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Neuropathology of major psychiatric disorders: A systematic review

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Abstract

Objective: The purpose of this paper is to review literature on the neuropathology of major psychiatric disorders.

Methods: Systematic reviews of neuropathology of psychiatric disorders were identified from 1972 to 2022 through the use of the PubMed database, using the keywords: 'neuropathology' AND 'schizophrenia' OR 'bipolar' OR 'major depression'. The search was then narrowed to systematic reviews.

Results: Ten systematic reviews were selected in this review. The neuropathological findings were identified and detailed for schizophrenia, bipolar disorder, and major depression, at the macroscopic and microscopic levels.

Conclusion: Most of the Psychiatric disorders showed cortical damage in certain areas of the brain especially the cingulate cortex, temporal lobe, and the amygdala. The main limitation of interpreting neuropathological findings in major psychiatric disorders is simply identifying and analyzing brain samples of sufficient quantity and quality for research.

Keywords: Neuropathology; Schizophrenia; Bipolar; Depression; Pathology

1. Introduction

Major psychiatric disorders such as Schizophrenia, Bipolar disorder, and Major Depression, are associated with some neuropathology, such as inflammatory, degenerative, and neoplastic processes [1, 2]. The special neuropathological interest in psychiatric disorders reflects the neurobiological importance of psychiatric disorders, and the need to identify the cellular, histological, and imaging characteristics of the structural brain abnormalities in psychiatric disorders. MRI findings, for instance, helped in targeting certain brain areas for neuropathological investigation such as the frontal lobe, and medial temporal lobe (hippocampal formation and amygdala) and striatum [1].

This systematic review aims at examining the literature on the neuropathology of major psychiatric disorders by focusing on the macroscopic and microscopic findings in the following disorders:

- Schizophrenia
- Bipolar disorder
- Major depression

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2. Material and methods

2.1. Search Strategy

Systematic reviews of neuropathology of psychiatric disorders were identified from 1972 to 2022 through the use of the PubMed database, using the keywords: 'neuropathology' AND 'schizophrenia' OR 'bipolar' OR 'major depression'. The search was then narrowed to systematic reviews.

3. Results

3.1. Overview

This systematic review of reviews explored the macroscopic and microscopic findings in major depression, bipolar disorder, and schizophrenia.

3.2. Schizophrenia

Schizophrenia is a mood disorder with significant progressive changes in perception, mood, cognitive abilities and behavior. Symptoms typically start between the late teens and early thirties. Symptoms should be present for at least 6 months and not secondary to another disorder [3]. These main symptoms can be positive symptoms including hallucinations, disorganized thinking and delusions. Some negative symptoms may be obvious as well; social withdrawal, apathy and flat affect [4]. Brain imaging technology advances, especially magnetic resonance imaging, have shown significant anatomical changes in the brain of patients with schizophrenia [5] .

3.2.1. Macroscopic picture:

In chronic schizophrenia patients, imaging studies showed enlarged ventricles with decrease volume in amygdala, temporal lobes, and parahippocampal gyrus [6-8]. In first- episode schizophrenia patients, enlarged lateral and third ventricles and decreases in overall brain volume, as well as basal ganglia, hippocampal and thalamic volumes were observed [9,10]. Recent studies have shown a progressive brain tissue volume decrease (mostly in the frontal and temporal gray matter areas) and lateral ventricles volume increase for up to 20 years after the first symptoms [11].

Progressive volume decreases in the frontal lobe have been reported many times [12], [13]. Cortical grey matter progressive deficits could be caused by pathological disease progression, drug effect [14], or some comorbidity as in alcoholism [15].

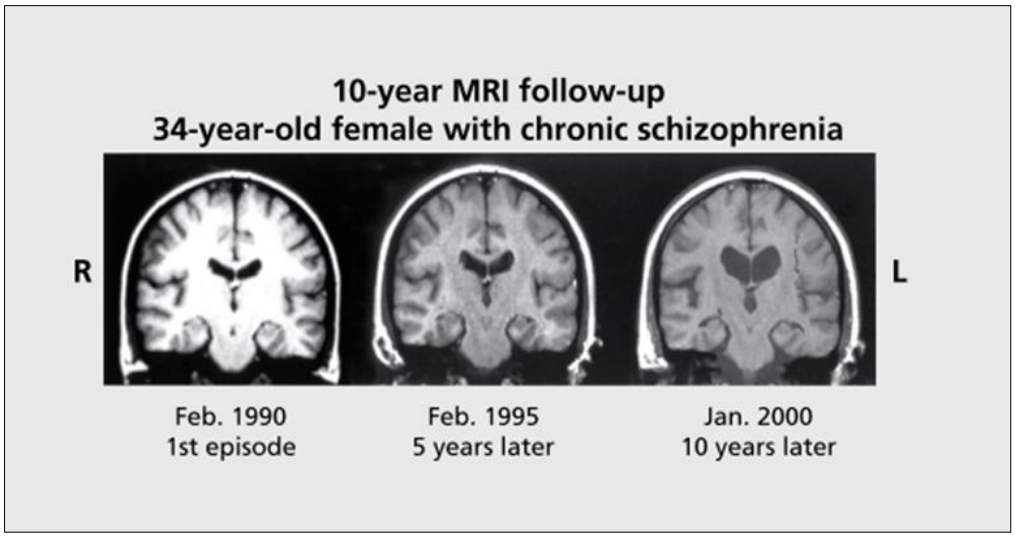

Figure 1 10-year brain MRI follow-up of a schizophrenia patient

Magnetic resonance imaging (MRI) of a female patient who initially was scanned at the time of hospitalization for a first episode of schizophrenia. At the tenth year of follow-up, at age 34, she was an outpatient with a diagnosis of chronic schizophrenia stabilized with predominantly negative symptoms with obvious progressive ventricular enlargement

(Weinberger DR, 1987). DeLisi LE, Szulc KU, Bertisch HC, Majcher M, Brown K. Understanding structural brain changes in schizophrenia. Dialogues Clin Neurosci. 2006;8(1):71-8. doi: 10.31887/DCNS.2006.8.1/ldelisi. [53]

3.2.2. Microscopic Picture

In the acute state of schizophrenia, microglia activation might be a factor cause for the damage of oligodendrocytes and myelinated fibers, in the subgroup of subjects with predominantly positive symptoms (SPPS). It was found that the prefrontal cortex (PFC) is one of the main areas affected in schizophrenia [16]. Psychotic symptoms and cognitive impairment were found to be associated with functional dysconnectivity of the PFC [17]. A link was observed between severity of positive symptoms and microstructure abnormalities in the PFC [18] and functional dysconnectivity in fronto-temporal cortex [19], [20]. Oligodendrocytes and myelin pathology are considered the basis for dysconnectivity in schizophrenia [21], [22].

Some changes have been reported in the PFC; reduced oligodendrocyte density [23]. [24], [25], [26], ultrastructural alterations of oligodendrocytes and myelinated fibers [27], [28], [29], altered intercortical myelin staining [30] and impaired differentiation of oligodendrocyte precursors [31]. Myelination abnormalities, reduced expression and dysregulation of oligodendrocyte and myelin related genes have been detected as well in the PFC in schizophrenia [32-34].

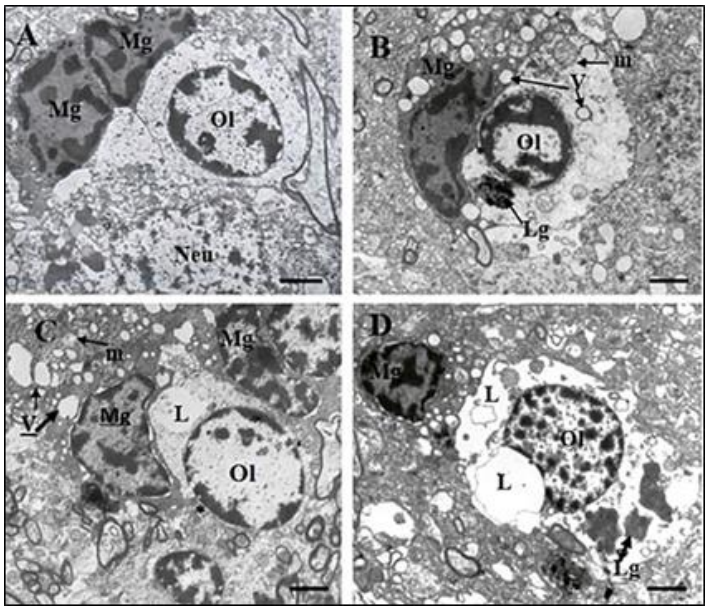

Figure 2 Electron microscopic picture comparison of the Prefrontal cortex of subgroup of predominantly positive symptoms (SPPS) with control subjects

These micrographs from layer 5 of the prefrontal cortex show microglia adjacent to oligodendrocytes from control brain (A) and from the SPPS subgroup (B–D). "Resting" microglia (A). Ameboid (activated) microglia (B). Dystrophic changes in microglia and oligodendrocytes: cytoplasm vacuolation, damaged mitochondria, accumulation of lipofuscin granules (C, D). Microglial cytoplasm contacts with oligodendrocyte nucleus (B, C, *). Focal lysis (L) of cytoplasm of oligodendrocytes adjacent to microglia (C, D). Mg, microglia; Ol, oligodendrocyte, m, mitochondria (arrows); V, vacuole (arrows), Lg, lipofuscin granule (arrows). (Scale bars = 1 μm). Uranova NA, Vikhreva OV, Rakhmanova VI, Orlovskaya DD. Ultrastructural pathology of oligodendrocytes adjacent to microglia in prefrontal white matter in schizophrenia. NPJ Schizophr. 2018 Dec 13;4(1):26. doi: 10.1038/s41537-018-0068-2. [54]

These micrographs from layer 5 of the prefrontal cortex show microglia adjacent to oligodendrocytes from the SPNS subgroup. Dark dystrophic microglia (A). Ameboid microglia (B), signs of apoptosis (dark nucleus and small rim of dark shrunken cytoplasm) (C, D). All microglia showed contacts with the nuclei of oligodendrocytes (A–D, arrows). A group (cluster) of three microglia surrounding dystrophic oligodendrocyte (D). Ol, oligodendrocyte; Mg, microglia. Scale bar=1 μm.

Uranova NA, Vikhreva OV, Rakhmanova VI, Orlovskaya DD. Ultrastructural pathology of oligodendrocytes adjacent to microglia in prefrontal white matter in schizophrenia. NPJ Schizophr. 2018 Dec 13;4(1):26. doi: 10.1038/s41537-018-0068-2. [54]

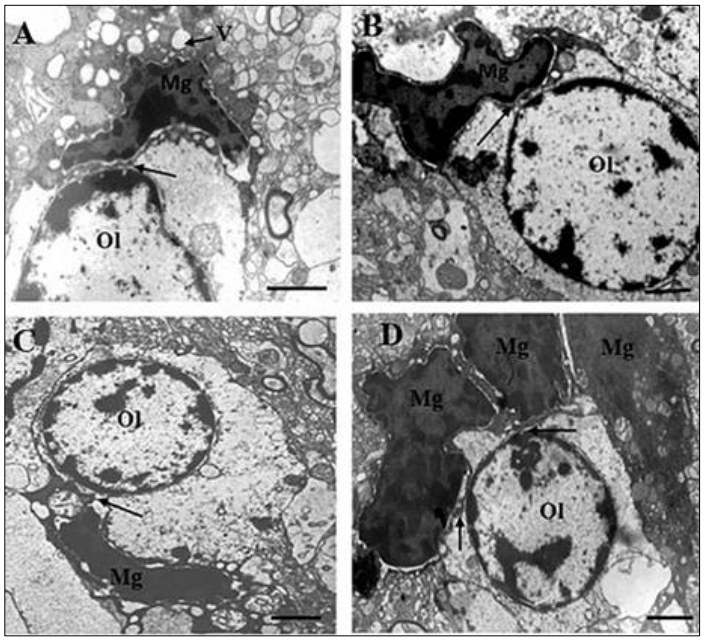

Figure 3 Electron microscopic picture of the Prefrontal cortex of subgroup of subjects with predominantly negative symptoms (SPNS)

3.3. Major depression

Major depressive disorder (MDD) is a common mood disorder that can negatively affect feelings, thoughts, and actions. MDD could impact one's ability to normally function in daily life as well as health-related quality of life (HRQoL) [35]. Symptoms include feelings of sadness, loss of interest/pleasure in activities once enjoyed, changes in appetite, insomnia or hypersomnia, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and thoughts of death/suicide [36]. The diagnosis of depression is made clinically and symptoms must be present for at least two weeks to make the diagnosis. The prevalence of at least one major depressive episode among adults in the U.S. was estimated to be 7.1% in 2017, representing roughly 17.3 million people. The highest prevalence of adults with a major depressive episode was among people aged 18-25 (13.1%) [37].

3.3.1. Macroscopic findings

Nonpsychotic disorders (OCD, anxiety disorders, MDD) showed greater gray matter loss in the hippocampus and amygdala [38]. These regions are all centered on the dorsal anterior cingulate cortex (dACC), which is part of a larger neural circuit, the anterior cingulo-insular network (aCIN). The aCIN is also sometimes referred to as the 'salience' network. These areas were shown to be affected not only in MDD and other non-psychotic disorders, but in most psychiatric disorders in general. The dACC and anterior insula are involved in self-regulation of emotions, thoughts, and behaviors, deficiencies of which are features of psychiatric illness [38]. Part of the anterior cingulate gyrus ventral to the genu of the corpus callosum, subgenual region sg24, was 40% smaller in 38 subjects with familial mood disorder compared to the 21 controls [39]. This volume decrease was left lateralized and was in both unipolar (MDD) and bipolar (BD) disorders [1].

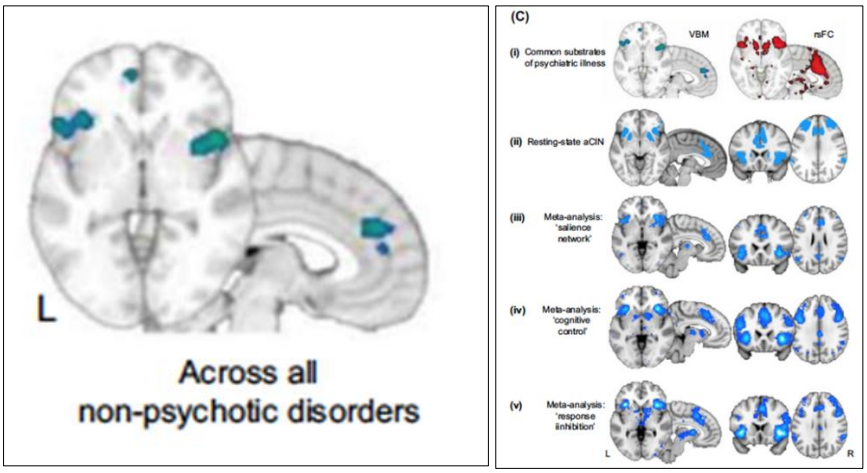

Figure 4 Brain MRI showing relationship between depression and white matter hyperintensities

MRI studies have shown a positive relationship between white matter hyperintensities (WMH), especially in the frontal lobe, and depression [40]. WMH have been shown to appear in excess in both unipolar and bipolar disorders [1]. These WMH are believed to be linked to risk factors or the presence of vascular disease [41] and indicate damage to white matter tracts [1, 42].

(Above, left) Regions showing gray matter loss in non-psychotic disorders (OCD, anxiety, MDD, substance abuse). Greater loss in the hippocampus and amygdala were noted. (Above, right) brain regions showing the common regions affected by psychiatric illness, the aCIN, the salience network, and the regions involved with response inhibition. Downar J, Blumberger DM, Daskalakis ZJ. The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation. Trends Cogn Sci. 2016 Feb;20(2):107-120. doi: 10.1016/j.tics.2015.10.007. [38]

3.3.2. Microscopic findings

The main positive findings in one study found decreased glial density in lamina VI and reduced neuronal size in laminae Vb and VI in the supra-genual part of the anterior cingulate cortex [1]. A large number of studies found that there were increased levels of inflammatory proteins (tumor necrosis factor (TNF), interleukin 6 (IL-6), and C-reactive protein (CRP)) in the serum or plasma of individuals with both MDD and BD. Pro inflammatory cytokines like these can reduce the availability of monoamines (serotonin, dopamine, norepinephrine) by upregulating synaptic reuptake and decreasing monoamine synthesis [43]. It has been demonstrated several times that elevations in CRP or IL-6 predicted the development of MDD and Psychosis [43].

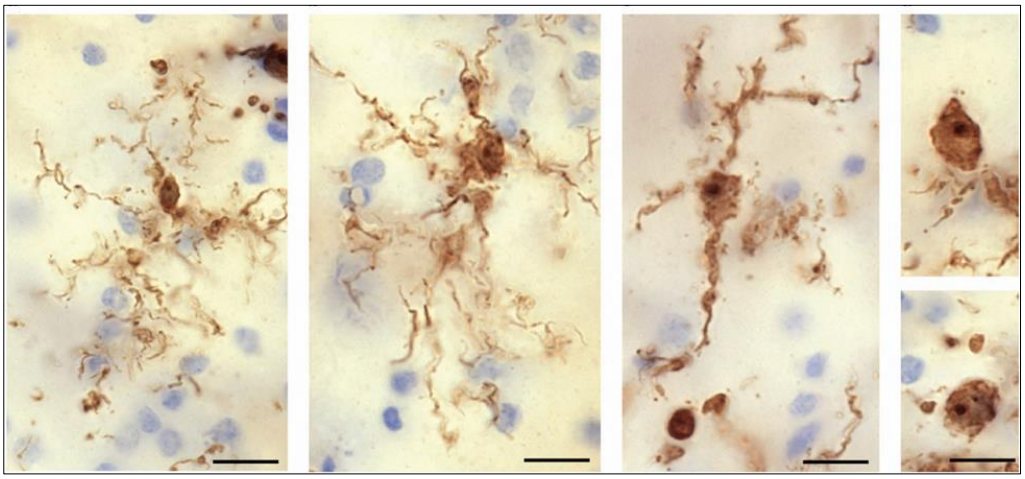

Figure 5 Microglial phenotypes in the ACC of depressed subjects

Positron emission studies have found evidence for microglial activation in the prefrontal cortex and anterior cingulate cortex in patients with MDD [43]. Anti-NMDA receptor antibodies also were found to be present in an increased frequency in patients initially diagnosed with MDD and post-partum psychosis. It has also become increasingly recognized that patients with MDD or psychosis may have a variant of autoimmune encephalitis [43].

Four main microglial phenotypes expressed in the ACC. (From left to right) Ramified microglial cell body with highly ramified processes, a primed microglia displaying a wider cell body, a reactive microglia with an ameboid-shaped cell body with a few ramified processes, ameboid microglia displaying either a couple ramified cell processes (above) or none at all (below). Taylor WD, Payne ME, Krishnan KR, Wagner HR, Provenzale JM, Steffens DC, MacFall JR. Evidence of white matter tract disruption in MRI hyperintensities. Biol Psychiatry. 2001 Aug 1;50(3):179-83. doi: 10.1016/s0006-3223(01)01160-x. [42]

3.4. Bipolar disorder

Bipolar Disorder (BD) is a brain disorder causing changes in a person's mood, energy and ability to function. BD is characterized by intense emotional states that last days to weeks with manic/hypomanic (abnormally happy or irritable) episodes or depressive (sad) episodes, hence BD is also often referred to as "manic depression". According to the DSM-5, [44] there are three mood disorders that share bipolar symptoms: Bipolar I Disorder, Bipolar II Disorder, and Cyclothymic Disorder. Bipolar I is defined by manic episodes lasting at least seven days or are severe enough to require hospitalization, depressive episodes can appear as well for at least 2 weeks. Bipolar II is characterized by a pattern of depressive and hypomanic episodes, but not full mania like in Bipolar I. Cyclothymic disorder is defined by periods of hypomanic symptoms and depressive symptoms lasting at least two years, but the symptoms do not meet the requirement for a hypomanic episode and depressive episode [45]. BD is a clinical diagnosis that lacks pathognomonic neuropathological findings such as in dementias for example, however morphological correlates of BD have been noted as described below [46].

3.4.1. Macroscopic findings

Thinning of gray matter multiple cortical regions, including the subgenual anterior cingulate cortex, reduced neuronal density in some amygadalar nuclei, and decreased calbindin positive neuron density in the PFC [46]. Downar and colleagues found that there was also a pattern of gray matter loss across medial prefrontal regions, insula, thalamus, and amygdala. They also noted increases in gray matter in the left and right striatum [38]. This trend was shared among the 'psychotic' disorders, such as BD and Schizophrenia. These regions, as stated in the section above on MDD, are part of the aCIN.

A prominent morphological abnormality in patients with BD was decreases in in the density/number of GABAergic neurons and glial cells [43]. Inflammation-associated white matter damage in the brain is associated with preterm births, interestingly it was also found that the risk of BD increases with decreased gestation time [43].

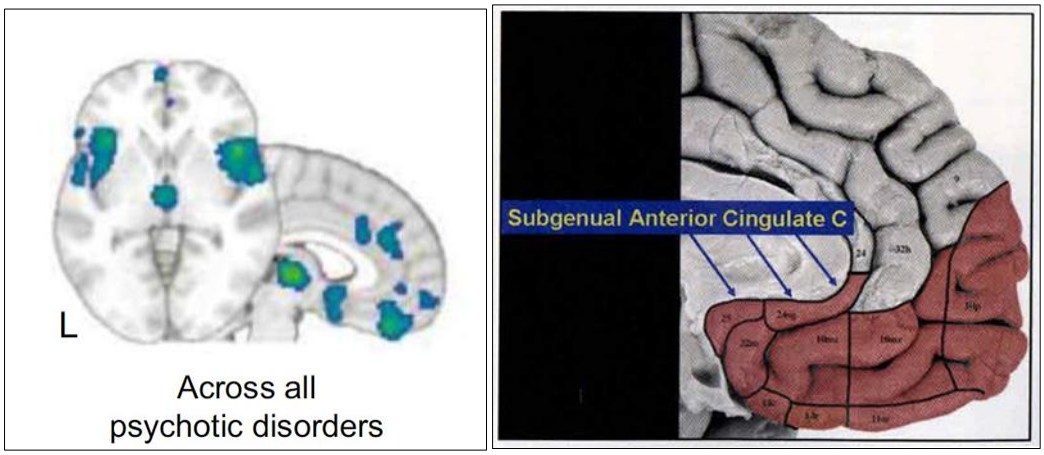

Figure 6 Brain cross sections in mood disorders

(Above, left) Brain regions showing loss of gray matter in across medial prefrontal regions, insula, thalamus, and amygdala. A trend that was shared among all psychotic disorders [38]. (Above, right) Gross dissection of a brain with the Subgenual ACC highlighted [39]. Thinning of gray matter was noted in the sgACC along with reduced neuronal density in some amygadalar nuclei, and decreased calbindin positive neuron density in the PFC [46]. Downar J, Blumberger DM, Daskalakis ZJ. The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation. Trends Cogn Sci. 2016 Feb;20(2):107-120. doi: 10.1016/j.tics.2015.10.007. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr. 2008 Aug;13(8):663-81. doi: 10.1017/s1092852900013754.

3.4.2. Microscopic findings

One notable negative finding was the absence of gliosis in patients with BD. This indicates that BD is not a neurodegenerative disease [46].Two notable positive findings, both in sg24, was the depths of laminae III, V, and VI were reduced by ~20% with neuronal density in these areas reduced by ~30% [1]. Another group found a decreased density of interneurons in lamina II and a trend towards lower pyramidal neuron density, but no change in glial density [47] or neuronal size [47] [1]. In area 24b of the Stanley Foundation brain series, decrements in three synaptic proteins: synaptophysin, complexin II, and growth-associated protein-43 [48] [1]. Another study [49] found reduced amounts of microtubule-associated proteins MAP1b and MAP2.

Research studies have shown mRNA expression of IL-1, IL-6, and TNF, and their associated receptors (IL-1R1, IL-1RA, TNFR1) to be significantly higher in the lymphocytes of patients with BD compared to healthy controls [43]. Diagnostically, elevated CRP levels have been shown to predict development of BD. Thryoperoxidase antibodies are significantly more common in patients with MDD and BD. This finding may be related to a shared genetic vulnerability to BD and autoimmune thyroiditis [43]. The evidence of microglial activation in mood disorders was robust, but smaller. These findings are complimented with the functional deficits in myelination, astrocytic glutamate recycling, and regulation of inhibitory/excitatory neurotransmission [43]. However, it is not possible at this time to draw a direct link between neuroinflammation and histopathology with the current data. Another systematic review by [46], found in fact that there was no neuropathological evidence for an inflammatory process in BD.

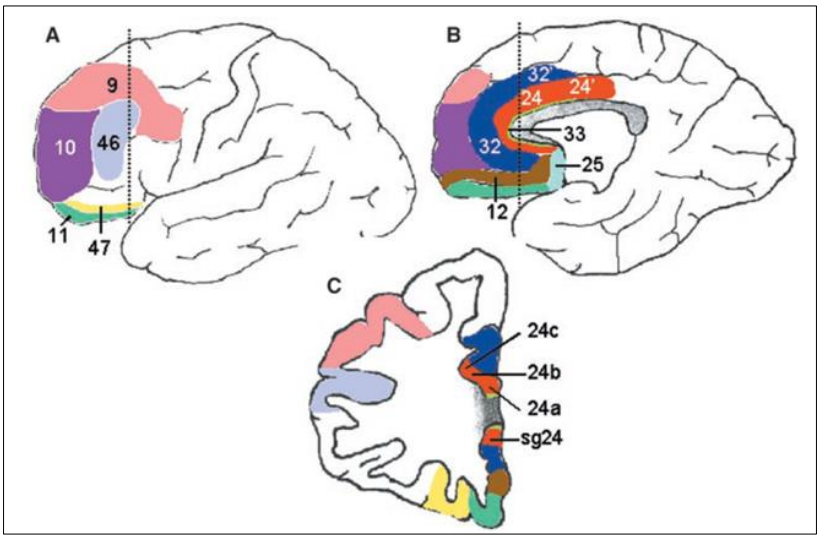

Figure 7 Frontal lobe map showing brain changes in mood disorders

(above): Map of the frontal lobe areas from the (A) lateral, (B) medial, and (C) coronal views. Subdivisions of the ACC are shown in areas 25, 25, 32, and 33. Reductions in laminar depth and glial density were noted in region 24 [1]. Harrison PJ. The neuropathology of primary mood disorder. Brain. 2002 Jul;125(Pt 7):1428-49. doi: 10.1093/brain/awf149.

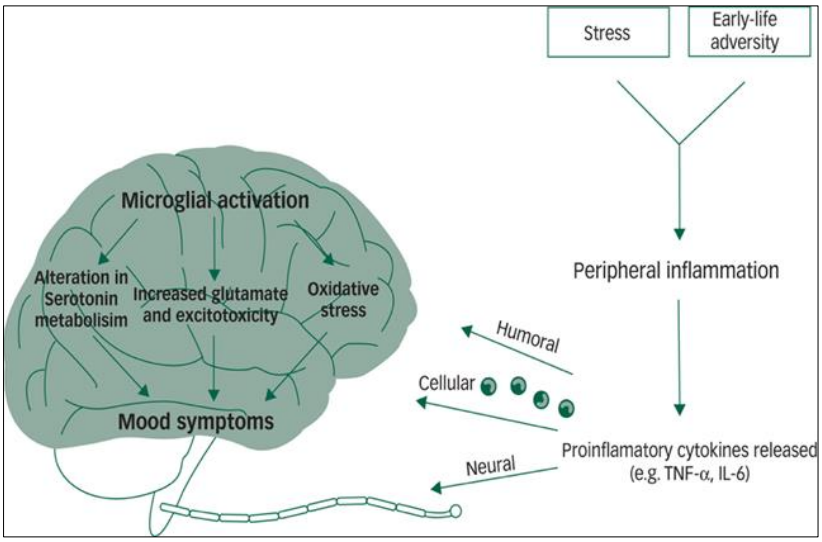

Figure 8 Brain inflammatory processes effect on mood disorders

(Above): Proposed framework for how inflammatory processes in the brain may contribute to mood disorders [55]. "Chronic stress and early-life adversity can lead to persistent activation of the inflammatory response system. Proinflammatory cytokines released by an activated immune response can reach the brain via three main routes: humoral, cellular and neural. These cytokines lead to alterations in serotonin metabolism, increased glutamate and oxidative stress. The downstream effect of these alterations in neural circuits may lead to the onset and persistence of mood symptoms. IL, interleukin; TNF, tumour necrosis factor." From: Jones, B., Daskalakis, Z., Carvalho, A., Strawbridge, R., Young, A., Mulsant, B., & Husain, M. (2020). Inflammation as a treatment target in mood disorders: Review. BJPsych Open, 6(4), E60. doi:10.1192/bjo.2020.43.

4. Discussion

A special neuropathological interest is directed into the major psychiatric disorders, such as Schizophrenia, major depression and Bipolar disorders. Histological and MRI findings of the structural brain abnormalities represent the insight into the world needed to be explored to reveal the mysteries around this important field.

In Schizophrenia (first episode and chronic), many imaging studies showed enlargement of the ventricles with the decrease in the volume of the amygdala and temporal lobes [6], [7], [8]. First episode Schizophrenia showed also decrease in the volume of the whole brain, thalamus, hippocampus and basal ganglia with progressive decrease in the frontal and temporal grey matter areas brain tissue and increase in lateral ventricles volume for up to 20 years after the first symptoms [11].

In Major depressive disorder, MRI showed grey matter damage in the amygdala and hippocampus [38], as well as white matter hyperintensities in the frontal lobe.

In Bipolar disorder, Downar and colleagues, found that there was also a pattern of gray matter loss across medial prefrontal regions, insula, thalamus, and amygdala. They also noted increases in gray matter in the left and right striatum [38]. This pattern was shared among some 'psychiatric' disorders, such as Bipolar disorder and Schizophrenia. These findings can be explained by the microscopic pictures of these major psychiatric disorders.

In Schizophrenia, oligodendrocytes and myelin pathology is considered the basis of dysconnectivity [21], [22], where activation of the microglia can cause damage of oligodendrocytes and myelinate fibers especially in subjects with positive symptoms. The prefrontal cortex was found to be one of the main areas affected [16].

In MDD, positive emission studies showed evidence of microglial activation in the prefrontal cortex and the anterior cingulate cortex [43]. Many studies have found that there is an increased plasma levels of inflammatory proteins in MDD

and BD. This can reduce monoamines (dopamine, serotonin, and norepinephrine) availability by upregulation of the synaptic reuptake and the decrease of monoamine synthesis [43].

In multiple research studies made for BD patients in comparison with healthy controls, it was found that mRNA expression of IL-1, IL-6, and TNF, and their receptors was significantly higher in the lymphocytes of the BD patients [43]. Mechawar & Savitz in 2016 found that thyroperoxidase antibodies were shown to be significantly higher in patients with MDD and BD. This might be related to a shared genetic vulnerability to BD and autoimmune thyroiditis. One negative finding noticed was the absence of gliosis in patients with BD. This finding showed that there was no neuropathological evidence for an inflammatory process in BD [46]. A smaller evidence was found of microglial activation in mood disorders. These findings are complimented with the functional deficits in myelination, astrocytic glutamate recycling, and regulation of inhibitory/excitatory neurotransmission [43].

5. Conclusion

Most of the Psychiatric disorders showed cortical damage in certain areas of the brain especially the cingulate cortex, temporal lobe, and the amygdala. The main limitation of interpreting neuropathological findings in major psychiatric disorders is simply identifying and analyzing brain samples of sufficient quantity and quality for research. This problem has been more hindering with the decrease in the rate of autopsies. This was much exaggerated by the fact that most deaths occur outside hospital and are transferred to the coroner, making collection of tissues for research practically difficult. Exclusion of potentially suitable subjects because of insufficient information such as clinical history, represents another challenge added to the decreased availability. Several centers described significant efforts in overcoming these problems and identifying suitable ways of consistent collection of brain tissue with adequate quality and quantity from subjects with psychiatric disorders and controls [50-53]. Further studies are needed to elaborate the specific pathology of each disorder, taking into consideration confounders that can affect the findings, such as treatment effects, substance use, and co-morbid psychiatric disorders.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to report regarding the content of this review article.

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