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Alexandros Lalousis, Paris; Wood, Stephen; Reniers, Renate; Schmaal, Lianne; Azam, Hannah; Mazziota, Antonella; Saeed, Hasson; Wragg, Charlotte; Upthegrove, Rachel

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Transdiagnostic structural neuroimaging features in depression and psychosis: A systematic review

Paris Alexandros Lalousis [a,b,*], Stephen Wood [a,b,c,d], Renate Reniers [a,b], Lianne Schmaal [c,d], Hannah Azam [a], Antonella Mazziota [a], Hasson Saeed [a], Charlotte Wragg [a], Rachel Upthegrove [a,b]

[a] Institute for Mental Health, University of Birmingham, Birmingham B15 2SA, United Kingdom
[b] Centre for Human Brain Health, University of Birmingham, Birmingham B15 2SA, United Kingdom
[c] Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne, Australia
[d] Centre for Youth Mental Health, The University of Melbourne, Parkville, Australia

A B S T R A C T

Background: Previous research suggests that there may be similarities in structural brain changes seen in patients with depression and psychosis compared to healthy controls. However, there is yet no systematic review collating studies comparing structural brain changes in depression and psychosis. Establishing shared and specific neuroanatomical features could aid the investigation of underlying biological processes.
Aims: To identify structural neuroimaging similarities and differences between patients with depression and psychosis.
Method: We searched PubMed, PsychInfo, Embase, NICE Evidence, Medline and the Cochrane Library were searched from inception to 30/06/2021 using relevant subject headings (controlled vocabularies) and search syntax. Papers were assessed for quality using the Newcastle-Ottawa Scale.
Results: Five-hundred and twenty papers were retrieved, seven met inclusion criteria. In narrative collation of results, grey matter volume (GMV) reductions were found in the medial frontal gyrus (MFG), hippocampus and left-sided posterior subgenual prefrontal cortex in both psychosis and depression. GMV reductions affected more brain regions in psychosis, including in the insula and thalamus. White matter volume (WMV) decline was found in both depression and psychosis. Reduced fractional anisotropy (FA) was more commonly seen in depression.
Conclusions: Our results suggest potential transdiagnostic patterns of GMV and WMV reductions in areas including the MFG, hippocampus, and left-sided posterior subgenual prefrontal cortex. These could be investigated as a future biomarker of transdiagnostic signature across mental illnesses. However, due to the limited number and poor quality of studies future research in large samples and harmonised imaging data is first needed.

1. Introduction

Depression and psychotic disorders constitute the major challenges of mental ill health to the world's population (Charlson et al., 2018; Vos et al., 2015; WHO | Depression and Other Common Mental Disorders, 2017). Major Depressive Disorder (MDD) has a lifetime prevalence rate of approximately 20% and is one of the most common and disabling psychiatric diseases globally (WHO | Depression and Other Common Mental Disorders, 2017). Psychotic disorders, including schizophrenia affect up to 3% of the world population (Charlson et al., 2018; World Health Organization, 1992) and are severely debilitating.

Despite depression and psychosis being two different diagnostic structures, they may share some aetiologies and maintenance processes. Depression in schizophrenia has long been a taxonomic challenge, with various approaches to address it including that core, deficit schizophrenia is "non-affective" and early more heterogeneous stages of psychosis have higher affective load (Upthegrove et al., 2017). Craddock and Owen (2010) argue genetic studies reinforce evidence that suggests a clear dichotomy between mood and psychotic disorders is absent.

Symptoms such as social withdrawal, blunted affect, anhedonia, avolition, and alogia are observed both in psychosis and depression (Krynicki et al., 2018). Social withdrawal, blunted affect, and alogia are associated with GMV reduction in the cerebellum, while anhedonia and avolition are negatively correlated with left anterior limb of internal capsule white-matter volume (WMV) and positively correlated with left superior longitudinal fasciculus WMV (Chuang et al., 2014; Meisenzahl et al., 2010). Structural magnetic resonance imaging (sMRI) has shown that patients with psychiatric disorders may have distinct brain changes compared to healthy controls. Depression and psychosis may share certain neuroanatomical characteristics; e.g. hippocampal grey matter volume (GMV) reductions are observed in both disorders (Chuang et al., 2014; Meisenzahl et al., 2010). Overlap in neuroanatomical characteristics between the two disorders may be suggestive of common aetiological mechanisms, with depression potentially playing an intrinsic role

* Corresponding author at: Institute for Mental Health, University of Birmingham, Birmingham B15 2SA, United Kingdom.
E-mail address: p.a.lalousis@bham.ac.uk (P. Alexandros Lalousis).

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in the pathogenesis of schizophrenia (Birchwood et al., 2005; Sönmez et al., 2013). However, to our knowledge there has been no previous systematic review of structural neuroimaging studies comparing depression to psychosis, and here we aim to address this gap. It should however be noted that there is an explicit lack of studies that directly compare the two (See Table 1).

2. Methods

The protocol was pre-registered on PROSPERO ID CRD42020190200 and is reported in line with Preferred Reporting lines for Systematic review and Meta-Analyses (PRISMA) guideline (Moher, 2009). Please see Fig. 1 for a PRISMA flow diagram documenting the study selection process.

2.1. Eligibility criteria

Eligibility criteria were established following PICOS format - patients/population, intervention, comparisons and outcomes (Liberati et al., 2009): a) only human participants; b) ages of 14–70 years; c) include participants with a diagnosis of major depressive disorder or recent onset depression AND patients with a diagnosis of first episode psychosis, or recent onset psychosis, or schizophrenia spectrum disorders, or schizophrenia, or schizophreniform disorders; d) studies reporting primary cross-sectional or longitudinal or follow up data; e) studies reporting GMV, or cortical thickness, or gyrification, or surface area, or white matter anisotropy or diffusion tensor imaging.

Studies including only bipolar disorder were excluded however, if these also included psychosis and depression, they were included as it may be possible to extract data from the relevant groups of interest. Animal studies, non-English language studies and pharmacological interventions were excluded.

Two authors (H.A. and C.W) screened titles and abstracts and then assessed eligible studies for potential inclusion with a thorough full text search. Two separate authors (A.M. and H.S.) checked the final list and any conflicts between authors were discussed and consensus achieved.

2.2. Information sources and search strategy

PubMed, PsychInfo, Embase, NICE Evidence, Medline and the Cochrane Library were searched from inception to 30/06/2021 using relevant subject headings (controlled vocabularies) and search syntax. See Supplementary Material and PROSPERO registration for full search terms.

A systematic search combining terms describing psychosis with AND to terms describing depression and with OR to terms describing different structural neuroimaging modalities was conducted on the following databases: PubMed, PsychInfo, Embase, NICE Evidence, Medline and the Cochrane Library from inception to 30/06/2020. The search terms were adjusted for different databases in subject headings and proximity operators. Please see supplement 1.1 for full details on the search strategy.

Reference lists from included studies were also hand searched for studies which met eligibility criteria that may not have been found from the databases.

3. Results

The systematic search identified 516 unique abstracts. Full text assessments was performed on 44 studies, with 37 of these excluded. Seven studies reporting on seven unique samples with a total of 1,452 participants fulfilled eligibility criteria were included in the review. The mean age of depression patients in the sample was 36.0 (12.1). The mean age of psychosis patients was 31.9 (8.8). Five studies investigated gray matter and three studies explored white matter. For details please see Table 2.

3.1. Overview of results

3.1.1. Grey matter

Five studies (Coryell et al., 2005; Jiang et al., 2019; Keller et al., 2008; Meisenzahl et al., 2010; Ota et al., 2013) identified: GMV reduction in the bilateral middle frontal gyrus was reported in both depression and psychosis; hippocampal GMV reductions both in depression and psychosis; bilateral amygdala GMV reduction in psychotic depression compared to non-psychotic depression, and reduced GMV in the insula and the thalamus in psychosis compared to depression.

3.1.2. White matter

Three studies (Cui et al., 2020; Kochunov et al., 2013; Ota et al., 2013) reported reduced WMV volume fractional anisotropy (FA) in the corpus callosum and bilateral anterior and posterior insula in depression compared to psychosis.

3.2. Risk of bias

The quality check was completed using the Newcastle-Ottawa Scale (NOS),

(Wells et al., 2000). Four out of the seven studies were rated 4 stars which is considered low quality. See Supplementary Table S1 for full details.

3.3. Gray matter volume

Jiang et al. (2019), conducted voxel-based-morphometric analysis of the total brain volume between patients with schizophrenia and major depressive disorder (MDD). Results found four clusters with significant group effects. In detail, lower GMV in the bilateral MFG, the medial prefrontal cortex (MPFC), and the rectus gyrus was found in patients with schizophrenia compared to patients with MDD. The authors investigated the correlation and causal effects between GMV alterations and clinical variables for each patient group. Specifically, in the schizophrenia group reduction in GMV was negatively correlated with PANSS negative scores. Using Granger Causality Analysis (GCA) they found that the causal link between the right cerebellum and the medial prefrontal cortex had a positive correlation with PANSS negative scores. Finally, authors found a significant negative correlation between GMV in the MPFC and the causal link between the right cerebellum and the MPFC. However, this was not the same for the depression group where no significant correlations or causal effects between GMV alterations and clinical features were observed.

Coryell et al. (2005) looked at GMV in the anterior and posterior Subgenual Prefrontal Cortex (SGPFC) in patients with psychotic depression compared to patients with schizophrenia and healthy controls. Results found that the SGPFC GMV did not significantly differ between patients with psychotic depression and schizophrenia. However, patients with psychotic depression reported the smallest volumes in the left-sided posterior SGPFC. The differences found in the left-sided posterior SGPFC volumes were compared with other structure measures within this region including cortical depth and surface area. Surface area did not differ significantly between groups; however, the depth of the surface area was significantly less in the psychotic depression group compared to the schizophrenia group. On follow up, increases in the posterior SGPFC volume were found in the psychotic depression group only.

Keller et al. (2008) performed a region of interest (ROI) analysis to investigate volumetric differences in amygdala and hippocampus in patients with psychotic depression and nonpsychotic depression. Patients with psychotic depression had marginally smaller bilateral amygdala volumes than patients with non-psychotic depression. The study found no significant differences in bilateral hippocampal volume between groups. However, researchers report that their sample of participants did not differ on measures of recurrent chronic depression,

Table 1
Data extraction table. GMV: grey matter volume; WM: white matter; WMV: white matter volume; VBM: Voxel-Based Morphometry; MRI: Magnetic Resonance Imaging; SCZ: schizophrenia; MDD: major depressive disorder; BP: Bipolar Disorder; PSDE: Psychotic Depression; NPSDE: Non-Psychotic Depression; HC: healthy controls; ROI: region of interest; FA: Fractional Anisotropy; SSRIs: selective serotonin reuptake inhibitors; F: female; M: male; FA: fractional anisotropy; HAM-D: Hamilton rating scale of depression; PANSS: Positive and negative syndrome scale; SD: standard deviation; AD: antidepressants; BDI: Beck's depression inventory; BAI: Beck's anxiety inventory; IMIE: Imipramine equivalent; MS: Mood stabilizers; AD: Antidepressants; TCA: tricyclic antidepressants; TAP: Typical antipsychotics; ATAP; Atypical antipsychotics. Duration of illness information was not available for all the included studies.

Study	Study Design	Sample size (N)	Age (M, (SD)) and duration of illness (M, (SD))	Patient medication	Setting	Mean symptom score	Type of neuroimaging	Coordinates (MNI or Talairach)
Coryell et al. (2005)	Case-Control	PSDE: 10 SCZ: 10 HC: 10	PSDE Age: 21.9 (4.9) PSDE Duration of illness (years): 4.7 (5.7) SCZ age: 22.2 (4.2) SCZ Duration of illness (years): 5.8 (6.0) HC age: 22.1 (6.0)	N/A	Iowa Longitudinal Study of the Outcome of Early Psychosis	N/A	MRI	N/A
Cui et al. (2020)	Case-Control	MDD: 85 BD: 42 SCZ: 68 HC: 95	MDD Age: 32.4 (8.7) MDD Duration of illness (months): 40.8 (55.8) SCZ Age: 28.5 (4.6) SCZ Duration of illness (months): 43.8 (43.6) HC mean age 30.2 (6.8)	MDD: 5 AP, 64 AD, 1 MS BD: 24 AP, 15 AD, 24 MS SCZ: 42 AP, 0 AD, 0 MS	Xinxiang Medical University hospital	PANSS-P (SCZ): 22.80 (3.79) PANSS-N (SCZ): 19.97 (5.22) BAI (MDD): 36.69 (12.12) BDI (MDD): 18.97 (7.24)	MRI for microstructural changes in WM	MNI coordinates
Jiang et al. (2019)	Case-Contr ol	SCZ: 20 MDD: 20 HC: 20	SCZ Age: 40.3 (13.8) MDD Age 41.8 (14.2) HC Age 41.4 (13.6)	SCZ: 20 ATAP and TAP MDD: 1 TCA, 15 SSRIs	Chengdu Mental Health Centre	PANSS-P (SCZ): 12.9 (5.6) PANSS-N (SCZ): 18.0 (7.0)PANSS-G (SCZ): 27.8 (5.3) HAM-D (MDD): 5.3 (1.3)	VBM analysis for whole brain GMV	MNI coordinates
Keller et al. (2008)	Case-Control	PSDE: 23 NPSDE: 19 HC: 22	PSDE Age: 26.5 (13.2) NPSDE: Age: 36.6 (11.9) HC Age: 32.2 (11.5)	PSDE: 16 AP, 15 AD, 4 MS NPDE: 0 AP, 11 AD, 2 MS	Stanford University or online and print advertisement	HAM-D (PSDE): 30.5 (4.7) HAM-D (NPSDE): 23.7 (3.2) BPRS (PSDE): 48.9 (7.8) BPRS (NPSDE): 33.2 (2.8)	MRI	Talairach coordinates
Kochunov et al. (2013)	Case-control	SCZ: 58 HC: 60 MDD: 132 HC: 351	SCZ Age: 37.1 (12.4) HC Age: 37.5 (12.1) MDD Age: 42.3 (12.1) HC Age: 41.5 (13.9)	SCZ: 3 TAP Rest of patients on ATAP or combination of TAP and ATAP 2 medication-free,	SCZ and HC: Maryland Psychiatric Research Centre MDD and HC: Genetics of Brain Structure and Function (GOBS) study.	BPRS (SCZ): 15.9 (11.7) BDI (MDD): 11.2 (9.0)	Fractional Anisotropy	N/A
Meisenzahl et al. (2010)	Case-control	SCZ: 89 MDD: 92 HC: 138	SCZ Age: 30.6 (9.1) MDD Age 44.6 (12.3) HC Age 33.3 (12.2) SCZ Duration of illness (years): 4.7 (5.9) MDD Duration of illness (years): 5.7 (7.5)	SCZ: 44 TAP, 63 ATAP, 3 medication-free MDD: 21 SSRI, 23 TCA, 42 other AD, 3 medication-free	Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University, Munich, Germany	PANSS-G (SCZ): 75.1 (22.1) HAM-D (MDD): 23.5 (6.7)	MRI	N/A
Ota et al. (2013)	Case-control	SCZ: 43 MDD: 41	SCZ Age: 38.6 (9.6) MDD Age: 41.9 (19.9)SCZ	SCZ: CPZ 540.6 (515.2) MDD: IMIE 102.6 (123.0)	N/A	PANSS-P (SCZ): 15.0 (6.0) PANSS-N (SCZ): 15.4	VBM and Fractional Anisotropy	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Sample size (N)	Age (M, (SD)) and duration of illness (M, (SD))	Patient medication	Setting	Mean symptom score	Type of neuroimaging	Coordinates (MNI or Talairach)
			Duration of illness (years) : 16.3 (6.1)MDD Duration of illness (years): 8.1 (7.5)			(6.6)PANSS-G (SCZ): 31.0 (10.4) HAM-D (MDD): 12.0 (7.7)		

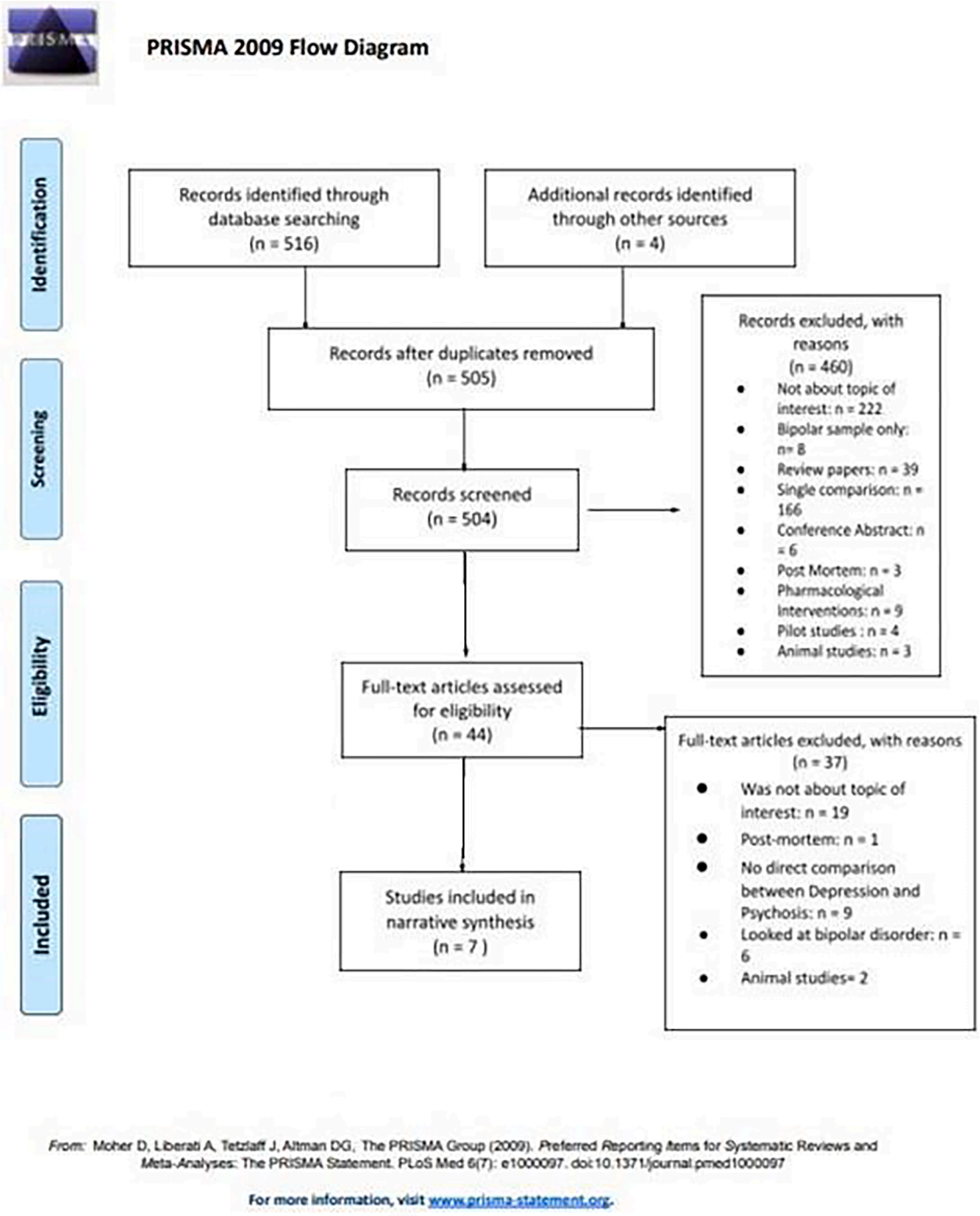

Fig. 1. PRISMA flow diagram documenting the study selection process including the identification, screening, eligibility and included studies stages.

Table 2
Table of results. ROI: region of interest; FA: Fractional Anisotropy; SCZ: schizophrenia; MDD: major depressive disorder; GMV: grey matter volume; WMV: white matter volume; ACC: anterior cingulate cortex; CC: corpus callosum; VBM: voxel-based morphometry: DTI: diffusion tensor imaging; SGPFC: subgenual prefrontal cortex; MPFC: medial prefrontal cortex; R: Right; L: Left.

Study	Analysis	Measured variables	Whole brain analysis done (Y/N)	Results
Coryell et al (2005)	Cortical area-depth and volume	GMV	Yes	Anterior SGPFC did not significantly differ between MDD with psychosis and MDD without psychosis. PsychoticMDD presented smaller volumes in the left-sided posterior SGPFC when comparison between MDD and SCZ post hoc pairwise test was conducted.
Cui et al (2020)	Voxel-wise FA	WM integrity	Yes	Reduced FA in MDD and SCZ (genu, body and splenium of CC, posterior anterior and superior CR. FA decreases found in genu and body of CC, bilateral anterior and posterior CR, and right superior CR
Jiang et al (2019)	VBM	GMV	Yes	Lower GMV in bilateral MFC in SCZ compared to MDD. Decrease in GMV in MPFC in SCZ than MDD
Keller et al (2008)	ROI analysis	GMV and WMV	No (region of interest analysis) amygdala and Hippocampus	Smaller R and L amygdala volume in MDD with psychosis compared to MDD without psychosis. No significant differences identified by subgroup analysis. No significant hippocampal volume differences.
Kochunov et al (2013)	DTI-FA	WMV	Yes	Age-related WM decline higher in SCZ patients in five specific regions. No significant WM decline in MDD patients.
Meisenzahl et al. (2010)	Hippocampal volume	GMV and WMV	Yes	Significance in the volume of the left and right Anterolateral region of the thalamus, ant. medial of the thalamus as well as the Central lateral. A significance as also seen in the FA of the R Subcallosal ACC and L rostral ACC
Ota et al (2013)	ACC, CC, Thalamus, Insula	GMV and WMV	ROI	Significant effect of diagnosis on bilateral hippocampal volumes GM and WM

which might be the reason for no differences in hippocampal volume.

Meisenzahl et al. (2010) looked at differences in hippocampal volume between patients with depression and schizophrenia and found a significant effect of diagnosis on reduced bilateral hippocampal GMV and hippocampal WMV. Furthemore, when studying differences between patients with first episode of depression and recurrently ill patients with depression the authors reported found no significant differences concerning hippocampal volume measurements.

Ota et al. (2013) found that patients with schizophrenia showed reduced GMV in the bilateral anterior and right posterior insula and the bilateral anterolateral, anteromedial, central lateral, central medial, and posterior regions of the thalamus.

3.4. White matter volume and integrity

Cui et al. (2020) examined white matter integrity and found that the depression group exhibited more extensive FA reductions compared to the schizophrenia group. Compared to the schizophrenia group the depression group also had significantly reduced FA measurements in the bilateral anterior section of the anterior corona radiata (CR). Results also showed significantly reduced FA in the anterior and posterior portions of the anterior CR in depression patients compared to patients with schizophrenia. In contrast, the similarities between depression and schizophrenia can be seen in the overlapping regions with decreased FA which were primarily in the posterior section of the anterior CR. Depression patients who were on medication had significantly lower FA values in the left anterior CR in comparison to depression patients who were not on medication. Finally, the effect of symptom severity and duration of illness on these results did not survive correction for multiple comparisons in voxel-wise and ROI analysis.

Kochunov et al. (2013) showed that a quadratic diagnosis by age interaction was significant in five white matter tracts with the impact of the diagnosis of schizophrenia by age factor indicating that the rate of age-related rate decline was two times as high than in the healthy control group. Also results in the schizophrenia cohort showed that higher age-related decline in FA was present in all twelve tracts analysed. Specifically, the age-of-intercept for average FA was 32.4 years but regionally it was from 27.7 years for the genu of the CC to 49.9 years for the thalamic radiation. The age-of-intercept was negatively correlated with normative age of FA peak suggesting earlier onset of accelerated aging in FA in schizophrenia in tracts that are normally matured slowly. On the other hand, in the depression group, patients demonstrated higher age-related decline in FA for seven tracts compared to HC of which none were statistically significant (genu of CC, body of CC, internal capsule, external capsule, Cingulum, SLF and inferior frontal occipital). Therefore, this suggests no evidence of tract-specific

accelerated aging in the normal lifespan of depression patients.

Finally, Ota et al. (2013) found that patients with depression exhibited reduced FA in the CC, bilateral anterior and posterior insula, anterolateral and posterior regions of the thalamus, and left rostral and right subcallosal regions of the thalamus.

4. Discussion

This is the first systematic review to summarise the results from structural brain imaging studies directly comparing patients with psychosis and depression. Our findings suggest that patients show GMV and WMV reductions in a number of similar areas, with some studies suggesting that GMV loss in the insula and thalamus may have some specificity to psychosis. Studies report WMV loss in depression and psychosis, with some potential for specificity in CR and CC FA reductions to depression.

Five studies reported on GMV in depression and psychosis. Overall, they suggest that patients with psychosis and depression show reductions in GMV in the left-sided posterior subgenual prefrontal cortex, the MFG, and the hippocampus. In schizophrenia, the greatest reductions are found in the MFG. In one study, an increase in the posterior subgenual prefrontal cortex volume was found only in the depression group upon follow-up. Some of these studies reported no significant differences in GMV between the two groups: including no significant differences in the female brain, subgenual prefrontal cortex as well as one study reporting no hippocampal GMV volume differences between both groups. Four studies reported on WMV and a transdiagnostic pattern of decreased WMV in both depression and psychosis was identified. This included FA reductions and WMV decline. Two studies found significantly reduced FA specifically in depression. This suggests that both psychosis and depression patients display significantly reduced patterns of WM integrity, with some studies indicating this is more common in depression patients.

Existing literature has demonstrated that depression and psychosis share common etiologies and symptoms which indicates that both disorders may be presenting transdiagnostic mechanisms (Correll & Schooler, 2020; Upthegrove et al., 2017). The literature for amygdala and hippocampal volume in depression and psychosis is conflicting, similar to our results. Part of Keller et al. (2008) results align with a systematic review which also found no significant differences between the two disorders when examining the hippocampus (O'Connor & Agius, 2015). Keller et al. (2008) found volume reductions in the right and left amygdala whereas O'Connor and Agius (2015) found no distinctions. They suggest that reductions in amygdala volume in patients with psychosis contribute to adverse implications such as severe anxiety and fear (Keller et al., 2008). Reduced hippocampal volume has also been closely linked to psychosis in the literature (Haukvik et al., 2018), causing implications such as intensified symptom severity and impaired learning and memory functioning (Arnold et al., 2014). This supports Meisenzahl et al's (2010) findings where patients with psychosis displayed a greater reduction in hippocampal volume compared to patients with depression.

Research comparing depression and psychosis directly is limited, especially in regards to brain structure, suggesting further evidence is needed to disentangle transdiagnostic signatures and specificity of each of the two disorders. Although comorbidities of depression and psychosis are common (Correll and Schooler, 2020; Kambeitz et al, 2015; Lalousis et al., 2021; Lalousis et al., 2022), the existing literature is sparse when investigating brain structure and its impact on diagnosis, symptom severity, and prognosis. Our results highlight that patients with depression and psychosis exhibit reductions in GMV and WMV with GMV loss being more prominent in psychosis. Coryell et al. (2005), however, found that patients with psychotic depression exhibited more GMV loss than patients with schizophrenia – a result going against the GMV loss hierarchy suggested by our results.

Our findings are in line with previous results showing WMV and FA disparities in both schizophrenia (Kelly et al., 2018) and depression (Jiang et al., 2017; Wise et al., 2016). Furthermore, literature has also suggested that GMV reductions have been found in both psychosis and depression, such as (Arnone et al., 2012) systematic review on depression, which found both WMV and GMV reductions in patients with depression as well as a significant amount of WMV lesions which have been associated with depression and cognitive decline. Moreover, (Steen et al., 2006) *meta*-analysis documented that patients with first episode psychosis experienced GMV loss, with continuous decline found over time. Subsequent systematic reviews confirmed this, with reduced GMV being found in both patients with schizoaffective disorder and patients with schizophrenia (Madre et al., 2016). A novelty in our findings is that GMV reductions were suggested to be more prevalent in psychosis, with WMV reductions being more prevalent in depression. This finding should however be approached with caution, as some studies did not follow this pattern such as Coryell et al. (2005) who found GMV reductions in both depression and schizophrenia compared to healthy controls and volume loss in the left-sided posterior subgenual prefrontal cortex being significantly lower in the depression group.

The relevance of WMV reductions in the aetiology of depression still remains in question. WMV in patients with depression has been show to increase after serotonin and norepinephrine reuptake inhibitor (SNRI) or selective serotonin reuptake inhibitor (SSRI) medication compared to recovered patients and healthy controls (Zeng et al., 2012). This implies that SSRIs and SNRIs could possibly reverse WMV reductions, suggesting that WMV may play a role in the aetiology of depression (Zeng et al., 2012).

On the contrary, medication for schizophrenia has shown to cause further impairment in brain structure (Zhang et al., 2018; Zhang et al., 2016). Studies have demonstrated how antipsychotic drug treatment can further reduce GMV as it can cause neuronal and cell complications (Zhang et al., 2016). However, it can be argued that GMV reductions may be a result of the disorder's severity and need for higher doses of medication (Zhang et al., 2016). Yet, studies show that antipsychotic medication for schizophrenia increases GMV in the thalamus, which modulates perception, thoughts, and feelings (Yue et al., 2016), resulting in improvements in positive symptoms.

Structural brain imaging findings can differ between individuals with recent onset versus chronic psychiatric disorders due to a variety of factors. Age-related changes in brain development and plasticity may influence the degree and extent of structural abnormalities seen on imaging. Neurodegenerative processes may also play a role, with chronic disorders potentially leading to progressive changes in brain structure. Additionally, medication effects may differ between those with recent onset versus chronic disorders, potentially affecting brain structure differently. Als, the cumulative illness burden associated with chronic disorders may result in greater structural abnormalities compared to those with recent onset disorders. All of these factors may differentially affect brain structure depending on the duration and severity of the disorder, and on the age of the individual and should be taken into account when interpreting the findings of this systematic review.

To date, this is the first systematic review which has provided an overview of structural neuroimaging brain comparisons between depression and psychosis. Key strengths of this systematic review include that it reduced reviewer bias as its approach of validly assessing individual studies is objective and reproducible (Bero, 2006; Collins and Fauser, 2005), it used a standardised search method in multiple databases, it was pre-registered, authors were consistently cross-referencing, and efficient quality checks were performed. However, limitations included the lack of coordinate information which prevented the conduction of a *meta*-analysis, the lack of individual studies directly comparing depression and psychosis, lack of controls for medication exposure, small sample sizes, and heterogeneity of symptoms. Four out of the 7 studies (Coryell et al., 2005; Kochunov et al., 2013; Ota et al, 2013; Cui et al., 2020) scored 4 on the NOS guidelines, indicating low quality. Furthermore, there is a large body of literature that examines

structural abnormatlities in depression and psychosis separately that could not be incorporated in the introduction. Finally, our inclusion criteria selected for studies from 2005 and 2020 in order to have as many studies as possible included in this systematic review. The advances in the technology of neuroimaging is quite fast moving and such a large time range introduces problems in the intepreptation of results. Our interepretation of the results should be viewed under these limitations.

5. Conclusions

We identified a pattern of GMV reductions and WMV reductions in areas such as the MFG, hippocampus, and left-sided posterior subgenual prefrontal cortex in both depression and psychosis. GMV loss was seen specifically in the insula and thalamus in psychosis. However, the lack of literature directly comparing brain structure in depression and psychosis is further heightened by the poor quality of the studies and future high-quality studies, including those utilising large data sets is needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103388.

References

Arnold, S. et al. (2014) "Hippocampal Volume Is Reduced in Schizophrenia and Schizoaffective Disorder But Not in Psychotic Bipolar I Disorder Demonstrated by Both Manual Tracing and Automated Parcellation (FreeSurfer)", Schizophrenia Bulletin, 41(1), pp. 233-249.

Arnone, D. et al. (2012) "Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses", European Neuropsychopharmacology, 22(1), pp. 1-16. doi: 10.1016/j.euroneuro.2011.05.003.

Bero, L., 2006. Evaluating systematic reviews and meta-analyses. J. Law Policy 14 (2). https://brooklynworks.brooklaw.edu/jlp/vol14/iss2/4.

Birchwood, M., Iqbal, Z., Upthegrove, R., 2005. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. Eur Arch Psychiatry Clin Neurosci 255, 202–212. https://doi.org/10.1007/s00406-005-0588-4.

Chuang, J.-Y., Murray, G.K., Metastasio, A., Segarra, N., Tait, R., Spencer, J., Ziauddeen, H., Dudas, R.B., Fletcher, P.C., Suckling, J., 2014. Brain structural signatures of negative symptoms in depression and schizophrenia. Front. Psych. 5 https://doi.org/10.3389/fpsyt.2014.00116.

Collins, J., Fauser, B., 2005. Balancing the strengths of systematic and narrative reviews. Hum. Reprod. Update 11 (2), 103–104. https://doi.org/10.1093/humupd/dmh058.

Correll, C., Schooler, N., 2020. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr. Dis. Treat. 16, 519–534. https://doi.org/10.2147/NDT.S225643.

Coryell, W., Nopoulos, P., Drevets, W., Wilson, T., Andreasen, N.C., 2005. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am. J. Psychiatry 162 (9), 1706–1712.

Craddock, N., Owen, M.J., 2010. The Kraepelinian dichotomy – going, going... but still not gone. Br J Psychiatry 196, 92–95. https://doi.org/10.1192/bjp.bp.109.073429.

Cui, Y., Dong, J., Yang, Y., Yu, H., Li, W., Liu, Y., Si, J., Xie, S., Sui, J., Lv, L., Jiang, T., 2020. White matter microstructural differences across major depressive disorder, bipolar disorder and schizophrenia: a tract-based spatial statistics study. J. Affect. Disord. 260, 281–286.

Haukvik, U.K., Tamnes, C.K., Söderman, E., Agartz, I., 2018. Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: a systematic review and meta-analysis. J. Psychiatr. Res. 104, 217–226.

Jiang, Y., Duan, M., Chen, X.i., Zhang, X., Gong, J., Dong, D., Li, H., Yi, Q., Wang, S., Wang, J., Luo, C., Yao, D., 2019. Aberrant prefrontal–thalamic–cerebellar circuit in schizophrenia and depression: evidence from a possible causal connectivity. Int. J. Neural Syst. 29 (05), 1850032.

Jiang, J., Zhao, Y.-J., Hu, X.-Y., Du, M.-Y., Chen, Z.-Q., Wu, M., Li, K.-M., Zhu, H.-Y., Kumar, P., Gong, Q.-Y., 2017. Microstructural brain abnormalities in medication-free patients with major depressive disorder: a systematic review and meta-analysis of diffusion tensor imaging. J. Psychiatry Neurosci. 42 (3), 150–163.

Kambeitz, J., Kambeitz-Ilankovic, L., Leucht, S., Wood, S., Davatzikos, C., Malchow, B., Falkai, P., Koutsouleris, N., 2015. Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. Neuropsychopharmacology 40 (7), 1742–1751.

Keller, J., Shen, L., Gomez, R.G., Garrett, A., Solvason, H.B., Reiss, A., Schatzberg, A.F., 2008. Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. Am. J. Psychiatry 165 (7), 872–880.

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O. A., Arango, C., Banaj, N., Bouix, S., Bousman, C.A., Brouwer, R.M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., Chen, J., Chen, J.-x., Chen, X., Chiapponi, C., Cho, K.K., Ciullo, V., Corvin, A.S., Crespo-Facorro, B., Cropley, V., De Rossi, P., Diaz-Caneja, C.M., Dickie, E.W., Ehrlich, S., Fan, F.-m., Faskowitz, J., Fatouros-Bergman, H., Flyckt, L., Ford, J.M., Fouche, J.-P., Fukunaga, M., Gill, M., Glahn, D.C., Gollub, R., Goudzwaard, E.D., Guo, H., Gur, R. E., Gur, R.C., Gurholt, T.P., Hashimoto, R., Hatton, S.N., Henskens, F.A., Hibar, D.P., Hickie, I.B., Hong, L.E., Horacek, J., Howells, F.M., Hulshoff Pol, H.E., Hyde, C.L., Isaev, D., Jablensky, A., Jansen, P.R., Janssen, J., Jönsson, E.G., Jung, L.A., Kahn, R. S., Kikinis, Z., Liu, K., Klauser, P., Knöchel, C., Kubicki, M., Lagopoulos, J., Langen, C., Lawrie, S., Lenroot, R.K., Lim, K.O., Lopez-Jaramillo, C., Lyall, A., Magnotta, V., Mandl, R.C.W., Mathalon, D.H., McCarley, R.W., McCarthy-Jones, S., McDonald, C., McEwen, S., McIntosh, A., Melicher, T., Mesholam-Gately, R.I., Michie, P.T., Mowry, B., Mueller, B.A., Newell, D.T., O'Donnell, P., Oertel-Knöchel, V., Oestreich, L., Paciga, S.A., Pantelis, C., Pasternak, O., Pearlson, G., Pellicano, G.R., Pereira, A., Pineda Zapata, J., Piras, F., Potkin, S.G., Preda, A., Rasser, P.E., Roalf, D.R., Roiz, R., Roos, A., Rotenberg, D., Satterthwaite, T.D., Savadjiev, P., Schall, U., Scott, R.J., Seal, M.L., Seidman, L.J., Shannon Weickert, C., Whelan, C.D., Shenton, M.E., Kwon, J.S., Spalletta, G., Spaniel, F., Sprooten, E., Stäblein, M., Stein, D.J., Sundram, S., Tan, Y., Tan, S., Tang, S., Temmingh, H.S., Westlye, L.T., Tønnesen, S., Tordesillas-Gutierrez, D., Doan, N.T., Vaidya, J., van Haren, N.E.M., Vargas, C.D., Vecchio, D., Velakoulis, D., Voineskos, A., Voyvodic, J. Q., Wang, Z., Wan, P., Wei, D., Weickert, T.W., Whalley, H., White, T., Whitford, T. J., Wojcik, J.D., Xiang, H., Xie, Z., Yamamori, H., Yang, F., Yao, N., Zhang, G., Zhao, J., van Erp, T.G.M., Turner, J., Thompson, P.M., Donohoe, G., 2018. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. Mol. Psychiatry 23 (5), 1261–1269.

Kochunov, P., Glahn, D.C., Rowland, L.M., Olvera, R.L., Winkler, A., Yang, Y.-H., Sampath, H., Carpenter, W.T., Duggirala, R., Curran, J., Blangero, J., Hong, L.E., 2013. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biol. Psychiatry 73 (5), 482–491.

Krynicki, C.R., Upthegrove, R., Deakin, J.F.W., Barnes, T.R.E., 2018. The relationship between negative symptoms and depression in schizophrenia: a systematic review. Acta Psychiatr. Scand. 137 (5), 380–390. https://doi.org/10.1111/acps.12873.

Lalousis, P. A., Wood, S. J., Schmaal, L., Chisholm, K., Griffiths, S. L., Reniers, R. L. E. P., Bertolino, A., Borgwardt, S., Brambilla, P., Kambeitz, J., Lencer, R., Pantelis, C., Ruhrmann, S., Salokangas, R. K. R., Schultze-Lutter, F., Bonivento, C., Dwyer, D., Ferro, A., Haidl, T., … PRONIA Consortium. (2021). Heterogeneity and Classification of Recent Onset Psychosis and Depression: A Multimodal Machine Learning Approach. *Schizophrenia Bulletin, sbaa185*. 10.1093/schbul/sbaa185.

Lalousis, P.A., Schmaal, L., Wood, S.J., Reniers, R.L.E.P., Barnes, N.M., Chisholm, K., Griffiths, S.L., Stainton, A., Wen, J., Hwang, G., Davatzikos, C., Wenzel, J., Kambeitz-Ilankovic, L., Andreou, C., Bonivento, C., Dannlowski, U., Ferro, A., Lichtenstein, T., Riecher-Rössler, A., Romer, G., Rosen, M., Bertolino, A., Borgwardt, S., Brambilla, P., Kambeitz, J., Lencer, R., Pantelis, C., Ruhrmann, S., Salokangas, R.K.R., Schultze-Lutter, F., Schmidt, A., Meisenzahl, E., Koutsouleris, N., Dwyer, D., Upthegrove, R., 2022. Neurobiologically Based Stratification of Recent-Onset Depression and Psychosis: Identification of Two Distinct Transdiagnostic Phenotypes. Biological Psychiatry 0. https://doi.org/10.1016/j.biopsych.2022.03.021.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. 62 (10), e1–e34. https://doi.org/10.1136/bmj.b2700.

Madre, M., Canales-Rodríguez, E.J., Ortiz-Gil, J., Murru, A., Torrent, C., Bramon, E., Perez, V., Orth, M., Brambilla, P., Vieta, E., Amann, B.L., 2016. Neuropsychological and neuroimaging underpinnings of schizoaffective disorder: a systematic review. Acta Psychiatr. Scand. 134 (1), 16–30. https://doi.org/10.1111/acps.12564.

Meisenzahl, E.M., Seifert, D., Bottlender, R., Teipel, S., Zetzsche, T., Jäger, M., Koutsouleris, N., Schmitt, G., Scheuerecker, J., Burgermeister, B., Hampel, H., Rupprecht, T., Born, C., Reiser, M., Möller, H.-J., Frodl, T., 2010. Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study. Eur. Arch. Psychiatry Clin. Neurosci. 260 (2), 127–137.

Moher, D., 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med 151, 264. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.

O'Connor, S., Agius, M., 2015. A systematic review of structural and functional MRI differences between psychotic and nonpsychotic depression. Psychiatr. Danub 27 (Suppl 1), S235–S239.

Ota, M., Ishikawa, M., Sato, N., Hori, H., Sasayama, D., Hattori, K., Teraishi, T., Noda, T., Obu, S., Nakata, Y., Higuchi, T., Kunugi, H., 2013. Discrimination between schizophrenia and major depressive disorder by magnetic resonance imaging of the female brain. J. Psychiatr. Res. 47 (10), 1383–1388.

Sönmez, N., Romm, K.L., Andreasssen, O.A., Melle, I., Røssberg, J.I., 2013. Depressive symptoms in first episode psychosis: a one-year follow-up study. BMC Psychiatry 13, 106. https://doi.org/10.1186/1471-244X-13-106.

Steen, R.G., Mull, C., Mcclure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br. J. Psychiatry 188 (6), 510–518. https://doi.org/10.1192/bjp.188.6.510.

Upthegrove, R., Marwaha, S., Birchwood, M., 2017. Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? Schizophr. Bull. 43 (2), 240–244. https://doi.org/10.1093/schbul/sbw097.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. and Tugwell, P., (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis.

Wise, T., Radua, J., Nortje, G., Cleare, A.J., Young, A.H., Arnone, D., 2016. Voxel-based meta-analytical evidence of structural disconnectivity in major depression and bipolar disorder. Biol. Psychiatry 79 (4), 293–302. https://doi.org/10.1016/j.biopsych.2015.03.004.

World Health Organization. (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization.

Yue, Y., Kong, L.i., Wang, J., Li, C., Tan, L., Su, H., Xu, Y., Zuo, X.-N., 2016. Regional abnormality of grey matter in schizophrenia: effect from the illness or treatment? PLoS One 11 (1), e0147204.

Zeng, L. et al. (2012) "Antidepressant Treatment Normalizes White Matter Volume in Patients with Major Depression", PLoS ONE, 7(8), p. e44248. doi:10.1371/journal.pone.0044248.

Zhang, Y. et al. (2016) "Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation", Translational Psychiatry, 6 (12), pp. e982-e982. doi: 10.1038/tp.2016.238.

Zhang, X., Zhang, Y., Liao, J., Jiang, S., Yan, J., Yue, W., Zhang, D., Yan, H., 2018. Progressive grey matter volume changes in patients with schizophrenia over 6 weeks of antipsychotic treatment and their relationship to clinical improvement. Neurosci. Bull. 34 (5), 816–826. https://doi.org/10.1007/s12264-018-0234-6.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J., Whiteford, H.A., 2018. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr Bull 44, 1195–1203. https://doi.org/10.1093/schbul/sby058.

Vos, T., Barber, R.M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V.L., Ferrari, A.J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J., Hansen, G.M., Hanson, S.W., Heuton, K.R., Higashi, H., Kassebaum, N., Kyu, H., Laurie, E., Liang, X., Lofgren, K., Lozano, R., MacIntyre, M.F., Moradi-Lakeh, M., Naghavi, M., Nguyen, G., Odell, S., Ortblad, K., Roberts, D.A., Roth, G.A., Sandar, L., Serina, P.T., Stanaway, J.D., Steiner, C., Thomas, B., Vollset, S.E., Whiteford, H., Wolock, T.M., Ye, P., Zhou, M., Ávila, M.A., Aasvang, G.M., Abbafati, C., Ozgoren, A.A., Abd-Allah, F., Aziz, M.I.A., Abera, S.F., Aboyans, V., Abraham, J.P., Abraham, B., Abubakar, I., Abu-Raddad, L.J., Abu-Rmeileh, N.M., Aburto, T.C., Achoki, T., Ackerman, I.N., Adelekan, A., Ademi, Z., Adou, A.K., Adsuar, J.C., Arnlov, J., Agardh, E.E., Al Khabouri, M.J., Alam, S.S., Alasfoor, D., Albittar, M.I., Alegretti, M.A., Aleman, A.V., Alemu, Z.A., Alfonso-Cristancho, R., Alhabib, S., Ali, R., Alla, F., Allebeck, P., Allen, P.J., AlMazroa, M.A., Alsharif, U., Alvarez, E., Alvis-Guzman, N., Ameli, O., Amini, H., Ammar, W., Anderson, B.O., Anderson, H.R., Antonio, C.A.T., Anwari, P., Apfel, H., Arsenijevic, V.S.A., Artaman, A., Asghar, R.J., Assadi, R., Atkins, L.S., Atkinson, C., Badawi, A., Bahit, M.C., Bakfalouni, T., Balakrishnan, K., Balalla, S., Banerjee, A., Barker-Collo, S.L., Barquera, S., Barregard, L., Barrero, L.H., Basu, S., Basu, A., Baxter, A., Beardsley, J., Bedi, N., Beghi, E., Bekele, T., Bell, M.L., Benjet, C., Bennett, D.A., Bensenor, I.M., Benzian, H., Bernabe, E., Beyene, T.J., Bhala, N., Bhalla, A., Bhutta, Z., Bienhoff, K., Bikbov, B., Abdulhak, A.B., Blore, J.D., Blyth, F.M., Bohensky, M.A., Basara, B.B., Borges, G., Bornstein, N.M., Bose, D., Boufous, S., Bourne, R.R., Boyers, L.N., Brainin, M., Brauer, M., Brayne, C.E., Brazinova, A., Breitborde, N.J., Brenner, H., Briggs, A.D., Brooks, P.M., Brown, J., Brugha, T.S., Buchbinder, R., Buckle, G.C., Bukhman, G., Bulloch, A.G., Burch, M., Burnett, R., Cardenas, R., Cabral, N.L., Nonato, I.R.C., Campuzano, J.C., Carapetis, J.R., Carpenter, D.O., Caso, V., Castaneda-Orjuela, C.A., Catala-Lopez, F., Chadha, V.K., Chang, J.-C., Chen, H., Chen, W., Chiang, P.P., Chimed-Ochir, O., Chowdhury, R., Christensen, H., Christophi, C.A., Chugh, S.S., Cirillo, M., Coggeshall, M., Cohen, A., Colistro, V., Colquhoun, S.M., Contreras, A.G., Cooper, L.T., Cooper, C., Cooperrider, K., Coresh, J., Cortinovis, M., Criqui, M.H., Crump, J.A., Cuevas-Nasu, L., Dandona, R., Dandona, L., Dansereau, E., Dantes, H.G., Dargan, P.I., Davey, G., Davitoiu, D.V., Dayama, A., De la Cruz-Gongora, V., de la Vega, S.F., De Leo, D., del Pozo-Cruz, B., Dellavalle, R.P., Deribe, K., Derrett, S., Des Jarlais, D.C., Dessalegn, M., deVeber, G.A., Dharmaratne, S.D., Diaz-Torne, C., Ding, E.L., Dokova, K., Dorsey, E.R., Driscoll, T.R., Duber, H., Durrani, A.M., Edmond, K.M., Ellenbogen, R.G., Endres, M., Ermakov, S.P., Eshrati, B., Esteghamati, A., Estep, K., Fahimi, S., Farzadfar, F., Fay, D.F., Felson, D.T., Fereshtehnejad, S.-M., Fernandes, J.G., Ferri, C.P., Flaxman, A., Foigt, N., Foreman, K.J., Fowkes, F.G.R., Franklin, R.C., Furst, T., Futran, N.D., Gabbe, B.J., Gankpe, F.G., Garcia-Guerra, F.A., Geleijnse, J.M., Gessner, B.D., Gibney, K.B., Gillum, R.F., Ginawi, I.A., Giroud, M., Giussani, G., Goenka, S., Goginashvili, K., Gona, P., de Cosio, T.G., Gosselin, R.A., Gotay, C.C., Goto, A., Gouda, H.N., Guerrant, R. l, Gugnani, H.C., Gunnell, D., Gupta, Rajeev, Gupta, Rahul, Gutierrez, R.A., Hafezi-Nejad, N., Hagan, H., Halasa, Y., Hamadeh, R.R., Hamavid, H., Hammami, M., Hankey, G.J., Hao, Y., Harb, H.L., Haro, J.M., Havmoeller, R., Hay, R.J., Hay, S., Hedayati, M.T., Pi, I.B.H., Heydarpour, P., Hijar, M., Hoek, H.W., Hoffman, H.J., Hornberger, J.C., Hosgood, H.D., Hossain, M., Hotez, P.J., Hoy, D.G., Hsairi, M., Hu, H., Hu, G., Huang, J.J., Huang, C., Huiart, L., Husseini, A., Iannarone, M., Iburg, K.M., Innos, K., Inoue, M., Jacobsen, K.H., Jassal, S.K., Jeemon, P., Jensen, P.N., Jha, V., Jiang, G., Jiang, Y., Jonas, J.B., Joseph, J., Juel, K., Kan, H., Karch, A., Karimkhani, C., Karthikeyan, G., Katz, R., Kaul, A., Kawakami, N., Kazi, D.S., Kemp, A.H., Kengne, A.P., Khader, Y.S., Khalifa, S.E.A., Khan, E.A., Khan, G., Khang, Y.-H., Khonelidze, I., Kieling, C., Kim, D., Kim, S., Kimokoti, R.W., Kinfu, Y., Kinge, J.M., Kissela, B.M., Kivipelto, M., Knibbs, L., Knudsen, A.K., Kokubo, Y., Kosen, S., Kramer, A., Kravchenko, M., Krishnamurthi, R. V., Krishnaswami, S., Defo, B.K., Bicer, B.K., Kuipers, E.J., Kulkarni, V.S., Kumar, K., Kumar, G.A., Kwan, G.F., Lai, T., Lalloo, R., Lam, H., Lan, Q., Lansingh, V.C., Larson, H., Larsson, A., Lawrynowicz, A.E., Leasher, J.L., Lee, J.-T., Leigh, J., Leung, R., Levi, M., Li, B., Li, Yichong, Li, Yongmei, liang, J., Lim, S., Lin, H.-H., Lind, M., Lindsay, M. P., Lipshultz, S.E., Liu, S., Lloyd, B.K., Ohno, S.L., Logroscino, G., Looker, K.J., Lopez, A.D., Lopez-Olmedo, N., Lortet-Tieulent, J., Lotufo, P.A., Low, N., Lucas, R.M., Lunevicius, R., Lyons, R.A., Ma, J., Ma, S., Mackay, M.T., Majdan, M., Malekzadeh, R., Mapoma, C.C., Marcenes, W., March, L.M., Margono, C., Marks, G.B., Marzan, M. B., Masci, J.R., Mason-Jones, A.J., Matzopoulos, R.G., Mayosi, B.M., Mazorodze, T. T., McGill, N.W., McGrath, J.J., McKee, M., McLain, A., McMahon, B.J., Meaney, P. A., Mehndiratta, M.M., Mejia-Rodriguez, F., Mekonnen, W., Melaku, Y.A., Meltzer, M., Memish, Z.A., Mensah, G., Meretoja, A., Mhimbira, F.A., Micha, R., Miller, T.R., Mills, E.J., Mitchell, P.B., Mock, C.N., Moffitt, T.E., Ibrahim, N.M., Mohammad, K.A., Mokdad, A.H., Mola, G.L., Monasta, L., Montico, M., Montine, T.J., Moore, A.R., Moran, A.E., Morawska, L., Mori, R., Moschandreas, J., Moturi, W.N., Moyer, M., Mozaffarian, D., Mueller, U.O., Mukaigawara, M., Murdoch, M.E., Murray, J., Murthy, K.S., Naghavi, P., Nahas, Z., Naheed, A., Naidoo, K.S., Naldi, L., Nand, D., Nangia, V., Narayan, K.M.V., Nash, D., Nejjari, C., Neupane, S.P., Newman, L.M., Newton, C.R., Ng, M., Ngalesoni, F.N., Nhung, N.T., Nisar, M.I., Nolte, S., Norheim, O.F., Norman, R.E., Norrving, B., Nyakarahuka, L., Oh, I.H., Ohkubo, T., Omer, S.B., Opio, J.N., Ortiz, A., Pandian, J.D., Panelo, C.I.A., Papachristou, C., Park, E.-K., Parry, C.D., Caicedo, A.J.P., Patten, S.B., Paul, V.K., Pavlin, B.I., Pearce, N., Pedraza, L.S., Pellegrini, C.A., Pereira, D.M., Perez-Ruiz, F.P., Perico, N., Pervaiz, A., Pesudovs, K., Peterson, C.B., Petzold, M., Phillips, M.R., Phillips, D., Phillips, B., Piel, F.B., Plass, D., Poenaru, D., Polanczyk, G.V., Polinder, S., Pope, C.A., Popova, S., Poulton, R.G., Pourmalek, F., Prabhakaran, D., Prasad, N.M., Qato, D., Quistberg, D. A., Rafay, A., Rahimi, K., Rahimi-Movaghar, V., Rahman, S. ur, Raju, M., Rakovac, I., Rana, S.M., Razavi, H., Refaat, A., Rehm, J., Remuzzi, G., Resnikoff, S., Ribeiro, A.L., Riccio, P.M., Richardson, L., Richardus, J.H., Riederer, A.M., Robinson, M., Roca, A., Rodriguez, A., Rojas-Rueda, D., Ronfani, L., Rothenbacher, D., Roy, N., Ruhago, G. M., Sabin, N., Sacco, R.L., Ksoreide, K., Saha, S., Sahathevan, R., Sahraian, M.A., Sampson, U., Sanabria, J.R., Sanchez-Riera, L., Santos, I.S., Satpathy, M., Saunders, J.E., Sawhney, M., Saylan, M.I., Scarborough, P., Schoettker, B., Schneider, I.J., Schwebel, D.C., Scott, J.G., Seedat, S., Sepanlou, S.G., Serdar, B., Servan-Mori, E.E., Shackelford, K., Shaheen, A., Shahraz, S., Levy, T.S., Shangguan, S., She, J., Sheikhbahaei, S., Shepard, D.S., Shi, P., Shibuya, K., Shinohara, Y., Shiri, R., Shishani, K., Shiue, I., Shrime, M.G., Sigfusdottir, I.D., Silberberg, D.H., Simard, E.P., Sindi, S., Singh, J.A., Singh, L., Skirbekk, V., Sliwa, K., Soljak, M., Soneji, S., Soshnikov, S.S., Speyer, P., Sposato, L.A., Sreeramareddy, C.T., Stoeckl, H., Stathopoulou, V.K., Steckling, N., Stein, M.B., Stein, D.J., Steiner, T.J., Stewart, A., Stork, E., Stovner, L.J., Stroumpoulis, K., Sturua, L., Sunguya, B.F., Swaroop, M., Sykes, B.L., Tabb, K.M., Takahashi, K., Tan, F., Tandon, N., Tanne, D., Tanner, M., Tavakkoli, M., Taylor, H.R., Te Ao, B.J., Temesgen, A.M., Have, M.T., Tenkorang, E. Y., Terkawi, A.S., Theadom, A.M., Thomas, E., Thorne-Lyman, A.L., Thrift, A.G., Tleyjeh, I.M., Tonelli, M., Topouzis, F., Towbin, J.A., Toyoshima, H., Traebert, J., Tran, B.X., Trasande, L., Trillini, M., Truelsen, T., Trujillo, U., Tsilimbaris, M., Tuzcu, E.M., Ukwaja, K.N., Undurraga, E.A., Uzun, S.B., van Brakel, W.H., van de Vijver, S., Dingenen, R.V., van Gool, C.H., Varakin, Y.Y., Vasankari, T.J., Vavilala, M.S., Veerman, L.J., Velasquez-Melendez, G., Venketasubramanian, N., Vijayakumar, L., Villalpando, S., Violante, F.S., Vlassov, V.V., Waller, S., Wallin, M.T., Wan, X., Wang, L., Wang, J., Wang, Y., Warouw, T.S., Weichenthal, S., Weiderpass, E., Weintraub, R. G., Werdecker, A., Wessells, K.R.R., Westerman, R., Wilkinson, J.D., Williams, H.C., Williams, T.N., Woldeyohannes, S.M., Wolfe, C.D., Wong, J.Q., Wong, H., Woolf, A. D., Wright, J.L., Wurtz, B., Xu, G., Yang, G., Yano, Y., Yenesew, M.A., Yentur, G.K., Yip, P., Yonemoto, N., Yoon, S.-J., Younis, M., Yu, C., Kim, K.Y., Zaki, M.E.S., Zhang, Y., Zhao, Z., Zhao, Y., Zhu, J., Zonies, D., Zunt, J.R., Salomon, J.A., Murray, C.J., 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 386, 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4.

WHO | Depression and Other Common Mental Disorders [WWW Document], 2017. . WHO. URL http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/ (accessed 5.20.19).

Further reading

An der Heiden, W., Leber, A., Häfner, H., 2016. Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 266 (5), 387–396.

Berger, G.E., Bartholomeusz, C.F., Wood, S.J., Ang, A., Phillips, L.J., Proffitt, T., Brewer, W.J., Smith, D.J., Nelson, B., Lin, A., Borgwardt, S., Velakoulis, D., Yung, A. R., McGorry, P.D., Pantelis, C., 2017. Ventricular volumes across stages of schizophrenia and other psychoses. Aust. N. Z. J. Psychiatry 51 (10), 1041–1051.

Carrà, G., Crocamo, C., Bartoli, F., Angermeyer, M., Brugha, T., Toumi, M., Bebbington, P., 2019. The mediating role of depression in pathways linking positive and negative symptoms in schizophrenia. A longitudinal analysis using latent variable structural equation modelling. Psychol. Med. 1–9. https://doi.org/10.1017/S0033291719000321.

Fu, C., Steiner, H., Costafreda, S., 2013. Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiol. Dis. 52, 75–83. https://doi.org/10.1016/j.nbd.2012.05.008.

Fusar-Poli, P. et al. (2014) "Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials", Schizophrenia Bulletin, 41 (4), pp. 892–899. doi: 10.1093/schbul/sbu170.

Fusar-Poli, P., Solmi, M., Brondino, N., Davies, C., Chae, C., Politi, P., Borgwardt, S., Lawrie, S.M., Parnas, J., McGuire, P., 2019. Transdiagnostic psychiatry: a systematic review. World Psychiatry 18 (2), 192–207.

Hinney, B., Walter, A., Aghlmandi, S., Andreou, C., Borgwardt, S., 2021. Does hippocampal volume predict transition to psychosis in a high-risk group? A meta-analysis. Front. Psychol. 11 https://doi.org/10.3389/fpsyt.2020.614659.

Horan, W.P., Green, M.F., Kring, A.M., Nuechterlein, K.H., 2006. Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? J. Abnorm. Psychol. 115 (3), 496–508.

Izuo, N., Nitta, A., 2021. New insights regarding diagnosis and medication for schizophrenia based on neuronal synapse-microglia interaction. J. Personal. Med. 11 (5), 371.

Jones, M., Koh, J., Cheong, K., 2020. Synaptic pruning in schizophrenia: does minocycline modulate psychosocial brain development? Bioessays 42 (9), 2000046. https://doi.org/10.1002/bies.202000046.

Kambeitz, J., Cabral, C., Sacchet, M.D., Gotlib, I.H., Zahn, R., Serpa, M.H., Walter, M., Falkai, P., Koutsouleris, N., 2017. Detecting neuroimaging biomarkers for depression: a meta-analysis of multivariate pattern recognition studies. Biol. Psychiatry 82 (5), 330–338.

Karlsgodt, K., Sun, D., Cannon, T., 2010. Structural and functional brain abnormalities in schizophrenia. Curr. Dir. Psychol. Sci. 19 (4), 226–231. https://doi.org/10.1177/0963721410377601.

Koutsouleris, N., Meisenzahl, E.M., Borgwardt, S., Riecher-Rössler, A., Frodl, T., Kambeitz, J., Köhler, Y., Falkai, P., Möller, H.-J., Reiser, M., Davatzikos, C., 2015. Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. Brain 138 (7), 2059–2073. https://doi.org/10.1093/brain/awv111.

Kraus, C., Kadriu, B., Lanzenberger, R., Zarate Jr, C.A., Kasper, S., 2019. Prognosis and improved outcomes in major depression: a review. Transl. Psychiatry 9 (1), 1–17. https://doi.org/10.1038/s41398-019-0460-3.

Krueger, R.F., Eaton, N.R., 2015. Transdiagnostic factors of mental disorders. World Psychiatry 14 (1), 27–29.

LeMoult, J., Gotlib, I.H., 2019. Depression: a cognitive perspective. Clin. Psychol. Rev. 69, 51–66. https://doi.org/10.1016/j.cpr.2018.06.008.

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., Lyu, J., 2020. Changes in the global burden of depression from 1990 to 2017: findings from the Global Burden of Disease study. J. Psychiatr. Res. 126, 134–140. https://doi.org/10.1016/j.jpsychires.2019.08.002.

Moller, P., Husby, R., 2000. The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. Schizophr. Bull. 26 (1), 217–232. https://doi.org/10.1093/oxfordjournals.schbul.a033442.

Moritz, S., Birkner, C., Kloss, M., Jahn, H., Hand, I., Haasen, C., Krausz, M., 2002. Executive functioning in obsessive–compulsive disorder, unipolar depression, and schizophrenia. Arch. Clin. Neuropsychol. 17 (5), 477–483.

Nakahara, S., Matsumoto, M., van Erp, T.G., 2018. Hippocampal subregion abnormalities in schizophrenia: a systematic review of structural and physiological imaging studies. Neuropsychopharmacol. Rep. 38 (4), 156–166. https://doi.org/10.1002/npr2.12031.

Owen, M.J., O'Donovan, M.C., Thapar, A., Craddock, N., 2011. Neurodevelopmental hypothesis of schizophrenia. Br. J. Psychiatry 198 (3), 173–175. https://doi.org/10.1192/bjp.bp.110.084384.

Schlesselman, J.J. and Collins, J.A., (2003). Evaluating systematic reviews and meta-analyses. In *Seminars in reproductive medicine* (Vol. 21, No. 01, pp. 095-106). doi: 10.4103/0019-5154.127671.

Schothorst, P., Emck, C., van Engeland, H., 2006. Characteristics of early psychosis. Compr. Psychiatry 47 (6), 438–442. https://doi.org/10.1016/j.comppsych.2006.03.003.

Strauss, G.P., Hong, L.E., Gold, J.M., Buchanan, R.W., McMahon, R.P., Keller, W.R., Fischer, B.A., Catalano, L.T., Culbreth, A.J., Carpenter, W.T., Kirkpatrick, B., 2012. Factor structure of the brief negative symptom scale. Schizophr. Res. 142 (1-3), 96–98.

van Velzen, L.S., Kelly, S., Isaev, D., Aleman, A., Aftanas, L.I., Bauer, J., Baune, B.T., Brak, I.V., Carballedo, A., Connolly, C.G., Couvy-Duchesne, B., Cullen, K.R., Danilenko, K.V., Dannlowski, U., Enneking, V., Filimonova, E., Förster, K., Frodl, T., Gotlib, I.H., Groenewold, N.A., Grotegerd, D., Harris, M.A., Hatton, S.N., Hawkins, E. L., Hickie, I.B., Ho, T.C., Jansen, A., Kircher, T., Klimes-Dougan, B., Kochunov, P., Krug, A., Lagopoulos, J., Lee, R., Lett, T.A., Li, M., MacMaster, F.P., Martin, N.G., McIntosh, A.M., McLellan, Q., Meinert, S., Nenadić, I., Osipov, E., Penninx, B.W.J.H., Portella, M.J., Repple, J., Roos, A., Sacchet, M.D., Sämann, P.G., Schnell, K., Shen, X., Sim, K., Stein, D.J., van Tol, M.-J., Tomyshev, A.S., Tozzi, L., Veer, I.M., Vermeiren, R., Vives-Gilabert, Y., Walter, H., Walter, M., van der Wee, N.J.A., van der Werff, S.J.A., Schreiner, M.W., Whalley, H.C., Wright, M.J., Yang, T.T., Zhu, A., Veltman, D.J., Thompson, P.M., Jahanshad, N., Schmaal, L., 2020. White matter disturbances in major depressive disorder: a coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. Mol. Psychiatry 25 (7), 1511–1525.

The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines [WWW Document], 1992. URL https://apps.who.int/iris/handle/10665/37958 (accessed 5.20.19).