Glia Dysfunction in Major Mental Diseases

Subjects: Biology

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Microglia exert multiple functional roles and contribute to the building of the neuronal circuit through synaptic pruning and stripping during development; they participate in surveillance by secreting neurotrophic factors that react against infectious agents or toxic elements and engage in phagocytic debris clearance, including the removal of dying neurons. The role of glia dysfunction, particularly Bergmann Glia in glutamate removal, is well described in autism.

epigenetic DNA methylation glia astrocyte microglia autism schizophrenia bipolar disorder depression Alzheimer's disease

1. Glia Dysfunction in Autism

The role of glia dysfunction, particularly Bergmann Glia in glutamate removal, is well described in autism [1]. Single-cell RNA sequencing revealed that autism-associated transcriptome alterations in specific cortical cell types are related to “synaptic signaling of upper-layer excitatory neurons” and microglia [2]. A large whole-genome study of postmortem brain samples also indicated that DNA methylation alterations associated with autism are involved in the immune system, synaptic signaling, and neuronal regulation and are highly correlated with the affected genes in patients with chromosome 15q duplication and H3K27 acetylation [3].

Some important microglia genes, such as *TREM2* (as the microglia innate immune receptor gene involved in synapse pruning) are also linked to autism pathogenesis. In mice, the lack of expression of *TREM2* is associated with autism-like behavior and, in humans, a reduced *TREM2* protein level correlates with the severity of autism symptoms [4]. Additionally, decreased expression of *TREM2* is associated with increased expression of *TNFA*, a pro-inflammatory cytokine, and *NOS2* (nitric oxide synthase 2) in mice [5]. Interestingly, sodium valproate (an epigenetic drug that inhibits HDACs) decreases *TNF-α* and *NOS2* expression levels [6], hinting at an opportunity for autism epigenetic therapy using HDAC inhibitors. Experimental evidence indicates that *TREM2* is also regulated by microRNAs. In this regard, as it is known that the up-regulation of miRNA-34a (an NF-κB-sensitive miRNA) targets *TREM2* and down-regulates its expression in microglia cells [7], increased expression of miRNA34 a/b/c was also shown in cortical tubers of patients with tuberous sclerosis, an autism spectrum disease [8]. There is also evidence that *TREM2* expression is regulated by DNA methylation. For example, DNA hypomethylation of *TREM2* intron 1, which is associated with its increased expression, was shown in the blood cells of patients with SCZ and Alzheimer’s disease [9][10]. On the other hand, increased DNA methylation of CpG sites located upstream of the *TREM2* transcription start site is reported in the superior temporal gyrus of patients with Alzheimer’s disease [11].

However, in the hippocampus of patients with Alzheimer's disease, the higher levels of DNA methylation were reported to be due to the enrichment of 5-hydroxymethycytosine associated with upregulation of *TREM2* expression [12]. Considering these data, further study of the epigenetic dysregulation of *TREM2* is warranted in autism.

Methyl-CpG binding protein 2 (*MECP2*) is another important gene in the pathogenesis of autism spectrum syndrome, specifically in Rett syndrome. In general, Rett syndrome is due to the mutation of *MECP2* located in chromosome X. The disease appears mostly in females, as males affected by this mutation usually die shortly after birth. In addition to its mutation, promoter DNA hypermethylation of *MECP2*, associated with its reduced protein expression, was shown in the frontal cortex of male autistic patients [13]. Based on recent data, while neuronal *MECP2* expression is more than that observed in astrocytes, in males, a higher DNA methylation level of *MECP2* regulatory regions is associated with reduced expression of *MECP2* in astrocytes [14]. This supports the idea that astrocytic DNA hypermethylation of *MECP2* may be a mechanism for disease pathogenesis in male autistic patients. In this regard, previous animal studies have shown that the re-expression of astrocytic *MECP2* in globally *MECP2*-deficient mice improves their behavioral and molecular aberrations [15]. Furthermore, as microglia pathology due to *MECP2* dysfunction was later proposed as the leading cause of Rett syndrome and autism pathogenesis [16], it has been shown that MECP2 regulates the expression of "microglia genes in response to inflammatory stimuli" [17].

With the involvement of microglia, it is not surprising that the immune system and complement proteins, such as C1q, C3, and C4, as well as TGFB2, which contribute to synapse pruning during brain maturation [18], are among the key players in autism pathogenesis [19][20] and in other major mental diseases, such as SCZ [21][22]. Relatedly, whole-genome DNA methylation analysis uncovered epigenetic dysregulation of several complement genes such as *C1Q, C3,* and *ITGB2* (*C3R*), as well as several other inflammatory genes (e.g., *TNF-α*, *IRF8*, and *SPI1*) in postmortem brain samples of patients with autism [23]. Therefore, these findings (as summarized in **Table 1**) call for more studies on the astroglia-mediated epigenetic dysregulation of complement genes in autism.

Table 1. Genes linked to non-neuronal brain cell function and supporting evidence indicating their epigenetic dysregulation in mental diseases.

Gene	Active in	Functions	Phenotypes	Expression Status	Epigenetic Alteration(s)	References
TREM2	Microglia	synapse pruning	Autism	Decreased in brain	Increased miRNA-34a	[4][8]
			Alzheimer's Disease	Increased in blood cells	DNA hypo-methylation	[9]
			SCZ	Increased in blood cells	DNA hypo-methylation	[10]
				Superior temporal	DNA hyper-methylation	[11]

Gene	Active in	Functions	Phenotypes	Expression Status	Epigenetic Alteration(s)	References
				gyrus (No expression study)		
				Increased in hippocampus	DNA hypermethylation (higher 5-hydroxymethylcytosine)	[12]
MECP2	Astrocytes	Neurodevelopment and regulation of microglia genes	Autism	Reduced in the frontal cortex	DNA hyper-methylation	[13][14]
C1q, *C3* and *C4*	Microglia and astrocytes	Synapse pruning	Autism and SCZ	Increased in several brain areas (e.g., DLPFC)	Different DNA methylation alterations	[19][20][21] [22][23][24]
C3	Microglia	synapse pruning	Alzheimer's Disease	Increased in brain and middle temporal gyrus	DNA hypo-methylation	[25][26]
C4a	Microglia	synapse pruning	SCZ	Increased in blood cells	Not defined in SCZ (regulated by DNA methylation in ADHD)	[27][28]
SLC1A2/GLT1	Astrocytes	Glutamate transporter and extracellular synapse glutamate removal	SCZ, BD	Increased in brain	Regulated by miR-218, DNA methylation and histone acetylation	[29][30][31] [32]
			Depression	Reduced in lateral habenula	?	[33][34]
S100B	Mainly astrocytes	Hippocampal synaptogenesis	SCZ	Increased in blood cells and serum	DNA methylation alterations	[35][36]
MHC class I	Microglia	Synaptic pruning	SCZ	Reduced in brain (DLPFC) and blood	DNA methylation alterations	[23][37]
NDN	Astrocytes	Neurodevelopment, spine formation	SCZ and autism	?	DNA Hypo-methylation (Imprinted gene)	[38]
KCNJ10	Astrocytes	A potassium channel	Depressive symptoms	Increased in lateral	Regulated by DNA methylation	[34][39]

Gene	Active in	Functions	Phenotypes	Expression Status	Epigenetic Alteration(s)	References
				habenula		
NTRK2	Astrocytes	Astrocyte maturation	Suicide	Decreased in brain	DNA hyper-methylation	[40]
			SCZ [48][49]	Increased in DLPFC	?	[29]
GRIN2A	Astrocytes	Aβ cleanup	Depression	?	DNA hypermethylation	[41]
HMGB1	Microglia	Inflammation. stimulates microglia	Depression	Increased in hippocampal microglia and serum [50]	Regulated by DNA methylation, HDAC4&5, and miR-129	[42][43][44][45][46][47][51]

postmortem brain studies also revealed that the altered expression of genes that are important to glia or astrocyte functions (e.g., *SLC1A2* and *TGFB2*) is linked to psychiatric phenotypes [29]. Interestingly, as the expression of astrocytes' glutamate transporter, *GLT-1* (*SLC1A2*) exhibits >100% and 70% increases in the postmortem brains of patients with SCZ and psychotic BD, respectively [29]. The use of ceftriaxone (an antibiotic that selectively enhances *GLT-1* expression) could reduce prepulse inhibition (which is also reduced in SCZ patients) in rats, which could be reversed by dihydrokainate (DHK), an antagonist of *GLT-1* [52]. Other research findings indicate that *GLT-1* expression is regulated by diverse epigenetic mechanisms [30][31]. For instance, while miR-218 downregulates astrocytic *GLT-1* expression [32] and the hypo-expression of miR-218 increases susceptibility to stress, its reduced expression has been observed in the medial prefrontal cortices of patients with depression and suicide [53][54]. Regarding *TGFB2*, while its expression is increased in the postmortem brains of patients with SCZ and psychotic BD, due to its promoter DNA hypomethylation [29], other studies have shown that *TGFB2* is over-expressed in the neurons of patients with Alzheimer's disease [55][56]. It is also the only cytokine that is increased in the cerebrospinal fluid of these patients [57]. In vitro studies indicate that the expression of *TGFB2* is induced by toxic amyloid betas in both glial and neuronal cells. In turn, the increased *TGFB2* binds to the extracellular domain of amyloid beta precursor protein and triggers a neuronal cell death pathway in Alzheimer's disease. Interestingly, the degrees of *TGFB2*-induced cell death are larger in cells expressing a familial AD-related mutant *APP* than in those expressing wild-type *APP* [57][58]. Together, these data suggest the potential roles of *GLT-1* and *TGFB2* epigenetic alterations in the pathogenesis of neuropsychiatric diseases, indicating that they are legitimate targets for therapeutic interventions [59].

Other genes that are mainly expressed by astrocytes and glial cells (e.g., *S100B*, the S100 calcium-binding protein B) are also linked to SCZ pathogenesis in GWAS analysis. Moreover, just as a higher level of the S100B protein is reported in the blood cells of SCZ patients [35], an increased serum level of *S100B* was also reported in BD patients [60]. While *S100B* promotes hippocampal synaptogenesis after traumatic brain injury [61], there is experimental evidence that its expression is regulated by DNA methylation [36].

Another line of evidence in support of the role of astroglia in SCZ is the existence of D2-like receptors in astrocytes. While astroglia account for almost one-third of *DRD2* binding sites in the brain cortex, and *DRD3* is also expressed in astrocytes, mice deficient for this D2-like receptor or that are treated with a DRD3 antagonist do not show

astroglia inflammatory activity in response to LPS (lipopolysaccharide) challenge. It should be noted that, although microglia do not express *DRD3*, in *DRD3* deficient mice, the expression of *Fizz1*, an anti-inflammatory protein, is increased in glial cells (both in vitro and in vivo). This also attenuates microglial activation in response to LPS challenge [62]. The fact that commonly used antipsychotic drugs block DRD2-like receptors, and that the long-term use of olanzapine alters *DRD2* promoter DNA methylation levels [63], suggests that the effects of DRD2-like antagonists in SCZ treatment could be due to the inhibition of astroglia's inflammatory activity, mediated in part by *DRD2* epigenetic modifications.

Human major histocompatibility complex (*MHC*) genes are among other genes associated with microglia functions that are involved in SCZ pathogenesis in GWAS analyses [64][65]. MHC class I is involved in complement-mediated synaptic pruning [3] and exhibits reduced expression in the brains of SCZ patients [37]. Additionally, it has been shown that glia overactivity mediated by complement *C4A* (one of the genes of MHC III) and the increased expression of *C4A* may have deleterious effects in SCZ [27][66]. Notably, in a study of humanized glial chimeric mice, it was shown that mice with glial cells produced from the iPSC of patients with childhood-onset SCZ, exhibited premature glia migration into the cortex and reduced expansion of white matter and its hypomyelination compared to the mice with glia from the normal controls. This was associated with a delay in astrocytic differentiation and abnormality in astrocytic morphology, as well as reduced prepulse inhibition, increased anxiety, and sleep problems. Additionally, the cultured glial progenitor cells from SCZ patients exhibited aberrant expression of genes linked to glial differentiation as well as synapse-associated genes in the RNA-seq analysis, suggesting that the observed glial pathology originates from these cells [67]. In reference to potential clinical applications of these findings, it is noteworthy that as an exaggerated synapse pruning has been repeatedly reported in adolescents, particularly in SCZ patients [68], which could be mitigated by minocycline [69][70]; thus it is not surprising that the inhibition of microglia activity by minocycline is effective in the treatment of negative symptoms of SCZ in randomized double-blind studies [71][72].

In addition to the relation between genetic variations of the complement system and SCZ [66], there is also evidence that non-genetic alterations of the activity of complement system are associated with SCZ. For example, as summarized in **Table 1**, increased *C4* and *C1q* levels were reported in the prefrontal cortices of patients with SCZ [24] and the blood cells of antipsychotic-naive first-episode SCZ patients [28], as well as those with chronic SCZ and in individuals at high risk for psychosis; meanwhile, increased *C3* levels were also shown in the latter group [73]. There are also reports of increased levels of *C3a, C5a,* and *C5b-9* in drug-free patients with bipolar disorder [74], and of increased expression of *C1q, C4*, and factor B in the peripheral blood mononuclear cells of chronic BD patients [75]. Epigenetic analysis of different elements of the complement system in other mental diseases revealed those genes of the complement system that are linked to glial activity and are subjects of epigenetic dysregulation (**Table 1**). For instance, in whole-genome DNA methylation analysis, the epigenetic dysregulation of *C1q, C3,* and *ITGB2* (*C3R*) was reported in autism [23]. The DNA hypomethylation of *C3* associated with its increased expression was also shown in the postmortem brains of patients with Alzheimer's disease [25][26]. Furthermore, DNA methylation alterations affecting *C4A* and *C4B* expression were reported in a genome-wide DNA methylation analysis of patients with Attention-Deficit/Hyperactivity Disorder [76].

As epigenetic alterations are frequently reported in SCZ and autism and these diseases are more common in males, it is important to note that, in females, one of the X chromosomes is subject to random inactivation by DNA methylation. Hence, if the activity of any gene in one of the X chromosomes is imbalanced due to inherited or de novo mutations, in a female subject, half of the neighboring cells can work normally, partially balancing the tissue functions. For example, *SRPX2* (regulated by the complement C1q) which is localized chromosome X and is involved in language and cognitive development [77], exhibits expression reduced by almost 20% in the postmortem brains of SCZ patients [29]. Although the *SRPX2* gene codes a neuronal protein, C1q binds to *SRPX2*, inhibiting synapse eliminations [78]. Thus, a close cooperation between *SRPX2* and this complement is required for the fine tuning of synapse pruning in normal brain development. In cancer research, it has been shown that DNA methylation regulates *SRPX2* expression levels [79]. Therefore, DNA methylation alteration of *SRPX2* could be an interesting subject for further studies in SCZ, as well as in autism and dyspraxia, which are both more prevalent in males than in females. There is also a correlation between the expression of *MECP2*, a methyl CpG binding protein, and *SRPX2* expression [80], which warrants further research.

Other evidence related to astroglia epigenetic alterations in mental diseases comes from imprinted genes in which one copy of the parental alleles (in autosomes) is inactivated by DNA methylation. In this regard, whole-genome DNA methylation analysis for rare epigenetic variations identified that the NDN gene, which is highly expressed in astrocytes, was linked to SCZ as well as to autism pathogenesis [38]. This gene is exclusively expressed from the paternal allele and is in the Prader-Willi syndrome deletion region implicated in autism pathogenesis [81].

3. Astroglia Pathology and Dysfunction in Depression

In addition to SCZ and BD, there is evidence for astroglia dysfunctions in depression. For example, whole-transcriptome analysis using RNA-seq of human postmortem brain samples from drug-free individuals with MDD (major depressive disorder) and suicide revealed deficits in genes related to microglial and astrocytic cell functions [82]. Aberrant DNA methylation patterns specific to astrocytes were also shown in the prefrontal cortices of postmortem brain samples of patients with depression [83]. Another study reported the upregulation of astroglia's potassium channel gene (*Kir4.1* or *KCNJ10*) and reduced *GLT-1* (*SLC1A2*) activity (which removes ~90% of extracellular/synapse glutamate) and increased neuronal bursting activity of the lateral habenula as key factors in the induction of depression-like behaviors [33][34]. A recent study revealed that DNA methylation regulates *KCNJ10* expression in astrocytes [39]. Aberrant DNA methylation of *NMDAR* (more specifically, the hypermethylation of the *GRIN2A* subunit) was also reported in the hippocampus and prefrontal cortex of MDD patients [41]. However, in SCZ patients, DNA hypomethylation of *GRIN2B* was shown in blood cells [84]. Interestingly, ketamine, which is used to treat MDD, decreases neuronal bursting activity [85] by blocking glial *NMDAR* in the lateral habenula, which is considered to be the brain's "antireward" center [33][34]. Nevertheless, in rats, ketamine's effects on depressive-like behavior was attributed to its activity in the regulation of astrocytic *GLT-1*, and also through BDNF-TrkB signaling [86]. It has also been shown that ketamine alleviates DNA hypermethylation of *BDNF* in the medial prefrontal cortex and hippocampus in a mouse model of PTSD [87]. Furthermore, while *BDNF* and its receptor NTRK2 play key roles

in astrocytes' maturation and functions [88], DNA hypermethylation of *NTRK2* and its reduced expression was reported in the postmortem brains of patients who died by suicide [40].

HMGB1 is another microglia-associated gene involved in depression [42][89]. Animal studies have shown that unpredictable chronic stress can lead to microglia activation in the hippocampus and depressive-like symptoms [90]. This type of stress could increase *HMGB1* expression in the hippocampal microglia, and the infusion of *HMGB1* into the mice hippocampus could also induce depression [43]. Interestingly, the activation of the microglia, along with depressive symptoms, could be prevented by minocycline or imipramine [90]. While *HMGB1* is a well-known marker of inflammation, increased expression of *HMGB1*, associated with its promoter DNA's methylation alteration, was reported in cardiac progenitor cells following hypoxia and metabolic diseases [44][45], suggesting that DNA methylation is a mechanism for *HMGB1* regulation. However, in brain cells, *HMGB1* expression is also regulated by HDAC4&5 and miR-129 [46][47], the latter of which was shown to regulate neuronal migration in mice brains [91].

References

1. Chrobak, A.A.; Soltys, Z. Bergmann glia, long-term depression, and autism spectrum disorder. Mol. Neurobiol. 2017, 54, 1156–1166.
2. Velmeshev, D.; Schirmer, L.; Jung, D.; Haeussler, M.; Perez, Y.; Mayer, S.; Bhaduri, A.; Goyal, N.; Rowitch, D.H.; Kriegstein, A.R. Single-cell genomics identifies cell type–specific molecular changes in autism. Science 2019, 364, 685–689.
3. Wong, C.C.; Smith, R.G.; Hannon, E.; Ramaswami, G.; Parikshak, N.N.; Assary, E.; Troakes, C.; Poschmann, J.; Schalkwyk, L.C.; Sun, W. Genome-wide DNA methylation profiling identifies convergent molecular signatures associated with idiopathic and syndromic autism in post-mortem human brain tissue. Hum. Mol. Genet. 2019, 28, 2201–2211.
4. Filipello, F.; Morini, R.; Corradini, I.; Zerbi, V.; Canzi, A.; Michalski, B.; Erreni, M.; Markicevic, M.; Starvaggi-Cucuzza, C.; Otero, K. The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. Immunity 2018, 48, 979–991.e978.
5. Takahashi, K.; Rochford, C.D.; Neumann, H. Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J. Exp. Med. 2005, 201, 647–657.
6. Patnala, R.; Arumugam, T.V.; Gupta, N.; Dheen, S.T. HDAC inhibitor sodium butyrate-mediated epigenetic regulation enhances neuroprotective function of microglia during ischemic stroke. Mol. Neurobiol. 2017, 54, 6391–6411.
7. Alexandrov, P.N.; Zhao, Y.; Jones, B.M.; Bhattacharjee, S.; Lukiw, W.J. Expression of the phagocytosis-essential protein TREM2 is down-regulated by an aluminum-induced miRNA-34a in a murine microglial cell line. J. Inorg. Biochem. 2013, 128, 267–269.

8. Mills, J.D.; Iyer, A.M.; van Scheppingen, J.; Bongaarts, A.; Anink, J.J.; Janssen, B.; Zimmer, T.S.; Spliet, W.G.; van Rijen, P.C.; Jansen, F.E. Coding and small non-coding transcriptional landscape of tuberous sclerosis complex cortical tubers: Implications for pathophysiology and treatment. Sci. Rep. 2017, 7, 8089.
9. Ozaki, Y.; Yoshino, Y.; Yamazaki, K.; Sao, T.; Mori, Y.; Ochi, S.; Yoshida, T.; Mori, T.; Iga, J.-I.; Ueno, S.-I. DNA methylation changes at TREM2 intron 1 and TREM2 mRNA expression in patients with Alzheimer's disease. J. Psychiatr. Res. 2017, 92, 74–80.
10. Yoshino, Y.; Ozaki, Y.; Yamazaki, K.; Sao, T.; Mori, Y.; Ochi, S.; Iga, J.-I.; Ueno, S.-I. DNA methylation changes in intron 1 of Triggering receptor expressed on myeloid cell 2 in Japanese schizophrenia subjects. Front. Neurosci. 2017, 11, 275.
11. Smith, A.R.; Smith, R.G.; Condliffe, D.; Hannon, E.; Schalkwyk, L.; Mill, J.; Lunnon, K. Increased DNA methylation near TREM2 is consistently seen in the superior temporal gyrus in Alzheimer's disease brain. Neurobiol. Aging 2016, 47, 35–40.
12. Celarain, N.; Sánchez-Ruiz de Gordoa, J.; Zelaya, M.V.; Roldán, M.; Larumbe, R.; Pulido, L.; Echavarri, C.; Mendioroz, M. TREM2 upregulation correlates with 5-hydroxymethycytosine enrichment in Alzheimer's disease hippocampus. Clin. Epigenetics 2016, 8, 37.
13. Nagarajan, R.; Hogart, A.; Gwye, Y.; Martin, M.R.; LaSalle, J.M. Reduced MeCP2 expression is frequent in autism frontal cortex and correlates with aberrant MECP2 promoter methylation. Epigenetics 2006, 1, 172–182.
14. Liyanage, V.R.; Olson, C.O.; Zachariah, R.M.; Davie, J.R.; Rastegar, M. DNA methylation contributes to the differential expression levels of Mecp2 in male mice neurons and astrocytes. Int. J. Mol. Sci. 2019, 20, 1845.
15. Lioy, D.T.; Garg, S.K.; Monaghan, C.E.; Raber, J.; Foust, K.D.; Kaspar, B.K.; Hirrlinger, P.G.; Kirchhoff, F.; Bissonnette, J.M.; Ballas, N. A role for glia in the progression of Rett's syndrome. Nature 2011, 475, 497–500.
16. Derecki, N.C.; Cronk, J.C.; Lu, Z.; Xu, E.; Abbott, S.B.; Guyenet, P.G.; Kipnis, J. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. Nature 2012, 484, 105–109.
17. Cronk, J.C.; Derecki, N.C.; Ji, E.; Xu, Y.; Lampano, A.E.; Smirnov, I.; Baker, W.; Norris, G.T.; Marin, I.; Coddington, N. Methyl-CpG binding protein 2 regulates microglia and macrophage gene expression in response to inflammatory stimuli. Immunity 2015, 42, 679–691.
18. Presumey, J.; Bialas, A.R.; Carroll, M.C. Complement system in neural synapse elimination in development and disease. Adv. Immunol. 2017, 135, 53–79.
19. Fagan, K.; Crider, A.; Ahmed, A.O.; Pillai, A. Complement C3 expression is decreased in autism spectrum disorder subjects and contributes to behavioral deficits in rodents. Complex Psychiatry 2017, 3, 19–27.

20. Lin, P.; Nicholls, L.; Assareh, H.; Fang, Z.; Amos, T.G.; Edwards, R.J.; Assareh, A.A.; Voineagu, I. Transcriptome analysis of human brain tissue identifies reduced expression of complement complex C1Q Genes in Rett syndrome. BMC Genom. 2016, 17, 427.
21. Rey, R.; Suaud-Chagny, M.-F.; Bohec, A.-L.; Dorey, J.-M.; d'Amato, T.; Tamouza, R.; Leboyer, M. Overexpression of complement component C4 in the dorsolateral prefrontal cortex, parietal cortex, superior temporal gyrus and associative striatum of patients with schizophrenia. Brain Behav. Immun. 2020, 90, 216–225.
22. Woo, J.J.; Pouget, J.G.; Zai, C.C.; Kennedy, J.L. The complement system in schizophrenia: Where are we now and what's next? Mol. Psychiatry 2020, 25, 114–130.
23. Nardone, S.; Sharan Sams, D.; Reuveni, E.; Getselter, D.; Oron, O.; Karpuj, M.; Elliott, E. DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways. Transl. Psychiatry 2014, 4, e433.
24. Jenkins, A.K.; Lewis, D.A.; Volk, D.W. Altered expression of microglial markers of phagocytosis in schizophrenia. Schizophr. Res. 2023, 251, 22–29.
25. Lardenoije, R.; Roubroeks, J.A.; Pishva, E.; Leber, M.; Wagner, H.; Iatrou, A.; Smith, A.R.; Smith, R.G.; Eijssen, L.M.; Kleineidam, L. Alzheimer's disease-associated (hydroxy) methylomic changes in the brain and blood. Clin. Epigenetics 2019, 11, 164.
26. Wu, T.; Dejanovic, B.; Gandham, V.D.; Gogineni, A.; Edmonds, R.; Schauer, S.; Srinivasan, K.; Huntley, M.A.; Wang, Y.; Wang, T.-M. Complement C3 is activated in human AD brain and is required for neurodegeneration in mouse models of amyloidosis and tauopathy. Cell Rep. 2019, 28, 2111–2123.e2116.
27. Melbourne, J.K.; Rosen, C.; Feiner, B.; Sharma, R.P. C4A mRNA expression in PBMCs predicts the presence and severity of delusions in schizophrenia and bipolar disorder with psychosis. Schizophr. Res. 2018, 197, 321–327.
28. Hatzimanolis, A.; Foteli, S.; Stefanatou, P.; Ntigrintaki, A.-A.; Ralli, I.; Kollias, K.; Nikolaou, C.; Gazouli, M.; Stefanis, N.C. Deregulation of complement components C4A and CSMD1 peripheral expression in first-episode psychosis and links to cognitive ability. Eur. Arch. Psychiatry Clin. Neurosci. 2022, 272, 1219–1228.
29. Abdolmaleky, H.M.; Gower, A.C.; Wong, C.K.; Cox, J.W.; Zhang, X.; Thiagalingam, A.; Shafa, R.; Sivaraman, V.; Zhou, J.R.; Thiagalingam, S. Aberrant transcriptomes and DNA methylomes define pathways that drive pathogenesis and loss of brain laterality/asymmetry in schizophrenia and bipolar disorder. Am. J. Med. Genet. Part B Neuropsychiatr. Genetics 2019, 180, 138–149.
30. Kim, R.; Sepulveda-Orengo, M.T.; Healey, K.L.; Williams, E.A.; Reissner, K.J. Regulation of glutamate transporter 1 (GLT-1) gene expression by cocaine self-administration and withdrawal. Neuropharmacology 2018, 128, 1–10.

31. Perisic, T.; Holsboer, F.; Rein, T.; Zschocke, J. The CpG island shore of the GLT-1 gene acts as a methylation-sensitive enhancer. Glia 2012, 60, 1345–1355.
32. Hoye, M.L.; Regan, M.R.; Jensen, L.A.; Lake, A.M.; Reddy, L.V.; Vidensky, S.; Richard, J.-P.; Maragakis, N.J.; Rothstein, J.D.; Dougherty, J.D. Motor neuron-derived microRNAs cause astrocyte dysfunction in amyotrophic lateral sclerosis. Brain 2018, 141, 2561–2575.
33. Cui, W.; Mizukami, H.; Yanagisawa, M.; Aida, T.; Nomura, M.; Isomura, Y.; Takayanagi, R.; Ozawa, K.; Tanaka, K.; Aizawa, H. Glial dysfunction in the mouse habenula causes depressive-like behaviors and sleep disturbance. J. Neurosci. 2014, 34, 16273–16285.
34. Cui, Y.; Yang, Y.; Ni, Z.; Dong, Y.; Cai, G.; Foncelle, A.; Ma, S.; Sang, K.; Tang, S.; Li, Y. Astroglial Kir4. 1 in the lateral habenula drives neuronal bursts in depression. Nature 2018, 554, 323–327.
35. Aleksovska, K.; Leoncini, E.; Bonassi, S.; Cesario, A.; Boccia, S.; Frustaci, A. Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. PLoS ONE 2014, 9, e106342.
36. Gasparoni, G.; Bultmann, S.; Lutsik, P.; Kraus, T.F.; Sordon, S.; Vlcek, J.; Dietinger, V.; Steinmaurer, M.; Haider, M.; Mulholland, C.B. DNA methylation analysis on purified neurons and glia dissects age and Alzheimer's disease-specific changes in the human cortex. Epigenetics Chromatin 2018, 11, 41.
37. Kano, S.-I.; Nwulia, E.; Niwa, M.; Chen, Y.; Sawa, A.; Cascella, N. Altered MHC class I expression in dorsolateral prefrontal cortex of nonsmoker patients with schizophrenia. Neurosci. Res. 2011, 71, 289–293.
38. Garg, P.; Sharp, A.J. Screening for rare epigenetic variations in autism and schizophrenia. Hum. Mutat. 2019, 40, 952–961.
39. Boni, J.L.; Kahanovitch, U.; Nwaobi, S.E.; Floyd, C.L.; Olsen, M.L. DNA methylation: A mechanism for sustained alteration of KIR4. 1 expression following central nervous system insult. Glia 2020, 68, 1495–1512.
40. Ernst, C.; Deleva, V.; Deng, X.; Sequeira, A.; Pomarenski, A.; Klempan, T.; Ernst, N.; Quirion, R.; Gratton, A.; Szyf, M. Alternative splicing, methylation state, and expression profile of tropomyosin-related kinase B in the frontal cortex of suicide completers. Arch. Gen. Psychiatry 2009, 66, 22–32.
41. Kaut, O.; Schmitt, I.; Hofmann, A.; Hoffmann, P.; Schlaepfer, T.E.; Wüllner, U.; Hurlemann, R. Aberrant NMDA receptor DNA methylation detected by epigenome-wide analysis of hippocampus and prefrontal cortex in major depression. Eur. Arch. Psychiatry Clin. Neurosci. 2015, 265, 331–341.
42. Shan, W.; Xu, L.; Qiu, Z.; Wang, J.; Shao, J.; Feng, J.; Zhao, J. Increased high-mobility group box 1 levels are associated with depression after acute ischemic stroke. Neurol. Sci. 2022, 43, 3131–

3137.

43. Franklin, T.C.; Wohleb, E.S.; Zhang, Y.; Fogaça, M.; Hare, B.; Duman, R.S. Persistent Increase in Microglial RAGE Contributes to Chronic Stress-Induced Priming of Depressive-like Behavior. Biol. Psychiatry 2018, 83, 50–60.
44. Rohde, K.; Rønningen, T.; la Cour Poulsen, L.; Keller, M.; Blüher, M.; Böttcher, Y. Role of the DNA repair genes H2AX and HMGB1 in human fat distribution and lipid profiles. BMJ Open Diabetes Res. Care 2020, 8, e000831.
45. Su, J.; Fang, M.; Tian, B.; Luo, J.; Jin, C.; Wang, X.; Ning, Z.; Li, X. Hypoxia induces hypomethylation of the HMGB1 promoter via the MAPK/DNMT1/HMGB1 pathway in cardiac progenitor cells. Acta Biochim. Et Biophys. Sin. 2018, 50, 1121–1130.
46. He, M.; Zhang, B.; Wei, X.; Wang, Z.; Fan, B.; Du, P.; Zhang, Y.; Jian, W.; Chen, L.; Wang, L. HDAC 4/5-HMGB 1 signalling mediated by NADPH oxidase activity contributes to cerebral ischaemia/reperfusion injury. J. Cell. Mol. Med. 2013, 17, 531–542.
47. Yang, Y.; Huang, J.-Q.; Zhang, X.; Shen, L.-F. MiR-129-2 functions as a tumor suppressor in glioma cells by targeting HMGB1 and is down-regulated by DNA methylation. Mol. Cell. Biochem. 2015, 404, 229–239.
48. Alam, R.; Abdolmaleky, H.M.; Zhou, J.R. Microbiome, inflammation, epigenetic alterations, and mental diseases. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 2017, 174, 651–660.
49. Karthikeyan, A.; Patnala, R.; PJadhav, S.; Eng-Ang, L.; Thameem Dheen, S. MicroRNAs: Key players in microglia and astrocyte mediated inflammation in CNS pathologies. Curr. Med. Chem. 2016, 23, 3528–3546.
50. Han, V.X.; Patel, S.; Jones, H.F.; Dale, R.C. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat. Rev. Neurol. 2021, 17, 564–579.
51. Toker, L.; Mancarci, B.O.; Tripathy, S.; Pavlidis, P. Transcriptomic evidence for alterations in astrocytes and parvalbumin interneurons in subjects with bipolar disorder and schizophrenia. Biol. Psychiatry 2018, 84, 787–796.
52. Bellesi, M.; Melone, M.; Gubbini, A.; Battistacci, S.; Conti, F. GLT-1 upregulation impairs prepulse inhibition of the startle reflex in adult rats. Glia 2009, 57, 703–713.
53. Torres-Berrío, A.; Lopez, J.P.; Bagot, R.C.; Nouel, D.; Dal Bo, G.; Cuesta, S.; Zhu, L.; Manitt, C.; Eng, C.; Cooper, H.M. DCC confers susceptibility to depression-like behaviors in humans and mice and is regulated by miR-218. Biol. Psychiatry 2017, 81, 306–315.
54. Torres-Berrío, A.; Nouel, D.; Cuesta, S.; Parise, E.M.; Restrepo-Lozano, J.M.; Larochelle, P.; Nestler, E.J.; Flores, C. MiR-218: A molecular switch and potential biomarker of susceptibility to stress. Mol. Psychiatry 2020, 25, 951–964.

55. Chong, J.R.; Chai, Y.L.; Lee, J.H.; Howlett, D.; Attems, J.; Ballard, C.G.; Aarsland, D.; Francis, P.T.; Chen, C.P.; Lai, M.K. Increased transforming growth factor β2 in the neocortex of Alzheimer's disease and dementia with lewy bodies is correlated with disease severity and soluble Aβ 42 load. J. Alzheimer's Dis. 2017, 56, 157–166.

56. Gast, H.; Gordic, S.; Petrzilka, S.; Lopez, M.; Müller, A.; Gietl, A.; Hock, C.; Birchler, T.; Fontana, A. Transforming growth factor-β inhibits the expression of clock genes. Ann. N. Y. Acad. Sci. 2012, 1261, 79–87.

57. Noguchi, A.; Nawa, M.; Aiso, S.; Okamoto, K.; Matsuoka, M. Transforming growth factor β2 level is elevated in neurons of Alzheimer's disease brains. Int. J. Neurosci. 2010, 120, 168–175.

58. Hashimoto, Y.; Chiba, T.; Yamada, M.; Nawa, M.; Kanekura, K.; Suzuki, H.; Terashita, K.; Aiso, S.; Nishimoto, I.; Matsuoka, M. Transforming growth factor β2 is a neuronal death-inducing ligand for amyloid-β precursor protein. Mol. Cell. Biol. 2005, 25, 9304–9317.

59. Pajarillo, E.; Rizor, A.; Lee, J.; Aschner, M.; Lee, E. The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: Potential targets for neurotherapeutics. Neuropharmacology 2019, 161, 107559.

60. Da Rosa, M.I.; Simon, C.; Grande, A.J.; Barichello, T.; Oses, J.P.; Quevedo, J. Serum S100B in manic bipolar disorder patients: Systematic review and meta-analysis. J. Affect. Disord. 2016, 206, 210–215.

61. Baecker, J.; Wartchow, K.; Sehm, T.; Ghoochani, A.; Buchfelder, M.; Kleindienst, A. Treatment with the neurotrophic protein S100B increases synaptogenesis after traumatic brain injury. J. Neurotrauma 2020, 37, 1097–1107.

62. Montoya, A.; Elgueta, D.; Campos, J.; Chovar, O.; Falcón, P.; Matus, S.; Alfaro, I.; Bono, M.R.; Pacheco, R. Dopamine receptor D3 signalling in astrocytes promotes neuroinflammation. J. Neuroinflammation 2019, 16, 258.

63. Melka, M.G.; Castellani, C.A.; Laufer, B.I.; Rajakumar, N.; O'Reilly, R.; Singh, S.M. Olanzapine induced DNA methylation changes support the dopamine hypothesis of psychosis. J. Mol. Psychiatry 2013, 1, 19.

64. Bergen, S.; O'dushlaine, C.; Ripke, S.; Lee, P.; Ruderfer, D.; Akterin, S.; Moran, J.; Chambert, K.; Handsaker, R.; Backlund, L. Genome-wide association study in a Swedish population yields support for greater CNV and MHC involvement in schizophrenia compared with bipolar disorder. Mol. Psychiatry 2012, 17, 880–886.

65. Yue, W.-H.; Wang, H.-F.; Sun, L.-D.; Tang, F.-L.; Liu, Z.-H.; Zhang, H.-X.; Li, W.-Q.; Zhang, Y.-L.; Zhang, Y.; Ma, C.-C. Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11. 2. Nat. Genet. 2011, 43, 1228–1231.

66. Sekar, A.; Bialas, A.R.; de Rivera, H.; Davis, A.; Hammond, T.R.; Kamitaki, N.; Tooley, K.; Presumey, J.; Baum, M.; van Doren, V. Schizophrenia risk from complex variation of complement component 4. Nature 2016, 530, 177–183.

67. Windrem, M.S.; Osipovitch, M.; Liu, Z.; Bates, J.; Chandler-Militello, D.; Zou, L.; Munir, J.; Schanz, S.; McCoy, K.; Miller, R.H. Human iPSC glial mouse chimeras reveal glial contributions to schizophrenia. Cell Stem Cell 2017, 21, 195–208.e196.

68. Mallya, A.P.; Wang, H.-D.; Lee HN, R.; Deutch, A.Y. Microglial pruning of synapses in the prefrontal cortex during adolescence. Cereb. Cortex 2019, 29, 1634–1643.

69. Inta, D.; Lang, U.E.; Borgwardt, S.; Meyer-Lindenberg, A.; Gass, P. Microglia activation and schizophrenia: Lessons from the effects of minocycline on postnatal neurogenesis, neuronal survival and synaptic pruning. Schizophr. Bull. 2017, 43, 493–496.

70. Sellgren, C.M.; Gracias, J.; Watmuff, B.; Biag, J.D.; Thanos, J.M.; Whittredge, P.B.; Fu, T.; Worringer, K.; Brown, H.E.; Wang, J. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. Nat. Neurosci. 2019, 22, 374–385.

71. Chaudhry, I.B.; Hallak, J.; Husain, N.; Minhas, F.; Stirling, J.; Richardson, P.; Dursun, S.; Dunn, G.; Deakin, B. Minocycline benefits negative symptoms in early schizophrenia: A randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J. Psychopharmacol. 2012, 26, 1185–1193.

72. Levkovitz, Y.; Mendlovich, S.; Riwkes, S.; Braw, Y.; Levkovitch-Verbin, H.; Gal, G.; Fennig, S.; Treves, I.; Kron, S. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J. Clin. Psychiatry 2009, 70, 4863.

73. Laskaris, L.; Zalesky, A.; Weickert, C.S.; di Biase, M.A.; Chana, G.; Baune, B.T.; Bousman, C.; Nelson, B.; McGorry, P.; Everall, I. Investigation of peripheral complement factors across stages of psychosis. Schizophr. Res. 2019, 204, 30–37.

74. Reginia, A.; Kucharska-Mazur, J.; Jabłoński, M.; Budkowska, M.; Dołęgowska, B.; Sagan, L.; Misiak, B.; Ratajczak, M.Z.; Rybakowski, J.K.; Samochowiec, J. Assessment of complement cascade components in patients with bipolar disorder. Front. Psychiatry 2018, 9, 614.

75. Akcan, U.; Karabulut, S.; Küçükali, C.İ.; Çakır, S.; Tüzün, E. Bipolar disorder patients display reduced serum complement levels and elevated peripheral blood complement expression levels. Acta Neuropsychiatr. 2018, 30, 70–78.

76. Van Dongen, J.; Zilhão, N.R.; Sugden, K.; Heijmans, B.T.; AC't Hoen, P.; van Meurs, J.; Isaacs, A.; Jansen, R.; Franke, L.; Boomsma, D.I. Epigenome-wide association study of attention-deficit/hyperactivity disorder symptoms in adults. Biol. Psychiatry 2019, 86, 599–607.

77. Schirwani, S.; McConnell, V.; Willoughby, J.; Study, D.; Balasubramanian, M. Exploring the association between SRPX2 variants and neurodevelopment: How causal is it? Gene 2019, 685,

50–54.

78. Cong, Q.; Soteros, B.M.; Wollet, M.; Kim, J.H.; Sia, G.-M. The endogenous neuronal complement inhibitor SRPX2 protects against complement-mediated synapse elimination during development. Nat. Neurosci. 2020, 23, 1067–1078.
79. Øster, B.; Linnet, L.; Christensen, L.L.; Thorsen, K.; Ongen, H.; Dermitzakis, E.T.; Sandoval, J.; Moran, S.; Esteller, M.; Hansen, T.F. Non-CpG island promoter hypomethylation and miR-149 regulate the expression of SRPX2 in colorectal cancer. Int. J. Cancer 2013, 132, 2303–2315.
80. Orlic-Milacic, M.; Kaufman, L.; Mikhailov, A.; Cheung, A.Y.; Mahmood, H.; Ellis, J.; Gianakopoulos, P.J.; Minassian, B.A.; Vincent, J.B. Over-expression of either MECP2_e1 or MECP2_e2 in neuronally differentiated cells results in different patterns of gene expression. PLoS ONE 2014, 9, e91742.
81. Cahoy, J.D.; Emery, B.; Kaushal, A.; Foo, L.C.; Zamanian, J.L.; Christopherson, K.S.; Xing, Y.; Lubischer, J.L.; Krieg, P.A.; Krupenko, S.A. A transcriptome database for astrocytes, neurons, and oligodendrocytes: A new resource for understanding brain development and function. J. Neurosci. 2008, 28, 264–278.
82. Pantazatos, S.P.; Huang, Y.; Rosoklija, G.B.; Dwork, A.J.; Arango, V.; Mann, J.J. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: Evidence for altered glial, endothelial and ATPase activity. Mol. Psychiatry 2017, 22, 760–773.
83. Nagy, C.; Suderman, M.; Yang, J.; Szyf, M.; Mechawar, N.; Ernst, C.; Turecki, G. Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. Mol. Psychiatry 2015, 20, 320–328.
84. Fachim, H.A.; Loureiro, C.M.; Corsi-Zuelli, F.; Shuhama, R.; Louzada-Junior, P.; Menezes, P.R.; Dalton, C.F.; Del-Ben, C.M.; Reynolds, G.P. GRIN2B promoter methylation deficits in early-onset schizophrenia and its association with cognitive function. Epigenomics 2019, 11, 401–410.
85. Yang, Y.; Cui, Y.; Sang, K.; Dong, Y.; Ni, Z.; Ma, S.; Hu, H. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature 2018, 554, 317–322.
86. Liu, W.-X.; Wang, J.; Xie, Z.-M.; Xu, N.; Zhang, G.-F.; Jia, M.; Zhou, Z.-Q.; Hashimoto, K.; Yang, J.-J. Regulation of glutamate transporter 1 via BDNF-TrkB signaling plays a role in the anti-apoptotic and antidepressant effects of ketamine in chronic unpredictable stress model of depression. Psychopharmacology 2016, 233, 405–415.
87. Ju, L.-S.; Yang, J.-J.; Lei, L.; Xia, J.-Y.; Luo, D.; Ji, M.-H.; Martynyuk, A.E.; Yang, J.-J. The combination of long-term ketamine and extinction training contributes to fear erasure by Bdnf methylation. Front. Cell. Neurosci. 2017, 11, 100.
88. Holt, L.M.; Hernandez, R.D.; Pacheco, N.L.; Torres Ceja, B.; Hossain, M.; Olsen, M.L. Astrocyte morphogenesis is dependent on BDNF signaling via astrocytic TrkB. T1. Elife 2019, 8, e44667.

89. Zhang, H.; Ding, L.; Shen, T.; Peng, D. HMGB1 involved in stress-induced depression and its neuroinflammatory priming role: A systematic review. Gen. Psychiatry 2019, 32, e100084.
90. Kreisel, T.; Frank, M.; Licht, T.; Reshef, R.; Ben-Menachem-Zidon, O.; Baratta, M.; Maier, S.; Yirmiya, R. Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis. Mol. Psychiatry 2014, 19, 699–709.
91. Wu, C.; Zhang, X.; Chen, P.; Ruan, X.; Liu, W.; Li, Y.; Sun, C.; Hou, L.; Yin, B.; Qiang, B. MicroRNA-129 modulates neuronal migration by targeting Fmr1 in the developing mouse cortex. Cell Death Dis. 2019, 10, 287.