Tumour brain: Pretreatment cognitive and affective disorders caused by peripheral cancers

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People that develop extracranial cancers often display co-morbid neurological disorders, such as anxiety, depression and cognitive impairment, even before commencement of chemotherapy. This suggests bidirectional crosstalk between non-CNS tumours and the brain, which can regulate peripheral tumour growth. However, the reciprocal neurological effects of tumour progression on brain homeostasis are not well understood. Here, we review brain regions involved in regulating peripheral tumour development and how they, in turn, are adversely affected by advancing tumour burden. Tumour-induced activation of the immune system, blood–brain barrier breakdown and chronic neuroinflammation can lead to circadian rhythm dysfunction, sleep disturbances, aberrant glucocorticoid production, decreased hippocampal neurogenesis and dysregulation of neural network activity, resulting in depression and memory impairments. Given that cancer-related cognitive impairment diminishes patient quality of life, reduces adherence to chemotherapy and worsens cancer prognosis, it is essential that more research is focused at understanding how peripheral tumours affect brain homeostasis.

KEYWORDS
blood–brain barrier, cancer-related cognitive impairment, circadian rhythms, depression, hypothalamic–pituitary–adrenal axis, inflammation, stress, tumour brain

1 | INTRODUCTION

People that develop non-CNS tumours often acquire a variety of affective and cognitive symptoms, including depression, anxiety and cancer-related cognitive impairment (CRCI). Metabolic dysfunction and sleep disturbances are also common co-morbidities that could exacerbate cancer-related memory and mood disorders. These adverse effects have long been attributed to the side effects of antineoplastic treatments (Ahles & Root, 2018; Lange, Joly, et al., 2019). However, longitudinal clinical studies now often include pretreatment assessments and are beginning to detect affective and cognitive disorders in cancer patients with non-CNS tumours prior to surgery or the administration of antineoplastic therapy, including radiotherapy, chemotherapy and/or hormonal therapy (Ahles et al., 2008; Berman et al., 2014; Janelsins et al., 2014; Jansen et al., 2011; Olson & Marks, 2019; Wefel et al., 2004). Importantly, the studies mentioned here have controlled for confounding demographic variables, as well as the cognitive reserve of individuals.
Recently, the CNS has been shown to be a critical contributor to tumour initiation and progression, via both direct and indirect modulation of the tumour micro-environment (TME) (Faulkner et al., 2019; Mauffrey et al., 2019). The relatively new field of Cancer Neuroscience aims for a better understanding of the complex interactions between the TME and the nervous system, specifically the influence of peripheral neuronal activity in both tumour initiation and cancer progression (Monje et al., 2020). Neurotransmitters and their receptors are also being investigated as novel and promising therapeutic targets to halt tumour growth. However, the reciprocal effects of tumour growth on the CNS and brain are being largely overlooked. The existence of pre-treatment cognitive and affective disorders in people with non-CNS cancers indicates a bidirectional crosstalk between the TME and CNS, which is likely to occur indirectly, via modulation of the innate immune system, and/or directly, through neurotransmitter release (Monje et al., 2020; Olson & Marks, 2019). However, even though cancer-associated neurological disturbances have been reported in a variety of pretreatment peripheral cancers, the mechanisms underlying these phenomena are still unknown (Baekelandt et al., 2016; Berman et al., 2014). A better understanding of how extracranial tumour growth leads to neurological complications is critical to enhancing patient survival. Cancer-associated neurological disturbances often decrease the quality of life of people diagnosed with cancer, and this can have knock-on effects, such as reducing patient adherence to chemotherapy drug regimens and decreasing overall survival rates (Bender et al., 2014; Janelins et al., 2014). Here, we review how different brain regions are involved in tumour progression and how they, in turn, can be adversely affected by peripheral tumour growth (Table 1).

2 | BLOOD–BRAIN BARRIER

The blood–brain barrier (BBB) is formed by microvascular endothelial cells, which line the cerebral capillaries of the brain and spinal cord. The BBB plays a critical role in protecting the brain parenchyma from blood-borne molecules and cells (Kadry et al., 2020). Peripheral tumours are thought to affect brain function via disruption of the BBB and peripheral immune cell infiltration (Olson & Marks, 2019) (Figure 1). The BBB is highly plastic and is known to undergo significant modification in response to physiological and pathological stimuli (Erickson & Banks, 2018). Impairment of the BBB has been reported in various CNS pathologies and particularly those initiated by inflammation (Wardill et al., 2016). The neuro-damaging capabilities of immune cell-derived pro-inflammatory cytokines are well characterised, and they are gaining more and more attention as the primary drivers of chemotherap- y- and cancer-associated cognitive impairment. Although the neurotoxic side effects of chemotherapy were thought to be the main cause of BBB disruption in patients with cancer, the inflammatory environment created by the tumour itself is now being investigated as the initial source of BBB dysfunction. For example, some cytokines, such as IL-1β, alter the paracellular barrier via breakdown and translocation of tight junction proteins, whereas other cytokines, such as TNF-α, mainly target the intracellular caveolae. Moreover, peripheral tumours could activate MMPs, via the release of pro-inflammatory cytokines, which further disrupt the basement membrane and tight junctions of the BBB (Kadry et al., 2020; Wardill et al., 2016). When BBB integrity is compromised, solutes and immune cells from the periphery can cross over to the brain more easily, where they can disrupt cognitive function (Geng et al., 2018).

Tumour-induced peripheral inflammation was also shown to induce astroglisis in the brains of mice bearing Lewis lung carcinoma (Demers et al., 2018). Astrocytes are intimately linked with endothelial cells of the BBB via the direct contact of astrocyte endfeet with pericyte cells that wrap around CNS vasculature. Therefore, astrocytes are acutely tuned to sense changes in BBB permeability (Heithoff et al., 2021), although the exact contribution of astrocytes to the maintenance of BBB integrity remains disputed (Kubotera et al., 2019). Demers et al. (2018) evaluated BBB integrity and observed increased accumulation of fibrin levels around cerebral vasculature and subsequent endothelial cell activation, potentially via endothelial granule release of von Willebrand factor (vWF) (Demers et al., 2018). More recently, in a mouse model of pancreatic ductal adenocarcinoma, increased circulating immune cell infiltration was observed in conjunction with extensive neuroinflammation and cancer-associated cachexia (Burfeind, Zhu, Norgard, Levasseur, Huisman, Buenafe, et al., 2020a). Here, a distinct population of non-CNS neutrophils (CD45<sup>hi</sup>CD11b<sup>+</sup>) expressing the chemokine receptor CCR2 were shown to accumulate at the meninges surrounding the hippocampus (known as the velum interpositum) of tumour-bearing mice. Pharmacological blockade of CCR2 prevented the circulating neutrophils from entering the brain and reduced the symptoms of cancer-associated cachexia. The authors further showed that tumour-derived factors induced the expression of the chemokine CCL2 in brain macrophages, providing a potential mechanism underlying the recruitment of CCR2 expressing neutrophils to the brain (Burfeind, Zhu, Norgard, Levasseur, Huisman, Buenafe, et al., 2020a).

BBB integrity is also known to be disrupted by the release of extracellular vesicles (EVs) in systemic inflammatory diseases (Saint-Pol et al., 2020) (Figure 1). EVs are defined as membrane-derived vesicles (including apoptotic bodies, microvesicles and exosomes) and have been identified as important mediators of cell communication via the exchange of lipids, nucleic acids and protein products. Peripherally derived EVs can easily cross the BBB via the circumventricular organs and endothelial transcytosis (Balusu et al., 2016). Given the fact that a heterogeneous population of EVs are being released during tumour growth, their potential involvement in disrupting brain function in people with extracranial cancers is now receiving much attention (Koh et al., 2020). Recently, Morad et al. (2019) discovered that breast cancer-derived EVs can indeed cross the BBB via caveolin-independent endocytosis. Using a mouse model of triple-negative MDA-MB-231 cancer cells, the tumour-derived EVs were shown to down-regulate the expression of the late endosomal marker Ras-related protein 7 (Rab7) in brain endothelial cells, demonstrating the ability of tumour-derived EVs to compromise BBB integrity and enhance EV-mediated communication between the
**TABLE 1** A non-exhaustive list of rodent studies showing peripheral tumour-induced affective and cognitive disturbances, including central dysregulations in the BBB, hippocampus, hypothalamus and VTA

| Brain region                | Main function                                                                 | Cancer model                                                                 | Primary findings                                                                 | References                        |
|-----------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------|
| Blood-brain barrier (BBB)   | CNS protection and maintenance of brain homeostasis                            | Lewis lung carcinoma (LLC) in female C57BL/6J mice                           | Accumulation of fibrin in brain vasculature                                      | (Demers et al., 2018)             |
|                             |                                                                                |                                                                               | Astrocyte activation († GFAP)                                                   |                                   |
|                             |                                                                                |                                                                               | ⇒ Anxious and depressive-like behaviour                                          |                                   |
|                             |                                                                                |                                                                               | Pancreatic ductal adenocarcinoma in male and female C57BL/6J mice               | (Burfeind, Zhu, Norgard, Levasseur, Huisman, Buenafe, et al., 2020a)         |
|                             |                                                                                |                                                                               | Accumulation of non-CNS neutrophils (CD45<sup>high</sup>CD11b<sup>+</sup>)        |                                   |
|                             |                                                                                |                                                                               | Expressing CCR2 at velum interpositum                                            |                                   |
|                             |                                                                                |                                                                               | ⇒ Cachexia-like symptoms                                                        |                                   |
|                             |                                                                                | Triple-negative breast cancer (human MDA-MB-231) in female nu/nu nude mice    | Tumour-derived EVs cross the BBB via transcytosis and down-regulation of         | (Morad et al., 2019)             |
|                             |                                                                                |                                                                               | endothelial Rab7                                                                |                                   |
|                             |                                                                                | Triple-negative breast cancer (human MDA-MB-231) in female nu/nu nude mice    | Tumour-derived EVs decrease astrocytic expression of TIMP-2                      | (Morad et al., 2020)             |
|                             |                                                                                |                                                                               | Hipocampal inflammation († IL-1β, IL-6, TNF-α and IL-10 protein)                 |                                   |
|                             |                                                                                |                                                                               | ⇒ Anxious and depressive-like behaviour                                          |                                   |
|                             |                                                                                | N-Nitroso-N-methylurea (NMU)-induced mammary tumours in female Wistar rats    | Hippocampal inflammation († IL-6 and TNF-α mRNA)                                | (Yang et al., 2014)              |
|                             |                                                                                |                                                                               | ⇒ Hippocampal neurogenesis                                                       |                                   |
|                             |                                                                                |                                                                               | ⇒ BDNF and COX-2 mRNA                                                           |                                   |
|                             |                                                                                |                                                                               | ⇒ Depression-like behaviour and impaired object recognition memory               |                                   |
|                             |                                                                                | Colon carcinoma (CT26) in female BALB/c mice                                  | Hippocampal inflammation († IL-1β mRNA)                                        | (Norden et al., 2015)            |
|                             |                                                                                |                                                                               | ⇒ Fatigue and depressive-like behaviour                                          |                                   |
|                             |                                                                                | Colon adenocarcinoma (C26) in female BALB/c x DBA/2 F1 (CD2F1)                | Hippocampal inflammation († IL-1β protein and mRNA)                             | (Walker li et al., 2017)         |
|                             |                                                                                |                                                                               | ⇒ No effect on hippocampal neurogenesis                                          |                                   |
|                             |                                                                                |                                                                               | ⇒ No effect on hippocampal BDNF mRNA                                             |                                   |
|                             |                                                                                |                                                                               | ⇒ No depressive-like behaviour                                                   |                                   |
|                             |                                                                                | Mammary tumours (67NR, 4T07 or 4T1) in female BALB/c mice                     | No hippocampal inflammation (≠ IL-1β, TNF-α, IFN-γ and IL-6 mRNA)                | (Emmer et al., 2019)            |
|                             |                                                                                |                                                                               | Hypothalamus                                                                     |                                   |
|                             | Maintenance of homeostasis, hormonal regulation of sleep, growth, metabolism, | Non-small cell lung adenocarcinoma genetically induced in Kras<sup>LSL-G12D-p53<sub>fl/fl</sub></sup> in female BALB/c mice | Altered circadian insulin, glucose and lipid metabolism                         | (Masri et al., 2016)             |
|                             | reproduction, body temperature, stress response, reward, feeding and circadian |                                                                               | Aberrant HO-producing neuron activity                                            | (Borniger et al., 2018)          |
|                             | rhythms                                                                         |                                                                               | HO-mediated metabolic dysfunction                                                 |                                   |
|                             |                                                                                |                                                                               | ⇒ Sleep disruption                                                              |                                   |
|                             |                                                                                | Mammary tumours (67NR) in female BALB/c mice                                  | Disrupted central clock gene regulation (Clock and Per1 mRNA)                   | (Sullivan et al., 2019)          |
|                             |                                                                                |                                                                               | (Continues)                                                                     |                                   |
systemic circulation and CNS parenchyma (Morad et al., 2019). In a subsequent study, the group worked on elucidating the functional consequences of tumour-derived EV transport across the BBB (Morad et al., 2020). Astrocytes were found to be the main recipients of peripheral EVs within the brain via the non-canonical Cdc42-dependent, clathrin-independent carriers (CLIC)/GPI-anchored protein-enriched early endosomal compartment (CLIC/GEEC) endocytosis pathway. Upon tumour-derived EV infiltration, astrocytes were found to express significantly less tissue inhibitor of MMP-2 (TIMP2), which was hypothesised to promote a suitable micro-environment for growth of brain metastases. The authors further determined the EV factors that were driving the decrease in TIMP2 in astrocytes by evaluating a number of microRNAs (miRNAs) with the ability to target the 30 untranslated region (30-UTR) within the TIMP2 mRNA. A miRNA known as miR-301a-3p was found to be significantly increased in vitro and in vivo (Morad et al., 2020). Although the authors did not investigate the potential neurological effects of this EV-mediated decrease in TIMP2 expression and BBB disruption, it is likely that this could cause cognitive impairment. In the context of brain ageing, a decline in plasma and hippocampal TIMP2 levels is thought to be associated with age-related cognitive dysfunction. Systemic administration of TIMP2 was shown to increase hippocampal synaptic plasticity and to improve behaviour and memory function in aged mice (Castellano et al., 2017). Moreover, several miRNAs have already been identified for their involvement in neuropathological diseases. For example, cerebral miR-30 directly impairs hippocampal synaptic transmission and plasticity, and miR-301b was shown to accelerate microglial activation and cognitive impairment (Song et al., 2019; Tang et al., 2019). These findings suggest that tumour-derived EVs could contribute to tumour-associated neurological disorders through the shuttling of miRNAs that disrupt BBB integrity and/or directly alter neuronal function. Further investigation of tumour-derived brain-infiltrating EVs and their contents is likely to uncover more mediators capable of causing affective and cognitive disorders in cancer patients (Koh et al., 2020).

### 3 | HIPPOCAMPUS

Although there is little evidence of direct crosstalk between the periphery and the hippocampus, this limbic structure is one of the main brain regions investigated in studies of CRCIs and mood disorders in pretreatment cancer patients. This is due to the critical role of the hippocampus in the processing of sensory stimuli and in memory formation, consolidation and retrieval (Opitz, 2014). Moreover, the dentate gyrus of the hippocampus is one of only a few brain regions that display lifelong neurogenesis, a process particularly

| Brain region | Main function | Cancer model | Primary findings | References |
|--------------|--------------|--------------|-----------------|------------|
| Pancreatic ductal adenocarcinoma in male C57BL/6J mice | Absence of endocrine and immune system rhythms | | | |
| Hypothalamic microgliosis (Iba1+ cells) | | | | (Burfeind, Zhu, Norgard, Levasseur, Huismann, Michaelis, et al., 2020b) |
| Hypothalamic astrogliosis (GFAP+ cells) | | | | |
| Cachexia-like symptoms | | | |
| Ventral tegmental area (VTA) | Regulation of motivation, reward and addiction | Melanoma (B16F10) in male OF1 mice | Central inflammation (IL-6 and TNF-α mRNA) | (Lebeña et al., 2014) |
| | | | Dopaminergic and serotonergic VTA input to striatum and prefrontal cortex | |
| | | | (DOPAC, DA, 5-HT and 5-HIAA) | |
| | | | Depressive-like behaviour | |
| | | | Cachexia-like symptoms | |
| | | | (Burfeind, Zhu, Norgard, Levasseur, Huismann, Michaelis, et al., 2020b) |
| Lewis lung carcinoma (LLC) and melanoma (B16) in male C57BL/6J mice | Optogenetic VTA activation attenuated tumour growth and decreased NA levels in the bone marrow | | (Ben-Shaanan et al., 2018) |
| Mammary tumours (MDA-231 and MCF-7) in male BALB/c nude mice | Optogenetic VTA activation within the mPFC had an anxiolytic effect and attenuated tumour progression | | Reduced anxiety-like behaviour |
| | | | (Xu et al., 2020) |

Abbreviations: 5-HIAA, 5-hydroxy indoleacetic acid (serotonin metabolite); BDNF, brain-derived neurotrophic factor; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid (dopamine metabolite); EVs, extracellular vesicles; GFAP, glial fibrillary acidic protein; HO, hypocretin/orexin; mPFC, medial prefrontal cortex; NA, noradrenaline; TIMP-2, tissue inhibitor of MMP-2.
important in the positive mood-enhancing mechanism of action of several antidepressant medications (Kang et al., 2015). To date, most neuroimaging studies in humans with non-CNS tumours have focused on chemotherapy-related brain abnormalities, such as the diffuse decrease in grey and white matter volumes, the decrease in neuronal stem cell (NSC) proliferation in the dentate gyrus and subtle inward deformation of the hippocampus, which correlates with self-reported impairments in episodic memory (Deprez et al., 2018; Simo et al., 2013). However, there is also evidence for the presence of structural and functional hippocampal changes in chemotherapy-naïve cancer patients, including hippocampal atrophy and the inability to deactivate regions within the posterior cingulate, which receives input from the hippocampus (Berman et al., 2014; Cimprich et al., 2010; Perrier et al., 2020; Scherling et al., 2012). Moreover, the cognitive domains that are commonly affected in people with non-CNS cancer before treatment, such as working memory, explicit memory, processing speed and executive function, all point towards the presence of hippocampal aberrations (Hermelink et al., 2007; Lange, Léger, et al., 2019; Meyers et al., 2005; Wefel et al., 2004). Given that increased levels of circulating inflammatory factors have been positively associated with cognitive dysfunction in people with cancer, prior to chemotherapy (Cheung et al., 2015; Lyon et al., 2016; Patel et al., 2015), and that the hippocampus is particularly vulnerable to stress and inflammation (Conrad, 2008), researchers have suggested a role for tumour-induced inflammation in pretreatment hippocampal dysfunction (Santos & Pyter, 2018; Schrepf, Lutgendorf, & Pyter, 2015). However, confounding factors, such as tissue trauma-related stress responses, anaesthesia-mediated immune suppression and opportunistic infection-driven systemic inflammation after surgery, can complicate the interpretation of these findings and make it difficult to attribute cognitive dysfunction directly with tumour burden-associated inflammation (Emmer et al., 2019; Joly et al., 2015; Kim, 2018; Lange, Léger, et al., 2019). Although the direct effects of peripheral tumour growth on the hippocampal formation is unclear in humans, several rodent studies support tumour-associated inflammation as a potential mechanism for hippocampal dysfunction (Norden et al., 2015; Pyter et al., 2009; Santos et al., 2019; Yang et al., 2014).

Tumour-associated systemic inflammation has been a major focus in trying to decipher the causes of pretreatment CRCI in people diagnosed with peripheral cancers. Of note, a wide variety of inflammatory mediators, including but not limited to IL-1β, IL-6 and TNF-α, have been associated with the systemic inflammatory response of peripheral cancers (Colotta et al., 2009). Pyter et al. (2009) observed a significant increase in hippocampal protein expression of IL-1β, IL-6,
TNF-α and IL-10 expression in rats with N-nitroso-N-methylurea (NMU)-induced mammary tumours. Here, tumour-bearing mice showed depressive-like behaviour based on the Porsolt forced swim test, which was not observed by NMU exposure alone (i.e., before tumour development), indicating that tumour growth itself was responsible for the central inflammatory response (Pyter et al., 2009). The increased production of pro-inflammatory cytokines in response to tumour growth is thought to signal to the brain via humoral and neural signalling (Dantzer, 2018). IL-10 is classically known as an anti-inflammatory cytokine. However, the role of IL-10 in cancer is ambiguous, and it teeters between immune stimulation and immune suppression (Zhao et al., 2015). Yang et al. (2014) assayed the serum levels of circulating cytokines in a BALB/c mouse model 2 weeks after inoculation with a colon carcinoma cell line (CT26) (Yang et al., 2014). In this study, an increase in the levels of serum IL-6 was observed, as well as increased mRNA levels of hippocampal IL-6 and TNF-α, which correlated with a decrease in the numbers of proliferating hippocampal neurons and a decrease in the mRNA levels of brain-derived neurotrophic factor (BDNF) and COX-2 in the hippocampus. In this study, tumour-inoculated mice showed depressive-like behaviour in the tail suspension test. This study suggests that peripheral tumour growth alone can cause neurological dysfunctions through IL-6-mediated inflammatory signalling, a reduction of hippocampal neurogenesis and decreased levels of hippocampal BDNF and COX-2 (Yang et al., 2014). However, although this study by Yang et al. (2014) suggests that depressive-like behaviour and memory impairments may be attributed to a decrease in hippocampal COX-2 expression, contrasting findings have been observed in tumour-bearing mice treated with low dose-aspirin. Aspirin, an anti-inflammatory non-selective COX inhibitor, prevented tumour-induced memory impairments, although it did not affect tumour-induced sickness or tumour growth, in 4T1 or EO771 mammary tumour mouse models (Walker et al., 2018). Moreover, human studies suggest that using aspirin in the year prior to receiving a cancer diagnosis reduced the risk of developing depression, anxiety and stress-related disorders in the year following a cancer diagnosis (data were adjusted for sociodemographic factors, comorbidities and cancer characteristics). Interestingly, aspirin was more protective than other non-steroidal anti-inflammatory drugs (NSAIDs) (Hu et al., 2020). Furthermore, the decrease in hippocampal BDNF mRNA that was observed in CT26-induced colon carcinoma by Yang et al. (2014) was not extended to other tumour models, including 4T07 and 4T1 mammary tumour models (Walker li et al., 2017) and NMU-induced ductal mammary tumours (Pyter et al., 2010). These observations highlight that tumour-induced changes in the hippocampus are highly cancer specific.

Using the C26 colon adenocarcinoma in vivo model, Norden et al. (2015) observed an increase in fatigue and depressive-like behaviour in the voluntary wheel running activity paradigm and in the sucrose preference and forced swim tests (Norden et al., 2015). They reported that the increase in cancer-related fatigue and depression was associated with an increase in pro-inflammatory IL-1β and IL-6 mRNA expression in the cortex and hippocampus. Microglial immunoreactivity was also significantly increased in the cortex, although no changes were observed in the hippocampus (Norden et al., 2015). This suggests an increase in neuroinflammation and microglial priming in the brain in response to peripheral colon cancer.

More recently, Santos et al. (2019) examined changes in pro-inflammatory cytokines in response to mammary tumour growth and in response to an additional LPS-mediated immune challenge (Santos et al., 2019). Moreover, the extent to which mammary tumour resection could attenuate the tumour-induced neuroinflammatory response was also investigated. An in vivo mouse model of non-metastatic mammary carcinoma (67NR cell line in BALB/c mice) was used. This was important to differentiate between the effects of peripheral tumour burden and blood-borne metastatic cancer cells that can invade and grow in CNS tissue. The protein levels of circulating TNF-α, IL-1β and IL-6 markedly increased in the plasma of both control and tumour-bearing mice following LPS stimulation. However, in the brain, the tumour-bearing cohort showed an attenuated neuroinflammatory response following peripheral immune challenge, compared with control mice. Although the mRNA levels of TNF-α, IL-1β and IL-6 increased in the hippocampus, hypothalamus and frontal cortex of control mice, this inflammatory response was much weaker in the brains of tumour-bearing mice following LPS stimulation. This is interesting in the context of the large body of literature describing how peripheral cancer growth is largely immunosuppressive and that immune modulation is a mechanism employed by tumours to evade destruction by cells of the innate immune system (Nguyen & Spranger, 2020). Interestingly, tumour resection restored the neuroinflammatory response to a peripheral immune challenge, measured as raised levels of hippocampal IL-6 and IL-1β, but not TNF-α. Their results indicate that peripheral tumour growth can significantly dampen neuroinflammatory pathways in the brain. However, no baseline mRNA levels (i.e., prior to the LPS challenge) were measured in the tumour-bearing mice and they did not investigate if the attenuated neuroinflammatory response had any effect on cognitive or affective functioning (Santos et al., 2019). Therefore, it is difficult to assess whether tumour-mediated attenuation of neuroinflammation has beneficial or detrimental effects on cognition and behaviour. In another study, 67NR mammary tumours were surgically resected 14 days prior to LPS-mediated immune challenge (Emmer et al., 2019). No changes in circulating inflammatory protein markers were observed between control mice (vehicle injection + sham surgery without removal of the mammary gland), mastectomy surgery mice (vehicle injection + removal of the mammary gland) and tumour mastectomy mice (tumour injection + removal of the mammary gland). However, mRNA expression of pro-inflammatory markers - IL-1β, TNF-α, CD68 and the IL-4 receptor α-subunit - was significantly increased in the hippocampus of tumour-bearing mice that had mastectomy surgery, in comparison with control mice. Of note, at the time of mastectomy, there were no significant differences in the hippocampal mRNA expression of the markers IL-1β, TNF-α, IFN-γ and IL-6 between tumour- and vehicle-injected animals (Emmer et al., 2019). Overall, these studies indicate that the hippocampus is particularly vulnerable to the presence of a peripheral tumour and is
likely very susceptible to off-target actions of tumour-induced systemic inflammation. Therefore, much of the cognitive and affective disturbances in people with non-CNS tumours could be the result of a chronic low-level systemic inflammation that affects key brain structures involved in memory and the regulation of mood, such as the hippocampus (Figure 2).

4 | HYPOTHALAMUS

The hypothalamus maintains essential physiological processes, including sleep, growth, metabolism, reproduction, body temperature, stress response, reward, feeding and circadian rhythms, mainly via the secretion of neurotransmitters. The disruption of many of these processes is linked to tumour initiation and progression (Masri & Sassone-Corsi, 2018). The hypothalamus is divided into three main regions (supraoptic, tuberal and mammillary) and three areas (paraventricular, medial and lateral). Each zone within the hypothalamus contains specific subsets of neurons, also known as nuclei, with specialised functions. In the context of cancer-associated neurological dysfunction, only a subset of hypothalamic nuclei have been investigated thus far, including the lateral nuclei (involved in sleep, metabolism and arousal via hypocretin/orexin [HO]-producing neurons), the paraventricular nucleus within the supraoptic medial hypothalamus (involved in the hypothalamic–pituitary–adrenal [HPA]-mediated stress response) and the suprachiasmatic nuclei (SCN), within the medial anterior hypothalamus (involved in regulating the vast majority of processes within the human body according to a 24-h cycle, known as the circadian rhythm) (Hall & Guyton, 2011) (Figure 3a).

4.1 | HO neurons in the lateral nuclei

Sleep disturbances, especially insomnia, are a common problem in people with extracranial cancers prior to, during and after antineoplastic therapy (Fiorentino & Ancoli-Israel, 2007). Unfortunately, poor sleep has been correlated with impaired ‘quality-of-life’ scores, metastatic spread and even increased mortality in cancer patients (Collins et al., 2017; Palesh et al., 2014). Thus, it appears that tumour growth promotes unhealthy sleep patterns, and reciprocally, poor sleep can further stimulate cancer progression (Walker & Borniger, 2019). Moreover, sleep disruption has also been associated with weight gain, metabolic dysfunction and the development of a chronic inflammatory state, which could further contribute to cancer progression (Walker & Borniger, 2019). However, the underlying mechanisms remained unclear until Borniger et al. (2018) investigated the involvement of the brain in cancer-associated sleep disruption and metabolic dysfunction (Borniger et al., 2018).

Borniger et al. (2018) observed a marked increase in the circulating levels of IL-6 in mammary tumour-bearing mice (67NR), in conjunction with a disrupted sleeping pattern. These tumour-induced changes were associated with aberrant activity of HO-producing neurons (Borniger et al., 2018). Lateral hypothalamic HO neurons project throughout the brain to regulate a variety of functions, including

![Figure 2](https://example.com/figure2.png)

**Figure 2** Peripheral tumour growth may affect the hippocampus, primarily via systemic inflammation. Increased levels of circulating inflammatory cytokines (e.g., IL-6, TNF-α and IL-1β), in response to peripheral tumour growth, appear to indirectly trigger an inflammatory response in the hippocampus. Because peripheral tumour growth is capable of altering various organ systems (e.g., hepatic metabolism, gut microbiome and spleen myeloid immune cell populations), tumour-derived signals are likely to be amplified and propagated to the brain via modulation of peripheral tissue physiology. In addition, tumour-induced systemic inflammation has been linked to a reduction in hippocampal neurogenesis, as well as the decreased expression of brain-derived neurotrophic factor (BDNF) and COX-2. Whereas the communication between the periphery and the brain is thought to occur via neural and humoral signalling, the exact mechanism is still unclear. Figure was created with BioRender.com
motivation, wakefulness, anxiety and reproductive behaviour. Furthermore, HO neurons send projections to various sympathetic output nuclei, which makes them reciprocally sensitive to metabolic signals arriving from the periphery, including leptin, ghrelin, glucose, pH and CO₂ (Sakurai, 2007). Inhibition of HO neuron signalling, using a dual HO receptor antagonist, almorexant, ameliorated the observed sleep abnormalities, but not the IL-6-mediated peripheral inflammation (Borniger et al., 2018). These results indicate a link between peripheral tumour growth and dysregulation of central neuromodulators involved in maintaining healthy sleep/wake cycles (Figure 3b).

In general, sleep abnormalities have been shown to affect neuronal activity and connectivity across multiple brain regions, including the dorsolateral and medial prefrontal cortex (PFC), thalamus, posterior cingulate cortex (PCC) and hypothalamus. The heterogeneous array of potential brain changes, including alterations in one’s attention span, working memory, emotion, reward and hippocampal learning, can result in disruption of human behaviour across nearly all domains of cognition and affection (Krause et al., 2017). The extent to which sleep deprivation affects the brain depends on several factors, including other co-morbidities, gender, coping mechanisms.
and cognitive reserve (Krause et al., 2017). Hypothalamic HO neurons send excitatory projections to the paraventricular nucleus of the thalamus, the arcuate nucleus, the VTA (which contains dopaminergic neurons), the locus coeruleus (which contains noradrenergic neurons), dorsal raphe (which contains serotonergic neurons) and tuberomammillary nucleus (which contains histaminergic neurons) (Sakurai, 2007). HO neurons not only regulate neurotransmitter release but also modulate calcium-mediated synaptic plasticity via their G protein-coupled receptors (GPCRs), OX1 and OX2 (Kukkonen & Leonard, 2014). Moreover, HO neurons are strongly connected to the autonomic output nuclei in the brainstem, the sympathetic nervous system (SNS) and, most importantly, the HPA axis (Sakurai, 2007). Indeed, optogenetic stimulation of HO neurons was shown to activate the HPA axis, resulting in increased levels of circulating glucocorticoids (Bonnavion et al., 2015). This suggests that tumour-induced activation of HO-producing neurons in the hypothalamus could lead to sleep disturbances and, over time, contribute to the affective and cognitive disturbances reported in people with non-CNS tumours (Li et al., 2020) (Figure 3b).

People that develop peripheral cancers often suffer from metabolic dysfunction, which can manifest as weight loss, anorexia, skeletal muscle wasting, atrophy of adipose tissue and cancer-associated cachexia. Cancer cachexia is multifactorial and is characterised by ongoing, unintentional weight loss and progressive functional impairment. Unlike previously suggested, cancer-associated weight loss also occurs in pretreatment cancer patients, as weight loss is observed in up to 34% of patients at the time of diagnosis, across various different cancer types and even in early stage cancers (Stage I —17.6%) (Gannavarapu et al., 2018). This phenomenon has been predominantly blamed on the inflammatory side effects of tumour growth, although clinical trials with anti-inflammatory agents show limited effects (Cole et al., 2018). In the same study mentioned above by Borniger et al. (2018), non-metastatic mammary tumour growth caused an increase in circulating levels of IL-6, alongside impaired hepatic glucose processing (Borniger et al., 2018). However, blocking IL-6 signalling using a monoclonal antibody did not rescue the observed hepatic abnormalities. Given the ability of HO neurons to also regulate metabolism, the authors hypothesised the involvement of HO neurons. Here, blocking HO signalling using the antagonist, almorexant, attenuated the hyperglycaemia and partly rescued the expression of genes involved in gluconeogenesis and glycolysis (ldha, gck and slc2a4) (Borniger et al., 2018).

In the human body, the orexigenic peptide ghrelin excites HO-producing neurons, whereas leptin inhibits their activity. Although ghrelin is predominantly produced and secreted by the stomach, ghrelin-producing neurons and their receptors have been identified in the CNS, including the hypothalamus (So et al., 2018). Previous studies have shown that central and peripheral administration of ghrelin to rodents activates various brain regions, including the hypothalamus, indicating that peripheral ghrelin can reach the brain (Cabral et al., 2015). Interestingly, ghrelin has been shown to be highly expressed in a multitude of extracranial cancer tissues such as colorectal, liver, pancreatic, thyroid, ovarian, prostate and breast cancers, although the data remain controversial (Soleymana-Jahi et al., 2019). This peripheral ghrelin imbalance could potentially cause a disruption in the negative feedback loop of HO neurons. Moreover, in the hippocampus, ghrelin interacts with the growth hormone secretagogue receptor (GHSR-1a), causing a conformational change in the receptor and leading to a wide array of physiological changes. Because GHSR expression is relatively high within the hippocampus, ghrelin was shown to promote LTP, spatial learning and memory formation (Mainardi et al., 2015; Ribeiro et al., 2014). In contrast, hyperactivation of hypocretin neurons has also been shown to cause insomnia, panic attacks, anxiety and depression (Nollet et al., 2012). Although a promising target to explain neurological dysfunction in pretreatment cancer patients, ghrelin, and its actions on HO-secreting neurons within the hypothalamus, has not been directly linked to the phenomenon of CRCI.

Whereas HO-secreting neurons are activated by ghrelin and hypoglycaemia, their activity is inhibited by the production of leptin (Yamanaka et al., 2003). Borniger et al. (2018) observed significantly reduced serum leptin levels in non-metastatic 67NR mammary tumour-bearing mice, in conjunction with aberrant HO neuron activity (Borniger et al., 2018). Leptin, a key peripheral signal, is also known to regulate the medio-basal hypothalamus. The medio-basal hypothalamus includes the arcuate nucleus and median eminence and contains crucial neuronal populations that control food intake and energy expenditure, including leptin-sensitive neuropeptide Y (NPY), agouti-related protein (AGRP) and GABA (NAG)-containing neurons and pro-opiomelanocortin (POMC)-expressing neurons (Pan & Myers, 2018). In addition to neuronal cell populations, the microglial cells within the medio-basal hypothalamus are highly responsive to inflammatory stimuli and metabolic perturbations (Valdearcos et al., 2019). Although microgliosis within the medio-basal hypothalamus is mostly studied in the context of obesity, Burfeind, Zhu, Norgard, Levasseur, Huisman, Michaelis, et al. (2020b) recently demonstrated that microgliosis within the medio-basal hypothalamus also occurs during cancer cachexia. The authors used a mouse model of pancreatic ductal adenocarcinoma, which is nearly always accompanied by cachexia. Here, microglia were shown to respond to tumour-derived factors and infiltrate the medio-basal hypothalamus, where they assumed an activated state. Interestingly, microglial depletion, or prevention of their activation using an antagonist against the colony stimulating factor 1 receptor, worsened cachexia. Moreover, antagonist-treated animals had significantly higher levels of circulating cortisol, which indicates activation of the HPA-axis. Overall, this study demonstrates a protective role for microglial activation within the hypothalamus in the context of cancer-associated cachexia (Burfeind, Zhu, Norgard, Levasseur, Huisman, Michaelis, et al., 2020b). However, the effects of localised microgliosis on cognitive and affective functioning in patients with cancer cachexia are yet to be determined.

4.2 HPA axis in the paraventricular nuclei

As previously mentioned, many hypothalamic processes are influenced by the HPA axis, which is primarily driven by the
paraventricular nucleus of the hypothalamus (DeMorrow, 2018). The HPA axis is known to be activated by internal and external stimuli, which are perceived as a threat by higher order cognitive centres. These regions identify the threat to homeostasis and send excitatory signals to the hypothalamus to initiate the synthesis and release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH is transported to the anterior pituitary gland via the hypophysial portal blood vessels, which connect the hypothalamus and the pituitary gland. Simultaneously, AVP is transported to the posterior pituitary gland via axonal transport. Once CRH and AVP reach the pituitary gland, the hormones act synergistically to stimulate the production and secretion of the adrenocorticotropic hormone (ACTH) from POMC-expressing corticotropic cells. ACTH is then released into the general circulation and makes its way to the adrenal glands, located on top of the kidneys. Here, ACTH induces the synthesis of fast-acting catecholamines, such as noradrenaline and adrenaline and the more slow-acting glucocorticoids, such as cortisol, which are released into the bloodstream. Under normal circumstances, glucocorticoid secretion is regulated via a negative feedback system. However, disturbances in the HPA signalling cascade are common in a variety of chronic diseases, such as cancer (Herman et al., 2016). Basal levels of HPA-axis hormones are necessary to maintain homeostatic organ and tissue function, whereas the smallest perturbations in steroid concentration can have a serious impact on the body's physiology. Glucocorticoids act via glucocorticoid (Type II) and mineralocorticoid (Type I) receptors to which they bind with different affinities. The mineralocorticoid receptor has a high affinity for glucocorticoids and is heavily occupied during the diurnal cycle. However, stress-induced elevations of the glucocorticoid concentrations increase the occupation of the lower-affinity glucocorticoid receptors (McEwen, 2007). On the other hand, stress-induced catecholamines can bind, with varying affinities, to G protein-coupled α- and β-adrenergic receptor subtypes to regulate SNS tone. Adrenergic receptors are expressed on a wide variety of tissues in the body and play major roles in modulating physiological processes, including smooth muscle cell constriction, myocardial contractility, heart rate and immune system function (Maletic et al., 2017).

Aberrant activation of the HPA axis and the subsequent production of catecholamines and glucocorticoids, which are strong regulators of metabolic state, immune function and circadian rhythms, are commonly reported in people with cancer (Weinrib et al., 2010). Psychological distress, which can begin with a cancer diagnosis and continue during treatment, is commonly experienced by people with cancer (Anunziata et al., 2011). Stress hormones, both cortisol and noradrenaline, have been shown to have a severe impact on disease progression and prognosis (Volden & Conzen, 2013). Thaker et al. (2004) were one of the first to show that elevated circulating levels of catecholamines resulted in increased tumour burden, angiogenesis and invasiveness of ovarian carcinoma cells in an orthotopic mouse model (Thaker et al., 2006). These findings were later corroborated in other cancer mouse models, which showed accelerated tumour progression in the presence of stress hormones, caused by disrupting anti-tumour immunity and other endocrine effects on tumour metabolism, angiogenesis, oncogenesis and DNA repair (Flaherty et al., 2017; Zhang et al., 2019). In humans with adrenocortical carcinoma, glucocorticoid excess was associated with low amounts of tumour-infiltrating lymphocytes and poor overall survival (Landwehr et al., 2020). In turn, altered cortisol responses and aberrant adrenergic signalling in cancer patients have also been correlated with neurological issues, such as cancer-related fatigue, anxiety, depression and potentially CRCI (Andreotti et al., 2015; Schmidt et al., 2016; Weinrib et al., 2010).

The HPA axis not only regulates the immune system, but the reverse also happens. For example, immune-neuroendocrine feedback has been shown to play a role in viral infections. Immune cells can dampen their own activity via the production of pro-inflammatory cytokines and the subsequent release of glucocorticoid hormones, which, in turn, attenuates the production of pro-inflammatory mediators by immune cells (Silverman et al., 2005). A similar mechanism could be happening in people with cancer prior to receiving treatment. For example, the pro-inflammatory cytokine, IL-6, is a potent inflammatory cytokine released by various cells within the TME, and increased serum levels of IL-6 have been demonstrated in various cancers (Masjedi et al., 2018). IL-6 was shown to be a potent activator of the adrenal axis following LPS-mediated immune activation (Bethin et al., 2000). Moreover, in colon or pancreatic tumour-bearing mice, an IL-6-mediated decrease in hepatic ketogenesis was associated with a glucocorticoid-mediated stress response, decreased anti-tumour immunity and decreased immunotherapy efficacy (Flint et al., 2016). In patients undergoing glucocorticoid therapy, serum levels of IL-6 are significantly reduced (Fujio et al., 2016). However, in the presence of neoplastic cell growth, the HPA negative feedback loop appears disrupted, which is likely to lead to the observed neurocognitive and neuropsychological disturbances in cancer patients. Interestingly, IL-6 and hyperactivity of the HPA axis also play a crucial role in the aetiology of depression. Jehn et al. (2010) found a strong correlation between increased plasma levels of IL-6 and HPA-axis dysfunction in cancer patients diagnosed with depression (Jehn et al., 2010). This faulty HPA feedback system is thought to be due to desensitised glucocorticoid receptors in the brain. Pro-inflammatory cytokines, including those produced in response to tumour growth, contribute to this desensitisation of glucocorticoid receptors by impairing the nuclear translocation and/or transcriptional function of these receptors (Silverman & Sternberg, 2012). Tumour cells, in conjunction with recruited immune cells, not only produce inflammatory cytokines but also secrete various other bioactive peptides that can affect the HPA axis. For example, intra-tumour production of CRH has been reported in human ovarian cancer (Minas et al., 2007) and in human melanoma cells (Sato et al., 2002). Prolonged activation of the HPA axis and chronic exposure to increased concentrations of glucocorticoids can have a range of pathological effects on the brain, such as decreased hippocampal volumes and decreased dendritic branching of immature dentate granule cells (Dioli et al., 2019) (Figure 3c). Another frequently reported side effect of HPA-axis dysfunction is the disruption of circadian rhythms, which are regulated by the SCN within the hypothalamus (Dumbell et al., 2016).
4.3 | Suprachiasmatic nuclei

The master regulator of the circadian system is located within the hypothalamus, known as the paired SCN. The SCN regulate neuronal activity, body temperature, hormone release, immune function, sleep and feeding in a 24-h cycle based on light–dark input from the retinal ganglion cells (Dumbell et al., 2016). Cancers have been linked to disruptions in the circadian rhythm (Sulli et al., 2019). Moreover, disruption of the circadian rhythm is strongly associated with brain dysfunction, suggesting that tumour-induced disruption of the circadian rhythm could alter brain function in cancer patients (Cash et al., 2015; Logan & McClung, 2019). For example, people with breast cancer display altered levels of circulating leukocytes and melatonin and report disturbances in their sleep–wake cycle. These observations were associated with behavioural co-morbidities, including fatigue and memory impairment (Ahles & Root, 2018; Payne, 2011).

Using a mouse model of lung adenocarcinoma, Masri et al. (2016) showed that tumour growth can disrupt the circadian metabolic rhythm as assessed by transcriptomic and metabolic analysis of the liver. Here, tumour growth in a distal organ led to alterations in liver metabolism, demonstrated by inhibition of hepatic insulin signalling, increased glucose production and deregulated lipid metabolism, which likely further drive tumorigenesis (Hadadi et al., 2020; Kinouchi & Sassone-Corsi, 2020). Whereas the authors stated that lung adenocarcinoma did not affect the core components of the circadian clock, they did not examine any core components, such as the hypothalamus (Masri et al., 2016). Thus, Sullivan et al. (2019) further explored the impact of mammary tumour growth on central circadian rhythm regulation (Sulli et al., 2019). After quantification of clock-related gene expression in the hypothalamus, two core clock-regulating genes (Clock and Per1) and four additional clock-related genes (Aanat, Camk2a, Creb1 and Mnt1a) were found to be differentially expressed in mammary tumour-bearing mice (67NR). Alongside hypothalamic gene expression changes, the researchers observed a significantly higher percentage of running wheel locomotor activity during the light phase of a 14:10 light–dark cycle in tumour-bearing mice, in comparison with non-tumour-bearing controls and tumour-resected animals. Moreover, the normal 24-h rhythm in circulating corticosterone and circulating neutrophils (CD11b+Ly6G+) was absent in tumour-bearing mice (Sullivan et al., 2019). Their findings confirm that peripheral tumour growth, independent of harsh cancer treatments, can disrupt the central molecular clock, as well as the physiological rhythms of the endocrine and immune systems (Figure 3d). They provide a potential explanation for the behavioural co-morbidities seen in cancer patients. However, the exact mechanism of how tumour growth causes circadian rhythm dysregulation is still unclear but is likely to be due to tumour-secreted factors, such as inflammatory cytokines. For example, abnormal diurnal cortisol rhythms in people with epithelial ovarian cancer prior to treatment were associated with increased levels of the pro-inflammatory cytokine, IL-6, and overall decreased survival (Schrepf, Thaker, et al., 2015) (Figure 3d).

5 | MIDBRAIN VENTRAL TEGMENTAL AREA

The midbrain ventral tegmental area (VTA) is commonly known for its role in motivational behaviours and in the brain’s reward system. However, more recently, the VTA has gained attention because of its ability to modulate tumour progression via the production of the neurotransmitter, dopamine (Ben-Shaanan et al., 2018; Xu et al., 2020). The VTA is one of the primary sources of dopamine within the brain. Dopamine is important in regulating motivation, mood and cognition and also exerts various actions in the periphery, such as blood pressure regulation and modulation of both the innate and adaptive immune systems (Zhang et al., 2017). Dopamine primarily mediates its effects via dopamine receptors, which are GPCRs and can be divided into two subgroups, D1-like (DRD1) and D2-like (DRD2), depending on their binding affinities. Dopamine synthesis relies on hydroxylation of L-tyrosine by tyrosine hydroxylase (TH), resulting in L-DOPA production. This step is followed by the decarboxylation of L-DOPA by the aromatic amino acid decarboxylase (DOPA decarboxylase) (Matt & Gaskill, 2020). Whereas the dopamine receptors and proteins required for dopamine synthesis are primarily expressed in dopaminergic neurons, various immune cells and cells from peripheral tissues express the required receptors and enzymes for dopamine activity and synthesis. For example, T lymphocytes express all dopamine receptors, as well as TH, the dopamine transporter (DAT) and catechol-O-methyltransferase (COMT), which is necessary for the degradation of dopamine. This indicates that T cells also have the capacity to take up, synthesise, store and release dopamine (Pacheco et al., 2009). Various immune functions, including cytokine secretion, chemotaxis and cell adhesion, are regulated via dopamine. Besides directly responding to dopamine, immune cells are also indirectly influenced by dopaminergic regulation within the CNS. Hyper-activation of the central dopaminergic system in the mouse VTA was shown to enhance phagocytic activity of splenic dendritic cells and macrophages (Ben-Shaanan et al., 2016). In turn, immune dysfunction is likely to affect dopaminergic signalling in both the CNS and periphery (Mackie et al., 2018).

Until now, cancer biologists have mainly focused on peripheral dopamine and its receptors (Zhang et al., 2017), and therefore, the central dopaminergic system has received little attention for its ability to modulate tumour progression. Several epidemiological studies have suggested that people with schizophrenia, associated with hyper-reactive dopaminergic systems, are relatively protected from developing cancer (Li et al., 2018). However, gender and the type of cancer studied are two important variables because men showed a significant decrease in the incidence of colorectal cancer, whereas women with schizophrenia may have a higher risk of developing breast cancer (Wu Chou et al., 2017). Similarly, the development of Parkinson’s disease, marked by declining dopamine levels, was associated with a lower risk of smoking-related cancers and a higher risk of developing malignant melanoma and breast cancer (Driver et al., 2007). Smaller primary tumours, reduced angiogenesis and a reduced metastatic potential of the tumour were observed following mammary
tumour implantation (MADB106) in Wistar APO-SUS rats with high dopaminergic reactivity, compared with those in APO-UNSUS rats with low dopaminergic reactivity (Teunis et al., 2002). More recently, chemogenetic activation of VTA-dopaminergic neurons was shown to reduce primary tumour volumes in two lung cancer mouse models (LCC and B16 melanoma) (Ben-Shaanan et al., 2018). To study how activation of VTA-dopaminergic neurons within the brain could signal to the primary tumour, the SNS was ablated using the neurotoxin 6-hydroxydopamine (6-OHDA). In mice that received 6-OHDA, activation of VTA-dopaminergic neurons no longer reduced tumour burden. The authors further showed that VTA activation altered the levels of noradrenaline in the bone marrow. Subsequently, this reduced the number of myeloid-derived suppressor cells (MDSCs), which normally promote tumour growth via stimulation of angiogenesis and inhibition of anti-tumour immunity. These findings indicate that central VTA stimulation, and thus enhanced levels of reward and motivation in mice, can modulate the immune system via SNS-mediated suppression of MDSCs (Ben-Shaanan et al., 2018). This emphasises the important translational implications of these rodent studies and suggests that those people who keep active, remain motivated and receive enough emotional support and VTA reward system activation after a cancer diagnosis may show reduced tumour growth/aggressiveness or better responses to chemotherapy treatments (Mehta et al., 2019; Van der Gucht et al., 2020).

The effects of stress and the activation of neural circuitry controlling emotions on tumour progression has been investigated in breast tumour-bearing mice (MDA-231, MCF-7 and 4T1) by subjecting them to unpredictable chronic mild stress (UCMS) (Xu et al., 2020). TH-positive neuronal terminals within the medial PFC (mPFC), which receives dopaminergic afferents from the VTA, were activated via optogenetic stimulation. Here, optogenetic activation of TH-positive terminals within the mPFC rescued anxiety-like behaviour in UCMS stressed tumour-bearing mice. Furthermore, repeated optogenetic stimulation of VTA-TH inputs in the mPFC attenuated the enhanced tumour progression observed in chronically stressed mice. The authors attributed this beneficial effect to reduced serum levels of the stress-related hormones, noradrenaline and corticosterone, in the VTA-TH-activated mice (Xu et al., 2020).

Given the known roles of the VTA in regulating mood, the studies discussed above have uncovered a potential physiological mechanism underlying how a patient’s psychological status may modulate anti-tumour immunity and cancer progression. However, could modulation of tumour progression by the VTA-dopaminergic axis and the SNS have physiological consequences that act back on the brain? In chronic neurological conditions, such as depression, the SNS is known to be continuously activated without the balancing counteractions of the parasympathetic nervous system. This results in immune system activation and increased levels of systemic pro-inflammatory cytokines, which is often reported in patients with depression (Won & Kim, 2016). Therefore, chronic activation of the SNS by the presence of a peripheral tumour could prime the immune system and increase peripheral inflammation that, over time, may lead to depression in people with untreated cancers (Sforzini et al., 2019). Indeed, inflammation-driven alterations to metabolic pathways, such as the indoleamine 2,3-dioxygenase (IDO)-kynurenine and tryptophan 2,3-dioxygenase (BH4) pathways, have been shown to cause substantial alterations in the synthesis of dopamine, 5-HT and noradrenaline and are likely to be the cause of depressive symptoms in cancer patients (Vancassel et al., 2018). In a mouse model inoculated with B16F10 melanoma cells, for example, the tumours induced depressive-like behaviour, as assessed by the tail suspension test, and led to increased levels of IL-6 and TNF-α in the brain (Lebeña et al., 2014). This corresponded with a decrease in dopaminergic activity in the striatum and a decrease in 5-HT in the PFC, with both regions receiving dopaminergic inputs from the VTA (Lebeña et al., 2014).

These alterations in monoamine turnover have been ascribed to tumour-induced dysfunction of metabolic processes within the brain. With this in mind, Kovalchuk et al. (2018) performed direct flow injection/MS (DI-MS) to assess the effects of extra-cranial tumour growth (including lung cancer, pancreatic cancer and sarcoma) on the brain metabolome in mice (Kovalchuk et al., 2018). The authors demonstrated that non-CNS tumour growth affected protein biosynthesis, and amino acid and sphingolipid metabolism. Of five different pathways that were commonly affected in all three cancer types, protein biosynthesis was significantly up-regulated in all three groups. Moreover, amino acid metabolism (including phenylalanine and tyrosine), as well as valine, leucine and isoleucine degradation, was commonly affected (Kovalchuk et al., 2018). Decreased amino acid levels or the deregulation of their metabolic machinery in the brain can cause neuronal death and apoptosis. Moreover, the observed alterations in catecholamine biosynthesis and increased levels of phenylalanine and tryptophan are known to cause neurotransmitter imbalances in levels of 5-HT, dopamine and noradrenaline (Xu et al., 2016). These findings further support the notion that tumour-induced inflammation can cause dysfunctions in monoaminergic systems, which in turn can lead to altered neural signalling in the affected brain regions (Figure 4).

Peripheral tumours are also likely to modulate the CNS by influencing the vagus nerve. The vagus nerve is the main component of the parasympathetic nervous system and relays inflammatory, satiety and metabolic cues to the brain. The vagal afferent fibres terminate within the nucleus tractus solitarius (NTS) in the brain stem, which further projects the information to higher brain regions, including the hypothalamus, locus coeruleus and amygdala (Breit et al., 2018). The vagus nerve has been implicated in various diseases, including cancer. Elevated vagal tone, measured by heart rate variability (HRV), is thought to exert a protective effect on cancer prognosis via the inhibition of oxidative stress, inflammation and sympathetic activity. However, rodent studies investigating the effects of vagal denervation have uncovered both protective and detrimental effects on tumour initiation, progression and metastasis (Partecke et al., 2017; Zhao et al., 2014).
In response to peripheral cancers, the vagus nerve is thought to inform the brain about tumour growth via inflammatory signals. In response, the brain can modulate tumour growth via the neuroendocrine and immune systems (Giese-Davis et al., 2015). Activation of the vagus nerve has been recorded electrophysiologically following peripheral administration of the pro-inflammatory cytokines IL-1β and TNF-α (Tsaava et al., 2020). On one hand, vagal nerve stimulation (VNS) has been shown to be predominantly neuroprotective and ameliorates LPS-induced cognitive dysfunction in mice (Huffman et al., 2019). On the other hand, stress, which is common in cancer patients, inhibits the vagus nerve and has deleterious effects on the gastrointestinal tract and gut microbiota (Bonaz et al., 2018). As such, the vagus nerve also serves as a connection between the enteric nervous system (ENS) and the CNS, also known as the gut–brain axis. The gut–brain axis is responsible for monitoring the body's physiological homeostasis by connecting emotional and cognitive brain areas to peripheral functions, such as immune activation and enteroendocrine signalling. Neuroactive compounds, such as ACh and 5-HT, released by the gut microbiota reach the CNS via the blood and circumventricular organs or via the vagus nerve (Bonaz et al., 2018). Altered compositions of the gut microbiota have been linked to neurological complications, including depression and anxiety (Breit et al., 2018). Given that dysbiosis of the gut microbiome has been reported in cancer patients, gut–brain signalling via the vagus nerve could be another potential pathway for neurological dysfunction in...
pre-treatment cancer patients, although this link is yet to be established (Whisner & Athena Aktipis, 2019).

7 | CONCLUSION

Neurological complications can exert devastating effects on people that develop extra-cranial cancers and can seriously affect their quality of life, their ability to tolerate and complete complex treatment regimens and could even shorten their overall survival rate. Whereas the neurological implications of anti-invasive therapies have received a substantial amount of interest, the existence of cognitive and affective disorders, before treatment has started, indicates that the full aetiology of these complications cannot be solely explained by the anti-cancer treatment itself. The compounding inflammatory and overall disruptive nature of peripheral tumour growth is now being recognised as a major challenge for the CNS (Cerulla Torrente et al., 2020). However, our understanding of how peripheral tumours affect critical functions within the brain is still limited. Elucidation of the molecular mechanisms by which extra-cranial tumours can induce affective and cognitive disorders promises to improve quality of life and treatment outcome in cancer patients. Moreover, the development of novel targeted neurotherapeutic agents that stimulate specific brain regions that are deregulated in cancer will help to overcome hurdles in current treatment strategies. In addition, holistic non-pharmacological approaches to cancer treatment, such as mindfulness and meditation, have already been shown to attenuate inflammation and reduce stress in breast cancer patients via stimulation of the dopaminergic VTA (Bower et al., 2015; Dutcher et al., 2020). However, significantly more research is needed to understand how peripheral tumours communicate with and affect the brain (Box 1). Neuro-immunologists and cancer biologists must work together with oncologists and psychiatrists to develop new ways to treat the whole body, including the brain and mind, if we are to truly beat cancer and give people back their full quality of life after treatment, which is very much dependent on maintaining their cognitive health.

Box 1. Outstanding questions

1. Which (sub)types of cancer correlate with a higher risk of developing tumour-induced affective and cognitive disturbances?
2. What strategies can be applied in the clinic to ameliorate affective and cognitive disturbances in cancer patients before they receive treatment?
3. Can the existence of affective and cognitive disorders, before treatment, predict vulnerability to the development of long-lasting chemotherapy-induced affective and cognitive impairments?
4. Can the brain fully recover after having experienced tumour-induced neurological dysfunctions (i.e., when the tumour is no longer present)?
5. Does an event of tumour-induced neurological dysfunction earlier in life increase vulnerability to the development of age-related neurological disorders?

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Cidlowski et al., 2019; Alexander, Fabbro et al., 2019a,b; Alexander, Kelly et al., 2019a,b).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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