Mondal and Huse *Acta Neuropathologica Communications* (2025) 13:85
https://doi.org/10.1186/s40478-025-02009-9

Acta Neuropathologica Communications

REVIEW Open Access

Neurotransmitter power plays: the synaptic communication nexus shaping brain cancer

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Abstract
Gliomas and brain metastases are notorious for their dismal prognosis and low survival rates, a challenge exacerbated by our incomplete grasp of the complex dynamics that govern brain cancers. Recently, a groundbreaking paradigm shift has emerged, highlighting the crucial role of synaptic communication between neurons and brain tumor cells in reshaping neuronal signaling to favor tumor growth. This review delves into the pivotal interplay of synaptic mechanisms, focusing on excitatory glutamatergic and inhibitory GABAergic pathways. Glutamatergic synapses utilize glutamate to propagate excitatory signals, while GABAergic synapses employ gamma-aminobutyric acid (GABA) to inhibit neuronal firing. Glutamatergic signaling can be broadly classified into ionotropic (NMDAR, AMPAR and kainite receptors) and metabotropic subtypes. The harmonious orchestration of these synaptic types is essential for normal brain function, and their dysregulation is implicated in neurodegenerative disorders such as Alzheimer's disease and epilepsy. Emerging evidence reveals that glioma and brain metastatic cells exploit these synaptic pathways and neurotransmitters to enhance their proliferation and survival. In this review, we will first explore the intricate mechanisms underlying glutamatergic and GABAergic signaling. Next, we will summarize recent advancements in understanding how brain cancer cells hijack these pathways to their advantage. Finally, we will propose novel therapeutic strategies aimed at disrupting the aberrant neuron-tumor synaptic communication, offering potential treatment strategies for combating these otherwise incurable brain cancers.

Introduction

Glioma and brain metastasis pose significant challenges to neuro-oncologists due to their clinically intractable nature, aggressive phenotype, and the lack of effective therapeutic regimes for combating them. While gliomas are a diverse group of primary brain tumors arising from glial and/or neuroepithelial progenitors, brain metastasis represent secondary tumors that have homed to the brain from primary malignancies elsewhere in the body, most frequently originating from lung and breast carcinoma, along with malignant melanoma. Gliomas, particularly high-grade variants, are associated with significant mortality with over 15,000 deaths annually in the United States [1]. Brain metastasis are the most common type of intracranial tumors and about 10–26% of patients succumbing to systemic cancer harbor brain metastasis at time of death [2]. In the United States, about 98,000-170,000 cases of brain metastasis occur each year [2], arising in 9–10% of all cancer diagnoses [3]. Overall, brain and other central nervous system tumors are the most prevalent form of cancer in children and rank as the 10th leading cause of death among both adult men and women in the United States [4]. Beyond the poor

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prognosis associated with these tumors, affected patients often suffer from neuro-cognitive deficits and poor overall quality of life (QoL). These factors underscore the severe impact of brain cancer on patient outcomes, reflecting the challenges associated with treating gliomas and metastatic brain disease.

Despite extensive research, significant knowledge gaps remain regarding the precise mechanism(s) driving gliomas and brain metastasis. Emerging evidence of the dynamic interplay between the nervous system and brain cancer cells has evolved our understanding of cancer-neuronal crosstalk and how it shapes the tumor microenvironment. Cancer cells can effectively hijack neuronal signaling pathways to promote their growth and survival. It has been shown that glioma cells can influence synaptic activity and release neurotransmitters that alter the neuronal microenvironment, enhancing tumor invasiveness and proliferation and promoting resistance to therapy [5–7]. Cancer cells can also exploit the neuronal infrastructure for their benefit, utilizing neuronal-derived growth factors and signaling molecules to support their own proliferation and metastatic potential, while impairing cognition [8, 9].

Neurotransmitters are essential chemical mediators that facilitate communication between neurons and other cells within the nervous system. As such, they play an indispensable role in regulating a range of physiological functions, including mood, cognition, muscle control and other autonomic processes. Multiple recent studies have elucidated how neurotransmitters are associated with tumor cell growth and proliferation [31, 32]. A wide array of neurotransmitters have been implicated in cancer, including acetylcholine, glutamate, gamma-aminobutyric acid (GABA), dopamine, serotonin, norepinephrine, neuropeptides, such as substance P and neuropeptide NPY, adenosine triphosphate (ATP) and gases such as nitric oxide [33, 103].

The extent to which neuronal factors influence cancer outgrowth in the central nervous system (CNS) is increasingly recognized. Functional synapses between neurons and tumor cells have been identified in both gliomas and breast-to-brain metastases [10–12]. This phenomenon of "tumor synaptogenesis" enables cancer cells to integrate into existing neural networks, receiving synaptic input in the form of neurotransmitters that fuel their growth. Brain tumor cells express functional receptors for neurotransmitters, particularly glutamate, the most abundant excitatory neurotransmitter in the CNS [13]. Glutamatergic signaling between neurons and tumor cells appears to activate pathways driving tumor cell proliferation in both pediatric and adult high-grade gliomas [10, 11, 73]. Inhibitory GABAergic synapses have also been implicated in brain cancer. An emerging body of literature points to the role of GABA as a potent regulator of cancer cell proliferation and metastasis, beyond its established function as the primary inhibitory neurotransmitter in the mammalian CNS. Aberrant GABAergic signaling has been implicated in promoting tumor growth, invasion, stemness and metastasis in a variety of cancer types, ranging from colon and pancreatic cancer to lung and breast cancer [20–25]. By contrast, other studies have described a tumor-suppressive role of GABA [100, 101]. These discrepant results could reflect the diverse subunits of GABA receptors. Regardless, the role of GABAergic synapses in brain cancers, particularly brain metastasis, remains understudied and largely unexplored.

Given this rapidly evolving domain of neuro-oncology, this article will address recent literature supporting a functional role for glutamate and GABA neurotransmitters in brain cancer, including the phenomenon of glutamatergic and GABAergic synaptic transmission, already subjected to reviews elsewhere [31, 32, 72, 102]. Building on this exciting development, we will also detail relevant literature covering additional mechanisms by which glutamatergic and GABAergic signaling pathways influence primary and secondary brain tumor formation and propose potential therapeutic strategies to combat this varied pathobiology.

Messengers of chaos: glutamate and GABA neurotransmitters' role in regulating brain cancers

The glutamate neurotransmitter acts upon either the ionotropic NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainate receptors, or group 1–3 metabotropic receptors (mGluR1-mGluR8). NMDA receptors (NMDARs) are distinguished by their voltage-dependent activation, requiring both glutamate and glycine to initiate their function. They facilitate the passage of calcium (Ca^{2+}), sodium (Na^{+}), and potassium (K^{+}) ions, and are essential for synaptic plasticity and long-term potentiation (LTP), both critical processes for learning and memory. By contrast, AMPARs act more rapidly, mediating fast synaptic transmission by allowing Na^{+} and, to a lesser degree, Ca^{2+} to enter the cell. AMPARs are crucial for immediate glutamate response and regulating synaptic strength. Kainate receptors, though structurally similar to AMPARs, play distinct roles in modulating neurotransmitter release and regulating neuronal excitability. They contribute to both presynaptic and postsynaptic signaling, helping to fine-tune synaptic transmission and plasticity. Finally, mGluRs are a class of G-protein-coupled receptors that regulate intracellular signaling pathways, impacting key processes like neurotransmitter release, synaptic plasticity, and neuroprotection. Group I mGluRs are predominantly excitatory, activating phospholipase C to enhance cellular responses, while Groups II and III

typically exert inhibitory effects by reducing neurotransmitter release through the suppression of adenylate cyclase activity.

Multiple studies have demonstrated how glutamate regulates functionally relevant signaling cascades in brain cancer [37]. Elevated concentrations of glutamate in the extracellular space have been shown to drive tumor growth and proliferation in the context of glioblastoma (GBM) [34]. Additionally, NMDAR activation on human GBM cells appears to promote cell survival and migration, while antagonizing NMDARs increases radiosensitivity by impairing the repair capacity of DNA double-strand breaks (DSBs) [35]. AMPARs have been shown to be highly expressed on glioma cells and activated AMPARs evoke Ca^{2+} influx, triggering apoptosis [36]. AMPARs have also been found to be highly expressed in high-grade gliomas and silencing the GluR1 subunit of these receptors disrupts AMPA-driven signaling and suppresses glioma growth [74]. Ishiuchi et al. have demonstrated that malignant glioma cells release glutamate into the extracellular space, thereby activating Ca^{2+}-permeable AMPAR and Akt pathway signaling. This activation promotes glioma cell growth and enhances migratory capacity. Furthermore, blockage of Ca^{2+}-permeable AMPARs suppresses GBM migration and induces apoptosis [75]. Similarly, overexpression of GluR1 enhances β1 integrin expression on glioma cells and promotes perivascular and subependymal invasion [41]. Increased expression of mGluR3 has also been found to correlate with higher fatality rates in GBM patients while blocking mGluR1/3 appears to inhibit GBM proliferation [38]. Arcella et al. have shown that treatment with a mGluR2/3 antagonist reduces growth of GBM cells in vivo [40], and the mGluR5 receptor has also been demonstrated to increase glioma cell line proliferation under hypoxic conditions [13]. By contrast, mGluR4 appears to suppress tumor growth and induce apoptosis in GBM cells [39]. Taken together, these findings illustrate the complex, contrasting, and contextualized effects glutamatergic signaling pathways exert on brain cancer development.

GABA, the primary inhibitory neurotransmitter in the CNS, acts on two main receptor classes: GABAA and GABAB. GABAA receptors function as ligand-gated ionotropic receptors, while GABAB receptors are G protein-coupled and metabotropic. The presence of GABA receptor subunits has been widely reported in brain tumors, including glioma [27, 42, 93, 94] and medulloblastoma [45, 96, 97]. The observed effects of GABA of glioma specifically and brain tumors more broadly are notably heterogeneous, possibly reflecting the diversity of the GABA receptors and their subunits. Activated GABAA receptors have been shown to curb the proliferation of glioma cells, reducing tumor growth and increasing survival in vivo models. However, ionotropic activity driven by endogenous GABAA receptor signaling has also been found to sustain the quiescent state of a subset of tumor-initiating glioma stem-like cells, which are crucial contributors to tumor recurrence and resistance to therapy [42]. Other work has demonstrated that benzodiazepine induction of GABAA receptors inhibits the growth of neuroblastoma cells and induces apoptosis [43]. Similarly, targeting Myc-driven medulloblastoma with a α5-GABAA receptor agonist appears to decrease cell viability and sensitize to cisplatin and gamma irradiation [45]. By contrast, recent work has shown that propofol-induced activation of the signaling axis involving GABAAR-Src-ZDHHC5-EZH2 promotes glioma growth [44] and that upregulation of glutamate decarboxylase 1 (GAD1), which is a master regulator of the GABA neurotransmitter pathway, facilitates brain metastasis [46]. Interestingly, GABA secreted by B cells has also been shown to drive cytotoxic T cell and macrophage suppression, thereby creating an immunosuppressive tumor microenvironment. GABAergic signaling has also been demonstrated to regulate oncogenesis by modulating the cAMP, EGFR, AKT, MAPK/ERK, and MMP downstream oncogenic signaling pathways [25].

In the context of GBM, D'Urso et al. demonstrated that the microRNA miR-155 inhibits GABRA1 which in turn leads to increased tumor growth [26], while Smits et al. have demonstrated a positive correlation between expression of GABAA receptor ρ2 subunit and favorable outcome in diffuse astrocytoma [27]. Human breast cancer cells have also been shown to proliferate and metastasize to the brain by catabolizing GABA into succinate, thus utilizing GABA as an onco-metabolite. Also, the GABAA receptor, GABA transporter, GABA transaminase, parvalbumin, and reelin have all been found to be highly expressed in breast cancer metastases to the brain [28]. Finally, Dahn et al. has shown by metabolite profiling that upregulation of systemic GABA levels results in greater breast cancer brain metastasis [29]. It must be noted that while the GABAA receptor has 19 distinct subunits, the GABAB receptor has two subunits- GABAB1 and GABAB2. The dichotomous and disparate effects of GABA on tumorigenesis likely depend on which GABA receptor subunits are being activated, the downstream signaling pathways induced, the tumor type, and the origin of the tumor in question. It is crucial to assess the impact of various GABA receptor subunits on brain tumor growth and metastasis by conducting functional studies that involve selectively knocking down these GABA receptor subunits, either individually or in combination.

Takes Two to Tango: Forging of Glutamatergic and GABAergic synaptic contacts and neuronal activity promotes brain cancers

An emerging body of research has demonstrated the ability of cancer cells to effectively hijack synaptic communication between neurons to facilitate growth and proliferation. From utilizing secreted paracrine factors and neurotransmitters to mimicking neural cells themselves, brain cancers adopt a wide array of mechanisms to shape neuronal circuitry for survival advantage. Venkatesh et al. have demonstrated that neuronal activity and paracrine factors secreted by neurons like neuroligin-3 (NLGN3) and BDNF can drive glioma proliferation [47]. NLGN3 binding drives multiple oncogenic signaling pathways like the PI3K-mTOR, SRC and RAS pathways, while also upregulating the expression of synapse-associated genes in glioma cells and promoting neuron-to-glioma synapses [50]. Through analogous mechanisms, insulin-like growth factor-1 (IGF1) released by olfactory receptor neurons, also appears to promote glioma growth [48]. Pan et al. demonstrated that the germline neurofibromatosis 1 (NF1) mutation increases NLGN3 shedding within the optic nerve in response retinal neuronal activity, resulting in growth of NF1-associated optic pathway gliomas [49]. Glioma cells themselves have been shown to promote neuronal hyperexcitability and glioma-associated seizures by secreting synaptogenic factors like glypican-3 and thrombospondin-1 (TSP-1) [57], while also leveraging glutamate-mediated mechanisms through the xc-cystine-glutamate transporter system [58], which in turn drives glioma cell proliferation. Krishna et al. have shown that the high-grade glioma-mediated secretion of TSP-1 drives remodeling of functional neural circuits in the brain [9]. Taken together, these intriguing recent findings paint a picture of neuronal excitability and brain tumor growth existing in a mutually reinforcing, positive feedback loop.

Additionally, synapses facilitate the spread of tumor cells by allowing them to migrate along neuronal structures. The synapse-like connections between tumor cells and neurons enable the cancer cells to exploit the brain's highly interconnected architecture, spreading to distant regions more effectively. It has also been shown that glutamate release confers growth advantage of gliomas in the brain and activation of NMDARs facilitates tumor proliferation [14]. Furthermore, increased neuronal activity and hyperexcitability appears to promote glioma progression [15, 16]. For instance, Huang-Hobbs et al. have found that callosal projection neurons located in the hemisphere contralateral to primary GBM tumors promote cancer progression and infiltration. Brain-derived neurotrophic factors (BDNFs) and other growth factors released during synaptic activity have also been widely implicated in cancer progression, angiogenesis, and metastasis [17, 18].

Glioma cells enhance neuronal and peritumoral excitability and seizure susceptibility through multiple mechanisms, including the non-synaptic release of glutamate [51], depletion of GABAergic associated inhibitory interneurons [52], or secretion of synaptogenic factors like glypican-3 [53], further contributing to heightened neuronal activity. Interestingly, mutations in the PIK3CA oncogene have been shown to differentially regulate release of synaptogenic proteins, pointing to PI3K pathway activity as a potentiator of neuron-to-glioma signaling [60]. These disruptions collectively fuel tumor growth and create a hyperactive neural environment that supports glioma progression. Additionally, multiple studies have demonstrated in elaborate detail through electron microscopy and electrophysiology experiments the existence of bona fide glutamatergic synapse formation between neurons and glioma cells in both pediatric and adult high-grade gliomas [10, 11]. These neuron-to-glioma synapses appear to be regulated by calcium permeable AMPARs. Moreover, Venkataramani et al. [11] have shown that glutamatergic neuron-to-glioma synapses, through their impact on calcium signaling within tumor microtube-mediated cell networks, play a critical role in advancing brain tumors by promoting glioma invasion and accelerating tumor growth. Furthermore, these malignant glioma cells' glutamatergic AMPAR synapses are further strengthened by neuronal secretion of BDNF, while glutamate-evoked depolarizing currents promote glioma proliferation [59]. Glioblastoma cell functionality has been shown to rely on a population of cells that are characterized by rhythmic intercellular Ca^{2+} waves which activate oncogenic MAPK and NF-κB pathways, ultimately driving tumor growth [54]. Gliomas are also known to form an intricate network of gap junctional connectivity between themselves through ultra-long microtubular extensions, which helps them establish a malignant network in brain [55].

More recently, GABAergic synaptic activity has also been shown to facilitate glioma growth. Barron et al. have demonstrated the presence of tumor-promoting GABAergic neuron-to-glioma synapses mediated by GABAA receptors in diffuse midline gliomas (DMGs) [30]. These GABAergic synaptic inputs appear to have a depolarizing effect on DMGs due to expression of cation–chloride cotransporters, such as the Na-K-Cl cotransporter NKCC1, which subsequently leads to the increased intracellular chloride concentration in tumor cells. Membrane depolarization induced by this GABAergic signaling ultimately drives proliferation of DMG cells in vivo. Moreover, treatment with either the benzodiazepine lorazepam, a GABA signaling agonist, or levetiracetam, a GABAergic antagonist, increase or decrease

proliferation, respectively, in patient derived DMG xenografts. Finally, other recent work [56] has shown that the differentiation pattern of pediatric gliomas harboring H3G34 mutations, diffuse hemispheric gliomas (DHGs), bear close resemblance to the in situ spatial and phenotypic characteristics of early GABAergic interneuron development, pointing to potential therapeutic vulnerabilities targeting GABA signaling in this tumor type.

The effect of synaptic communication on brain metastasis remains to be elucidated in detail. Douglas Hanahan's group demonstrated for the first-time that glutamatergic NMDARs are significantly upregulated in brain metastatic patient samples and knocking down these receptors attenuates brain metastatic outgrowth [12]. This pathobiology appears to engage pseudo-tripartite synapses at glutamatergic terminals wherein glutamate released by neuron-neuron synapses is utilized by peri-synaptic breast cancer cells to fuel their own growth. Breast-to-brain metastases express elevated levels of the NMDAR subunit GluN2B, and exogenous NMDA or glutamate activates both single-channel currents and upregulates intracellular calcium transients in brain-metastatic tumor cells while ligand-stimulated NMDAR induces calcium influx in neurons, leading to phosphorylation of the transcription factor CREB (cAMP response element-binding protein) at Ser133 [12, 19]. Additionally, the suppression of GluN2B in breast to brain metastatic cells has been shown to reduce brain tumor burden and extend survival in mice, indicating that NMDAR synapses facilitate cancer cell proliferation within the brain. Interestingly, NMDAR subunit epsilon-2 (NR2b) expression has been found in multiple cancer types, including glioma [19].

Taken together, the dynamic and complex interplay between synaptic communication and brain cancer progression is a critical frontier in understanding how tumors thrive within the brain's complex microenvironment (Fig. 1). Glutamatergic and GABAergic synapses, through their influence on excitatory and inhibitory signaling, appear to play a central catalytic role in dictating the growth, invasion, and survival of brain tumors. Glioma cells exploit these pathways, forming connections with neurons, integrating into neural networks, and using synaptic and paracrine signaling to facilitate growth and proliferation. Emerging evidence suggests that brain metastasis from different primary organs co-opt similar mechanisms to hijack the neuronal signaling machinery.

Therapeutic implications for brain cancers: striking at the heart of synaptic communication and neuronal activity

The emerging field of cancer neuroscience and the developments described above have revealed promising therapeutic possibilities. We explore below some of the potential therapeutic regimes, based on interactions between cancer cells and CNS constituents, that could be used to combat gliomas and brain metastasis (Table 1).

Firstly, neuronal hyperexcitability has been widely reported to be a promoter of glioma and potentially brain metastasis as well. Accordingly, repurposing FDA-approved anti-epilepsy drugs (AEDs) towards the treatment of brain cancers represents an intriguing strategy. This class of drugs impairs neuronal hyperexcitability, downregulating voltage gated calcium channels (VGCC) and synaptogenesis. Both broad spectrum AEDs such as levetiracetam (Keppra) and valproic acid (Depakote), and narrow-spectrum AEDs such as gabapentin (Neurontin) and phenytoin (Dilantin) could be evaluated for anti-brain cancer benefits, as could the recent FDA approved cannabinoid Epidiolex, the N-type VGCC inhibitor, Phα1β and its recombinant form CTK 01512-2, which have already shown efficacy in preventing glioma progression [68]. Valproate combined with whole brain radiotherapy was demonstrated to significantly improve the median overall survival in patients with breast cancer brain metastasis [104], and an early valproic acid regimen demonstrably improved overall survival in mice xenografted with breast cancer brain metastatic cells [99].

Second, studies have revealed that glioma and neuronal networks communicate through gap junctions. Gap-junction inhibitors have been shown to be effective anti-convulsants and are well tolerated in patients with migraines [61]. Interestingly, tonabersat, a gap-junction modulator, has shown therapeutic efficacy for GBM when combined with radiotherapy and temozolomide [62]. Such findings point to a potential therapeutic benefit of commonly used gap junction blockers such as Quinine, Anandamide, Mefloquine, Oleamide, and Carbenoxolone among others, either alone or in combination with radiotherapy/chemotherapy. Glutamate transport (GluTs) inhibitors like threo-beta-benzyloxyaspartate (TBOA) could be similarly tested.

Third, increased synaptogenesis is a widely observed feature of brain cancers. This raises the possibility of blocking synapse formation to aid cancer therapy. Neuroligin, a post-synaptic adhesion molecule which binds pre-synaptic neurexin, has been demonstrated to be pivotal in regulating both GABAergic and glutamatergic synaptogenesis [63], synaptic adhesion, and regulating pre-synaptic formation [64]. It would be prudent to evaluate the effect of inhibiting the entire family of neuroligins (NLGN1, NLGN2, NLGN3, NLGN4X and NLGN5) and their pre-synaptic binding partner neurexins (NRXN1, NRXN2, and NRXN3). Moreover, the ADAM10 metalloprotease has been demonstrated to regulate neuroligin levels on the cell surface through cleavage from the postsynaptic membrane, specifically neuroligin-1 and neuroligin-3. Aclinical trial of ADAM10 inhibitor (INCB7839) to target neuron-glioma interactions in the

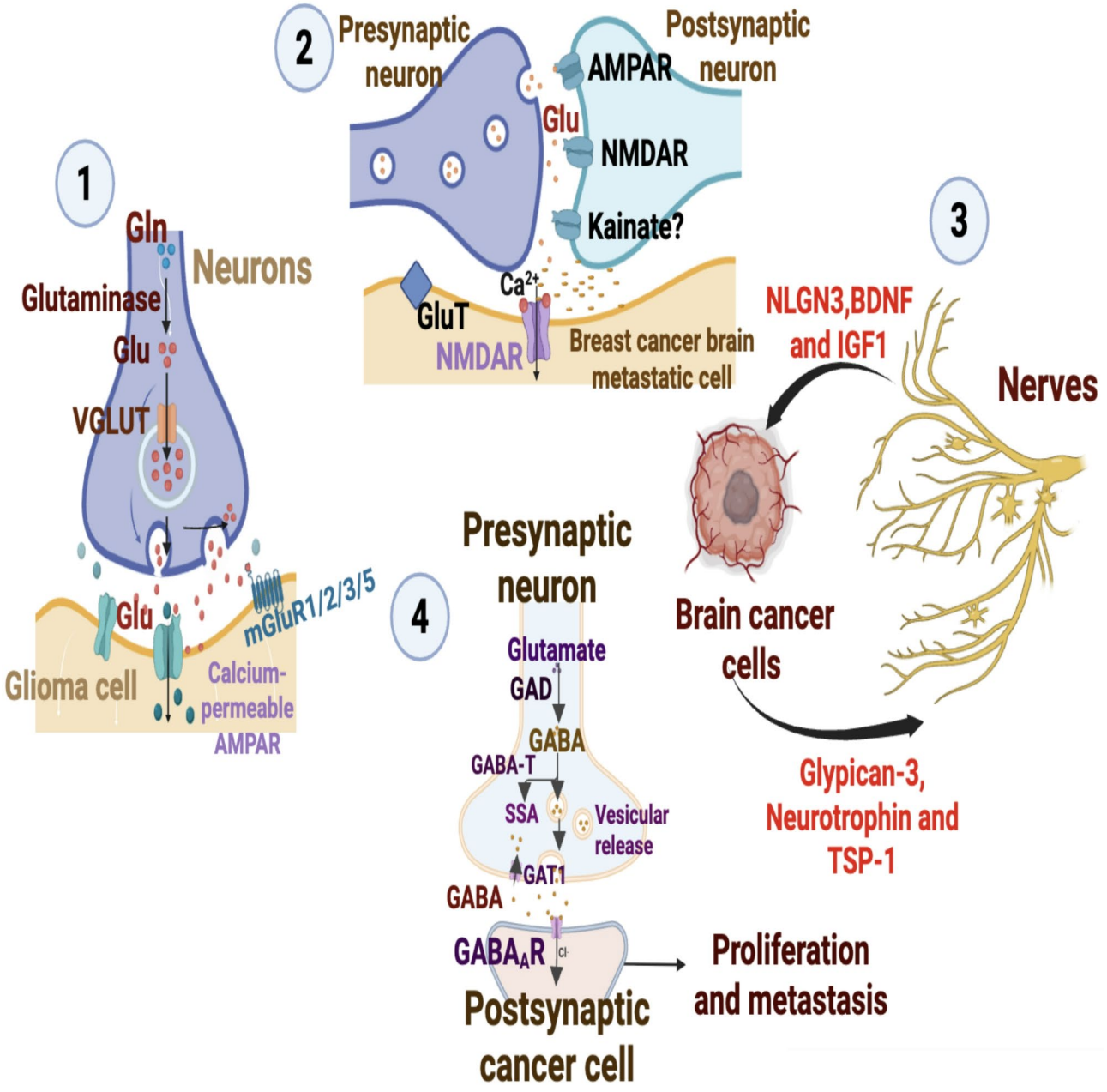

Fig. 1 Synaptic communication and neuronal activity promotes glioma and brain metastasis. (1) Direct synaptic communication between neurons and cancer cells dictates glioma proliferation. Glutamate released by the neurons are taken up by glioma cells with upregulated AMPAR expression. (2) Tripartite-like synapses between neurons and breast cancer brain metastatic cells have also been reported as an indirect method of neuronal-cancer cell communication. Glutamate released by the neurons is taken up the proximal breast cancer brain metastatic cells through an NMDAR mediated pathway, promoting metastasis. (3) An intricate crosstalk exists between brain cancer cells and nerves. While brain cancer cell-derived factors such as Glypican-3, Neurotrophins and TSP-1 promote neurogenesis and thereby cancer proliferation, nerves release paracrine factors such as NLGN3, BDNF and IGF1 which promote the proliferation of brain cancer cells. (4) Brain cancer can also utilize the GABA neurotransmitter released by presynaptic neurons and uptake GABA by overexpressing GABAA-receptors. GABA taken up by cancer cells can be metabolized to promote brain cancer proliferation and metastasis. (Abbreviations: GluT- Glucose transporters; NLGN3- neuroligin 3; BDNF- Brain-Derived Neurotrophic Factor; IGF1- Insulin-like growth factor 1; Gln- Glutamine; VGLUT- vesicular glutamate transporters; Glu-Glutamate; GAD- glutamic acid decarboxylase; GABA-T-GABA transaminase; GAT1- GABA transporter 1; TSP-1- Thrombospondin-1; SSA- Succinic semialdehyde) (Created with BioRender)

Table 1 A comprehensive overview of the different classes of drugs that could be utilized to target the upregulation of synaptic communication and neuronal hyperexcitability in brain cancers, along with their mechanism of action and reported therapeutic implications

Class of Drugs	Mechanism of Action	Reported effects on brain cancers
Anti-epilepsy drugs (AEDs) - Levetiracetam (Keppra) - Valproic acid (Depakote) - Gabapentin (Neurontin) - Phenytoin (Dilantin)	Impairs neuronal hyperexcitability, downregulates voltage gated calcium channels (VGCC) and synaptogenesis	Levetiracetam use was associated with prolonged survival in patients with GBM treated with concurrent TMZ chemoradiotherapy [80]. Valproic acid and Gabapentin have been reported to improve outcomes in GBM patients [81, 82].
Gap-junction inhibitors - Tonabersat - Quinine - Anandamide - Mefloquine - Oleamide - Carbenoxolone	Impedes the electrical synaptic transmission between glioma and neuronal networks	Tonabersat was found to be an effective adjuvant treatment for GBM in mice models [83]. Mefloquine has been demonstrated to inhibit GBM angiogenesis and growth [84], while oleamide induces cell death in GBM RG2 cells [85].
Synaptogenesis inhibitors - INCB7839 (ADAM10/17 inhibitor) - LSKL (TSP-1 inhibitor) - ZW251 (Glypican-3 targeting antibody drug conjugate) - Pregabalin	Impair cancer growth by blocking synapse formation.	NCT04295759 is an ongoing clinical trial to test the efficacy of INCB7839 in inhibiting neuron-glioma interactions in pediatric glioma patients. Silencing thrombospondin-1 has been reported to inhibit GBM invasion and growth [86]. Pregabalin was found to be effective in primary brain tumor patients [87].
AMPAR inhibitors - Fycompa (Perampanel) - Becampanel - Fanapanel - Tezampanel	Impede tumorigenesis by downregulating AMPAR.	Perampanel has been demonstrated to have anti-proliferative effects on GBM cells [88]. A currently ongoing phase IIa clinical trial, PerSurge (NOA-30), aims to evaluate the efficacy of Perampanel on GBM patients [89]. EU-CT registration number: 2023-503938-52-00 30.11.2023
NMDAR inhibitors - Memantine - Amantadine - Ketamine - Dizocilpine - Ifenprodil	Impair NMDAR and downstream calcium signaling pathways in cancer cells, which promote glioma progression and metastasis.	Ketamine has been shown to suppress the proliferation of rat glioma cells [90] and inhibit the migration of glioma cells [91]. Blocking NMDAR signaling with Memantine or Ifenprodil suppressed the survival and migration of GBM cells [35].
GABA receptor antagonists - Flumazenil - Gabazine - THIP - TPMPA - Levetiracetam GABA-A receptor agonists - QHii066 - KRM-II-08 - Moxidectin	Inhibit GABAergic synaptic transmission to suppress brain cancers. GABA-A receptor agonists have shown efficacy in medulloblastoma, inducing HOXA5, upregulating p53, and promoting mitochondrial membrane depolarization through chloride-anion efflux.	Levetiracetam was found to suppress GABAergic neuron-to-glioma synaptic transmission, reduced glioma proliferation and improved the survival of mice injected with Diffuse midline glioma (DMG) xenografts [30]. QHii066 and KRM-II-08 have been shown to promote medulloblastoma cell apoptosis by inducing mitochondrial membrane depolarization and cell cycle arrest, while Moxidectin inhibited pediatric medulloblastoma progression by suppressing the PKA-Gli1 signaling axis [95, 98].

context of pediatric glioma patients is currently ongoing (NCT04295759). Proteins such as the SLITRK (SLIT and NTRK-like family, member 1) family of transmembrane receptors, which regulates synapse formation and neurite outgrowth, along with its binding partner LAR-type receptor phosphotyrosine-phosphatases (LAR-RPTPs) and KIRREL3 which regulates synapse formation [92] could also be targeted to combat brain cancers. Additionally, since thrombospondin and glypican-3 are core regulators of synaptogenesis, the potent thrombospondin (TSP-1) inhibitor LSKL and glypican-3 targeting antibodies could be evaluated for efficacy against gliomas and brain metastasis. Gabapentin and pregabalin, which have been demonstrated to inhibit synaptogenesis [65, 66], also have potential for being used against brain cancers. Inhibiting neurogenesis using nerve growth factor antibodies such as tanezumab and fulranumab, and GW441756, a potent, selective inhibitor of the NGF receptor tyrosine kinase A, also holds promise [67]. The neurotrophin receptors TrkB and TrkC are novel targets in glioma. Emerging evidence suggests that targeting axon guidance and dendrite growth modulating molecules and their regulators, including the semaphorins,

netrin family, and the SLIT-ROBO complex can potentially attenuate brain cancers [78, 79].

Finally, there is tremendous potential in therapeutically targeting synaptic signaling/communication to combat brain cancers. AMPAR upregulation is a common feature across gliomas and brain metastasis. Fycompa (Perampanel), a non-competitive antagonist of AMPAR, has shown anti-seizure efficacy in brain tumor patients in retrospective studies [69]. Its efficacy, along with other AMPAR antagonists such as Becampanel, Fanapanel and Tezampanel should be studied in large prospective investigations. Encouragingly, Talampanel, a well-tolerated AMPAR blocker, was found to increase median survival in newly diagnosed GBM patients when used in combination with radiation and temozolomide [70]. Targeting NMDARs also represents a promising strategy, particularly for brain metastasis, where they have been implicated in tumor promotion [12]. Memantine and the Dextromethorphan are two FDA-approved NMDAR antagonists that could be evaluated for efficacy in the context of brain metastasis and gliomas. Other NMDAR channel blockers such as Dizocilpine, Amantadine, Ifenprodil and Ketamine could be similarly tested. Downregulating GABAergic synaptic communication with GABA receptor inhibitors or by downregulating IQSEC3 [77] could be potentially evaluated. GABA-A receptor antagonists such as flumazenil and gabazine, GABA-B receptor antagonists such as 4,5,6,7-tetrahydroisoxazolo[5,4-c] pyridin-3-ol (THIP), and GABA-C receptor antagonists such as 1,2,5,6-tetrahydropyridin-4-methylphosphinic acid (TPMPA) are all promising therapeutic candidates. GABA-A receptor agonists such as QHii066 and KRM-II-08 have been shown to induce apoptosis in medulloblastoma cells, while Moxidectin inhibits pediatric medulloblastoma progression [95, 98]. Inhibitors against potassium voltage-gated channels like KCNC1, which mediate slow currents and are predominately expressed in inhibitory GABAergic interneurons, could also be utilized to target brain cancers, as KCNC1 has been previously implicated in glioma proliferation and invasion [71, 76].

Conclusion

Glioma and brain metastasis are each in urgent need of innovative therapeutic strategies. In this review, we aimed to first focus on summarizing the role of glutamate and GABA neurotransmitters in fueling brain cancers. We also describe the latest advances and discoveries documenting the extent to which glutamatergic and GABAergic synaptic communication promotes tumor progression and metastasis. Finally, we propose potential mechanisms by which this aberrant synaptic communication can be therapeutically targeted to improve the prognosis of patients afflicted by brain cancers. The fact that neuronal interactions can facilitate the expression of cancer hallmarks [73] while cancer itself can then enhance neuronal circuitry in a positive feed-back loop further underscores the clinical relevance of therapeutically targeting neuron-cancer cell interactions. Further research into the fascinating domain of cancer neuroscience promises to unravel the complexities governing neuron-brain cancer crosstalk for tangible patient benefit.

Acknowledgements
Not applicable.

Author contributions
J.M. and J.T.H. wrote the initial manuscript, revised, and finalized the manuscript.

Funding
JM is supported by the Cancer Prevention and Research Institute of Texas (CPRIT) Graduate Scholar Training Program Fellowship (RP210028) and the Schissler Foundation Fellowship.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
J.T.H. serves as co-editor-in-chief of Acta Neuropathologica Communications.

Received: 18 November 2024 / Accepted: 13 April 2025
Published online: 30 April 2025

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