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# A narrative review of astrocytes and suicide in psychiatric disorders

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**Abstract.** Suicide is a real public health problem today, and in recent decades its possible neurobiological basis has been intensively studied. One particular strand of research has focused on suicide deaths and psychiatric disorders, with ample evidence for molecular mechanisms related to astrocytic abnormalities. The scope of the articles and their compilation over a period of many years has resulted in old, current and new knowledge being scattered across a large number of sources. The purpose of this narrative literature review is therefore to bring all this information together and summarize it in a single work that can be useful for those approaching this topic for the first time, for those looking for current evidence, and finally for those interested in exploring new frontiers of research. A comprehensive literature search has clearly shown that there are numerous converging findings indicating astrocyte changes in various biomarkers, particularly in the dorsolateral prefrontal cortex of suicidal individuals suffering from major depressive disorder. There is very little evidence for other brain regions and psychiatric disorders. Although these are preliminary results, they are encouraging and future studies could gradually overcome the limitations in the currently available literature and contribute to a better understanding of the etiopathological mechanisms of the occurrence of some of the main psychiatric pathologies leading to suicide.

**Keywords:** suicide, astrocytes, biomarkers, psychiatric disorders, major depressive disorder.

## LIST OF ABBREVIATIONS

ACC: anterior cingulate cortex
ALDH1L1: aldehyde dehydrogenase 1 family member L1
AQP4: aquaporin 4
CA: cornus ammonis
Cb: cerebellum
CN: caudate nucleus
CNR2: cannabinoid receptor 2
CRYAB: crystallin alpha B
DCN: dorsal caudate nucleus

dlPFC: dorsolateral prefrontal cortex
dvPFC: dorsoventral prefrontal cortex
EEAT1: excitatory amino acid transporter 1
EEAT2: excitatory amino acid transporter 1
GFAP: glial fibrillary acidic protein
GJA1: gap junction protein alpha 1 (also known as connexin 43 CX43)
GJB6: gap junction protein beta 6 (also known as connexin 30 CX30)
GLUL: glutamine synthetase (also known as glutamate-ammonia ligase)
GPR55: G protein-coupled receptor 55
GRIK2: glutamate ionotropic receptor kainate type subunit 2
H3K9me3: Histone 3 lysine 9 trimetylaition
HIPP: hippocampus
ICAM1: Intercellular Adhesion Molecule 1
LC: locus coeruleus
MD: mediodorsal thalamus
MDD: major depressive disorder
NEBL: nebulette
OFC: orbitofrontal cortex
PVRL3: poliovirus receptor-like 3 protein (also known as Nectin 3)
PVC: primary visual cortex
PMC: premotor cortex
ROPN1B: rhophilin associated tail protein 1B
S100b: S100 calcium binding protein B
SCZ: schizoprenia
SOX9: SRY-box transcription factor 9
TrkB.T1: truncated isoform of the receptor tyrosine receptor kinase B
VIM: vimentin

## 1. INTRODUCTION

Among the prevalent public health and social impact problems worldwide, suicide plays an extremely important role as one of the leading causes of death, accounting for approximately 800,000 deaths per year (Claveria, 2022). Globally, suicides are most commonly observed in men and adults, with incidence rates varying between population groups in different countries. In this context, the World Health Organisation gives a standardised suicide rate per age of 5.5 deaths per 100,000 inhabitants for Italy (WHO, 2019). Considering the impact that the phenomenon of suicide has at different levels (health, epidemiology, public health and economy), suicide prevention is one of the main priorities in the health sector. The World Health Organization (WHO) has also recognized the importance of this phenomenon and has identified suicide as one of the most important research topics for investigating the causes and identifying effective prevention measures (Tambuzzi et al., 2024). However, this is a challenging task, as suicide is a phenomenon with a multifactorial aetiology that varies even from country to country, although the most important risk factors include psychiatric illness, alcohol abuse, family dysfunctionality and childhood trauma, socioeconomic status and a previous suicide attempt (Turecki and Brent, 2016). However, of all the risk factors for suicide, psychiatric disorders are the most important, and the population with such disorders has a 10 to 30 times higher risk than the general population (Song et al., 2020). The most common psychiatric diagnoses associated with suicide include depressive syndromes, schizophrenic spectrum disorders and personality disorders. Of all these diagnoses, major depressive disorders have an increasing impact on the overall burden of disease and account for 65% to 90% of suicides (Tambuzzi et al., 2024).

In this general and multifaceted context, a number of studies have accumulated in recent decades that have brought to light the presence of organic-structural brain alterations in mentally ill individuals and those who have died by suicide, highlighting abnormalities in glial populations (astrocytes, microglia and oligodendrocytes) as a possible etiopathological role. In particular, possible correlations exist in postmortem gene expression in the brain, morphological changes, cytokines and neurotrophic factors that indicate an inflammatory response or altered neuroplasticity (Liu et al., 2022; Yamamoto et al., 2024). Of all glial cells, astrocytes are the most numerous and have the greatest influence on brain function. Having long been considered merely accessory cells, it has been shown to date that they play a much more important and complex role, performing diverse and complex neuronal functions such as: neuronal metabolism (Choi et al., 2012; Hall et al., 2014; Marina et al., 2020); regulation of synaptic function and neuronal plasticity (interaction with neurotransmitters) (Arizono et al., 2020; Corkrum et al., 2020); synaptic remodelling during early brain development (Chung et al., 2016; Koeppen et al., 2018); protection of neurons from toxic substances (role in blood-brain barrier and immune defence) (Correa et al., 2011; Bell et al., 2011); and response to pathological injury through a process known as reactive astrogliosis (Liddelow and Barres, 2017; Escartin et al., 2021). Therefore, astrocytes are known as particularly dynamic cells that, due to their multiple functions, are able to continuously regulate the physiology of the brain to meet the demands of neuronal activity in a timely manner. They are also able to respond with

functional and morphological changes to alterations in neurotransmitter systems, which play a role both in the pathophysiology of mood disorders (O'Leary and Mechawar, 2020) and in the therapeutic response to psychotropic and neuroprotective medications (Coyle and Schwarcz, 2000; Koyama, 2015). In particular, reduced expression of glutamate transporters has been found in people with depression, leading to a reduced ability of astrocytes to take up glutamate released by neurons at the synapse (Choudary et al., 2005; Bernard et al., 2011; Chandley et al., 2013; Medina et al., 2016). Thus, reduced astrocyte activity may contribute to dysfunction of the glutamatergic system, an essential mechanism for neuronal communication and synaptic plasticity (Miguel-Hidalgo et al., 2010; Parkin et al., 2018; Power and Sodhi, 2019). This may explain the correlation between altered astrocyte function and symptoms of major depression, a major cause of suicide (Rajkowska et al., 2013; Koyama, 2015). More in general, there has been evidence that astrocytic dysfunction can contribute also to the development of anxiety disorders and schizophrenia, which are other known risk factors for suicide (Rajkowska, 2000; Webster et al., 2001; Bowley et al., 2002; Webster et al., 2005; Altshuler et al., 2010; Kim et al., 2018). Over the years, however, it became apparent that a specific subpopulation of astrocytes expressing the glial fibrillary acidic protein (GFAP, the most important astrocyte marker) as a component of the intracellular intermediate filaments was altered (Lyck et al., 2008). In particular, Miguel-Hidalgo et al. were among the first to show that the density of immunoreactive (IR) GFAP astrocytes in the dorsolateral prefrontal cortex (dlPFC) of individuals suffering from major depression decreased in a positive correlation with age (Miguel-Hidalgo et al., 2000). In particular, in younger adults (30-45 years), the density of these astrocytes was below the minimum value of the range found in the healthy control group, in contrast to older depressed individuals (46-86 years). Si et al. further investigated these age-related changes in the dorsolateral prefrontal cortex and showed that the density of GFAP-IR atrocytes was significantly lower in depressed subjects under 60 years of age than in the healthy control population (Si et al., 2004). In addition, the density of GFAP-IR astrocytes was found to correlate with age at onset of depression. From this, the authors concluded that reduced GFAP levels may contribute to the pathophysiology of depression, particularly in relatively young people.

Precisely because of the importance of astrocytes in the overall function of the nervous system and their etiologic link to psychiatric disorders and suicide, research has focused mainly on them, with the result that old, current and new knowledge have accumulated and are scattered over many sources. Therefore, the aim of this narrative literature review is to summarize all this information specifically related to astrocytes in suicidal patients with psychiatric disorders in a single work that can be useful for those approaching this aspect for the first time, for those in search of insights, and finally for those interested in exploring new frontiers of research to find innovative approaches to prevent and protect the health of individual patients and the community as a whole.

## 2. MATERIAL AND METHODS

A literature search was conducted in the most common electronic databases (PubMed, Scopus, Medline, Google Scholar and Web of Science) up to October 15, 2024, in which the following combinations of text protocols "astrocytes" were combined individually and randomly with the Boolean operator "and": "suicide", "biomarker", "psychiatric disorder". Based on PubMed, the search for "astrocytes and suicide" yielded 125 articles. The combination "astrocytes and suicide and psychiatric disorder" yielded 50 articles. The addition of "biomarkers" reduced the number of articles. Of the total number, all articles dealing with the analysis of astrocytes in the postmortem brain of individuals who died by suicide and suffered from a psychiatric disorder were included. Therefore, all studies dealing only with suicide cases without psychiatric disorder were not the main focus of this review. All studies conducted on animals were excluded. The remaining databases were also reviewed, with duplicates removed. Overall, only English-language full-text articles were considered, with dated publications also included. Finally, all bibliographies of the selected articles were checked for further relevant articles.

## 3. RESULTS

The most important changes in the astrocyte population in the postmortem brain of suicidal patients with psychiatric disorders described in the literature so far are a lower astrocyte density and number, morphological alterations and changes in protein expression compared to control groups of healthy individuals. The majority of post-mortem studies on this topic had shown that in several regions of the prefrontal cortex of brains of individuals with depression and died by suicide, the density and number of different types of glial cells, especially astrocytes, had decreased (Yamamoto et al., 2024). In fact, Miguel-Hidalgo et al. reported a reduction in

glial packing density in the orbitofrontal cortex (OFC) in alcohol dependence (Miguel-Hidalgo et al., 2006). However, at the same time, Hercher et al. observed an increase of glial density in the anterior cingulate cortex (ACC) of suicide completers with alcohol dependence (Hercher et al., 2009). Furthermore, Torres-Platas et al. reported that cortical astrocytes positive for Golgi staining had significantly larger cell bodies and a greater number of nodes, an average number of branches, a total length of branches and a total number of spines, and more branching processes in the anterior cingulate cortex (ACC) of depressed suicides, suggesting a neuroinflammatory theory of depression and suicide (Torres-Platas et al., 2011). Finally, Hercher et al. pointed out that the spatial distribution of astrocytes in suicide victims with schizophrenia and bipolar disorder differed from that of the control group (Hercher et al., 2014).

### *3.1. Alterations in GFAP-IR astrocytes in suicide deceased and psychiatric disease*

The psychiatric condition that has been most studied in this context is major depressive disorder (MDD), since 2013, when Chandley et al. showed in a post-mortem study of the locus coeruleus (LC) of MDD patients that most decedents who died by suicide had a significantly lower density of GAFP-IR astrocytes than corresponding control subjects (Chandley et al., 2013). Later, Nagy et al. demonstrated that GFAP and its transcription were reduced in the dorsolateral prefrontal cortex (dlPFC; Nagy et al., 2015) of depressed suicidal patients (Table 1). Interestingly, Cobb et al. showed that there were a decrease in the density of GFAP-IR astrocytes in the hippocampus (HIPP) between patients with and without depressive suicide, and their density in certain areas (cornus ammonis – CA 2/3) was inversely correlated with the duration of depression and treatment in suicide victims (Cobb et al., 2016). Remarkably, it was significantly reduced only in depressed individuals not taking antidepressant medication, while this was not the case in depressed individuals receiving specific therapy (Table 1). Almost simultaneously, Torres-Platas et al. described a decrease in GFAP and its transcription in mediodorsal thalamus (MD) and caudate nucleus (CN) in the brains of depressed and suicide individuals and similar levels to healthy controls in primary visual cortex (PVC), premotor cortex (PMC) and cerebellum (Cb) (Torres-Platas et al., 2016; Table 1). Rajkowska et al. examined GFAP-IR astrocytes in the white matter adjacent to the dorsoventral prefrontal cortex (dvPFC) in individuals who suffered from depression and some of them died by suicide (Rajkowska et al., 2018). In these subjects, a reduction in the density and tissue coverage of GFAP-IR astrocytes was found, while the average size of the astrocytic bodies remained unchanged (Table 1). Even more recently, O'Leary et al. demonstrated by immunohistochemistry (IHC) that the density of GFAP-IR astrocyte subpopulations in the brain (dorsal caudate nucleus – DCN, dorsolateral prefrontal cortex – dlPFC, and mediodorsal thalamus – MD) of depressed individuals who died by suicide was statistically reduced compared to control groups of healthy individuals (O'Leary et al. 2021; Table 1).

With regard to other psychiatric disorders, changes in GFAP-IR atrocytes have been studied almost exclusively in postmortem brain tissue from individuals who did not die by suicide. For the purposes of this literature review, therefore, only the study by Zhang et al. must be considered, in which schizophrenia (SCZ) was assessed (Zhang et al., 2020). No changes in the mRNA concentration of GFAP in the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) between suicide and non-suicide patients with SCZ and their matched controls were reported (Table 1).

### *3.2. Alterations in other astrocytic markers in suicide deceased and psychiatric disease*

Since around 2010, another front of astrocyte research has been pursued with the aim of investigating regional variations in the distribution and morphology of astrocytes in the brains of suicidal and psychiatrically ill individuals. In fact, the GFAP protein identifies only part of the astrocytes and may only incompletely represent the astrocytic phenotype (O'Leary and Mechawar, 2020; Jurga at al., 2021). For this reason, other protein markers have also begun to be characterised.

The first to be studied in the postmortem brain of subjects with depression and suicide were glutamine synthetase (also known as glutamate-ammonia ligase, GLUL) and S100b (a calcium binding protein), whose mRNAs were examined by Klempan et al. only in the dorsolateral prefrontal cortex (dlPFC), with inconclusive results, as both not-statistically-significant increases and decreases were found (Klempan et al., 2009; Table 2).

The study of GLUL was later also taken up in two other articles (Nagy et al., 2015; Zhang et al., 2020). Nagy et al. examined the dorsolateral prefrontal cortex (dlPFC) in suicidal and depressed individuals and found a decrease in GLUL expression. On the other hand, Zhang et al. focused on the dorsolateral prefrontal cortex (dlPFC) of suicidal and schizophrenic individuals and reported a decrease in GLUL expression, that was not present in the anterior cingulate cortex (ACC) (very similar val-

**Table 1.** Astrocytic GFAP changes in suicide victims in relation to the psychiatric disorder they suffered from.

| Psychiatric disorder | Reference (year) | Astrocyte marker | Type | Brain areas | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | LC | dlPFC | HIPP | MD | CN | PVC | PMC | Cb | dvPFC | DCN | ACC |
| MDD | Chandley et al. (2013) | GFAP | Protein | ↓ | | | | | | | | | | |
| | | | mRNA | ↓ | | | | | | | | | | |
| | Nagy et al. (2015) | GFAP | mRNA | | ↓ | | | | | | | | | |
| | Cobb et. al. (2016) | GFAP | Protein | | | ↓ | | | | | | | | |
| | Torres-Platas et al. (2016) | GFAP | Protein | | | | ↓ | ↓ | » | » | » | | | |
| | | | mRNA | | | | ↓ | ↓ | » | » | » | | | |
| | Rajkowska et al. (2018) | GFAP | Protein | | | | | | | | | ↓ | | |
| | | | mRNA | | | | | | | | | ↓ | | |
| | O'Leary et al. (2021) | GFAP | IHC | | ↓ | | ↓ | | | | | | ↓ | |
| SCZ | Zhang et al. (2020) | GFAP | mRNA | | » | | | | | | | | | » |

ues compared to the control cases). The study of glutamate metabolism in relation to depression and suicide was further investigated by Zhao et al. (2016). The dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) were examined in young MDD patients who died by suicide, MDD patients who died from non-suicidal causes, and comparable control subjects. Components of the glutamate-glutamine cycle with astrocytic localization (GLUL and excitary aminoacid transporters, EAAT1 and EAAT2) were found to be decreased in the dorsolateral prefrontal cortex (dlPFC) of suicidal and depressed patients. EEAT1 (excitatory amino acid transporter 1) and EEAT2 (excitatory amino acid transporter 2) were further specifically studied by Chandley et al. in the locus coeruleus (LC) of suicidal and depressed subjects, showing a significant decrease (Chandley et al., 2013). A similar decrease in EEAT1 only was also demonstrated in the dorsolateral prefrontal cortex (dlPFC) by Nagy et al. (Nagy et al., 2015; Table 2).

On the other hand, S100b was examined in more detail by Zhang et al. in the brains of suicidal and depressed people with psychotic symptoms, who showed similar values to healthy controls in both dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) (Zhang et al., 2021; Table 2).

In chronological order, the new astrocytic marker studied was ICAM1 (Intercellular Adhesion Molecule 1) by Miguel-Hidalgo et al. which showed a decrease in orbitofrontal cortex (OFC) in suicidal and depressed individuals compared to control subjects (Miguel-Hidalgo et al., 2011; Table 2). Since then, no further studies have been conducted on this specific marker.

Subsequently, the GJA1 protein (gap junction protein alpha 1), also known connexin 43 (CX43), was examined in the orbitofrontal cortex (OFC) of the brain of suicidal individuals with depression and alcoholism, and no differences were found compared to healthy controls (Miguel-Hidalgo et al., 2014). The study of the GJA1 protein was not further developed in subsequent years; instead, mRNA analysis of this marker was preferred. Indeed, the mRNA levels of GJA1 were examined by Nagy et al. in the dorsolateral prefrontal cortex (dlPFC) of suicidal and depressed individuals, as well as GJB6 (gap junction protein beta 6, also known as connexin 30 – CX30), ALDH1L1 (aldehyde dehydrogenase 1 family member L1), and SOX9 (SRY-box transcription factor 9) (Nagy et al., 2015). A statistically significant decrease was demonstrated for all these markers compared to healthy controls (Table 2). GJA1 and GJB6 were further investigated by Nagy et al. in 2017, again in suicidal and depressed subjects, and showed a significant decrease in mRNA levels compared to controls in mediodorsal thalamus (MD), premotor cortex (PMC), primary visual cortex (PVC), and caudate nucleus (CN) (Nagy et al., 2017). In the cerebellum (Cb), however, a decrease in GJA1 was observed, while GJB6 increased. In 2019, Tanti et al. also examined GJB6 in suicidal and depressed subjects and demonstrated a significant decrease in mRNA levels compared to controls in the anterior cingulate cortex (ACC) (Tanti et al., 2019; Table 2).

More recently, the study of ALDH1L1 was also resumed in two articles on the brains of suicide people with schizophrenia (Zhang et al., 2020) and with depression (Zhang et al., 2021. It was found that ALDH1L1 was decreased in the dorsolateral prefrontal cortex (dlPFC) of suicidal and schizophrenic subjects, while there were no statistical differences in the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) of suicidal and depressed subjects compared to controls (Table 2).

The most recent area of research was conducted in 2021, when O'Leary et al. characterised another astro-

**Table 2.** Astrocytic changes in suicide victims in relation to the psychiatric disorder they suffered from.

| Psychiatric disorder | Reference (year) | Astrocyte marker | Type | Brain areas | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | dlPFC | ACC | LC | OFC | MD | PMC | PVC | CN | Cb |
| MDD | Klempan et al. (2009) | GLUL | mRNA | » | | | | | | | | |
| MDD | Nagy et al. (2015) | GLUL | mRNA | ↓ | | | | | | | | |
| SCZ | Zhang et al. (2020) | GLUL | mRNA | ↓ | » | | | | | | | |
| MDD | Zhao et al. (2016) | GLUL | Protein | ↓ | » | | | | | | | |
| MDD | Chandley et al. (2013) | EEAT1 | mRNA | | | ↓ | | | | | | |
| | | EEAT2 | mRNA | | | ↓ | | | | | | |
| MDD | Nagy et al. (2015) | EEAT1 | mRNA | ↓ | | | | | | | | |
| MDD | Zhao et al. (2016) | EEAT1 | mRNA | ↓ | » | | | | | | | |
| | | EEAT2 | mRNA | ↓ | » | | | | | | | |
| MDD | Klempan et al. (2009) | S100b | mRNA | » | | | | | | | | |
| MDD and psycothic symptons | Zhang et al. (2021) | S100b | mRNA | » | » | | | | | | | |
| MDD | Miguel-Hidalgo et al. (2011) | ICAM1 | IHC | | | | ↓ | | | | | |
| MDD and alcoholism | Miguel-Hidalgo et al. (2014) | GJA1 (CX43) | Protein | | | | » | | | | | |
| MDD | Nagy et al. (2015) | GJA1 (CX43) | mRNA | ↓ | | | | | | | | |
| MDD | Nagy et al. (2017) | GJA1 (CX43) | mRNA | | | | | ↓ | ↓ | ↓ | ↓ | ↓ |
| MDD | Nagy et al. (2015) | GJB6 (CX30) | mRNA | ↓ | | | | | | | | |
| MDD | Nagy et al. (2017) | GJB6 (CX30) | mRNA | | | | | ↓ | ↓ | ↓ | ↓ | |
| MDD | Tanti et al. (2019) | GJB6 (CX30) | mRNA | | ↓ | | | | | | | |
| MDD | Nagy et al. (2015) | SOX9 | mRNA | ↓ | | | | | | | | |
| MDD | Nagy et al. (2015) | ALDH1L1 | mRNA | ↓ | | | | | | | | |
| SCZ | Zhang et al. (2020) | ALDH1L1 | mRNA | ↓ | | | | | | | | |
| MDD | Zhang et al. (2021) | ALDH1L1 | mRNA | | » | | | | | | | |
| MDD | O'Leary et al. (2021) | VIM | IHC | ↓ | | | | ↓ | | | ↓ | |

cytic population using a new marker identified in vimentin (VIM), also a type III intermediate filament like GFAP (O'Leary et al., 2021). It had the additional advantage that it also highlights blood vessels and thus facilitated the identification of astrocytes. After an initial evaluation in healthy human brain tissue (O'Leary et al., 2020), this marker was used to further characterise astrocyte subpopulations in suicidal and depressed patients. In particular, it was demonstrated a statistically significant decrease of VIM-IR astrocytes in the dorsolateral prefrontal cortex (dlPFC), mediodorsal thalamus (MD), and caudate nucleus (CN) compared to healthy controls (Table 2). In view of the close connection between astrocytes and blood vessels, the density of the blood vessels was also examined in the same regions using the CD-31 marker. It was found that similar to GFAP-IR astrocytes, the density of VIM-IR astrocytes was also reduced in the brains of depressed suicide victims compared to control subjects. In contrast, the density of CD-31-positive blood vessels was similar between the two groups, except in the prefrontal white region, where vascularization was increased.

To date, astrocyte markers such as cannabinoid receptor 2 (CNR2; Garcia-Gutierrez et al., 2018), G protein-coupled receptor 55 (GPR55; Garcia-Gutierrez et al., 2018), crystallin alpha B (CRYAB; Ernst et al., 2011), truncated isoform of the receptor tyrosine receptor kinase B (TrkB.T1; Ernst et al., 2009), and aquaporin 4 (AQP4; Bernard et al., 2011; Rajkowska et al., 2013; Medina et al., 2016; Rosu et al., 2019; Genel et al., 2021) have not yet been studied in suicides of individuals who were affected by psychiatric disorders, but only in one of the two scenarios: patients with a psychiatric disorder not died by suicide or patients died by suicide but not

affected by any psychiatric disorders. Regarding AQP4 specifically, Medina et al. analysed a postmortem study group of 13 individuals affected by MDD, but only six of whom had died by suicide. Overall, a decrease in AQP4 mRNA expression was found in the hippocampus of the study subjects compared to the control group, but it is not possible to distinguish between those who died by suicide and those who did not (Medina et al., 2016).

Finally, for the sake of completeness, only one study is reported in which DNA methylation in the brains of suicidal and depressed individuals was investigated. The study conducted by Nagy et al. revealed a decrease in the methylation of the GRIK2 (glutamate ionotropic receptor kainate type subunit 2) and NEBL (nebulette) genes and an increase in the PVRL3 (poliovirus receptor-like 3 protein), also known as Nectin 3, and ROPN1B (rhophilin associated tail protein 1B) genes in the dorsolateral prefrontal cortex (dlPFC) compared to healthy subjects (Nagy et al., 2015).

There is also a single study in the literature on epigenetic silencing that shows an increased rate of silencing of the Histone 3 lysine 9 trimetylaition (H3K9me3), again in the dorsolateral prefrontal cortex (dlPFC) of suicidal and depressed individuals (Nagy et al., 2017).

## 4. DISCUSSIONS

In recent decades, much research has been conducted on suicide in general, and the study of the brains of suicide individuals has become increasingly important in determining possible organic causes of suicidal behaviour. In particular, the study of the postmortem neuroanatomy of the brains of individuals who have died by suicide continues to be of great interest due to the potential scientific implications that may arise (Yamamoto et al., 2024). Indeed, glial cells, particularly astrocytes, have been reported to be involved in suicide, although the pathological mechanism of glial activity and the risk of suicidal behaviour remain unclear. In this general context, another research focus has gradually been placed on the study of the neuroanatomy of the brain cells of people who died by suicide but were also affected by psychiatric disorders. The intensive research activity on this topic has led to many results being scattered in various publications. It was therefore considered useful to compile a review of the literature focusing specifically on the astrocytic changes described and reported to date.

It is clear, and on this point the literature agrees, that astrocyte populations in the brains of individuals suffering from psychiatric disorders who have died by suicide are characterised by changes in their density and number, with alterations in protein expression compared to control groups of healthy individuals. This has been particularly observed in major depression, a psychiatric disorder that has been by far the best studied to date (O'Leary and Mechawar, 2020). However, the overall picture became particularly complicated as research tried to investigate specific astrocyte subpopulations using specific markers in specific brain regions in different psychiatric pathologies. The results have been sometimes contradictory, but this is not surprising since, as clearly stated in the literature, any psychiatric disorder can be considered a confounding factor (Qi et al., 2019). It follows that although all studies that have contributed to this topic have been designed as case-control studies comparing suicide cases with psychiatric disorders with healthy control cases, each study person (i.e. with a psychiatric disorder) is an absolutely unique individual. In general, each person is difficult to categorise, and this is even more so when the main selection criteria concern psychiatric disorders and the suicide event. As mentioned above, suicide is a multifactorial event involving several aspects, and it is not yet known what influence neuroanatomy has on the ability to commit suicide, also because there is often a lack of appropriate case controls (Yamamoto et al., 2024). Furthermore, in all studies conducted, the degree of internal suffering of suicidal individuals was unknown, as was often the motivation. In most cases, information on the psychiatric illnesses from which the test subjects suffered was also missing. With a few exceptions, the duration and severity of the psychiatric illness were not known and, above all, any treatment the person was undergoing was not taken into account. And it is precisely here that the greatest limitation of all previous work in the literature on this topic (but also on suicide in general) becomes apparent, namely the little or no consideration of the role of the interaction of the individual's biology with the environment. Indeed, the literature shows that even the environment in the broadest sense, i.e. external exposure to air and water, the consumption of medicatons and stimulants (e.g. smoking, alcohol and illicit drugs) appears to make a non-negligible direct contribution to suicide (Tambuzzi et al., 2024). In addition, numerous environmental pollutants are considered neurotoxic due to their effects on brain cell plasticity and can cause the onset of psychiatric pathologies, which also indirectly contributes to suicide (Costa et al., 2017; Calderón-Garcidueñas et al., 2008; Jones and Miller, 2008; Munzel and Daiber, 2018). At the same time, it is obvious how difficult it can be to take all these variables into account in a single study.

Overall, it is very interesting, precisely because of the great inter-individual biological variability that characterises the suicide victims with a psychiatric disorder selected in the individual studies, that converging tendencies nevertheless emerge in this panorama. In addition to the general observations of reduced overall astrocyte density, significant results were obtained in the search for specific astrocyte markers, in particular GFAP. Over a period of about 20 years, almost all publications found that the population of GFAP-IR astrocytes was statistically reduced in the brains of individuals who had died by suicide and suffered from depression compared to healthy controls (Chandley et al., 2013; Nagy et al., 2015; Cobb et al., 2016; Torres-Platas et al., 2016; Rajkowska et al., 2018; O'Leary and Mechawar, 2020). This was demonstrated in several brain regions, but particularly in the dorsolateral prefrontal cortex (dlPFC) cortex, which was by far the most studied. This was also recently confirmed by O'Leary et al., not only in the dlPFC but also in the dorsal caudate nucleus (DCN) and mediodorsal thalamus (MD), confirming earlier observations that brain involvement is more extensive than it initially appeared (O'Leary et al., 2021). However, postmortem brain tissue from individuals with schizophrenia and bipolar disorder has also been shown to be affected, with a reduced number and density of GFAP-IR astrocytes, giving a picture of diffuse astrocytopathy (Webster et al., 2001; Altshuler et al., 2010). However, studies specifically focusing on suicide victims affected by psychiatric diseases other than depression are still lacking.

From all this it can be concluded that the presence of neuroanatomical changes in the number and density of GFAP-IR astrocytes in certain brain regions of persons with psychiatric disorder who have died by suicide has so far been documented quite solidly in the literature.

Equally interesting is the fact that the studies currently published in the literature seem to indicate that further changes in astrocyte biomarkers may occur in the brains of these individuals. In this overall picture, the most promising research fronts appear to lie in the analysis of the GLUL protein (Klempan et al. 2009; Nagy et al., 2015; Zhao et al., 2016; Zhang et al., 2020), ALDH1L1 (Nagy et al., 2015; Zhang et al., 2020, Zhang et al., 2021) and VIM (O'Leary et al., 2020; O'Leary et al., 2021). These are endocellular or membrane proteins that are directly involved in astrocyte metabolism in various ways and for which several studies have shown a statistically significant reduction in certain brain regions (again, mainly in the dorsolateral prefrontal cortex - dlPFC) of individuals who died by suicide and suffered from depression or in some cases even schizophrenia compared to healthy controls.

It is also of great importance that there are more recent confirmations for the above-mentioned proteins from studies after 2020, which prove the scientific significance of these results. As far as the other markers examined are concerned, the current results are still preliminary and in some cases cannot be clearly interpreted. Some of them, such as S100b and AQP4, have been studied more in the context of depression or suicide, but not yet sufficiently in situations where both variables coexist, i.e. suicide and psychiatric pathology. To date, there is also very limited evidence for studies of DNA methylation and gene silencing of astrocyte populations in the brains of suicidal and psychiatrically ill individuals.

Overall, it is clear that this is a ground-breaking field of research with very significant preliminary results. However, it also highlights the many limitations that currently exist. In particular, previous studies have only analysed European populations. In addition, brain regions have been discussed, such as the right or left hemisphere and white or grey matter, where astrocyte concentrations are known to differ (Pelvig et al., 2008; Verkhratsky et al., 2017; Forrest et al., 2023). Furthermore, the sample sizes were small, and the different methods and outcome measures used in the different studies may affect the reliability and accuracy of the results. In addition, as previously mentioned, the effects of medications and other medical therapies used in patients with psychiatric disorders on brain biology should be further discussed. Future research on this topic should take these aspects into account, and in particular it would be interesting to try to relate the data on drug therapy and exposure to possible toxic substances to those from neuroanatomical examination of the brain. The close relationship between astrocytes and the blood vessels of the brain, which form the blood-brain barrier, is well known (Kealy at al., 2020). It is therefore quite conceivable that when astrocyte density is reduced, as has already been described in the literature, defences against toxic substances of various kinds are less effective and brain cells, including the astrocytes themselves, are exposed to chronic stress, possibly leading to pathological changes and psychiatric disorders. Other variables not yet considered that should be investigated are the age and sex of the victims, the assessment of the post-mortem interval and whether the patient died during the day or at night, which could affect the markers of glial activation after death (Wruck and Adjaye, 2020; Cabrera-Mendoza et al., 2020; Yu et al., 2023).

Apart from these considerations, the fact that the researches have been conducted on postmortem human brain tissue is certainly a strength, as preclinical (ani-

mal) studies are of limited use in this particular area of research. Moreover, such an approach makes it possible to emphasise that, although often forgotten, much can be learned from the dead to contribute to the well-being of the living. And pursuing the goal of a better interpretation of suicide risk through a more careful assessment of suicide risk stratification, especially in special populations, is precisely one of these goals. Although these are still preliminary results, it is important that this line of research continues, as it could progressively contribute to a better understanding of the etiopathological mechanisms of the occurrence of some of the main psychiatric pathologies that lead to suicide. Moreover, it is possible that, based on this new knowledge, innovative therapeutic perspectives can be implemented, as well as new approaches to prevent and protect the health of individual patients and the community as a whole.

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