Ibrahim et al. (2012a) investigated MK-0657, a GluN2B antagonist that was administered orally to treatment resistant MDD patients for 12 days. The study design was a randomised, double blind, placebo controlled crossover trial. MADRS was the primary outcome measure although HAM-D was also completed. No significant improvement was noted on MADRS. Significant improvement was noted on BDI and HAM-D. No dissociative reactions were reported (Ibrahim et al., 2012a). Sample size was only 5 and therefore it is impossible to draw any real conclusions. In addition the conflicting mood rating scores further confuse the evidence. This is an interesting finding given the positive results of other GluN2B antagonists in MDD.

3.7.2.6. AZD6765 (Lanicemine)

AZD6765 is a low-trapping NMDA channel blocker that has little or no propensity for causing psychotomimetic effects (Mealing et al., 1999, Zarate et al., 2013a, Sanacora et al., 2014). AZD6765 has antidepressant-like properties in animal models such as the forced swim and learned helplessness tests (Zarate et al., 2013a). AZD6765 was administered i.v. in a double-blind, placebo-controlled crossover RCT in 22 medication free MDD (Zarate et al., 2013a). Significant reductions in MADRS scores were reported at 80 and 110 minutes post infusion but the response was transitory. There was a 16% additional response rate over placebo with AZD6765. The patient group had high levels of treatment resistance. In a further combination of studies Sanacora et al. (2014) reported a significant reduction in MADRS scores at 72 hours post initial infusion. Nausea and dizziness were the most commonly reported side effects, although no dissociative effects were noted. The MADRS reduction was maintained for 5 weeks following repeated infusions of AZD6765. However patients were allowed to remain on their background medication following the initial infusion which would confound results. Given the similar mechanism to ketamine AZD6765 would be expected to produce significant antidepressant effects of a similar effect size to ketamine.

Conclusions – drugs acting at NMDA receptors

The evidence for memantine and amantadine is inconclusive but they may have antidepressant effects in humans. The experimental compounds of GLYX-13, MK-0657 and AZD6765 all require further trials to demonstrate their antidepressant effect.

3.7.3. Drugs acting at AMPA receptors

3.7.3.1. RO4917523/AZD2066/Coluracetam

There are number of novel compounds which have been recently trialled. These include the mGlu₅ antagonists; RO4917523 and AZD2066. The latter have no antidepressant effects in patients with MDD on MADRS (Hashimoto et al., 2013). Older AMPAkinetics such as levetiracetam have not shown evidence of efficacy but several more potent compounds have been developed such as coluracetam (BCI-540) which is in clinical trials (Saricicek et al., 2011).

3.8. Conclusions and need for future studies

The current theory of NMDA antagonist's antidepressant effect is summarised with evidence in Table 11. If glutamate is an important mechanism of action of antidepressant drugs, the question arises whether they correct an illness-related abnormality. However, the answer is fairly inaccessible in living humans. Despite the 40% heritability of depression, no glutamate or other risk genes have yet been identified from large scale genome-wide association studies (Flint and Kendler, 2014). In principle determination of glutamate concentration in vivo in brain should be possible with [¹H] MRS. However, at commonly available 3T field strengths, it is difficult to separate the glutamate and glutamine peaks and the combined peak, called Glx, has been used. Nevertheless, several [¹H] MRS studies have reported reduced content of Glx in studies in the ACC, PFC, dlPFC, amygdala and hippocampus (Hasler et al., 2007, Block et al., 2009, Bhagwagar et al., 2008, Yildiz-Yesiloglu and Ankerst, 2006). More recent studies, however, report no difference when glutamine was removed from the spectra in the dlPFC and ACC (Nery et al., 2009, Taylor et al., 2009). Sanacora et al. (2004) reported increased glutamate content in OCC in a large sample of MDD. Inferences about synthesis and release from static concentrations are uncertain. A recent study using ¹³C glucose MRS found no evidence for altered glutamate/glutamine cycling in OCC in depression (Abdallah et al., 2014). The state of presynaptic glutamate release in-vivo in MDD remains uncertain.

In human post-mortem brain a number of studies have reported molecular and cytoarchitectural evidence of reduced astroglial numbers and function (Sanacora and Banasr, 2013). This has led to an important integrative theory that glial retraction allows glutamate i) to spill over onto extrasynaptic dendritic NMDA receptors which mediate cytotoxic depressogenic effects and ii) to

access extrasynaptic terminal mGlu₂ receptors resulting in inhibition of glutamate release. NMDA antagonists would reverse the deficient glutamate release and block the toxic stimulation of extrasynaptic NMDA receptors. However, the evidence for glial pathology is not entirely consistent. The sole study of glutamine synthetase, the glial enzyme that recycles glutamate to glutamine and back into the neurone, found no changes in MDD in post-mortem brain (Toro et al., 2006). The glial dysfunction theory suggests that drugs that increase glial uptake of glutamate could restore normal synaptic function. The antibiotic ceftriaxone appears to work in this way in animal models but there have been no trials in humans (Mineur et al., 2007).

Although a loss of glial cells in the vACC, rACC, dIPFC and OFC in MDD have been reported there are also reports of increases in glial cell numbers in the hippocampus and dentate gyrus (Rajkowska and Miguel-Hidalgo, 2007). A reduction in cell numbers and both in EAAT1 and EAAT2 seems to play a role in the frontolimbic regions (Miguel-Hidalgo et al., 2010, Choudhary et al., 2005, Sanacora and Banasr, 2013). A number of studies have reported reduced GluN1, GluN2A and GluN2B receptor subunits in post mortem brain in hippocampus (Law and Deakin, 2001, Block et al., 2009, Beneyto et al., 2007). There are also reductions reported in GluN2A and GluN2B in the PFC (Feyissa et al., 2009, Karolewicz et al., 2009a). If these effects are not artefacts of antemortem treatment or chronic illness, they are difficult to integrate with the efficacy of NMDA antagonists. Problems arise with consistency of study groups, use of concomitant medication prior to death and limited repetition of studies for different brain regions.

If we are to assume that synaptic glutamate is reduced in MDD then this would question the mechanism of drugs like ketamine acting simply through NMDA blockade creating an antidepressant effect. There is some evidence that ketamine works through glutamate release onto AMPA receptors (Maeng et al., 2008, Li et al., 2010b). Riluzole may also increase synaptic AMPA expression (Du et al., 2007). The psychotomimetic effects of ketamine are also reduced by lamotrigine suggesting an interaction with non-NMDA receptors (Anand et al., 2000, Deakin et al., 2008). Other NMDA receptor antagonists appear to be antidepressant such as amantadine, memantine and traxoprodil (Zarate et al., 2004a, Vale et al., 1971, Dietrich et al., 2000, Preskorn et al., 2008a). None of the above alternatives seem to offer the rapid antidepressant effect of ketamine.

It is important to note that this is not a mechanism separate from the function of traditional antidepressants. Although some differences in synaptic cascade have been noted (Li et al., 2010b) there are changes in both NMDA and AMPA receptors with fluoxetine (Ampuero et al., 2010). Desipramine and fluoxetine have also both shown effects at blocking NMDA induced currents (Szasz et al., 2007). Furthermore, there is evidence of downregulation of NMDA receptors following treatment with citalopram and fluoxetine in animals (Nowak et al., 1996, Nowak et al., 1998, Boyer et al., 1998). Increased expression of mGlu_{2/3} has been noted following imipramine treatment in animals (Matrisciano et al., 2007), while others have noted downregulation of mGlu_{2/3}, mGlu₄ and mGlu₇ with amitriptyline in an olfactory bulbectomy model of depression in mice (Wieronska et al., 2008). However, a recent proton magnetic resonance

spectroscopy [¹H] MRS study where MDD patients were treated with escitalopram for 6 weeks yielded no change in glutamate or glutamine despite improvement in HAM-D scores (Godlewska et al., 2014).

A range of studies have reported response to ketamine from 15% to 86% on mood rating scales (Denk et al., 2011, Abdallah et al., 2012). Peak effect seems to occur following the primary infusion. The antidepressant effect has only been prolonged with repeated infusions rather than riluzole or lamotrigine (Mathew et al., 2010a). Even so the evidence is unreliable. Inadequate sample sizes, lack of control groups and randomization and differences in patient group characteristics have plagued studies. Patients in these trials have had co-morbid disorders which have further worsened their reliability. There is also no active comparators except in one study (Murrough et al., 2013a) where they did not report the impressive HAM-D reductions initially reported by Berman et al. (2000) and Zarate et al. (2006a). No saline group was present to further demonstrate this.

Part of the problem remains that we have no reliable biomarkers of glutamate function in patients with depression; animal models do not always transfer well to humans. phMRI evidence of prolonged deactivation of the vACC with ketamine and prolonged activation with citalopram has been noted (Deakin et al., 2008, McKie et al., 2005). In fact Mayberg et al. (2005) has shown sustained remission in four of six patients following deep brain stimulation of the vACC (Mayberg et al., 2005). Recently Salvatore et al. (2010) has demonstrated using MEG that MDD patients with least engagement of rACC during a working memory task as a possible biomarker of antidepressant response to ketamine. This has not been investigated further.

The mechanism of ketamine appears to be in part through glutamate release onto non-NMDA receptors including AMPA and metabotropic receptors. There are also reported effects on 5-HT, dopamine and intracellular effects on the mTOR pathway amongst others (Maeng et al., 2008, Li et al., 2010b). Antidepressants increase AMPA function and citalopram glutamate cycling (Williams et al., 2007, Ampuero et al., 2010). This complete mechanism has not been well elucidated in humans. More recently animal models have demonstrated a neuroprotective and antidepressant effect of ketamine in preventing lipopolysaccharide induced inflammation and depressive symptoms in animal models (Walker et al., 2013).

Given the early promising results in clinical trials further proof of concept studies are required in animal and human models of MDD with new glutamate modifying drugs as our knowledge in this area expands. This is especially important for new and emerging compounds. The linked effects of glial loss, changes in Glx demonstrated in proton MRS and effects on resting state in the ACC suggest this is an area to focus on. Although the evidence that conventional antidepressants acting on glutamate systems is inconclusive, phMRI may suggest common networks of action. Furthermore if antidepressant treatments affect glutamate in the ACC this should be able to be correlated with changes in the DMN and SN.

Table 11 NMDA antagonists as antidepressants: summary of evidence

Therapeutic mechanism	Increases effect of glutamate non-NMDA receptors	Prevents overstimulation of NMDA receptors
Glutamate neurotransmission in depressed patients	<p>↓Glx (glutamine+glutamate) several proton MRS studies in MDD (Bhagwagar et al., 2008, Hasler et al., 2007, Block et al., 2009)</p> <p>↓ Gln/Cr, Gln/glx ratios decreased (Block et al., 2009)</p> <p>Increased mGlu₂, mGlu₅ and mGlu₇ in MDD (Karolewicz et al., 2009a, Feyissa et al., 2010)</p>	<p>Overstimulation of NMDA PM brain (Law and Deakin, 2001, Nudmamud-Thanoi and Reynolds, 2004, Beneyto et al., 2007, Feyissa et al., 2009)</p> <p>Glial deficiency and/or failure of glial glutamate uptake PM brain (Choudhary et al., 2005, Sanacora and Banasr, 2013, Miguel-Hidalgo et al., 2010)</p> <p>Post-mortem reductions in ionotropic and metabotropic glutamate receptors (Law and Deakin, 2001, Beneyto et al., 2007, Feyissa et al., 2009, Karolewicz et al., 2009a)</p>
Effects of glutamate drugs on depression	<p>Ketamine has antidepressant effects in MDD (Berman et al., 2000, Zarate et al., 2006a, Murrough et al., 2013a, Moghaddam et al., 1997, Maeng et al., 2008, Zhou et al., 2014)</p> <p>Lamotrigine antidepressant in BPD (Calabrese et al., 1999)</p>	<p>Lamotrigine did not block AD effects of single dose i.v. ketamine (Mathew et al., 2010b)</p> <p>Traxoprodil acts as antidepressant (Preskorn et al., 2008a)</p>
Glutamate and animal models of depression	<p>Ketamine increases glutamate release onto AMPA receptors (Moghaddam et al., 1997, Maeng et al., 2008, Zhou et al., 2014)</p> <p>AMPA agonism enhances antidepressant function (Zhou et al., 2014)</p> <p>GluA1 (AMPA) knockout mice depression-like with increased glutamate release onto NMDA receptors (Chourbaji et al., 2008)</p> <p>Riluzole increases synaptic AMPA receptor expression (Du et al., 2007)</p> <p>Ketamine activates synapse formation via mTOR pathway (Li et al., 2010b)</p>	<p>GluN2A knockout mice antidepressant effects (Boyce-Rustay and Holmes, 2006)</p> <p>Ceftriaxone increases EAAT2 gene transcription and is antidepressant-like in animals (Mineur et al., 2007)</p>
Effects of standard antidepressants on glutamate function in animals /humans	<p>Antidepressants increase AMPA function (Ampuero et al., 2010)</p> <p>Citalopram increases glutamate cycling (Williams et al., 2007)</p>	<p>Antidepressants down regulate NMDA function (Nowak et al., 1996, Nowak et al., 1998, Szasz et al., 2007, Boyer et al., 1998)</p>

3.9. Thesis hypotheses

From the review of literature in Chapters 1-3, the following hypotheses were drawn for the experimental chapters that follow:

- i) *Administration of antidepressant drugs to patients with MDD will increase the mean intensity of the ACC resting state network in SN and CEN structures (ACC, insula, superior frontal cortex, IPL) and reduce it in the DMN structures (mPFC and precuneus).*

This is based on the review of resting state studies (Chapter 2) (Dutta et al., 2014) which demonstrated increases in measures of intensity and connectivity in SN and CEN structures and decreases in DMN structures. These increases and decreases were reversed by antidepressant medication. Given the role of the ACC activity as a factor in treatment response central to the DMN switching, effects of antidepressant medication should occur most prominently in ACC correlated networks (Mayberg, 2003, Pizzagalli, 2011, Fu et al., 2013).

- ii) *Improvement in mood rating scores in drug treated groups will correlate positively with mean intensity of ACC RS component in SN structures (ACC and insula) and negatively with DMN structures (precuneus).*

ACC response has correlated with higher likelihood of improvement in mood to antidepressants (Fu et al., 2013). Furthermore patients administered conventional antidepressants were reported to have increased rACC metabolism in responders compared with non-responders (Mayberg et al., 1997). Due to the opposing roles of the DMN versus the SN and CEN, opposite effects should be expected in mood rating scale correlation to neural response.

- iii) *Trait abnormalities will be observed in the mean intensity of ACC RS component in DMN structures in cMDD and rMDD when administered an antidepressant.*

Rumination has been proposed as a trait marker of MDD (Nolen-Hoeksema, 2000). Rumination has been associated with vulnerability to MDD and with increased activity of the DMN (Johnson et al., 2009) Relapse in rMDD is observed with tryptophan depletion and therefore administration of an SSRI may demonstrate defective response of the 5-HT system in DMN structures (Delgado et al., 1990, Reilly et al., 1997).

- iv) *The same effects on mean intensity of ACC RS component in DMN, CEN and SN structures will be common to antidepressants with different mechanisms of action.*

Chapter Four: Effects of AZD6765 on resting state networks in major depressive disorder

4.1. Introduction

Chapter 3 (Dutta et al., 2015) reviewed the current interest in glutamate mechanisms in MDD as a promising target for the development of new antidepressants based on the rapid antidepressant effects of intravenous infusion of ketamine, (Berman et al., 2000, Zarate et al., 2006a). The mechanism of action appears to be in part through glutamate release onto non-NMDA receptors including α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors. However, there have been few studies at a neural systems level, of the mechanism of action of glutamate antidepressants and none on RS networks. Chapter 3 described a number of glutamate-active drugs, other than ketamine, with potential antidepressant effects including AZD6765 (lanicemene) a NMDA antagonist. A recent study in Manchester compared phMRI BOLD responses to ketamine and AZD6765 in depressed untreated participants meeting criteria for MDD (Downey D. et al., In press). Both drugs elicited responses in rACC that predicted improvement in mood occurring 24 hours and 7 days later. The present study re-analyzed the phMRI data to compare the drugs' effects on RS activity in rACC and in regions showing the rACC RS pattern.

That rACC BOLD signal predicted antidepressant effects are compatible with a number of lines of evidence. The ACC has been proposed as one of the 'central hubs' of the DMN because of its role in self-referential processing including rumination (Pizzagalli, 2011). Furthermore it has previously been suggested that normalisation of vACC hyperactivity is essential for symptom remission (Mayberg, 2003). Elevated CBF and metabolism are reported in PET studies of MDD (Drevets, 2000). Treatment response has been linked to reductions in metabolism in the vACC (Drevets et al., 2002). A recent meta-analysis of functional imaging studies also found increased activation of the rACC correlated with greater likelihood of treatment response to antidepressants (Fu et al., 2013). From the review of resting state studies (Chapter 2)(Dutta et al., 2014) several studies report reduced ACC RS activity when medicated patients were examined (Greicius et al., 2007, Wu et al., 2011, Guo et al., 2012b, Liu et al., 2013a, Sambataro et al., 2013) but reduced FnC following antidepressant treatment (Anand et al., 2005b, Posner et al., 2013). Antidepressant response to ketamine was predicted by increased pre-treatment rACC activity measured by MEG following exposure to fearful faces (Salvadore et al., 2009). Responders to conventional antidepressants were reported to have increased rACC metabolism compared with non-responders and with HC on PET (Mayberg et al., 1997). Finally, pretreatment response of the rACC predicts response to ketamine (Salvadore et al., 2009) and reductions in FnC between the ACC and other structures have been reported in healthy volunteers following ketamine infusion (Scheidegger et al., 2012).

In view of the foregoing evidence that ACC may have a key role antidepressant mechanisms, the present analysis of the effects of ketamine and lanicemine focused on the regional activity of RS component most prevalent in the ACC. The ACC is part of the DMN and the SN. The study was mainly observational. However, we expected the 2 drugs to have similar effects in reducing ACC RS signal strength in DMN regions, such as precuneus and mPFC, that are associated with

rumination, and increasing ACC RS signal strength in SN components such as the insula, which is associated with attention and switching to the CEN. Within the ACC itself, it was assumed that pHMRI BOLD signal evoked by the 2 drugs in ACC would be associated with a more prevalent ACC RS component.

4.2. Aims

The aims of this study were to determine whether:

- i) AZD6765, a novel NMDA receptor antagonist with similar receptor binding properties to ketamine, affects the mean intensity of ACC RS component.
- ii) AZD6765 and ketamine have prolonged effects on mean intensity of ACC RS component 24 hours after infusion
- iii) MADRS mood rating scores are correlated with mean intensity of ACC RS component of AZD6765 or ketamine infusion in HC and cMDD

4.3. Hypotheses

The hypotheses for the study were:

- i) *AZD6765 and ketamine compared with saline placebo will a) increase the mean intensity of ACC RS component in SN structures (ACC and insula) and CEN (superior frontal cortex, IPL) and b) reduce mean intensity of ACC RS in DMN structures (precuneus and mPFC)*
- ii) *The effects of AZD6765 and ketamine on day 1 should persist in the day 2 RS data 24 hours after infusion.*
- iii) *Improvement in MADRS mood rating scores in drug-treated groups will positively correlate with mean intensity of ACC RS component in the ACC and insula (SN) and negatively with the precuneus (DMN).*

4.4. Methods and materials

4.4.1. Ethics

The study protocol, subject information sheet and consent forms were approved by the Capenhurst Independent Research Ethics Committee (CIREC) Ref: 1029.

4.4.2. Study design and recruitment

The study (NCT1046630) was carried out in two centres using a randomized, double-blind, placebo-controlled, parallel-group design. After screening and consent, participants attended two successive experimental days and had a follow-up visit 7 days after drug infusion. At the beginning of each experimental day, Beck Depression Inventory (BDI) (Beck et al., 1961, Beck et al., 1996) self-ratings and Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery

and Asberg, 1979) interview ratings of mood were carried out. On Day 1 participants were randomized to receive intravenous saline, ketamine or AZD6765 during an hour-long scanning session. The MADRS but not the BDI was repeated after the infusion. Day 2 began with mood ratings 24 hours post infusion when near maximal antidepressant effects were expected.

4.4.3. Study recruitment

Male and female participants between the ages of 18 and 45 years with MDD were recruited by advertisement on a website with an online BDI and collection of contact details for those wishing to volunteer. Volunteers scoring at least 12 on the BDI underwent a brief telephone screen followed by consent and formal screening at the local research unit. Sixty-four participants were screened to ensure a maximum of 60 randomized participants across both centres.

4.4.4. Screening and randomisation

The inclusion criteria included the following: able to provide written informed consent; meeting DSM-IV Major Depressive Disorder (MDD) criteria - Single or Recurrent Episodes by Structured Clinical Interview (SCID) (First et al., 2002); not pregnant and use of effective contraception; not under psychiatric care. The exclusion criteria covered the following: lifetime history of psychosis or bipolar disorder; mood stabilizers or psychoactive drugs within 14 days; positive urine drug screen; clinically relevant medical illness; smoking and caffeine limits; left handedness, and MR scanning contraindication. The smoking limit was 10 cigarettes per day or the equivalent of this in tobacco. The caffeine limit was no more than 8 cups of caffeinated drinks per day. There were no specified alcohol consumption limits, however, participants were screened out at the investigator's discretion via medical history due to potential risks of administering the study medication. The research pharmacies at each site held separate randomization codes and dispensed the infusions on the day of the experiment labelled with a code number.

4.4.5. Study procedures

Experimental Day 1: PharmacoMRI Procedure

Participants completed the BDI and were interviewed for MADRS ratings and baseline dissociative symptoms using the Clinical Administered Dissociative States Scale (CADSS) (Bremner et al., 1998). They were cannulated. After baseline scans the participants received a constant intravenous infusion of AZD6765 (100 mg total dose), ketamine (0.5 mg/kg total dose) or placebo (0.9% saline) made up to 40mL over 1 hour.

Scanning was carried out on a Philips Achieva 3T MR scanner (Salford Royal Hospital, Salford) and a Siemens TimTrio 3T scanner (John Radcliffe Hospital, Oxford). Whole-brain echo-planar images (TR/TE = 3000/30 msec, in-plane resolution = 3 x 3 mm, slice-thickness = 2.5 mm with 0.5 mm slice gap, 45 ascending sequential slices) were acquired 5 minutes prior to and 40 min during the infusion (900 volumes in total). To maintain wakefulness, at 2 minute intervals participants rated subjective effects such as “drowsy” and “anxious” on a 4-point scale projected

on a screen. MADRS and CADSS ratings were repeated immediately after the infusion and at 4 hours.

Experimental Day 2 and Follow-up: 24 hr post infusion mood ratings and fMRI

Participants returned for 24 hour post infusion BDI and MADRS mood ratings. Participants also returned 8–11 days after treatment and completed questionnaires and safety assessments. The maximum total study duration was 42 days.

4.4.6. Image preprocessing

Images were preprocessed using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) run under MATLAB 2009a (The MathWorks, Inc., Natick, MA, USA; <http://www.mathworks.com>) in the standard way using realignment, normalisation and smoothing. SPM8 was used because this was the preferred software used within the research group.

4.4.7. Independent Component Analysis

Independent component analysis (ICA) is a data driven model-free method that allows the extraction and signal separation without specific assumptions regarding the data (McKeown et al., 1998). ICA allows the separation of signals into spatially independent components which represent multifocal neural networks. The component map is described by a distribution of values for each voxel. ICA allows unmixing of unknown source signals which are mixed together (GIFT Documentation Team, 2013). Both temporal and spatial correlation of the data are possible although spatial ICA is more common (Calhoun et al., 2001). Although ICA had been used to analyse individual data, Calhoun et al. (2001) proposed a method of entering all subjects into an group ICA and estimating one set of components.

The preprocessed images from all groups on day 1 and day 2 were ordered by site, treatment and day, before being entered into Group ICA of fMRI Toolbox (GIFT) software run under MATLAB 2009a. GIFT v1.3i (<http://icatb.sourceforge.net/groupica.htm>) uses spatial ICA to make group inferences about fMRI data. The final 25 minutes of the phMRI was used for day 1 and a 25 minute resting state scan used for day 2. GIFT split the data set into 20 components using the Infomax algorithm (Bell and Sejnowski, 1995) using default settings and regular ICA analysis. GIFT performed the following stages: initializing of parameters, group data reduction, ICA calculation, back reconstruction, component calibration and finally group statistics. The components were sorted by spatial correlation with to the ACC mask from the Talairach Atlas in the WFU (Wake Forest University) PickAtlas (Tzourio-Mazoyer et al., 2002, Maldjian et al., 2003, Maldjian et al., 2004, Maldjian et al., 2008) and then displayed. Each of the 20 components was also visually inspected via SPM[T] map overlaid upon the single subject T1 image from SPM8 to

identify any additional components representing the ACC. The component with the highest spatial correlation to the ACC was selected. Brain images of the intensity of the selected component for each individual were created in GIFT by back reconstruction. The individual component images for the component with the highest spatial correlation with the ACC, the ACC RS component images, were then entered into one-way ANOVAs, one for each day, to test for main effects of treatment.

Selection of the ACC independent component of interest

The 20 component maps for the AZ dataset are displayed below (radiological convention is followed which means the left side of the image corresponds to right side of the brain). These are derived from the day 1 and 2 data combined. The component map overlays are cluster thresholded at >20 voxels and height thresholded at $p < 0.001$ uncorrected demonstrating the positive and negative component. The components represent ACC correlated resting state statistically independent 'networks' that respond concurrently to drug challenge. The components with the highest spatial correlation to the ACC in this dataset were components 10 ($r = 0.473$), 7 ($r = 0.338$) and 6 ($r = 0.073$). Component 10 is highlighted in red in figure 3 below and was selected as the component of interest.

Treatment effects on the ACC RS component and correlations with MADRS scores

Individual maps of the amplitude of component 10 were entered into a one-way ANOVA in SPM with drug treatment group as the between subjects factor. The positive and negative ACC RS components were examined using SPM voxel-wise and regional MaRSBaR analysis.

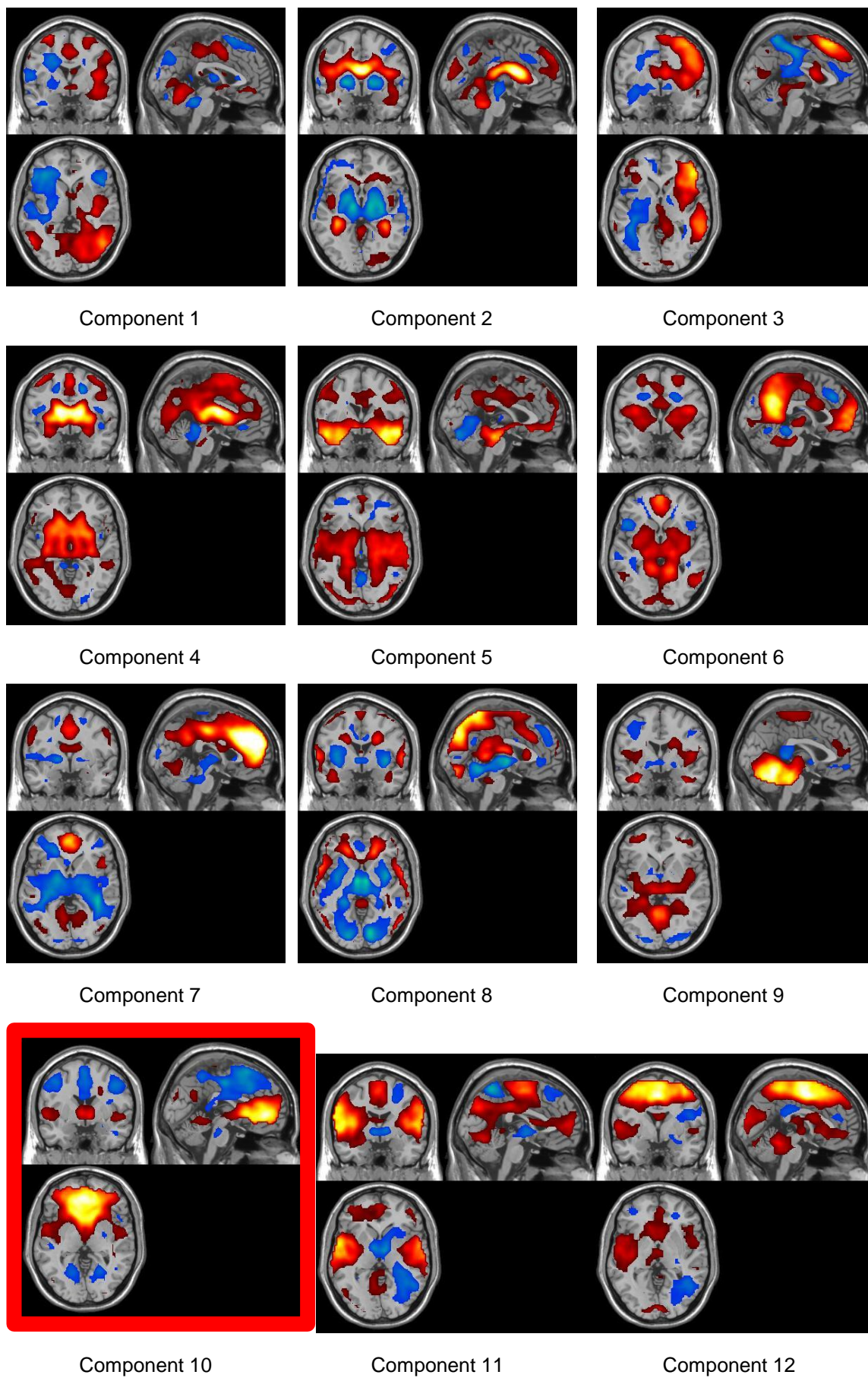
For the SPM voxel-wise analysis, contrasts were set up to test for differences between the groups, medication and group by medication interactions across the whole brain. Activated voxels were thresholded at an uncorrected $p = 0.001$ with an extent threshold that meet a cluster False Discovery Rate (FDR) corrected extent threshold of $pFDRc < 0.05$. The Montreal Neurological Institute (MNI) co-ordinates were entered into the WFU PickAtlas toolbox v2.4 in order to identify anatomical structures using the Talairach Atlas. Day 2 maps were subtracted from Day 1 maps to examine the day x treatment interaction using MaRSBaR regional analysis.

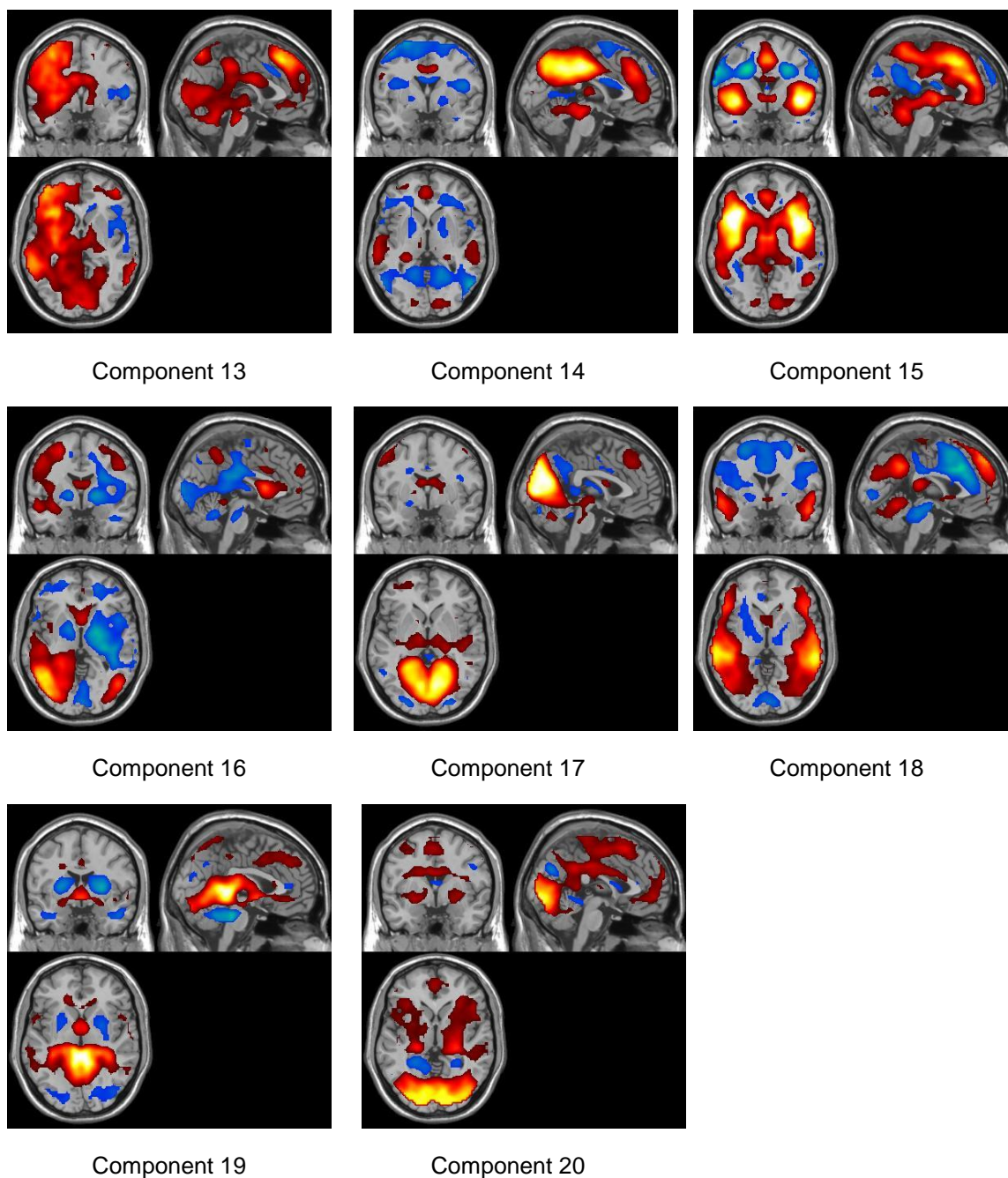
Regional analysis was performed using MarsBaR (Marseille Boite a Regions d'interet), a region of interest toolbox for SPM. For the selected ACC RS component GIFT produced a Talairach table of regions thresholded as above at $p < 0.001$ uncorrected and extent threshold set at 20 voxels. SPM clusters were acquired and masks written to ROI files. The images were viewed via MarsBaR and the centre of mass for each component calculated. Statistical results were extracted for p values, mean, t-statistic and standard error for each of the significant regions identified. The p-values were FDR corrected for the number of Talairach regions tested.

MADRS scores were analysed using t-tests for difference between baseline, 4 hour, 24 hour and 7 days post infusion. T-tests were also performed for group differences in baseline, 24 hour and 7 day BDI scores.

Areas showing significant correlation between improvement in MADRS scores and ACC RS (ICA component 10) amplitude were computed in SPM separately for the 3 treatment groups and for ketamine and AZD6765 combined (i.e. 4 analyses). Day 1 ICA data were correlated with 4 and 24 hour improvement scores using t-tests to investigate whether there was a correlation between the two. Day 2 ICA data were correlated with improvement at 24 hours.

Figure 3 AZ study mean component maps





4.5. Results

4.5.1. Demographics and mood rating scales

Table 12 displays the study demographics below for the AZ study. There were no significant differences in mean age between the groups. There was a significant difference between baseline MADRS between AZD6765 patients and those treated with ketamine and placebo. Over the entire study MADRS scores decreased in all groups. There was no significant effect of active treatments relative to placebo. There was also a significant difference between MADRS scores at 24 hours and 7 days post infusion between AZ and placebo but not AZ and ketamine or between

ketamine and placebo. There were significant differences between AZD6765 and placebo and a trend result for differences between ketamine and placebo for the baseline BDI score. There were also significant differences at 24 hours and 7 days post infusion between AZD6765 and placebo and at 7 days for ketamine compared to placebo. There was a significant reduction in MADRS scores for AZD6765 between baseline, 4 hours and 24 hours post infusion, for ketamine between baseline and 24 hours post infusion and for placebo between baseline, 24 hours and 7 days post infusion. There were significant reductions in BDI scores between baseline, 24 hours and 7 days for all drugs except between AZD6765 and 7 days post infusion. The groups were biased toward females in all study arms.

Table 12 Demographics and mood rating scales

	AZD6765 Current MDD	Ketamine Current MDD	Placebo Current MDD
Sample size	19	17	18
Mean Age	27.1	26.7	25.7
Males	7	6	8
Females	12	11	10
Baseline MADRS	28.3 (SD 6.2)*	23.2 (SD 5.8)	20 (SD 7.6)
4 hour MADRS	21.1 (SD 10.3)	19.6 (SD 5.4)	17.1 (SD 9.1)
24 hour MADRS	22.4 (SD 9.4) ^a	17.6 (SD 8.7)	14.1 (SD 10.1)
7 day MADRS	24.1 (SD 8.5) ^b	20.2 (SD 10) ^f	13.2 (SD 8.8)
Baseline BDI	34.6 (SD 9.6) ^c	29.8 (SD 8.7)	25.7 (SD 7.9)
24 hour BDI	27.3 (SD 11.3) ^d	21.7 (SD 9)	18.3 (SD 10.7)
7 day BDI	29.9 (SD 12.1) ^e	23.8 (SD 10.3)	16.7 (SD 10.1)

* = p<0.05 for difference between AZD6765 compared to ketamine and AZD6765 compared to placebo baseline MADRS scores; ^a = p<0.05 for difference between AZD6765 compared to placebo 24 hour MADRS scores; ^b = p<0.05 for difference between AZD6765 and placebo 7 day MADRS scores; ^c = p<0.05 for difference between AZD6765 and placebo for baseline BDI scores; ^d = p<0.05 for difference between AZD6765 and placebo for 24 hour BDI scores; ^e = p<0.05 for difference between AZD6765 and placebo and ketamine and placebo for 7 day BDI scores; ^f = p<0.05 for difference between ketamine and placebo for 7 day MADRS scores; SD = standard deviation

4.5.2. Effects of drug in regions expressing significant ACC RS activity - SPM voxel-wise analysis

Day 1

Table 13 details the results of the SPM voxel-wise analysis for day 1. Those results in highlighted in red are significant at $p_{FDR} < 0.05$. Overlays for significant results are plotted in Figure 4 (radiological convention is followed which means the left side of the image corresponds to right side of the brain).

AZD6765 produced greater increases in mean intensity of ACC RS component than ketamine in the superior temporal gyrus. There was no placebo corrected effect noted.

Day 2

There were no significant clusters for voxel-wise analysis of day 2.

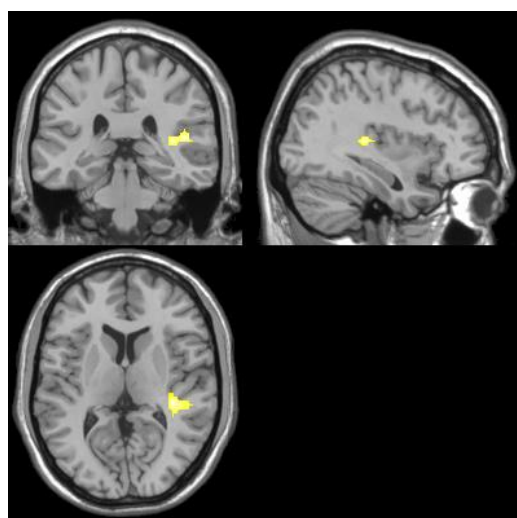
Day 1 minus day 2

There were no significant clusters for voxel-wise analysis of day 1 minus day 2.

Table 13 SPM voxel-wise analysis

Region	Side	Centre of Mass			No of voxels	p(FWEc)	q(FDRc)
		x	y	z			
Day 1 AZ>ketamine							
Superior Temporal Gyrus	L	-40	-36	9	76	0.019	0.008

Figure 4 SPM voxel-wise analysis contrast map – positive (red/yellow) and negative (blue) effect



AZ>ketamine
($p < 0.001$ uncorrected)

4.5.3. Effects of drug in regions expressing significant ACC RS activity - regional MarsBaR analysis

4.5.3.1. Drug modulation of day 1 positive ACC RS component

Table 14 details the results of the positive ACC RS component regional MarsBaR analysis for day 1. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 5 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

Hypothesis i a) Increases in ACC RS in SN and CEN. Neither ketamine nor AZD6765 produced the expected increase in ACC RS component in the ACC itself. Indeed there were no regions where ketamine significantly increased mean intensity of ACC RS component compared placebo although there was a trend ($p = .057$) result in the left mFG. However, AZD6765 had no effect on ACC RS in this region. The sole instance where the drugs had similar effects was in reducing ACC RS in the left insula but this was only statistically significant for AZ < placebo. In right insula, AZD6765 increased mean intensity of ACC RS as predicted. AZD6765 also significantly increased ACC RS in left mid cingulate and right IPL relative either to placebo or ketamine or both. AZD6765 reduced ACC RS relative to ketamine and non-significantly to placebo in right lentiform nucleus and left mFG.

Hypothesis i b) Decreases in ACC-DMN. No drug effects were observed on ACC RS in posterior DMN structures.

No areas survived correction for multiple comparisons.

4.5.3.2. Drug modulation of day 1 negative ACC RS component

Table 15 details the results of the negative ACC RS component regional MarsBaR analysis for day 1. Values in red are significant at $p_{FDR} < 0.05$ corrected for the number of regions tested. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 6 (radiological convention is followed which means the left side of the image corresponds to right side of the brain).

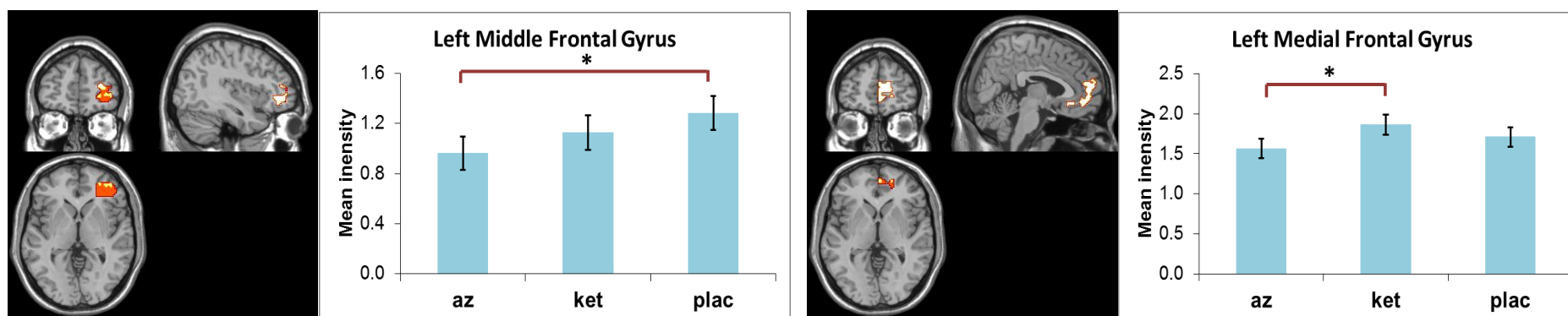
Ketamine reduced mean intensity of ACC RS component greater than placebo but did not survive FDR correction. AZD6765 significantly increased mean intensity of ACC RS component greater than ketamine in the right insula. This remained significant even after FDR correction.

Table 14 Component 10 positive ACC RS component regions that show differences between treatment groups on day 1

Region	Side	Centre of mass			No. of voxels	p						FDR	
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket		
Middle Frontal Gyrus	L	-34	44	-1	172	ns	(0.048)	ns	ns	ns	ns		
Medial Frontal Gyrus	L	-11	48	8	377	0.057	ns	(0.045)	ns	ns	ns		
Insula	L	-39	3	-2	79	ns	(0.024)	ns	ns	ns	ns		
Insula	R	41	-16	4	27	ns	0.016	0.036	ns	ns	ns		
Cingulate Gyrus	L	-16	8	33	16	ns	ns	0.043	ns	ns	ns		
Inferior parietal lobule	R	42	-66	43	33	ns	0.034	0.015	ns	ns	ns		
Lentiform nucleus	R	18	9	-3	53	ns	(0.075)	(0.049)	ns	ns	ns		

p -values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 5 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 1: *p<0.05 uncorrected.



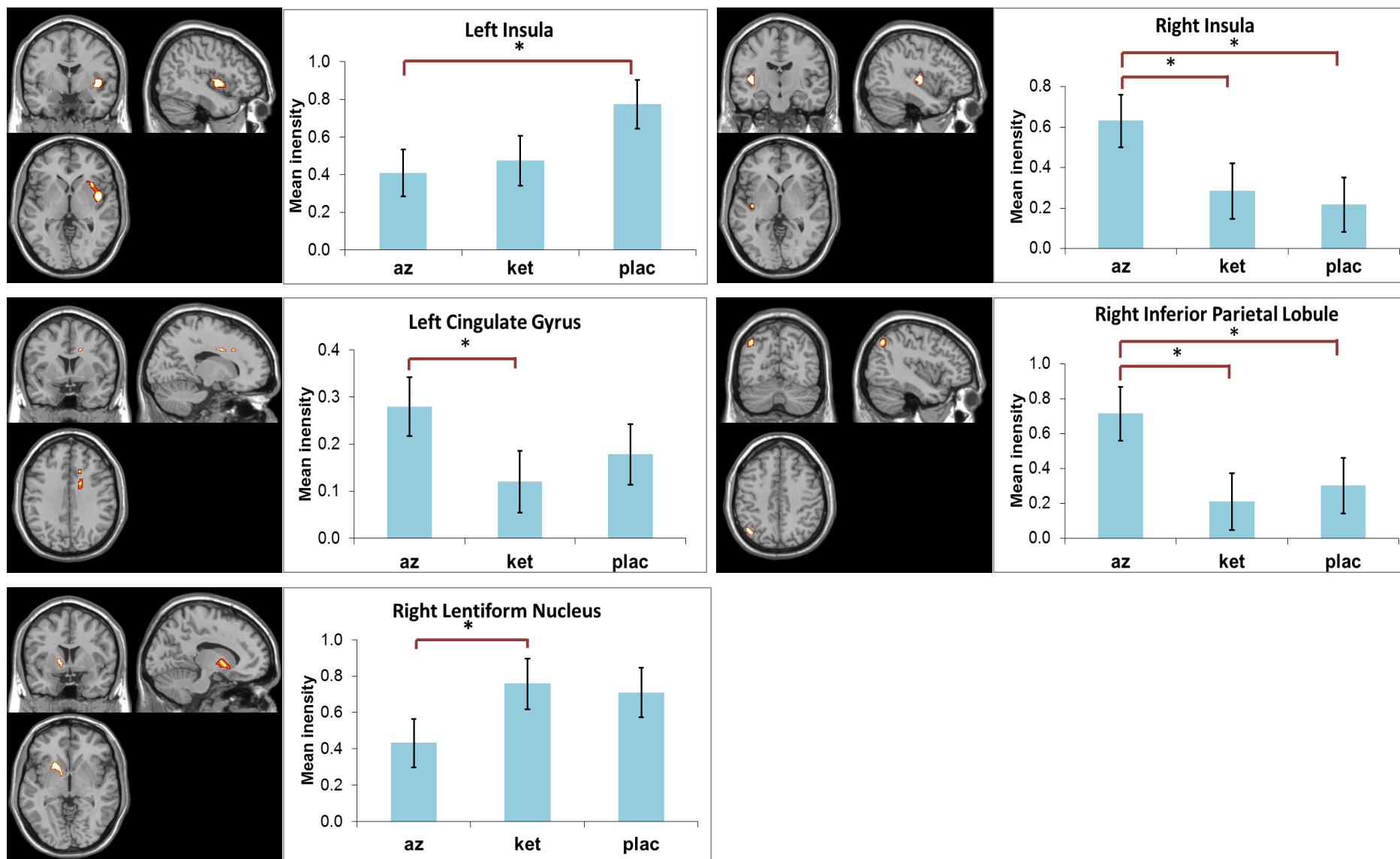


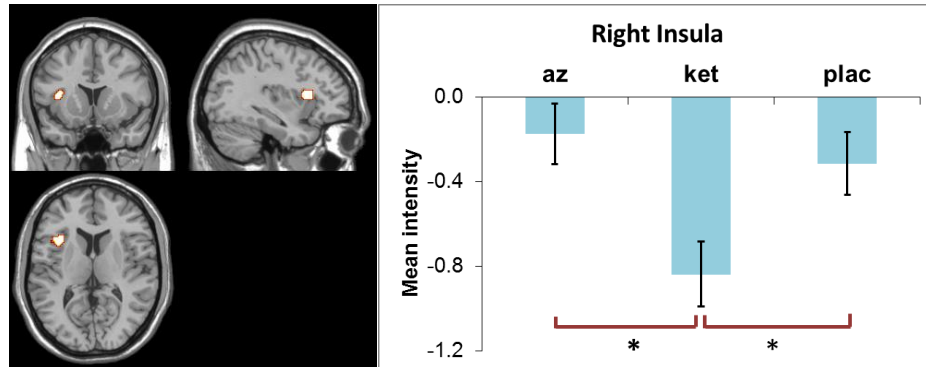
Table 15 Component 10 negative ACC RS component regions that show differences between treatment groups on day 1

Region	Side	Centre of mass			No. of voxels	p			FDR		
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket
Insula	R	37	16	9	36	(0.009)	ns	0.001	ns	ns	0.027

p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 6 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 1:

*p<0.05 uncorrected



4.5.3.3. Drug modulation of day 2 positive ACC RS component

Table 16 details the results of the positive ACC RS component regional MarsBaR analysis for day 2. Values in red are significant at $p_{FDR} < 0.05$ corrected for the number of regions tested, whilst those in italics show trend results. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 7 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

Overview. AZD6765 increased ACC RS in 8/13 regions showing a drug effect and decreased it in 5/13. 4 of the 5 areas showing decreases were in frontal cortical regions. Ketamine's effects broadly followed those of AZD6765 but only in right cuneus did both drugs differ significantly from placebo.

Hypothesis i a) Increases in ACC RS in SN and CEN. Neither ketamine nor AZD6765 pre-treatment produced the expected increase in ACC RS component in the ACC itself. Neither drug affected expression of the ACC RS component in the insula. AZD6765 significantly, and ketamine numerically, increased ACC RS in left superior frontal cortex relative to placebo, however the drugs showed the opposite reducing effect on the right side of this CEN region.

Hypothesis i b) Decreases in ACC-DMN. Both drugs reduced ACC RS component in MFG, AZD6765 significantly, relative to placebo. However, against prediction both drugs significantly increased ACC RS in right cuneus and to a lesser extent in left cuneus in a graded fashion relative to placebo (AZD6765 > ketamine > placebo).

Basal ganglia. The same (AZD6765 > ketamine > placebo).pattern of drug effects as in posterior DMN was seen the basal ganglia (caudate and lentiform nuclei). Several of the above effects of drug pre-treatment survived FDR correction (Table 16).

Hypothesis ii) The effects of AZD6765 and ketamine on day 1 should persist in the day 2 RS data 24 hours after infusion. Only 2 regions showed drug effects on both days. AZD6765 decreased ACC RS in left MFG relative to placebo on day 1 and relative to ketamine on day 2. Ketamine ACC RS showed very little difference from placebo. At identical coordinates in the right lentiform (ventral striatal region) AZD6765 increased ACC RS on day 2 but decreased it on day 1 ketamine's non-significant effects were intermediate between placebo and AZD6765.

4.5.3.4. Drug modulation of day 2 negative ACC RS component

Table 17 details the results of the negative ACC RS component regional MarsBaR analysis for day 2. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 8 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

Hypothesis i b) Decreases in ACC-DMN. AZD6765 significantly reduced ACC RS in the left precuneus as predicted. Ketamine followed a similar pattern of drug effects in both the left precuneus and right inferior parietal lobule with mean values between those of AZD6765 and placebo.

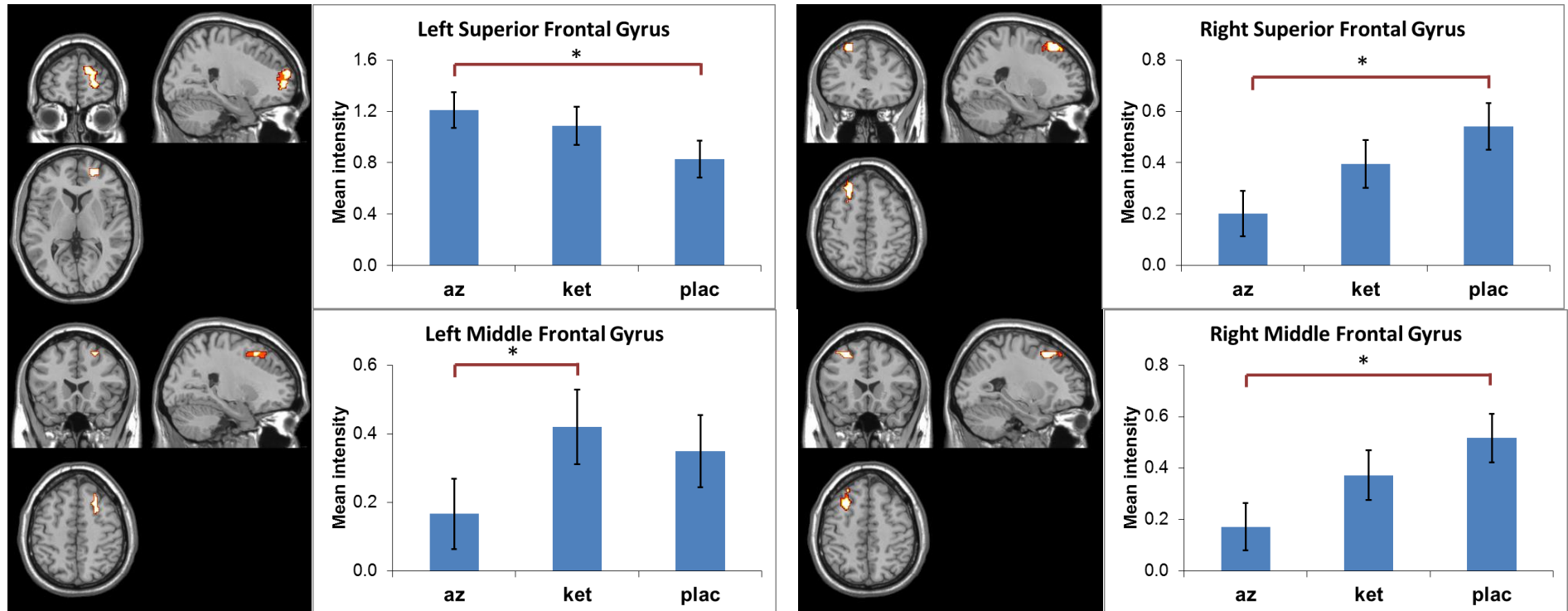
Table 16 Component 10 positive ACC RS component regions that show differences between treatment groups on day 2

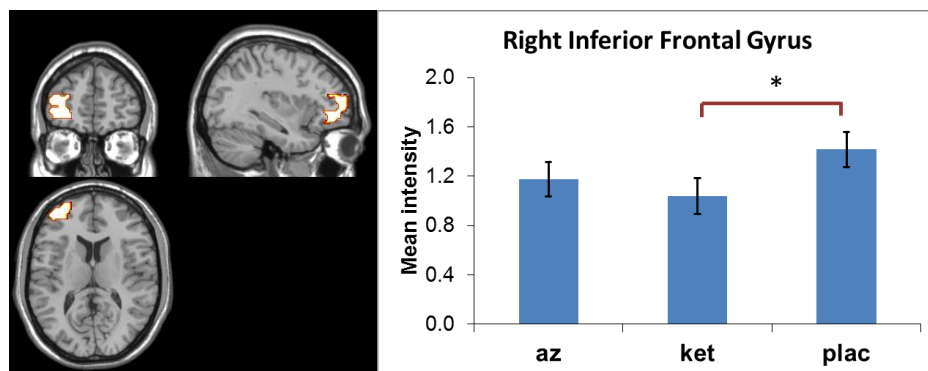
Region	Side	Centre of mass			No. of voxels	p			FDR		
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket
Superior Frontal Gyrus	L	-19	55	15	130	ns	0.031	ns	ns	ns	ns
Superior Frontal Gyrus	R	27	23	52	85	ns	(0.005)	ns	ns	ns	ns
Middle Frontal Gyrus	L	-24	18	50	230	ns	ns	(0.048)	ns	ns	ns
Middle Frontal Gyrus	R	29	22	50	62	ns	(0.006)	<i>(0.069)</i>	ns	ns	ns
Inferior Frontal Gyrus	R	35	47	2	284	(0.034)	ns	ns	ns	ns	ns
Hypothalamus	R	8	-1	-4	63	ns	0.006	<i>0.080</i>	ns	0.041	ns
Precentral Gyrus	L	-29	-28	59	181	0.022	ns	(0.016)	ns	ns	ns
Middle Occipital Gyrus	R	36	-75	7	48	ns	0.004	<i>0.051</i>	ns	0.035	ns
Cuneus	L	-20	-88	8	30	ns	0.038	<i>0.097</i>	ns	ns	ns
Cuneus	R	1	-90	24	120	0.043	0.002	ns	ns	<i>0.078</i>	ns
Caudate	R	10	13	5	110	ns	0.037	ns	ns	ns	ns
Lentiform nucleus	L	-18	8	-2	88	ns	0.003	0.049	ns	<i>0.052</i>	ns
Lentiform nucleus	R	19	9	-3	87	ns	0.003	0.028	ns	0.037	ns

p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

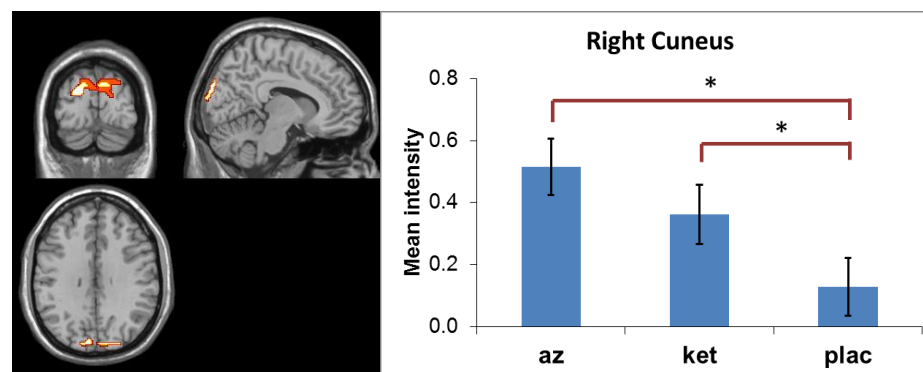
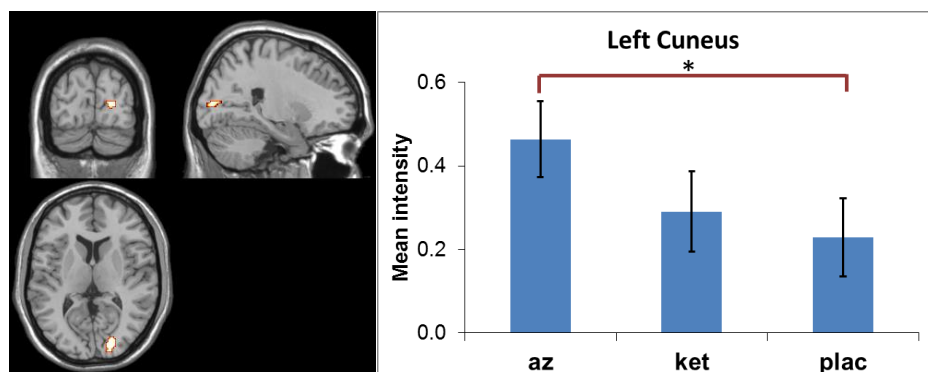
Figure 7 Overlays & histograms for regions of positive ACC RS component that show a significant difference between treatment groups on day 2:
 * $p < 0.05$ uncorrected

Pre-treatment group differences in frontal cortical regions

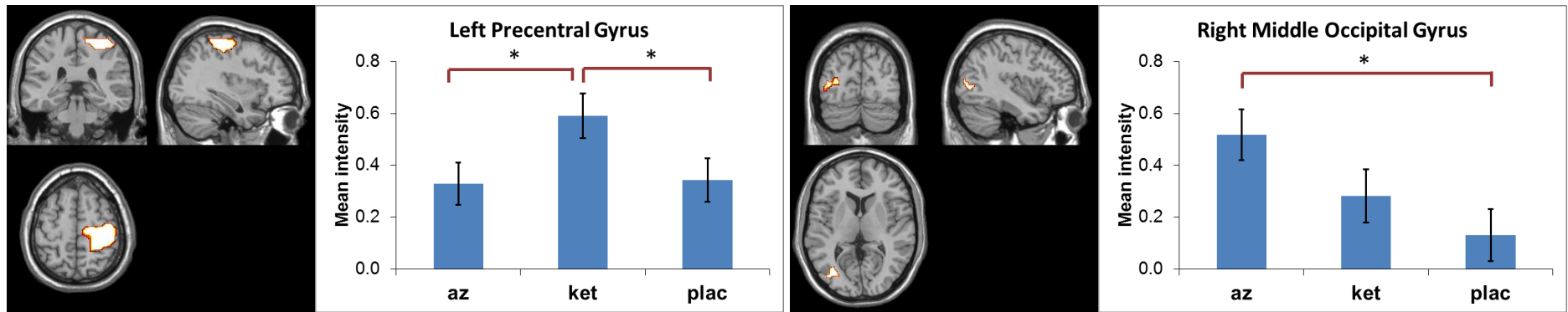




Pre-treatment group differences in the posterior DMN region



Pre-treatment group differences in other cortical regions



Pre-treatment group differences in basal ganglia regions and hypothalamus

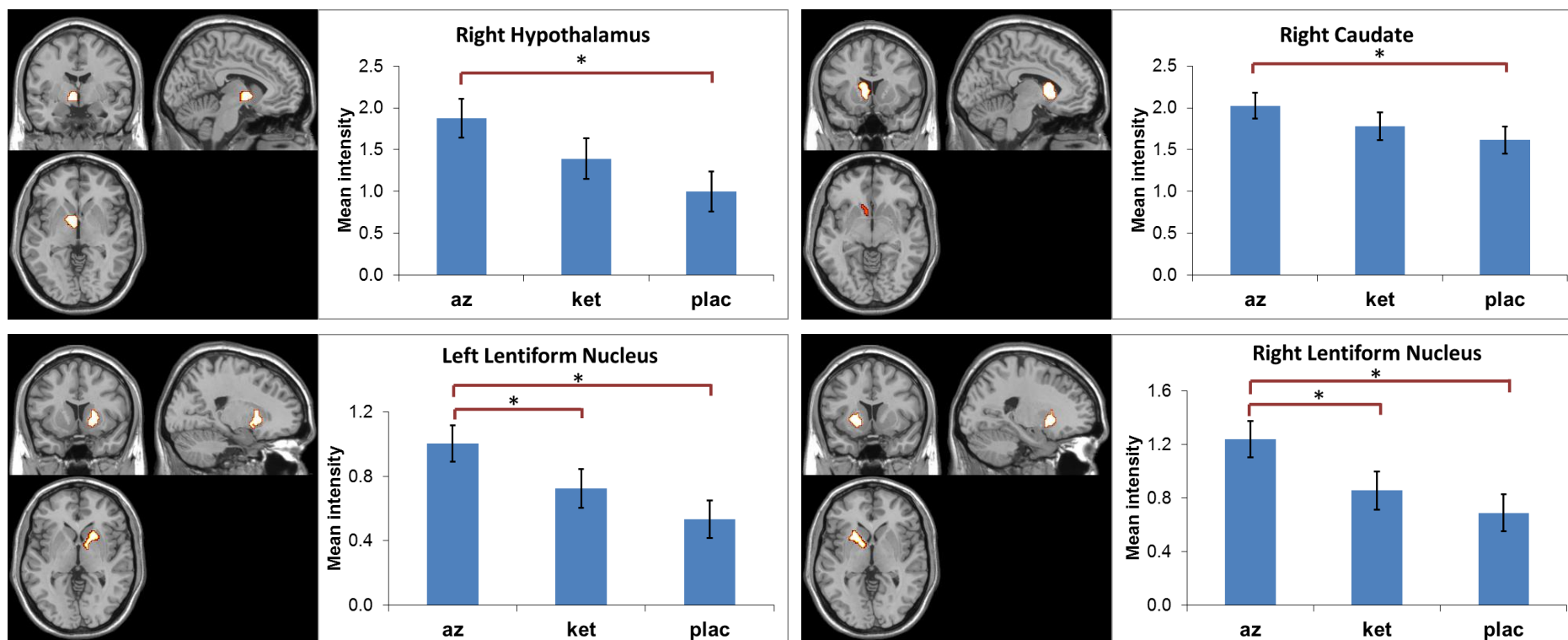


Table 17 Component 10 negative ACC RS component regions that show differences between treatment groups on day 2

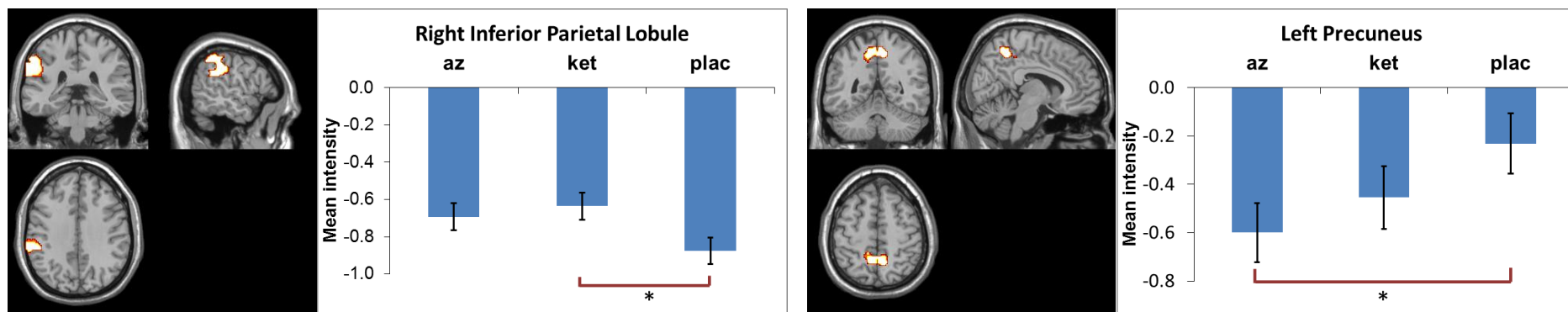
Region	Side	Centre of mass			No. of voxels	p			FDR		
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket
Inferior Parietal Lobule	R	56	-38	32	312	0.033	0.073	ns	ns	ns	ns
Precuneus	L	1	-51	51	134	ns	(0.020)	ns	ns	ns	ns

* = $p < 0.05$ uncorrected. p values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 8 Overlays & histograms for regions of negative ACC RS component that show a significant difference between treatment groups on day 2:

*** $p < 0.05$ uncorrected**

Pre-treatment group differences posterior default mode network regions



4.5.3.5. Drug effects on positive day 1-day 2 differences (day1>day2) in ACC RS component

Table 18 details the results of the positive ACC RS component regional MarsBaR analysis for day 1 minus day 2 (i.e. regions in which day 1 treatment group modified an overall decline in ACC RS intensity from day 1 to day 2). Day 1 minus day 2 effects represent, in pharmacological terms, the prolonged drug effects seen in previous trials of ketamine (see Chapter 3)(Dutta et al., 2015). Overlays and histograms for each region significant at $p<0.001$ uncorrected are shown in Figure 9 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

A day x treatment interaction, with greater reduction in mean intensity of ACC RS component from day 1 to day 2 with ketamine compared to AZD6765, but not with placebo, was observed in the left mFG; the significant day 1 differences (reported above and see asterisk in Figure 9) were lost by day 2. In right ACC the decline in ACC RS after placebo was significantly less than after AZD6765. Neither result remained significant following FDR correction.

4.5.3.6. Drug effects on negative day 1-day 2 differences (day1>day2) in ACC RS component

Table 19 details the results of the negative ACC RS component regional MarsBaR analysis for day 1 minus day 2 (i.e. regions in which day 1 treatment group modified an overall increase in ACC RS intensity from day 1 to day 2). Values in red are significant at $p_{FDR}<0.05$ corrected for the number of regions tested. Overlays and histograms for each region significant at $p<0.001$ uncorrected are shown in Figure 10 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

Hypothesis i a) Increases in ACC RS in SN and CEN. Ketamine and AZD6765 produced steeper increases in ACC RS component in three frontal regions. In each case the drugs reduced ACC RS in day 1 compared to placebo but this effect switched to the statistically significant increases previously reported on day 2 (see asterisks in Figure 10). The placebo treated group showed least increase from day 1 to 2. The interaction in right anterior insula (SN) is driven by differences between the 2 drugs in which ketamine non-significantly suppressed day 1 ACC RS component but by day 2 there was little difference between the groups. This anterior region of insula is distinct from the posterior region in which significant drug effects occurred on day 1.

Hypothesis i b) Decreases in ACC-DMN. In two closely adjacent posterior DMN regions (right posterior cingulate and cuneus) AZD6765 lessened the day1-2 increase seen in the placebo group and ketamine also showed lessening ($p=.06$) in posterior cingulate. However, the absolute drug group differences on day 1 and 2 were not significant.

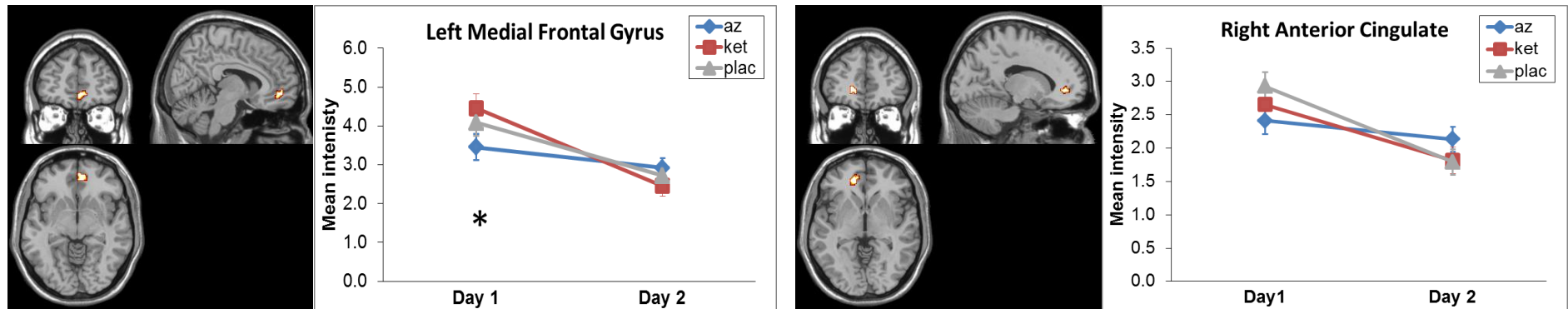
Basal ganglia The increase in ACC RS in right, left and medial ventral striatum (right and left lentiform nuclei and ventral caudate) on placebo was considerably and significantly accentuated by AZD6765 and non-significantly by ketamine to produce the increase reported on day 2.

Table 18 Component 10 positive ACC RS component (day 1 > day 2) regions that show a day x treatment group interaction

Region of Interest	Side	Centre of mass			No. of voxels	p						FDR	
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket	ket>plac	az>ket
Medial Frontal Gyrus	L	-6	47	-8	30	ns	ns	(0.014)	ns	ns	ns	ns	ns
Anterior Cingulate	R	13	44	-3	22	ns	(0.016)	ns	ns	ns	ns	ns	ns

p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 9 Overlays & line graphs for regions of positive ACC RS component that show a significant day x treatment group interaction: *p<0.05 uncorrected



Asterisks indicate significant treatment effects on day 1 or day 2

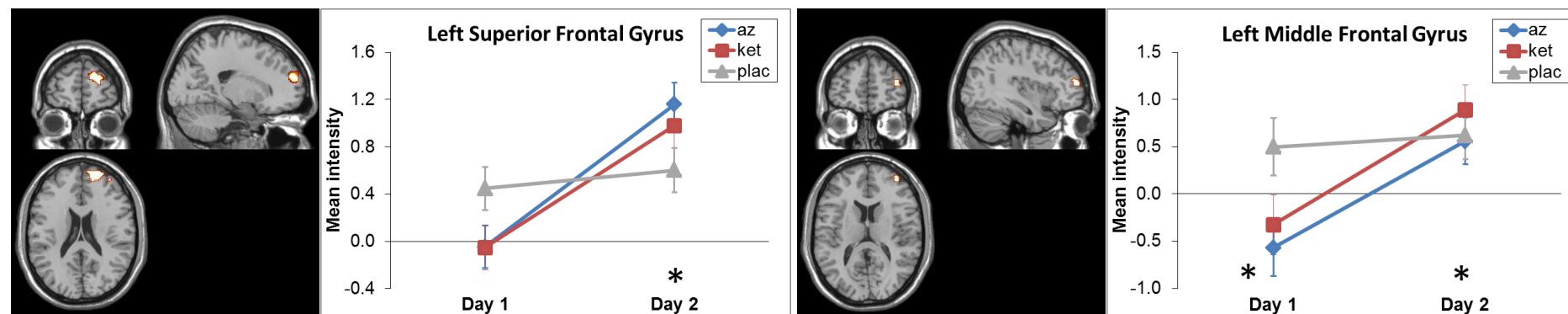
Table 19 Component 10 negative ACC RS component (day 2 > day 1) regions that show a day x treatment group interaction

Region of Interest	Side	Centre of mass			No. of voxels	p				FDR	
		x	y	z		ket>plac	az>plac	az>ket	ket>plac	az>plac	az>ket
Superior Frontal Gyrus	L	-19	58	20	75	(0.005)	(0.001)	ns	ns	(0.013)	ns
Middle Frontal Gyrus	L	-38	53	13	20	(0.014)	(0.018)	ns	ns	ns	ns
Inferior Frontal Gyrus	R	32	29	5	16	(0.049)	ns	ns	ns	ns	ns
Insula	R	37	17	7	36	ns	ns	0.014	ns	ns	ns
Posterior Cingulate	R	8	-42	41	58	<i>0.060</i>	0.012	ns	ns	ns	ns
Precuneus	R	4	-43	46	24	ns	0.027	ns	ns	ns	ns
Ventral caudate	L	2	4	-6	68	ns	(0.039)	ns	ns	ns	ns
Lentiform Nucleus	L	-16	9	-7	18	ns	(0.020)	ns	ns	ns	ns
Lentiform Nucleus	R	18	10	-7	29	ns	(0.003)	(0.021)	ns	(0.021)	ns

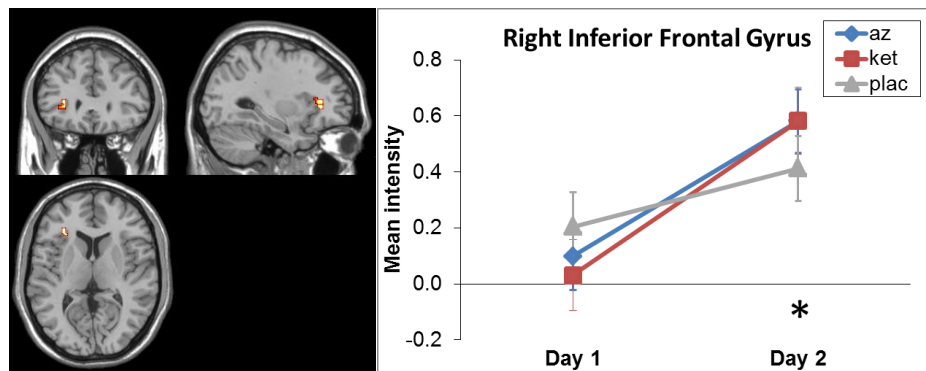
p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 10 Overlays & line graphs for regions of negative ACC RS component that show a significant day x treatment group interaction: *p<0.05 uncorrected

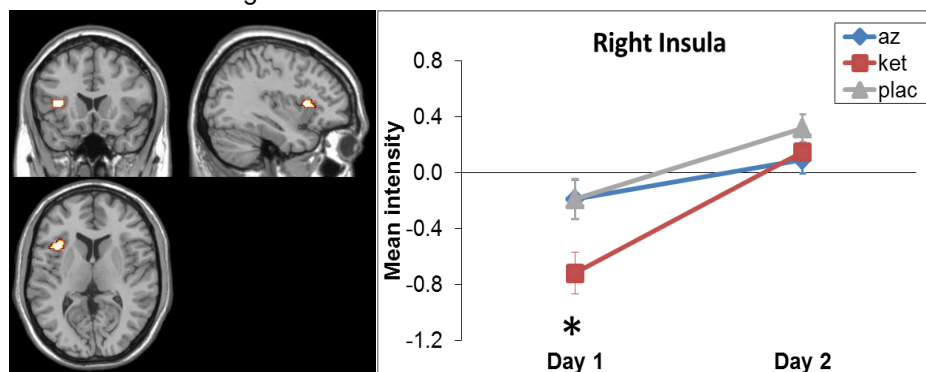
Frontal cortical regions



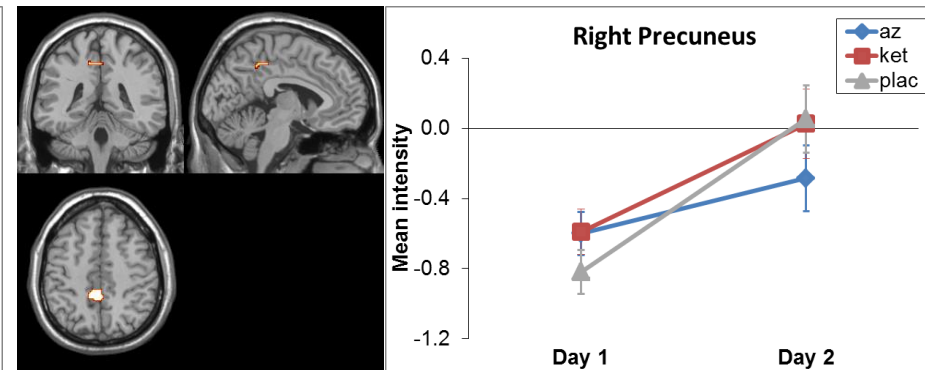
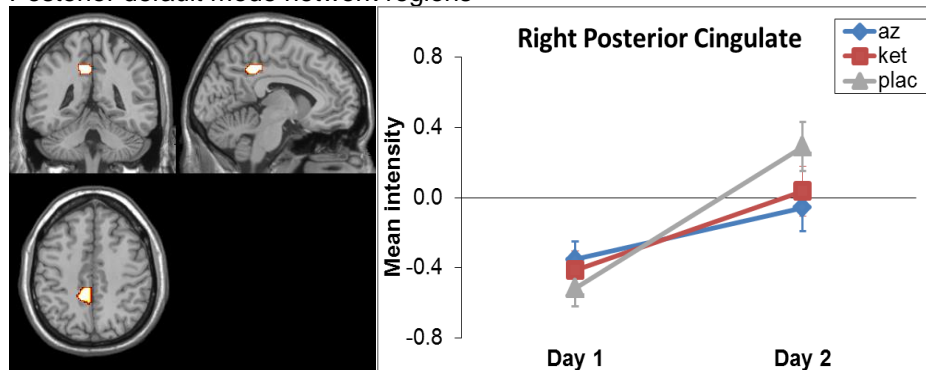
Asterisks indicate significant treatment effects on day 1 or day 2



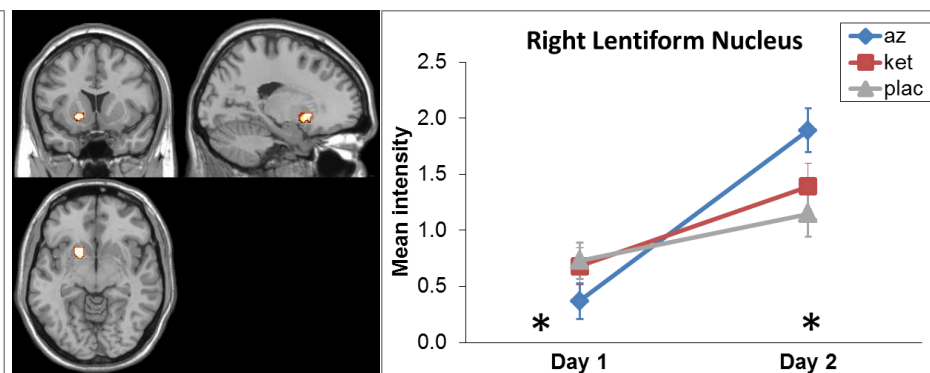
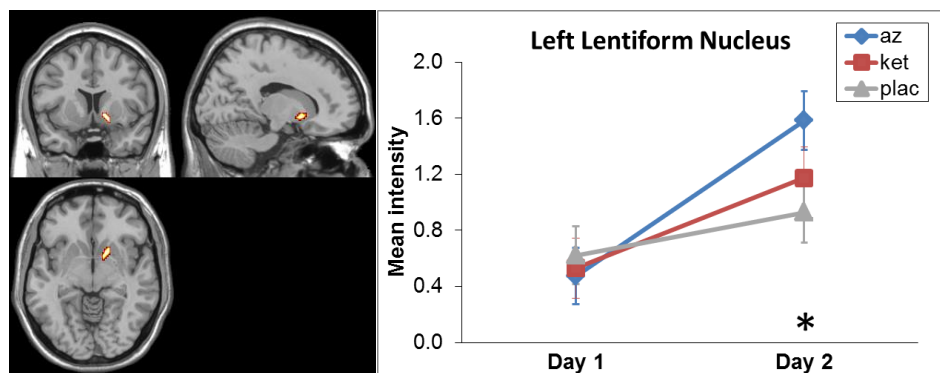
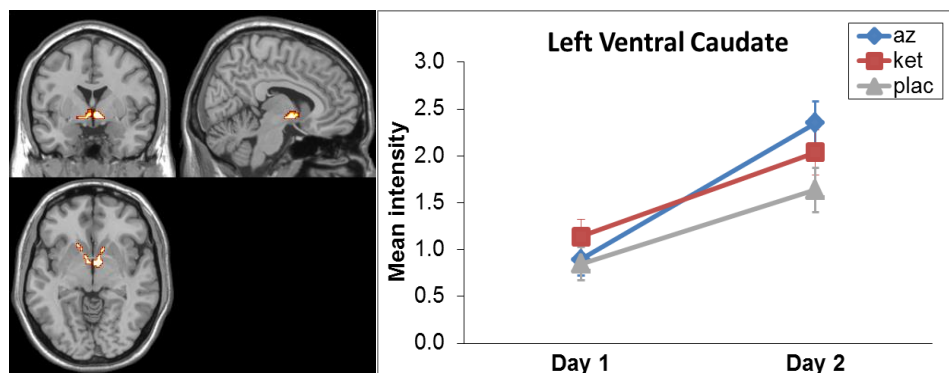
Saliency network regions



Posterior default mode network regions



Basal ganglia regions



4.5.4. Drug effects on ACC RS and MADRS mood rating scales

There was no overall effect of active treatments compared to placebo. This is surprising in the context of the results in Chapter 3 demonstrating the efficacy of ketamine. However, this was also a mechanistic trial and not one to demonstrate treatment response which might explain this. Therefore there was a reduced dosage of AZD6765 used and no bolus dosing of ketamine. There is still validity in correlating brain changes to MADRS scores to identify early onset of neural changes due to drug effects.

Significant voxel-wise correlations between the mean intensity of ACC RS component of component 10 and MADRS mood rating scales are detailed in Table 20. Regions are significant at $p_{FWEc} < 0.05$ and $p_{FDRc} < 0.05$. Overlays of significant results are plotted in Figure 4 (radiological convention is followed which means the left side of the image corresponds to right side of the brain).

There was no correlation between the day 1 component 10 mean intensity of ACC RS component and improvements in MADRS at 4 hour or 24 hour post dose MADRS for AZD6765, ketamine or placebo.

Day 2 ACC RS correlations with 24 hour MADRS improvement were seen after placebo in the precuneus, and after ketamine in the right posterior cingulate and left middle occipital gyrus. No such correlations were present in the AZD6765 ACC RS data. However, the combined AZD6765 and ketamine component images showed correlations in right IPL with 24 hour improvement in MADRS score.

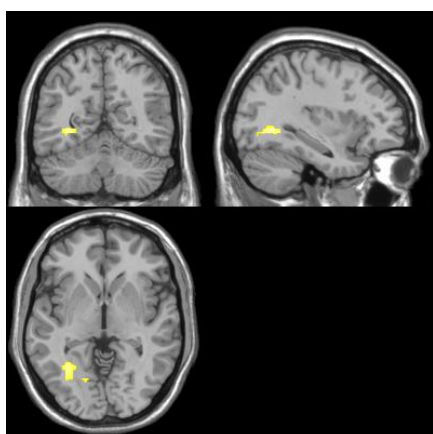
Differences between mean intensity of ACC RS component maps between day 1 and day 2 did not correlate with 24 hour improvement in the placebo or AZD6765 groups. This was because the trial was to examine drug mechanism rather than treatment response. There was, however, a positive correlation for the difference between day 1 and day 2 for ketamine mean intensity of ACC RS component to the 24 hour MADRS score difference in the left cingulate gyrus.

Table 20 Regions in which component 10 correlated with MADRS improvement

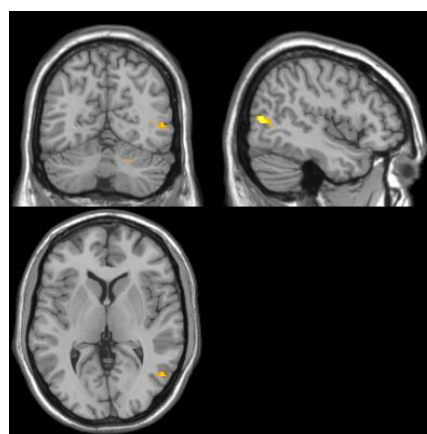
	4hr improvement	24hr improvement
Day1		
Placebo	ns	ns
Ketamine	ns	ns
AZD6765	ns	ns
Ketamine + AZD6765	R fusiform gyrus	right tranverse temporal gyrus, left middle temporal gyrus, left cerebellum
Day 2		
Placebo		precuneus
Ketamine		right PCC and left middle occipital gyrus
AZD6765		ns
Ketamine + AZD6765		right IPL
Day 1 – Day 2		
Placebo		ns
Ketamine		left cingulate gyrus
AZD6765		ns
Ketamine + AZD6765		ns

Figure 11 Significant MADRS mood rating scales correlations with component 10

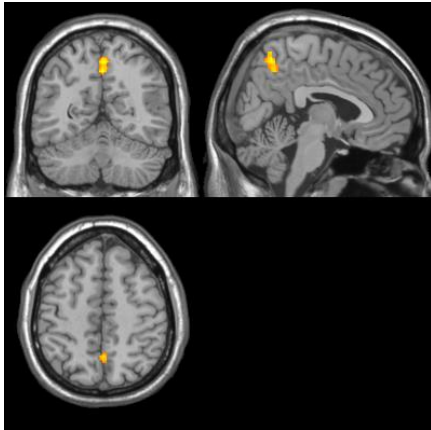
(All images $p < 0.001$ uncorrected)



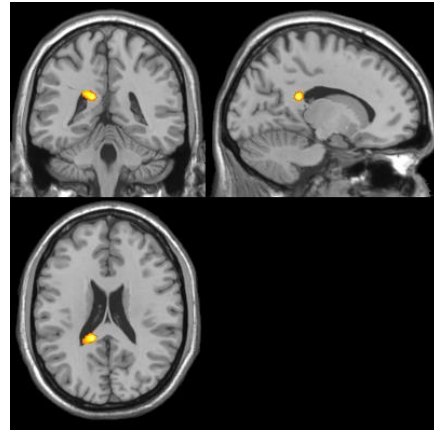
Day 1 AZD6765 + Ketamine positive correlation MADRS score difference 4h post dose with ACC RS in r-fusiform gyrus



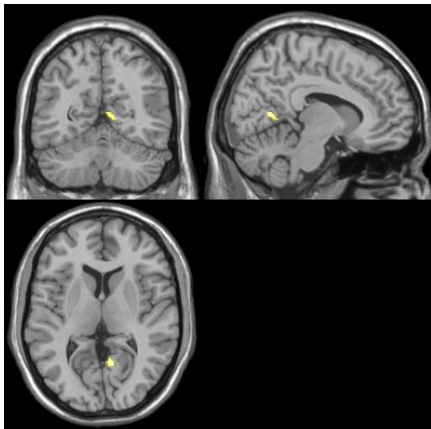
Day 1 AZD6765 + Ketamine negative correlation MADRS score difference 24h post dose with ACC RS in l-transverse/middle temporal gyrus & l-cerebellum



Day 2 Placebo positive correlation to MADRS score difference 24h post dose with ACC RS in precuneus



Day 2 Ketamine positive correlation to MADRS score difference 24h post dose with ACC RS in r-PCC



Day 2 AZD6765 + Ketamine positive correlation MADRS score difference 24h post dose with ACC RS in r-IPL



Day 1 - Day 2 Ketamine positive correlation MADRS score difference 24h post dose with ACC RS in I-cingulate gyrus

4.6. Discussion

4.6.1. Effects of drug in regions expressing significant ACC RS activity

4.6.1.1. SPM voxel-wise analysis

Day 1

AZD6765 produced greater increases in mean intensity of ACC RS component than ketamine in the left superior temporal gyrus (see Table 14). The superior temporal lobe has a key role in the interpretation of auditory information especially speech (Binder et al., 2000). In addition it has

functions in social interaction and emotional processing (Schaefer et al., 2006). In a previous study, ketamine produced significant reduction in BOLD compared to baseline in the bilateral superior temporal gyrus in HC (Deakin et al., 2008). This current result which is different from Deakin et al. (2008) may be due to the response of cMDD to AZD6765 causing an increase in mean intensity of ACC RS component.

4.6.1.2. Regional MarsBaR analysis

Drug modulation of day 1 positive/negative ACC RS component

There were no regions where ketamine significantly increased mean intensity of ACC RS component greater than placebo. Ketamine increased mean intensity of ACC RS component greater than AZD6765 in the right lentiform nucleus and left mFG. The literature is somewhat confusing regarding the mFG reporting both increased and decreased ALFF/fALFF in medicated MDD patients (Guo et al., 2012b, Liu et al., 2013a). Decreased ReHo is reported in unmedicated MDD compared to HC in the lentiform nucleus (Yao et al., 2009, Liu et al., 2010). Both these regions have demonstrated significant increases in BOLD signal activity in healthy volunteers following ketamine infusion (Deakin et al., 2008). However, in the current study MDD administered ketamine did not differentiate from placebo where the literature suggests a reduced response should occur following active drug.

AZD6765 increased mean intensity of ACC RS component greater than ketamine and placebo in the right IPL and right insula. AZD6765 also increased the mean intensity of ACC RS component more than ketamine in the right insula when the negative ACC RS component was examined. The insula has several reported functions including self-awareness, emotional regulation in the context of sensory experience, homeostasis and motor control. Reduced response occurs in the right insula in MDD when shown negative affective pictures (Lee et al., 2007). The findings replicated those of Anand et al. (2005a). More recently Liu et al. (2010) observed reduced ReHo in the right insula in unmedicated MDD and first degree relatives of MDD patients. However, in the current results ketamine and AZD6765 produce a different magnitude of effect on mean intensity of ACC RS component. Horn et al. (2010) reported that FnC of the anterior insula and rACC correlated positively with HAM-D scores. In the left anterior insula AZD6765 significantly reduced mean intensity of ACC RS component but this was not correlated to MADRS scores. The effects between the anterior and posterior insula are also different in magnitude. The results found in the insula therefore are not completely compatible with the literature.

Drug modulation of day 2 positive ACC RS component

Differences in frontal cortical regions

Ketamine increased mean intensity of ACC RS component greater than AZD6765 in the left MFG. Mean intensity of ACC RS component was increased on Day 2 in the ketamine group in the left MFG and reduced in the AZD6765 group compared to day 1. Ketamine therefore appears to

have more of a prolonged action in the left MFG. AZD6765 reduced mean intensity of ACC RS component greater than placebo in the right MFG and right superior frontal gyrus. Ketamine reduced the mean intensity of ACC RS component greater than placebo in the right MFG. AZD6765 reduced mean intensity of ACC RS component reflecting a similar pattern seen on day 1 in the left MFG in a more anterior region. In the superior frontal gyrus AZD6765 had opposite effects between the left and right sides, however the left superior frontal gyrus was somewhat more anterior than the right.

AZD6765 increased mean intensity of ACC RS component greater than placebo in left superior frontal gyrus. In the superior frontal gyrus AZD6765 had opposite effects between the left and right sides, however the left superior frontal gyrus was somewhat more anterior than the right.

Posterior default mode network regions

AZD6765 increased mean intensity of ACC RS component greater than placebo in left and right cuneus. These are regions where AZD6765 has a unique extended action since these are not observed with ketamine or placebo. Deakin et al. (2008) implicated the cuneus in memory recall, visual imagery and self-awareness. Increased BOLD during reward processing has been reported in the bilateral cuneus and left superior frontal gyrus in a meta-analysis of MDD patients and HC (Zhang et al., 2013b). This complements the current result. AZD6765 may therefore have unique effects on visual reward processing that require further investigation given the similar effects on the left and right cuneus.

Differences in other regions

Ketamine increased mean intensity of ACC RS component greater than AZD6765 in the left precentral gyrus and increased the mean intensity of ACC RS component in the right cuneus and left precentral gyrus greater than placebo. Tao et al. (2013) suggested the precentral gyrus as part of the risk/action circuit that works alongside the inferior frontal gyrus to maintain response inhibition. In comparison to healthy controls SPET of pre-treated MDD patients demonstrated hypoperfusion in the bilateral precentral gyrus (Richieri et al., 2011). Decreased left precentral gyrus ReHo has been noted in MDD patients compared to their first degree relatives and HC (Liu et al., 2010). Ketamine may therefore increase mean intensity of ACC RS component in a similar way to conventional antidepressants.

Differences in basal ganglia regions and hypothalamus

AZD6765 increased the mean intensity of ACC RS component in the right and left lentiform nucleus greater than ketamine and placebo. On day 1 AZD6765 reduced mean intensity of ACC RS component compared to ketamine and placebo, whereas on day 2 the effect was to increase mean intensity of ACC RS component. The lentiform nucleus comprises the putamen and the globus pallidus. Animal models suggest that the globus pallidus is involved in incentive related behaviour and expectation of reward (Schultz et al., 1992, McAlonan et al., 1993). Regional

cerebral blood flow in the left lentiform nucleus was inversely correlated to depressive symptoms and positively correlated to cognitive performance in a SPET study (Perico et al., 2005). Decreased ReHo was observed in MDD compared to healthy controls in the left lentiform nucleus (Yao et al., 2009). Decreased BOLD in the right lentiform nucleus in MDD in response to positive stimuli has been noted in a meta-analysis (Zhang et al., 2013b). Positive stimuli varied from reading words to implicit and explicit rating of emotional faces in the study. Guo et al. (2012b) reported increased ALFF in the putamen in medicated MDD although patients had varying medication profiles. The current finding is compatible with AZD6765 increasing mean intensity of ACC RS component. These are not acute effects, however, but prolonged actions after a single infusion. AZD6765 increased mean intensity of ACC RS component greater than placebo in right hypothalamus quite close to the caudate region.

Drug modulation of day 2 negative ACC RS component

Posterior default mode network regions

Ketamine reduced mean intensity of ACC RS component greater than placebo in the right IPL. AZD6765 reduced mean intensity of ACC RS component greater than placebo in the left precuneus. As noted previously this is likely to be an effect of switching between the DMN and other neural networks. The pattern in the right IPL is similar to that seen on day 1 except it is observed in the negative ACC RS component. It is possible that although ketamine continues to switch off the DMN, AZD6765 does not have sufficiently prolonged action leading to continued mean intensity of ACC RS component in the precuneus.

Drug effects on positive day 1 > day 2 differences in ACC RS component

A day x treatment interaction, with greater reduction in mean intensity of ACC RS component from day 1 to day 2 with ketamine compared to AZD6765, but not with placebo, was observed in the left mFG. A further day x treatment interaction occurred with placebo producing a greater reduction than AZD6765 in mean intensity of ACC RS component in the right ACC. Damage to the ACC causes emotional instability, autonomic dysfunction, apathy, inattention and akinetic mutism (Tow and Whitty, 1953, Kennard, 1955, Bush et al., 2000). Mayberg et al. (1997) first suggested that increased regional glucose metabolism in the rostral ACC distinguished responders from non-responders to antidepressants. This finding was replicated using paroxetine (Saxena et al., 2003). The current finding suggests little change between day 1 and day 2 in the right ACC when administered AZD6765 but does not fit with the literature since the results did not correlate with MADRS scores.

Drug effects on negative day 1 < day 2 differences in ACC RS component

Default mode network regions

A day x treatment interaction was observed between AZD6765 and placebo. AZD6765 produced less of a difference in mean intensity of ACC RS component than placebo in the right posterior cingulate. There was an effect of day for placebo only in the right posterior cingulate. AZD6765 produced more of a difference in mean intensity of ACC RS component than placebo in the left ACC. There was an effect of treatment for AZD6765 and ketamine but not placebo. There was a trend result for ketamine produced less of a difference in mean intensity of ACC RS component than placebo in the right posterior cingulate.

Salience network regions

A day x treatment interaction was observed between AZD6765 and ketamine. AZD6765 produced less of a difference in mean intensity of ACC RS component than ketamine in the right insula. An effect of day was noted for ketamine but not placebo or AZD6765. The insula and ACC are regions that fall within the salience and default mode networks. (Seeley et al., 2007, Elton and Gao, 2014). A recent study revealed decreased FnC between the DMN and CEN (also termed the task positive network) and increased FnC between the SN and DMN in MDD (Manoliu et al., 2013). The right anterior insular was reported to have reduced FnC within the SN and was postulated as a region modulating switching between the DMN and CEN (Manoliu et al., 2013, Sridharan et al., 2008). The results in the right insula are compatible with this hypothesis.

Basal ganglia regions

AZD6765 produced more of a difference in mean intensity of ACC RS component than placebo in the left and right lentiform nucleus. The lentiform nuclei in the current dataset are likely to be the putamen. Whilst the function of the putamen in MDD has been linked to the perception of disgust and hate it was not tested whether AZD6765 affected these emotions or not (Phillips et al., 1998, Sprengelmeyer et al., 1998, Zeki and Romaya, 2008).

4.6.2. Drug effects on ACC RS and MADRS mood rating scales

Day 1/Day 2 correlations

The AZD6765 group were significantly more depressed at baseline which makes the groups not directly comparable. It is not clear why the groups were more depressed than those receiving ketamine and placebo but may have been due to an initial phase of the study which incorporated only ketamine and placebo. There were very few effects of ketamine that correlated with 4 hour improvement in MADRS scores, and no correlation with 24 hour improvement. Day 2 Ketamine mean intensity of ACC RS component was positively correlated in the right cingulate to the 24 hour post dose difference in MADRS score. The cingulate region in the current dataset is most

likely the PCC. The PCC has functions related to learning, memory, reward, motivation and decision making (Pearson et al., 2011). The posterior cingulate shows decreased BOLD in MDD patients before treatment with increased BOLD after treatment (Fitzgerald et al., 2008a). ROI studies have demonstrated decreased FnC and regional homogeneity in currently depressed patients in the precuneus/PCC (Bluhm et al., 2009, Yuan et al., 2008). The PCC could, therefore, be another site of delayed action of ketamine altering connectivity in the DMN and is similar to the published literature.

The effects of ketamine on day 2 demonstrate neural correlates of effect of ketamine at 24 hours. In Zarate et al. (2006a) the most prominent antidepressant effect of ketamine was 24 hours after a single open label infusion. Although the current findings support the continued effects after a single infusion there are no resting state studies in humans that are directly comparable.

AZD6765 + Ketamine combined correlations

To increase power a correlation analysis was performed with the drug groups combined. The MADRS scores were analysed combining the data for AZD6765 and ketamine as one group. There were no regions where mean intensity of ACC RS component for AZD6765 and ketamine combined was correlated.

Day 1 component 10 mean intensity of ACC RS component images positively correlated with the 4 hour MADRS score difference in the right fusiform gyrus. The fusiform gyrus is part of the visual recognition network and is involved in the perception of facial emotion stimuli (Kawasaki et al., 2012, Tao et al., 2013). MDD severity has been correlated with neural response in this region (Surguladze et al., 2005). The increased ACC RS component intensity in the fusiform gyrus could be due to acute dissociative symptoms, although this was not evident on CADSS.

Day 2 component 10 images mean intensity of ACC RS component for AZD6765 and ketamine combined was positively correlated with the right IPL. The IPL has been described as part of the posterior DMN being related to self-related cognition and autobiographical memory retrieval (Wang et al., 2012a, Vilberg and Rugg, 2008, Harrison et al., 2008). Decreased responses of the IPL have been reported following antidepressant treatment using emotional processing fMRI tasks in MDD (Delaveau et al., 2011). This could reflect restoration of the normal switching off mechanism of the DMN. Improvement in MDD in the current dataset correlated with the commencement of changes within the posterior DMN.

4.7. Limitations and future studies

A major limitation of the present study is the lack of a non-depressed control group to determine whether drug effects act to correct RS abnormalities in depression. The limitations of this study include lack of functional imaging prior to AZD6765 or ketamine administration. No filtering was applied to the dataset to compensate for the physiological noise produced by cardiac or

respiratory cycles; however this will have been filtered out by the spatial ICA. No examination was made of the signal to noise ratio of the fMRI data between groups to see if this confounded results. The next step in the current analysis would be to consider FnC between part of the DMN and other brain regions to observe the effects of ketamine and AZD6765. Comparison with an accepted antidepressant such as citalopram would have been beneficial. Further examination of the effects of ketamine and AZD6765 as adjunct treatments to reduce time to response may be beneficial. Attempting to combine response to AZD6765 with genetic analysis may also yield prognostic genetic biomarkers.

4.8. Conclusions

Acute i.v. ketamine had no statistically significant effects on the distribution of ACC RS activity. This was surprising in view of its direct effect on BOLD signal in ACC and by inference neural activation, in the same study. However, in Downey D. et al. (In press) the region examined was the more ventral portion of the ACC. In addition the entire infusion dataset was used rather than the last 25 minutes as here. In Downey et al.'s analysis there was a decline in overall drug effect in later time bins which might explain the lack of positive drug effects. No consistent changes similar to Deakin et al. (2008) were noted where decreased BOLD signal was reported in the ACC in healthy volunteers. Furthermore, AZD6765, with a very similar neurochemical action to ketamine, influenced ACC RS in a number of regions; decreases in middle frontal cortex, opposite effects in left and right insula, no effect on posterior DMN structures and decreasing ACC RS in ventral striatal regions. The lack of effect of ketamine might simply indicate that too low a dose was used. There was also no bolus used and a lack of dissociative effects which have been suggested to be important in therapeutic effect. Indeed, quantitatively the effects of ketamine tended to be intermediate between the placebo and AZD6765 groups.

There were no clear-cut dissociable effects of acute AZD6765 or ketamine on anatomical components of the ACC RS network that related to subsequent improvement in mood as predicted by hypothesis iii. Given that measures of intensity were used it might be that analysis of resting state connectivity may demonstrate a different picture of increased connectivity without changes in intensity.

Ketamine and AZD6765 evoked statistically significant delayed changes in ACC RS measured 24 hours after infusion. This was most clearly revealed by controlling for acute effects (day 1-day 2). In general both drugs ultimately increased frontal cortical expression of the ACC RS sometimes after an initial decrease on day 1. The results are compatible with hypothesis i a) that antidepressants increase SN or CEN ACC connectivity assuming the frontal regions affected are part of these networks.

Both drugs decreased the ACC RS in posterior cingulate, a classic component of the DMN. This is compatible with hypothesis i b) that dampening an overactive ruminative default mode network is an antidepressant mechanism.

AZD6765 strikingly increased ACC RS in ventral striatal regions implicated in reward. The precise implications of increased networking between ACC and reward mechanisms are not clear but they suggest the drug might have particular efficacy for anhedonia in depression. Whether similar non-significant effects of ketamine indicate a similar pro-reward efficacy for ketamine cannot be excluded.

There was no compelling evidence for hypothesis ii) that the NMDA functional antagonists work by exerting an acute effect on ACC RS that persists since there were no persistent effects shared by both drugs from day 1 to day 2. It appears instead that delayed effects are important, in some case triggered by opposing immediate effects.

Chapter Five: Effects of citalopram on resting state networks in major depressive disorder

5.1. Introduction

MDD is characterised by excessive negative inner reflection about the personal past, present and future, encapsulated in the concept of rumination. There is evidence that the tendency to ruminate is a personality trait that predisposes to depression and relapse (Nolen-Hoeksema, 2000, Michalak et al., 2011). Self-referential processing is associated with the DMN and is dysfunctional in MDD (Bluhm et al., 2008). Furthermore increased connectivity between the DMN and ACC has been reported in MDD compared to HC (Greicius et al., 2007, Sheline et al., 2010). From the review of resting state studies (Chapter 2)(Dutta et al., 2014), several studies reported decreased ALFF, fALFF and FnC of the ACC and insula in unmedicated MDD and increased in medicated and first episode MDD samples. Increased response of the rACC correlated with higher likelihood of treatment response to antidepressants (Fu et al., 2013). Moreover, Mayberg (2003) suggested that reduction of vACC hyperactivity was essential for symptom remission. Thus MDD could involve a central impairment in the ability to switch out of the DMN and engage systems concerned with external demands such as the CEN and SN via the ACC (Seeley et al., 2007, Belleau et al., 2014).

Antidepressants could be used to correct dysfunctional connectivity between resting state networks (Kennedy et al., 2001, Anand et al., 2005b). Selective serotonin reuptake inhibitors (SSRIs) are used frequently in the management of a variety of anxiety and depressive disorders (Deakin, 1998). Tryptophan depletion leads to relapse in rMDD, so trait vulnerability may be produced in the serotonin system by a MDD episode (Delgado et al., 1990, Reilly et al., 1997). 5-HT is clearly necessary for the antidepressant efficacy of SSRIs (Delgado et al., 1990), however, it remains far from clear whether there is a disease-related abnormality of 5-HT function in depression.

In the previous chapter both drugs reduced the mean intensity of ACC resting state (RS) component in the PCC (DMN region). This suggests changes in the DMN could correlate with acute antidepressant response. It was also demonstrated that both ketamine and AZD6765 increased mean intensity of ACC RS component in the insula, IPL and lentiform nucleus. Liu et al. (2010) previously observed reduced ReHo in the right insula in unmedicated MDD. IPL gray matter increase has been reported in rMDD patients compared to cMDD and HC, suggesting that this region returns to normal function on recovery from MDD (Salvadore et al., 2011). Changes in the insula, IPL and lentiform nuclei may therefore be common to the recovery following antidepressant treatment.

One approach to probing dynamic 5-HT functioning is to evoke acute 5-HT release using intravenous administration of the SSRI citalopram and to monitor the CNS effects using phMRI (McKie et al., 2005). In the experiment, combining acute citalopram infusion with ICA analysis of the ACC RS component allows exploration of the acute effects of citalopram in cMDD, rMDD and HC.

Citalopram Study 1 - Healthy controls vs current MDD vs remitted MDD after citalopram

5.2. Aims

- i) To determine whether an acute i.v. citalopram infusion affects the mean intensity of ACC RS component differently in HC, cMDD and rMDD.
- ii) To determine whether MADRS mood rating scores are correlated with the effects on the mean intensity of ACC RS component following an acute i.v. citalopram infusion in HC, cMDD and rMDD.

5.3. Hypotheses

- i) *Acute i.v. citalopram will increase the mean intensity of ACC RS component in cMDD > HC > rMDD.*
- ii) *Citalopram will reverse increased DMN and decreased SN and CEN activity in MDD.*
- iii) *Acute i.v. citalopram will increase the mean intensity of the ACC RS component in cMDD in the insula, IPL and lentiform nuclei.*
- iv) *MADRS scores will correlate with mean intensity of ACC RS component in regions of the DMN including precuneus/PCC, mPFC and ACC.*

5.4. Methods and materials

5.4.1. Ethics

Approval was gained from the local research ethics committee prior to commencement for each study.

5.4.2. Study design and recruitment

The effects of acute citalopram infusion on cMDD, rMDD and HC in previously unmedicated participants was investigated. The data presented are a combination of two datasets for REMEDi (Remission Mechanisms in Depression) and NewMood (New Molecules in Mood Disorders) studies.

5.4.3. Study recruitment

Both REMEDi and NewMood studies were performed at the University of Manchester with participants recruited via advertisement. Patients' illness severity was established using MADRS and the seven item Clinical Anxiety Scale adapted from the HAM-A. Currently depressed patients were required to have a MADRS score of ≥ 20 . Patients in remission were required to have a

MADRS score of ≤ 10 . Recruitment was conducted at the University of Manchester. Informed consent was obtained from all participants. Each individual was compensated for participation in the relevant study.

5.4.4. Screening and randomisation

Exclusion criteria were any unstable medical condition, neurological disorders, history of significant head trauma, lifetime history of substance or alcohol abuse, and contraindication to MRI scanning. For HC a positive family history of psychiatric disorders was an additional criterion for exclusion. The research pharmacy held separate randomization codes and dispensed the infusions on the day of the experiment labelled with a code number.

5.4.5. Image acquisition

Images were acquired on a Philips Intera 1.5 Tesla MR scanner housed within the Wellcome Trust Clinical Research Facility, Manchester. The acquisition parameters were single shot echo planar imaging sequence with an ascending and sequential slice order: TR (Time to repetition) was 2.1 seconds and TE (Echo Time) 40ms. A qualified radiographer performed all MR scans.

5.4.6. Study procedures

Both NewMood and REMEDi studies had identical imaging protocols. In both studies 7.5mg citalopram was infused i.v. for 7.5 minutes at 5 minutes post commencement of scanning. The NewMood study contained both HC and rMDD who received citalopram whereas the REMEDi study contained another set of HC and cMDD who received citalopram or placebo as part of a RCT.

5.4.7. Independent Component Analysis

Overview

The HC dataset from NewMood and REMEDi studies were combined. The preprocessed images were separated into treatment (citalopram or placebo for REMEDi only) drug and group (HC from NewMood, HC from REMEDi, rMDD from NewMood and cMDD from REMEDi) order before being entered into Group ICA of fMRI Toolbox (GIFT) software run under MATLAB 2009a.

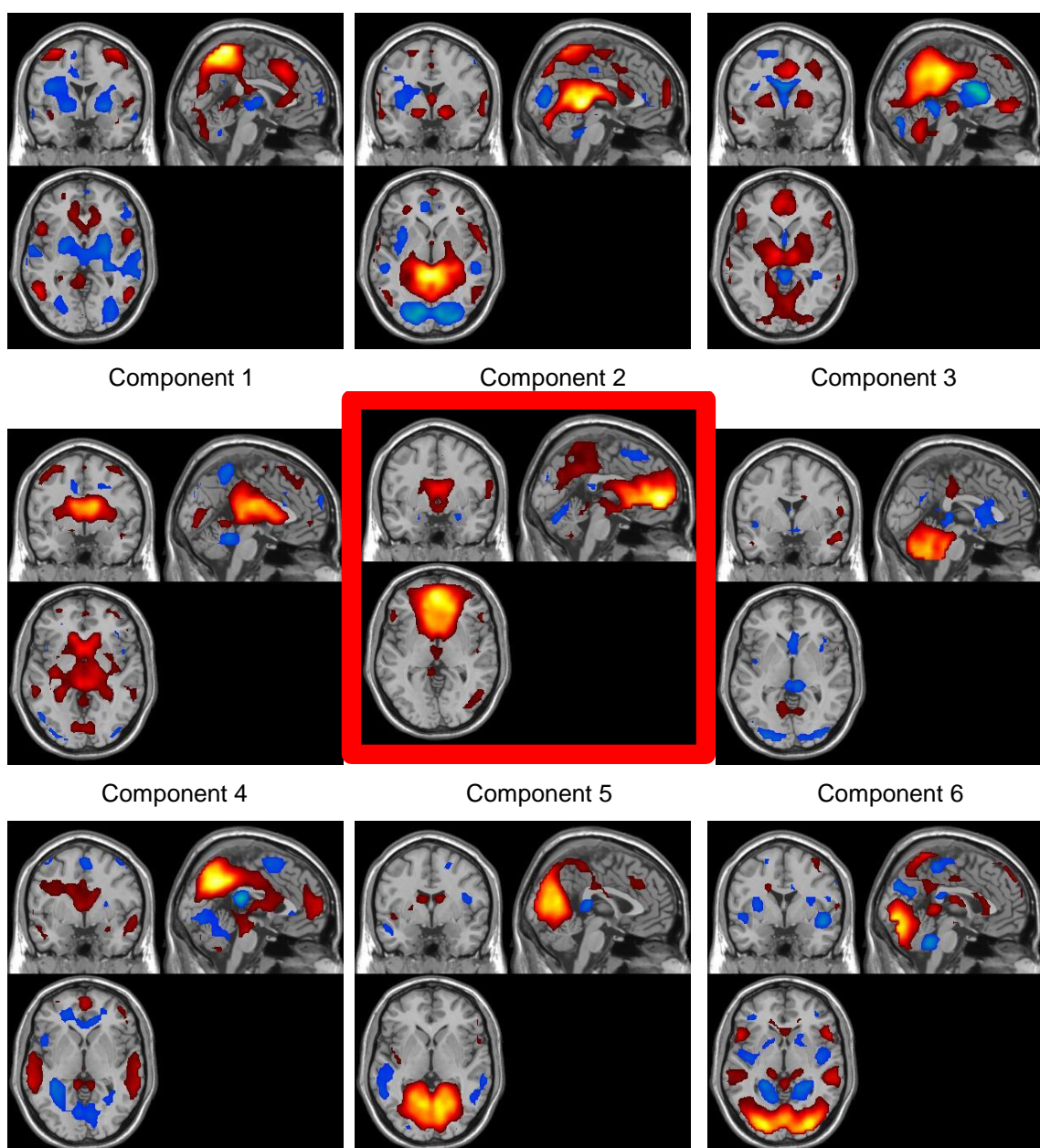
Selection of the ACC independent component of interest

The 20 component maps for the combined NewMood and REMEDi datasets are displayed in Figure 12 below. The component map overlays are cluster thresholded at >20 voxels and height thresholded at $p < 0.001$ uncorrected demonstrating the positive and negative component. The components represent ACC correlated resting state statistically independent 'networks' that respond concurrently to drug challenge. The components with the highest spatial correlation to the ACC in this dataset were components 5 ($r=0.454$), 19 ($r=0.079$) and 14 ($r=0.072$). Component 5 is highlighted in red and was selected as the component of interest.

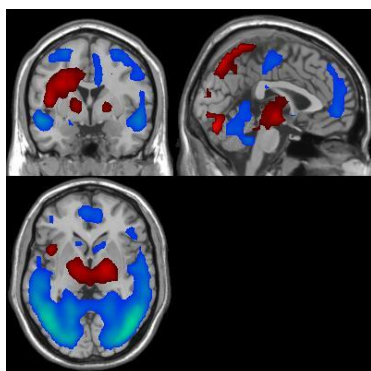
Treatment effects on the ACC RS component and correlations with MADRS scores

The ACC RS component images, resulting from the back reconstruction, were then entered into a one way ANOVA to test for the differences between the HC, rMDD and cMDD groups and a two-way ANOVA to test for the interaction between treatment (citalopram or placebo) and group (HC or cMDD). The positive and negative ACC RS components were examined using SPM voxel-wise and regional MaRSBaR analysis (see section 4.4.7). Areas showing significant correlation between improvement in MADRS scores and ACC RS (ICA component 5) amplitude were computed in SPM separately for the 3 groups in citalopram study 1 (HC, rMDD and cMDD) and for the 4 groups in citalopram study 2 (HC citalopram, HC placebo, cMDD citalopram and cMDD placebo). MADRS scores were also analysed using t-tests for difference between baseline scores.

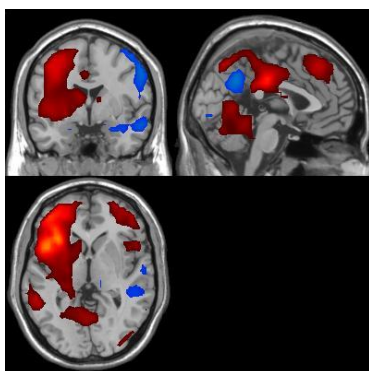
Figure 12 Citalopram study 1 & 2 mean component maps



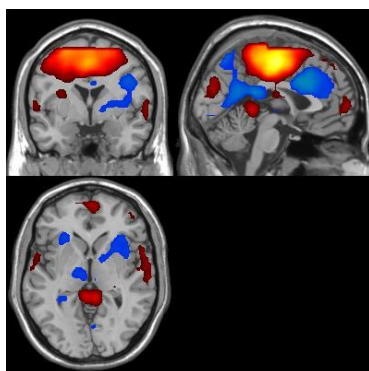
Component 7



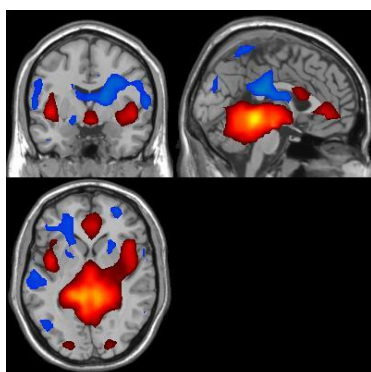
Component 8



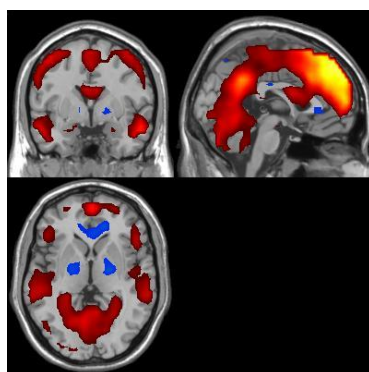
Component 9



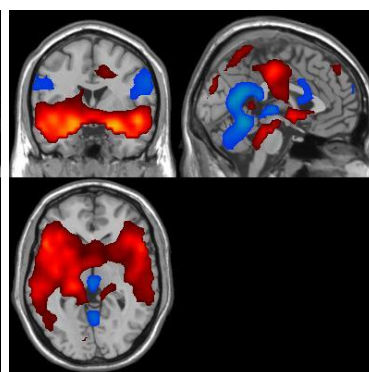
Component 10



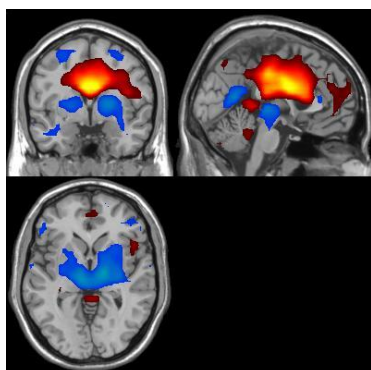
Component 11



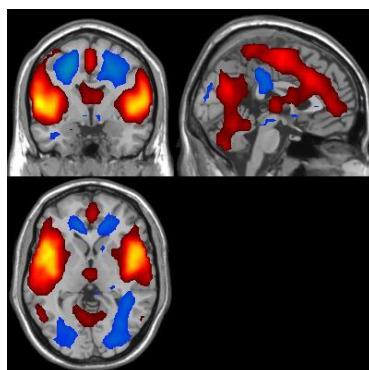
Component 12



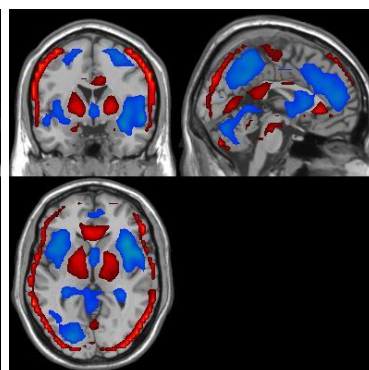
Component 13



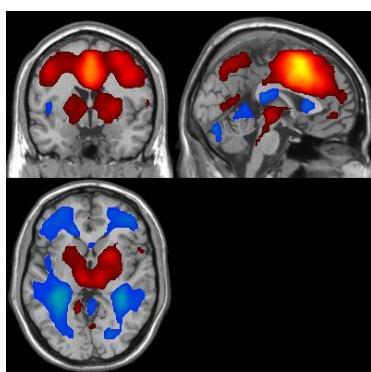
Component 14



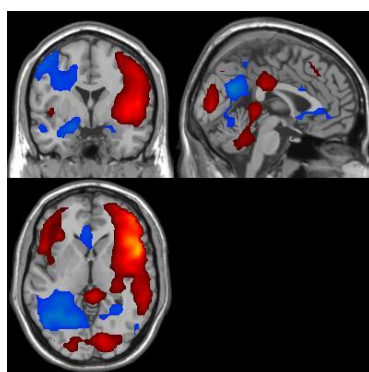
Component 15



Component 16



Component 17



Component 18

Component 19

Component 20

5.5. Results

5.5.1. Demographics

Table 21 displays the study demographics below for citalopram study 1 – the difference in mean intensity of ACC RS component after an acute citalopram infusion between the groups. There were no significant differences in mean age between the groups. The baseline MADRS scores were significantly increased in the cMDD group compared to rMDD and HC. The groups were biased toward females in all groups.

Table 21 Demographics and mood rating scales

	Healthy Controls	Remitted MDD	Current MDD
Citalopram (NewMood)	14	14	-
Citalopram (REMEDI)	15	-	24
Total numbers	29	14	24
Baseline MADRS	0.6 (SD 1.3)	1.8 (SD 2.4)	26.8 (SD 4)*
Mean Age	31.6 (SD 9.8)	33.4 (SD 11.6)	35.9 (SD 8.5)
Males	8	2	8
Females	21	12	16

* = $p < 0.05$ for cMDD compared to rMDD and HC; SD = standard deviation

5.5.2. Effects of group in regions expressing significant ACC RS activity - SPM voxel-wise analysis

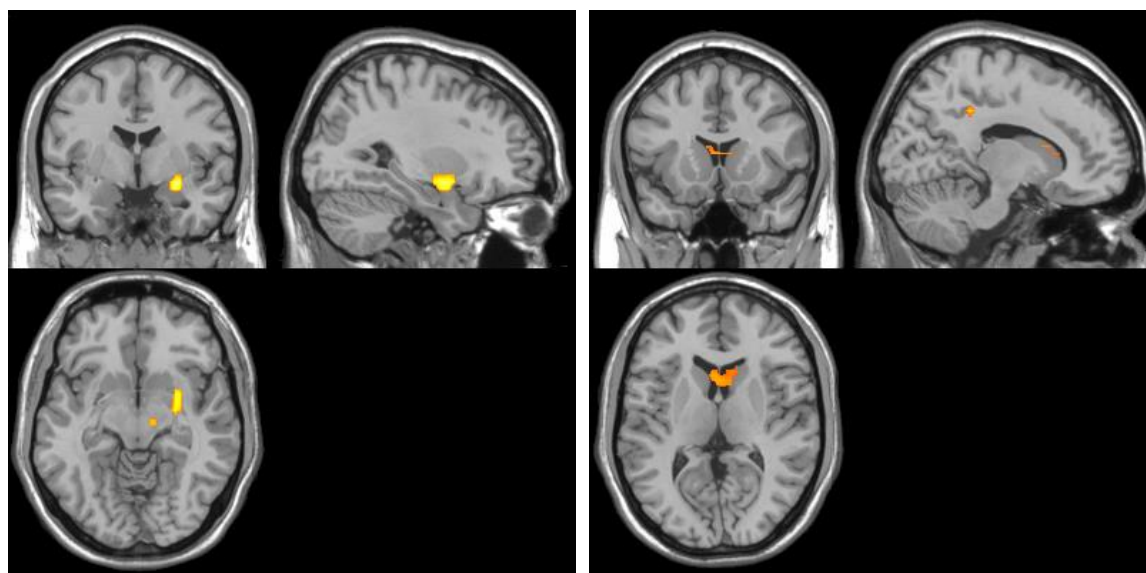
Table 22 details the results of the SPM voxel-wise analysis. Those results highlighted in red are significant at $p_{FDRc} < 0.05$, whilst those in red italics show trend results. Overlays for significant results are plotted in Figure 13 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

cMDD had reduced mean intensity of ACC RS component after citalopram infusion in the left amygdala, right posterior cingulate cortex and left insula compared to HC (Figure 13a). cMDD patients showed increased mean intensity of ACC RS component in the left cingulate gyrus and caudate compared to HC (Figure 13b).

Table 22 SPM voxel-wise analysis

Region	Side	Centre of Mass			No of voxels	p(FWEc)	q(FDRc)
		x	y	z			
HC > cMDD							
Amygdala	L	-20	-10	-12	68	0.001	0.002
Insula	L	-34	-19	18	28	0.053	0.038
Posterior Cingulate Cortex	R	-3	-34	18	42	0.012	0.012
cMDD > HC							
Caudate	L	-1	12	8	42	0.012	0.033
Cingulate Gyrus	L	-19	-43	36	33	0.030	0.043
HC > rMDD / rMDD>HC							
No significant regions							

Figure 13 SPM voxel-wise analysis contrast maps



a) HC > cMDD ($p < 0.001$) – l-amygdala, l-insula & r-PCC

b) cMDD > HC ($p < 0.001$) – l-caudate & l-cingulate gyrus

5.5.3. State vs trait effects on positive ACC RS component – regional MarsBaR analysis

Table 23 details the results of the positive ACC RS component regional MarsBaR analysis. Values in red are those that survive correction for the number of regions investigated at $p_{FDR} < 0.05$. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 14 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant. State abnormalities are marked in the top left hand corner of the histograms in Figure 14.

Three patterns were discerned from the histograms in Figure 14:

- 1) Trait abnormalities were those where both cMDD and rMDD had similar responses following citalopram infusion but both were different from HC. Trait-like decreases in ACC RS component were seen right medial frontal gyrus, left anterior cingulate and bilateral precuneus although the differences did not survive FDR correction.
- 2) State-dependent changes in which the cMDD group separated from responses in rMDD and HC were seen in the frontal and cingulate areas and in the posterior DMN components cuneus and cingulate. Specifically, state-dependent increases in cMDD ACC RS component were seen in left superior and middle frontal gyri and right cuneus, and decreases in left inferior frontal gyri and bilateral posterior cingulate.
- 3) A third mixed state & trait pattern showed opposite differences between the two depressed groups and HCs (cMDD>HC>rMDD) in the basal ganglia caudate and lentiform nuclei. The mixed pattern of group differences in left and right caudate involved the most statistically significant effects in this analysis and they survived FDR correction. Furthermore the whole brain analysis corroborates increased ACC RS component in left caudate in cMDD.

5.5.4. State vs trait effects on negative ACC RS component – regional MarsBaR analysis

Table 24 details the results of the negative ACC RS component regional MarsBaR analysis. Values in red are those that survive correction for the number of regions investigated at $p_{FDR} < 0.05$. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 15 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

There were no trait abnormalities within the negative ACC RS component. State abnormalities were present in the right thalamus. State abnormalities are marked in the top left hand corner of the histograms in Figure 15.

HC had decreased mean intensity of ACC RS component in the right thalamus and right IPL. The differences in the right thalamus survived FDR correction. rMDD patients had decreased mean

intensity of ACC RS component in the right thalamus compared to cMDD. cMDD patients had greater mean intensity of ACC RS component values in the left parietal lobe which remained significant even after FDR correction.

5.5.5. State vs trait effects on ACC RS and MADRS mood rating scales

There were no regions that demonstrated significant correlation of the mean intensity of ACC RS component with baseline MADRS scores

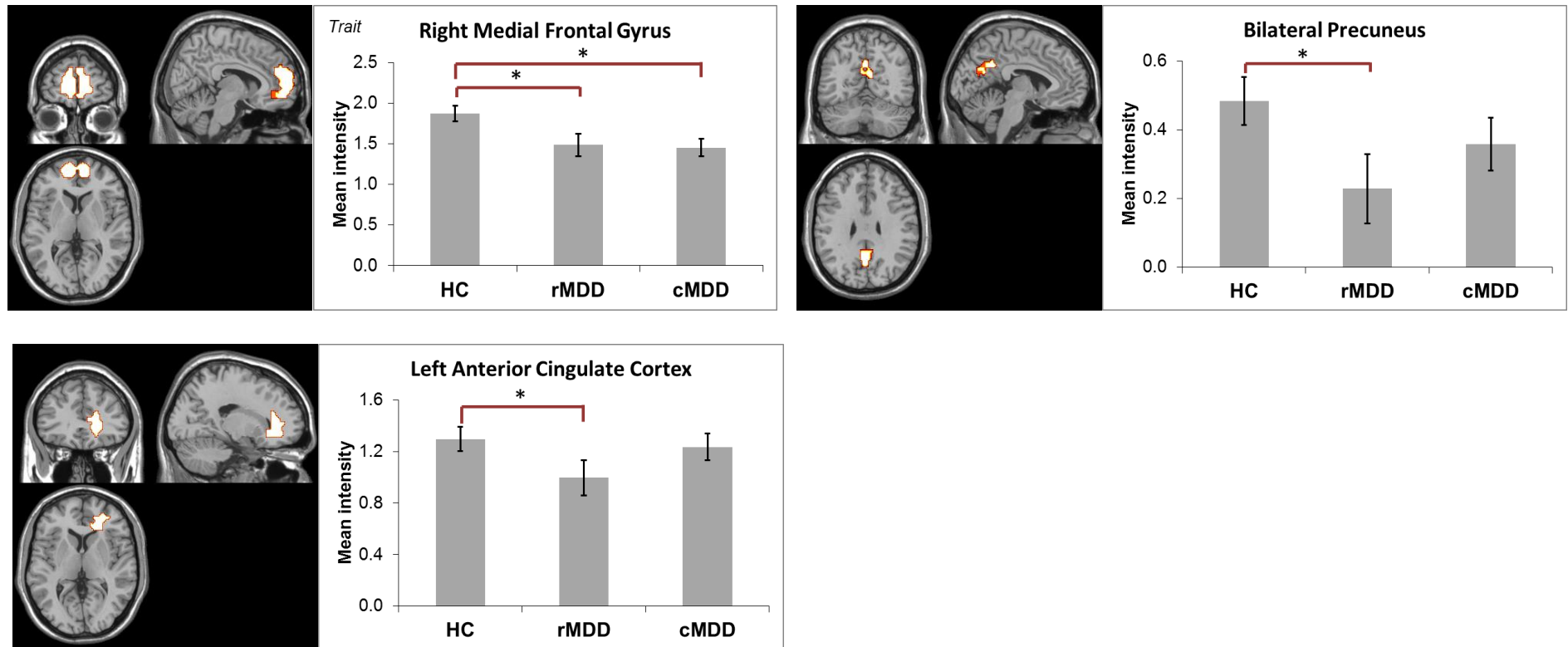
Table 23 Component 5 positive ACC RS component regions that show differences between groups

Region of Interest	Side	Centre of mass			No. of voxels	p			FDR		
		x	y	z		HC>rMDD	HC>cMDD	rMDD>cMDD	HC>rMDD	HC>cMDD	rMDD>cMDD
Superior Frontal Gyrus	L	-18	55	15	147	ns	0.037	ns	ns	ns	ns
Medial Frontal Gyrus	R	0	52	9	381	0.013	0.002	ns	ns	0.062	ns
Middle Frontal Gyrus	L	-30	48	1	101	ns	ns	0.032	ns	ns	ns
Inferior Frontal Gyrus	L	-53	25	2	28	ns	(0.010)	(0.023)	ns	(0.042)	ns
Anterior Cingulate Cortex	L	-20	37	2	116	0.038	ns	ns	ns	ns	ns
Posterior Cingulate	B/L	1	-38	36	109	ns	(0.003)	(0.027)	ns	(0.014)	ns
Precuneus	B/L	-1	-62	27	68	0.021	ns	ns	ns	ns	ns
Cuneus	R	21	-85	17	30	ns	0.003	0.007	ns	0.044	ns
Caudate	L	-10	9	8	74	0.076	(<0.001)	(<0.001)	ns	(0.002)	(<0.001)
Caudate	R	11	10	8	67	0.012	(<0.001)	(<0.001)	ns	(0.001)	(<0.001)
Lentiform Nucleus	R	18	8	-2	49	ns	ns	(0.023)	ns	ns	ns

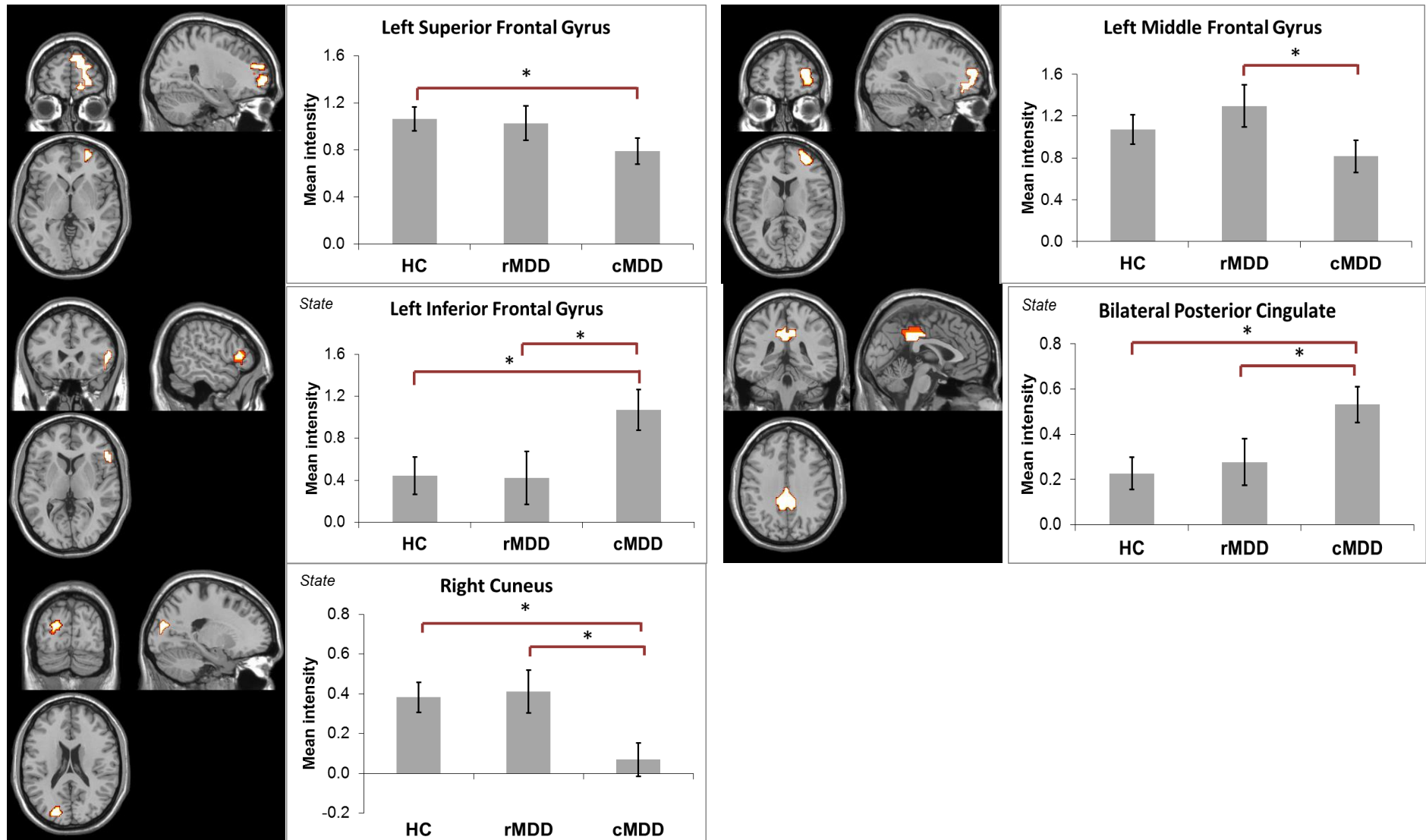
p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 14 Overlays & histograms for regions of positive ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected

Trait or possible trait difference (cMDD = rMDD \neq HC)



State dependent or possible state dependent difference (cMDD < > rMDD = HC)



Mixed state-trait differences (cMDD > HC > rMDD)

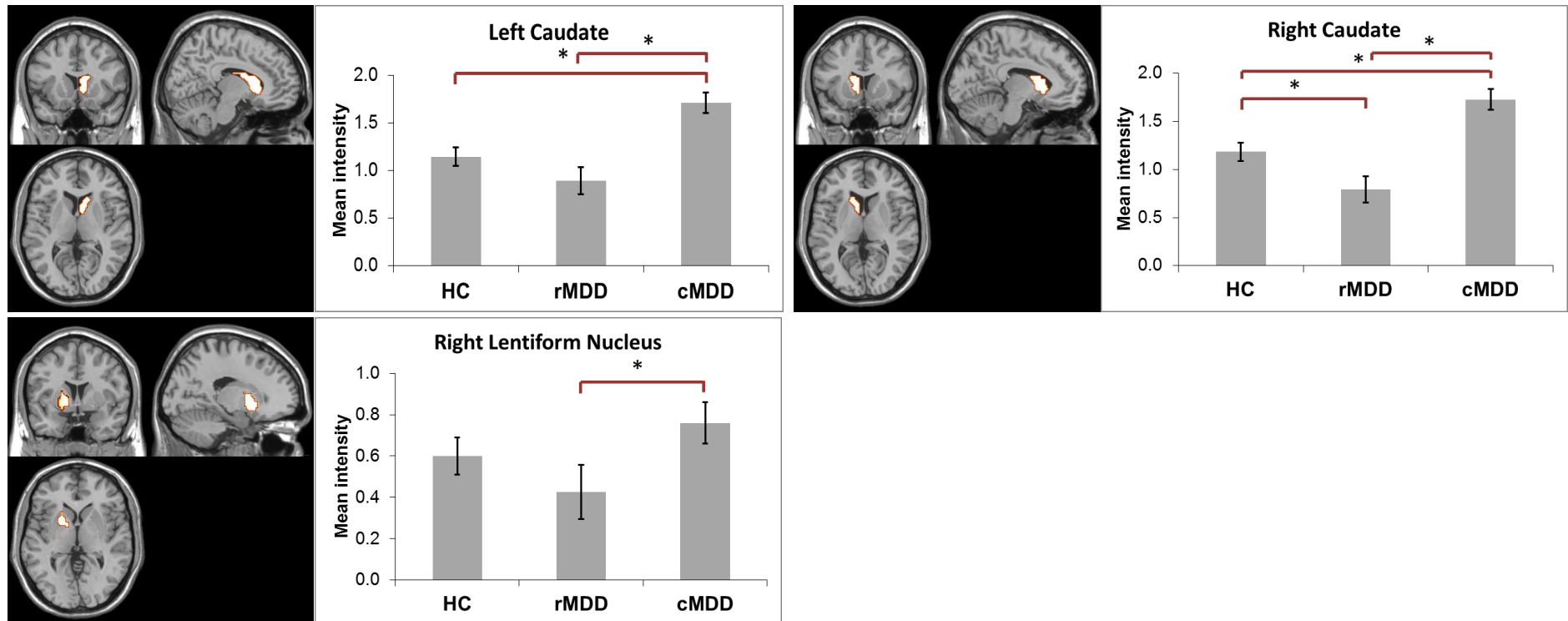


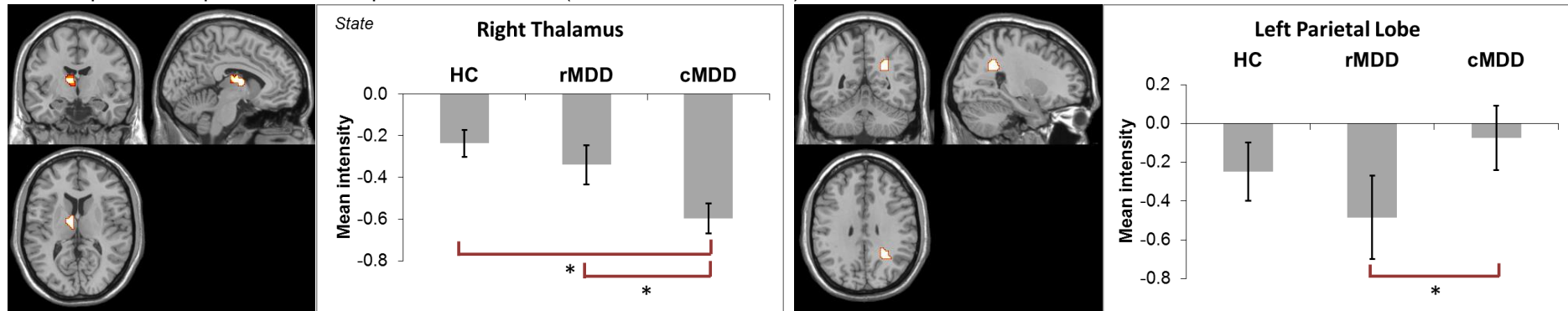
Table 24 Component 5 negative ACC RS component regions that show differences between groups

Region of Interest	Side	Centre of mass			No. of voxels	p			FDR		
		x	y	z		HC>rMDD	HC>cMDD	rMDD>cMDD	HC>rMDD	HC>cMDD	rMDD>cMDD
Thalamus	R	15	-38	13	42	ns	0.000	0.016	ns	0.001	<i>0.097</i>
Parietal Lobe	L	-26	-50	28	29	<i>0.052</i>	0.080	(0.004)	ns	ns	(0.045)
Inferior Parietal Lobule	R	50	-49	43	127	ns	0.044	ns	ns	ns	ns

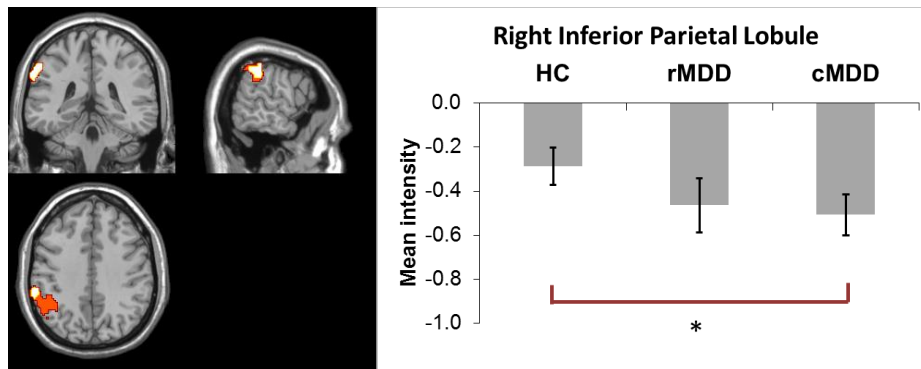
p-values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 15 Overlays & histograms for regions of negative ACC RS component that show a significant difference between groups: * = $p < 0.05$ uncorrected

State dependent or possible state dependent difference (cMDD < > rMDD = HC)



Possible trait difference (cMDD = rMDD < > HC)



5.6. Discussion

5.6.1. State vs trait effects on positive ACC RS component after acute citalopram

Trait differences (cMDD = rMDD < > HC)

The right medial frontal gyrus was the only region with fully statistically justified trait abnormality. Remitted depressed participants showed non-significant trait decreases in ACC RS anterior cingulate and bilateral precuneus. These are part of the DMN although the frontal regions may also overlap with the SN. Mean intensity of ACC RS component in the right mFG was increased in HC more than remitted and currently depressed groups. McKie et al. (2005) previously demonstrated the effects of acute citalopram i.v. increasing BOLD in the mFG in healthy volunteers. Decreased glucose metabolism in the right mFG has been reported in those who developed MDD following cancer diagnosis (Kumano et al., 2007). This is compatible with the current result with increased mean intensity of ACC RS component in HC compared to both MDD groups. Since in this study all ACC RS data were obtained under acute citalopram treatment, it is not possible to be certain whether trait abnormalities are due to differences in the intensity of the RS networks themselves or in their responsivity to citalopram.

Other regions observed to have trait abnormality which was not statistically significant was the bilateral precuneus, although there was no significant difference between cMDD and HC. The precuneus is part of the posterior DMN and central to connectivity with other regions (Fransson and Marrelec, 2008). Both increased and decreased FnC of the precuneus in cMDD has previously been reported by researchers (Greicius et al., 2007, Bluhm et al., 2009, Zhu et al., 2012). Increased ALFF was noted in rMDD when compared to cMDD females (Jing et al., 2013). The current findings show a different picture of probable trait abnormalities with no difference between cMDD and rMDD and HC and cMDD.

Trait differences therefore appear to be within regions of the DMN. This suggests that abnormal DMN functioning might persist despite recovery from MDD.

State dependent differences (cMDD < > rMDD = HC)

Regions showing state dependent abnormalities were the left inferior frontal gyrus, bilateral posterior cingulate and right cuneus. cMDD patients had greater mean intensity of ACC RS component in the left inferior frontal gyrus than HC or rMDD. Guo et al. (2011b) reported decreased ReHo in the left inferior frontal gyrus in unmedicated tr MDD patients. However there is no evidence to support unilateral left inferior frontal gyrus response in MDD following acute i.v. citalopram. Other regions of potential state dependent abnormality included the left superior frontal gyrus and left middle frontal gyrus but where cMDD failed to have significant difference in mean intensity of ACC RS component.

Increased mean intensity of ACC RS component in cMDD is seen in the MaRSBaR regional analysis bilaterally in the PCC. In the SPM voxel-wise analysis, however, HCs had greater mean intensity of ACC RS component than cMDD patients in the right PCC. The PCC is part of the DMN associated with rumination and emotional self-judgement (Nejad et al., 2013). It would be expected that cMDD patients would have greater mean intensity of ACC RS component in this area prior to treatment (Cooney et al., 2010). Matthews et al. (2010) in a randomized fMRI study of 15 HC reported a reduction in BOLD of bilateral PCC when performing self-evaluation tasks following escitalopram treatment (Matthews et al., 2010). In the current results, HC had increased mean intensity of ACC RS in the PCC following citalopram rather than a reduction. It is not clear why the SPM voxel-wise analysis differs from the regional MarsBaR analysis.

In the SPM voxel-wise analysis cMDD patients were noted to have increased mean intensity of ACC RS component in the right caudate compared to HC following citalopram. Increased response in the right caudate in healthy volunteers is associated with reward prediction, response and learning from positive feedback (Smoski et al., 2009, Elliott et al., 2000a). Monkul et al. (2012) observed increased blood flow in the right caudate in unmedicated MDD during a PET study. In a meta-analysis though, however, Arnone et al. (2012a) reported that there were no individual volume differences when the each side of the caudate was examined in MDD patients but an overall reduction for the bilateral caudate. The caudate therefore tends to be hyporesponsive in MDD patients. In the current study it is hypothesized that citalopram had an acute effect increasing mean intensity of ACC RS component in MDD. This would make sense given the previous research suggesting reduced blood flow and volume in the caudate.

HCs and rMDD patients had greater mean intensity of ACC RS component than cMDD patients in the right cuneus. The cuneus alongside the lingual gyrus are key regions in the visual recognition circuit (Tao et al., 2013, Guo et al., 2012b). Meta-analysis has revealed the cuneus also has significantly reduced resting state BOLD in MDD (Alcaro et al., 2010). Increased BOLD has also previously been reported following citalopram in healthy volunteers (McKie et al., 2005) and it can be assumed that mean intensity of ACC RS component should increase in MDD following treatment given the evidence of a similar effect from previous studies with fluoxetine (Fu et al., 2007). The current results support this. In the previous chapter, both ketamine and AZD6765 groups on day 2 had increased mean intensity of ACC RS component in the right cuneus, further supporting the suggestion of a state dependent effect.

In the current dataset, HC had greater mean intensity of ACC RS component than cMDD patients in the left superior frontal gyrus. Also in the current result, rMDD appear to produce a similar response to HC and cMDD. In the previous chapter both AZD6765 and ketamine on AZ study day 2 increased mean intensity of the ACC RS component compared to placebo in MDD. Therefore although there are suggested functional and structural abnormalities there are no persistent effects of MDD in the superior frontal gyrus.

Mixed state-trait differences (cMDD>HC>rMDD)

There were a number of areas on MaRSBaR regional analysis with opposite differences between the two depressive groups. These regions included the left and right caudate and lentiform nuclei. The left ACC mean intensity of ACC RS component was increased in HC significantly more than in rMDD. The area identified here is probably part of the rACC rather than vACC. The rACC has an important role in anhedonia and emotional processing (Walter et al., 2009). Horn et al. (2010) demonstrated that FnC between the rACC and anterior insula was positively correlated with HAM-D scores. In the current dataset rMDD patients continue to have defective responses of the rACC. Assuming that antidepressant medications reduce FnC in MDD (McCabe and Mishor, 2011), remitted patients must retain some of the previous aberrant connectivity despite remission of symptoms.

5.6.2. State vs trait effects on negative ACC RS component

State dependent difference (cMDD < > rMDD = HC)

State abnormalities were present in the right thalamus. HC and rMDD patients had increased mean intensity of ACC RS component than cMDD in the right thalamus. The thalamus in this dataset is probably the pulvinar nucleus and more caudal than the thalamic BOLD noted by McKie et al. (2005) following citalopram administration in healthy volunteers. A recent large MRI trial revealed smaller bilateral thalamus volumes in unmedicated MDD compared to HC (Nugent et al., 2013). Greater FnC between the thalamus and DMN has been previously been reported by Greicius et al. (2007) in medicated MDD. Anand et al. (2007) reported decreased FnC between the rACC, amygdala, pallidostriatum and medial thalamus prior to antidepressant treatment which improved following sertraline. Higher degrees of self-relatedness to negative emotional stimuli correlate with reduced BOLD signal in the dorsomedial thalamus (Grimm et al., 2009). Where volume reduction has been reported it would be expected that trait rather than state abnormalities would be observed.

Possible trait difference (cMDD = rMDD < > HC)

The possible state abnormalities are regions that were not statistically significant. The discussion is therefore a speculative one of non-significant results. The right IPL was an area of potential trait abnormality, whilst potential state dependent abnormality was evident in the left parietal lobe. HC had increased mean intensity of ACC RS component compared to cMDD in the right IPL. The IPL acts as a switching region between functional networks (Daniels et al., 2010). It integrates sensory information from a number of different modalities and has functions in retrieval of autobiographical memory (Vilberg and Rugg, 2008), reward (Zhang et al., 2013b), decision making (Dosenbach et al., 2007) and attention (Fox et al., 2006). Wang et al. (2012a) observed decreased ALFF bilaterally in the IPL and fALFF in the right IPL in first episode unmedicated MDD patients compared to HC. The cross-sectional nature of the current study meant effects of therapy were not examined. In the current dataset decreased mean intensity of ACC RS

component in the right IPL in HC demonstrates that citalopram produced similar effects to those seen with glutamate based antidepressants such as AZD6765 and ketamine. The IPL is part of the DMN along with the right mFG and bilateral precuneus observed in the positive ACC RS component, which are altered by acute citalopram infusion.

Regions found only on SPM voxel-wise analysis

Two regions not found in the MarsBaR regional analysis was the left amygdala and insula. The left amygdala was another area where HCs had increased mean intensity of ACC RS component compared to cMDD. PET studies have demonstrated elevated CBF and metabolism in the amygdala primary unmedicated MDD (Drevets, 2000). Treatment response has been linked to reductions in metabolism in the left amygdala (Drevets et al., 2002, Carlson et al., 2013). The finding is therefore different to the previous literature with increased mean intensity of ACC RS in HC compared to MDD.

The left insula was noted to have increased mean intensity of ACC RS component in HC compared to cMDD. Guo et al. (2011b) reported decreased ReHo in the left insula in tr MDD compared to HC. Veer et al. (2010) reported decreased FnC between the amygdala and left insula in MDD. Chronic treatment with paroxetine decreased metabolism in a PET imaging study of the posterior insula in MDD (Kennedy et al., 2001). The area identified in Kennedy et al. (2001) was a similar region to that observed in the current analysis. The acute effects of citalopram in HC suggest increased mean intensity of ACC RS component and do not fit with the literature. This may be because the studies investigate the effect of chronic treatment.

In summary, there were a number of areas where changes were noted related to emotional and visual processing with links also to the default mode and salience networks. The most significant effects surround the effects in the caudate and the cingulate gyrus in cMDD. State abnormalities were observed in the left inferior frontal gyrus, bilateral posterior cingulate, left caudate and right cuneus, whilst trait abnormalities were observed in the right mFG. It is impossible to know whether the abnormalities reflect group differences in the ACC RS per se or the response of ACC RS to citalopram challenge due to the lack of placebo control.

5.7. Conclusions

Basal ganglia regions Mixed state-trait differences were noted in the left and right caudate and right lentiform nuclei following acute i.v. citalopram. Therefore as predicted in hypotheses i) acute i.v. citalopram increased the mean intensity of ACC RS component in cMDD > HC > rMDD. and iii) that iii) acute i.v. citalopram would increase the mean intensity of the ACC RS component in the lentiform nuclei. The effects in the caudate were the most significant since they survived FDR correction. Predicted increases in ACC RS component were present in the lentiform but were present unilaterally.

DMN/SN/CEN regions Trait-like changes were observed in the DMN regions in the right mFG and bilateral precuneus. In these regions, cMDD had decreased mean intensity of ACC RS in accordance with the hypotheses ii) that acute citalopram would decrease ACC-DMN RS response. State dependent increases in ACC RS component in cMDD were also observed in the PCC. However there were some state dependent changes in the posterior DMN (right cuneus) which were contrary to hypothesis ii where cMDD had decreases in ACC RS component. There are probably both state and trait dependent effects within the DMN.

No effects were observed in the insula as predicted, and effects in the left ACC did not differentiate HC from cMDD. There were no effects in the SN as predicted in hypothesis ii) that a reversal in decreased SN activity would occur. Increased ACC RS activity predicted in CEN in hypothesis ii) also did not occur, but there were decreases in ACC RS activity in the left superior frontal gyrus and right IPL.

MADRS score correlation There was no correlation of any regions with MADRS scores. Therefore acute activity of the DMN regions does not correlate MDD severity. It was hoped that state dependent changes in DMN activity would correlate with an improvement in mood.

5.8. Limitations and future studies

The limitations of the study include the lack of functional imaging prior to citalopram administration and lack of placebo control for each group. The study sample size was small and future studies would require higher numbers. The analysis combined data from two studies (REMEDi and NewMood) which whilst utilising the same protocol would have sampled patients at different timepoints. Furthermore no filtering was applied to the dataset to compensate for the physiological noise produced by cardiac or respiratory cycles; however this should have been filtered out by the spatial ICA.

Further examination of the effects of chronic citalopram administration on MDD patients should be considered. A more longitudinal approach with repeated imaging over a number of weeks and months would allow investigation of the effects in responders and non-responders.

Citalopram Study 2 - Healthy controls vs current MDD after citalopram or placebo infusion

Citalopram study 2 was a placebo controlled trial to examine the acute effects of i.v. citalopram on cMDD compared to HC as a comparator to citalopram study 1. Citalopram study 1 examined potential trait abnormalities shared by cMDD and rMDD groups in response to citalopram challenge but did not have a placebo control.

5.9. Aims

- i) To determine whether an acute i.v. citalopram infusion affects the mean intensity of ACC RS component differently in HC and cMDD.
- ii) To determine whether MADRS mood rating scores are correlated with the effects on the mean intensity of ACC RS component following an acute i.v. citalopram infusion in HC and cMDD.

5.10. Hypotheses

- i) *Acute i.v. citalopram will increase the mean intensity of ACC RS component in cMDD > HC.*
- ii) *Acute i.v. citalopram will reverse increased DMN and decreased SN and CEN activity in MDD*
- iii) *Acute i.v. citalopram will increase the mean intensity of the ACC RS component in cMDD in the insula, IPL and lentiform nuclei.*
- iv) *MADRS scores will correlate with mean intensity of ACC RS component in regions of the DMN including precuneus/PCC, mPFC and ACC.*

5.11. Results

5.11.1. Demographics

Table 25 displays the study demographics below for citalopram study 2. There were no significant differences in mean age between the groups. The baseline MADRS scores were significantly increased in the cMDD groups compared to the HC groups. This was regardless of whether they were treated with placebo or citalopram. There was no difference between the HC on citalopram and placebo on MADRS. There were no differences between cMDD patients whether treated with citalopram or placebo. The groups were biased toward females in all groups.

Table 25 Demographics and mood rating scales

	Healthy Controls Citalopram	Healthy Controls Placebo	Current MDD Citalopram	Current MDD Placebo
Sample size	15	11	24	13
Baseline MADRS	0.2 (SD 0.6)*	0.0 (SD 0.3) ^a	26.8 (SD 4)	27.5 (SD 4.9)
Mean Age	33.3 (SD 10.1)	32.7 (SD 8.6)	35.9 (SD 8.5)	36 (SD 10)
Males	5	3	8	3
Females	10	8	16	10

* = $p < 0.05$ for healthy controls citalopram compared to current MDD citalopram and current MDD placebo compared to current MDD; ^a = $p < 0.05$ for healthy controls placebo compared to current MDD placebo and current MDD citalopram; SD= standard deviation

5.11.2. SPM voxel-wise analysis

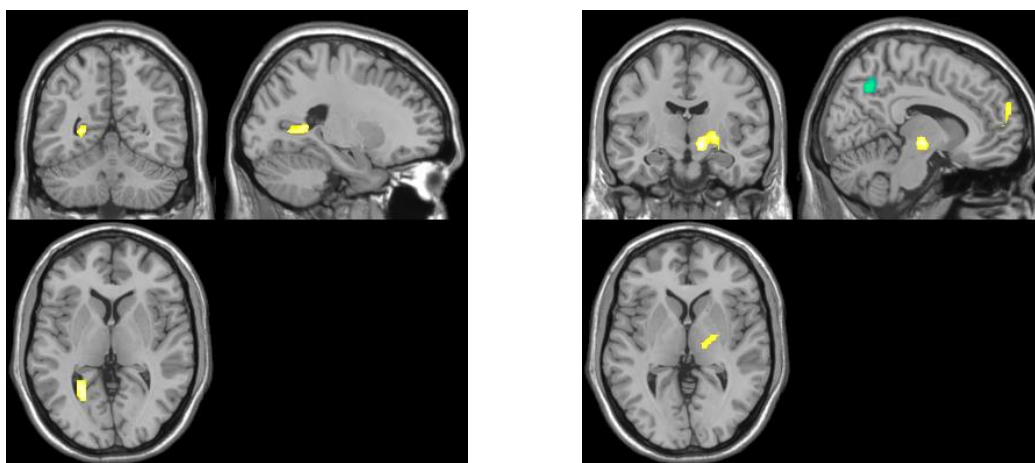
Table 26 details the results of the SPM voxel-wise analysis. Those results highlighted in red are significant at $p_{FDRc} < 0.05$, whilst those in red italics show trend results. Overlays for significant results are shown in Figure 16 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

There were no regions within the positive effect of group. Negative effect of group was demonstrated in the right PHG. Effect of group did not take into account effects of treatment. Positive interaction was noted in the left brainstem and left mFG. A negative interaction was noted in the left precuneus. HCs treated with citalopram had significantly increased mean intensity of ACC RS component in the left mFG whereas cMDD patients treated with citalopram had significantly increased mean intensity of ACC RS component in the left precuneus.

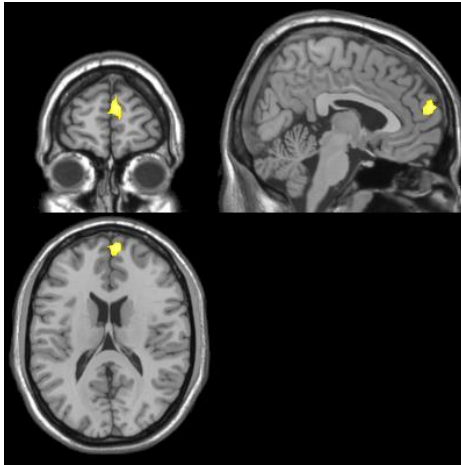
Table 26 SPM voxel-wise analysis

Region	Side	Co-ordinates			No of voxels	p(FWEc)	q(FDRc)
		x	y	z			
Positive effect of group (cMDD< HC)							
No significant regions							
Negative effect of group (HC< cMDD)							
Parahippocampal Gyrus	R	27	-56	1	36	0.025	0.033
Positive Interaction (HC(cital-plac)>cMDD(cital-plac))							
Medial Frontal Gyrus	L	-8	56	20	33	0.034	0.033
Brainstem	L	-12	-14	-10	79	0.001	0.001
Negative Interaction (cMDD(cital-plac)>HC(cital-plac))							
Precuneus	L	-8	-63	35	50	0.006	0.011
HC (cital - plac)							
Medial Frontal Gyrus	L	-4	57	13	39	0.018	0.041
cMDD (cital - plac)							
Precuneus	L	-7	-61	41	33	0.034	0.050

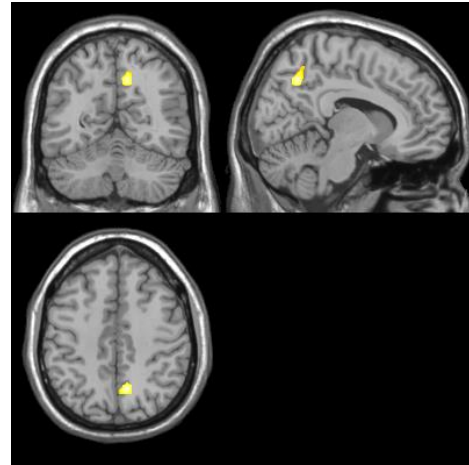
Figure 16 SPM voxel-wise analysis contrast maps – positive (yellow) and negative (blue) effects are plotted at peak-level threshold of $p=0.001$ and extent threshold of $p_{FDRc}<0.05$



a) Negative effect of group (HC < cMDD)
– r-PHG



b) Interactions – positive (l-mFG & brainstem)
and negative (l-precuneus)



c) HC (cital-plac) – l-mFG

d) cMDD (cital-plac) – l-precuneus

5.11.3. Drug modulation of positive ACC RS component – regional MarsBaR analysis

Table 27 details the results of the positive ACC RS component regional MarsBaR analysis. Values in red are those that survive correction for the number of regions investigated at $p_{FDR} < 0.05$. Overlays and histograms for each region significant at $p < 0.001$ uncorrected are shown in Figure 17 (radiological convention is followed which means the left side of the image corresponds to right side of the brain). Regions are reported from anterior to posterior with left and right regions reported together where significant.

Table 27 shows there were several main and interacting effects of citalopram and diagnosis.

Increases in ACC RS component in the untreated MDD group were seen in frontal regions and posterior cingulate. Decreased ACC RS component expression in MDD was present in midline bilateral precuneus and adjacent paracentral lobule, thalamus, temporal cortex. There minimal differences in the basal ganglia.

Effects of citalopram were almost exclusively confined to HCs, with increases in frontal regions and decreases in thalamus and temporal cortex. Thus citalopram did not reverse increases or decreases in ACC RS component in MDD. The single exception is that citalopram reversed the decrease in ACC RS component in precuneus.

5.11.4. Drug modulation of negative ACC RS component – regional MarsBaR analysis

There was no negative effect at the thresholds used above.

5.11.5. Drug effects on ACC RS component and MADRS mood rating scales

There were no regions that demonstrated significant correlation with baseline MADRS scores

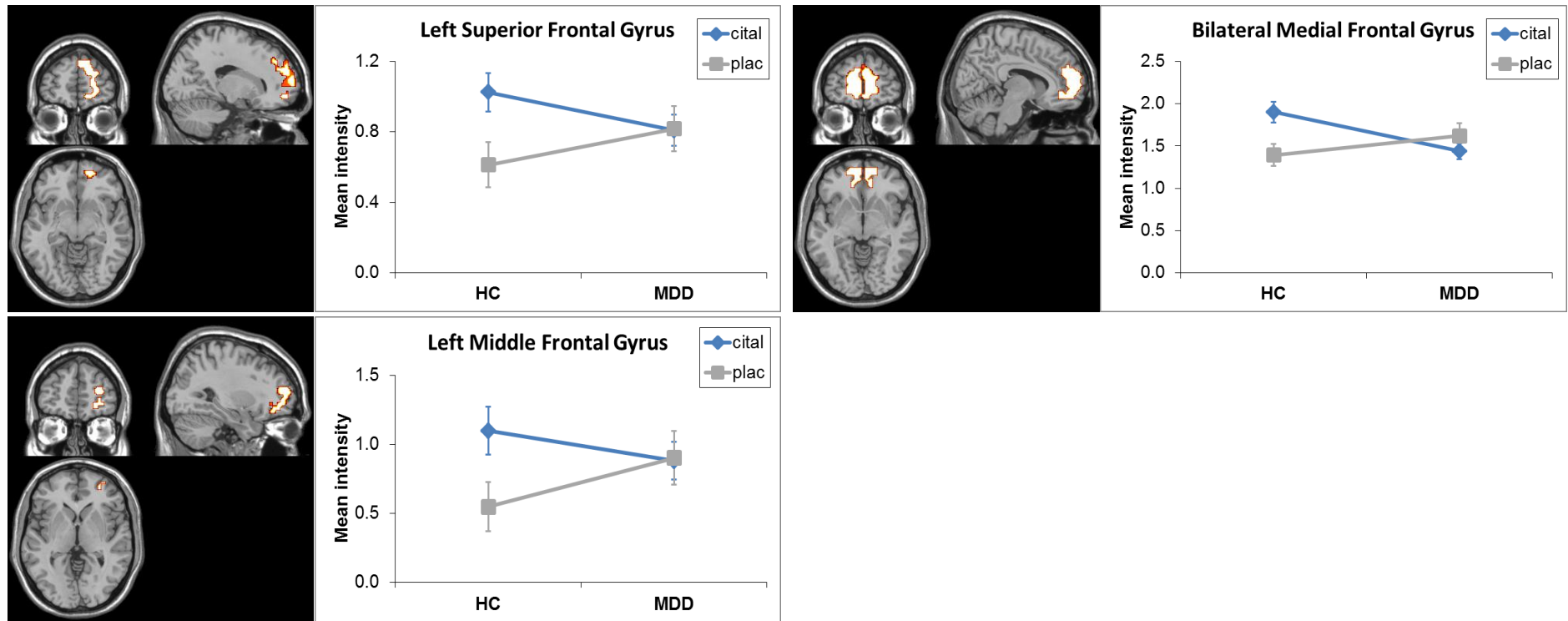
Table 27 Component 5 Positive ACC RS component regions that show drug, group, and drug x group interactions

Region	Side	Centre of mass			No of voxels	p						FDR	
		x	y	z		Positive Effect of Drug <i>cital>plac</i>	Positive Effect of Group <i>HC>cMDD</i>	Positive Interaction <i>HC(cital-plac)>MDD(cital-plac)</i>	Positive Effect of Drug <i>cital>plac</i>	Positive Effect of Group <i>HC>cMDD</i>	Positive Interaction <i>HC(cital-plac)>MDD(cital-plac)</i>		
Superior Frontal Gyrus	L	-17	55	16	143	0.043	ns	0.036	ns	ns	ns		
Medial Frontal Gyrus	B/L	0	52	10	386	ns	ns	0.004	ns	ns	ns		
Middle Frontal Gyrus	L	-28	48	0	74	<i>0.064</i>	ns	0.050	ns	ns	ns		
Posterior Cingulate	B/L	4	-40	36	116	ns	(0.048)	ns	ns	ns	ns		
Precuneus	B/L	1	-56	42	131	0.041	0.005	(0.025)	ns	ns	ns		
Paracentral Lobule	R	2	-42	57	53	0.022	0.050	ns	ns	ns	ns		
Thalamus	R	9	-10	11	24	(0.029)	<i>0.068</i>	ns	ns	ns	ns		
Temporal Lobe	L	-44	-17	-13	22	(0.015)	ns	ns	ns	ns	ns		
Superior Temporal Gyrus	L	-57	-24	7	54	(0.041)	ns	(0.018)	ns	ns	ns		
Middle Temporal Gyrus	R	45	-71	11	23	(0.039)	ns	ns	ns	ns	ns		
Caudate	L	-10	10	7	71	ns	(0.033)	ns	ns	ns	ns		
Caudate	R	11	10	8	70	ns	(0.047)	(0.033)	ns	ns	ns		
Lentiform Nucleus	L	-16	8	-3	28	0.027	ns	ns	ns	ns	ns		

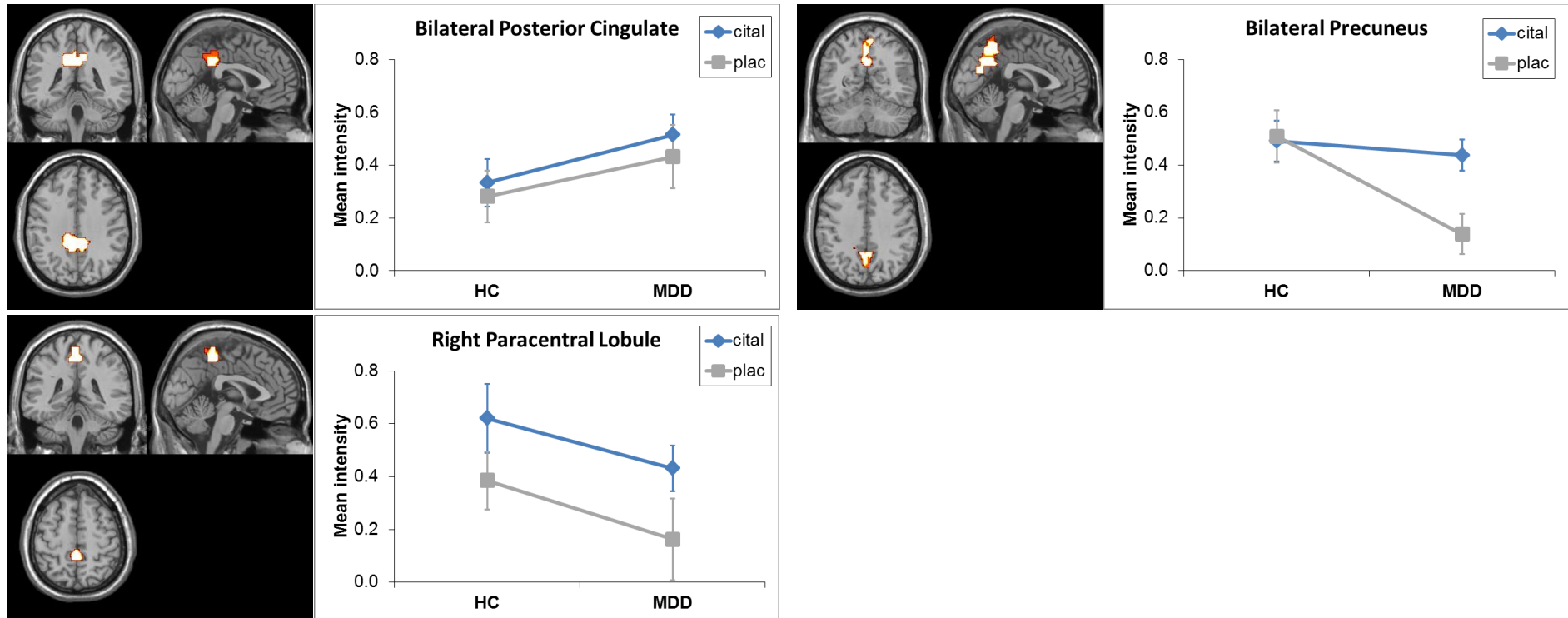
p -values in brackets represent significance in the opposite direction. ns = p-values > 0.1; B/L = bilateral; L = left; R = right; FDR = false discovery rate

Figure 17 Overlays & line graphs for regions of positive ACC RS component that show a significant difference of drug, group or drug x group interaction

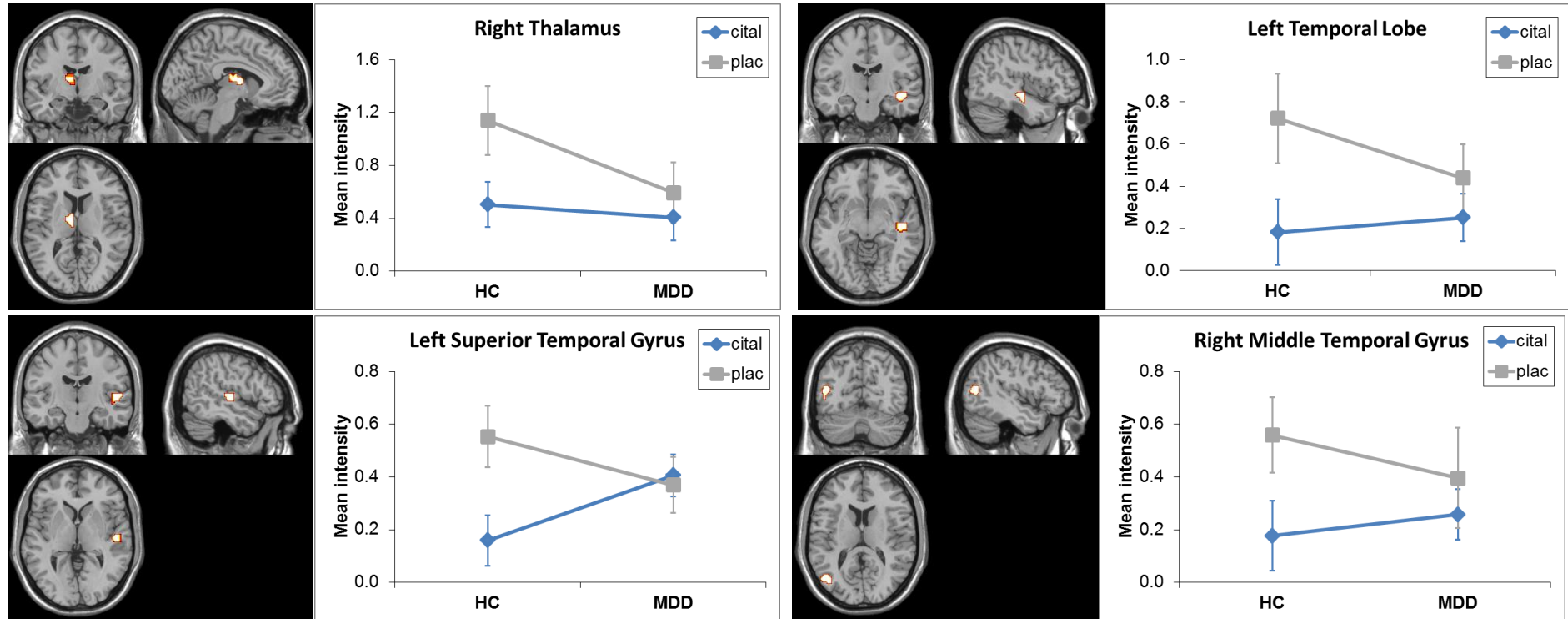
Differences in frontal cortical/anterior DMN structures



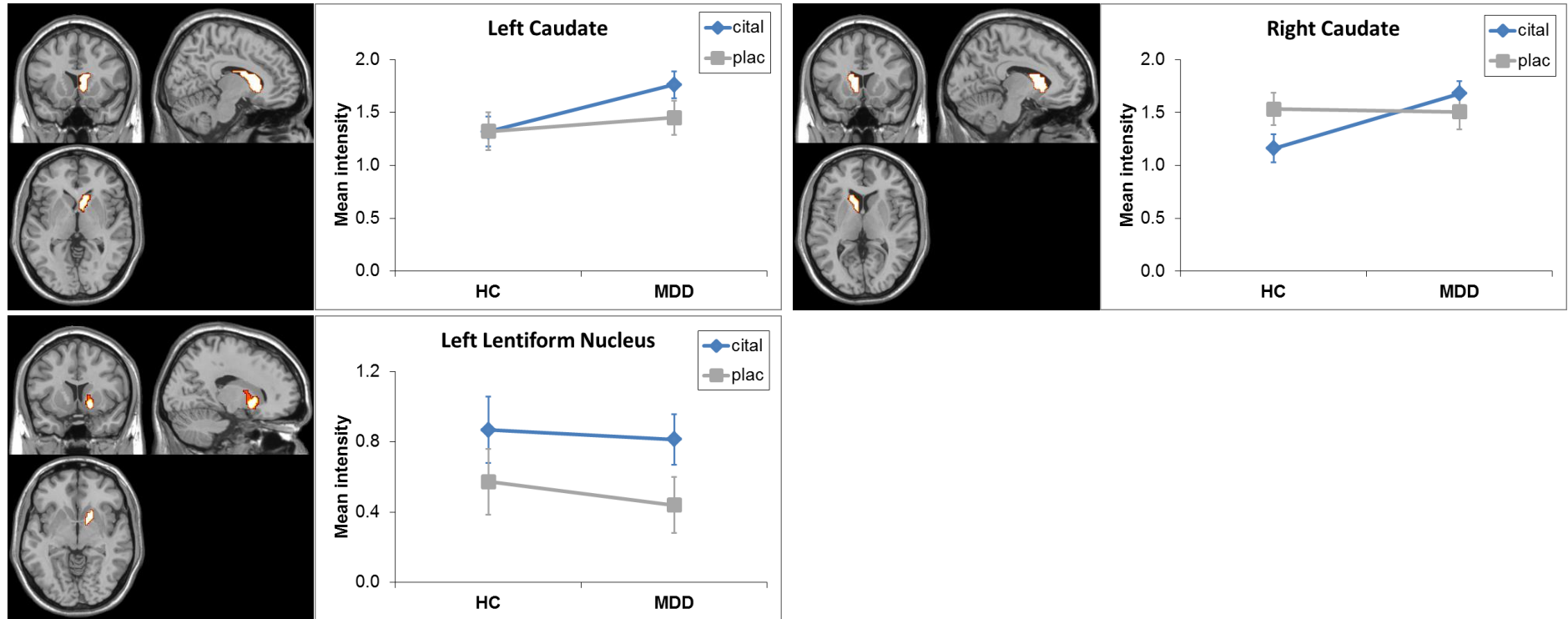
Differences in posterior DMN regions



Differences in temporal and lateral regions



Differences in basal ganglia regions



5.12. Discussion

5.12.1. Drug modulation of positive ACC RS component

Overview

Citalopram increased ACC RS in all frontal regions and posterior midline DMN components but decreased it in the thalamus and temporal cortical regions in HCs. Citalopram induced increases in ACC RS component were almost entirely confined to the HC group with minimal increases in the MDD, producing significant drug by group interactions. This suggests that MDD is associated with impaired 5-HT functioning in terms of its modulatory effect on ACC connectivity in the DMN. 5-HT appears to increase ACC RS intensity in the core DMN but to disengage correlated activity in temporal cortex and thalamus. The sole instance in which citalopram increased ACC RS component in cMDD was in the bilateral precuneus, in which citalopram restored a marked reduction of ACC RS to the levels seen in the HCs.

MDD was associated with increases in ACC RS in anterior frontal and posterior regions of the DMN as hypothesised. However, three adjacent areas of the DMN region showed different abnormalities. Posterior cingulate showed the predicted increase in ACC RS component in MDD but ACC RS intensity in the paracentral lobule and precuneus was decreased in MDD. Therefore the idea that the entire DMN is overactive in depression mediating rumination and self-absorption is probably an oversimplification.

Differences of drug and group in frontal cortical/anterior DMN structures

Positive interaction was noted in the left superior frontal gyrus, bilateral mFG and left MFG. This means citalopram produced a greater difference mean intensity of ACC RS component in HC than in cMDD. In all three regions there was no additional effect of citalopram over placebo in MDD, suggesting impaired 5-HT functioning in these regions in depression or more particularly in how 5-HT modulates connectivity with the ACC. MDD patients and their siblings have been observed to have increased fALFF compared to HC in the MFG (Liu et al., 2013a). Matthews et al. (2010) discovered that the response in the left MFG following administration of chronic escitalopram was affected by self-referential processing. In the current dataset neuropsychological tasks occurred prior to citalopram infusion and it may be that patients began to ruminate on these tasks during the resting state scan. In citalopram study 1 there was a similar reduction of mean intensity of ACC RS in the right mFG in cMDD. Similarly no effect of ketamine or AZD6765 was observed in cMDD when compared to placebo in the AZ study, supporting the findings of the current study.

In the SPM voxel-wise analysis, a positive interaction was noted in the left mFG highlighting that the mean intensity of ACC RS component difference between citalopram and placebo in HC was more than the same difference in cMDD. The origins of the positive interaction relate to the

difference in HC in the mFG. Gray matter deficits have been reported in the left mFG in first episode medication naïve MDD patients (Lai and Wu, 2014). In the current dataset whilst there is a normal response to citalopram in HC, there is no effect in cMDD suggesting an impaired responsivity of the 5-HT synapses in mFG.

There was also a positive effect of drug in the left superior frontal gyrus with citalopram increasing mean intensity of ACC RS component. The superior frontal gyrus has roles in working memory (du Boisgueheneuc et al., 2006), as a connecting node between the DMN and CEN and a role in the motor control of speech (Li et al., 2013b). Richieri et al. (2011) previously reported hypoperfusion in rCBF of the superior frontal gyrus bilaterally on SPET in MDD compared to HC. Interestingly rMDD patients had reduced gray matter volume in the superior frontal gyrus compared to controls and non-remitters (Li et al., 2010a). Citalopram therefore acts in both HC and cMDD in the same way as noted in citalopram study 1. AZD6765, however, increased mean intensity of ACC RS above placebo in MDD subjects, different to the current finding.

Differences of drug and group in posterior DMN structures

A negative interaction was noted in the left precuneus highlighting that the mean intensity of ACC RS component difference between citalopram and placebo in cMDD was more than the difference between treatments in HC. The origins of the negative interaction relate to the difference in cMDD. The precuneus is part of the posterior aspect of the DMN (Fransson and Marrelec, 2008). There is a specific effect of citalopram in the precuneus in the current dataset that maintained the mean intensity of ACC RS component. Greicius et al. (2007) reported increased FnC between the DMN and precuneus in medicated MDD. Other authors have reported converse findings of increased resting state FnC of the precuneus with a reduction following antidepressant administration (Li et al., 2013a). Decreased ReHo reflecting reduced neural activity has been noted in the left precuneus in medicated tr MDD (Wu et al., 2011). In the current dataset effects are noted only following the entire dosage being infused so there is no comparison to pre-treatment state. The current finding would support reports of increased response from a pre-treatment state in cMDD but not a reduction.

Differences of drug and group in thalamus, temporal and lateral regions

Citalopram maintained the mean intensity of the ACC RS component in the right thalamus producing a negative effect of drug. Bilateral thalamic volume reduction has been observed by Nugent et al. (2013) using MRI in medication free MDD compared to rMDD and HC. The right thalamus has been reported to have increased FnC with the DMN in MDD (Greicius et al., 2007). In addition increased CBF and glucose metabolism has been reported in the left medial thalamus in MDD (Drevets et al., 1992). This is similar to the current results where HC had increased mean intensity of ACC RS component in the right thalamus. The results from citalopram study 2 are different from citalopram study 1 where cMDD showed reduced mean intensity of ACC RS compared to HC.

A negative effect of drug was observed in the right middle temporal gyrus, where citalopram decreased mean intensity of ACC RS component more than placebo. The temporal cortex has been implicated in the regulation of emotional planning of events and transient periods of sadness in HC (Partiot et al., 1995, Beauregard et al., 1998). fALFF has also been observed to be reduced in the bilateral middle temporal gyrus in first episode treatment naïve MDD (Wang et al., 2012a). This is seen in the HC group in the current results with increased mean intensity of ACC RS component.

There is an effect of drug and of group on the mean intensity of the ACC RS component in the right paracentral lobule, meaning that both citalopram and placebo produced reductions. The paracentral lobule is in close proximity to the primary somatosensory cortex, precuneus and superior and IPL. Straube and Miltner (2011) suggested that somatosensory associated regions may be relevant to emotional processing related to body sensation. In the current results whilst citalopram increased mean intensity of ACC RS component in both groups there was a reduction in MDD compared to HC. This was evident even with placebo. Increased mean intensity of ACC RS component in this region in the current dataset following citalopram may be due to increased sensitivity to emotional perception of body sensation stimuli.

Differences of drug and group in basal ganglia structures

A negative effect of group, with cMDD participants having increased mean intensity of ACC RS component compared to HC, was noted in the left and right caudate. A negative interaction was also noted in the right caudate. In the current dataset the left caudate has little effect either due to group or drug while in the right there appear to be differences in HC but no difference in MDD. Reduced connectivity between precuneus/PCC and the bilateral caudate has been reported (Bluhm et al., 2009). The inference is that changes in DMN may have effects on the caudate. The nature and role of this is unclear.

There was a positive effect of drug in the left lentiform nucleus. Here citalopram increased mean intensity of ACC RS component regardless of group. In the lentiform nucleus citalopram appears to maintain the mean intensity of the ACC RS component in cMDD and HC while there is a decrease with placebo. The lentiform nucleus comprises the putamen and globus pallidus and is part of the basal ganglia. Animal models suggest that the globus pallidus is involved in incentive related behaviour and expectation of reward (Schultz et al., 1992, McAlonan et al., 1993). The putamen is proposed to have a number of functions. These include perception of contempt and disgust and may be part of the motor system activated in the context of hate (Phillips et al., 1998, Sprengelmeyer et al., 1998, Zeki and Romaya, 2008). Increased ALFF in the putamen in medicated MDD has been reported by Guo et al. (2012b). Jing et al. (2013) also reported increased fALFF and ALFF in the right putamen in MDD. In the current results mean intensity of ACC RS component was reduced in MDD compared to HC which increased with citalopram therefore is compatible with Guo et al. (2012b). AZD6765 showed similar effects on the lentiform nucleus on day 2 increasing mean intensity of ACC RS above placebo.

Differences of drug and group in other regions

On SPM voxel-wise analysis mean intensity of ACC RS component was increased in the cMDD group compared to the HC group in the right PHG. The PHG is known to have important functions in memory and emotional regulation (Manns et al., 2003). Bluhm et al. (2009) reported increased posterior DMN (precuneus and PCC) connectivity with the PHG bilaterally in early MDD. The co-ordinates reported were more anterior than reported here. Metabolic changes in a PET study, post open label i.v. ketamine, revealed an inverse correlation between MADRS scores and metabolic changes in the right PHG (Carlson et al., 2013). Glucose hypermetabolism has previously been reported in the right PHG in untreated MDD (Aihara et al., 2007). In the current results HC responded differently whether they received citalopram or not compared to cMDD. This is contrary with the findings of increased metabolism and FnC changes before treatment and after ketamine.

A positive interaction was noted in the left brainstem. The brainstem is the source of many neurotransmitters affected in MDD. The structures involved include the raphe nuclei and locus coeruleus (Lin et al., 2011). Effects in MDD and of antidepressant drugs should be expected in these regions as has been reported in animal models (West et al., 2009). There are a number of studies which have reported reduced brainstem size in MDD especially in the raphe nuclei (Shah et al., 1992, Lee et al., 2011, Soriano-Mas et al., 2011). The raphe nuclei have been known to have a role in inhibition of behavioural activity in animal models (Eagle et al., 2009). The locus coeruleus provides stimulatory noradrenaline input to the paraventricular nucleus leading to activation of the HPA axis and secretion of cortisol (Song et al., 2014). The locus coeruleus via its projections has roles in arousal, attention, memory and response to stress (Benarroch, 2009). In the current dataset the increased mean intensity of ACC RS component in cMDD after acute citalopram in the brainstem may relate to an initial activating effect of citalopram.

5.13. Conclusions

DMN regions In hypothesis i) it was predicted that acute i.v. citalopram would increase the mean intensity of ACC RS component in cMDD > HC, citalopram increased ACC RS in all frontal regions and midline posterior midline DMN components in HC but decreased in the thalamus and temporal cortical regions. Citalopram did not reverse increased DMN activity as predicted in hypothesis ii. The SPM voxel-wise analysis demonstrated that negative interaction was due to effects in the precuneus in cMDD where no effects were observed in controls but citalopram maintained the mean intensity of the ACC RS component.

An opposite effect was seen in the left mFG. The positive interaction was driven by effects in the left mFG in HC where citalopram increased mean intensity of the ACC RS component. This effect was not observed in cMDD suggesting impaired responsivity of the 5-HT synapses in the mFG.

SN/CEN No effects were seen in the SN or CEN that demonstrated a reversal of decreased ACC RS activity.

Other regions Although citalopram did maintain the mean intensity of the ACC RS component in the left lentiform nucleus in cMDD, there was no interaction. Therefore citalopram did acutely increase the mean intensity of the ACC RS component in cMDD as predicted in hypothesis iii but this occurred in HCs as well.

No effects were observed in the insula or IPL. It was predicted in hypothesis ii) that citalopram would increase mean intensity of the ACC RS component in cMDD in the insula and IPL. Regions where citalopram had the same effect in MDD as placebo tended to be midline structures which it could be argued are linked to DMN abnormalities.

MADRS scores No regions demonstrated significant correlation with baseline MADRS scores. Therefore ACC-DMN RS activity following acute i.v. citalopram is not related to severity. It has been predicted that MADRS scores would correlate with mean intensity of ACC RS component in regions of the DMN. However it is important to note that this was a mechanistic trial rather a trial to examine response to treatment.

5.14. Limitations and future studies

As with citalopram study 1 the limitations of the study include lack of functional imaging prior to citalopram administration. Furthermore no filtering was applied to the dataset to compensate for the physiological noise produced by cardiac or respiratory cycles; however this should have been filtered out by the spatial ICA. Sample size was also small.

Further examination of the effects of acute and chronic citalopram administration on MDD patients should be considered in conjunction with neuropsychological tests examining reward, rumination and mood.

Chapter Six: General discussion

6.1. Overview

MDD is a common and debilitating illness which has been recognised for two thousand years, yet our understanding of the pathophysiology remains poor. MDD has a huge impact in terms of suicide, disability, treatment costs and indirect effects on the wider economy. Treatment resistance remains a significant problem (Mulrow et al., 2000). Despite 70 years of research since the first discoveries about the action of antidepressants on monoamines, conclusive evidence that MDD involves abnormal monoamine function that is corrected by antidepressants has been lacking. Perhaps the most certain finding is that SSRIs correct MDD in the short term by increasing synaptic 5-HT availability. Recent evidence points to glutamate abnormalities in MDD and this evidence was systematically reviewed in Chapter 3. At a neural systems level, again conclusive evidence is lacking that a particular system is consistently under or overactive or underdeveloped or damaged in MDD. This may reflect the possibility that MDD may have many different routes of pathogenesis. There is evidence that particular functional systems mediating reward, emotion processing, autonomic responses, attention and executive control are dysfunctional in MDD. Functional systems can be identified in the patterns of correlated activity across different brain regions in the resting state when the brain is not engaged by external cognitive demands. This is currently producing a large literature which is reviewed in chapter 2. The experimental part of the thesis investigated whether the putative glutamatergic antidepressant drugs ketamine and AZD6765 had similar effects on RS networks and whether these effects were similar to those of the established antidepressant citalopram using data from previous pHMRI studies in Manchester.

The status of glutamate in MDD

Clinically, a single intravenous infusion of ketamine has alleviated depressive symptoms in patients within hours of administration (Berman et al., 2000, Zarate et al., 2006a). This effect can last for up to 14 days. There are now 45 trials of ketamine that demonstrate improvements in mood, with repeated infusions producing continued recovery (see Chapter 3). Intranasal and intramuscular forms of ketamine have also provided comparable response in MDD symptoms to i.v. administration. Other modulators of glutamate release have shown promise as antidepressants including riluzole, traxoprodil, GLYX-13, MK-0657 and AZD6765 (lanicemine). One limitation is that although there is an antidepressant effect of glutamate based drugs the mechanism has not been fully elicited. A further difficulty in interpreting trial evidence is the lack of suitable placebo control for the psychotomimetic effects of ketamine following i.v. administration. Although there is unequivocal evidence for some glutamate based antidepressant effects, this has not been observed to occur as rapidly as with ketamine.

Post mortem studies have reported reduced astrocytes, which remove glutamate from the synaptic cleft, in MDD (Rajkowska and Stockmeier, 2013, Sanacora and Banasr, 2013). In addition post-mortem studies have revealed reductions in ionotropic and metabotropic glutamate

receptors in hippocampal and PFC regions in MDD (Law and Deakin, 2001, Beneyto et al., 2007, Feyissa et al., 2009, Karolewicz et al., 2009a). The effects of SSRI antidepressants have also been linked to alterations in NMDA function in animal models (Ampuero et al., 2010). These changes, however, have not been linked to changes in glutamate when investigated using [^1H] MRS in humans (Taylor et al., 2010, Taylor et al., 2012). At commonly available 3T field strengths, it is difficult to separate glutamate and glutamine peaks and the combined peak called Glx to be used. This may be one factor why no differences using [^1H] MRS have been reported. It is therefore unclear whether glutamate antagonists correct abnormal glutamate function in MDD. A further limitation is the lack of reliable biomarkers of glutamate function in MDD.

The mechanism of ketamine appears to be in part through glutamate release onto non-NMDA receptors including AMPA and metabotropic receptors (Maeng et al., 2008). Riluzole may also increase synaptic AMPA expression (Du et al., 2007). The psychotomimetic effects of ketamine are also reduced by lamotrigine suggesting an interaction with non-NMDA receptors (Anand et al., 2000, Deakin et al., 2008). MDD involves decreased AMPA signalling due to reduced glutamate release which corrected by NMDA ion channel receptor blockers causing disinhibition of glutamate release. The hypothesis predicts that novel NMDA antagonists should share antidepressant effects with ketamine and act on similar systems in the brain which overlap with the actions on RSNs.

Resting state networks in MDD and antidepressant effects

RSN research in MDD but has largely focussed on the DMN rather than the SN, AN or CEN. RSN networks are significant in their correlation to psychiatric and MDD psychopathology. A number of different methodologies each with their own limitations have been used to examine networks of neural activity that may be related to clinical presentation. These methods examine either intensity (e.g. ReHo, ALFF, fALFF) or connectivity (e.g. FnC, ICA). ICA used in this thesis was chosen because of the model-free data driven approach that can not only give an idea of correlated network structures, but in combination with regional MarsBaR analysis, an idea of the functional alteration produced within that structure. FnC does not identify the region that is dysfunctional. The thesis method combines elements of FnC and investigation of individual brain structures as part of a RSN, therefore offering the strengths of both measures.

Reduced ALFF, fALFF and FnC of the ACC and insula was reported in unmedicated cMDD with increased ALFF, fALFF and FnC noted in medicated cMDD compared to HC. Findings in the dlPFC, mPFC and CEN were not consistent. There was increased ALFF, fALFF and FnC of the precuneus, caudate and IPL in unmedicated cMDD which reduced following antidepressant treatment. These conclusions suggest overactivity of the DMN and underactivity of the SN which could be corrected by antidepressant treatment. Trials of antidepressants on resting state network appear to support a reduction in FnC of the DMN. Varying conventional antidepressants have been used with limited repetition of studies which is a limitation of the evidence. However, the same reduction in FnC observed with conventional antidepressants is also seen with i.v.

administration of ketamine, but trials have only been in healthy volunteers. DMN connectivity of dmPFC, rACC, mPFC and PCC was reduced 24 hours after *i.v.* infusion of S-ketamine. S-ketamine was also shown to reduce FnC between the vACC and dmPFC. There have been no investigations of the effects of ketamine on RSN in MDD. There is limited evidence that investigated the effects of rMDD on RSN to draw conclusions. There were no studies of the effect of acute antidepressant drug treatment on RSN in MDD. This meant that predictions regarding the effects of citalopram in the experiments in this thesis were made on the basis of chronic antidepressant treatment reports. The expectation was that AZD6765 and ketamine would acutely affect the DMN and SN in MDD correlated to mood improvement and that a similar response would be seen with acute citalopram infusion.

6.2. Summary of findings

There are no trials examining the effects of acute administration of antidepressants on resting state networks. The experiments in this thesis therefore focussed on the acute effects of *i.v.* citalopram and AZD6765 on MDD populations using the mean intensity of the ACC RS component through ICA, SPM voxel-wise analysis and regional MarsBaR analysis.

Comparison of selected components demonstrating ACC RS activity

Both components 5 and 10 were spatially similar in that they contain regions of the ACC, caudate, insula, superior, inferior, middle and medial frontal gyri, superior, inferior and middle temporal gyri, inferior parietal lobule, superior occipital gyrus, PCC, precuneus, basal ganglia and thalamus.

AZD6765 study

The AZ study compared AZD6765, ketamine and placebo in cMDD and HC immediately after infusion and 24 hours later. The two drugs have very similar pharmacological actions in blocking the ion channel gated by the NMDA glutamate receptor. The Manchester group had previously shown the drugs had similar effects in increasing BOLD signal in anterior cingulate cortex (Downey D. et al., In press). The present analysis investigated whether they had similar or distinct effects on RS networks. Several RSN studies had previously reported increased ACC RS activity in medicated cMDD compared to HC. The ACC was believed to be a central hub for alteration in RS activity. Furthermore there had been numerous trials reported prolonged effects of ketamine and AZD6765 correlated to improvement in mood rating scales. The hypothesis was that ketamine and AZD6765 acting through a similar mechanism would reduce ACC RS component in DMN structures such as precuneus and mPFC that are associated with rumination, and increasing it in SN components such as the insula associated with attention and switching to CEN. The effects of both drugs would be prolonged and correlate with MADRS scores. Based on the hypotheses, the predictions were i) AZD6765 and ketamine compared with saline placebo will a) increase the mean intensity of ACC RS component in SN structures (ACC and insula) and

CEN (superior frontal cortex, IPL) and b) reduce mean intensity of ACC RS in DMN structures (precuneus and mPFC) ii) the effects of AZD6765 and ketamine on day 1 should persist in the day 2 RS data 24 hours after infusion and iii) improvement in MADRS mood rating scores in drug-treated groups would positively correlate with mean intensity of ACC RS component in the ACC and insula (SN) and negatively with the precuneus (DMN) .

On day 1 AZD6765 significantly increased mean intensity of ACC RS component in the right insula, right IPL and left cingulate gyrus greater than ketamine or placebo. There was significantly decreased mean intensity of ACC RS component in the left insula in the AZD6765 group compared to placebo. Ketamine increased mean intensity of ACC RS component greater than AZD6765 in the right lentiform nucleus and left mFG. On day 2 AZD6765 reduced mean intensity of ACC RS component in the left and right MFG compared to ketamine. AZD6765 increased mean intensity of ACC RS component greater than ketamine and placebo in the left and right lentiform nuclei. There were very few effects of ketamine that correlated with 4 hour improvement in MADRS scores, and no correlation with 24 hour improvement. There was no correlation with MADRS score improvement for AZD6765 for either day. The rapid effects of AZD6765 might therefore be due to resetting of the interface between DMN and salience networks via the ACC and IPL but were not correlated to MADRS score improvement. Downey D. et al. (In press) reported an increased BOLD response in the ACC. The resting state analysis of AZD6765 examined the ACC correlated network and therefore is somewhat different. It is also important to note that the last 25 minutes of the pHMRI dataset was analysed whereas Downey et al. used the entire dataset. When Downey et al. examined the entire dataset there was some decline in response in later time bins which might explain the limited effects seen in the current analysis.

Citalopram studies

Following on from the AZ study it was useful to compare the effects of glutamate based antidepressants on RS activity with a conventional antidepressant. The previous RS literature had suggested that chronic antidepressant treatment reduced FnC and increased ALFF/fALFF in the ACC RS. It was also demonstrated that both ketamine and AZD6765 increased mean intensity of ACC resting component in the insula, IPL and lentiform nuclei. It was therefore hypothesised that the DMN is dysfunctional in MDD and switching via the ACC and IPL might correlate with MADRS scores. Antidepressant response had been linked to ACC activity and therefore correlated activity might produce a common effect in RSN as part of the onset of antidepressant action. The predictions were: i) acute i.v. citalopram would increase the mean intensity of ACC RS component in cMDD > HC > rMDD ii) citalopram would reverse increased DMN and decreased SN and CEN activity in MDD iii) acute i.v. citalopram would increase the mean intensity of the ACC RS component in cMDD in the insula, IPL and lentiform nuclei and iv) MADRS scores would correlate with mean intensity of ACC RS component in regions of the DMN including precuneus/PCC, mPFC and ACC.

There were two citalopram studies. Citalopram study 1 compared cMDD, rMDD and HC. All received citalopram. rMDD had increased mean intensity of ACC RS component in the PCC compared to cMDD on SPM voxel-wise analysis. Reduced mean intensity of ACC RS component was noted in the right PCC, left PHG and insula in cMDD compared to HC on SPM voxel-wise analysis. Acute i.v. citalopram produced reductions in these regions which form part of the DMN and SN. Increased mean intensity of ACC RS component in cMDD, compared to HC and rMDD, was noted in bilateral posterior cingulate and left inferior frontal gyrus on regional MaRSBaR analysis.

The right medial frontal gyrus was the only region where trait abnormality was identified. Regions with state abnormalities were the left inferior frontal gyrus, bilateral posterior cingulate, right cuneus and right thalamus. rMDD had reduced mean intensity of ACC RS component in DMN regions including ACC and precuneus compared to HC. Reduced mean intensity of ACC RS component in cMDD, compared to HC and rMDD, was observed in the right thalamus, IPL and left parietal lobe. Effects in the right IPL were opposite to those seen with AZD6765, with a decrease in mean intensity of ACC RS component following i.v. citalopram. There was no correlation of any regions with MADRS scores. The lack of a true control group makes it difficult to make inferences based on these results. However there were reductions in mean intensity in regions of the posterior DMN and salience network on SPM voxel-wise analysis following i.v. citalopram. Previous responders to medication might therefore be predicted by the initial response in the ACC and precuneus.

Citalopram study 2 compared i.v citalopram with placebo in cMDD and HC. The predictions were: i) citalopram would increase the mean intensity of ACC RS component in cMDD > HC, ii) citalopram would reverse increased DMN and decreased SN and CEN activity in MDD, iii) citalopram would increase the mean intensity of the ACC RS component in cMDD in the insula, IPL and lentiform nuclei and iv) MADRS scores will correlate with mean intensity of ACC RS component in regions of the DMN including precuneus/PCC, mPFC and ACC..

SPM voxel-wise analysis demonstrated that negative interaction was due to effects in the precuneus in cMDD where no effects were observed in controls but citalopram maintained the mean intensity of the ACC RS component. The positive interaction was driven by effects in the left mFG in HC where citalopram increased mean intensity of the ACC RS component. On regional MaRSBaR analysis, positive drug x group interaction was noted in the left superior frontal gyrus, bilateral mFG and left MFG. Negative drug x group interaction was noted in the bilateral precuneus, left superior temporal gyrus and right caudate. Although citalopram did maintain the mean intensity of the ACC RS component in the left lentiform nucleus in cMDD, there was no interaction. In the right middle temporal gyrus, left temporal lobe and right thalamus while citalopram increased mean intensity of the ACC RS component in HC, this effect was not observed in cMDD. No effects were observed in the insula or IPL as predicted. No regions demonstrated significant correlation with baseline MADRS scores.

The acute effects of i.v. citalopram may therefore be due to effects on regions of the DMN. Acute citalopram restores the precuneus component of the ACC-precuneus resting state network in MDD, suggesting reduced 5-HT function may mediate this abnormality. Citalopram increases the medial prefrontal component of ACC RS in controls, but not in depressed patients. MDD may involve an impaired sensitivity to 5-HT modulation of medial prefrontal control of the ACC in resting state networks

6.3. Possible abnormal resting state networks in MDD

Significant RSN regions affected by citalopram, AZD6765 or ketamine in the resting state experiments will be examined in the context of commonality between drug effects, and consideration as possible networks to investigate in the future. The graphical results from MarsBaR analysis are summarised in Figure 18 below.

6.3.1. Frontal cortical network – Medial and superior frontal gyri

Medial frontal gyrus

In the AZ study, ketamine increased mean intensity of ACC RS component greater than AZD6765 in the left mFG on day 1 of the AZ study. In citalopram study 1, mean intensity of ACC RS component was increased in HC compared to rMDD and cMDD in the right mFG. This represented a trait abnormality in response to citalopram infusion. In citalopram study 2, positive drug x group interaction was noted in the left mFG on SPM voxel-wise analysis and bilaterally on regional MarsBaR analysis. There was no effect of citalopram in cMDD suggesting a 5-HT abnormality.

From the review of resting state networks (Chapter 2)(Dutta et al., 2014) changes in ALFF in the mFG/ACC were reported as both increased and decreased. Increased BOLD response of the mFG and ACC has been linked to aspirational thinking in MDD and memory retrieval tasks (Johnson et al., 2009, Werner et al., 2009). Gray matter deficits have been reported in the left mFG in first episode medication naïve MDD patients (Lai and Wu, 2014). Prior to symptom onset decreased metabolism in the right mFG compared to controls on PET imaging has been reported (Kumano et al., 2007). Given the trait abnormalities noted in citalopram study 1 this region requires further investigation. The effects in the mFG may be related to acute drug effects and episodes of MDD may produce trait vulnerability due to cognitive dysfunction.

Superior frontal gyrus

On day 2 of the AZ study, AZD6765 reduced mean intensity of ACC RS component greater than placebo in the right superior frontal gyrus while the opposite effect was seen in the left superior frontal gyrus on day 2. In citalopram study 1, HC had increased mean intensity of ACC RS component in the left superior frontal gyrus compared to cMDD. In citalopram study 2 there was a

positive drug x group interaction in the left superior frontal gyrus in addition to a positive effect of drug, on regional MarsBaR analysis there was no effect of citalopram in cMDD.

The superior frontal gyrus has a role as a connecting node between the DMN and CEN (Li et al., 2013b). Ketamine and citalopram infusions in healthy volunteers have produced increased BOLD signal in the superior frontal gyrus (McKie et al., 2005, Deakin et al., 2008). Richieri et al. (2011) previously reported hypoperfusion in rCBF of the superior frontal gyrus bilaterally in MDD. From the review of resting state networks (Chapter 2)(Dutta et al., 2014) increased FnC has also been reported between the PCC/precuneus and superior frontal gyrus in unmedicated MDD. Antidepressant medication therefore reduces the response of the superior frontal gyrus in MDD compared to HC and may be a region involved in the prolonged antidepressant action of drugs like AZD6765 through modulation of the DMN.

6.3.2. Posterior DMN – Precuneus and inferior parietal lobule

Precuneus

In the negative ACC RS component in the AZ study day 2 a further reduction in mean intensity of ACC RS component was observed in the AZD6765 treatment group compared to placebo. This effect was not observed with ketamine. The mean intensity of ACC RS component in the precuneus was increased in HC compared to rMDD in citalopram study 1. Although the mean intensity of ACC RS component in cMDD was also increased this was not significant when compared to rMDD. In citalopram study 2, a significant drug x group interaction was observed in the bilateral precuneus where citalopram was found to normalise the reduced mean intensity of ACC RS component in cMDD back to the level observed in HC both with and without citalopram.

The findings in the precuneus are probably the most noteworthy of all the results from the citalopram study. There was a clear group x treatment interaction where the reduced mean intensity of ACC RS component observed in cMDD under placebo was normalised to HC levels under citalopram. These effects were not seen with ketamine which questions whether rapid antidepressant effects involve the precuneus at all. An effect of AZD6765 on day 2, however, may suggest the similar effects occur with citalopram and AZD6765 but on a different time scale. As part of the posterior DMN, the precuneus has a central role in rumination (Fransson and Marrelec, 2008, van Buuren et al., 2010). Reductions in gray matter density and ALFF have previously been reported in relation to rMDD as have correlations with disease duration and severity (Salvadore et al., 2011, Jing et al., 2013). The findings in the bilateral precuneus are therefore in accordance with the literature. Changes in FnC both before and after treatment have also been reported (Li et al., 2013a, Liu et al., 2013a). Increased FnC between the precuneus and the DMN normalised following treatment (Li et al., 2013a, Greicius et al., 2007). Clearly there is a role for the precuneus in MDD and further work could examine the ruminative response following drug infusion in conjunction with fMRI.

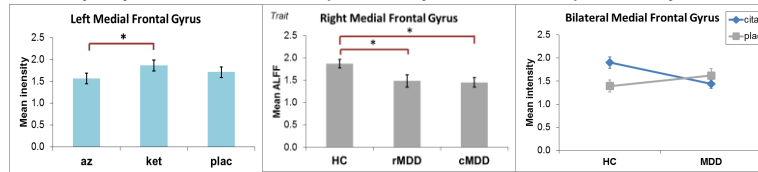
Figure 18 Summary MarsBaR analysis results of possible abnormal RSNs in MDD

Medial frontal gyrus

AZ study day 1

Citalopram study 1

Citalopram study 2

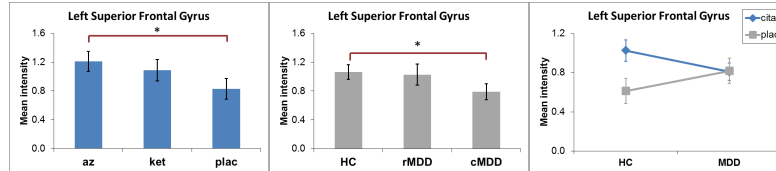


Superior Frontal Gyrus

AZ study day 2

Citalopram study 1

Citalopram study 2



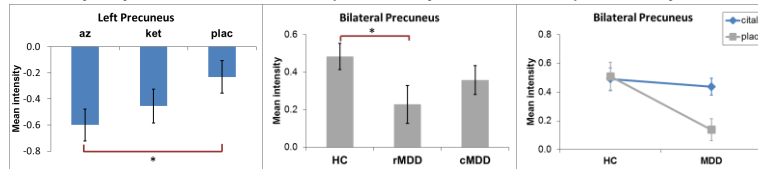
Frontal cortical network

Precuneus

AZ study day 2

Citalopram study 1

Citalopram study 2



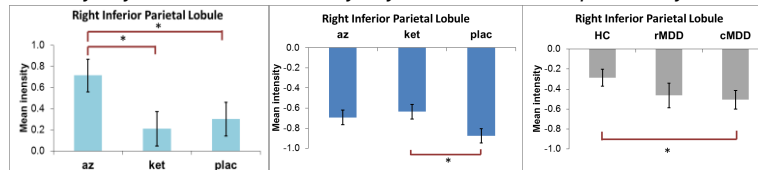
Posterior default mode network

Inferior Parietal Lobule

AZ study day 1

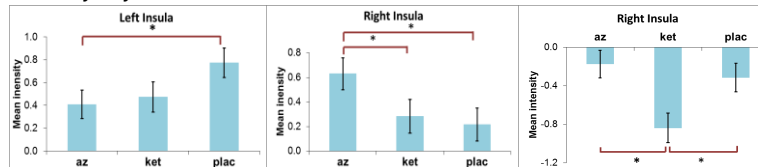
AZ study day 2

Citalopram study 1



Insula

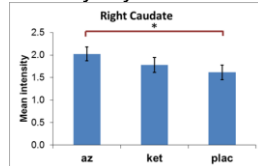
AZ study day 1



Salience network

Caudate

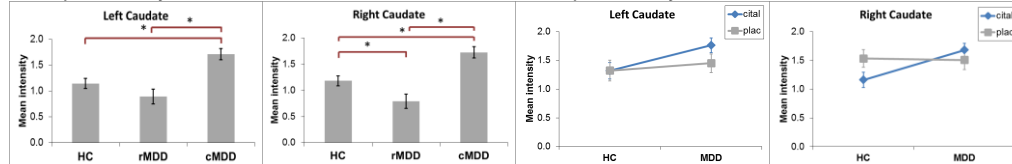
AZ study day 2



Basal ganglia network

Citalopram study 1

Citalopram study 2

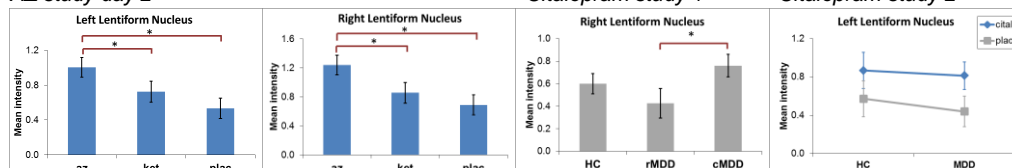


Lentiform nucleus

AZ study day 2

Citalopram study 1

Citalopram study 2



Inferior parietal lobule

AZD6765 increased mean intensity of ACC RS component greater than ketamine or placebo during acute administration. This acute effect was not observed 24 hours after infusion. In citalopram study 1 there was reduced mean intensity of ACC RS component in cMDD compared to rMDD and HC when examining the negative ACC RS component for the right IPL.

The IPL region has been proposed as a switching region between networks (Daniels et al., 2010). Decreased FnC has been noted between the IPL and a number of other structures including the cerebellum and vACC (Guo et al., 2013b, Zhou et al., 2010). Furthermore, Zhu et al. (2012) reported that decreased FnC of the posterior DMN and IPL correlated with autobiographical memory performance. Increased ALFF has also been reported (Daniels et al., 2010, Wang et al., 2012a). It may be that AZD6765 causes a level of dissociative experience which produces these effects. Decreased response of the IPL has been reported following antidepressant treatment when examined emotional processing tasks and fMRI in MDD (Delaveau et al., 2011). Moreover gray matter increase has been discovered in rMDD patients compared to cMDD and HC suggesting that this region returns to normal function on recovery from MDD (Salvadore et al., 2011).

6.3.3. Salience Network - Insula

AZD6765 produced significantly increased mean intensity of ACC RS component compared to ketamine and placebo on day 1 of the AZ study in the right insula. Conversely in the left insula there was significantly reduced mean intensity of ACC RS component compared to placebo. In citalopram study 1, there was an effect of HC having increased mean intensity of ACC RS component in the left insula. Recent PET ligand studies have revealed reduced 5-HT₂ receptor distribution and increased binding potential of the 5-HT transporter in the insula in unmedicated MDD (Biver et al., 1997, Cannon et al., 2007). It is therefore postulated that acute effects of AZD6765 may rely on increased 5-HT₂ binding. The opposite effects in the insula may be due to the lateralization of emotional processing. The right insula has been implicated in hunger, survival, negative affect and avoidance whilst the left insula has been implicated in aspects of safety and positive affect (Duerden et al., 2013)

The insula is an important structure in MDD as it has a number of potential functions ranging from emotional awareness to risk anticipation and physiological awareness (Craig, 2009). The insula also functions as part of the salience network in addition to the ACC (Seeley et al., 2007, Elton and Gao, 2014). Insula volume may predict treatment response in MDD (Chen et al., 2007). Decreased ReHo is noted in MDD patients and their first degree relatives in the right insula (Liu et al., 2010). Additionally MDD symptom clusters have also been positively correlated to ReHo in the insula (Yao et al., 2009). Chronic treatment with antidepressants appears to decrease metabolism in the insula (Kennedy et al., 2001). The right anterior insula was reported to have reduced FnC within the salience network and was postulated as a region modulating switching

between the DMN and CEN in MDD (Manoliu et al., 2013, Sridharan et al., 2008). Acute AZD6765 may therefore have effects in resetting the switching between the DMN, CEN and salience network.

6.3.4. Basal ganglia network – caudate and lentiform nuclei

Caudate

In the AZ study increases in mean intensity of ACC RS component were only noted for AZD6765 compared to placebo on day 2 and in the right caudate only. These were not observed when comparing ketamine to placebo on day 2. The caudate was observed to have increased mean intensity of ACC RS component on voxel-wise analysis in the cMDD group compared to HC in citalopram study 1. Using MarsBaR regional analysis, citalopram caused an increase in mean intensity of ACC RS component in cMDD but a reduction in rMDD compared to HC. As all groups in this study were administered citalopram it is difficult to decipher if this is a true effect of drug or group. However, a significant drug x group interaction was observed in citalopram study 2 in the left caudate. This interaction was driven by citalopram increasing the mean intensity of ACC RS component compared to placebo to a greater extent in MDD than HC. In HC placebo had the same effect as citalopram.

In the current studies, effects in the caudate are more evident in the citalopram rather than the AZ studies. Therefore although the caudate has been put forward as a trait marker of vulnerability to MDD it appears only as a marker of an acute episode in the current results (Norbury et al., 2010). There has been reports of both volume reduction bilaterally in one meta-analysis of MDD patients (Arnone et al., 2012a). Furthermore decreased metabolism and CBF has also been reported in the caudate in primary unmedicated MDD (Drevets, 2000). Decreased connectivity between the precuneus and the caudate bilaterally has been suggested to reflect problems with reward processing networks possibly explaining symptoms of reduced motivation and anhedonia (Bluhm et al., 2009). The exact mechanism behind this however is not clear. Given the effects of 5-HT_{2C} agonists on increasing BOLD signal in the caudate in healthy volunteers, the mechanism seen following acute citalopram infusion is also likely to involve 5-HT (Anderson et al., 2002), especially given high 5-HT selectivity of citalopram and mechanism preventing reuptake via the 5-HT transporter (Hyttel, 1994). Further FnC analysis may help to elucidate the role of the caudate in MDD.

Lentiform Nucleus

Significantly increased mean intensity of ACC RS component was reported on day 2 for AZD6765 compared to ketamine and placebo. The effect was bilateral and driven by the effects 24 hours after infusion rather than the acute effects. Significant increase in mean intensity of ACC RS component was observed for cMDD compared to rMDD in citalopram study 1 but only in

the right lentiform nucleus. In citalopram study 2, citalopram normalised the mean intensity of ACC RS component in the left lentiform nucleus in MDD but placebo led to a reduction.

The effects in the lentiform nucleus are most noticeable on day 2 of the AZ study. Part of the difficulty in interpretation of these results is that the lentiform nucleus comprises two functionally independent structures; the globus pallidus and the putamen. Placebo, however, caused a reduction in mean intensity of ACC RS component in both AZ and citalopram studies. Reduced cerebral blood flow in the lentiform nucleus has been correlated with increasing severity of MDD symptoms on SPET (Perico et al., 2005). ALFF and fALFF have been reported to be increased in the putamen in medicated MDD (Guo et al., 2012b, Jing et al., 2013). Decreased ReHo and BOLD signal have also been reported in the lentiform nucleus (Zhang et al., 2013b, Yao et al., 2009). This suggests an involvement of the basal ganglia in MDD and therefore the dopamine system in the extended actions of AZD6765 and possibly citalopram.

6.4. Conclusions on the effect of antidepressants on resting state networks

A systematic review of a rapidly expanding literature concluded that MDD is probably associated with increased DMN and decreased SN and CEN intensity and connectivity despite the wide range of methods used and their lack of standardization, the prevalence of small single centre studies, the lack of definition of the networks and a general lack of replication using the same methods. Antidepressant drugs have been reported to reverse some of the abnormalities. Very few studies have investigated the effect of acute antidepressant administration on RS networks to understand their mechanism of action and as possible biomarkers of efficacy.

A systematic review of novel rapid acting antidepressant drugs based on glutamate found 45 studies reporting acute but transient effects of i.v. ketamine. The subjective effects of ketamine make blind comparison with placebo almost impossible. However, the effects are compatible – animal behavioural studies and MRS evidence both demonstrate glutamate abnormalities in MDD. Meta-analytic studies suggest the ACC may be a focus of antidepressant action. Independent component analysis identified RS networks focussed on the ACC in 2 independent data sets. The key conclusions were:

- i) Acute infusions of AZD6765 have more potent effects than ketamine at the doses used on the intensity of ACC RS
- ii) At the dose tested novel putative antidepressant AZD6765 had more effects on ACC RS than ketamine.
- iii) Trait abnormalities were present in regions of the mFG and precuneus suggesting DMN abnormalities were present.
- iv) Citalopram prevented the reduction observed with placebo in mean intensity of ACC RS component in the precuneus in MDD.

- v) There was no difference in effect in cMDD in the mFG of acute citalopram infusion suggesting possible 5-HT abnormality.

Comparison of data from other antidepressants might help to develop further hypotheses regarding why drug effects seen with citalopram were not also seen with AZD6765 or ketamine. A larger experiment would need to be constructed. A region of interest analysis using the centre of mass for each of the regions could be completed in cMDD, rMDD and HC participants. Patients would be administered citalopram, reboxetine, bupropion or saline on a randomised basis. Additional to this MRS could be completed for the precuneus to examine changes in neurotransmitter levels. This could be first performed in healthy volunteers followed by repetition in rMDD and cMDD compared to HC.

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Appendix



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Review article

Resting state networks in major depressive disorder



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ABSTRACT

Resting state functional magnetic resonance imaging (fMRI) examines the spontaneous low frequency neural activity of the brain to reveal networks of correlated neural activity. A number of different methodologies, each with its own advantages and disadvantages, have been used to examine networks of neural activity that may be related to clinical presentation. Major depressive disorder (MDD) research has largely focused on the default mode network (DMN), which is most active at rest and may relate to negative rumination. However, other networks can be discerned in the resting state such as salience and affective and cognitive control networks, all of which may be relevant to MDD psychopathology. This article reviews the rapidly increasing literature on resting state networks. A number of state- and trait-dependent abnormalities have been reported in MDD in a wide variety of regions including the cerebellum, lingual gyrus, anterior cingulate cortex (ACC), middle frontal gyrus (MFG), dorsolateral prefrontal cortex (dlPFC), amygdala and insula. Current and chronic medication is often a potential confound. Few trials have examined the immediate or delayed effects of antidepressants on resting state networks. This article presents a novel approach to the analysis of drug effects, the identification of signatures of efficacy, and thus for drug development.

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Contents

1. Resting state networks	140
2. Default mode and salience networks	140
3. Other resting state networks in MDD	141
4. Resting state fMRI studies in MDD	141
5. Effect of antidepressant drugs on the default mode and salience networks	148
6. Using an NMDA receptor antagonist to probe resting state networks	149
7. Summary	149
Funding	149
References	149

Abbreviations: AMYG, amygdala; AN, affective network; ant, anterior; ACC, anterior cingulate cortex; BD, bipolar disorder; BPD, bipolar depression; b/l, bilateral; CES-D, Center for Epidemiologic Studies Depression Scale; Cohe-ReHo, coherence based regional homogeneity; cMDD, current major depressive disorder; Cr, creatinine; FnC, functional connectivity; fALFF, fractional amplitude of low frequency fluctuations; ALFF, amplitude of low frequency fluctuations; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FG, fusiform gyrus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; Glx, glutamate + glutamine; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; hx, history; INS, insula; IPL, inferior parietal lobule; LG, lingual gyrus; MDD, major depressive disorder; MFG, middle frontal gyrus; mFG, medial frontal gyrus; MMSE, mini mental state examination; mOFC, medial orbitofrontal cortex; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; MTG, middle temporal gyrus; PCC, post cingulate cortex; PHG, parahippocampal gyrus; post, posterior; OCC, occipital cortex; rACC, rostral anterior cingulate cortex; rMDD, remitted major depressive disorder; ROI, region of interest; ReHo, regional homogeneity; sibsMDD, healthy siblings of MDD patients; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; T, Tesla; THAL, thalamus; trMDD, treatment resistant major depressive disorder; TR, Repetition time; tx, treatment; vlPFC, ventrolateral prefrontal cortex; VMHC, Voxel-mirrored homotopic connectivity; vmPFC, ventromedial prefrontal cortex; vACC, ventral anterior cingulate cortex; vPFC, ventral prefrontal cortex

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1. Resting state networks

The resting state refers to regional neural activity of the brain when humans or animals are awake and alert but not actively involved in any activity that requires attention or a goal-directed action (Raichle et al., 2001, Broyd et al., 2009). Resting state functional magnetic resonance imaging (fMRI) studies of major depressive disorder (MDD) have focused on several distinct networks containing brain regions that have been shown to have correlated oscillating blood oxygenation level dependent (BOLD) signals. Veer et al. (2010) identified a total of 13 functionally relevant resting state networks (RSNs) from a study of 19 recovered depressive patients and 19 healthy controls. The 13 functionally relevant RSNs were the following: (1) primary visual, (2) lateral visual, (3) medial visual, (4) sensory-motor, (5) right lateral, (6) left lateral, (7) precuneus, (8) ventral stream, (9) medial temporal, (10) salience, (11) task positive, (12) auditory, and (13) default mode (Veer et al., 2010), all of which have previously been demonstrated in healthy volunteers (Damoiseaux et al., 2006).

Resting state networks are most frequently assessed first by identifying regions that show correlated activity of over time against a region of interest (ROI; seed-based correlation) or that emerge from independent components analysis (ICA). ICA is able to extract from the BOLD time series a number of spatially independent components that can be interpreted as a network showing similar BOLD activity levels (Rosazza and Minati, 2011). The degree to which the component is present is expressed as a power function. Direct comparisons of the different analytic methodologies have identified similar networks (Bluhm et al., 2008). An alternative method of regional homogeneity (ReHo) analyses the differences in neural activity between one voxel and its nearest neighbours. It assumes that the haemodynamic characteristics of the neighbouring voxels will be similar and also that a cluster of voxels will demonstrate synchronised activity (Liang et al., 2013). Abnormal ReHo is therefore likely to be related to temporal changes in BOLD signal (Zang et al., 2004). Other measures include Uddin and colleagues' "network homogeneity", where voxels are compared with all other voxels in the brain network (Uddin et al., 2008), "integrated local correlation" (Deshpande et al., 2009) and Greicius et al.'s (2004) "goodness of fit" model (Greicius et al., 2004). New techniques for the analysis of the resting state have also emerged. These include analysing the fractional amplitude of low frequency fluctuations (fALFF) or the amplitude of low frequency fluctuations (ALFF) and voxel-mirrored homotopic connectivity. Fractional ALFF is the fractional component of the low frequency range of the ALFF, which is close to the spontaneous resting neural activity (Zou et al., 2008).

There are strengths and weaknesses with each of these methods. ICA is a model-free, data-driven approach. However, the number of components to be generated in ICA during the analysis will affect the number of spatially distinct networks detected. Components can be functional networks or physiologically linked regions but may also be imaging artefacts. It is also difficult to compare components between groups and participants (Uddin et al., 2008). In the ROI-based method, seed placement can be somewhat arbitrary, affecting the patterns of functional connectivity observed (Uddin et al., 2008). Furthermore, the ROI-based method is more susceptible to contamination from other non-neural low frequency fluctuations when compared with the ICA-based approach (Greicius et al., 2007). Kuhn and Gallinat have also commented that the seed-voxel-based analysis approach is highly dependent on the positioning of the seed voxel and may therefore produce inconsistent results (Kuhn and Gallinat, 2011).

The newer method of network homogeneity is better suited to examining longer range connectivity and group differences in pathology since it allows comparison of one voxel with all the other voxels in a particular network. However, the network of

interest needs to be identified and well characterised before analysis. This makes network homogeneity less useful in paediatric populations (Uddin et al., 2008) as there is the potential to miss differences between networks that might otherwise be demonstrated. Greicius et al.'s (2004) "goodness of fit" model suffers from similar problems because the data are matched to a spatial template that is selected before analysis. They attempted to alleviate this by examining the four "best-fit" components. These are then matched using an automated process followed by the examination of the differences between them (Greicius et al., 2004).

The advantage of regional homogeneity (ReHo) is the model-free nature of the method which allows discovery of unpredicted BOLD response. However, regional homogeneity can be affected by the level of spatial smoothing, cluster size and volume examined (Zang et al., 2004). This method was reported to be insensitive to phase variability, such as random noise across the time series, leading to an improvement in sensitivity to detect differences in spontaneous neural activity (Guo et al., 2012a). Integrated local correlation was introduced to alleviate the problems of ReHo. ReHo uses only the neighbouring voxels, whereas in integrated local correlation the integration of the spatial correlation function for each voxel is used. Integrated local correlation is also reported to be unaffected by fluctuations from cardiac and respiratory cycles except around large blood vessels (Deshpande et al., 2009).

Functional connectivity (FnC) provides information about the correlation between a set of pre-specified brain regions. As FnC is not data-driven, it does not demonstrate changes in specific brain regions and will not identify the part of the network that is dysfunctional (Zang et al., 2007; Zou et al., 2008). ALFF allows detection of spontaneous BOLD signal changes without these challenges. However, greater regional ALFF is especially prevalent around large blood vessels and cisternal areas (Zang et al., 2007; Zou et al., 2008) due to physiological noise. To improve the approach, Zou et al. (2008) used the ratio of the power of the low frequency range (0.01–0.08 Hz) to the whole frequency range (0–0.25 Hz), termed fractional ALFF (fALFF).

2. Default mode and salience networks

Raichle et al. first coined the phrase "default mode" to describe correlated brain activity in its resting state (Raichle et al., 2001). The default mode network (DMN), one of several resting state networks of brain regions that show high levels of functional connectivity in the resting brain, includes the posterior cingulate cortex (PCC)/precuneus, medial prefrontal cortex (mPFC), ventral anterior cingulate cortex (vACC), and lateral and inferior parietal cortex. Because the network is most active at rest, it has been associated with self-referential processing (Bluhm et al., 2008). Different components have been emphasised by different authors. For example, Franco et al. (2009) emphasised the ACC (Brodmann area (BA) 11/32), dorsolateral and superior frontal gyrus (BA 8/9/10), inferior frontal cortex (BA 47), PCC (BA 23/31), posterior parietal lobule (BA 7/39/40), inferior temporal gyrus (BA 19/37) and parahippocampal gyrus (BA 30/36) (Franco et al., 2009). The most consistently defined parts of the DMN are the precuneus/PCC and the mPFC. The PCC is believed to be related to the monitoring of internal and external environments (Raichle et al., 2001), whilst the mPFC is thought to be involved in social cognition and observing the psychological states of self and others. The DMN therefore interfaces task performance and emotion (Simpson et al., 2001). Self-referential tasks have demonstrated increased response in the dorsomedial prefrontal cortex (dmPFC) whilst reduced response was observed in the ventral mPFC when affective stimuli were presented (Gusnard et al., 2001).

The DMN is suppressed by external task requirements, and it has been termed the task-negative network inversely correlated with task-positive networks (TPN). The TPN typically involves the dlPFC, medial temporal cortex, parietal lobe, insula bilaterally and supplementary motor area, and it is related to task performance activation (Biswal et al., 1995; Fox et al., 2005; Broyd et al., 2009). Hamilton and colleagues compared DMN dominance over TPN in fMRI data from 17 depressed individuals and 17 healthy controls. DMN dominance has been shown to have a significant positive correlation with scores on the Ruminative Responses Scale depression subscale and a negative correlation with scores on the self-reflection subscale (Hamilton et al., 2011). In this study, however, participants were not questioned about their symptoms at the time of scanning. The authors also noted that the right fronto-insular cortex (r-FIC) activated at DMN peaks whereas in controls it activated at TPN peaks. The r-FIC is therefore thought to control switching between DMN and TPN. DMN response is attenuated when task-related activations are seen (Raichle et al., 2001; Broyd et al., 2009). More complex and demanding tasks cause greater suppression of the task-negative DMN (McKiernan et al., 2006) and the DMN may remain intact when performing simple sensory tasks, during conscious sedation, and the early stages of sleep (Greicius et al., 2003). Abnormalities of the DMN have been reported in depression, anxiety, dementia, schizophrenia, epilepsy, autism and attention deficit hyperactivity disorder (Broyd et al., 2009). The specificity of such changes has not so far been investigated. It is possible some may relate to transdiagnostic neurobiological processes.

FnC is the temporal correlation between fluctuations in the BOLD signal that is measured using fMRI at different anatomical sites (Fox and Raichle, 2007). Bluhm et al. have reported that there are gender differences in the DMN, with women having increased PCC/precuneus and bilateral medial frontal connectivity in an ROI analysis, and greater activity in bilateral superior frontal gyrus and right angular gyrus (Bluhm et al., 2008). Age has also been demonstrated to alter the DMN and FnC. Task-negative attenuations in the DMN are less sensitive to cognitive demand in older adults, whilst there is reduced FnC between regions of the DMN in older adults (Bluhm et al., 2008; Esposito et al., 2008).

The salience network, another RSN, is involved in filtering information to support behaviour choice. It is structurally correlated to the ACC and insula. (Seeley et al., 2007; Elton and Gao, 2014). The insula is thought to be important in the early evaluation of the significance of sensory and affective stimuli presented. This involves perception of the body's physiological responses (Craig, 2002; Lovero et al., 2009). The rostral ACC (rACC) is classically engaged by errors in task performance (error-related brain activation) along with the mPFC, insula, precuneus and PCC (Menon et al., 2001). These regions form parts of both the salience network and the DMN. Some of the structures are related to self-referential thinking (mPFC) and monitoring of eye movements and spatial memory (PCC) (Vogt et al., 1992; Ridderinkhof et al., 2004). It is hypothesised that in MDD there will be increased activation of the salience network and increased activity in the DMN.

3. Other resting state networks in MDD

Other networks of importance in MDD include the affective network and the cognitive control network. The cognitive control network (CCN) is involved in complex cognitive tasks and working memory, decision making and conflict resolution (Corbetta and Shulman, 2002; Sheline et al., 2010). The CCN contains the dorsal ACC, dlPFC and portions of the parietal lobe; overlapping with regions of the DMN (Alexopoulos et al., 2012). The affective network

includes the amygdala, temporal poles, pallidum, insula and superior temporal gyrus. The role of this network is emotional regulation and processing (Zeng et al., 2012). Abnormalities have previously been noted in the affective network between the amygdala and the hippocampus/parahippocampal gyrus, OFC and temporal poles in MDD (Zeng et al., 2012; Zhang et al., 2014). However, these studies were limited by lack of control for physiological effects. Overall there are fewer studies that have examined the cognitive control and affective network abnormalities in MDD when compared with those investigating the DMN and salience networks. The populations used in previous resting state studies are complicated by age-related or diagnostic issues that affect the findings and limit reliability (Alexopoulos et al., 2012). To the best of our knowledge, there are no published studies that examine the effects of antidepressants on the CCN or affective network.

4. Resting state fMRI studies in MDD

Table 1 shows fMRI studies of resting state networks in MDD. Studies of adolescents were excluded due to difficulty with emerging MDD diagnoses as were those studies without a control group. Whilst most studies examined the DMN, others examined the resting state activity and connectivity of specific structures using the various methods highlighted above. No studies investigated changes in the salience network. Two studies examined the affective network (Sheline et al., 2010; Zhang et al., 2014). Patients in most studies were unmedicated either before or during the study. The scanner's magnetic field strength varied between 1.5 and 4 T. Six studies incorporated a treatment-resistant MDD group (Lui et al., 2011; Wu et al., 2011; Guo et al., 2011b; Guo et al., 2012b; Guo et al., 2012a; Guo et al., 2013b). In these studies there are varying effects on the cerebellum and the lingual, fusiform and temporal gyri. However, the reported patterns are inconsistent. First episode patients were included in 14 studies (Zhou et al., 2010; Guo et al., 2011a; Peng et al., 2011; Cao et al., 2012; Wang et al., 2012; Guo et al., 2012a; Peng et al., 2012; Ye et al., 2012; Zhu et al., 2012; Wang et al., 2013; Guo et al., 2013a; Liu et al., 2013b; Guo et al., 2013c; Zhang et al., 2014). A few studies report consistent changes in reduced ALFF, fALFF and ReHo in the left parahippocampal gyrus (Guo et al., 2011a; Guo et al., 2013c; Liu et al., 2013b). Findings from "late life" depression were reported in five studies (Kenny et al., 2010; Bohr et al., 2012; Liu et al., 2012a; Yue et al., 2013; Andreescu et al., 2013). No studies corrected for cardiac or respiratory cycles when using seed region analyses.

Seventeen studies used a seed ROI functional connectivity method (Anand et al., 2005a; Anand et al., 2007; Anand et al., 2009; Bluhm et al., 2009; Horn et al., 2010; Kenny et al., 2010; Sheline et al., 2010; Zhou et al., 2010; Lui et al., 2011; Bohr et al., 2012; Cao et al., 2012; Liu et al., 2012b; Peng et al., 2012; Ye et al., 2012; Andreescu et al., 2013; Guo et al., 2013b; Tang et al., 2013) whilst 12 used ReHo to show differences in connectivity (Yuan et al., 2008; Yao et al., 2009; Liu et al., 2010; Guo et al., 2011a; Guo et al., 2011b; Peng et al., 2011; Wu et al., 2011; Guo et al., 2012a; Liu et al., 2012a; Liang et al., 2013; Ma et al., 2013; Yue et al., 2013). Two of these studies also used coherence-based ReHo (Guo et al., 2012a; Liu et al., 2012a).

Spatial ICA was used in five studies. Each of the studies reported increased functional connectivity of the DMN in MDD in structures such as the ventral anterior cingulate cortex, orbito-frontal cortex, hippocampus and thalamus (Greicius et al., 2007b; Zhu et al., 2012; Li et al., 2013; Guo et al., 2013c; Sambataro et al., 2013). This suggests that these structures form interconnecting circuits as has been suggested in the limbic-cortical dysregulation model of MDD (Mayberg, 2003). Li et al. (2013) reported that

Table 1
Resting State Network fMRI Studies in MDD sorted by methodology.

Studies using amplitude of low frequency fluctuations (ALFF)					
Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
Guo et al. (2012b)	18 trMDD (med) 17 cMDD (med) 17 HC	cMDD mFG, ACC, post CER, MTG, inferior occipital gyrus, FG, putamen, caudate, IFG trMDD mFG, ant CER, LG, middle occipital gyrus, cuneus	cMDD ITG, ant CER trMDD ACC/mFG, post CER	Varying medication profiles. trMDD had longer episode duration.	trMDD higher ALFF in DMN and lower ALFF in visual recognition network compared to treatment responsive
Jing et al. (2013)	19 cMDD (med) 19 rMDD 19 HC	cMDD & rMDD r-precuneus, I-LG cMDD r-precuneus, I-LG	rMDD r-putamen cMDD r-mFG, r-putamen	All female population. Varying medication profile. No correction for multiple comparisons. ALFF positive correlation with number of episodes, fALFF positively correlated with disease duration.	r-mFG could be biomarker for MDD. DMN nodes still affected even when medicated.
Zhang et al. (2014)	32 cMDD 1st episode 35 HC	b/l OFC	b/l INS, b/l temporal lobe, I-fusiform cortices and mid occipital gyrus decreased I-OFC-AMYG FnC	Due to young age could not guarantee diagnosis of MDD and not BD.	Decreased ALFF in OFC suggests hypofunctioning of emotional regulation in AN
Studies using fractional amplitude of low frequency fluctuations (fALFF)					
Guo et al. (2013a)	24 cMDD 1st episode 24 HC	FnC IPL and b/l ITG positive correlation with severity	I-Crus I and I-cerebellar lobule VI FnC right hippocampus negative correlation with severity		Abnormal fALFF regions as seeds. Increase CER ALFF may be disease state phenomenon.
Liu et al. (2013a)	22 cMDD (19 med) 22 sibsMDD 26 HC	cMDD I-precuneus, r-precentral, b/l postcentral gyri, I-mid occipital gyrus, b/l LG, I-superior and I-inferior occipital gyri sibsMDD	cMDD r-mFG/ACC, I-MFG, r-IPL, r-precuneus, I-precentral gyrus, I-angular gyrus, r-ventrolateral IFG, sibsMDD b/l LG, I-MFG, r-MTG		Varying medication profiles. I-MFG endophenotype for MDD. r-dorsal mFG may be state marker for MDD. DMN/CCN abnormalities seen in siblings.
Liu et al. (2013b)	22 cMDD 1st episode 19 HC	r-mFG/ACC, r-precuneus r-post CER, I-PHG, r-MFG,	I-superior occipital gyrus/cuneus		Control group from previous study. Abnormal regions part of cortical-limbic dysregulation model of MDD.
Wang et al. (2012)	18 cMDD 1st episode 18 HC	I-ITG, bilateral inferior parietal lobule and r-LG, left DLPFC, bilateral mOFC, MTG and r-IPL	r-fusiform gyrus, ant and post CER, r-precentral gyrus, ITG, bilateral FG,		No correlations with severity. May be related to disturbances of multiple emotion and cognition networks
Studies using ALFF, fALFF or FnC within Independent component analysis (ICA) defined networks					
Guo et al. (2013c)	24 cMDD 1st episode 24 HC	I-PHG	I-dmPFC		Mood rating scales not completed in controls. dmPFC may be a marker of severity. No network effects noted
Greicius et al. (2007)	28 cMDD (med) 20 HC		precuneus, vACC, OFC and THAL		Varying medication profile. 25 ICA components used. length of MDD episode positively correlated with FnC in vACC. vACC FnC may indicate treatment response. vACC dysfunction may be related to CCN or salience network.
Li et al. (2013)	24 cMDD 29 HC		post DMN/precuneus		Normalised following treatment. Abnormal FnC of ant DMN may be biomarker
Sambataro et al. (2013)	20 cMDD (14 med) 20 HC		DMN+vACC, r-lateral temporo-parietal cortex and PCC, rACC, r-hippocampus		Varying medication profile. Mood rating scales not completed in controls. MDD reported to be 'mild'. 30 ICA components used. MDD characterised by widespread increases in DMN connectivity.
Zhu et al. (2012)	35 cMDD 1st episode 35 HC	b/l PCC/precuneus and angular gyrus – associated with overgeneral memory	dmPFC/vACC, vmPFC, medial orbital PFC – associated with rumination.		Dissociation of ant and post DMN is MDD trait.
Studies using Regional Homogeneity (ReHo)					
Guo et al. (2011a)	17 cMDD 1st episode 17 HC	I-post CER and PHG, r-post central gyri and FG	r-ITG		Mood rating scales not completed in HC. Short illness episode duration. Limbic-cortical network dysregulation.
Peng et al. (2011)	16 cMDD 1st episode 16 HC	I-THAL, temporal lobe, post CER and bilateral occipital lobe			Longer TR (3 s). Limbic-cortical network dysregulation.
Guo et al. (2011b)	24 trMDD 19 HC	I-INS, STG, IFG, LG, culmen	I-STG, tuber, culmen, r-cerebellar tonsil and b/l FG		Short medication washout. Mood rating scales not completed in controls. Abnormality of prefrontal-amygdala-pallidothalamic-midolothalamic mood circuit.
Wu et al. (2011)	22 trMDD (med) 22 cMDD (med) 26 HC	trMDD + cMDD – I-inferior mPFC, I-post FG, I-inferior frontal area, I-IPL, I-caudate, trMDD – I-precuneus/SPL, I-IFG, I-post FG, b/l IPL cMDD – I-prefrontal gyrus	trMDD + cMDD – b/l ACC and mFG, r-insula, r-PHG trMDD – I-mid cingulate, b/l ACC and mFG, r-MTG, r-INS, r-STG cMDD – I-mPFC, r-PHG		Limbic-cortical network dysregulation suggested. DMN/salience network and CCN regions affected more in trMDD.
Liang et al. (2013)	16 cMDD 17 BPD 16 HC	I-PHG, r-precentral gyrus, I-postcentral, precentral and cingulate gyri	r-IPL, r-precuneus, I-middle occipital lobe		Longer TR (3 s). DM/Salience network may be affected.
Liu et al. (2010)	15 MDD	cMDD –	cMDD – b/l IPL, I-IFG, I-post CER		Regions of salience network and CCN affected.

Table 1 (continued)

Studies using amplitude of low frequency fluctuations (ALFF)					
Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference
		15 1st degree relatives 15 HC	r-INS, r-MFG, r-lentiform nucleus, l-ant CER, l- STG, l-precentral gyrus, l-postcentral gyrus, relatives – r-INS and l-CER	relatives – l-precentral gyrus	Siblings 9 years older on average.
Ma et al. (2013)	19 MDD sub-threshold (Elderly) 18 HC		l-dIPFC, r-OFC, l-postcentral gyrus, l-MFG and l-ITG	b/l INS and r-dIPFC	Concomitant medical conditions and medication. Longer TR (3 s) No correlation with CES-D.
Yue et al. (2013)	22 MDD 'late onset' (1st episode) 30 HC		r-MFG, l-SFG, l-AMYG + r-occipital and r-parietal lobe, r-AMYG + l-parietal lobe	l-AMYG + b/l putamen/frontal lobe, r-AMYG + frontal lobe	Not properly corrected for multiple comparisons. MDD patients significantly less educated. More severe on HAM-D scoring. Long duration of illness (mean 5 years) Longer TR (3 s). No correction for multiple comparisons.
Yao et al. (2009)	22 MDD 22 HC		r-PCC, r-INS, r-vACC, l-dACC, r-OFC, r-FG, l-lentiform nucleus r-OFC correlated with cognitive disturbance, r-post cingulate gyrus and r-INS with retardation, r-vACC and r-INS with hopelessness		Dysfunctional limbic–cortical–striatal–pallidal–thalamic circuit. Regions of DMN/ Salience Network have decreased ReHo.
Yuan et al. (2008)	18 rMDD 14 HC		l-MFG, b/l precuneus, b/l SFG, r-STG, r-MTG, r-FG, r-postcentral gyrus	r-SFG, b/l putamen, l-postcentral gyrus	Decreased ReHo in DMN regions even after remission. Trait marker.
Studies using coherence based Regional Homogeneity (ReHo)					
Guo et al. (2012a)	23 trMDD 22 cMDD 1st episode 19 HC		trMDD l-CER (b/l CER when compared to cMDD) cMDD b/l SFG	trMDD l-FG	Treatment resistant group not clearly established. Mood rating scales not completed in controls. Significant difference in MMSE scores. Mood rating scales not completed in controls. No correlation
Liu et al. (2012a)	15 cMDD 'late life' (1st episode) 15 HC		r-ACC, l-dIPFC, b/l mPFC, r-precuneus, r-angular gyrus, l-caudate	l-post CER, STG, r-postcentral gyrus, b/l supplementary motor area	Decreased Cohe-ReHo in CCN/DMN regions.
Studies using Region of Interest (ROI) methodology and functional connectivity (FnC)					
Anand et al. (2007)	12 MDD 11 HC		ACC + AMYG/striatum/THAL		Mood rating scales not completed in controls. No correction for multiple comparisons. FnC increased, ALFF reduced following treatment.
Anand et al. (2009)	11 BD (5 BPD) 15 MDD 15 HC		rACC + dorsomedial THAL / r-AMYG		No correction for multiple comparisons. More severe decreases in BPD than MDD.
Anand et al. (2005)	15 MDD 15 HC		b/l ACC + l-medial THAL, ACC and r-medial THAL, ACC + l-pallidostriatum.		Mood rating scales not completed in controls. Long duration of illness (mean 6 years). No correction for multiple comparisons.
Andreescu et al. (2013)	47 cMDD (elderly) (med) 46 HC		b/l MFG. Treatment responsive – l-dACC, r-dIPFC, r-cuneus	r-precuneus Treatment responsive – r-mPFC, l-precuneus, l-striatum	Participants gathered from several other trials. Controls significantly older and higher MMSE score. Longer TR (3 s) but 4 T MR scanner.
Bluhm et al. (2009)	14 cMDD (1 med) 15 HC		Precuneus/PCC + b/l caudate		Mood rating scales not completed in controls.
Cao et al. (2012)	42 cMDD 1 st episode 32 HC		l-hippocampus + b/l MFG	r-hippocampus + r-IPL	Increased DMN FnC. ant DMN FnC increased after treatment.
Guo et al. (2013b)	23 trMDD (med) 22 cMDD (med) 19 HC		cMDD l-MFG, b/l IPL connexions with various cerebellar lobules trMDD l-MFG, b/l ITG, r-IPL, l-IFG connexions with various cerebellar regions trMDD v MDD r-precuneus, l-IPL, r-angular gyrus connexions with various cerebellar regions	cMDD r-precuneus, r-mFG, l-PHG, l-calcarine, l-LG, r-IFG, r-IFG, l-middle occipital gyrus, b/l middle temporal gyrus, l-calcarine, r-FG connexions with various cerebellar lobules trMDD b/l PHG, b/l LG, r-SFG, r-IFG, l-MTG, r-STG connexions with various cerebellar regions	Decreased DMN FnC in trMDD and cMDD. Increased FnC in both groups in visual recognition network
Horn et al. (2010)	18 MDD 22 HC		Glx/Cr ratio in rACC negatively correlated with FnC between rACC + ant INS cortex	FnC between rACC + ant INS cortex positively correlated to HAM-D	Varying severity of MDD. No correction for multiple comparisons.
					Salience network/DMN linked to reduced glutamate function

Table 1 (continued)

Studies using amplitude of low frequency fluctuations (ALFF)						
Reference	Population	Decreased in MDD	Increased in MDD	Other findings/comment	Inference	
Kenny et al. (2010)	16 MDD 'late life' (12 med) 17 HC			b/l precuneus, l-caudate + l-precentral, r-sub-gyral, b/l paracentral lobule, b/l THAL, l-postcentral gyrus, r-caudate + b/l cingulate, r-INS, l-precentral gyrus, l-MFG, l-paracentral lobule, r-postcentral gyrus, r-IPL, r-supramarginal gyrus, r-STG	Varying medication profiles. Mood rating scales not completed on controls.	Increased DMN FnC.
Liu et al. (2012b)	20 MDD 20 HC		various PCC, precuneus, mPFC, FG, LG, OFC, STG, SFG connexions with various cerebellar lobules	temporal cortical connexions with various cerebellar regions		Reduced DMN FnC with CER.
Lui et al. (2011)	28 trMDD 32 cMDD 48 HC		cMDD ACC + l-MTG, l-parietal cortex, r-IFG, l-AMYG + l-cingulate cortex, l-frontal + r-INS, b/l cingulate cortex, l-hippocampus + cingulate cortex, l-putamen, l-parietal cortex, l-INS + l-precuneus, r-parietal cortex, l-MTG, r-occipital cortex, r-cingulate cortex, l-THAL + r-IFG, r-AMYG + l-cingulate cortex, r-INS + r-hippocampus, l-INS, r-occipital cortex, l-precuneus, r-MTG, r-putamen + l-precuneus, r-THAL + cingulate cortex, r-hippocampus + r-IFG, r-INS, l-cingulate cortex trMDD l-frontal + precuneus, r-parietal cortex, l-THAL + r-INS, r-putamen, r-cingulate cortex, l-MFG, l-hippocampus + l-MTG, r-INS + r-precuneus, r-cingulate cortex, r-putamen + l-MFG and r-IFG, r-THAL + r-IFG, l-MFG, l-putamen, r-INS	trMDD > MDD l-AMYG + cingulate cortex, r-INS + cingulate cortex, r-precuneus	Mood rating scales not completed on controls.	Decreased DMN FC. More widespread decreases in cMDD.
Peng et al. (2012)	16 cMDD 1st episode 16 HC		THAL + b/l parietal lobe, r-cingulate gyrus, r-precuneus	rACC + PHG/l-parietal lobe/l-frontal lobe	Longer TR (3 s). No correction for multiple comparisons.	Multiple networks may be affected.
Ye et al. (2012)	22 cMDD 1st episode 30 HC		r-dIPFC + r-parietal lobe	r-dIPFC + l-dACC, l-PHG, l-THAL, l-precentral gyrus	Varying medication profiles.	No inference.
Zhou et al. (2010)	18 cMDD 1st episode 20 HC		PCC + l-mPFC/l-lateral parietal cortex + l-INS/IFG, r-ant temporal cortex + l-inferior parietal gyrus, l-ant temporal cortex + l-inferior parietal gyrus, l-PHG + l-inferior parietal gyrus, r-CER + left inferior parietal gyrus/postcentral gyrus, l-CER + l-MFG	mPFC + r-PCC/precuneus, l-medial SFG + mPFC/OFC, l-lateral parietal cortex + mPFC/OFC, precuneus, r-ant temporal cortex + mOFC/rectal gyrus, b/l PCC/precuneus, l-ant temporal cortex + r-precuneus, mOFC/rectal gyrus, l-PHG + r-precuneus		Multiple changes in DMN FC
Sheline et al. (2010)	18 cMDD 17 HC			b/l dmPFC. FnC positively correlated with HAM-D scores		dmPFC interconnects DMN, CCN & AN
Tang et al. (2013)	28 cMDD 30 HC		b/l AMYG + vPFC		More severe MDD	Limbic-cortical network dysregulation
Bohr et al. (2012)	14 cMDD 'late life' (8 med) 16 HC			caudate + r-precuneus, b/l paracingulate, b/l supramarginal gyrus, b/l cingulate gyrus, b/l lateral OCC, l-central operculum, l-precentral gyrus, b/l parietal operculum, r-angular gyrus	Varied age of onset and number of episodes. Mixed medicated and unmedicated patients.	Increased DMN FnC
Wang et al. (2013)	17 cMDD 1st episode 17 HC		mOFC, PHG, FG, middle occipital gyri and cuneus. FG negative correlation to illness duration, MFG, IFG, CER, crus II negative correlation to cognition			No inference
Studies using whole brain functional connectivity (FC)						
Veer et al. (2010)	19 cMDD 19 HC		b/l AMYG + l-INS, left frontal pole, b/l LG, r-STG		Significant difference in educational level between groups. Some patients in remission according to MADRS score. Mixed 1 st episode and recurrent MDD.	Abnormal FnC in AN, visual recognition network
Wang et al. (2014)	18 cMDD w/o neglect hx (17 med) 20 cMDD with neglect hx (18 med) 20 HC		without neglect hx b/l vmPFC/vACC with neglect hx b/l vmPFC/vACC, dlPFC, dmPFC, vPFC, INS, caudate, THAL, PHG, hippocampus, AMYG, CER		Varying medication profiles. Mood rating scales not completed in controls. Higher education and longer duration of illness in those without childhood neglect history. Recall bias.	Childhood neglect leads to widespread FnC reductions in MDD greater than those without.
Zeng et al. (2012)	24 cMDD 29 HC		ACC, mPFC, AMYG, PCC, INS, PHG, hippocampus, THAL, ITG, temporal poles, globus pallidus, STG, LG, FG, inferior occipital and calcarine gyrus			DMN, AN and visual recognition network all affected in cMDD.

All populations were unmedicated unless otherwise stated. Those medicated indicated by (med).

increases in FnC of the DMN normalised following treatment with antidepressants (Li et al., 2013). ALFF/fALFF was used in seven studies (Guo et al., 2012b; Wang et al., 2012; Jing et al., 2013; Liu et al., 2013a; Guo et al., 2013a; Liu et al., 2013b; Zhang et al., 2014). ICA was combined with fALFF in two studies (Guo et al., 2013c; Sambataro et al., 2013). Three studies examined whole brain functional connectivity (Veer et al., 2010; Zeng et al., 2012b; Wang et al., 2013a).

ALFF/fALFF has been used to examine treatment-resistant, remitted and first episode MDD. The results highlight similar themes, which include increased ALFF in the cerebellum and increased functional connectivity between the cerebellum and hippocampus (Guo et al., 2012b; Guo et al., 2013a). The cerebellum has connections to a number of frontal and limbic regions (such as the amygdala and hippocampus) that are important in emotional and cognitive processing (Schmahmann and Caplan, 2006). ALFF changes were less consistent between anterior and posterior lobes of the cerebellum; Wang et al. (2012) reported increased ALFF in both the anterior and posterior lobes whilst Guo et al. (2012b) reported increased ALFF in the posterior lobe only. Additionally, reduced ReHo in first episode MDD in the posterior cerebellum was reported in two studies (Guo et al., 2011a; Peng et al., 2011).

The lingual gyrus was consistently reported to have reduced ALFF even in siblings of patients with MDD (Guo et al., 2012b; Jing et al., 2013; Liu et al., 2013a). This finding was also reported in first episode MDD (Wang et al., 2012). The lingual gyrus has been reported to be within the visual recognition network and is believed to have a role in the perception of emotions when facial stimuli are presented (Jing et al., 2013; Tao et al., 2013). The other interesting finding was that changes in ALFF in the mFG/ACC were reported as both increased (Guo et al., 2012b; Liu et al., 2013a) and decreased (Liu et al., 2013b). The finding of increased fALFF in the mFG/ACC in siblings may suggest these areas as biomarkers for MDD. Liu et al. have suggested this abnormality may relate to the insula since it has reciprocal connections to the inferior frontal gyrus, ACC and mFG (Liu et al., 2013a).

ReHo studies report abnormalities in a number of areas. The studies considered treatment-resistant, subthreshold and later onset MDD. Decreased ReHo was reported in the posterior cerebellum in two studies. Several studies reported decreased ReHo in the insula (Yao et al., 2009; Guo et al., 2011b), ACC (Yao et al., 2009; Liu et al., 2012a) and dorsolateral prefrontal cortex (dlPFC) (Liu et al., 2012a; Ma et al., 2013). It is known that the ACC plays a central part in cognition, emotional regulation and attention functions (Elliott et al., 1997). The left and right sides of the dlPFC have been suggested to manage emotional judgment and anticipation of emotional judgment (Nitschke and Mackiewicz, 2005). It has been demonstrated that the insula is associated with emotional response to interoceptive sensory stimuli (Reiman et al., 1997).

The ROI functional connectivity (FnC) studies examined a number of different brain areas and populations including both first episode and later onset MDD. Anand et al. (2005a) reported findings of decreased FnC between the ACC, amygdala and thalamus (Anand et al., 2005a; Anand et al., 2007; Anand et al., 2009). Liu et al. (2012b) reported decreased FnC between the PCC/precuneus, ventromedial prefrontal cortex (vmPFC), hippocampus, orbitofrontal cortex (OFC) and superior frontal gyrus. These findings were extended by Guo et al. (2013b), who reported decreased cerebellar FnC with the right precuneus, inferior parietal lobule and angular gyrus. First episode MDD appears to have decreased vACC and PFC/inferior parietal lobule connectivity (Zhou et al., 2010). These regions seem to have decreased FnC with the ACC, hippocampus, insula, amygdala and thalamus (Liu et al., 2011). There is also some agreement regarding increased FnC of the caudate and cingulate and precentral gyrus. The problem in comparing these studies is that the population sample and seed

regions used are generally not the same between studies. Overall, large studies are needed in the future using a standardised methodology.

The whole brain FnC studies present some further curious findings. Wang et al. (2014) reported on patients with MDD with or without a history of neglect. It is interesting to note that the findings of decreased connectivity in the ACC, hippocampus, parahippocampal gyrus and insula are present both in the neglect group and in the study of Zeng and colleagues (2012) where neglect was not considered. This would suggest the effects of a history of neglect on FnC in MDD could be altered by antidepressant treatment.

5. Effect of antidepressant drugs on the default mode and salience networks

There are limited studies investigating the effects of antidepressants on RSNs. van Wingen et al. (2013) demonstrated that 2 weeks of oral duloxetine reduced the connectivity between the mPFC, lateral parietal cortex and dlPFC regions of the DMN in healthy volunteers. Reduced connectivity between the left dmPFC and left hippocampus was observed after 7 days of oral citalopram administered to healthy volunteers (McCabe et al., 2011). Whilst McCabe and Mishor (2011) discovered reduced functional connectivity in the amygdala and vmPFC following the selective serotonin reuptake inhibitor (SSRI) citalopram, these differences were not observed with the norepinephrine reuptake inhibitor (SNRI) reboxetine (McCabe and Mishor, 2011). Interestingly there is considerable doubt as to the clinical efficacy of reboxetine, which may explain this finding (Eyding et al., 2010).

In MDD antidepressant treatment appears to normalize abnormalities in the DMN, but the reported effects are inconsistent, possibly due to the limited number of studies. In a small study investigating the effect of 6 weeks of oral sertraline on MDD patients, Anand et al. (2005b) discovered that connectivity between ACC, medial thalamus and pallidostriatum normalised following treatment at rest and when exposed to positive and neutral pictures (Anand et al., 2005b). Andreescu et al. (2013) explored the effects of antidepressants in 'late-life' MDD in a sample of 47 MDD patients and 46 healthy controls. Patients received either SSRI or SNRI medications following the first MR session. After 12 weeks of treatment, there was greater functional connectivity between the mFG and dACC, which disappeared after adjustment for white matter hyperintensity (Andreescu et al., 2013). However, several participants were lost to follow-up before the post-treatment scan. Posner et al. (2013) also examined the effects of duloxetine, but in patients with dysthymia. Using the PCC as a seed region, they observed DMN connectivity following a 10-week course of oral duloxetine. DMN connectivity was normalised between the PCC and right lateral parietal cortex in the treatment arm (Posner et al., 2013). A similar methodology was used by Li et al. (2013), but patients were prescribed a variety of SSRI or SNRI medications after the first MR session. They observed effects on the anterior and posterior subnetworks of the DMN. Antidepressant treatment normalised the increased connectivity observed in the precuneus before treatment (Li et al., 2013).

Although significant effects of antidepressant treatment on the DMN were found, their importance is unclear. No studies are available on the effects of antidepressants on the AN, CCN or salience network. Few resting state studies are available to draw reliable conclusions on the role of the affective and cognitive control networks in MDD. There is also no evidence of any correlations of the DMN changes with improvements in clinical mood rating scales. There are variations between drug treatment

and seed ROIs used in analysis. Furthermore, there is also no clear evidence of the effects in first episode and remitted MDD.

6. Using an NMDA receptor antagonist to probe resting state networks

There is increasing evidence of rapid antidepressant actions of antagonists of *N*-methyl D-aspartate glutamate receptor function such as ketamine and lanicemine (AZD6765) (Berman et al., 2000; Zarate et al., 2006; Zarate et al., 2013). Ketamine has also shown effects on the DMN in healthy volunteers. DMN connectivity of the dmPFC, rACC, mPFC and PCC was reduced 24 h after i.v. infusion of S-ketamine. S-Ketamine was also shown to reduce functional connectivity between the vACC and dmPFC. No change in mood was noted. (Scheidegger et al., 2012). An earlier fMRI study of ketamine pharmacological challenge (phMRI) also found increases in the BOLD signal in the PCC, precuneus and cerebellum in healthy volunteers following acute i.v. administration of racemic ketamine (Deakin et al., 2008).

In view of the reduced connectivity between the vACC and dmPFC due to ketamine reported by Scheidegger et al. (2012) in healthy volunteers, it would be expected that NMDA antagonists would normalise DMN abnormalities in MDD as this effect has been observed with accepted antidepressants in MDD (Anand et al., 2005b; Li et al., 2013). The ACC has been proposed as one of the 'central hubs' of the DMN because of its role in self-referential processing including rumination (Pizzagalli, 2011). Furthermore, it has previously been suggested that normalisation of vACC hyperactivity is essential for symptom remission (Mayberg, 2003).

There is a growing body of evidence to suggest that pretreatment activity of the rACC is predictive of response to antidepressants and ketamine (Salvadore et al., 2009). Decreased BOLD signals have been correlated with reduced glutamate in the rACC (Walter et al., 2009). The rACC also has higher densities of AMPA, kainate and GABA_B receptors than the vACC (Palomero-Gallagher et al., 2009). Several studies have established that NMDA antagonists disable normal inhibitory controls from GABA interneurons on cortical pyramidal neurons, increasing release of glutamate onto non-NMDA receptors. (Bustos et al., 1992; Liu and Moghaddam, 1995). Animal studies have revealed that blockade of AMPA receptors prevents the emergence of the antidepressant effect in forced swim and learned helplessness tests (Maeng et al., 2008). Magnetic resonance spectroscopy (MRS) studies suggest in humans that ketamine disinhibits glutamate release in the ACC (Rowland et al., 2005), although this may be depend on the rate of infusion (Taylor et al., 2012). Experimental drug-challenge studies on RS networks combined with neurochemical measures using MRS in patients and volunteers holds great promise for neuropsychopharmacological insights into MDD.

7. Summary

The resting state consists of the spontaneous low frequency neural activity in correlated brain regions. It can be analysed using a number of methods, each with its own limitations. MDD research has largely focussed on the DMN rather than resting state networks such as the salience network. There is an increasing volume of studies examining the resting state in MDD, leading to interesting findings in the cerebellum, lingual gyrus, ACC, MFG, dIPFC, amygdala and insula. The DMN findings following antidepressant treatment in MDD suggest it would be beneficial to investigate resting state networks using NMDA receptor antagonists with comparisons made to traditional antidepressants. It is hypothesised that resting state fMRI following i.v. administration of an NMDA antagonist such as ketamine would demonstrate the functional neural correlates of the rapid antidepressant response.

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Review article

Ketamine and other potential glutamate antidepressants

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ABSTRACT

The need for rapid acting antidepressants is widely recognised. There has been much interest in glutamate mechanisms in major depressive disorder (MDD) as a promising target for the development of new antidepressants. A single intravenous infusion of ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist anaesthetic agent, can alleviate depressive symptoms in patients within hours of administration. The mechanism of action appears to be in part through glutamate release onto non-NMDA receptors including α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors. However these are also reported effects on 5-HT, dopamine and intracellular effects on the mammalian target of rapamycin (mTOR) pathway. The effects of SSRI (Selective Serotonin Reuptake Inhibitor) antidepressants may also involve alterations in NMDA function. The article reviews the effect of current antidepressants on NMDA and examines the efficacy and mechanism of ketamine. Response to ketamine is also discussed and comparison with other glutamate drugs including lamotrigine, amantadine, riluzole, memantine, traxoprodil, GLYX-13, MK-0657, RO4917523, AZD2066 and Coluracetam. Future studies need to link the rapid antidepressant effects seen with ketamine to inflammatory theories in MDD.

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Contents

1. Introduction	2
2. Efficacy of ketamine in MDD	2
2.1. Methodology of studies	2
2.2. Response to ketamine infusion	2
2.3. Biomarkers of response to ketamine	6
2.4. Trials to identify mechanisms of ketamine effects	6
2.5. Mechanisms of action of ketamine	7
3. Effects of other glutamate drugs on MDD (clinical studies)	7
3.1. Modulators of glutamate release	7
3.1.1. Lamotrigine	7
3.1.2. Riluzole	8
3.2. Drugs acting at NMDA receptors	8
3.2.1. Memantine	8
3.2.2. Amantadine	8
3.2.3. Traxoprodil (CP-101,606)	8
3.2.4. GLYX-13	8
3.2.5. MK-0657	8
3.3. Drugs acting at AMPA receptors	8
3.3.1. RO4917523/AZD2066/Coluracetam	8
4. Conclusions and need for future studies	8
References	10

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1. Introduction

The need for rapid acting antidepressants is widely recognised. Despite the introduction of selective serotonin reuptake inhibitors (SSRI) and several other mechanisms of antidepressant action revolving around monoamine theory in the 1980s, response rates have not improved beyond approximately 60% (Mulrow et al., 2000). Naturalistic studies have observed remission of major depressive disorder (MDD) in only 28% of patients after first line treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Trivedi et al., 2006). Furthermore second and third line treatments demonstrated declining rates of remission in spite of various augmentation strategies (Nierenberg et al., 2006; Trivedi et al., 2008). This has led to interest in new targets for antidepressant action over recent years including neurokinin, corticotrophin releasing factor, intracellular signalling cascades and modulation of glucocorticoid, cytokine, opioid and cannabinoid receptors (Pacher and Kecskemeti, 2004).

Interest in the role of glutamate in depression and antidepressant effects goes back to pharmacological studies in the late 1980s. Reynolds and Miller (1988) reported that tricyclic antidepressants had zinc-like functional effects on the NMDA receptor – they occluded the ion channel associated with the NMDA glutamate receptor. Trullas and Skolnick (1990), on the basis of stress and antidepressant effects on long-term potentiation in the hippocampus, proposed and demonstrated that functional antagonists at the NMDA receptor had antidepressant-like behavioural effects in animals. Berman et al. (2000) made the seminal human observation that a single intravenous infusion of ketamine (a NMDA receptor antagonist anaesthetic agent) alleviated depressive symptoms in patients within hours of administration and peaking some days later (Berman et al., 2000; Zarate et al., 2006a). These effects were replicated by Zarate et al. (2006a) and in bipolar depressive disorder by Diazgranados et al. (2010b). These findings stimulate a number of questions about the role of glutamate in MDD; what is the effectiveness of different glutamate drugs, what is their mechanism of action and how do they affect the glutamate system in MDD?

2. Efficacy of ketamine in MDD

2.1. Methodology of studies

The clinical studies of ketamine are summarised in Table 1. Five of the studies were double-blind crossover randomised controlled trials (RCTs) (Berman et al., 2000; Zarate et al., 2006a; Diazgranados et al., 2010b; Zarate et al., 2012b; Sos et al., 2013). One trial was a double blind RCT (Murrough et al., 2013a). The remaining RCTs were not double blinded. Of the remaining trials, a single blind study observed the effect of ketamine when used as part of an anaesthetic in patients with MDD undergoing orthopaedic surgery (Kudoh et al., 2002). The remaining studies were either open label (Correll and Futter, 2006; Machado-Vieira et al., 2009b; Phelps et al., 2009; Salvatore et al., 2009; aan het Rot et al., 2010; Paslakis et al., 2010; Okamoto et al., 2010; Salvatore et al., 2010; Ibrahim et al., 2011, 2012b; Salvatore et al., 2012; Carlson et al., 2013; Duncan et al., 2013a; Murrough et al., 2013b; Rasmussen et al., 2013) or crossover studies (Paul et al., 2009; Valentine et al., 2011). Mathew et al. (2010) used open label i.v. ketamine examining the effects of lamotrigine pre-treatment and riluzole maintenance treatment. Two studies, which were open label, compared drug effects in MDD patients and healthy volunteers (Salvatore et al., 2009; Okamoto et al., 2010). Although the majority of studies included only patients with MDD, two studies were carried out in bipolar depression and another included one bipolar depressive

into the trial group (Berman et al., 2000; Diazgranados et al., 2010b; Zarate et al., 2012b).

Most studies used ketamine 0.5 mg/kg by intravenous infusion over 40 minutes but some used lower dosages (Correll and Futter, 2006; Sos et al., 2013). Higher doses of 1.0 mg/kg and 1.5 mg/kg have been used as anaesthetic during ECT and preoperatively prior to orthopaedic surgery (Kudoh et al., 2002; Goforth and Holsinger, 2007). A problem common to all studies is that the immediate subjective effects of ketamine reveal the treatment condition so the use of saline placebo infusions does not maintain the blind. One study used midazolam as an active placebo with no saline control group (Murrough et al., 2013a). A number of trials allowed the use of concomitant medications including other antidepressants (Kudoh et al., 2002; Stefanczyk-Sapieha et al., 2008; Diazgranados et al., 2010b; Irwin and Igiewicz, 2010; Rasmussen et al., 2013). A number of studies had MDD patients with comorbid anxiety disorders (Salvatore et al., 2009; Salvatore et al., 2010; Valentine et al., 2011).

The majority of studies used reduction in the Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D) as primary outcome measures except one (Messer et al., 2010). However these scales may have limited validity when used more frequently than weekly. Some studies included measures of psychotomimetic effects (Phelps et al., 2009; Diazgranados et al., 2010b; Ibrahim et al., 2011, 2012b; Zarate et al., 2012b; Carlson et al., 2013; Murrough et al., 2013a, 2013b; Lapidus et al., 2014).

The main problems with the studies are that they employed small sample sizes – most less than 20 participants in the active treatment groups. The samples in seven of the studies had statistically significant differences in patient characteristics between controls and depressives. They included differences in baseline MADRS scores, age, number and severity of episodes (Phelps et al., 2009; Salvatore et al., 2009; Diazgranados et al., 2010b; Mathew et al., 2010; Valentine et al., 2011; Sos et al., 2013). The time points at which MADRS was measured limited understanding the time of the peak effect of ketamine. Additionally, data were read from graphical data in the papers which may have led to errors.

2.2. Response to ketamine infusion

All the studies agree that the antidepressant effect of ketamine begins within 24 hours of a single intravenous infusion and can last up to 14 days. However, there is some variability in the response. The peak reduction on HAM-D scores varied from 15% (Abdallah et al., 2012) to 86% (Denk et al., 2011). Similar changes were seen in the Beck Depression Inventory (BDI) and MADRS scores. The response rates following ketamine infusion range from 20% (Rasmussen et al., 2013) to 90% (aan het Rot et al., 2010). In bipolar depression peak reduction in mood rating scales was noted as early as 40 minutes after start of infusion (Diazgranados et al., 2010a; Zarate et al., 2012b). The antidepressant effect noted in the bipolar depression study (Diazgranados et al., 2010a) occurred earlier but was less sustained than noted by Zarate et al. (2006a) in MDD. Furthermore, lower response rates were noted in bipolar depression than in MDD at the end of day 1 (42% in bipolar depression vs. 71% in MDD) in the ketamine group (Diazgranados et al., 2010a, Zarate et al., 2006a).

Eight studies examined whether repeated doses of ketamine cause a more sustained effect than single dosage (Correll and Futter, 2006; Stefanczyk-Sapieha et al., 2008; Liebrecht et al., 2009; aan het Rot et al., 2010; Messer et al., 2010; Murrough et al., 2013b; Rasmussen et al., 2013; Szymkowicz et al., 2013). aan het Rot et al. (2010) demonstrated relapse in depressive symptoms could be delayed by up to 19 days after the final i.v. ketamine infusion when repeated infusions of ketamine were used. However, patients had

Table 1
Clinical studies of ketamine in major depressive disorder.

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Berman et al. (2000)	Double blind placebo controlled crossover RCT	7 MDD	0.5 mg/kg IV/40 min	HAM-D	-42% ^a	-7% ^a	3 days	50%	Patients aware of placebo
Diazgranados et al. (2010b)	Double blind crossover RCT	18 BPD TR	0.5 mg/kg IV/ 40 min + lithium/ valproate	MADRS	-48% ^a	-18% ^a	40 min	56%	Earlier peak reduction at 40 mins. Concurrent use of lithium/ valproate. Differing sample characteristics (some rapid cycling BD). Patients aware of placebo
Mathew et al. (2010)	Double blind RCT	13 MDD (placebo + ketamine)	0.5 mg/kg IV/ 40 min + lamotrigine/ placebo	MADRS	-60% ^b	No placebo	1 day	65%	No saline control. Higher BMI than in other studies. Ketamine administered open label. Pre-treatment effects
Sos et al. (2013)	Double blind placebo controlled crossover RCT	27 MDD (lamotrigine + ketamine)	0.27 mg/kg i.v./10 min then 0.27 mg/kg i.v./ 20 min + current antidepressant	MADRS	-28%	-2% ^a	1 day	37%	Mixed patient group differed in number of episodes and baseline MADRS score between those who had placebo and ketamine first
Zarate et al. (2006a)	Double blind placebo controlled crossover RCT	18 MDD TR	0.5 mg/kg IV/40 min	HAM-D	-56%	-9.8%	1 day	71%	Inpatient sample. Some had history of substance misuse. Patients aware of placebo
Zarate et al. (2012b)	Double blind placebo controlled crossover RCT	15 BPD TR	0.5 mg/kg IV/ 40 min + lithium/ valproate	MADRS	-50% ^a	-6% ^a	40 min	79%	Patients aware of placebo
Murrough et al. (2013a)	Double blind placebo controlled RCT	47 MDD (ket) 25 MDD (midazolam)	0.5 mg/kg IV/40 min	MADRS	-55%	-27% midazolam	1 day	64%	Longer duration of illness and current episode in patients receiving ketamine. Active comparator but no saline control
Abdallah et al. (2012)	Single blind placebo controlled RCT	8 MDD (thiopental + ketamine)	0.5 mg/kg i.v. as anaesthesia for ECT	HAM-D	-15% ^a	-16% ^a	Not reported		No significant difference after first or subsequent ECT sessions. Concurrent use of antidepressants and other medications. Differences between groups in medication used. Longer seizure duration in ketamine group
Yousefi et al. (2014)	Double blind placebo controlled RCT	15 MDD (thiopental) 14 MDD (ketamine)	1-2 mg/kg i.v. as anaesthesia for ECT	HAM-D	-32%	-13%	2 days		Significant difference in HAM-D favouring ketamine. Longer seizure duration with ketamine and increased electrical dose for ECT
Lapidus et al. (2014)	Double blind placebo controlled crossover RCT	18 MDD TR	50 mg intranasal	MADRS	-43% ^a	-17% ^a	1 day	44%	Patients aware of placebo. Concurrent use of psychotropic medications
Kudoh et al. (2002)	Single blind, parallel group RCT	35 MDD (ket) 35 MDD (no ket) 25 CON (ket)	1.5 mg/kg propofol + 2 µg/kg fentanyl i.v. ± 1.0 mg/kg ketamine i.v. anaesthetic	HAM-D	-22%	-17%	1 day		Concurrent use of antidepressants and other medications. Higher dosages of ketamine than in other trials. No detail of length of infusion or whether bolus dosing occurred
Loo et al. (2012)	Single blind RCT	17 MDD/ 5 BPD (ket) 17 MDD/ 7 BPD (saline)	0.5 mg/kg i.v. following anaesthesia for ECT	MADRS	-51%	-56%	Not reported		No significant differences in MADRS score reduction. High rate of dropout. Significantly higher thiopentone dose in placebo group. Small sample size. Variation between unilateral and bilateral ECT and dosage reported
Rasmussen et al. (2014)	Single blind RCT	21 MDD (ket) 17 MDD (methohexital)	1.0 mg/kg i.v. as anaesthetic prior to ECT	HADS	Baseline scores not present	Baseline scores not present	Not reported		No significant differences in HADS score reduction. No baseline scores reported. Variation between unilateral and bilateral ECT. Differences in confusion, visual disturbance and seizure motor effects

Table 1 (continued)

Reference	Methodology	Population	Ketamine preparation	Primary outcome measure	Peak reduction in mean rating scale score		Peak time of ketamine response	Ketamine response rate	Comment
					Ketamine	Control			
Wang et al. (2012)	Single blind RCT	12 MDD (propofol) 12 MDD (ketamine) 16 MDD (ketamine + propofol)	0.8 mg/kg i.v. as part of anaesthetic for ECT	HAM-D	-79% ^a	-60% ^a	1 day		No significant differences in HAM-D score reduction. Variation between unilateral and bilateral ECT and dosage reported. Concurrent use of antidepressant drugs
Paul et al. (2009)	Open label crossover trial	2 Recurrent MDD	0.5 mg/kg i.v./ 50 min + 0.25 mg/kg 5-ketamine/30 min 7 days apart	HAM-D	-58%	No placebo	1 day	50%	Response not measured before 1 day. Older mean age. One patient showed no change. Open label. No saline control group
Valentine et al. (2011)	Open label crossover trial	10 MDD	0.5 mg/kg i.v./40 min	HAM-D	-29% ^a	-10% ^a	3 days ^a		Older mean age of patients. Co-morbid anxiety disorders. Heterogeneous sample with regard to number of MDD episodes and severity of MDD
Salvadore et al. (2009)	Open label case control	11 MDD TR 11 CON	0.5 mg/kg i.v./40 min	MADRS	-36%	No placebo	230 min		No saline control of ketamine infusion. Older mean age of patients. High levels of co-morbid anxiety
Kranaster et al. (2011)	Open label case control	16 MDD (ket) 26 MDD (thiopental)	5-ketamine (mean dose 46.7 mg)	HAM-D	-76%	-73%	Not reported		No significant differences in HAM-D score reduction. Mixed group. Some were psychotic. Retrospective study. Variable number of ECT sessions
Okamoto et al. (2010)	Open label case control	11 MDD TR (ket) 20 MDD TR (propofol)	0.86 mg/kg i.v. bolus or 0.94 mg/kg propofol (mean dose) ketamine anaesthesia prior to ECT	HAM-D	-78%	-76% (propofol)	28 days ^d		Continued current antidepressant after ECT. No true control group
aan het Rot et al. (2010)	Open label trial	10 MDD TR	0.5 mg/kg IV/40 min × 6	MADRS	-67% ^a	No placebo	240 min ^e	90% ^f	Older mean age of patients. Repeat infusions given as outpatients and had reducing efficacy. Open label. No saline control group
Carlson et al. (2013)	Open label trial	20 MDD	0.5 mg/kg i.v./40 min	MADRS	-44%	No placebo	40 min	30%	No saline control group. Open label
Diazgranados et al. (2010b)	Open label trial	33 MDD TR	0.5 mg/kg i.v./40 min	MADRS	-44% ^{a,b}	No placebo	40 min		No saline control group. Mood rating scale score differences in those with suicidal ideation
Duncan et al. (2013a)	Open label trial	30 MDD TR	0.5 mg/kg i.v./40 min	MADRS	-46%	No placebo	240 min	40%	No saline control group. Open label. Positive correlation between baseline delta sleep ratio and response to ketamine
Ibrahim et al. (2011)	Open label trial	40 MDD TR	0.5 mg/kg i.v./40 min	MADRS	-44% ^{a,b}	No placebo	40 min		No saline control group. Response to treatment whether previously responded to ECT or not
Ibrahim et al. (2012b)	Open label trial	42 MDD TR	0.5 mg/kg i.v./40 min + /- riluzole/placebo	MADRS	-39% ^{a,b}	No placebo	1 day	62%	Underpowered study. Hospital inpatients. No saline control group. Open label
Machado -Vieira et al. (2009b)	Open label trial	23 MDD TR	0.5 mg/kg i.v./40 min	MADRS	-42% ^{a,b}	No placebo	40 min	48%	Most patients obese. Very high number of episodes of MDD (Mean 32). No saline control group
Murrough et al. (2013b)	Open label trial	24 MDD TR	0.5 mg/kg IV/ 40 min - × 6 infusions	MADRS	-59% ^{a,c}	No placebo	2 h	71%	Open label trial. Part of previous study. Protocol change removed patient exclusion if non-response halfway through. Not all received multiple dosing
Phelps et al. (2009)	Open label trial	26 MDD TR	0.5 mg/kg i.v./40 min	MADRS	-42% ^{a,b}	No placebo	40 min	43%	Significant baseline differences in mood rating scale scores
Rasmussen et al. (2013)	Open label trial	10 MDD	0.5 mg/kg i.v./100 min × 4	MADRS	-34% ^{a,c}	No placebo	Post-infusion	20% ^f	No saline control group. Open label. Variable number of completed infusions. Concurrent use of other medications
Salvadore et al. (2010)	Open label trial	15 MDD	0.5 mg/kg i.v./40 min	MADRS	-37%	No placebo	230 min		Older mean age of patients. Large number with co-morbid anxiety disorder. No saline control group. Open label
Salvadore et al. (2012)	Open label trial	14 MDD	0.5 mg/kg i.v./40 min	MADRS	-25%	No placebo	230 min		No saline control group. Some participants from previous trials. Older mean age of patients. Open label
Chilikuri et al. (2014)	Open label trial	27 MDD	0.5 mg/kg i.v./40 min or 0.5 mg/kg IM or 0.25 mg/kg IM	HAM-D	59% - IV 60% - IM	No placebo	120 min		0.25 mg/kg IM dose produced reduction in HAM-D of 57%. No saline control group. Open label

Chazemi et al. (2014)	Single blind RCT	9 MDD (ket) 9 MDD (ket+ECT)	0.5 mg/kg i.v./45 min × 3	HAM-D	−42%	−14% ECT	1 day	77%	No saline control group. Continued use of other psychotropic medication
Messer et al. (2010)	Open label case series	2 MDD TR	0.5 mg/kg IV/40 min × 2 – × 6	BDI	−35% ^a	No placebo	Not reported		Open label. No saline control group. Both patients markedly overweight and had medical comorbidities
Jarventausta et al. (2013)	Single blind RCT	16 MDD TR (S-ket+ propofol) 16 MDD TR (propofol)	0.4 mg/kg S-ketamine bolus prior to anaesthetic for ECT	MADRS	−73% ^a	−73% ^a (propofol)	Not reported		No additional benefit of S-ketamine. Concurrent use of antidepressants. No active comparator
Pasłakis et al. (2010)	Open label case series	4 MDD	1.25 mg/kg oral S-ketamine for 14 days+ current antidepressant	HAM-D	−43%	No placebo	14 days ^c	50%	Open label. No saline control group. Potential augmentation effect of current antidepressants
Segmüller et al. (2013)	Open label case series	6 MDD TR	0.25 mg/kg S-ketamine IV/40 min × 6 + current antidepressant	HAM-D	−55%	No placebo	120 min	50%	Open label. No saline control group. Older mean age and long illness duration. Potential augmentation effect of current antidepressants
Szymkowitz et al. (2013)	Open label case series	3 MDD TR	0.5 mg/kg i.v./40 min × 6	MADRS	Data unclear	No placebo	Data unclear		Open label. No saline control group. Patients taking other medications. All patients responded after repeated infusions
Correll and Futter (2006)	Case reports	2 MDD	0.1–0.3 mg/kg/h.v.for 5 days	HAM-D	−73%	No placebo	4 days		Open label. No saline control group. Patients markedly overweight
Denk et al. (2011)	Case report	1 MDD TR	0.25 mg/kg i.v. S-ketamine/40 min	MADRS	−86%	No placebo	Post-infusion		Open label. No saline control group
Glue et al. (2011)	Case report	2 MDD	0.5/0.7/1.0 mg/kg IV/40 min	MADRS	−34% ^a	No placebo	Not reported		Open label. No saline control group. Ascending dosages. Peak effect seen after 0.7 mg/kg
Goforth and Holsinger (2007)	Case report	1 Severe MDD with psychotic features	100 mg IM anaesthesia prior to ECT	MADRS	−60%	No placebo	3 days		Open label. No control group
Irwin and Iglewicz (2010)	Case reports	2 MDD	0.5 mg/kg PO	HAM-D	−41%	No placebo	60 min		Open label. No control group. Several concurrent psychotropic medications. Comorbid anxiety disorders also present
Liebreinz et al. (2009)	Case report	1 MDD TR	0.5 mg/kg IV/50 min × 2	HAM-D	−57% ^a	No placebo	1 day		Open label. No saline control group. Polysubstance dependence
Stefanzyk-Sapieha et al. (2008)	Case report	1 MDD TR	0.5 mg/kg i.v./60 min × 2	HAM-D	−43% ^a	No placebo	60 min		Open label. No saline control group. Diagnosis of metastatic prostate cancer. Several concurrent medications

Abbreviations: BDI=Beck Depression Inventory; BPD=Bipolar Depression; CON=Controls; HADS=Hospital Anxiety and Depression Scale; HAM-D=Hamilton Depression Rating Scale; IM=Intramuscular; IV=Intravenous; ket=Ketamine; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; PO=oral; pla=Placebo; RCT=Randomised Controlled Trial; Response=50% reduction in scores; TR=treatment resistant.

^a Calculated from graphical data presented in paper.

^b Only ketamine data presented here.

^c In two cases.

^d Maximal reduction after 8th ECT session.

^e After 1st infusion.

^f After final session of ECT.

previously participated in riluzole and ketamine trials by the same group and had shown response to ketamine. Repeated i.v. ketamine dosing demonstrated improved mean reductions in MADRS scores compared to single i.v. ketamine infusion (85% after 6th infusion vs. 67% after 1st infusion) (aan het Rot et al., 2010). Murrough et al. (2013b) administered a regime of open label ketamine three times a week over 12 days. Whilst there were a number of methodological problems, those who responded had a median time to relapse of 18 days (Murrough et al., 2013b). Rasmussen et al. (2013) further demonstrated that repeated infusions improved response rates to ketamine utilising a slower infusion rate of 0.5 mg/kg i.v. over 100 minutes. Correll and Futter (2006) had observed the benefits of 5 days continuous i.v. ketamine infusion. Although onset of efficacy appeared no quicker than with single or repeated i.v. infusions, remission was maintained for at least 12 months from discontinuing i.v. ketamine.

2.3. Biomarkers of response to ketamine

A number of biomarkers of ketamine response have been suggested (Zarate et al., 2013). These include pre-treatment predictor effects of ketamine and the effect of ketamine as a correlates or predictors. Response to i.v. ketamine was associated with increases in circulating brain derived neurotrophic factor (BDNF) and slow wave EEG sleep activity on the night of ketamine infusion in one study of treatment resistant MDD patients (Duncan et al., 2013b). Baseline delta sleep ratio has also been correlated with MADRS score reductions following ketamine infusion (Duncan et al., 2013a). Plasma BDNF levels were negatively correlated to MADRS scores following ketamine infusion but not midazolam, an active control, in another sample of treatment resistant MDD (Haile et al., 2014). This finding has previously been observed in MDD patients on standard antidepressants (Kurita et al., 2012) but another ketamine study did not observe changes in BDNF (Machado-Vieira et al., 2009b). Increased BDNF function may be explained by the results of a recent study which demonstrated that MDD patients with Val/Val BDNF allele at rs6265 (Val66Met single nucleotide polymorphism) exhibited increased antidepressant response to ketamine (Laje et al., 2012).

Ketamine responders, at 230 minutes according to MADRS, have significantly lower D- and L-serine plasma concentrations compared to non-responders (Moaddel et al., 2014). Baseline D-Serine levels in ketamine responders were also associated with higher Clinician Administered Dissociative States Scale (CADSS) scores. This is opposite to the findings of a previous study of standard antidepressants which revealed non-response corresponded to lower D- and L-serine levels (Maes et al., 1998). Luckenbaugh et al. (2014) has recently suggested that the dissociative but not psychotomimetic effects of ketamine are a biomarker of final response in a meta-analysis of ketamine effects in bipolar disorder and MDD patients. The prolonged antidepressant effects of ketamine may also be related to the half-life of active metabolites such as dehydronorketamine and hydroxynorketamine which have been reported to be present up to 3 days following dosing (Zarate et al., 2012a; Zhao et al., 2012).

There is also pre-treatment predictor effects observed. Increased pre-treatment rostral anterior cingulate cortex (ACC) activity measured by magnetoencephalographic recordings (MEG), has predicted response to ketamine infusion following exposure to fearful faces although there was no control group or MEG recording following ketamine (Salvadore et al., 2009). Cornwell et al. (2012) reported increased cortical excitability on MEG within the period of antidepressant response, with responders to ketamine having increased γ -band responses in the somatosensory cortex using MEG. In another study MDD patients with the least engagement of the pregenual ACC during a working memory task (N-back) had

the greatest improvement in mood within 4 hours of ketamine infusion (Salvadore et al., 2010).

Pre-treatment neurotransmitter and metabolic abnormalities have been reported. Salvadore et al. (2012) discovered pre-treatment glutamate+glutamine (Glx)/glutamate ratio in the dorsomedial/dorsal anterolateral prefrontal cortex negatively correlated with improvement in depressive symptoms following ketamine in MDD patients. A preliminary PET study has demonstrated decreased metabolism in the right habenula, insula, ventrolateral and dorsolateral prefrontal cortices (dlPFC) following ketamine infusion (Carlson et al., 2013). The effects in the ACC, neurotransmitter and metabolic abnormalities suggest it may be possible to identify ketamine responders by the effects in the ACC and PFC.

Several studies have found biological predictors of, or association with, the effects of ketamine but so far there are no replicated findings and their clinical utility and relevance to the mechanism of action of ketamine remain uncertain. Some clinical predictors of ketamine response in MDD have also been reported. They include family history of alcohol dependence (Phelps et al., 2009) and in bipolar depression increased peripheral vitamin B12 levels (Permoda-Osip et al., 2013). Across both MDD and bipolar depression improvement was correlated with higher body mass index and fewer previous suicide attempts (Niciu et al., 2014). However, the current biomarkers are not currently practical for clinical usage.

2.4. Trials to identify mechanisms of ketamine effects

Eight mechanistic trials using i.v. ketamine have been carried out (Paul et al., 2009; Machado-Vieira et al., 2009b; Mathew et al., 2010; Paslakis et al., 2010; Denk et al., 2011; Ibrahim et al., 2012b; Duncan et al., 2013a; Segmiller et al., 2013; Sos et al., 2013). One study investigated the effect of lamotrigine on ketamine response in treatment resistant MDD. Mathew et al. (2010) randomised patients to receive lamotrigine pre-treatment followed by open label i.v. ketamine as well as riluzole maintenance treatment in an attempt to prolong the duration of the effects of ketamine. Lamotrigine acts by inhibiting glutamate release. Riluzole modulates glutamate release but also enhances synaptic AMPA receptor expression (Du et al., 2007) and blocks NMDA receptor activation (Kalia et al., 2008). Mathew et al. (2010) hypothesised that lamotrigine would block the enhanced glutamate release produced by administration of ketamine and riluzole would prolong the effects of ketamine. Lamotrigine failed to attenuate psychotomimetic symptoms produced by ketamine or enhance its antidepressant effects. Furthermore riluzole did not sustain response in those patients that had responded to i.v. ketamine infusion and the same negative result was reported by (Ibrahim et al., 2012b). Both lamotrigine and riluzole reduce glutamate release and their lack of effect on ketamine's efficacy in the Mathew et al. (2010) study suggests that antidepressant effects were not dependent on a secondary increase in glutamate release. Serum levels of lamotrigine were not measured.

Two open-label case studies investigated the S-isomer of ketamine which has a higher affinity than the R-isomer for the phencyclidine site of the NMDA receptor site (Paul et al., 2009; Paslakis et al., 2010). S-ketamine has a 4 fold greater anaesthetic potency and higher frequency of psychotomimetic side effects in humans (Kohrs and Durieux, 1998). One study compared single infusions of the two isomers 7 days apart in two patients (Paul et al., 2009). They found one patient did not improve. The second patient had 58% reduction after initial racemic ketamine infusion and 46% reduction following the second infusion of S-ketamine 7 days later. The other S-ketamine study exploited the use of oral S-ketamine preparation as add on therapy (Paslakis et al., 2010). 4 patients showed a mean improvement

in HAM-D of 43% after 14 days treatment. Others have examined the adjunctive effects of S-ketamine with propofol and ECT (Jarventausta et al., 2013). There are no trials of R-ketamine reported. However, in an animal model R-ketamine immobility times were significantly reduced in the forced swim and tail suspension tests 7 days following ketamine infusion compared to S-ketamine (Zhang et al., 2014). There were no changes in sucrose preference, a model of anhedonia, in animals. These studies suggest S-ketamine does not have the same efficacy as racemic ketamine and that R-ketamine in animal models is more potent and long acting than S-ketamine.

Alternative routes of administration have recently been examined. Lapidus et al. (2014) reported comparable improvement in mood with intranasal ketamine in a randomised, double-blind placebo controlled trial although there was no group that received i.v. ketamine as a comparator. Chilukuri et al. (2014) observed that 0.25 mg/kg IM ketamine produced the similar reductions in HAM-D to i.v. ketamine in MDD in an open label parallel group trial.

One difficulty in evaluating ketamine studies is that patients are not blind to treatment because of the dissociative effects of the ketamine making an appropriate sham/placebo treatment hard to envisage. The psychotomimetic effects of ketamine also make its use problematic in clinical practice. Slow infusion of low dose ketamine is not associated with serious psychotomimetic side-effects but a drawback to clinical use is that the benefits are short-lasting.

2.5. Mechanisms of action of ketamine

Ketamine works by “trapping block” channel closure and slow open-channel blocking/unblocking kinetics of the NMDA receptor (MacDonald et al., 1991; Machado-Vieira et al., 2009a). Because non-competitive NMDA receptor antagonists like ketamine produce a block only when the channel is in its open state after activation; it is use-dependent (Huettner and Bean, 1988). This means that the drug will act selectively at the site of excess NMDA activation (Mealing et al., 1999). One consequence of blockade of the NMDA receptor-associated ion-channel is that glutamate release is increased (Moghaddam et al., 1997) and is thus available to act on non-NMDA glutamate receptors. The increase in glutamate release is known to have behavioural effects in animals because the effects of ketamine-like drugs are blocked by glutamate antagonists that act on AMPA receptors (Maeng et al., 2008). A number of animal and human studies have attempted to determine whether increased glutamate release (possibly acting on AMPA receptors) or the primary NMDA block is the mechanism of antidepressant effect of ketamine.

Ketamine subunit selectivity for GluN1/GluN2A (Narita et al., 2001) and GluN2B (De Vry and Jentsch, 2003) has been discovered in an animal drug discrimination model utilising using compounds to mimic the behavioural effects of ketamine. The response to ketamine in rats was mimicked by PCP and dizocilpine (antagonists at GluN1/GluN2A/GluN2B) but was only partly reproduced by the GluN2B receptor antagonist ifenprodil (Narita et al., 2001). This would suggest the psychotomimetic effects of ketamine are produced by GluN1/GluN2A subunits rather than GluN1/GluN2B. An in-vitro receptor binding study found evidence that ketamine binds to the high affinity D2 receptor and to 5-HT_{1A} (Fukumoto et al., 2014), and 5-HT₂ receptors Ketamine increases extra-cellular dopamine and serotonin levels in the medial prefrontal cortex in rats when given acutely (Hirota and Lambert, 1996; Lindfors et al., 1997). However i.v. ketamine failed to displace raclopride binding in humans (Kegeles et al., 2002). An interaction with μ - and κ -opioid has been also been suggested (Wong et al., 1996; Hirota et al., 1999).

Ketamine is antidepressant-like in animal models of MDD. It reduced immobility in the forced swim test, onset of behavioural despair and anhedonia in rats (Yilmaz et al., 2002). Li et al. (2010) presented evidence that suggested that the rapid action of ketamine

could be mediated by activation of the mammalian target of rapamycin (mTOR) signalling cascade in the prefrontal cortex (PFC) seen in rats. mTOR has been linked to local protein synthesis in synapses and the formation of new synapses. This might account for the delayed antidepressant effects that emerge long after the disappearance of ketamine from the circulation. The authors demonstrated transient increases in brain preparations of mTOR, 4E binding protein (4E-BP1), P70S6 kinase (p70S6K) phosphorylation, extracellular regulated kinase (ERK) and protein kinase B following administration of low dose ketamine to rats. These increases were associated with antidepressant behavioural actions with ketamine, but not conventional antidepressants such as imipramine or fluoxetine. Pre-treatment with an AMPA receptor antagonist NBQX blocked these molecular effects completely as was also reported by Zhou et al. (2014). This further supports the theory that ketamine's antidepressant effects are mediated by increased release of glutamate onto non-NMDA receptors. Such findings have encouraged interest in drugs which enhance AMPA receptor function, the AMPAkinases or positive allosteric modulators (see Section 3).

That ketamine increases glutamate release in humans was confirmed using [¹H]MRS by Rowland et al. (2005) although this was not corroborated by Taylor et al. (2012). However, two studies reported effects of ketamine in healthy volunteers were blocked by pre-treatment with lamotrigine. The rationale was that lamotrigine is an anticonvulsant that decreases glutamate release by acting on sodium channels in the nerve terminals. In a human pharmacological-challenge MRI (phMRI) study, Deakin et al. (2008) found that i.v. ketamine in healthy volunteers evoked increases in blood oxygen level dependent (BOLD) signal in a variety of cortical and subcortical brain regions and this itself suggested increases in glutamate activation. Furthermore these effects were prevented by pre-treatment with lamotrigine. Both Deakin et al. (2008) and Anand et al. (2000) reported that lamotrigine blocked most of the dissociative and mild psychotomimetic effects of ketamine. However, in both studies the only subjective effect that was not attenuated by lamotrigine was euphoria which was actually augmented in the Anand et al. (2000) study. This suggests that ketamine's immediate effects on mood may be mediated directly by NMDA blockade and not by the secondary effect of increased glutamate release. However, the delayed antidepressant effect seen in patients might involve different mechanism from the acute effect on mood in volunteers.

3. Effects of other glutamate drugs on MDD (clinical studies)

3.1. Modulators of glutamate release

3.1.1. Lamotrigine

Lamotrigine is an anticonvulsant that stabilizes neuronal membranes and prevents glutamate release via inhibition of cation channels (Leach et al., 1991; Grunze et al., 1998; Pisani et al., 2004). Lamotrigine is also thought to affect 5-HT, noradrenaline and dopamine uptake (Southam et al., 1998).

In bipolar depression, a multicentre double-blind randomized controlled trial of lamotrigine (50 mg daily or 100 mg twice daily for 7 weeks) in 192 outpatients demonstrated significant improvement in the Clinical Global Impression (CGI), HAM-D and MADRS. (Calabrese et al., 1999). However, Calabrese et al. (1999) noted rashes, headaches and a small proportion manic or hypomanic episodes. A recent meta-analysis reported lamotrigine was effective in bipolar depression (Geddes et al., 2009). Unfortunately these positive results have not translated to studies in humans in MDD comparing lamotrigine to placebo (Amann et al., 2011; Reid et al., 2013).

3.1.2. Riluzole

Another inhibitor of glutamate release originally used in the treatment of amyotrophic lateral sclerosis is riluzole. It acts to inhibit glutamate release through inactivation of sodium channels with a similar mechanism to lamotrigine (Benoit and Escande, 1991; Wang et al., 2004). Riluzole also enhances synaptic AMPA receptor expression (Du et al., 2007) and blocks NMDA receptor activation (Kalia et al., 2008). There were significant improvements in the MADRS with response rate of 32% overall in an open labelled trial of riluzole alone over 6 weeks in 19 patients with treatment resistant MDD (Zarate et al., 2004). As with lamotrigine headaches were a significant proportion of the adverse effects as were gastrointestinal side effects and restlessness. There was a short drug washout period prior to commencement, and varying length of medication (Zarate et al., 2004). A similar positive result was found in an open label study of 14 patients with bipolar depression of riluzole up to 200 mg/day in combination with lithium. Improvements in the MADRS and CGI during the 8 week trial period were reported. There was no control group (Zarate et al., 2005). Concomitant use of lithium may have also affected the results given its reported effects on NMDA receptors (Nonaka et al., 1998).

However, as noted previously, riluzole did not maintain the acute antidepressant effects of ketamine in Mathew et al. (2010) leading to early trial termination. Brennan et al. (2010) reported riluzole 100–200 mg significantly decreased HAM-D, MADRS and CGI-S scores in bipolar disorder depression in an open label trial. The lack of control group was a problem. Follow up was very frequent which may have also improved scores. In addition some patients were also continuing to use antidepressants and antipsychotics. Open label augmentation of current antidepressant therapy using riluzole by Sanacora et al. (2007) reported significant improvements in both anxiety and depressive symptoms. Overall, there is good evidence to support the antidepressant effect of riluzole in MDD and other conditions (Sanacora and Banasr, 2013).

3.2. Drugs acting at NMDA receptors

3.2.1. Memantine

Memantine is derivative of amantadine and an NMDA receptor antagonist used in the treatment of moderate to severe Alzheimer's dementia (Hashimoto, 2009). It may have agonist activity at dopamine D₂ receptors (Seeman et al., 2008). Zarate and colleagues reported on 32 patients with MDD in a double-blind placebo controlled trial of memantine versus placebo for 8 weeks (Zarate et al., 2006b). No difference was noted between the treatment groups in MADRS scores at the end of the trial. Differences between this and previous ketamine studies in humans were explained by lower NMDA receptor affinity, faster open channel blocking/unblocking kinetics and partial trapping channel closure of memantine (Zarate et al., 2006b). A 12 week open label trial of memantine in 8 patients however found MADRS scores improved within 1 week of treatment, continued till week 8 and were maintained till the end of the trial. At 12 weeks mean improvement was 16.7 points. There was no washout period or control group, and patients were not excluded from taking other medications (Ferguson and Shingleton, 2007). Somnolence, headaches, dizziness and anxiety were all noted as side effects in this trial (Ferguson and Shingleton, 2007). The evidence for memantine's antidepressant effect is not clear.

3.2.2. Amantadine

Amantadine is an NMDA antagonist commonly prescribed for the treatment of Parkinson's disease and has been used as an antiviral. It is thought to inhibit NMDA responses through stabilisation of the

ion channel and a more rapid rate of closure (Blanpied et al., 2005). Noradrenergic mechanisms may also be a factor in the action of amantadine (Moryl et al., 1993). Amantadine has been shown to improve mood in humans with "chronic depressive syndrome" when given up to 200 mg/day for 4 weeks (Vale et al., 1971). Use as an adjunctive therapy in major and bipolar depression has been trialled open label in 25 patients with 68% having > 50% reduction on the HAM-D (Dietrich et al., 2000). However there is no RCT evidence to support its efficacy in depression and as such the evidence is limited and unreliable.

3.2.3. Traxoprodil (CP-101,606)

CP-101,606 is an GluN2B subunit selective NMDA receptor antagonist which has been studied as adjunctive therapy to paroxetine (Preskorn et al., 2008). Patients initially had 6 weeks of open-label treatment with paroxetine 40 mg/day. Non-responders (30 patients) were then randomized to CP-101,606 intravenous infusion or placebo. Non-response was defined as improvement of 20% or less on the HAM-D. They continued on paroxetine 40 mg/day for another 4 weeks till the end of the study. The addition of CP-101,606 produced a 60% response rate versus 20% for placebo on the HAM-D with 33% meeting criteria for remission by day 5. Response was maintained in 42% of patients till 15 days after. The dosing of CP101,606 was reduced to 0.5 mg/kg for 1.5 hours for half the patients. This was done for safety reasons due to the high number of dissociative effects caused by CP-101,606 at higher doses but will have led to methodological bias (Preskorn et al., 2008).

3.2.4. GLYX-13

GLYX-13 is a novel NMDA receptor glycine site functional partial agonist. It recently completed phase II trials and was reported to have antidepressant effects within 24 hours which last up to 7 days in MDD patients who had failed one or more antidepressant medications. There were no dissociative effects (Burch, 2012).

3.2.5. MK-0657

Ibrahim et al. (2012a) investigated MK-0657, a GluN2B antagonist that was administered orally to treatment resistant MDD patients for 12 days. The study design was a randomised, double blind, placebo controlled crossover trial. MADRS was the primary outcome measure although HAM-D was also completed. No significant improvement was noted on MADRS. Significant improvement was noted on BDI and HAM-D. No dissociative reactions were reported (Ibrahim et al., 2012a). Sample size was only 5 and therefore it is impossible to draw any real conclusions. In addition the conflicting mood rating scores further confuse the evidence.

3.3. Drugs acting at AMPA receptors

3.3.1. RO4917523/AZD2066/Coluracetam

There are number of novel compounds which have been recently trialled. These include the mGlu₅ antagonists RO4917523 and AZD2066. The latter no antidepressant effects in patients with MDD on MADRS (Hashimoto et al., 2013). Older AMPAkinases such as levetiracetam have not shown evidence of efficacy but several more potent compounds have been developed such as Coluracetam (BCI-540) which is in clinical trials (Saricicek et al., 2011).

4. Conclusions and need for future studies

The current theory of NMDA antagonist's antidepressant effect is summarised with evidence in Table 2.

If glutamate is an important mechanism of action of antidepressant drugs, the question arises whether they correct an illness-related abnormality. However, the answer is fairly inaccessible in

Table 2
NMDA antagonists as antidepressants: summary of evidence.

Therapeutic mechanism	Increases effect of glutamate on non-NMDA receptors	Prevents overstimulation of NMDA receptors
Glutamate neurotransmission in depressed patients	↓Glx (glutamine+glutamate) several proton MRS studies in MDD (Hasler et al., 2007; Block et al., 2009; Bhagwagar et al., 2008) ↓Gln/Cr, Gln (glutamine)/glx ratios decreased (Block et al., 2009) Increased mGlu ₂ , mGlu ₅ and mGlu ₇ in MDD (Karolewicz et al., 2009; Feyissa et al., 2010)	Overstimulation of NMDA PM brain (Law and Deakin, 2001; Nudmamud-Thanoi and Reynolds, 2004; Beneyto et al., 2007; Feyissa et al., 2009) Glial deficiency and/or failure of glial glutamate uptake PM brain (Choudhary et al., 2005; Miguel-Hidalgo et al., 2010; Sanacora and Banasr, 2013) Post-mortem reductions in ionotropic and metabotropic glutamate receptors (Law and Deakin, 2001; Beneyto et al., 2007; Feyissa et al., 2009; Karolewicz et al., 2009)
Effects of glutamate drugs on depression	Ketamine has antidepressant effects in MDD (Moghaddam et al., 1997; Berman et al., 2000; Zarate et al., 2006a; Maeng et al., 2008; Murrough et al., 2013a; Zhou et al., 2014) Lamotrigine antidepressant in BPD (Calabrese et al., 1999)	Lamotrigine did not block AD effects of single dose i.v. ketamine (Mathew et al., 2010) Traxoprodil acts as antidepressant (Preskorn et al., 2008)
Glutamate and animal models of depression	Ketamine increases glutamate release onto AMPA receptors (Moghaddam et al., 1997; Maeng et al., 2008; Zhou et al., 2014) AMPA agonism enhances antidepressant function (Zhou et al., 2014) GluA1 (AMPA) knockout mice depression-like with increased glutamate release onto NMDA receptors (Chourbaji et al., 2008) Riluzole increases synaptic AMPA receptor expression (Du et al., 2007) Ketamine activates synapse formation via mTOR pathway (Li et al., 2010)	GluN2A knockout mice antidepressant effects (Boyce-Rustay and Holmes, 2006) Ceftriaxone increases EAAT2 gene transcription and is antidepressant-like in animals (Mineur et al., 2007)
Effects of standard antidepressants on glutamate function in animals/humans	Antidepressants increase AMPA function (Ampuero et al., 2010) Citalopram increases glutamate cycling (Williams et al., 2007)	Antidepressants down regulate NMDA function (Nowak et al., 1996; Boyer et al., 1998; Nowak et al., 1998; Szasz et al., 2007)

living humans. Despite the 40% heritability of depression, no glutamate or other risk genes have yet been identified from large scale genome-wide association studies (Flint and Kendler, 2014). In principle determination of glutamate concentration in vivo in brain should be possible with [¹H]MRS. However, at commonly available 3T field strengths, it is difficult to separate glutamate and glutamine peaks and the combined peak called Glx has been used. Nevertheless, several studies have shown reduced content of Glx in studies in the ACC, PFC, dlPFC, amygdala and hippocampus (Yildiz-Yesiloglu and Ankerst, 2006; Hasler et al., 2007; Bhagwagar et al., 2008; Block et al., 2009). More recent studies, however, report no difference when glutamine when glutamate is removed from the spectra in the dlPFC and ACC (Nery et al., 2009; Taylor et al., 2009) while Sanacora et al. (2004) reported increased glutamate content in occipital cortex in a large sample of MDD. Inferences about synthesis and release from static concentrations are uncertain. However, a recent study using ¹³C glucose MRS found no evidence for altered glutamate/glutamine cycling in occipital cortex in depression (Abdallah et al., 2014). The state of presynaptic glutamate release in-vivo in MDD remains uncertain.

In human post-mortem brain a number of studies have reported molecular and cytoarchitectural evidence of reduced astroglial numbers and function (Sanacora and Banasr, 2013). This has led to an important integrative theory that glial retraction allows glutamate (i) to spill over onto extrasynaptic dendritic NMDA receptors which mediate cytotoxic depressogenic effects and (ii) to access extrasynaptic terminal mGlu₂ receptors resulting in inhibition of glutamate release. NMDA antagonists would reverse the deficient glutamate release and block the toxic stimulation of extrasynaptic NMDA receptors. However, the evidence for glial pathology is not entirely consistent. The sole study of glutamine synthetase, the glial enzyme that recycles glutamate to glutamine and back the neurone, found no changes in MDD in post-mortem brain (Toro et al., 2006). The glial dysfunction theory suggests that drugs that increase glial uptake of glutamate could restore normal

synaptic function. The antibiotic ceftriaxone appears to work in this way in animal models but there have been no trials in humans.

A number of studies have reported reduced rather than increases in NMDA GluN1, GluN2A and GluN2B receptor subunits in post-mortem brain in hippocampus. (Law and Deakin, 2001; Beneyto et al., 2007; Block et al., 2009) and of GluN2A and GluN2B in the PFC (Feyissa et al., 2009; Karolewicz et al., 2009). Findings are inconsistent across brain regions and different studies. If these effects are not artefacts of antemortem treatment or chronic illness, they are difficult to integrate with the efficacy of NMDA antagonists.

If we are to assume that synaptic glutamate is reduced then this would question the mechanism of drugs like ketamine acting simply through NMDA blockade creating an antidepressant effect. There is some evidence that ketamine works through glutamate release onto AMPA receptors (Maeng et al., 2008; Li et al., 2010). Riluzole may also increase synaptic AMPA expression (Du et al., 2007). The psychotomimetic effects of ketamine are also by reduced by lamotrigine suggesting an interaction with non-NMDA receptors (Anand et al., 2000; Deakin et al., 2008). Other NMDA receptor antagonists appear to be antidepressant such as amantadine, memantine and traxoprodil (Vale et al., 1971; Dietrich et al., 2000; Zarate et al., 2004; Preskorn et al., 2008). None of the above though seems to offer the rapid antidepressant effect of ketamine.

This is not a mechanism separate from the function of traditional antidepressants. Although differences in synaptic cascade have been noted (Li et al., 2010) there are changes in both NMDA and AMPA receptors with fluoxetine (Ampuero et al., 2010). Desipramine and fluoxetine have also both shown effects at blocking NMDA induced currents (Szasz et al., 2007). Furthermore, there is evidence of downregulation of NMDA receptors following treatment with citalopram and fluoxetine in animals (Nowak et al., 1996, 1998; Boyer et al., 1998). Increased expression of mGlu_{2/3} has been noted following imipramine treatment in animals (Matrisciano et al., 2007), while others have noted downregulation of mGlu_{2/3}, mGlu₄ and mGlu₇ with amitriptyline in an olfactory bulbectomy model of

depression in mice (Wieronska et al., 2008). However, a recent proton magnetic resonance spectroscopy [¹H]MRS study where MDD patients were treated with escitalopram for 6 weeks yielded no change in glutamate or glutamine despite improvement in HAM-D scores (Godlewska et al., 2014).

A range of studies have reported response to ketamine from 15% to 86% on mood rating scales (Denk et al., 2011; Abdallah et al., 2012). Peak effect seems to occur following the primary infusion. The antidepressant effect has only been prolonged with repeated infusions rather than riluzole or lamotrigine (Mathew et al., 2010). Even so the evidence is unreliable. Inadequate sample sizes, lack of control groups and randomisation and differences in patient group characteristics have plagued studies. Patients in these trials have had co-morbid disorders which have further worsened their reliability. There is also no active comparators except in one study (Murrough et al., 2013a) where they did not report the impressive HAM-D reductions initially reported by Berman et al. (2000) and Zarate et al. (2006a). However, no saline group was present to further demonstrate this.

Part of the problem remains that we have no reliable biomarkers of glutamate function in patients with depression; animal models do not always transfer well to humans. pHMRI evidence of prolonged deactivation of the subgenual cingulate with ketamine and prolonged activation with citalopram has been noted (McKie et al., 2005; Deakin et al., 2008). In fact Mayberg et al. (2005) has shown sustained remission in four of six patients following deep brain stimulation of the subgenual cingulate (Mayberg et al., 2005). Recently Salvatore et al. (2010) has demonstrated using MEG that MDD patients with least engagement of pregenual cingulate during a working memory task as a possible biomarker of antidepressant response to ketamine. These have not been investigated further.

The mechanism of ketamine appears to be in part through glutamate release onto non-NMDA receptors including AMPA and metabotropic receptors. However these are also reported effects on 5-HT, dopamine and intracellular effects on the mTOR pathway amongst others (Maeng et al., 2008; Li et al., 2010). This complete mechanism has not been well elucidated in humans. More recently animal models have demonstrated a neuroprotective and antidepressant effect of ketamine in preventing lipopolysaccharide induced inflammation and depressive symptoms in animal models. This has been reported as due to the inhibition of indoleamine 2,3-dioxygenase (an enzyme that catalyses tryptophan through the kynurenine pathway) (Walker et al., 2013). Given the early promising results in clinical trials further proof of concept studies are required in animal and human models of depression with new glutamate modifying drugs as our knowledge in this area expands.

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