

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

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This is an interesting review on a topic not widely developed in the scientific literature but of great interest.

However, it lacks depth in the topic covered and is lost in collateral considerations. A complete revision of the review is needed.

- Both the introduction and chapter 2 are extremely confusing, repetitive, and do not address a clear need for this review. There are very good reviews on the essence of glial cells, their functions in the healthy brain, their physiological adaptive responses, and their reactions in different pre-pathological and pathological scenarios. In the introduction, it would be enough to mention their functions, and in chapter 2, glial responses in physiology and then in pathology in a generic way. I don't know why there is so much emphasis on pain (if it is important in suicidal behavior, it should be addressed later). Table 1 is meaningless. Glial cells are present in ALL regions of the CNS, and their dysfunction is present in ALL neurodegenerative diseases (not in 4) and in ALL (?) mental illnesses. It makes no sense to base the table on laboratory catalogs rather than on references for specific diseases.

The key, in general terms and later analyzed in chapters 3 and 4, is to show glial reactions. Gliosis is an ambiguous term but highly indicative of important changes, initially defensive and, if chronic, neurotoxic. Reactive changes (A1 and A2 as well as M1 and M2; pro-inflammatory and anti-inflammatory, respectively) are very important in the pathogenetic courses of brain diseases.

- The important chapters are 3 and 4. Table 2 should be moved (after revision) to the beginning of chapter 3. Each subchapter could contain a table showing the findings in the brains and blood samples studied (morphological gliosis/non-gliosis - increase/decrease in glial elements-, pro-inflammatory and/or anti-inflammatory phenotypic changes). Fig. 2 is illustrative (it should indicate what MDD, SUD, etc. are) but it should perhaps be expanded with more detailed tables for each subchapter. Figure 3 is not well designed: e.g., neuronal degeneration and glial dysfunction JOINTLY occur in neurodegenerative diseases. The genes are not solely glial, it is not indicated whether there is hyper- or hypo-gliosis/atrophy or only phenotypic changes, and which neuronal-neuroglial systems are affected. Table 2 is better specified but the references are poorly made (this table may be a summary of the tables I proposed above).

- - Perhaps it would be interesting to add a chapter on treatments to prevent suicide, both in general and those dedicated to regulating glial dysfunctions.
- - Other considerations: a) I consider Fig. 1 to be unnecessary: Furthermore, "location" does not reflect reality (i.e., among synapses (?); most frequent in the white matter (there exists different subsets), the brain colored regions are not explained b) "Glial cells exhibit multifaceted functions and represent essential contributors to various physiological ... demonstrated by recent research" Many decades. C) "Those in the CNS (neocortex) are represented by three major lineages as follows: astroglia, microglia, oligodendrocytes and their progenitors NG2-glia" = Those in the CNS are represented by three major lineages as follows: astroglia, microglia and oligodendroglia (including the OL-progenitors or NG2 cells)
- This reviewer does not like the designation of neuroglial cells as non-electrical/non-neuronal cells, although he is aware of its use by some authors. Many astroglial cells have close relationships with the electrical currents of the circuits and have ion channels that facilitate them (Bhoi R, Mitra T, Tejaswi K, Manoj V, Ghatak S. Role of Ion Channels in Alzheimer's Disease Pathophysiology. J Membr Biol. 2025 Jun;258(3):187-212. doi: 10.1007/s00232-025-00341-8). Astroglia and oligodendroglia are epithelial cells derived from glioblasts during development or in certain areas of the adult brain and microglia derive from mesodermal cells as well described by the author.