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A SYSTEMATIC REVIEW OF STRUCTURAL AND FUNCTIONAL MRI DIFFERENCES BETWEEN PSYCHOTIC AND NONPSYCHOTIC DEPRESSION

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SUMMARY

Background: *Psychotic depression is widely accepted as a specific subtype of unipolar major depression. Magnetic resonance imaging studies have begun to investigate the neurobiological changes that differentiate this subtype of major depression from non-psychotic depression. Any differences may eventually be useful in aiding diagnosis patients for whom there is diagnostic uncertainty. This review collates the currently available evidence.*

Subjects and methods: *A systematic search of the Medline, PubMed, Embase & Web of Science databases was used to identify all articles comparing structural grey matter or functional magnetic resonance imaging (MRI) differences between adults (18+) with previously diagnosed psychotic and nonpsychotic depression in predefined regions of interest (hippocampus, amygdala, cingulate, insula & frontal cortices). The results were collated and organised according to brain region.*

Results: *There is a paucity of studies addressing structural and functional changes differentiating these two disorders and recommendations regarding use of these modalities in diagnosis cannot be made. From the available studies decreases in frontal cortex grey matter volumes may differentiate psychotic from non-psychotic depression whilst further studies are required to confirm decreases in insula cortex volumes. fMRI studies show associations between altered activity in these two regions and cognitive impairments in patients with psychotic depression. The volumes of putative emotional processing regions including the amygdala, hippocampus and anterior cingulate show no difference between psychotic and nonpsychotic depression.*

Conclusions: *Structural and functional changes in the higher associative regions of the frontal and insular cortices appear to differentiate psychotic and nonpsychotic depression to a greater degree than changes in putative emotional processing regions. The quality of the evidence both in terms of numbers of studies available and sample sizes involved is very poor but in regard to directing future study, understanding the neurobiology of psychotic depression may benefit from a more detailed assessment of these two regions.*

Key words: *affective disorders – psychotic - magnetic resonance imaging – neuroimaging – review - systematic*

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INTRODUCTION

In recent years there has been an appreciation that structural and functional neuroimaging could be of significant benefit in the diagnosis of psychiatric disorders (Gur 2002). Whilst several studies have assessed the clinical potential of neuroimaging in schizophrenia (Gur 2007) and bipolar disorder (Konarski 2008), no studies have yet assessed the potential of neuroimaging for differentiating the different subtypes of unipolar depression outlined in DSM-V.

Psychotic depression is one subtype of major depression and it is a condition that is often subject to misdiagnosis (Wagner 2011) because the symptoms crossover with other conditions including melancholic depression, schizophrenia, schizoaffective disorder or even dementia. This can result in significantly poorer patient outcomes, as this condition requires its own unique treatment profile (Rothschild 2013). It is therefore a condition that would greatly benefit from any objective input into the diagnostic process.

Although a variety of neuroimaging techniques exist, structural & functional magnetic resonance imaging (MRI) are seen as the most promising modalities for analysing subtle changes in the morphology or activity of cerebral regions of interest.

Previous research has identified MRI changes in putative emotional processing including the hippocampus, amygdala and the cingulate gyrus as central to the pathophysiology of major depression (Arnone 2012), whilst changes in the insula cortex (Price 2010) and frontal lobe (Knoble 1997) have been implicated in the pathophysiology of psychosis.

The aim of this review is to determine whether MRI can be used to discern reliable structural gray matter or functional activity differences in these regions between psychotic and nonpsychotic unipolar depression.

SUBJECTS AND METHODS

A systematic search was conducted using 4 electronic databases (PubMed, Medline, Embase & Web of Science). A list of 61 search terms was produced and this search strategy was adapted for each database (Appendix 1 and 2). The search was supplemented by bibliographic cross-referencing.

Inclusion criteria include production of original clinical data, full publication by January 2014, adult

participants (>18 years) and direct comparison of size/activation using MRI between clinically confirmed psychotic and nonpsychotic depression. Regions of interest (ROI) were defined as the hippocampus, amygdala, cingulate gyrus, insula cortex and frontal cortex. For structural studies, only changes in gray matter were included. For functional studies all studies were included regardless of test paradigm.

Exclusion criteria included a diagnosis of post-partum or puerperal psychosis, schizoaffective disorder, unspecified affective psychosis, psychotic bipolar disorder, cyclothymic depression or atypical depression. Any structural studies addressing white matter changes were excluded, as were studies using MR Spectroscopy or Positron Emission Tomography (PET) imaging. Finally articles were excluded if they were published as review articles or conference abstracts. Multiple publications by the same author were screened to avoid inclusion of repeat results.

RESULTS

The search identified a total of 16,915 papers across the four databases (Figure 1), which reduced to 15,912 having removed duplicate publications. 15,875 papers could be excluded based on analysis of the title and abstract. 37 papers were read in full to assess for eligibility with 8 papers meeting all of the inclusion criteria. Of these 8 studies, 6 were structural grey matter studies and 2 were functional studies (Table 1). There was significant heterogeneity in design between the included studies preventing any sensible meta-analytic collation.

Emotional processing regions

Three studies addressed gray matter volumes in the hippocampus and amygdala and none of these studies found any significant difference in volume between the two patient groups. Currently no studies have addressed volume difference in the cingulate cortex.

Frontal Cortex

One study (Simpson 1999) found decreased frontal lobe volume in psychotic depression whilst another (Kim 1999) identified decreased prefrontal cortex volumes. Both of these studies involved elderly patients using medication. A study addressing frontal cortex changes in young, un-medicated, first-episode adults found no difference between the patient groups (Salokangas 2002). One study (Vassilopoulou 2013) looked specifically at the subgenual prefrontal cortex and found no difference between the groups.

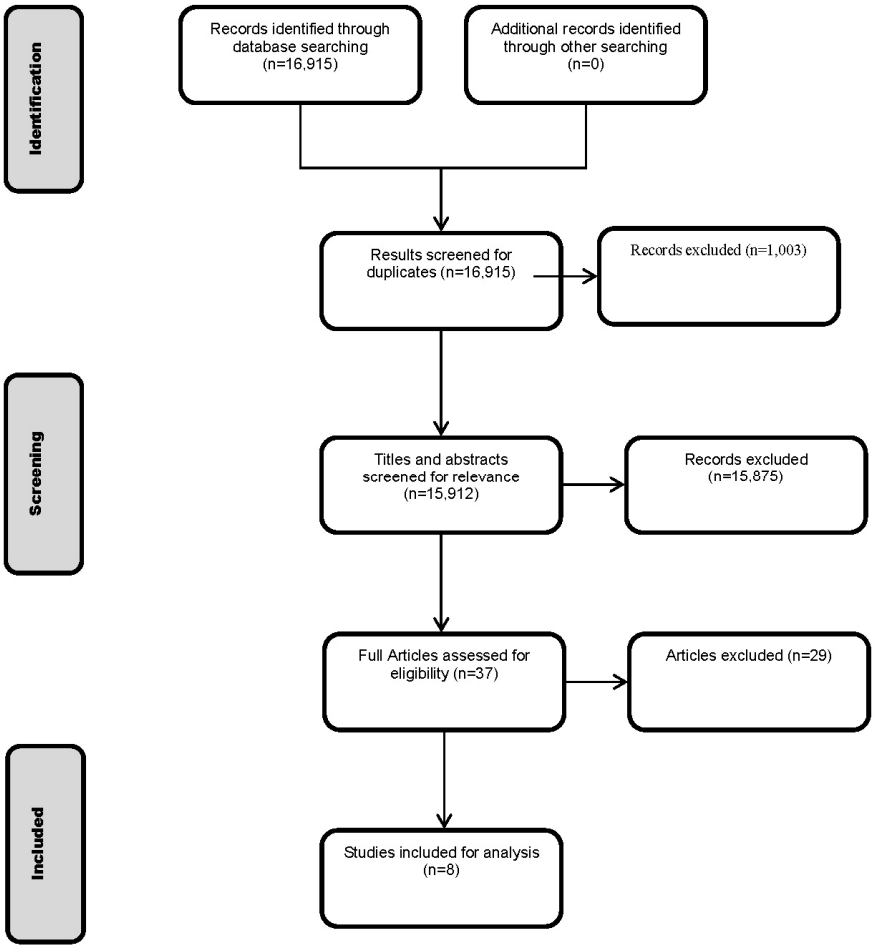

Figure 1. PRISMA Diagram

Table 1. Structural & Functional MRI Studies comparing Psychotic and Non-Psychotic Depression

Structural Studies	Hippo-campus	Amygdala	Frontal Cortex	In-sula	Sample (n)	Age (mean)	Treatment Profile	DSM	MRI Features
Vassilopoulou et al. 2013	NSD	NSD	NSD (Subgenual)	-	PD=17, NPD=22	PD=52, NPD=53	Antidepressants, Antipsychotics (> in PD)	DSM-III-R	Phillips Intera 1.5T Thickness 3mm
Keller et al. 2008	NSD *	NSD	-	-	PD=23, NPD=19	PD=37, NPD=37	Antidepressants, Antipsychotics (> in PD)	DSM-IV	GE Signa 3T Thickness 1.5mm
Kim et al. 1999	NSD	NSD	SD (PFC <in PD, p=0.03)	-	PD=19, NPD=26	Elderly (PD=65, NPD=65)	Not disclosed	DSM-III-R	GE Signa 1.5T Thickness 1.5mm
Salokangas et al. 2002	-	-	NSD	-	PD=20, NPD=17	PD=34, NPD=38	Un-medicated (first-episode)	DSM-IV	Siemens 1.5T, Thickness 5.4mm
Simpson et al. 1999	-	-	SD (Frontal < in PD; left: p=0.026, right: p=0.09)	-	PD=10, NPD=34	Elderly (PD=75, NPD=74) ***	ECT (> in PD) & Antidepressants	DSM-III-R	GE Vectra 0.5T (Frontal 2x8 slices)
Cohen et al. 2013	-	-	-	NSD **	PD=20, NPD=19****	PD=36, NPD=37	Antidepressants, Antipsychotics (> in PD) ****	DSM-IV	GE Signa 3T Thickness 1.5mm
Functional Studies	**Para-digm**	**Results**			**Sample (n)**	**Age (mean)**	**Treatment Profile**	**DSM**	**MRI Features**
Kelley et al. 2013	Decla-rative memory	PD: Encoding <right insula (p=0.003)	PD: Poorer retrieval>LM FG (p = 0.03)		PD=16, NPD=15	PD=36, NPD=36	Antidepressants, Antipsychotics (> in PD), Anxiolytics	DSM-IV	GE Signa 3T Thickness 4mm SPM5
Garrett et al. 2011	Working memory (n-back)	NPD < in DLPFC (p=0.007)			PD=16, NPD=15	PD=34, NPD=40	Not Available *****	DSM-IV	GE Signa 3T Thickness 4mm SPM5

PD = psychotic depression, NPD = nonpsychotic depression, SD = significant difference, NSD = no significant difference, PFC = prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, LMFG = left middle frontal gyrus; * Non-significant trend for smaller amygdala in PD (left: p=0.01, right p=0.08); ** Significant correlation between psychosis severity and anterior insula volume; ***Mean ages for entire cohorts, subsets of which underwent MRI scanning; **** Subjects are the same as for Keller et al, 2008; ***** Comparison of medicated vs non-medicated PD showed no difference

Insula Cortex

Only one study addressed changes in insula cortex volumes. This study (Cohen 2013) found no significant difference between the two patient groups but did demonstrate a significant correlation between the volume of the anterior insula and the degree of psychosis.

fMRI Studies

One study (Garret 2011) found that the non-psychotic group showed decreased activation in the dorsolateral prefrontal cortex in a working memory task. Another study from the same group and using the same patient group (Kelley 2013) showed that the psychotic group had decreased activation in the right insula cortex during encoding of a declarative memory task, as well as poorer retrieval which was associated with increased activation in the left middle frontal gyrus.

DISCUSSION

There is a paucity of evidence regarding both structural grey matter changes and functional activation changes between psychotic and nonpsychotic depression. In particular the number of relevant studies available is small and all such studies have small sample sizes. The available evidence is insufficient to comment on whether structural and functional MRI could help clinicians identify psychotic depression in those with a degree of diagnostic uncertainty.

More studies are needed to expand the evidence base and the evidence presented could be used to direct future research. The fact that none of the 3 identified studies found any significant difference in the volume of the hippocampus or the amygdala, suggests that changes in these areas have less potential as a diagnostic tool. The lack of studies addressing changes in the cingulate cortex highlights an obvious area for future study.

The changes in the frontal cortex between the two disorders is currently inconclusive but further work in this area may lead to a metric that could be of diagnostic benefit. In particular, studies should investigate volume changes in specific regions of the frontal lobe to determine the sub-regions driving the observed differences in some studies.

Further studies are required to identify whether changes in the volume of the insula cortex could be of diagnostic benefit but the correlation between psychosis severity and anterior insula volume in major depression, suggests that such investigations would be prudent.

The fact that both of the available fMRI studies identified the prefrontal cortex and the insula cortex as

regions of interest strengthens the proposition that further investigations in these areas may yet lead to a metric of diagnostic benefit. However both fMRI studies involved the same cohort of patients so these results need replication in other, distinct patient populations. Undoubtedly more fMRI studies are needed, preferably using the same test paradigm, to assess the potential of this modality in diagnostic differentiation.

It is perhaps intuitive that the frontal cortex and the insula may differentiate psychotic from nonpsychotic depression since they have been implicated in psychotic episodes in schizophrenia. Further, a recent review of imaging studies in affective psychosis (Bussatto 2013) also identified the insula and prefrontal cortex as key areas differentiating psychotic depression from nonpsychotic depression, however their suggestion that the hippocampus may also be useful in this regard, does not apply when considering MRI as a potential diagnostic tool, as this was based on PET studies.

CONCLUSIONS

This review highlights a lack of MRI evidence regarding the differences between psychotic and nonpsychotic depression. Further studies addressing these differences, perhaps with a particular focus on the frontal and insular cortices, may eventually lead to a metric which can aid psychiatric diagnosis in those patients for whom the diagnosis is not clear from the history.

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Appendix 1. Database Search Terms: OVID Medline and EMBASE

1	Psychotic depression
2	Depressive psychosis
3	Depression with psychosis
4	Affective disorders, Psychotic/ or Affective psychosis
5	Psychotic disorders/ or Psychotic
6	Psychosis
7	Hallucination$ or Hallucinations/
8	Delusion$ or Delusions/
9	Depression/ or Depression$
10	Depressive Disorder, Major/ or Depressive$ or Depressive Disorder/ or Depressive Disorder, Treatment-Resistant/
11	Affective disorder$ or Mood Disorders/
12	Mood Disorder$
13	Affective Symptoms/ or Emotional Disorder$
14	Melancholic$
15	Unipolar Depression$
16	Depressive Disorder, Major/ or Major Depression$
17	5 or 6 or 7 or 8
18	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
19	17 and 18
20	Magnetic Resonance Imaging/ or MRI
21	Magnetic Resonance Imaging$
22	Neuroimaging/ or Neuroimaging
23	Neuroimage
24	Brain Scan
25	Scan
26	Imaging
27	Medical Imaging or Diagnostic Imaging/
28	Structural MRI
29	Structural Magnetic Resonance Imaging
30	Structural Scan
31	Structural Brain Scan
32	Voxel$
33	fMRI
34	Functional MRI
35	Functional Magnetic Resonance Imaging
36	Functional Brain Scan
37	Functional Activation
38	Brain Activation
39	BOLD
40	BOLD Signal
41	Hippocampus or Hippocampus/
42	Hippocampal
43	Hippocampal Gyrus
44	Amygdala or Amygdala/
45	Medial Temporal Lobe
46	Gyrus Cinguli/ or Cingulate
47	Cingulate Gyrus
48	Cingulate Cortex
49	Insula$
50	Insula$ Cortex
51	Frontal Lobe/ or Frontal Cortex
52	Frontal Lobe
53	Frontal Gyrus
54	Prefrontal Cortex/ or Prefrontal
55	Prefrontal Cortex
56	Prefrontal Gyrus
57	Volume
58	Thickness
59	Depth
60	Activity
61	Activation
62	Grey Matter
63	Gray Matter
64	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 57 or 58 or 59 or 60 or 61 or 62 or 63
65	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
66	64 and 65
67	1 or 2 or 3 or 4 or 19
68	66 and 67

Appendix 2. Database Search Terms: PubMed and Web of Science

Psychotic depression OR depressive psychosis OR depression with psychosis OR affective psychosis) OR ((psychotic OR psychosis OR hallucination$ OR delusion$) AND (depression OR depressive OR affective disorder OR mood disorder OR emotional disorder OR melancholic OR unipolar depression OR major depression)) AND ((MRI OR magnetic resonance imaging OR neuroimaging OR neuroimage OR brain scan OR scan OR imaging OR medical imaging OR structural MRI OR structural magnetic resonance imaging OR structural scan OR structural brain scan$ OR voxel$ OR fMRI OR functional MRI OR functional magnetic resonance imaging OR functional brain scan$ OR functional activation OR brain activation OR BOLD OR BOLD signal OR activation OR activity OR thickness OR depth OR size OR volume OR grey matter OR gray matter) AND (hippocampus OR hippocampal OR hippocampal gyrus OR amygdala OR medial temporal lobe OR cingulate OR cingulate cortex OR cingulate gyrus OR insula OR insula cortex OR insular OR insular cortex OR frontal cortex OR frontal gyrus OR frontal lobe OR prefrontal OR pre-frontal OR prefrontal gyrus OR pre-frontal gyrus OR prefrontal cortex OR pre-frontal cortex))

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