Journal of Affective Disorders 295 (2021) 893–903

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Changes in glial gene expression in the prefrontal cortex in relation to major depressive disorder, suicide and psychotic features

Lin Zhang [a], Ronald W.H. Verwer [a], Juan Zhao [a], Inge Huitinga [b,c], Paul J. Lucassen [c], Dick F. Swaab [a,*]

[a] Neuropsychiatric Disorders Group, Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences, University of Amsterdam, Meibergdreef 47, Amsterdam 1105 BA, the Netherlands
[b] Neuroimmunology Group, Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands
[c] Brain Plasticity Group, Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Major depressive disorder
Suicide
Psychotic features
Glia
Prefrontal cortex

ABSTRACT

Background: To establish whether major depressive disorder (MDD), suicidal behaviors and psychotic features contribute to glial alterations in the human prefrontal cortex.
Materials and methods: We compared mRNA expression using real-time qPCR of 17 glia related genes in the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) between 24 patients with MDD and 12 well-matched controls without psychiatric or neurological diseases. The MDD group was subdivided into i) MDD who died of suicide (MDD-S) or natural causes (MDD-NS) and ii) MDD with or without psychotic features (MDD-P and MDD-NP). The results were followed up with confounder factor analysis.
Results: Astrocyte gene aldehyde dehydrogenase-1 L1 (ALDH1L1) showed an increased expression in the DLPFC of MDD-NS and the ACC of MDD-NP. S100 calcium-binding protein B (S100B) was upregulated in the DLPFC of MDD compared to the controls. Microglial markers CD11B and purinergic receptor 12 (P2RY12) both showed decreased expression in the ACC of MDD-NS. CD68 was increased in the DLPFC of MDD in both, MDD-S and MDD-P, compared to the controls. In addition, there was increased translocator protein (TSPO) expression in the DLPFC of MDD, especially MDD-NS. In the ACC, this gene had a lower expression in MDD-P than in MDD-NP. Myelin basic protein (MBP) mRNA in the DLPFC increased in MDD, in relation to psychotic features, but not to suicide.
Limitations: Sample volumes are relatively small.
Conclusions: Different glial functions in MDD were related to specific brain area, suicide or psychotic features.

1. Introduction

One-third of individuals with major depressive disorder (MDD) attempt suicide during their lifetime (Dong et al., 2019). Suicidal behavior is often associated with psychotic symptoms (Ma et al., 2019), while the presence of psychotic features in MDD predicts a double mortality rate, and a 2–5 times higher completion of suicide attempts during the acute episodes (Nelson et al., 2018; Suominen et al., 2009; Zalpuri and Rothschild, 2016). This elevated suicide mortality rate does not respond to antidepressants (Suominen et al., 2009), while tricyclic antidepressants have been reported to have a low impact but potentially exacerbate psychotic symptoms in patients with MDD (Glassman et al., 1975; Kantrowitz and Tampi, 2008). In addition, while family history of depression remains unclear among patients with MDD and psychotic features, family members of patients with psychotic features have a higher vulnerability to develop psychotic features (Nelson et al., 2018), which points to independence of psychotic features and MDD. Thus, the evidence above indicates that suicide and psychotic features can be considered as two heterogeneous conditions (Cardinal and Bullmore, 2011; Holma et al., 2010) that may be to a certain degree independent factors in MDD severity.

Based on previous work on neuronal abnormalities in both dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), changes in neuron-glia interactions have been implicated as the neurobiological underpinning of MDD (Zhao et al., 2015,2018, 2016). In our studies, glial-driven functional brain changes have been explored in

* Corresponding author.
E-mail address: d.f.swaab@nin.knaw.nl (D.F. Swaab).

https://doi.org/10.1016/j.jad.2021.08.098
Received 26 May 2021; Received in revised form 17 July 2021; Accepted 28 August 2021
Available online 4 September 2021
0165-0327/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

MDD pathophysiology, and several suicide-/psychotic features-related specific glial alterations have been described in bipolar disorder and schizophrenia (SCZ) (Zhang et al., 2020a,2020b). Within this framework, the pathological studies on the two regions that reported glial abnormalities required some follow up. Firstly, they mainly focused on the white, and not the grey matter, and are thus, intuitively, difficult to align to the neuronal changes in the cortex (Gittins and Harrison, 2011; Mosebach et al., 2013; Rajkowska et al., 2015; Schnieder et al., 2014; Schnieder et al., 2018; Torres-Platas et al., 2014; Webster et al., 2005). Secondly, age-dependent glial changes, that may indicate a compensatory response to, or underlying cause of, the neuronal dysfunction, have been found that complicate the pattern of glial pathology in MDD (Miguel-Hidalgo et al., 2000; Rajkowska and Stockmeier, 2013; Vostrikov and Uranova, 2011). Our earlier studies pointed out that MDD and suicide may differ in the alterations of key stress-related genes transcripts (Zhao et al., 2019). However, in studies on MDD so far, patients who died of suicide or non-suicidal causes were often lumped together (Ernst et al., 2011; Mosebach et al., 2013; Rajkowska et al., 2013). Additionally, suicide victims were compared to control subjects losing sight of the fact that the far majority of suicide cases have an underlying psychiatric illness (Klempan et al., 2009a; Lutz et al., 2017; Nagy et al., 2015; Schnieder et al., 2018; Torres-Platas et al., 2014; Zhao et al., 2019). Moreover, none of the glia-related studies has so far analyzed psychotic features as a subgroup of patients with MDD. This may at least partly be an explanation for inconsistencies in the literature.

Therefore, we investigated here the expression levels of 17 glia-related genes in the prefrontal cortex (PFC) in MDD, taking into account suicide and psychotic features as separate subsets.

2. Materials and methods

2.1. Brain samples

RNA samples were obtained from the Stanley Medical Research Institute (SMRI, Bethesda, MD, USA). Permission for the use of brain material was provided by the next of kin. Diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. All brain regions were microscopically examined to exclude patients with pathological signs of neurodegeneration or other lesions. Exclusion criteria included subjects over age 70, subjects with a history of seizures or other neurological disorders that might affect brain pathology. The cause of death for 17 of 24 patients with MDD was suicide. Eleven patients with MDD had a history of psychotic features. The other cases and all control subjects died of natural causes or accidents.

The SMRI provided us with RNA from the isolated grey matter of the DLPFC (Brodmann area 46) and ACC (Brodmann area 24). They were obtained from patients with MDD (MDD, N = 24) and matched controls (Ctr, N = 12) without a history of suicidal behavior or any major psychiatric diagnosis. We distinguished the following subsets within the MDD group: 1) patients with MDD who died of suicide (MDD-S) or natural causes (MDD-NS) and 2) patients with or without psychotic features (MDD-P or MDD-NP). All groups were matched for age, brain pH, post-mortem interval, brain weight, history and severity of alcohol/substance abuse (Tables 1 and **S1**). All demographic information and medical data, including any lifetime use of antidepressants or a history of substance abuse, were provided by the SMRI. All analyses were performed by investigators unaware of the diagnosis.

2.2. Quantitative real-time PCR

RNA isolation and cDNA synthesis were performed as described before (Zhao et al., 2018). RNA integrity value (RIN), an indicator of human post-mortem tissue RNA quality (Stan et al., 2006), did not show any significant difference between the diagnostic groups in the SMRI material (RIN value of the ACC/DLPFC from MDD-S: 7.69 ± 0.66; MDD-NS: 7.49 ± 0.56; MDD-P: 7.56 ± 0.26; MDD-NP: 7.69 ± 0.10 and the control group: 7.73 ± 0.95, mean ± SEM). For cDNA synthesis, an equal quantity of RNA (300 ng) for each sample was used for the synthesis of cDNA, mixed with a 4.1 ml mixture of oligo dT (100 mg ml-1) and 10 x hexanucleotide (Roche, Basel, Switzerland) (40:1 for the oligo-dT and hexanucleotide mixture), heated to 80°C for 10 min, after which the tubes were quickly transferred to ice. Then 1 ml reverse transcriptase Superscript II RT (Invitrogen Life Technologies) was added together with a mixture of 5 ml 5 first-strand buffer, 2.5 ml 100 mM dithiothreitol, 1.5 ml 10 mM dNTPs and 0.5 ml RNase inhibitor. The synthetic reaction was allowed to proceed for 1 h at 42°C, after which cDNA was stored at -20°C or used immediately. Additional information on all tested genes and the sequences for each primer pair is shown in **Table S2**. cDNA template (equivalent to 5 ng of total RNA) was amplified in a final volume of 20 µl using an SYBR Green PCR master mix (Applied Biosystems, CA, USA) and a mixture of forward and reverse primers (each 2 pmol/µl).

Data were acquired and processed automatically by the Applied Biosystems 7300 Real-Time PCR System. The specificity of amplification was checked by melting curve analysis and electrophoresis of the products on an 8% polyacrylamide gel. Sterile water and RNA samples without the addition of reverse transcriptase during cDNA synthesis served as negative controls. The linearity of each qPCR assay was tested by preparing a series of dilutions of the same stock cDNA in multiple plates. To reduce the effect of sample variability, reference genes were selected based on expression stability measurement (Vandesompele et al., 2002) and the proportion of explained variability regarding all target genes. The higher stability of a reference gene means that its variance was relatively lower than the other considered reference genes. Further, if the expression of a reference gene reflects the variability of the samples well, it is expected that its application should reduce the overall variability of the target genes. Briefly, we used the following reference genes: actin beta (ACTβ), glyceraldehyde-phosphate dehydrogenase (GAPDH), hypoxanthine phosphoribosyltransferase 1 (HPRT1), tubulin alpha (TUBα), tubulin beta (TUBβ) and ubiquitin C (UBC). For the comparisons in the DLPFC, the specific selection was ACTβ, TUBα, TUBβ and UBC; in the ACC, the corresponding selection was ACTβ, TUBβ and UBC.

Table 1
Demographic information on the control and MDD subjects.

	Ctr	MDD	F or x^2	*P*
Age (years, range)	47 (24-63)	42 (24-63)	1.23	0.64
Gender (M/F)	8/4	13/11	0.51	0.47
Race	11W, 1H	23W, 1H	0.26	0.61
PMD (hours, range)	25.3 (9–40)	29.7 (13–65)	1.35	0.30
Brain pH	6.6 (6.31–6.91)	6.6 (6.3–6.9)	1.47	0.81
Brain Weight (gram, range)	1445 (1200–1595)	1469 (1170–1780)	1.69	0.63
Side of Brain Frozen (L/R)	6/6	15/9	0.51	0.47
Psychotic Features	-	11		
Alcohol hx	6	16	0.94	0.33
Severity of Alcohol abuse[1]	2.08 (0-5)	1.92 (0-5)	1.07	0.82
Drug hx	4	8	0.00	1.00
Severity of Substance abuse[1]	0.75 (0–4)	1.04 (0–4)	1.35	0.59
Fluphenazine (lifetime, range)	-	1121 (0–6500)		

Abbreviation: Ctr, control; F, female; hx, history; L, left; M, male; MDD, major depressive disorder; PMD, postmortem delay; R, right.
[1] Substance abuse and alcohol abuse was rated on a scale of 0-5.

2.3. Statistical analysis

Statistical analysis was conducted with IBM SPSS (version 20, SPSS) and TIBCO S+ software (version 8.2.0, TIBCO, Seattle, WA, USA). The

gene expression values were ^{10}log-transformed before they were further processed for statistical analysis. The transformation of the essentially exponential expression data facilitates the application of reference gene correction and enables the application of conventional statistical methods. Thus, the residuals of the combination of selected reference genes can be simply subtracted from the original target gene values to obtain corrected gene expression values.

Given the higher variability in human postmortem data, that may not sufficiently conform to commonly assumed theoretical distributions of test statistics, we applied a non-parametric resampling procedure (Zhao et al., 2018). Resampling was performed without replacement in two-group comparisons, thereby providing an alternative for the t-test. We generated 9999 replicates consisting of randomly reallocated patients over the two groups in each comparison to obtaining a permutation NULL distribution of the test statistic. The obtained NULL distribution mimics the hypothesis that the patients from either group belong to one and the same group (Davison and Hinkley, 1997). As test statistic, we used T = (mean (group2) – mean (group1)) /se. In this formula, se is the standard error of the difference in means. If our data are normal with unknown, unequal variances in group2 and group1, while group1 and group2 observations belong to the same group, T should approximate the t-distribution with Welch modified degrees-of-freedom. In that case, the observed T-value would be sufficient to decide whether the two groups should be considered as one or not. If it is uncertain how appropriate the t-distribution is, the 9999 permutation T-values together with the real observed T-value constitute a sample of 10,000 “resampled observations”, that can be used to estimate how unusual the observed T-value is (Davison and Hinkley, 1997). Since the observed T-value can be on either side of the mean, testing was done two-sided (Zhao et al., 2018). P-values were corrected for multiple testing using the Benjamini-Hochberg criterion (Benjamini and Hochberg, 1995). After statistical analysis, group mean expression levels were back-transformed and expressed as fold-changes to compare their mutual differences (relative mRNA values in the figures). Figures were made with Graphpad Prism 8.1.2.

3. Results

3.1. Gene transcripts encoding astrocytic markers

As an indication for changes in astrocyte-related functions in the PFC of patients with MDD, we analyzed qPCR values of three gene transcripts: aldehyde dehydrogenase 1 family, member L1 (ALDH1L1), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B).

In the DLPFC, S100B was the only gene that showed a significant increase (fold change = 1.25, $P = 0.037$) in patients with MDD. In suicide- or psychotic features-related subset comparisons, however, no significance was found. A trend for an increase was found for ALDH1L1 (fold change = 1.32, $P = 0.061$) in patients with MDD. The elevated transcript level of this gene was significant in the MDD-NS group (fold change = 1.60, $P = 0.023$). Psychotic features did not significantly confound the detected change in astrocytic transcripts (see Table 2B).

For the ACC, no changes were found between patients with MDD and controls, neither following subgrouping for suicide. However, in patients with MDD who did not have psychotic features, ALDH1L1 expression was higher than those with psychotic features (fold change = 1.38, $P = 0.034$) and the control subjects (fold change = 1.43, $P = 0.034$).

3.2. Gene transcripts encoding microglial markers

To assess whether MDD, suicide and psychotic features may be accompanied by gene expression changes of proteins characteristic for microglia, we tested the expression levels of the following 10 microglial markers. They are CD11B (CR3), CD45, CD68, chemokine (C-X3-C motif) receptor 1 (CX3CR1), human leukocyte antigen-DR alpha chain (HLA-DRA), ionized calcium-binding adapter molecule 1 (IBA1), purinergic receptor 12 (P2RY12), transmembrane protein 119 (TMEM119), triggering receptor expressed on myeloid cells 2 (TREM2) and translocator protein (TSPO).

Among these genes, both CD68 and TSPO revealed more than 20% increases in MDD in the DLPFC (CD68: fold change = 1.22, $P = 0.037$; TSPO: fold change = 1.25, $P = 0.020$), and for CD68 in the suicide completers (MDD-S vs. Ctr: fold change = 1.23, $P = 0.033$). TSPO expression in MDD-NS (MDD-NS vs. Ctr: fold change = 1.40, $P = 0.014$) significantly increased compared to the controls. For CD68, another elevation is present in patients with MDD and psychotic symptoms relative to the controls (fold change = 1.32, $P = 0.015$).

In the ACC, no alterations were observed in the two-group comparisons. However, we found some genes differently expressed between MDD subgroups. For example, both CD11B and P2RY12 were approximately reduced by half in non-suicidal patients with MDD, but not in suicide completers compared to the controls (CD11B: MDD-NS vs. Ctr: fold change = -1.49, $P = 0.031$; MDD-S vs. MDD-NS: fold change = 1.59, $P = 0.065$. P2RY12: MDD-NS vs. Ctr: fold change = -1.47, $P = 0.046$; MDD-S vs. MDD-NS: fold change = 1.68; $P = 0.065$). Additionally, TSPO showed opposite expressions between patients with and without psychotic features (MDD-P vs. MDD-NP: fold change = -1.27, $P = 0.034$). These variable alterations per subgroup account for the unchanged transcript levels between MDD and controls.

3.3. Gene transcripts encoding oligodendrocytic markers

In addition, we investigated the following 4 oligodendrocyte genes: myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte transcription factor 2 (OLIG2) and myelin proteolipid protein (PLP).

In the DLPFC, MDDs showed increased MBP expression compared to the controls (fold change = 1.22, $P = 0.003$), but the subgroup of suicide completers did not specially contribute to this elevation (MDD-S vs. Ctr: fold change = 1.20, $P = 0.023$; MDD-NS vs. Ctr: fold change = 1.26, $P = 0.023$; MDD-S vs. MDD-NS: $P = 0.289$). Interestingly, the expression of this gene in patients with psychotic features increased 30% compared to the controls (fold change = 1.30, $P = 0.010$).

No changes were detected for oligodendrocyte markers from two- or three-group comparisons regarding MDD, suicide or psychotic features in the ACC.

An overview of significant changes is presented in Figs. 1–3. For more details, we refer to Tables 1 and 2A–C.

3.4. Sex differences

We did not find significant differences between the sexes, neither in the MDD nor in the matched control group.

3.5. Confounder analysis

The *P*-values for matching for possibly confounding factors are given in Tables 1, **S1B** and **S1C**. There were no significant differences. Correlations between glia expression and non-matched factors, i.e. age of onset, disease duration and lifetime antipsychotic use, have been done and these factors did not alter our conclusions.

4. Discussion

We have found alterations in gene expression in astrocytes, microglia and oligodendrocytes in the DLPFC and ACC in relation to MDD, suicide and psychotic features. As discussed below, altered neuronal functions behind these changed glial transcripts may include dopamine (DA) and gamma-aminobutyric acid (GABA) signaling, blood-brain barrier (BBB) permeability and central nervous system (CNS) injury, microglia

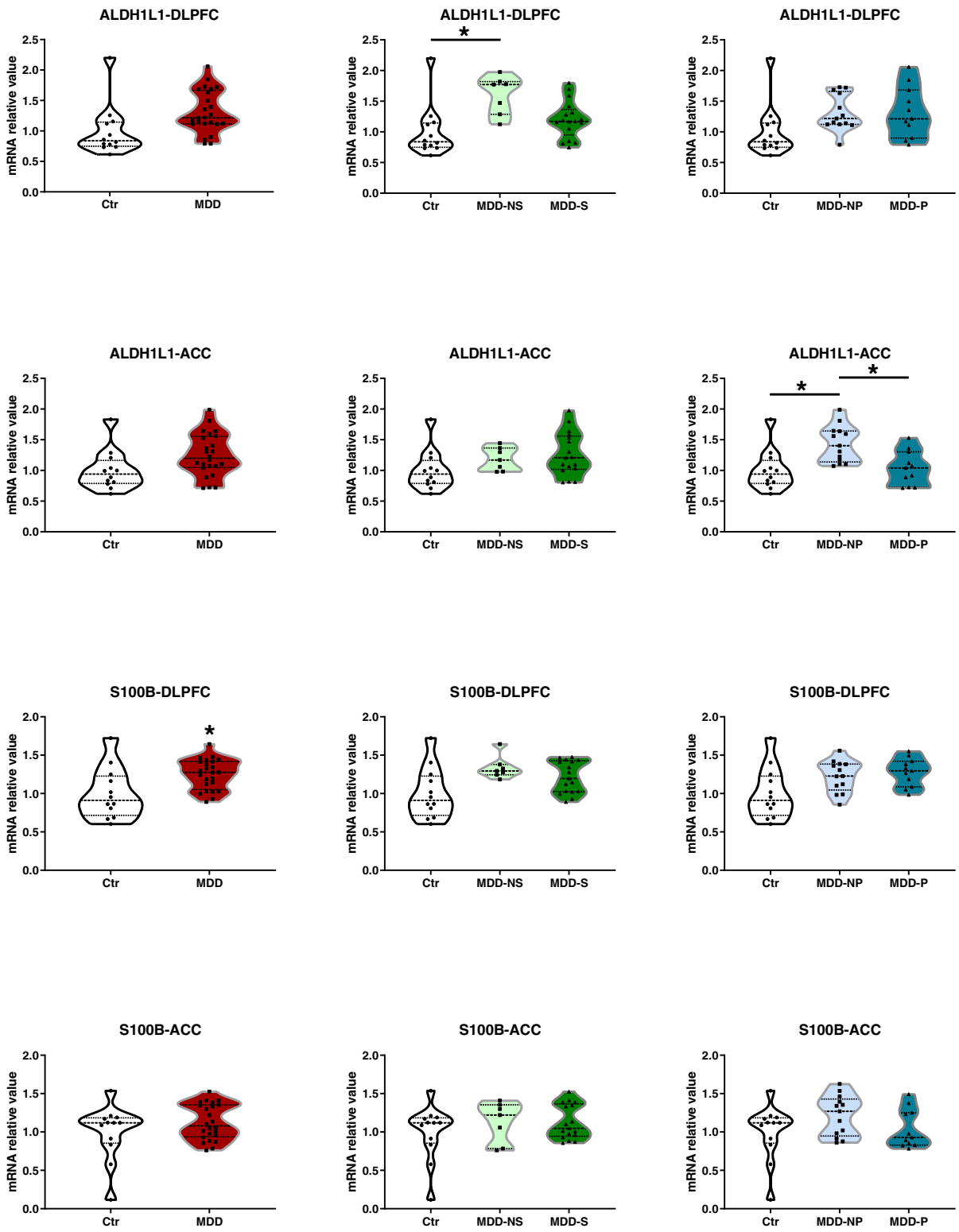


Fig. 1. Transcript levels of astrocyte related genes (ALDH1L1 and S100B) in the DLPFC and ACC in controls (Ctr) and patients with major depressive disorder (MDD) that died of suicide (MDD-S) or other causes than suicide (MDD-NS), and patients with (MDD-P) or without psychotic features (MDD-NP). Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; * indicates $0.01 \leq P < 0.05$.

phagocytosis, innate immune response and neuroinflammation, platelet coagulation and myelin stability.

In our previous study, we have found that patients with SCZ who died of non-suicidal causes presented elevated ALDH1L1 mRNA in the DLPFC (Zhang et al., 2020a). This present data show an increased expression of this gene in MDD, an effect that was not confounded by age (Barley et al., 2009). Although dopaminergic impairments may trigger psychotic symptoms (Pai et al., 2019), lower DA metabolites have been found in body fluids of suicide attempters (Roy et al., 1989, 1992), a change that was notably unrelated to the underlying psychiatric disorder (Pitchot et al., 2001). One possible explanation could be the stronger affinity of immunoglobulin G for DA found in the cerebral spinal fluid

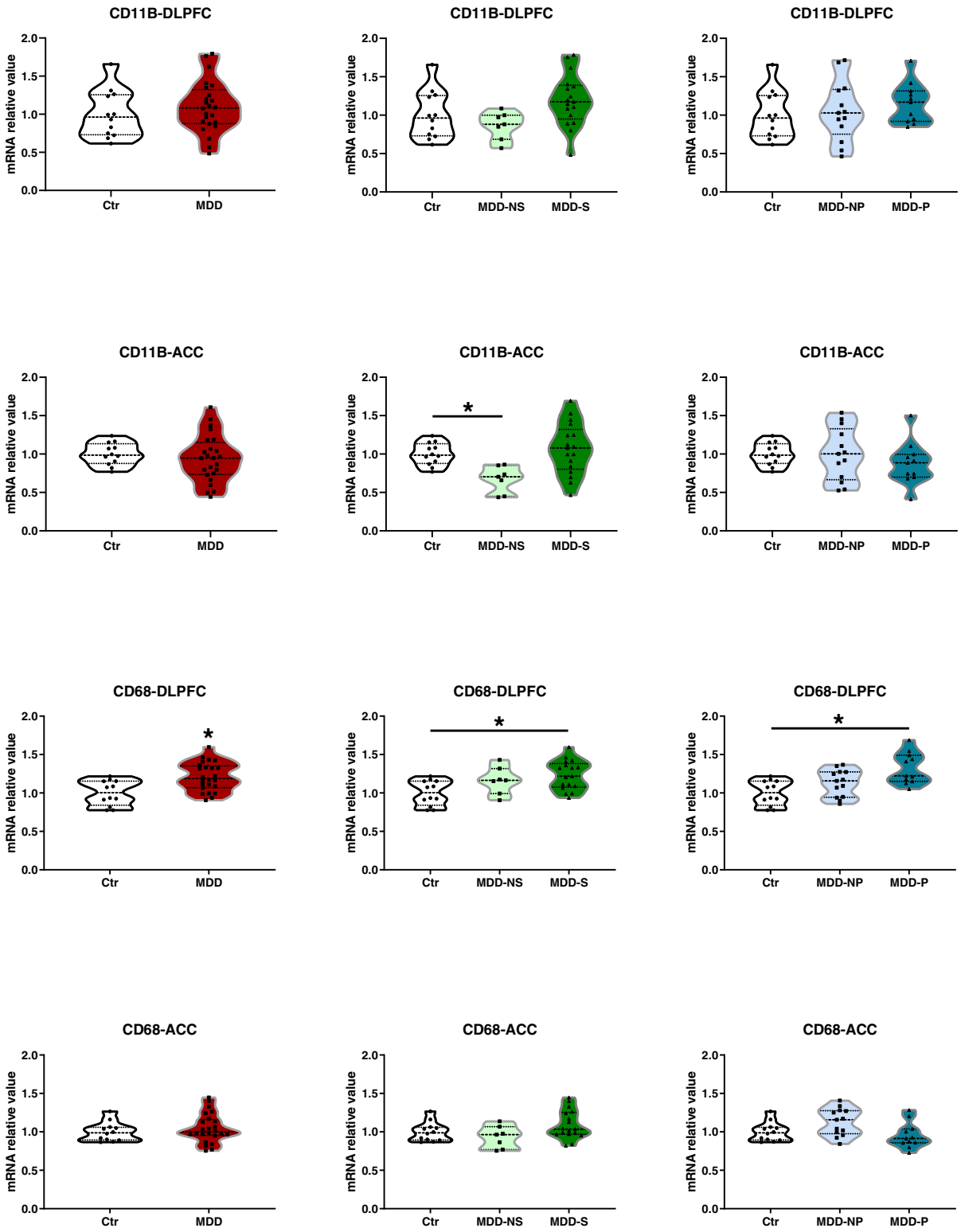


Fig. 2. Transcript levels of microglia related genes (Fig. 2A CD11B and CD68; Fig. 2B P2RY12 and TSPO) in the DLPFC and ACC in controls (Ctr) and patients with major depressive disorder (MDD) that died of suicide (MDD-S) or other causes than suicide (MDD-NS), and patients with (MDD-P) or without psychotic features (MDD-NP). Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; * indicates $0.01 \leq P < 0.05$.

(CSF) of subjects with suicide attempts (Bergquist et al., 2002). However, although D2 dopaminergic dysfunction was reported to be related to DAD2 receptor (DAD2R) polymorphisms in suicide attempters (Suda et al., 2009), this possibility was not supported by other studies showing an unchanged binding in subcortical regions known to control DA synthesis, comparing suicide cases with controls (Allard and Norlen, 1997, 2001; Fitzgerald et al., 2017; Pare et al., 1969). One could thus assume that the binding of DA to DAD2R in the DLPFC of patients with suicide is not as strong as in non-suicides. In addition, in the ACC, we found an exclusive increase of ALDH1L1 expression in nonpsychotic

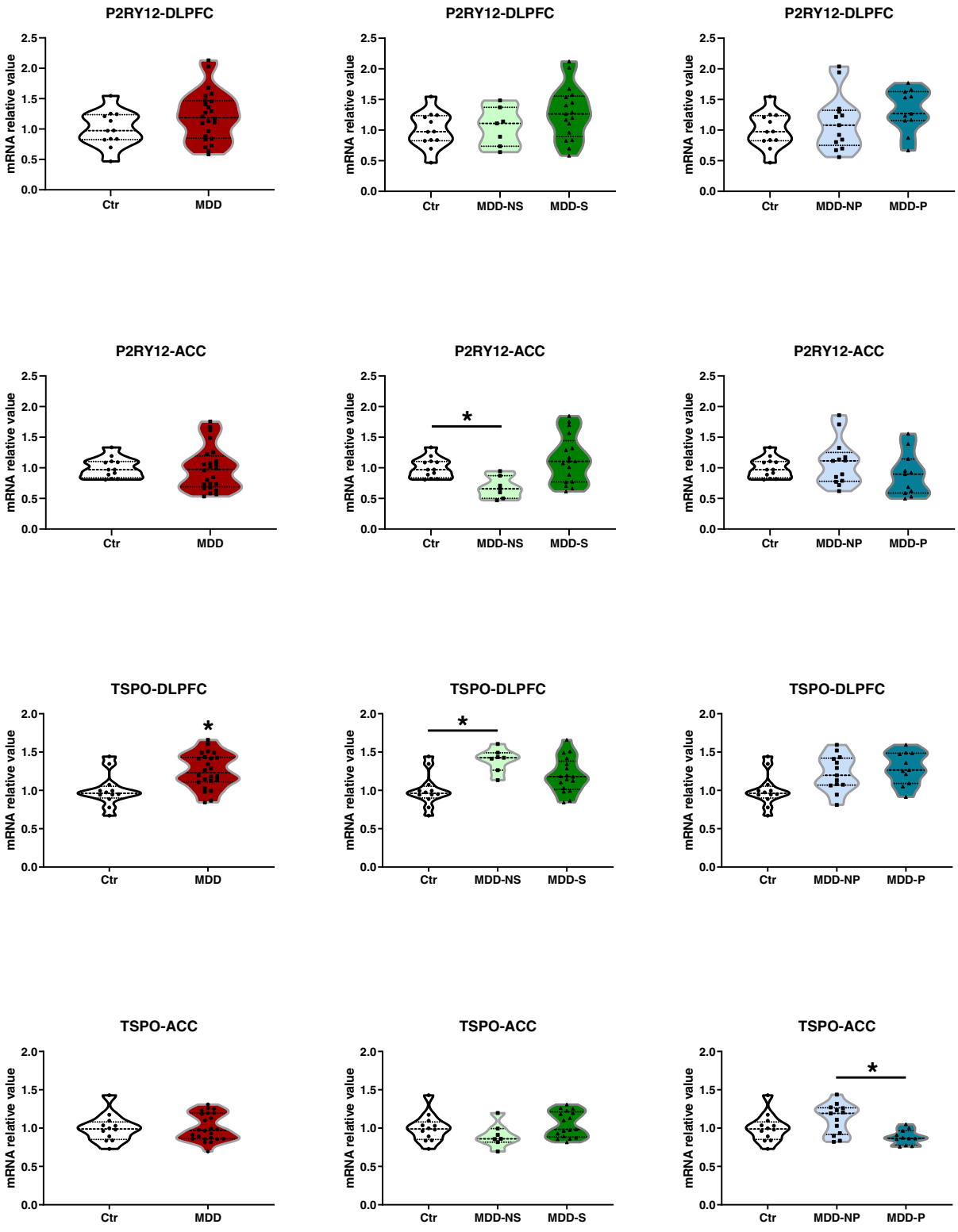


Fig. 2. (*continued*).

MDDs, suggesting that region-specific changes in DAD2R could be involved in MDD pathogenesis (Larisch et al., 1997). On basis of these observations, we presume that the ACC, but not the DLPFC, may serve as a specific DA binding site that presents different binding abilities when comparing MDD and psychotic features per se Suhara et al. (2002), Takahashi et al. (2006).

The elevated S100B expression we observed in MDD brain samples may contribute to the increased S100B levels reported in peripheral blood (Gos et al., 2013; Hamidi et al., 2004; Schroeter et al., 2013). However, CSF S100B was reported to remain unchanged in MDD, likely reflecting different alterations among different brain areas (Schmidt et al., 2015). An alternative possibility, i.e. that a compromised BBB permeability could affect the DLPFC of depressed patients, awaits further study (Loftis et al., 2018). Klempan et al. (2009b) reported

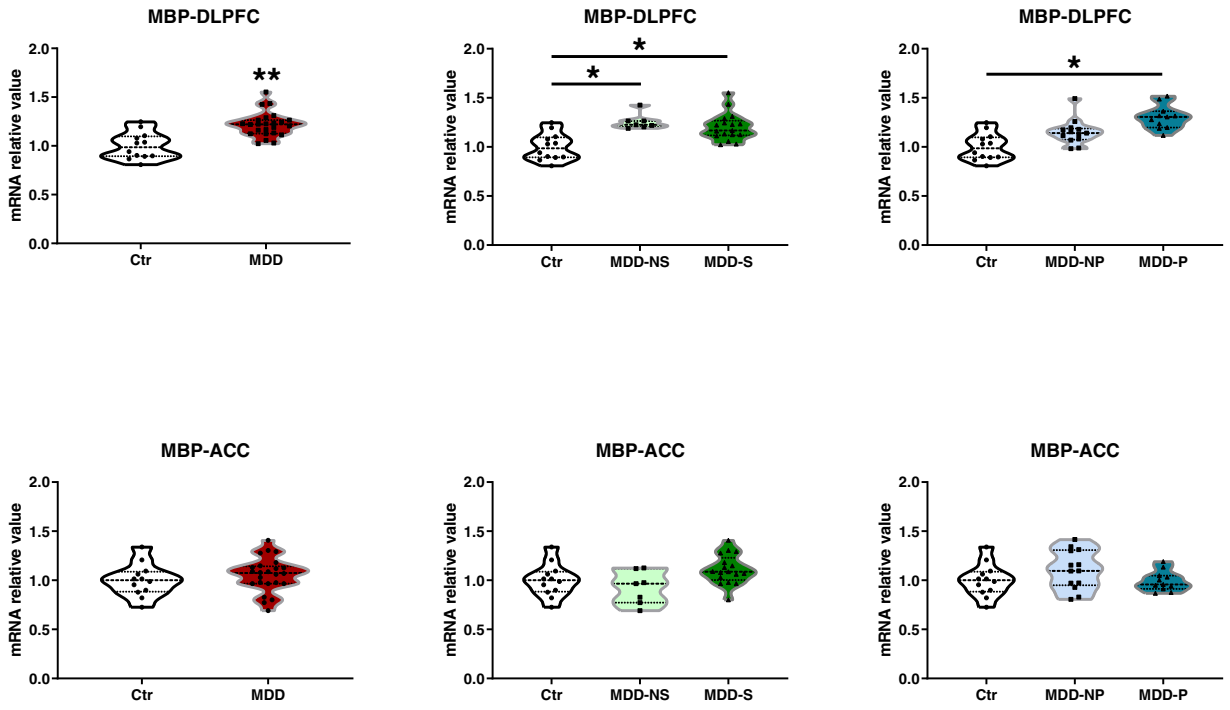


Fig. 3. Transcript levels of oligodendrocyte related genes (MBP) in the DLPFC and ACC in controls (Ctr) and patients with major depressive disorder (MDD) that died of suicide (MDD-S) or other causes than suicide (MDD-NS), and patients with (MDD-P) or without psychotic features (MDD-NP). Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; * indicates $0.01 \leq P < 0.05$, ** indicates $0.001 \leq P < 0.01$.

Table 2A
Alterations in glia gene expression in MDD as compared to their matched control group.

	DLPFC			ACC		
	Fold change	P-perm	BHadj-p	Fold change	P-perm	BHadj-p
Astrocyte genes						
ALDH1L1	1.32	0.018	0.061	1.25	0.030	0.503
GFAP	1.16	0.072		1.05	0.696	
S100B	**1.25**	**0.009**	**0.037**	1.13	0.197	
Microglia genes						
CD11B	1.10	0.416		-1.06	0.237	
CD45	1.22	0.403		1.20	0.391	
CD68	**1.22**	**0.003**	**0.020**	1.04	0.453	
CX3CR1	1.07	0.777		-1.03	0.564	
HLA-DRA	1.33	0.135		-1.01	0.804	
IBA1	1.13	0.305		1.01	0.718	
P2RY12	1.22	0.129		1.00	0.506	
TMEM119	1.44	0.025	0.070	1.07	0.509	
TREM2	1.13	0.413		1.07	0.618	
TSPO	**1.25**	**0.004**	**0.020**	1.01	0.929	
Oligodendrocyte genes						
MBP	**1.22**	**0.000**	**0.003**	1.05	0.368	
MOG	1.18	0.141		1.07	0.524	
OLIG2	1.06	0.426		1.00	0.941	
PLP	1.22	0.065		-1.06	0.640	

Note: ACC: anterior cingulate cortex; BHadj-p: P value of Benjamini-Hochberg's adjustment; Ctr: control; DLPFC: dorsolateral prefrontal cortex; MDD: major depressive disorder; P-perm: P value of permutation test.

reduced levels of S100B transcripts in the DLPFC of MDD-S relative to controls, while in our comparison, we did not find any significant alteration. However, a previous rodent study showed that drug overdose increased S100B concentration in CSF (Vicente et al., 2007) and there are five suicide victims in our collection who died of a drug overdose, this may have contributed to a higher S100B expression in the MDD-S abolishing significance.

CD11B expression decreased in MDD, confirming observations in rodent models. In both depression models, neonatal (early life stress) and adult (social defeat stress), CD11B expression was found to be decreased in the PFC (Ambrée et al., 2018; Giridharan et al., 2019). Our data indicate that there is no increased neuro-inflammation in non-suicidal individuals with MDD. Given the unchanged CD68 expression found after our three-group comparison, we deduce that reduced innate inflammatory state and synapse pruning may be present in the ACC in patients with MDD who died naturally (Michailidou et al., 2015). In human postmortem studies, complement C3b was found to be deposited in peripheral capillaries of suicide completers (Thorell, 1989; Varis et al., 1993). Our current data showed a trend for an increase in CD11B, a C3 receptor, in MDD-S compared to the rest of the patients, which supports this finding. Additionally, a reduced hypo-thrombotic state has been found in peripheral plasma of patients with MDD relative to suicide attempters and healthy controls and independent of suicidality. It should be noted that this condition went together with a higher pro-coagulant activity, solely in MDDs who had presented suicidal behaviors. In our ACC data, P2RY12, a key regulator in platelet aggregation (Dorsam and Kunapuli, 2004), showed a similar crosstalk suggesting that, in suicide, an increased platelet aggregation may be induced by capillary injury that activated complement system (Yang et al., 2016).

We found an increase of CD68 mRNA in the DLPFC in suicide completers. This is an extension of the finding that some types of microglia in the prefrontal white matter were associated with suicide (Schnieder et al., 2014). These observations also agree with previous studies reporting a peripheral and cerebral increase of monokines, that is mainly produced by monocytes and macrophages, and are indicative of microglia activation in suicide. For instance, plasma tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) were both increased in MD patients with suicidality (Li et al., 2013; Monfrim et al., 2014), while TNF-α levels in patients who attempted suicide seem to be even higher compared to those who only displayed suicidal ideation (Janelidze et al., 2011). In addition, in the PFC of suicidal patients, an increased expression of cytokines, that promote monocyte-macrophage activation (IL-4 and IL-13), or are centrally secreted by macrophages

Table 2B
Alterations in glia gene expression in MDD in relation to suicide.

	Fold change			*P*-perm			BHadj.p		
	MDD-S/MDD-NS	**MDD-S/Ctr**	**MDD-NS/Ctr**	**MDD-S/MDD-NS**	**MDD-S/Ctr**	**MDD-NS/Ctr**	**MDD-S/MDD-NS**	**MDD-S/Ctr**	**MDD-NS/Ctr**
DLPFC-astrocyte genes									
ALDH1L1	-1.34	1.20	**1.60**	0.009	0.077	**0.002**	0.061	0.224	**0.023**
GFAP	-1.09	1.13	1.24	0.407	0.127	0.073			
S100B	-1.10	1.21	1.34	0.120	0.030	0.008	0.267	0.139	0.061
DLPFC-microglia genes									
CD11B	1.38	1.19	-1.16	0.015	0.136	0.352	0.087	0.267	0.485
CD45	1.15	1.26	1.10	0.587	0.335	0.852			
CD68	1.06	**1.23**	1.16	0.420	**0.003**	0.079	0.522	**0.033**	0.420
CX3CR1	1.27	1.14	-1.12	0.134	0.394	0.388			
HLA-DRA	1.29	1.42	1.10	0.345	0.112	0.542			
IBA1	1.33	1.21	-1.10	0.043	0.113	0.652	0.167	0.267	0.722
P2RY12	1.21	1.28	1.05	0.233	0.076	0.742			
TMEM119	1.38	1.57	1.14	0.106	0.010	0.514	0.267	0.061	0.610
TREM2	1.18	1.17	-1.00	0.325	0.264	0.882			
TSPO	-1.16	1.20	**1.40**	0.033	0.024	**0.001**	0.142	0.121	**0.014**
DLPFC-oligodendrocyte genes									
MBP	-1.04	**1.20**	**1.26**	0.185	**0.001**	**0.001**	0.349	**0.014**	**0.014**
MOG	1.06	1.20	1.13	0.702	0.123	0.310			
OLIG2	1.11	1.10	-1.01	0.338	0.285	0.976			
PLP	1.10	1.26	1.14	0.513	0.051	0.231			
ACC-astrocyte genes									
ALDH1L1	1.06	1.26	1.19	0.687	0.041	0.071	0.876	0.218	0.259
GFAP	1.08	1.06	-1.02	0.516	0.571	0.907			
S100B	1.00	1.13	1.13	0.923	0.223	0.491			
ACC-microglia genes									
CD11B	1.59	1.07	**-1.49**	0.005	0.801	**0.001**	0.065	0.930	**0.031**
CD45	1.40	1.30	-1.07	0.161	0.195	0.760			
CD68	1.17	1.09	-1.07	0.058	0.138	0.307			
CX3CR1	1.33	1.05	-1.27	0.093	0.876	0.081			
HLA-DRA	1.55	1.12	-1.38	0.049	0.521	0.147	0.226	0.738	0.375
IBA1	1.50	1.12	-1.34	0.006	0.188	0.012	0.065	0.432	0.087
P2RY12	1.68	1.14	**-1.47**	0.004	0.399	**0.002**	0.065	0.683	**0.046**
TMEM119	1.17	1.12	-1.05	0.402	0.392	0.9798			
TREM2	1.47	1.19	-1.24	0.008	0.115	0.0428	0.071	0.326	0.218
TSPO	1.16	1.05	-1.10	0.080	0.445	0.2662			
ACC-oligodendrocyte genes									
MBP	1.20	1.11	-1.08	0.017	0.074	0.3378	0.107	0.259	0.638
MOG	-1.04	1.05	1.10	0.908	0.472	0.7442			
OLIG2	1.05	1.04	-1.04	0.685	0.839	0.8374			
PLP	1.05	-1.05	-1.10	0.555	0.805	0.5188			

Note: ACC: anterior cingulate cortex; BHadj-p: P value of Benjamini-Hochberg's adjustment; Ctr: control; DLPFC: dorsolateral prefrontal cortex; MDD: major depressive disorder; MDD-NS: MDD patients died of non-suicidal reasons; MDD-S: MDD patients died of suicide; P-perm: P value of permutation test.

(IL-1β and TNF-α), supports a CD68-driven microglial activation in suicide completers with MDD (Pandey et al., 2012; Tonelli et al., 2008). Of note, Steiner et al. reported an increased microgliosis in the DLPFC of patients who accomplished suicide and included both patients with MDD and SCZ (Steiner et al., 2008). Since we previously found an unchanged CD68 expression in the PFC of SCZ patients that committed suicide, their observation may be influenced by a large number of MDD-S cases. In addition, enhanced microglial phagocytosis has been assumed to participate in the pathophysiology of psychotic diseases that could be inhibited by antipsychotics (Chen et al., 2013; Rački et al., 2016). We here provide additional molecular proof showing that CD68 was increased in the DLPFC of patients with MDD and psychotic features.

A positron emission tomography (PET) study showed that TSPO was increased in the frontal cortex in patients with MDD who did not present with severe suicidality (Li et al., 2018). This is in line with our results in the DLPFC, but not the ACC. TSPO, as a benzodiazepine receptor, was believed to be associated with the effects of GABA at the $GABA_A$ receptors (Costa et al., 2011). These receptor subunits were already shown to be increased more in MDD-NS than in MDD-S versus controls in the same cohort (Zhao et al., 2018). Another PET study, however, presented a suicidality-specific TSPO elevation in the ACC, but not in the DLPFC (Holmes et al., 2018). We tend to consider the suicidal category (ideation in their patients, but actual completion in ours) and brain region (middle frontal cortex includes BA9 and BA46) to be the main reasons explaining why our results differ. In addition, a distinction was noticed related to the psychotic symptoms in MDD. In vivo, a psychotic features-dependent reduction in frontal grey matter volume was noticed in TSPO imaging, which indicates that MDD pathophysiology may at least in part be driven by microglial deficits (Collste et al., 2017; Selvaraj et al., 2018). In our data, the DLPFC did not show psychotic features-related alterations in TSPO expression, which is consistent with an imaging study on patients with a high risk for psychotic features (Hafizi et al., 2018a, 2018b).

Our data together with the findings of others indicate that changes in oligodendrocyte related transcripts in MDD may be Brodmann area-specific and differ between the grey and white matter (Mosebach et al., 2013; Pantazatos et al., 2017; Rajkowska et al., 2015). We did not find evidence to support the possibility that suicide is an independent factor in oligodendrocyte expression. This is in agreement with two Canadian studies indicating that suicide does not contribute to altered oligodendrocytic activities in the PFC (Lutz et al., 2017; Tanti et al., 2017). Data from blood samples report higher MBP transcripts in patients with first-episode psychosis compared to healthy controls (Ota et al., 2015; Santoro et al., 2015). However, postmortem studies in the human brain did not reveal elevated oligodendrocyte-related gene expression in relation to psychosis (Aston et al., 2005; Barley et al., 2009; Chandley et al., 2013; Matthews et al., 2012). Thus, the increased

Table 2C
Alterations in glia gene expression in MDD in relation to psychotic features.

	Fold change			p-perm			BHadj.p		
	MDD-P/MDD-NP	**MDD-P/Ctr**	**MDD-NP/Ctr**	**MDD-P/MDD-NP**	**MDD-P/Ctr**	**MDD-NP/Ctr**	**MDD-P/MDD-NP**	**MDD-P/Ctr**	**MDD-NP/Ctr**
DLPFC-astrocyte genes									
ALDH1L1	1.00	1.32	1.31	0.855	0.053	0.014	0.099	0.172	0.891
GFAP	1.00	1.17	1.16	0.985	0.106	0.094			
S100B	1.04	1.28	1.22	0.477	0.013	0.033	0.626	0.099	0.152
DLPFC-microglia genes									
CD11B	1.10	1.16	1.05	0.305	0.140	0.856			
CD45	1.25	1.37	1.10	0.207	0.133	0.928			
CD68	1.17	**1.32**	1.13	0.021	**0.001**	0.077	0.105	**0.015**	0.217
CX3CR1	1.21	1.18	-1.02	0.157	0.193	0.588			
HLA-DRA	1.19	1.46	1.22	0.295	0.055	0.491			
IBA1	1.21	1.25	1.03	0.275	0.185	0.640			
P2RY12	1.17	1.32	1.13	0.193	0.036	0.535	0.339	0.152	0.665
TMEM119	-1.21	1.29	1.56	0.290	0.162	0.019	0.445	0.330	0.105
TREM2	1.30	1.29	-1.01	0.057	0.047	0.717	0.172	0.172	0.813
TSPO	1.05	1.29	1.22	0.452	0.004	0.017	0.623	0.075	0.105
DLPFC-oligodendrocyte genes									
MBP	1.13	**1.30**	1.15	0.008	**0.000**	0.007	0.078	**0.010**	0.078
MOG	-1.06	1.14	1.21	0.559	0.299	0.104			
OLIG2	-1.07	1.07	1.10	0.485	0.736	0.314			
PLP	-1.02	1.21	1.23	0.762	0.178	0.057			
ACC-astrocyte genes									
ALDH1L1	**-1.38**	1.04	**1.43**	**0.002**	0.698	**0.002**	**0.034**	0.831	**0.034**
GFAP	-1.32	-1.12	1.18	0.011	0.200	0.108	0.138	0.425	0.374
S100B	-1.17	1.04	1.21	0.104	0.663	0.110			
ACC-microglia genes									
CD11B	-1.14	-1.14	1.00	0.404	0.128	0.646			
CD45	-1.57	-1.09	1.43	0.015	0.611	0.034	0.149	0.820	0.245
CD68	-1.18	-1.05	1.13	0.022	0.392	0.055	0.189	0.572	0.341
CX3CR1	-1.15	-1.12	1.03	0.335	0.305	0.983			
HLA-DRA	1.02	1.00	-1.02	0.928	0.863	0.792			
IBA1	-1.19	-1.10	1.09	0.162	0.228	0.599			
P2RY12	-1.22	-1.12	1.08	0.151	0.186	0.701			
TMEM119	-1.25	-1.06	1.18	0.159	0.930	0.248			
TREM2	-1.19	-1.03	1.16	0.197	0.645	0.308			
TSPO	**-1.27**	-1.14	1.12	**0.001**	0.060	0.139	**0.034**	0.341	0.403
ACC-oligodendrocyte genes									
MBP	-1.12	-1.01	1.11	0.105	0.991	0.166			
MOG	-1.15	-1.01	1.14	0.270	0.948	0.260			
OLIG2	-1.21	-1.11	1.09	0.082	0.383	0.400			
PLP	-1.20	-1.17	1.03	0.102	0.247	0.726			

Note: ACC: anterior cingulate cortex; BHadj-p: P value of Benjamini-Hochberg's adjustment; Ctr: control; DLPFC: dorsolateral prefrontal cortex; MDD: major depressive disorder; MDD-NP: MDD patients did not report psychotic features; MDD-P: MDD patients reported psychotic features; P-perm: P value of permutation test.

MBP expression we report in the DLPFC may be the first possible cortical region from where the increased plasma MBP levels are derived. This suggests stronger demyelination in patients with MDD and psychotic features, especially when MBP increases BBB permeability by inducing cerebral inflammation (D'Aversa et al., 2013).

In conclusion, differential changes were observed in the expression of several glial transcripts, in relation to MDD, suicide and psychotic features that were region-specific. Overall, MDD shows glia-related changes that may be relevant for BBB integrity, microglial phagocytosis, DA and GABA signaling, and myelination. While both suicide and psychotic features confound microglial phagocytosis, only psychotic features impact myelin stability.

5. Limitations

Inherent to postmortem studies is the sample volumes in this study relatively small. However, subjects of the collection studied have been well matched to reduce the output variabilities. Correlation analysis between glia expression and fluphenazine lifetime dosage has been performed but we did not find significance.

Role of funding source

This research was supported by the 'Stichting Vrienden van het Herseninstituut'.

CRediT authorship contribution statement

Lin Zhang: Visualization, Data curation, Writing – original draft. **Ronald W.H. Verwer:** Formal analysis. **Juan Zhao:** Writing – review & editing. **Inge Huitinga:** Visualization, Writing – review & editing. **Paul J. Lucassen:** Writing – review & editing. **Dick F. Swaab:** Visualization, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

None to declare.

Acknowledgments

Postmortem brain samples were obtained from the Stanley Medical Research Institute (Director: Dr. Maree J Webster) Depression Collection. We thank Arja Sluiter and Dr. Yuting Hu for their technical support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.098.

References

Allard, P., Norlen, M., 1997. Unchanged density of caudate nucleus dopamine uptake sites in depressed suicide victims. J. Neural Transm. 104, 1353–1360.

Allard, P., Norlén, M., 2001. Caudate nucleus dopamine D2 receptors in depressed suicide victims. Neuropsychobiology 44, 70–73.

Ambrée, O., Ruland, C., Scheu, S., Arolt, V., Alferink, J., 2018. Alterations of the innate immune system in susceptibility and resilience after social defeat stress. Front. Behav. Neurosci. 12 https://doi.org/10.3389/fnbeh.2018.00141.

Aston, C., Jiang, L., Sokolov, B., 2005. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. Mol. Psychiatry 10, 309.

Barley, K., Dracheva, S., Byne, W., 2009. Subcortical oligodendrocyte-and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorder. Schizophr. Res. 112, 54–64.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B (Methodol.) 57, 289–300.

Bergquist, J., Träskman-Bendz, L., Lindström, M.B., Ekman, R., 2002. Suicide-attempters having immunoglobulin G with affinity for dopamine in cerebrospinal fluid. Eur. Neuropsychopharmacol. 12, 153–158.

Cardinal, R.N., Bullmore, E.T., 2011. The Diagnosis of Psychosis. Cambridge University Press.

Chandley, M.J., Szebeni, K., Szebeni, A., Crawford, J., Stockmeier, C.A., Turecki, G., Miguel-Hidalgo, J.J., Ordway, G.A., 2013. Gene expression deficits in pontine locus coeruleus astrocytes in men with major depressive disorder. J. Psychiatry Neurosci. JPN 38, 276.

Chen, M.L., Wu, S., Tsai, T.C., Wang, L.K., Tsai, F.M., 2013. Regulation of macrophage immune responses by antipsychotic drugs. Immunopharmacol. Immunotoxicol. 35, 573–580.

Collste, K., Plavén-Sigray, P., Fatouros-Bergman, H., Victorsson, P., Schain, M., Forsberg, A., Amini, N., Aeinehband, S., Farde, L., Flyckt, L., 2017. Lower levels of the glial cell marker TSPO in drug-naive first-episode psychosis patients as measured using PET and [11 C] PBR28. Mol. Psychiatry 22, 850.

Costa, B., Da Pozzo, E., Chelli, B., Simola, N., Morelli, M., Luisi, M., Maccheroni, M., Taliani, S., Simorini, F., Da Settimo, F., 2011. Anxiolytic properties of a 2-phenyl-indolglyoxylamide TSPO ligand: stimulation of *in vitro* neurosteroid production affecting GABAA receptor activity. Psychoneuroendocrinology 36, 463–472.

D'Aversa, T.G., Eugenin, E.A., Lopez, L., Berman, J.W., 2013. Myelin basic protein induces inflammatory mediators from primary human endothelial cells and blood–brain barrier disruption: implications for the pathogenesis of multiple sclerosis. Neuropathol. Appl. Neurobiol. 39, 270–283.

Davison, A.C., Hinkley, D.V., 1997. Bootstrap Methods and Their Application. Cambridge University Press.

Dong, M., Zeng, L.N., Lu, L., Li, X.H., Ungvari, G.S., Ng, C.H., Chow, I.H., Zhang, L., Zhou, Y., Xiang, Y.T., 2019. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. Psychol. Med. 49, 1691–1704.

Dorsam, R.T., Kunapuli, S.P., 2004. Central role of the P2Y 12 receptor in platelet activation. J. Clin. Investig. 113, 340–345.

Ernst, C., Nagy, C., Kim, S., Yang, J.P., Deng, X., Hellstrom, I.C., Choi, K.H., Gershenfeld, H., Meaney, M.J., Turecki, G., 2011. Dysfunction of astrocyte connexins 30 and 43 in dorsal lateral prefrontal cortex of suicide completers. Biol. Psychiatry 70, 312–319.

Fitzgerald, M.L., Kassir, S.A., Underwood, M.D., Bakalian, M.J., Mann, J.J., Arango, V., 2017. Dysregulation of striatal dopamine receptor binding in suicide. Neuropsychopharmacology 42, 974. Official publication of the American College of Neuropsychopharmacology.

Giridharan, V.V., Réus, G.Z., Selvaraj, S., Scaini, G., Barichello, T., Quevedo, J., 2019. Maternal deprivation increases microglial activation and neuroinflammatory markers in the prefrontal cortex and hippocampus of infant rats. J. Psychiatr. Res. 115, 13–20.

Gittins, R.A., Harrison, P.J., 2011. A morphometric study of glia and neurons in the anterior cingulate cortex in mood disorder. J. Affect. Disord. 133, 328–332.

Glassman, A.H., Kantor, S.J., Shostak, M., 1975. Depression, delusions, and drug response. Am. J. Psychiatry 132 (7), 716–719.

Gos, T., Schroeter, M.L., Lessel, W., Bernstein, H.G., Dobrowolny, H., Schiltz, K., Bogerts, B., Steiner, J., 2013. S100B-immunopositive astrocytes and oligodendrocytes in the hippocampus are differentially afflicted in unipolar and bipolar depression: a postmortem study. J. Psychiatr. Res. 47, 1694–1699.

Hafizi, S., Da Silva, T., Meyer, J.H., Kiang, M., Houle, S., Remington, G., Prce, I., Wilson, A.A., Rusjan, P.M., Sailasuta, N., 2018a. Interaction between TSPO-a neuroimmune marker-and redox status in clinical high risk for psychosis: a PET–MRS study. Neuropsychopharmacology 43, 1700–1705.

Hafizi, S., Guma, E., Koppel, A., Da Silva, T., Kiang, M., Houle, S., Wilson, A.A., Rusjan, P.M., Chakravarty, M.M., Mizrahi, R., 2018b. TSPO expression and brain structure in the psychosis spectrum. Brain Behav. Immun. 74, 79–85.

Hamidi, M., Drevets, W.C., Price, J.L., 2004. Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. Biol. Psychiatry 55, 563–569.

Holma, K.M., Melartin, T.K., Haukka, J., Holma, I.A., Sokero, T.P., Isometsä, E.T., 2010. Incidence and predictors of suicide attempts in DSM–IV major depressive disorder: a five-year prospective study. Am. J. Psychiatry 167, 801–808.

Holmes, S.E., Hinz, R., Conen, S., Gregory, C.J., Matthews, J.C., Anton-Rodriguez, J.M., Gerhard, A., Talbot, P.S., 2018. Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: a positron emission tomography study. Biol. Psychiatry 83, 61–69.

Janelidze, S., Mattei, D., Westrin, Å., Träskman-Bendz, L., Brundin, L., 2011. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain Behav. Immun. 25, 335–339.

Kantrowitz, J.T., Tampi, R.R., 2008. Risk of psychosis exacerbation by tricyclic antidepressants in unipolar major depressive disorder with psychotic features. J. Affect. Disord. 106, 279–284.

Klempan, T.A., Ernst, C., Deleva, V., Labonte, B., Turecki, G., 2009a. Characterization of QKI gene expression, genetics, and epigenetics in suicide victims with major depressive disorder. Biol. Psychiatry 66, 824–831.

Klempan, T.A., Sequeira, A., Canetti, L., Lalovic, A., Ernst, C., Turecki, G., 2009b. Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. Mol. Psychiatry 14, 175.

Schroeter, M.L., Sacher, J., Steiner, J., Schoenknecht, P., Mueller, K., 2013. Serum S100B represents a new biomarker for mood disorders. Curr. Drug Targets 14, 1237–1248.

Larisch, R., Klimke, A., Vosberg, H., Löffler, S., Gaebel, W., Müller-Gärtner, H.W., 1997. *In Vivo* evidence for the involvement of dopamine-D2Receptors in striatum and anterior cingulate gyrus in major depression. Neuroimage 5, 251–260.

Li, H., Sagar, A.P., Kéri, S., 2018. Microglial markers in the frontal cortex are related to cognitive dysfunctions in major depressive disorder. J. Affect. Disord. 241, 305–310.

Li, Z., Qi, D., Chen, J., Zhang, C., Yi, Z., Yuan, C., Wang, Z., Hong, W., Yu, S., Cui, D., 2013. Venlafaxine inhibits the upregulation of plasma tumor necrosis factor-alpha (TNF-α) in the Chinese patients with major depressive disorder: a prospective longitudinal study. Psychoneuroendocrinology 38, 107–114.

Loftis, J.M., Valerio, J., Taylor, J., Huang, E., Hudson, R., Taylor-Young, P., Chang, M., Ho, S.B., Dieperink, E., Miranda, J.L., 2018. S100B and inflammatory cytokine levels in blood as potential markers of blood–brain barrier damage and psychiatric impairment in comorbid hepatitis C viral infection and alcohol use disorder. Alcohol. Clin. Exp. Res. 42, 1466–1475.

Lutz, P.-E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J.J., Zhou, Y., Chen, G.G., Wakid, M., Shaw, M., Almeida, D., 2017. Association of a history of child abuse with impaired myelination in the anterior cingulate cortex: convergent epigenetic, transcriptional, and morphological evidence. Am. J. Psychiatry 174, 1185–1194.

Ma, Y.J., Wang, D.F., Yuan, M., Zhang, X.J., Long, J., Chen, S.B., Wu, Q.X., Wang, X.Y., Patel, M., Verrico, C.D., 2019. The prevalence, metabolic disturbances and clinical correlates of recent suicide attempts in Chinese inpatients with major depressive disorder. BMC Psychiatry 19, 144.

Matthews, P.R., Eastwood, S.L., Harrison, P.J., 2012. Reduced myelin basic protein and actin-related gene expression in visual cortex in schizophrenia. PloS One 7, e38211.

Michailidou, I., Willems, J.G., Kooi, E.J., van Eden, C., Gold, S.M., Geurts, J.J., Baas, F., Huitinga, I., Ramaglia, V., 2015. Complement C 1q-C 3–associated synaptic changes in multiple sclerosis hippocampus. Ann. Neurol. 77, 1007–1026.

Miguel-Hidalgo, J.J., Baucom, C., Dilley, G., Overholser, J.C., Meltzer, H.Y., Stockmeier, C.A., Rajkowska, G., 2000. Glial fibrillary acidic protein immunoreactivity in the prefrontal cortex distinguishes younger from older adults in major depressive disorder. Biol. Psychiatry 48, 861–873.

Monfrim, X., Gazal, M., De Leon, P.B., Quevedo, L., Souza, L.D., Jansen, K., Oses, J.P., Pinheiro, R.T., Silva, R.A., Lara, D.R., 2014. Immune dysfunction in bipolar disorder and suicide risk: is there an association between peripheral corticotropin-releasing hormone and interleukin-1β? Bipolar Disord. 16, 741–747.

Mosebach, J., Keilhoff, G., Gos, T., Schiltz, K., Schoeneck, L., Dobrowolny, H., Mawrin, C., Müller, S., Schroeter, M.L., Bernstein, H.G., 2013. Increased nuclear Olig1-expression in the pregenual anterior cingulate white matter of patients with major depression: a regenerative attempt to compensate oligodendrocyte loss? J. Psychiatr. Res. 47, 1069–1079.

Nagy, C., Suderman, M., Yang, J., Szyf, M., Mechawar, N., Ernst, C., Turecki, G., 2015. Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. Mol. Psychiatry 20, 320.

Nelson, J.C., Bickford, D., Delucchi, K., Fiedorowicz, J.G., Coryell, W.H., 2018. Risk of psychosis in recurrent episodes of psychotic and nonpsychotic major depressive disorder: a systematic review and meta-analysis. Am. J. Psychiatry 175, 897–904.

Ota, V.K., Noto, C., Santoro, M.L., Spindola, L.M., Gouvea, E.S., Carvalho, C.M., Santos, C.M., Xavier, G., Higuchi, C.H., Yonamine, C., 2015. Increased expression of NDEL1 and MBP genes in the peripheral blood of antipsychotic-naive patients with first-episode psychosis. Eur. Neuropsychopharmacol. 25, 2416–2425.

Pai, S., Li, P., Killinger, B., Marshall, L., Jia, P., Liao, J., Petronis, A., Szabó, P.E., Labrie, V., 2019. Differential methylation of enhancer at IGF2 is associated with abnormal dopamine synthesis in major psychosis. Nat. Commun. 10, 2046.

Pandey, G.N., Rizavi, H.S., Ren, X., Fareed, J., Hoppensteadt, D.A., Roberts, R.C., Conley, R.R., Dwivedi, Y., 2012. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J. Psychiatr. Res. 46, 57–63.

Pantazatos, S.P., Huang, Y., Rosoklija, G.B., Dwork, A.J., Arango, V., Mann, J.J., 2017. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: evidence for altered glial, endothelial and ATPase activity. Mol. Psychiatry 22, 760.

Pare, C., Yeung, D., Price, K., Stacey, R., 1969. 5-Hydroxytryptamine, noradrenaline, and dopamine in brainstem, hypothalamus, and caudate nucleus of controls and of patients committing suicide by coal-gas poisoning. Lancet 294, 133–135.

Pitchot, W., Hansenne, M., Ansseau, M., 2001. Role of dopamine in non-depressed patients with a history of suicide attempts. Eur. Psychiatry 16, 424–427.

Rački, V., Petrić, D., Kučić, N., Gržeta, N., Jurdana, K., Rončević-Gržeta, I., 2016. Cortical gray matter loss in schizophrenia: could microglia be the culprit? Med. Hypotheses 88, 18–21.

Rajkowska, G., Stockmeier, C.A., 2013. Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue. Curr. Drug Targets 14, 1225–1236.

Rajkowska, G., Hughes, J., Stockmeier, C.A., Miguel-Hidalgo, J.J., Maciag, D., 2013. Coverage of blood vessels by astrocytic endfeet is reduced in major depressive disorder. Biol. Psychiatry 73, 613–621.
Rajkowska, G., Mahajan, G., Maciag, D., Sathyanesan, M., Iyo, A.H., Moulana, M., Kyle, P.B., Woolverton, W.L., Miguel-Hidalgo, J.J., Stockmeier, C.A., 2015. Oligodendrocyte morphometry and expression of myelin–Related mRNA in ventral prefrontal white matter in major depressive disorder. J. Psychiatr. Res. 65, 53–62.
Roy, A., De Jong, J., Linnoila, M., 1989. Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients: a 5-year follow-up study. Arch. Gen. Psychiatry 46, 609–612.
Roy, A., Karoum, F., Pollack, S., 1992. Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. Arch. Gen. Psychiatry 49, 447–450.
Santoro, M.L., Gadelha, A., Ota, V.K., Cunha, G.R., Asevedo, E., Noto, C.S., Spindola, L. M., Pan, P.M., Talarico, F., Mansur, R.B., 2015. Gene expression analysis in blood of ultra-high risk subjects compared to first-episode of psychosis patients and controls. World J. Biol. Psychiatry 16, 441–446.
Schmidt, F.M., Mergl, R., Stach, B., Jahn, I., Schönknecht, P., 2015. Elevated levels of cerebrospinal fluid neuron-specific enolase (NSE), but not S100B in major depressive disorder. World J. Biol. Psychiatry 16, 106–113.
Schnieder, T.P., Trencevska, I., Rosoklija, G., Stankov, A., Mann, J.J., Smiley, J., Dwork, A.J., 2014. Microglia of prefrontal white matter in suicide. J. Neuropathol. Exp. Neurol. 73, 880–890.
Schnieder, T.P., Zhou Qin, I.D., Trencevska-Ivanovska, I., Rosoklija, G., Stankov, A., Pavlovski, G., Mann, J.J., Dwork, A.J., 2018. Blood vessels and perivascular phagocytes of prefrontal white and gray matter in suicide. J. Neuropathol. Exp. Neurol. 78, 15–30.
Selvaraj, S., Bloomfield, P.S., Cao, B., Veronese, M., Turkheimer, F., Howes, O.D., 2018. Brain TSPO imaging and gray matter volume in schizophrenia patients and in people at ultra high risk of psychosis: an [11C] PBR28 study. Schizophr. Res. 195, 206–214.
Stan, A.D., Ghose, S., Gao, X.-M., Lewis-Amezcua, K., Hatanpaa, K.J., Tamminga, C.A., 2006. Human postmortem tissue: what quality markers matter? Brain research 1123, 1–11.
Steiner, J., Bielau, H., Brisch, R., Danos, P., Ullrich, O., Mawrin, C., Bernstein, H.-G., Bogerts, B., 2008. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J. Psychiatr. Res. 42, 151–157.
Suda, A., Kawanishi, C., Kishida, I., Sato, R., Yamada, T., Nakagawa, M., Hasegawa, H., Kato, D., Furuno, T., Hirayasu, Y., 2009. Dopamine D2 receptor gene polymorphisms are associated with suicide attempt in the Japanese population. Neuropsychobiology 59, 130–134.
Suhara, T., Okubo, Y., Yasuno, F., Sudo, Y., Inoue, M., Ichimiya, T., Nakashima, Y., Nakayama, K., Tanada, S., Suzuki, K., 2002. Decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia. Arch. Gen. Psychiatry 59, 25–30.
Suominen, K., Haukka, J., Valtonen, H.M., Lönnqvist, J., 2009. Outcome of patients with major depressive disorder after serious suicide attempt. J. Clin. Psychiatry 70, 1372–1378.
Takahashi, H., Higuchi, M., Suhara, T., 2006. The role of extrastriatal dopamine D2 receptors in schizophrenia. Biol. Psychiatry 59, 919–928.
Tanti, A., Kim, J., Wakid, M., Davoli, M., Turecki, G., Mechawar, N., 2017. Child abuse associates with an imbalance of oligodendrocyte-lineage cells in ventromedial prefrontal white matter. Mol. Psychiatry 23, 2018–2028.
Thorell, L., 1989. Is electrodermal measurement a complement in assessing suicide risk? Lakartidningen 86, 525.
Tonelli, L.H., Stiller, J., Rujescu, D., Giegling, I., Schneider, B., Maurer, K., Schnabel, A., Möller, H.J., Chen, H.-H., Postolache, T.T., 2008. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. Acta Psychiatr. Scand. 117, 198–206.
Torres-Platas, S.G., Cruceanu, C., Chen, G.G., Turecki, G., Mechawar, N., 2014. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav. Immun. 42, 50–59.
Vandesompele, J., De Preter, K., Pattyn, F., Poppe, B., Van Roy, N., De Paepe, A., Speleman, F., 2002. Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. Genome Biol. 3. http://genomebiology.com/2002/3/7/research/0034. research0034. 0031.
Varis, J., Rantala, I., Pasternack, A., Oksa, H., Jäntti, M., Paunu, E., Pirhonen, R., 1993. Immunoglobulin and complement deposition in glomeruli of 756 subjects who had committed suicide or met with a violent death. J. Clin. Pathol. 46, 607–610.
Vicente, É., Tramontina, F., Leite, M.C., Nardin, P., Silva, M., Karkow, A.R., Adolf, R., Lucion, A.B., Netto, C.A., Gottfried, C., 2007. S100B levels in the cerebrospinal fluid of rats are sex and anaesthetic dependent. Clin. Exp. Pharmacol. Physiol. 34, 1126–1130.
Vostrikov, V., Uranova, N., 2011. Age-related increase in the number of oligodendrocytes is dysregulated in schizophrenia and mood disorders. Schizophr. Res. Treat. 2011. https://doi.org/10.1155/2011/174689.
Webster, M., O'grady, J., Kleinman, J., Weickert, C., 2005. Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder and schizophrenia. Neuroscience 133, 453–461.
Yang, Y., Chen, J., Liu, C., Fang, L., Liu, Z., Guo, J., Cheng, K., Zhou, C., Zhan, Y., Melgiri, N.D., 2016. The extrinsic coagulation pathway: a biomarker for suicidal behavior in major depressive disorder. Sci. Rep. 6, 32882.
Zalpuri, I., Rothschild, A.J., 2016. Does psychosis increase the risk of suicide in patients with major depression? A systematic review. J. Affect. Disord. 198, 23–31.
Zhang, L., Verwer, R.W., Lucassen, P.J., Huitinga, I., Swaab, D.F., 2020a. Prefrontal cortex alterations in glia gene expression in schizophrenia with and without suicide. J. Psychiatr. Res. 121, 31–38.
Zhang, L., Verwer, R.W., Lucassen, P.J., Huitinga, I., Swaab, D.F., 2020b. Sex difference in glia gene expression in the dorsolateral prefrontal cortex in bipolar disorder: Relation to psychotic features. J. Psychiatr. Res. 125, 66–74.
Zhao, J., Lucassen, P.J., Swaab, D.F., 2019. Suicide is a confounder in postmortem studies on depression. Biol. Psychiatry 86, e37–e40.
Zhao, J., Qi, X.R., Gao, S.F., Lu, J., van Wamelen, D., Kamphuis, W., Bao, A.-M., Swaab, D., 2015. Different stress-related gene expression in depression and suicide. J. Psychiatr. Res. 68, 176–185.
Zhao, J., Verwer, R., Gao, S.F., Qi, X.R., Lucassen, P., Kessels, H., Swaab, D., 2018. Prefrontal alterations in GABAergic and glutamatergic gene expression in relation to depression and suicide. Journal of Psychiatr. Res. 102, 261–274.
Zhao, J., Verwer, R., van Wamelen, D., Qi, X.R., Gao, S.F., Lucassen, P., Swaab, D., 2016. Prefrontal changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters in depression with and without suicide. J. Psychiatr. Res. 82, 8–15.