

Review

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[Maya Nahi Abou Chahla](#) *

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Review

The Interplay Between Suicidal Behavior and Mental Disorders: Focus on the Role of Glial Cells

Maya N Abou Chahla

Lebanese International University, Faculty of Biological Sciences, Lebanon; maya.aboushahla@liu.edu.lb
(M.N.A.C.); Tel.: +961-70609487 (M.N.A.C.)

Abstract: Glial cells have shown to possess vital and surprising roles in the brain rather than just being silent supportive cells to neurons. Different glial populations of the central nervous system in involved brain regions play various functions, express different proteins and result in fluctuating effects when altered. Glial cells pathologies were detected in most mental disorders including suicidal behavior. Suicidal behavior represents a health problem of high importance worldwide where protective measures are required to be taken at many levels. Studies on patients with mental disorders that represent risk factors for suicidal behavior, revealed multiple changes in the glia at diverse levels including variations regarding the expressed glial markers. This review summarizes the role of glia in some psychiatric disorders and highlights the crosslink between changes at the level of glial cells and development of suicidal behavior in patients with an underlying psychiatric condition; In addition, the interplay and interconnection between suicidal behavior and other mental diseases will spot the light on the routes of personalized therapy involving glial-related drugs.

Keywords: glial cells; glial pathology; suicidal behavior; glial markers; mental disorders

1. Introduction

Glial cells (glia) or “glue” cells are numerous non-electrical/non-neuronal cells in the brain (33–66% of brain mass). They are found in the central nervous system (CNS) and the peripheral nervous system (PNS). Those in the CNS (neocortex) are represented by three major lineages as follows: astrocytes, microglia, oligodendrocytes and their progenitors NG2-glia [1]. Glial cells of the PNS include satellite glial cells (SGCs), enteric glial cells, myelinating and non-myelinating schwann cells [2], [3]. Glial cells have a wide array of functions with variations between CNS and PNS [2]. Glial cells represent half of the total CNS cells; and they outnumber neurons with region-specific variations sometimes. The proper use of cell or stage specific molecular markers (Table 1) that usually have variable sensitivity and specificity determines differentiation, functional diversification and fate specification of glia [4], [5]. Each of these cells play its own roles and secrete its own factors and gliotransmitters. The main functions played by glial cells are regulatory roles [6], crucial roles involving the synapses, and they participate in the control of the neural processes in the CNS and PNS [7], [8], [9]. The neurophysiological mechanisms performed by glial cells include synaptic remodeling, neuronal development, neuropathic pain [10]. They also represent a vital metabolic and structural component of the nervous system [11]. Glial cell populations were meant to support and sustain neuronal cells initially [12]; However, these cells now are being reconsidered for having critical roles underlying a healthy or diseased brain. They contribute to neuroinflammation, neuropathic pain, CNS damage and neurodegeneration [12], [13]. Moreover, glial cells are involved in maintaining neuronal health and regulating brain function and activity by mutual interaction with the neurons. Modern tools helped in investigating the role of glial cells in healthy and diseased brain [14]. Regulation of neuronal activity occurs by tripartite synapses (receptors, transporters, ion channels) and glio-transmission. Maturation of neural development necessitates synapse formation and synapse pruning referred to consolidation of neural wiring.

Some features in glial cells facilitate their interaction with neurons in early stages of brain development. Synaptic patterning is also involved [15]. The hallmark of various psychiatric diseases is the synaptic dysfunction.

Suicidal behavior (SB) is a very complex behavior and a multifactorial phenomenon with multiple aspects [16], [17]. SB has several phenotypes starting from suicidal ideation, suicide attempts and suicide. These phenotypes are complex and involve many risk factors. Suicide is considered as a leading cause of death globally by WHO. Novel knowledge about SB is recently provided by advancements in metabolic, transcriptomics and proteomic studies performed in post-mortem brains and blood of individuals with SB; In addition to data from systems biology *in silico* to decipher the key mechanisms and involved markers underlying this behavior. Research indicated the involution of alterations in neuroplasticity, immune responses, energy homeostasis, neurotransmission (glutamatergic and GABAergic systems) and pathways associated with glial cells (mainly microglia and astrocytes). In other words the neurobiology of suicide is related to noradrenergic and HPA axis hyperactivity, glutamatergic, dopaminergic and GABAergic, serotonergic systems dysfunction, microgliosis, signaling failure, and glial cells abnormalities [18]. Moreover, concentrating on the balance between excitatory and inhibitory synapses and pathways associated with psychiatric disorders is very key for understanding SB. Further mechanisms such as gliogenesis, cortical connection formation, and mRNA splicing associated transcriptional factors need to be further studied to fill the missing gaps leading to SB [19].

2. Glial Cells

2.1. Glial Cells Functions

Astrocytes, oligodendrocytes and microglia (Figure 1) are the major cells in the CNS involved in defense against invasion, maintaining brain homeostasis and stress [20]. Each of these glial cells play a specific role and provide a metabolic support for neurons. The neurophysiological processes regulated by glial cells include neuropathic pain, neuronal development and synaptic remodeling [10]. In other words, glia are involved in regulating blood flow and metabolism, modulating synapse formation, functionality and elimination, and in producing myelin [5]. CNS glial cells seem to participate in brain functions and development [11]. Glial cells support and interact with neurons and shape neuronal circuits as well. Out of the three populations available in the CNS, astrocytes are the most abundant group located among synapses and blood vessels and implicated in the maintenance of homeostatic and metabolic functions, involved in synapse formation, plasticity and transmission, and astrocyte-conditioned media contains variable excitatory and inhibitory synaptogenic features depending on the involved brain region. They also maintain an ideal milieu for an appropriate neuronal function and maintenance of blood brain barrier. Astrocytes also conserve water balance in the CNS, due to the presence of aquaporin AQP4. Besides, they regulate and represent the main controllers of K^+ homeostasis which plays a critical role in neuronal activity [14], [21]. Moreover, astrocytes are involved in the maintenance of glutamate/GABA balance in the CNS [22]. On the other hand, the microglia enter the CNS during embryogenesis; they are yolk-sac derived cells of mesodermal origin and are highly active and possess the repopulation capacity [1], [23]. During brain injury, microglia undergo the mechanism of self-defense for being the brain resident innate immune cells [24]. In addition, they are involved in phagocytosis, impact synaptic functions and elimination, and very vital for a proper neuronal activity [14]. The cells that control the neuronal axons diameter affecting and sculpting their electrical and structural properties are the oligodendrocytes (NG2 glia is their precursor cell). They play a myelinating role in the white matter of the CNS to insure a saltatory conduction or action potential propagation against the axons and provide axons with trophic support [25], [26], express the glutamine synthetase (GS) enzyme and involved in the excitatory glutamatergic transmission in the CNS as well. They connect with the astrocytes via connexins gap junctions (GJs) in the panglial syncytium, which serves a necessary function especially regarding long-distance siphoning of K^+ ions from the paranodal peri-axonal

space to the cerebrospinal fluid or the blood vessels. Like astrocytes, they maintain K^+ homeostasis as well [14], [25]. Oligodendrocytes progenitor cells (OPCs), identified as NG2-glia, contribute to CNS function and dysfunction too. They play a crucial role in brain plasticity, by modulating neurotransmission and interacting with neurons and other glia. It has been reported through clinical studies that NG2-glia are involved in responding to stress, and their role in stress-related psychiatric diseases is still disputable. Studies also showed that early life adversity causes long-lasting changes in NG2-glia [27].

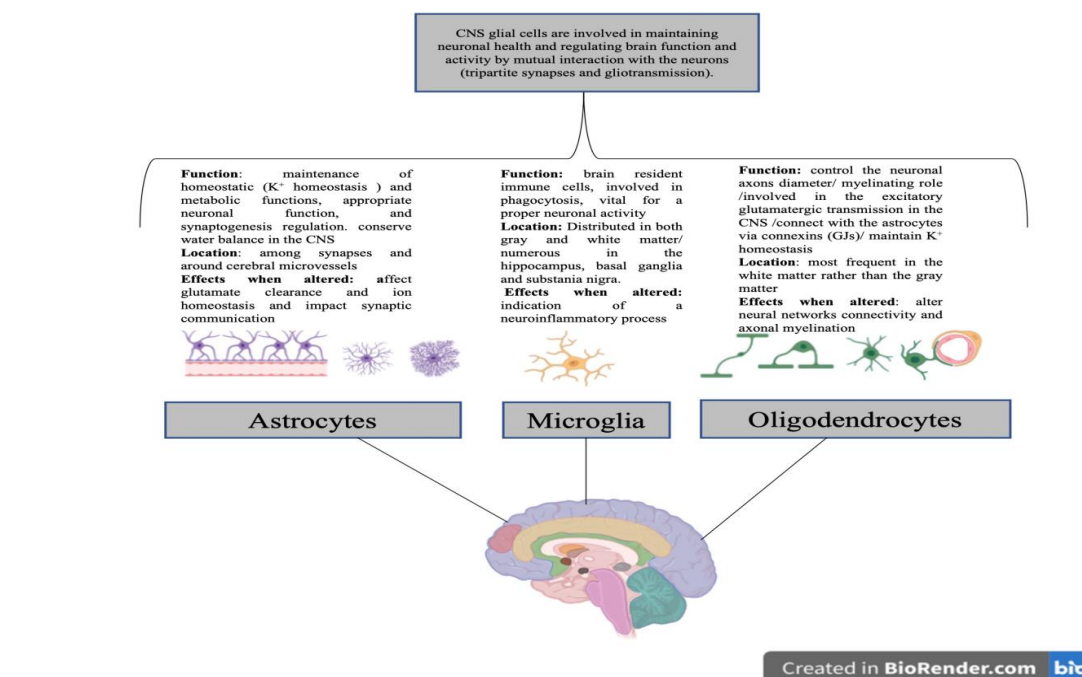


Figure 1. CNS glial cells: General Overview (Created in BioRender.Com (Accessed on 15 December 2024).

2.2. Glia-Pathologies: Markers Involved

Recently, knowledge about glial cells in health and disease have increased incredibly. According to “gliocentric theory”, alterations and abnormalities in glial cells are responsible of the pathophysiology of mental disorders. But the question to be resolved is how these abnormalities develop and their impact on cognitive and emotional disturbances [28]. Brain pathologies, especially neurodegenerative diseases (NDs), revealed progressive dysfunction in glial cells and damaged neurons. Genes expressed in glial cells were mutated in patients with NDs. These genes include: apolipoprotein E (*APOE*), cluster of differentiation 33 (*CD33*), glucosylceramidase Beta 1 (*GBA1*) and granulin precursor (*GRN*), and triggering receptor of myeloid cells 2 (*TREM2*) [29]. Spatial and temporal heterogeneity of glial cells leading to glia-mediated neurodegeneration were reported in NDs. Involved pathways also described the roles of α -synuclein (α -syn), G-protein-coupled receptors (GPCRs), pattern recognition receptors (PRRs), toll-like receptors (TLRs), NOD-like receptors and glial extracellular vesicles [30] in pathological conditions [29]. Three main brain regions depict alterations in glial cell functions; the limbic areas (hippocampus (HC) included), the prefrontal cortex and the amygdala. Progressive plasticity in the amygdala and regressive plasticity in both prefrontal cortex and HC are results of failure in adopting to the varying neurophysiology as a response to stress [22]. The unique protein composition of glial cells implies their diverse roles, and these compositions vary according to activity or disease condition [5].

Glial cells play essential roles in brain’s reaction to disease or injury [23]. For instance, astrocytes response to diseases (also known as astrogliosis) is common in several brain injury and diseases. Astrogliosis combined with the extracellular matrix form what is known as the glial scar that in some context has a prejudicial effect on neural repair and regeneration. In the CNS, one oligodendrocyte is

able to contact and myelinate many axons at a time. This intimate interaction between axons and oligodendrocytes can be disrupted by injury or disease, a condition known as dys-myelination (or demyelination). Demyelination is a result of autoimmune, metabolic, genetic hypoxic-ischemic or mechanical insults. This could lead to the loss of axonal support and thus result in permanent loss, disability and degeneration of axons. Moreover, the microglia after injury undergo dramatic changes in protein expression and shape to protect the brain and release cytokines and phagocytose dead cells and debris. They also strip dysfunctional synapses. The loss of microglial main role and behavior can result in behavioral deficits and impaired learning-dependent synaptic plasticity [5]. In brief, dysfunctional astrocytes affect glutamate clearance and ion homeostasis and impact synaptic communication. Dysfunctional oligodendrocytes alter neural networks connectivity; And hyperactivation of microglial is an indication of a neuroinflammatory process [28]. Furthermore, a study has likewise indicated the significant role of N6-methyladenosine (m6A), an epitranscriptomic modification, in glial cells of the mammalian brains that affects the cells functions by regulating gene expression patterns thus resulting in the development of neurological diseases [31]. The understanding of which abnormality leads to which, and the sequence of events and the main cause of abnormalities will draw the unique and intersecting pathways between mental disorders.

Table 1. Glial Biomarkers of the CNS.

Glial Cells	Markers Expressed	Brain Region	Brain/Mental Disorders	Reference
Astrocytes	- S100B - MAO-B - GFAP - ALDH1L1 - Acyl-CoA Synthetase Bubblegum Family Member 1 (ACSBG1) - Nuclear factor 1A-type (NFIA) - SOX9 - Glutamate transporter 1 (GLT-1 or EAAT2/SLC1A2) - Glutamate-aspartate transporter (GLAST or EAAT1/SLCA3)	- Prefrontal cortex - amygdala - Hippocampus - Cerebral cortex - White matter of cerebellum	- Schizophrenia - MDD - Alzheimer's disease - Amyotrophic Lateral Sclerosis (ALS)	[4], [23], [32], [33]

	- Glutamine synthase (GS) - Fatty acid binding protein 7 (FABP7) - Aldolase C (ALDOC) - Aquaporin 4 (AQP4) - Zinc Finger And BTB Domain Containing 20 (ZBTB20) - Brain lipid binding protein (BLBP)			
Microglia	- Ionized calcium binding adaptor 1 (IBA1) - CX3CR1 - Cluster of Differentiation (CD68) - P2RY12 - Beta-hexosaminidase subunit beta (HEXB) - CD206 - Integrin alpha M (ITGAM/CD11b) - CD45 - Transmembrane protein 119 (TMEM119) - IBA1	- Hippocampus - Basal ganglia - Substantia nigra - Olfactory telencephalon	- Schizophrenia - MDD - Suicidal Behavior - Alzheimer's disease - Parkinson's disease - Amyotrophic Lateral Sclerosis (ALS) - CNS tumors	[4], [32]

	- Surface glycoprotein F4/80 - Apolipoprotein E (ApoE) - TREM2 - Osteopontin (Spp1) - Cystatin 7 (CST7) - Translocator protein (TSPO)			
Oligodendrocytes	- Transcription factor SOX10 - OLIG2 - Platelet-derived growth factor receptor alpha (PDGFRA) - NG2 - NK2 Homeobox 2 (NKX2.2) - Crenarchaeal Chromatin Protein 1 (CC1) - Myelin Regulatory Factor (MYRF) - Myelin proteins (MOG, MAG, MBP) - Monoclonal antibody O4 - TMEM10 (Opalin) - PLP - Aspartoacylase (ASPA)	- Gray matter of cerebral cortex - White matter (Corpus callosum)	- Schizophrenia - Bipolar disorder - Major depression disorder	[4], [32]

	- Carbonic anhydrase 2 (CA II)			
Ependymal Cells	- Monoclonal antibody (RC1) - BLBP	- Line the ventricles of the brain	- Depression - Anxiety	[5]

3. Glial Cells and SB

The precise role of glial-associated mechanisms and processes in the pathophysiology of disease still poorly understood and requires further investigations by applying and implementing new methods and diverse study groups [34]. Glial cells association to SB was based on morphological changes, postmortem brain gene expression, cytokines and neurotrophic factors [20]. Suicide represents a major health issue gradually rising worldwide and is considered as an independent disorder with a unique genetic-molecular background [35], [36], [37]. In humans, a subcortical brain region called the hippocampus- part of the limbic-cortical-hypothalamic circuit- is rich with glucocorticoid receptors and is very sensitive to stress seems to be implicated in the pathophysiology of suicide. Suicidal samples show a smaller HC accompanied with histopathological changes by neuroimaging studies, with anatomical and functional differences in the hippocampal subregions [35].

The pathophysiology of suicide is mainly caused by disruption of serotonergic functions - serotonin deficiency- in the dorsal raphe nucleus (DRN); the DRN itself is composed of several important subregions, and is implicated in sending serotonergic projections to other locations such as the HC, thalamus, frontal cortex, nucleus accumbens, striatum, habenular complex and lateral septal nuclei [38]. Further evidence for the role of glial cells, especially microglia, in suicide was revealed through the analysis of the cerebrospinal fluid and serum/plasma of patients, in addition to positron emission tomography (PET) imaging and postmortem studies. Most studies involving SB demonstrated its association with alteration in cytokines levels- mainly interleukin (IL)-6- released by microglia (IL-2, IL-6, IL-8, vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF)- α [38]. Collective studies also revealed that astrocytes-related suicides are associated with abnormalities and changes in methylation, transcription and protein content. For instance, the major marker for astrocytes glial fibrillary acidic protein (*GFAP*), showed a reduced transcription in caudate nucleus, mediodorsal thalamic nucleus (MD), locus ceruleus (LC) and dorsolateral prefrontal cortex

(DLPFC) by real time polymerase chain reaction (PCR) unlike in the cerebral cortex (Cb), primary visual cortex (PVC), and primary motor cortex (PMC) [20]. Only in suicides, the prefrontal cortical GFAP (sp4005) protein was identified indicating the higher phosphorylation state might be implicated in the pathophysiology of SB. Other astrocytic markers with decreased transcriptional levels in the DLPFC include S100 calcium-binding proteins B (S100B), Aldehyde dehydrogenase 1 family member L1 (ALDH1L1), glutamate-ammonia ligase (GLUL), SRY-Box Transcription Factor 9 (SOX9) and solute-carrier family 1 member 3 (SLC1A3) [20]. Besides, about eight post-mortem studies on the brains of suicide victims revealed morphological changes (increased cell density) in microglial, supporting the relationship between SB and dysregulation of microglial, and in most cases, independent of a psychiatric illness [17].

4. Suicidal Behavior and Mental Disorders

Studies about mental diseases and their interconnected basis have increased in the last decade. Different groups with different variables showed multiple and complex variations and repetition is needed to confirm results, indeed. It is also interesting here to understand the behavior of glial cells and their expression profiles under different circumstances or triggers. Mental disorders represent a high-risk factor for the predisposition of SB. SB phenotypes and severity vary from one patient to another based on the underlying psychiatric state or illness [39].

Brain gene expression profiling of individuals who died of suicide but with dual diagnosis (co-occurrence of one or more mental disorder or one substance-use disorder in an individual) was distinct from those of suicide with a single disorder highlighting the presence of common disrupted pathways [40]. Most mental disorders or diseases have a tight connection with inflammation/neuroinflammation. Yet, the mechanisms underlying the full image of inflammatory dysfunction is not fully elucidated. The possible pivotal player is the microglial dysfunction which when over-activated in response to neuroinflammation, secretes proinflammatory cytokines excessively modifying the glutamate signaling and the kynurenine pathway. This overactivation of microglia leads to consequent glutamate release as a result of increased astrocytic activity; This is toxic to the CNS. Moreover, the change in the products of the kynurenine pathway (as a result of excessive microglial activation) will in turn impact the serotonergic, glutamatergic and dopaminergic signaling pathways (Figure 2) [41].

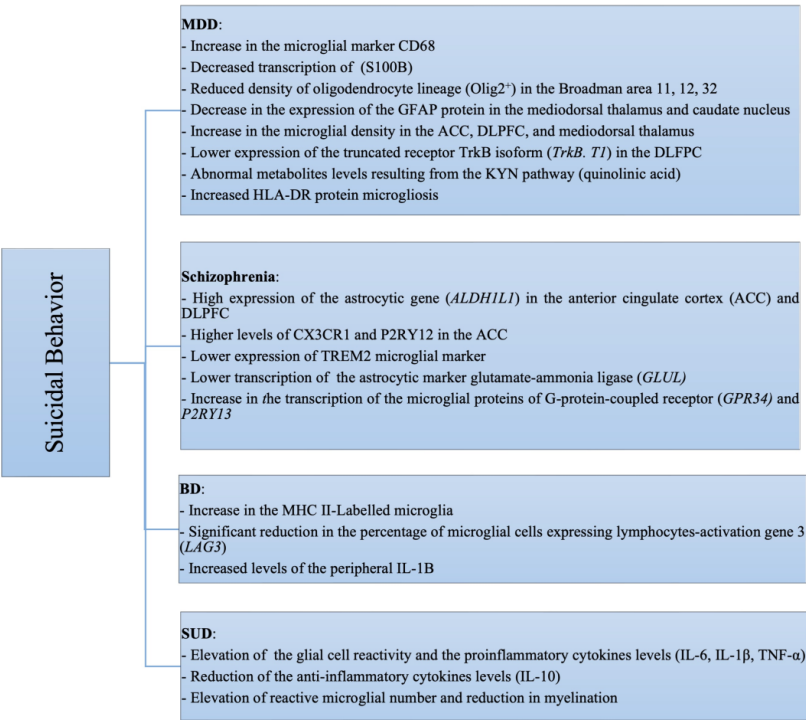


Figure 2. Recent data about alterations linking SB to some mental disorders.

4.1. SB and Major Depressive Disorder (MDD)

MDD is a common mental disease (reported in about 350 million individuals) in which the patient suffers from permeant low mood and related-changes in biological functions, thoughts and behavior. MDD patients reveal dysregulation in HPA axis, cardiac autonomic regulation and immune system; Still, MDD pathogenesis and precise etiology are partially understood [42].

Studies confirmed a relationship between different types of mental disorder affected by alterations in glial gene expression and differ with different brain regions [43]; and in MDD patients brain studies, reports showed significant reduction in glial numbers in the ventromedial PFC and amygdala [28]. Another study involving 17 glial related genes in the DLPFC have shown an increase in the microglial marker CD68 in patients with MDD and died of suicide compared to controls. Other genes transcripts such as the myelin basic protein (MBP) mRNA in the DLPFC were increased with MDD patients experiencing psychotic features but not suicide [44]. Postmortem investigations in MDD suicide completers showed a decreased transcription of S100 calcium-binding protein B (S100B) in their prefrontal cortex. This marker is specifically expressed by protoplasmic astrocytes located in gray matter (and found in myelinating oligodendrocytes in the white matter) that exhibit special morphological patterns. Another study of depressed suicide samples with child abuse history reported a reduced density of oligodendrocyte lineage (Olig2⁺) in the Broadman area (BA) 11, BA12 and BA32 in comparison to controls, that is associated with an increased density of mature oligodendrocytes (Adenomatous Polyposis Coli protein (APC⁺) and Reticulon-4 (Nogo⁺)) indicating a shift into a more mature phenotype of OL lineage.

Depressed suicides PFC showed that the mRNA expression for some astrocyte-related genes (including the astrocytic GFAP), was importantly decreased and the methylation associated with those genes was also decreased. Another study revealed that the mediodorsal thalamus and caudate nucleus experience a significant decrease in the expression of the GFAP protein and the mRNA unlike the primary motor, cerebral or visual cortex of depressed suicide subjects [45]. In addition, compared to controls, suicidal patients with depression showed an increase in the microglial density in the ACC, DLPFC, and mediodorsal thalamus. This was also confirmed by another study that reported an increase in the microglial density in the white matter of the PFC for the same type of patients. Samples from depressed suicidal patients also showed an increase in the primed microglial cells in the white matter of the dorsal ACC [38]. Repeated stress exposure of patients with MDD can cause microglial inflammation or even SB. In comparison to controls, depressed suicides showed a lower expression of the truncated receptor TrkB isoform (*TrkB. T1*) in the DLPFC and frontal eye field (FEF) [20], [46]. Several studies also focused on the role of the Monoamine oxidase (MAO) and the severity of MDD and other neuro- and mental pathologies. *MAO-B* is expressed by the fibrous white matter astrocytes and cortical astrocytes in the frontal, temporal and occipital lobes. This gene is closely related to disorders such as MDD and its knockdown can lead from mild to aggressive behavioral changes that might lead to suicide; but further investigation of this gene's expression profiles is required, particularly for *MAO-B*, to better understand its role in brain disorders [47], [48], [49], [50], [51], [52].

Glial alterations can lead to defective information processing in the PFC in addition to emotional and cognitive disturbances as seen in MDD patients. This causes loss of interest and impaired decision making and tendency to SB; Similar results are reported in patients with reduction in hippocampal neurogenesis [22]. Glial cells can also affect the kynurenine (KYN) pathway in the CNS. Abnormal metabolites levels resulting from the KYN pathway (quinolinic acid) were recorded in the HC of suicidal depressed patients which showed a decrease when compared to healthy control subjects [38]. The hippocampal subregions of the individual with MDD who died of suicide, showed that more neurons but fewer astrocytes exits in the *Cornu Ammonis* (CA) 2/3 subareas of HC, and fewer granular neurons but more glia with larger nuclei were found in the dentate gyrus (DG) indicating a functionally distinct role of the basic circuits of HC in suicidal development [35]. Furthermore, studies showed an increased HLA-DR protein microgliosis in suicide patients with

MDD. Few other studies involving the DLPFC and ACC of suicide patients with MDD reported no variation in the transcription of the microglial markers (major histocompatibility complex, class II, DR- α (*HLA-DRA*), *CD68*, Integrin alpha M (*ITGAM*), chemokine receptor (*CX3CR1*), and Allograft inflammatory factor 1 (*AIF1*)), oligodendrocytes proteins (Myelin oligodendrocyte glycoprotein (*MOG*), Proteolipid protein (*PLP*) and Oligodendrocyte transcription factor (*OLIG2*) and the astrocytic marker (*ALDH1L1*) [20].

4.2. SB and Schizophrenia

Samples from schizophrenic patients also shown to have suicidal-related differences and a heterogeneity in glial gene alterations through post-mortem RNA-sequencing of transcriptional profiles in the DLPFC examination. Results of studies revealed a high expression of the astrocytic gene (*ALDH1L1*), an astrocytic marker in the anterior cingulate cortex (ACC) and DLPFC in schizophrenic patients who died by suicide in comparison to controls. On the other hand, the following microglial markers – *CX3CR1* and purinergic receptor (*P2RY12*)- in the ACC were higher in schizophrenic suicidal patients compared to schizophrenic non-suicidal, unlike the triggering receptor expressed on myeloid cells 2 (*TREM2*) microglial marker whose expression was lower [34]. However, clinical findings on schizophrenic brains showed no change (normal) in glial cell numbers unlike other disorders [28].

Other research involving postmortem studies and PET scans showed discrepancies in the findings concerning microglial activation in schizophrenia due to the effect of comorbid factors such as suicidal tendencies [38]. In comparison to non-suicides, suicide patients with schizophrenia indicated an elevation of microglial markers (*TREM2*, *P2RY12*, and *CX3CR1*) in the ACC and a lower transcription of astrocytic markers (glutamate-ammonia ligase (*GLUL*) and *ALDH1L1*) in the DLPFC. Moreover, the MBP protein was decreased in the anterior PFC. Furthermore, the microglial density of HLA-DR protein was increased for the same category of patients in the following brain regions DLPFC, MD, ACC and HC. The transcription of the microglial proteins of G-protein-coupled receptor (*GPR34*), *P2RY12*, and *P2RY13* was also increased [20]. The pathogenesis of schizophrenia is also related to alterations in glial-cell derived neurotrophic factor (GDNF) and GFAP; Their serum levels in schizophrenic patients were lower than in healthy controls [53].

4.3. SB and Bipolar Disorder (BD)

BD is a psychiatric and behavioral condition characterized by functional disability, cognitive impairment and fluctuating mood states [54]. BD progression and pathophysiology involve several important brain mechanisms such as oxidative stress, abnormalities in both glutamatergic and monoaminergic neurotransmission, reductions in neurotrophins, mitochondrial dysfunctions and impairments in neuroplasticity. Remarkable reduction in glial cells density has been reported in BD patients in the ventromedial and dorsolateral PFC, and ACC [28]. Many Studies have revealed a link between suicidal behavior and bipolar disorder [54], [55]. It is estimated that in patients with BD, the risk of suicidal behavior increases 20-30 times in comparison to healthy controls; and BD represents the psychiatric condition with the highest frequency of SB. It is also indicated that in patients with such psychiatric disorders, the testosterone hormone (high or low) might have a contribution to suicidality as it seems to affect behavior and mood and regulate the pro-active and re-active aspects of aggression. Patients with BD have a reduced quality of life and experience manic and hypomanic episodes at least once. It is estimated that for men and women with BD, respectively, suicidal attempts are about 19% and 34% [56], [57]. Suicidal risk in BD patients increases with rapid cycling, the early onset of BD, and the presence of familial and genetic risk factors that differ between countries and regions [57].

On another level, a study revealed a well-recognized increase in the MHC II-Labelled microglia only and hippocampal microglial density (labeled by microglial specific marker *P2RY12*) as well compared to controls. Furthermore, there was a significant reduction in the percentage of microglial cells expressing lymphocytes-activation gene 3 (*LAG3*) in suicidal BD patients. This study also

confirms the absence of correlations between the density of activate microglia and *LAG3* expression levels [55]. In addition, the peripheral IL-1 β levels are increased in suicide BD patients compared with non-suicide BD patients. Besides, the deficiency of serotonin is one of the biological basis underlying BD. In addition, there is a role played by the activated glycogen synthase kinase-3 β (GSK-3 β) in the Wnt signaling pathway and the progression of BD. Moreover, microglia during neuroinflammation provide a link between those two pathways [54].

4.4. SB and Borderline Personality Disorder (BPD)

BPD represents a severe personality disorder with abnormal patterns of behavior and inner experience. BPD patients usually suffer from other coexisting mood or mental illnesses including MDD, BD, or substance use disorders (SUDs). Individuals with BPD are characterized by a wide range of behaviors including SB [58]. A study as detected that suicidal risk increase more in case of BPD than in patients with affective disorders. Among personality disorders, BPD is considered as the most suicidal. The suicidal tendencies in patients with BPD are due to the high reactivity of emotions with anxiety, tense relationships, episodic depression in addition to in impulsiveness in decision making. In 87% of the cases, suicidal attempts occurred suddenly without prior planning [59]; and 10% of BPD patients die by suicide after a mean of three-lifetime suicide attempts and a long course of unsuccessful treatment [60]. Further investigations are required at the molecular levels and glial markers alterations to assess the precise molecular link and variations between BPD suicidal and non-suicidal patients.

4.5. SB and Attention Deficit Hyperactivity Disorder (ADHD)

Inattention, hyperactivity and impulsivity are the main characteristics of ADHD which is a common neurodevelopmental disorder that disrupts the brain functioning. ADHD is diagnosed in males more than in females and estimated to have a stable rate of 7.2% over the past 40 years. Suicide and ADHD are significantly associated to each other in different age groups and in children [61]. The risk of SB increased in groups diagnosed with ADHD as some studies confirmed [62], [63], [64], [65], [66]. Studies have revealed that glial markers other than the S100B have differences in different groups of study. For instance, ADHD patients showed lower level of the toxic 3-hydroxykynurenine (3HK) [67]. Whereas patients with ADHD sensitive to allergy especially children, show also higher levels of IL-10 and IL-6 [62].

4.6. SB and Post-Traumatic Stress Disorder (PTSD)

PTSD patients are characterized by poor brain health [68]; it is a mental illness that results after a trauma caused by an incident leading to anxiety or physical damage (mental shock). In Adults, PTSD represents a risk factor of SB [69], [70]. Glial -mainly astrocytic- dysfunction in PTSD represents an emerging area of investigation [71]. According to studies, changes in glial activation were detected in PTSD patients, and PTSD is linked to neuroinflammation. The GFAP is released by the glial cells after reacting to stress and is considered as a putative biomarker of pro-glial activation. Moreover, it is postulated that GFAP distributions are associated with PTSD severity [68]. PTSD is associated with the unnatural cause of death, suicide [72], [73]. Based on reports, diseases in glia (Astrocytes and microglia) can cause structural, functional and behavioral changes related to PTSD. Furthermore, increased levels of inflammatory cytokine biomarkers (C-reactive protein, TNF- α , NF-k β , IL-1, and IL-6) were reported in PTSD patients in comparison to controls [74].

4.7. SB and Anxiety Disorders

Ascending evidence exists to confirm the association between suicide and anxiety but the precise role of anxiety in SB is not yet understood. And since SB is multifactorial, the patient must be evaluated at several levels including anxiety, personality, depression and others to assess his SB. Anxiety is a neuropsychiatric impairment that usually follows blast related traumatic brain injury

(bTBI). Two brain regions, the motor cortex and the HC play a critical role in the manifestation of anxiety. Glial pathological changes such as astrocyte pathology (GFAP) and dendritic alteration (microtubule-associated protein, MAP2) can contribute to anxiety [75].

4.8. SB and Substance Use Disorders (SUDs)

According to statistics, almost 40 million people are affected by SUD. Research reported that functional changes in the pathways that deal with self-control and stress response are usually affected by SUD or drug addiction; in addition, to brain circuits that control pleasure or rewards as well. Opioids (morphine) and psychostimulants (methamphetamine or cocaine) seem to elevate the glial cell reactivity and the proinflammatory cytokines levels as well (IL-6, IL-1 β , TNF- α). On the other hand, the levels of anti-inflammatory cytokines levels were reduced (IL-10). It has also been reported that SUD change the glutamate neurotransmission and metabolism by GLT-1 (Specific astrocytic glutamate transporter) and decrease astrocyte cell number, but elevate reactive microglial number and decrease myelination by impairing oligodendrocytes as well. These events represented by glial dysfunction affect the permeability of blood brain barrier (BBB), increase neurotoxicity and thus promote further addictive behavior [76].

According to various studies, SB and SUDs are substantially associated, and SUD is comorbid with various other psychiatric disorders and can result in suicide [76], [77], [78], [79]. Recent data confirms that 13.3 % of patients suffering from SUD seem to be associated with unplanned suicide. SUDs refer to the use of substance in an unhealthier pattern leading to significant life's impairment. Substances such as cannabis [80], heroin, alcohol, cocaine, methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), nicotine and methamphetamine are substances that have deleterious effect on suicide as well [81].

5. Conclusions

Suicidal behavior is a multifactorial independent mental disorder, as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, that demands huge attention and efforts worldwide to decrease its consequences on society. Understanding the role of glial cells and their interconnected missions in diverse psychiatric illnesses, will have an impact on the personalized methods of therapy and will pave and clarify the routes leading to SB. Astrocytes, microglia and oligodendrocytes with their diverse and different roles are separately considered a wide topic of huge impact on mental disorders and the pathological conditions in the brain. Glial pathologies differ in variable psychiatric disorders. Their differences have diverse effects on neurons. The discrepancies vary from the density of glial cells to the secreted markers and expressed proteins, to the affected brain regions. Different age groups diagnosed with SB and other psychiatric disorder have to be monitored to assess the initial trigger/s causing this disruption in the natural pathways and the initial understandable language between glia and neurons in a "healthy" brain. This complexity that surrounds the multiple combinations of events requires extensive research of wide and diverse groups of patients to better address the interplay between the SB and other psychiatric disorders at the level of alterations in the glial cells. It is also essential to navigate and map the interlocking and separate/unique pathways leading to mental disorders. What leads to what! and under which conditions the involved mechanisms are well-orchestrated or disrupted is a huge matter of interest and intricacy that remains a mysterious debate. This represents the key that requires a huge amount of research efforts to be unlocked. Advancement in artificial intelligence and technologies combined with social and medicinal interventions are promising in defining glial-related drug targets, and in predicting the possibility of occurrence of a specific mental disorder and/or SB, and also to map the unique or intersecting pathways among psychiatric disorders to pave possible effective and preventive measures at younger ages.

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