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Review

White matter abnormalities in major depression: Evidence from post-mortem, neuroimaging and genetic studies

Ming Wei Tham ^{a,b}, Puay San Woon ^a, Min Yi Sum ^a, Tih-Shih Lee ^c, Kang Sim ^{a,*}

^a Institute of Mental Health/Woodbridge Hospital, 10, Buangkok View, Singapore 539747, Singapore

^b School of Biological Sciences, Nanyang Technological University, Singapore

^c Duke-NUS Graduate Medical School, Singapore

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ABSTRACT

Background: Until more recently, most studies have examined the changes in brain gray matter in major depressive disorder (MDD) with less studies focusing on understanding white matter pathology in MDD. Studies of brain white matter volume changes, connectivity disruptions, as well as genetic factors affecting myelination can throw light on the nature of white matter abnormalities underpinning MDD.

Methods: We review the state of the art understanding of white matter changes in MDD from the extant neuropathology, neuroimaging and neurogenetic studies.

Results: Overall, data are sparse and mostly conducted in older patients with MDD. Post-mortem studies have highlighted pathology of white matter in prefrontal brain region in terms of decreased oligodendrocyte density, reductions in the expression of genes related to oligodendrocyte function, molecular changes in intercellular cell adhesion molecule (ICAM) expression levels and suggestion of possible mechanism of ischemia. Structural magnetic resonance imaging studies have revealed deep white matter hyperintensities which are associated with clinical severity, and treatment responsiveness.

Limitations: There is a particular dearth of genetic studies related to white matter pathology, studies of younger depressed subjects and specifically probing cortical and subcortical white matter pathology together in MDD.

Conclusions: Future investigations would want to study white matter changes in different cerebral regions and incorporate multimodal and longitudinal levels of examination in order to better grasp the neural basis of this condition.

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Contents

1.	Introduction	0
2.	Materials and methods	0
3.	Results	0
3.1.	White matter changes in post-mortem studies (see Table 1)	0
3.2.	White matter changes in neuroimaging studies (see Table 2)	0
3.3.	Genetic studies involving myelination genes/cerebral white matter in MDD (see Table 3)	0
4.	Discussion	0
4.1.	Making sense of white matter and specific lesions	0
4.2.	Clinical importance and future directions	0
4.3.	Limitations	0

* Corresponding author. Tel.: +65 63892000; fax: +65 63855900.
 E-mail address: kang_sim@imh.com.sg (K. Sim).

5. Conclusion	0
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References	0

1. Introduction

Major depressive disorder (MDD) is a mood disorder in which an individual experiences at least a two week period of pervasive low mood which can be accompanied by other features such as reduced interest and/or pleasure in all activities, significant loss or gain in appetite or weight, loss of sleep or excess sleep, fatigue, low self-worth, poor concentration, agitated or slowed motor activity, and suicidal tendencies (APA, 1994). The World Health Organization's (WHO) world health report on mental health estimates the global point prevalence of MDD to be 1.9% for men and 3.2% for women, with 5.8% of men and 9.5% of women experiencing a depressive episode within a year (WHO, 2001). MDD is associated with a huge disease burden, including the burden on the afflicted individual, their caregivers/significant others, and the impact on their quality of life and level of psychosocial functioning at work, school or in their interactions with the people around them. The WHO report listed MDD as the fourth leading contributor to burden on people and society among all diseases (WHO, 2001).

Given the enormity of the burden of disease and the extent of treatment resistance, the search for neurobiological bases of MDD has taken greater urgency. Current approaches include neuroimaging, genomic and molecular approaches. In terms of neuroimaging studies, they can be divided into structural, functional and chemical studies. Structural imaging methods include the use of structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI) methods. Functional imaging approaches include positron emission tomography (PET) and functional MRI studies and chemical studies involve the use of magnetic resonance spectroscopy (MRS). These studies compare the structure and function of various brain regions of patients with MDD with normal controls to determine pathology in terms of specific brain volume differences, white matter disruptions, changes in glucose metabolism, functional activations during cognitive tasks as well as brain chemical levels in vivo. Genetic studies allow a better understanding of candidate genetic factors and functional pathways that may underlie the pathophysiology of MDD. When genetic approaches are combined with other approaches such as neuroimaging strategies, they can be useful tools in highlighting brain changes that may be mediated by underlying genetic factors which are integral to neural function including neuronal organization, neuronal signaling and inter-neuronal communication.

Up to more recently, most studies have examined the changes in brain gray matter in MDD with less studies focusing on understanding white matter pathology in MDD (Drevets et al., 2008; Rigucci et al., 2010). In this review paper, we aimed to review and summarize our state of the art understanding of white matter pathology in MDD from the existing literature of relevant neuropathology, neuroimaging

and neurogenetic studies. We first detail these studies, discuss the observed trends from these studies and then comment on the limitations, clinical implications and future research directions.

2. Materials and methods

The literature search was conducted using the National Center for Biotechnology Information (NCBI) PubMed/Medline to identify relevant research articles related to MDD that were published until June 2010. The keywords used included major depressive disorder, major depression, unipolar depression, mood disorder, myelin, white matter, oligodendrocytes, post-mortem, neuroimaging, white matter hyperintensities and genetic.

The articles were included in the review if: (1) the journal article was published in English, and (2) they were related to post-mortem neuropathology, neuroimaging or neurogenetic studies involving brain white matter changes in MDD. Further searches via the Scopus database were made using the bibliographies in the main articles and relevant papers were obtained.

3. Results

3.1. White matter changes in post-mortem studies (see Table 1)

The majority of the available studies investigated the prefrontal cortex (PFC) and in older individuals with depression (Cotter et al., 2002; Koenigs and Grafman, 2009; Regenold et al., 2007; Thomas et al., 2002a, 2003b). The post-mortem study by Thomas et al. (2003a) found ischemic demyelination of white matter in PFC suggesting pathological processes underlying these white matter lesions. Pro-inflammatory Intracellular Cell Adhesion Molecules (ICAM) were used (Thomas et al., 2002a, 2003b) to examine the extent of ischemia-induced white matter lesions. While a non-significant increase in ICAMs was observed in white matter of MDD subjects in an earlier study (Thomas et al., 2002a,b), a significant increase of CAMs was noted in a subsequent study by the same team (Thomas et al., 2003b). The study by Regenold et al. (2007) found that the dorsolateral PFC and ventromedial PFC displayed less intense myelin staining in MDD subjects compared to controls (Regenold et al., 2007) indicating increased deep white matter lesions in PFC (Table 1).

Decreases in glial cells number and density have been noted in the deeper prefrontal cortical layers (Cotter et al., 2002) but were observed to be unchanged in other studies involving prefrontal regions (Khundakar et al., 2009, 2010) and temporal white matter (Beasley et al., 2009). A lower density of oligodendroglial cells was found in layer VI of prefrontal cortex of subjects with MDD (Uranova et al., 2004) and a significant decrease in the expression of genes related to oligodendrocyte function was found in the temporal cortex of

Table 1

Post-mortem studies involving white matter in depression.

Author	Patients	Controls	Ages	Gender	Methods	Region	Results
Thomas et al. (2002a)	20 DSM-4 MDD	20	75.0 ± 7.37 (patient)	N/A	Immunohistochemistry to localize Cell Adhesion Molecules (CAM) in brain tissue and image analysis to quantify CAM	Dorsolateral prefrontal cortex (dlPFC)	Significant increased CAM expression in gray matter of dlPFC
			74.2 ± 7.46 (control)			Anterior cingulate cortex (ACC)	Non significant increase in CAM expression in white matter of dlPFC
Cotter et al. (2002)	15 DSM-4 MDD	15	46.5 ± 9.3 (patient)	9M, 6F (patient)	Spatial point pattern techniques and two-dimensional measures of cell size and density	PFC Area 9, neurons and glial cells	Glial cell density and neuron size decreased compared to controls
			48.1 ± 10.7 (control)	9M, 6F (control)		Occipital cortex (OCC)	
Thomas et al. (2002b)	20 DSM-4 MDD	20	All elderly	N/A	MRI 1.0 T	Whole brain	Hyperintensities (perivascular and deep white matter) due to dilated perivascular spaces, ischemic demyelination, and oligemic demyelination
Thomas et al. (2003a)	20 DSM-4 MDD	20	Elderly	N/A	T2 imaging, histopathological analysis In vitro MRI coronal slices of brain tissue	Hyperintensities investigated Periventricular white matter hyperintensities (PVH)	Similar pathological basis of PVH in patients and controls
Thomas et al. (2003b)	20 DSM-4 MDD	20	Above 60 years	N/A	Histopathology and immunocytochemistry stains Quantitative image analysis for vascular cell adhesion molecule (VCAM-1) Intercellular cell adhesion molecule (ICAM-1)	Dorsolateral prefrontal cortex (dlPFC) Anterior cingulate cortex (ACC) Occipital cortex (OCC)	dlPFC: significant increase of ICAM-1 in white matter compared to controls ACC and OCC: no significant difference
Uranova et al. (2004)	15 DSM-4 MDD	15	46.5 ± 9.3 (patient)	9M, 6F (patient)	Optical disector methodology	Prefrontal region	A significant reduction in density of oligodendrocytes in MDD
			48.1 ± 10.7 (control)	9M, 6F (control)			
Hamidi et al. (2004)	8 DSM-4 4 MDD	10	77.7 (patient)	5M, 3F (patient)	Nissl method	Amygdala	Lower density of total glia and oligodendrocytes in the amygdala of MDD
			64.6 (control)	9M, 1F (control)			
Regenold et al. (2007)	15 DSM-4 MDD	15	46.5 ± 9.3 (patient)	9M, 6F (patient)	Myelin staining of fixed dorsolateral prefrontal cortex brain sections by Kluver and Barrera method Staining intensity was quantified by digital image analysis and expressed as a percent of gray matter staining for a given section	Ventromedial prefrontal cortex (vmPFC)	Less intense staining compared to control
			48.1 ± 10.7 (control)	9M, 6F (control)		Dorsolateral prefrontal cortex (dlPFC)	
Khundakar et al. (2009)	17 MDD	10	76.1 ± 7.05 (patient)	5M, 12F (patient)	Disector and nucleator methods to estimate neuronal density and volume and glial density of cells	Dorsolateral prefrontal cortex	No glial cell differences
			77.0 ± 7.69 (control)	4M, 6F (control)			
Khundakar et al. (2010)	13 MDD	11			Optical disector and nucleator methods	Orbitofrontal cortex	No changes were found in glial cell, pyramidal or non-pyramidal neuron density, or in non-pyramidal and pyramidal neuron volume in the orbitofrontal cortex

Abbreviations: MDD, major depressive syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; PFC, prefrontal cortex; CAM, Cell Adhesion Molecule; dlPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; OCC, occipital cortex; WMH, white matter hyperintensities; PVH, periventricular hyperintensities; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; NAA, N-acetylaspartate; Cho, choline; PT, planum temporale.

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Table 2

Neuroimaging studies involving white matter in depression.

Author	Patients	Controls	Ages	Gender	Methods	Region	Results
O'Brien et al. (1996)	60 DSM-3R MDD	39	71.2 ± 7.9 (patient)	18M, 42F (patient)	T2-weighted MRI scans	Deep white matter lesions (DWML) and periventricular lesions (PVL)	DWML were significantly more common in depressed subjects
Kumar et al. (2004)	8 DSM-4 MDD	8	71.4 ± 11.0 (control) 71.5 ± 5.13 (patient)	20M, 19F (control) 1M, 7F (patient)	Magnetization transfer (MT)	Anterior cingulate gray matter	Genu and splenium of the corpus callosum, right caudate nucleus, putamen, and occipital white matter found with lower MT ratios compared to controls
			74.1 ± 8.9 (control)	2M, 6F (control)	MT ratios (indicating integrity of the macromolecular protein pool) were also obtained	Head of the caudate nucleus Putamen Periventricular frontal and occipital white matter Genu and splenium of the corpus callosum	
Videbech et al. (2004)	41 DSM-3R MDD	46	41.4 ± 12.5 (patient)	12M, 29F (patient)	MRI 1.5 T	Prefrontal, anterior cingulate, striatal, thalamus, cerebellum regions	No significant difference in activations between the two groups. Stroop interference time correlated with number of white matter lesions especially in frontal-striatal regions and insula
			41.1 ± 11.6 (control)	16M, 30F (control)	Six positron emission tomography (PET) scans Stroop test administered		
Heiden et al. (2005)	31 DSM-4 MDD	N/A	68.0 ± 6.5 (patient)	8M, 23F (patient)	Longitudinal study	Periventricular white matter hyperintensities (PVWMH)	Subjects with greater degree of WMH showed significantly higher Hamilton Depression Rating Scale (HAM-D) after 5 years, more severe course of depression, and lower Mini-Mental State Examination (MMSE) scores
					21 out of 31 reassessed after 5 years	Deep white matter hyperintensities (DWMHs)	
Hickie et al. (2005)	47 DSM-4 MDD	21	52.8 ± 12.6 (patient)	N/A	MRI 1.5 T Volumetric assessment of hyperintensities	Deep white matter (DWM), periventricular (PV), and subcortical (SC) hyperintensities	No significant difference in lesion severity compared to control DWM and SC lesions were associated with histories of hypertension and diabetes Strong correlation between B12 and DWM
			54.7 ± 9.1 (control)				Hypofolatemia, hypertension and increased age: greater severity of total brain WMH compared to control
Iosifescu et al. (2005)	50 DSM-4 MDD	35	40.6 ± 10.3 (patient)	33M, 17F (patient)	MRI 1.5 T	Whole brain MRI	Greater severity of subcortical WMH compared to control
			39.2 ± 9.8 (control)	21M, 14F (control)	Serum folate, vitamin B12, homocysteine and cholesterol levels measured Cardiovascular risk factors also measured	Detect T2 white matter hyperintensities (WMH)	
Papakostas et al. (2005)	50 DSM-4 MDD	N/A	41.2 ± 10.2 (patient)	33M, 17F (patient)	MRI 1.5 T to detect T2 WMH	Brain MRI	Subjects with severe subcortical WMHs and/or hypofolatemia had poor response to anti-depressants

Table 2 (continued)

Author	Patients	Controls	Ages	Gender	Methods	Region	Results
Chen et al. (2006)	14 DSM-4 MDD	11	75.1 ± 6.3 (patient)	6M, 8F (patient)	Cardiovascular risk factors were assessed, serum folate, vitamin B12 and homocysteine levels were measured Fluoxetine 20 mg/day for 8 weeks Ultrasound intima-media thickness (IMT) measurements of the carotid arteries	T2 WMH Carotid arteries.	Higher correlation between IMT and WMH in depressed compared to controls
			72.6 ± 8.1 (control)	4M, 7F (control)	MRI 3.0 T	Cerebral MRI scans	
Iosifescu et al. (2006)	19 DSM-4 MDD (Treatment) 65 DSM-4 MDD (No Treatment)	35	39.6 ± 7.6 (treatment)	9M, 10F (Treatment)	MRI 1.5 T	White matter hyperintensities (WMH)	No significant difference in number of WMH between groups Left hemisphere subcortical WMH correlated to lower treatment response
			40.7 ± 10.2 (no treatment) 39.2 ± 9.8 (control)	41M, 24F (No Treatment) 21M, 14F (control)	Voxel-based analysis	Cardiovascular risk factors	
Hickie et al. (2007)	32 DSM-4 MDD	17	55.5 ± 11.9 (patient)	15M, 17F (patient)	Longitudinal study	White matter lesions	Periventricular (PV) and deep white matter (DWM) lesions are associated with low rCBF
			55.4 ± 9.6 (control)	8M, 9F (control)	MRI 1.5 T scans	Caudate nucleus	
Ma et al. (2007)	14 DSM-4 MDD	14	28.9 ± 8.0 (patient)	2M, 12F (patient)	Single photon emission computerized tomography (SPECT) Regional cerebral blood flow (rCBF) Diffusion tensor imaging (DTI) 1.5 T	Whole brain white matter	Lower fractional anisotropy (FA) values observed in right middle frontal gyrus, left lateral occipito-temporal gyrus, subgyral and angular gyri of the right parietal lobe compared to controls
Potter et al. (2007)	83 DSM-4 MDD	47	27.1 ± 6.7 (control) 60 and above	2M, 12F (control) N/A	MRI 1.5 T	Brain MRI	Noncompletion of the SoC occurred in approximately 19% of depressed participants compared to controls (2%); failure to complete the SoC was associated with greater volume of white matter lesions in the left prefrontal cortex
Li et al. (2007)	19 DSM-4 MDD	20	28.1 ± 7.4 (patient)	4M, 15F (patient)	Cognitive task assessment Stockings of Cambridge subtest (SoC) of the Cambridge Automated Neuropsychological Testing Battery (CANTAB) DTI 1.5 T	Prefrontal white matter: (4 mm inferior, and 0, 4, 8, 12, 16 and 20 mm superior to the anterior commissure (AC)–posterior commissure (PC) plane)	Significantly lower fractional anisotropy (FA) values in prefrontal white matter at bilateral 20 mm, right 16 mm and right 12 mm above the AC–PC
			26.7 ± 6.9 (control)	4M, 16F (control)			

(continued on next page)

Table 2 (continued)

Author	Patients	Controls	Ages	Gender	Methods	Region	Results
Kim et al. (2008)	22 DSM-4 MDD	25	38.5 ± 9.7 (patient)	0M, 22F (patient)	MRI 1.5 T images were analyzed using optimized voxel-based morphometry to examine group differences in regional gray and white matter volume	Caudate (left and right)	Reduced gray matter volumes in caudate and thalamus compared to controls. No group differences in white matter volume
Zou et al. (2008)	45 DSM-4 MDD	45	35.3 ± 11.3 (control) 33.2 ± 8.9 (patient)	0M, 25F (control) 15M, 30F (patient)	DTI 3.0 T	Thalamus (left and right) Whole brain	Significant decrease in FA in left hemisphere (including anterior limb of the internal capsule and the inferior parietal portion of the superior longitudinal fasciculus)
Chen et al. (2009)	27 DSM-4 MDD	19	31.0 ± 10.3 (control) 72.6 ± 4.7 (patient) 71.2 ± 7.2 (control)	15M, 30F (control) 8M, 19F (patient) 6M, 13F (control)	Voxel-based analysis 3-T proton magnetic resonance spectroscopy Ratios of N-acetylaspartate (NAA), choline (Cho) and myo-inositol to creatine ratios were calculated from spectra obtained	Left frontal white matter, left periventricular white matter, left basal ganglia	Left frontal white matter: lower NAA/creatine ratio compared to controls Left basal ganglia: higher Cho/creatine and myo-inositol/creatine ratios compared to controls
Weber et al. (2010)	38 DSM-4 MDD	62	66.0 ± 6.2 (patient) 71.0 ± 7.3 (control)	7M, 31F (patient) 14M, 48F (control)	Neuropsychological evaluation Personality assessment	Limbic regions	No significant difference in WMH in depressed compared to controls
Dalby et al. (2009)	22 DSM-4 MDD	22	57.4 ± 4.6 (patient) 59.2 ± 7.3 (control)	7M, 15F (patient) 7M, 15F (control)	MRI 3.0 T MRI 3.0 T	Whole brain White matter lesions (WML): localization, volume, number	Higher WML density in left superior longitudinal fasciculus and the right frontal projections of the corpus callosum No significant difference in volume and number compared to controls
Kieseppä et al. (2010)	16 DSM-4 MDD	20	48.4 ± 10.3 (patient) 42.0 ± 11.6 (control)	2M, 14F (patient) 10M, 10F (control)	DTI 1.5 T Voxel-based analysis	Left sagittal striatum, right cingulate cortex, posterior body of corpus callosum	Left sagittal striatum: lower fractional anisotropy (FA) values compared to control Right cingulate cortex, posterior body of corpus callosum: suggestive of decrease in FA
Abe et al. (2010)	21 DSM-4 MDD	42	48.1 ± 13.5 (patient) 48.0 ± 13.2 (control)	11M, 10F (patient) 22M, 20F (control)	MRI 1.5 T Voxel-based analysis T1 images DTI on T2 echo-planar images	Whole brain : gray and white matter volumes Mean diffusivity (MD) Fractional anisotropy (FA)	No significant difference in FA and white matter volume compared to controls FA tended to correlate negatively with total days depressed in the right anterior cingulate and the left frontal white matter

Abbreviations: MDD, major depressive syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; PFC, prefrontal cortex; MT, magnetization transfer; WMH, white matter hyperintensities; PVWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; HAM-D, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Exam; DWM, deep white matter; PV, periventricular; SC, subcortical; IMT, intima-media thickness; SPECT, single photon emission computerized tomography; rCBF, regional cerebral blood flow; FA, fractional anisotropy; DTI, diffusion tensor imaging; SoC, Stockings of Cambridge subtest; CANTAB, Cambridge automated neuropsychological testing battery; AC, anterior commissure; PC, posterior commissure; NAA, N-acetyl aspartate; Cho, choline; WML, white matter lesions; MD, mean diffusivity.

MDD (Aston et al., 2005). Disruptions in frontal circuits and their inter-relationships and interactions with non frontal regions based on earlier studies need to be further clarified (Chen et al., 2009; Hickie et al., 2007; Ma et al., 2007; Thomas et al., 2003a,b). In addition, periventricular white matter

hyperintensities (PVWMH) have been noted in the subcortical regions which can affect microvascular blood flow to the frontal regions of the brain (Hickie et al., 2007).

In sum, post-mortem studies have highlighted pathology of white matter in prefrontal brain region in terms of

Table 3

Genetic studies involving myelination genes or cerebral white matter in depression.

Author	Patients	Controls	Ages	Gender	Methods	Region	Results
Aston et al. (2005)	12 DSM-4 MDD	14	46.3 ± 3.0 (patient)	9M, 3F (patient)	Post-mortem study	Gene expression in middle temporal gyrus	Myelination and myelination-related genes and transcription factors are significantly decreased in patients Structural components of myelin (<i>CNP</i> , <i>MAG</i> , <i>MAL</i> , <i>MOG</i> , <i>MOBP</i> , <i>PMP22</i> , <i>PLLP</i> , and <i>PLP1</i>) Synthesis of myelin constituents (<i>ASPA</i> and <i>UGT8</i>) Regulation of myelin formation (<i>ENPP2</i> , <i>EDG2</i> , <i>TF</i> , and <i>KLK6</i>) Significant changes in multiple genes involved in axonal growth/synaptic function
			49.0 ± 3.0 (control)	9M, 5F (control)	Microarray transcript profiling		
Hashimoto et al. (2006)	373 DSM-4 MDD	717	54.0 ± 16.0 (patient)	147M, 226F (patient)	MRI	Association study	Carriers of Cys704 allele of the Ser704Cys single-nucleotide polymorphism (SNP) associated with an increased risk of developing MDD Decreased FA values in prefrontal white matter
			41.3 ± 16.9 (control)	351M, 366F (control)	Genetic analysis (SNP genotyping)		
Novak and Tallerico (2006)	15 DSM-4 MDD	15	45.0 ± 3.0 (patient)	8M, 7F (patient)	Post-mortem study	Nogo gene and variants (A, B and C)	Nogo B significantly reduced in patient compared to control
			47.0 ± 3.0 (control)	8M, 7F (control)	Quantitative real-time PCR (polymerase chain reaction)		
Frodl et al. (2008)	60 DSM-4 MDD	60	44.2 ± 11.8 (patient)	29M, 31F (patient)	MRI 1.5 T on hippocampal volumes	5-HTTLPR gene, chromosome 17q11.2	La/La: smaller hippocampal gray and white volumes compared to (controls, La/(Lg + S) and (Lg + S)/(Lg + S) patients) La/(Lg + S) and (Lg + S)/(Lg + S): no significant difference compared to controls
			41.6 ± 12.3 (control)	29M, 31F (control)	PCR on serotonin transporter gene (5-HTTLPR) genotypes		

Abbreviations: MDD, major depressive syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; DISC, Disrupted-in-schizophrenia; SNP, single-nucleotide polymorphism.

decreased oligodendrocyte density, molecular changes in intercellular cell adhesion molecule (ICAM) expression levels and suggestion of the possible mechanism of ischemia, with interactions between prefrontal and non frontal regions as well as cortical and subcortical brain regions.

3.2. White matter changes in neuroimaging studies (see Table 2)

The majority of the studies listed in Table 2 involved magnetic resonance imaging (MRI) studies. Generally, structural MRI studies were conducted in older subjects more than 35 years of age and diffusion tensor imaging (DTI) studies were conducted on individuals less than 35 years of age except for two studies (Abe et al., 2010; Kiesepää et al., 2010). Two structural MRI studies evaluated periventricular and deep or subcortical white matter hyperintensities and found no significant differences in lesion severity (Hickie et al., 2005) and lesion number (Iosifescu et al., 2006) between MDD subjects and controls in contrast to earlier studies (O'Brien et al., 1996; Iosifescu et al., 2005) which documented greater number and severity of total brain and subcortical white matter

hyperintensities. These periventricular and deep white matter hyperintensities were associated with lower regional cerebral blood flow on single photon emission computerized tomography (SPECT) imaging (Hickie et al., 2007). In terms of clinical associations, the presence of these white matter intensities in MDD seemed to indicate a more severe illness and poorer treatment outcomes in that white matter hyperintensities were associated with more severe ratings on Hamilton Depression Rating Scale (HAM-D), lower Mini-Mental State Examination (MMSE) scores (Heiden et al., 2005) and poorer anti-depressant treatment response (Iosifescu et al., 2006; Papakostas et al., 2005). In terms of correlations with other clinical factors, hypofolatemia was associated with more accentuated subcortical white matter hyperintensities (Iosifescu et al., 2005) which is in turn correlated with poorer anti-depressant treatment response in patients with MDD (Papakostas et al., 2005). Vitamin B12 levels and hypertension were associated with the presence of deep white matter hyperintensities underscoring the need to examine the role of metabolic and vascular factors in the context of white matter changes (Hickie et al., 2005; Papakostas et al., 2005).

In terms of diffusion tensor imaging (DTI), studies reported lower fractional anisotropy (FA) values within the cortical and subcortical brain regions (Kieseppä et al., 2010; Li et al., 2007; Ma et al., 2007; Zou et al., 2008). Specifically, the affected regions included the frontal gyrus (Li et al., 2007; Ma et al., 2007), parietal lobe and occipito-temporal gyrus (Ma et al., 2007), inferior parietal portion of the superior longitudinal fasciculus (Zou et al., 2008), anterior limb of the internal capsule (Zou et al., 2008), and left striatum (Kieseppä et al., 2010). The presence of reduced FA in frontal and parietal regions within a younger cohort of patients with MDD (Li et al., 2007; Ma et al., 2007) makes it necessary to chart the trajectories over time in order to better understand how these disruptions of these cortical–subcortical circuitries interact with treatment, course of illness and psychopathology.

In addition to MRI and DTI imaging techniques, other imaging methods used included Magnetization Transfer Imaging (MTI), ultrasound intima-media thickness (IMT) measurements and proton magnetic resonance spectroscopy (H-MRS) (Chen et al., 2006, 2009; Kumar et al., 2004). Chen et al. (2009) observed lower N-acetylaspartate (NAA) to creatine ratios in frontal white matter of patients with MDD compared to normal controls, indicating perturbations of neuron integrity and possible glial dysfunction in the same brain regions (Chen et al., 2009). IMT measurements of carotid arteries found greater ultrasound correlations with white matter lesions in MDD, indicating that ischemic damage may underlie these lesions (Chen et al., 2006). Lower MTI ratios were observed in MDD subjects compared to controls in the occipital white matter, caudate nucleus and corpus callosum indicating compromised structural integrity in white matter of more widespread brain regions (Kumar et al., 2004).

In brief, MRI studies found that the presence of brain white matter hyperintensities, which were associated with different clinical parameters (symptoms, folate and vitamin B12 levels) and treatment response. Decreased FAs found in diverse brain regions suggest disruptions of white matter integrity and cortical–subcortical circuitry. In addition, findings from other imaging techniques such as H-MRS, MTI and IMT suggest possible neuronal injury and ischemic damage underlying these white matter changes.

3.3. Genetic studies involving myelination genes/cerebral white matter in MDD (see Table 3)

Genetic studies investigating the white matter related genes in depression are shown in Table 3. Regarding non white matter genes, MDD patients with the La/La genotype of the Serotonin transporter gene (5-HTTLPR) showed smaller white matter volumes in the hippocampus (Frodl et al., 2008). Myelin and myelin associated genes in MDD were reported to be significantly decreased in their transcripts and these genes are important for axon growth (Aston et al., 2005; Novak and Talerico, 2006), signal transduction and synaptic function (Aston et al., 2005).

Carriers of the Cys704 allele of the Disrupted-in-schizophrenia 1 (DISC1) gene displayed lower FA values in the prefrontal white matter (Hashimoto et al., 2006), suggesting that smaller white matter volumes in medial temporal lobe and disruptions in prefrontal white matter

integrity may be mediated through genetic effects involving serotonin and DISC1 genes.

4. Discussion

4.1. Making sense of white matter and specific lesions

White matter comprises mainly myelinated axons. White matter hyperintensities (WMH) refer to areas of bright intensities observed during MRI scans. These areas of intensities or white matter lesions (WML) indicate the presence of affected white matter, which can be related to features such as decreased myelin content; loss of axon number, smaller axons coupled with losses in ependymal cell layer, reactive gliosis and increased peri-ependymal extracellular fluid content (Pantoni and Garcia, 1995). Pantoni and Garcia (1995) observed that cerebral ischaemia contributed to the development of WML which eventually paved the way for the proposed vascular depression theory. The theory suggests that WML are caused by localized ischemic damage (Herrmann et al., 2008), which are supported by current studies (Chen et al., 2006; Hickie et al., 2007; Thomas et al., 2002a, 2003b) which studied older patients with MDD. Post-mortem WML studies by Thomas et al. (2002a) found evidence for the presence of cell adhesion molecules indicating inflammation consistent with ischemia and ischemia-induced demyelination. The study by Chen measured intima-media thickness (IMT) or thickness of the carotid arteries using ultrasound and found evidence of cerebral ischemic changes in MDD. The higher IMT scores found in MDD subjects suggested greater atherosclerosis, with the consequence of lowered cerebral blood flow (Chen et al., 2006). Similar findings were observed in the study by Hickie on the blood flow within the caudate nucleus and WML. The study found that periventricular and deep white matter lesions were associated with major changes to cerebral blood flow in the caudate nucleus (Hickie et al., 2007). Together, these findings suggest that the presence of WML especially in elderly patients with MDD may be related to underlying cerebral ischemia in the context of background risk factors including age and other medical conditions such as hypertension, hyperlipidaemia, and ischemic heart disease and are consistent with the vascular depression theory (Herrmann et al., 2008).

White matter lesions can serve as prognosis indicators in MDD (Heiden et al., 2005; Kumar et al., 2004), even in the context of lack of specific differences in the nature and number of WMLs (Dalby et al., 2009; Iosifescu et al., 2006; Weber et al., 2010). The presence of WMLs indicated more severe psychopathology (Heiden et al., 2005) and poorer anti-depressant response (Iosifescu et al., 2006). It would be crucial to find out whether these white matter lesions can change with treatment and illness course and their impact on clinical presentations and subsequent outcomes. Subjects with MDD in the study by Heiden et al. (2005) were found with lower Mini-Mental State Examination (MMSE) scores, indicating that white matter lesions may underlie early cognitive impairments or that their association with predisposition towards more severe depressive symptoms may interact with neuropsychological functioning. Deficits in processing speed, working memory, episodic memory and executive functioning in MDD can affect the daily functioning

and increase the morbidity and worsen the quality of life of these individuals (Weber et al., 2010).

The frontal lobes are involved in executive function including conscious thought, decision making and moderating socially-appropriate behavior (Santröck, 2005; Sherwood, 2007) as well as control of voluntary motor activity, speech (Sherwood, 2007). The integrative theory of PFC function by Miller and Cohen (2001) posits that the PFC is the command centre for cognitive control. It is proposed that the PFC integrates sensory inputs, memories and bias signals to generate a desired cognitive behavior (Miller and Cohen, 2001) and in this aspect, the presence of white matter lesions in the PFC regions could provide the neural basis for some of the cognitive deficits observed.

4.2. Clinical importance and future directions

MDD has been clinically studied with interactive models using a combination of both the biopsychosocial (BPS) and diathesis-stress model. The BPS model proposes that MDD results from a combination of factors relating to biological (brain changes and genetic factors), psychological (thoughts, behaviors and emotions) and social factors (Santröck, 2007). The diathesis-stress model proposes that MDD manifests itself when subjects with predisposed vulnerabilities are exposed to stressful events (Caspi et al., 2003; Haefel et al., 2008). In short, interactive models investigate the interplay of biological, psychological, and social factors and trigger in the etiology of MDD. The findings of this systematic review should be viewed in the context of biological factors within a web of other interrelated and interactive non biological factors. Based on the interactive models, psychological and social factors should be further investigated in the context of biological factors such as white matter lesions to provide a comprehensive formulation and understanding of MDD. Nevertheless, the findings suggest that deep white matter hyperintensities may be potential clinical biomarkers denoting more severe illness, course, and correlation with cognitive deficits and poorer response to antidepressants (Heiden et al., 2005; Iosifescu et al., 2006; Videbeck et al., 2004). Future replication studies are needed to validate these and other findings. These biological factors may potentially serve as tools to aid the clinician in pharmacological management of MDD and prognostication in an era of personalized and evidence based medicine.

Future studies may want to involve larger recruitment targets and adopt multimodal ways to better examine these white matter changes by incorporating different imaging modalities and in combination with approaches in genomics, lipidomics, and metabolomics which are relevant to understanding white matter changes in MDD. Longer follow up studies are warranted to track the developmental trajectories of clinical symptoms and white matter changes over time. The adoption of more standardized rating scales for clinical symptoms and neurocognitive profile would facilitate comparisons across studies in larger samples. Studies linking white matter lesions with cognitive processes and functioning are important in determining how white matter lesions can affect the cognitive control and relate to clinical factors and aspects of psychosocial functioning such as work performance.

In terms of genetic studies, studies looking into associations of white matter and related genes to MDD offer

potential for better biological understanding of MDD. Genome wide association and copy number variation studies in MDD are wanting. Transcriptional profiling analysis could be pursued in the frontal lobes or PFC regions given the strong associations of these regions with WML in MDD subjects. The wide array of structural myelin genes (CNP, MAG, MAL, MOG, MOBP, PMP22, PLLP, and PLP1) and myelin synthesis genes (ASPA, UGT8, ENPP2, EDG2, TF, and KLK6) in the study by Aston et al. (2005) could be further investigated to determine their expression profiles in the other related brain regions.

4.3. Limitations

There are several limitations of the present studies. First, there is a paucity of genetic studies or studies linking genetic factors and other biological substrates such as neuroimaging parameters, molecular factors and clinical symptoms and overall functioning. The transcriptional profiling of white matter genes by Aston et al. (2005) provides an excellent profile of genes for further WML gene studies which can be used for correlation with other genetic factors to elucidate possible gene–gene and epistatic interactions that may occur to predispose the individual towards MDD.

Second, most studies focus on studying MDD in the age ranging 40s and above. While findings found the correlation between ischemia and WML in elderly patients (Chen et al., 2006; Hickie et al., 2007; Thomas et al., 2002b, 2003a), it is unclear whether they apply in younger age spectrum. However, isolated findings suggest that prefrontal WML can occur in young patients which may persist or change with over time (Li et al., 2007). Examination of similar biological processes across the age spectrum including younger and more elderly patients may offer a more complete and comprehensive understanding of the neural basis affecting brain white matter in MDD.

Third, longitudinal studies are needed to chart progressive white matter changes in MDD. Factors which may pose as challenges include difficulty with recruitment, high drop-out rates, lack of assured resources for proper tracking and follow-up. Fourth, while predominance of studies highlighted deep white matter lesions and in frontal regions, further studies are warranted and should specifically look for other non frontal and subcortical changes in order to better understand any aberrations involving cortical and subcortical circuitries. In this regard, the anterior cingulate cortex was analyzed for the presence of cell adhesion molecules although no significant differences were found between MDD subjects and controls (Thomas et al., 2003b). On the whole, given that the frontal lobe have subdivisions with specialised functions as is the case with the other brain regions (Santröck, 2005), efforts should be garnered to examine white matter changes in other interrelated brain regions.

Fifth, glial cells serve a multiplicity of functions by maintaining homeostasis, providing structural support, supplying nutrients and aiding in myelin formation (Sherwood, 2007). While Cotter et al. (2002) found that glial cells were decreased in the prefrontal region, Khundakar et al. (2009; 2010) failed to find any group differences in glial cells at the orbitofrontal and dorsolateral prefrontal cortices and Beasley et al. (2009) observed that the total glial cell density remained unchanged in superior temporal gyrus. The extant

findings should provoke further specific investigations into changes in specific subpopulations of glial cells at different brain regions along the course of MDD along with genetic/genomic and clinical correlates which can potentially throw light on the pathophysiology of white matter changes and psychopathology in MDD.

5. Conclusion

In sum, our review mainly found studies that reported cerebral white matter lesions involving deep white matter and especially frontal cortical regions in patients with MDD which are associated with vascular ischemic markers, clinical severity, and treatment responsiveness. These white matter changes are supported by few findings of disruptions of white matter fibre integrity through DTI studies. Existing findings may support the vascular depression theory, and serve as biological factors within the interactive model of factors impacting depression. While efforts to study white matter changes in MDD have been initiated, future investigations would want to drill deeper into wider cerebral regions and extend to multimodal levels of examination in order to better grasp the neural basis of this condition.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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