Neuroscience and Biobehavioral Reviews 83 (2017) 474–488

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Major depressive disorder and anxiety disorders from the glial perspective: Etiological mechanisms, intervention and monitoring

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ARTICLE INFO

Keywords:
Glia
Major depressive disorder
Anxiety disorders
Early trauma
Brain imaging
Astrocyte
Oligodendrocyte
Microglia
Radial glia
Psychiatric disorders

ABSTRACT

Despite intense ongoing research efforts, the etiology of psychiatric disorders remains incompletely understood. Among biological factors playing a role in Major Depressive Disorder (MDD) and Anxiety Disorders (ANX), emerging evidence points to the relevance of different types of glia cells and efficient neuron-glia interactions. Here, we review recent findings highlighting the involvement of central nervous system (CNS) glia in MDD and ANX etiology and treatment response. Additionally, several relatively underexplored topics will be discussed: (1) glial response to non-pharmacological therapies, (2) impact of early life adversity on glia, (3) influence of lifestyle factors on glia in the context of MDD and ANX, and (4) monitoring glial functions in patients. It can be concluded that despite the sequence of events is still unclear, alterations in glial cell types are common and somewhat overlapping in ANX, MDD and corresponding animal models. Furthermore, glia are responsive to a variety of treatment and lifestyle options. Looking forward, new research developments can lead to novel types of therapeutic or symptom-relieving approaches targeting glia.

1. Introduction

Psychiatric illnesses constitute a major disease burden in the world, with Major Depressive Disorder (MDD; all abbreviations found in Table 1) being the single leading cause of time loss due to disability for both males and females (Kessler et al., 2005b; World Health Organization, 2016). MDD has lifetime prevalence of around 16%, and this number is projected to increase (Kessler et al., 2003; Lopez et al., 2006; World Health Organization, 2016). Anxiety disorders (ANX) have lifetime prevalence of around 28% (Kessler et al., 2005a). While MDD and ANX are highly heterogeneous diagnostic categories (Nandi et al., 2009), they display significant comorbidity and may share some etiological mechanisms (Avenevoli et al., 2001; Gorwood, 2004; Ruscio and Khazanov, 2017).

A fundamental obstacle to treating MDD and ANX effectively has been an incomplete understanding of the underlying biological mechanisms and of exactly how drugs and other interventions work at the molecular-cellular level. The earliest evidence-based theories on MDD and ANX focused on a deficit of monoamines, in particular, serotonin (Dell'osso and Lader, 2013; Hyman, 2013). While monoaminergic theories of the etiological mechanisms of these diseases have been refined over the years (Booij et al., 2015), it has also become increasingly clear that alterations in monoamine systems are not sufficient to explain the full spectra of MDD and ANX phenotypes and treatment responses.

In the search for underlying mechanisms, the importance of non-neuronal cell types, most notably immune cells and glia, has been increasingly recognized (Di Benedetto and Rupprecht, 2013). Glia comprise several morphologically and functionally distinct cell types that are found in central and peripheral nervous system and are at least as abundant as neurons (Hilgetag and Barbas, 2009). Glia are crucially involved in the regulation of nervous system development (Rakic, 1971, 1972), formation of vasculature and blood-brain-barrier (BBB) (Siqueira et al., 2017), signal transmission (Baumann and Pham-Dinh, 2001; Bunge et al., 1962; Pomeranz et al., 1968), synapse formation (Ango et al., 2008; Elmariah et al., 2005; Pfrieger and Barres, 1997; Sild et al., 2016) and neuroplasticity (Araque et al., 1999; Panatier et al., 2006; Papouin et al., 2017). Such variety of functions has prompted research of glial participation in the etiology of psychiatric disorders and as possible drug targets (Di Benedetto and Rupprecht, 2013; Manev et al., 2003). Accumulating evidence points to glial alterations in all major psychiatric conditions, although schizophrenia and MDD have received the most research attention in this context (Bernstein et al.,

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http://dx.doi.org/10.1016/j.neubiorev.2017.09.014
Received 3 July 2017; Received in revised form 8 August 2017; Accepted 11 September 2017
Available online 14 September 2017

Table 1
Abbreviations.

Abbreviation	Meaning
5-HT	5-Hydroxytryptamine
ACC	Anterior Cingulate Cortex
AD	Antidepressant
ANX	Anxiety Disorders
ATP	Adenosine Triphosphate
BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
CNS	Central Nervous System
EE	Environmental Enrichment
FGF	Fibroblast Growth Factor
GAD	Generalized Anxiety Disorder
GDNF	Glial Cell Line-Derived Neurotrophic Factor
GFAP	Glial Fibrillary Acidic Protein
GLAST	Glutamate Aspartate Transporter
GLT-1	Glutamate Transporter 1
GR	Glucocorticoid Receptor
HDAC	Histone Deacetylase
HDACi	Histone Deacetylase Inhibitor
LPS	Bacterial Lipopolysaccharide
MDD	Major Depressive Disorder
mPFC	Medial Prefrontal Cortex
NG2	Neural/Glial Antigen 2
OCD	Obsessive Compulsive Disorder
OD	Oligodendrocyte
PFC	Prefrontal Cortex
RG	Radial Glia
SAD	Seasonal Affective Disorder
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TSPO	18 kDa Translocator Protein
VEGF	Vascular Endothelial Growth Factor
VGF	VGF Nerve Growth Factor Inducible

2015; Dallerac and Rouach, 2016; Di Benedetto and Rupprecht, 2013; Elsayed and Magistretti, 2015; Laskaris et al., 2016; Rajkowska and Stockmeier, 2013; Rial et al., 2015; Takahashi and Sakurai, 2013; Wang et al., 2017).

The present review focuses specifically on glial roles in the most common mental disorders, MDD and ANX. Furthermore, the notion that these two psychiatric conditions are often co-morbid may imply some commonalities in glial alterations. However, roles of glia have been much less explored in ANX than in MDD. In addition to a broad overview of the potential roles of glia in MDD and ANX etiology, several topics less discussed elsewhere will be covered here: glial response to different types of therapies, impact of early life adversity on glia, effect of lifestyle factors on glia, and the possibilities of monitoring glial properties as indicators for diagnoses and treatment response. The overall aim of this article is to give a timely, yet concise overview of multiple perspectives of how glial cells may participate in the etiology and treatment of MDD and ANX.

This review starts with a brief introduction to central nervous system (CNS) glia development and subtypes, followed by an overview of findings of glial alterations in MDD, ANX and related animal models. Next, since exposure to early life adversity is a major risk factor for development of MDD and ANX in later life (Heim and Nemeroff, 2001; Kessler et al., 2010), a section is devoted to glial responses to different types of early life stress. We will discuss how glia are affected by pharmacological and non-pharmacological MDD and ANX treatments and lifestyle factors. Some means of monitoring glial function in living humans will be covered. The overarching hypothesis of this review article is that glial alterations that are present in MDD and ANX may serve as important cues for the disease etiology and as targets for therapeutic approaches.

2. Overview of central nervous system glia and their functions

Central nervous system (CNS) glia, which include astrocytes, oligodendrocytes, NG2 cells, radial glia, microglia and ependymal cells – carry out a number of crucial support and regulatory functions in the mature CNS that are outlined in Table 2. Importantly, glia are also critically involved in the development of the CNS from very early prenatal stages. Radial glia derive directly from the nervous system stem cells (neuroepithelial cells) and are already present when the first immature neurons form in the CNS (in humans around gestational week 4) (Barry et al., 2014; Gotz and Huttner, 2005; Rakic, 1972). From there on, radial glia serve as guidance substrates for neuronal migration (Rakic, 1972), direct growing axons to their target locations (Norris and Kalil, 1991; Silver et al., 1982) and induce angiogenesis (Siqueira et al., 2017) thus structurally organizing the CNS neural network. Furthermore, radial glia themselves are progenitors for neurons (Kriegstein and Alvarez-Buylla, 2009; Noctor et al., 2001) and other glia (*i.e.*, astrocytes, oligodendrocytes and ependymal cells) that appear slightly later in the development (Budday et al., 2015; Pinto and Gotz, 2007). In contrast, microglia are not derived from radial glia but from yolk sac macrophage precursors, and enter the brain around the time of neurogenesis (Ginhoux et al., 2010; Reemst et al., 2016). Deviations in glial functions during development have already been shown to cause major neurodevelopmental diseases like lissencephaly (Wu and Wang, 2012). Lissencephaly patients experience intellectual disability and a number of other problems, which are thought to result from abnormal neuronal migration and neurogenesis, due to radial glial failure to adopt their correct morphology (Pawlisz and Feng, 2011).

Furthermore, during development a critical structure for brain protection, the blood-brain barrier (BBB), is formed as an interaction of blood vessels with microglia, astrocytes, pericytes and neurons (Abbott,

Table 2
Glial subtypes in the central nervous system.

Type of glia	Key characteristics	For more info, recent reviews
Astrocytes	Coordinate synapse formation, maintenance and plasticity; provide energy substrates to neurons; regulate extracellular ionic and neurotransmitter balance; release neurotrophic factors, regulate vasculature tone.	Dallerac and Rouach (2016), Lundgaard et al. (2014), Vasile et al. (2017)
Oligodendrocytes	Produce insulating myelin sheeth around the axons (necessary for high velocity electrical conduction).	Bergles and Richardson (2015), Michalski and Kothary (2015)
NG2 glia	Considered largest population of resident progenitor cells for oligodendrocytes, astrocytes and possibly neurons. Respond to trauma with fast proliferation as primary source of remyelinating cells.	Eugenin-von Bernhardi and Dimou (2016), Vigano and Dimou (2016)
Microglia	Phagocyte immune cells of the central nervous system. Can adopt pro- or anti-inflammatory forms. In addition to pathogens, thought to phagocytose neurons and synapses to sculpt neural circuits, sometimes in a destructive way.	Hong et al. (2016), Prinz and Priller (2014), Ransohoff and El Khoury (2015)
Radial glia	Progenitors of neurons and other glia. Directional scaffolds for migrating neuroblasts and axons. Regulate synapse formation and maintenance.	Barry et al. (2014), Malatesta and Gotz (2013), Sild and Ruthazer (2011)
Ependymal cells	Progenitors for neurons and glia. Participate in maintenance of blood-brain barrier, neuroendocrine events and thought to coordinate directional movement of cerebrospinal fluid.	Del Bigio (2010), Kyrousi et al. (2017)

2005; Siqueira et al., 2017). An incomplete BBB has been suggested to be a major contributing factor in neurological and psychiatric disorders including migraine, MDD and schizophrenia (DosSantos et al., 2014; Shalev et al., 2009).

In conclusion, in addition to the versatile roles of glia in the adult CNS, glia are crucial for proper formation of the CNS in early development. More research is required to elucidate whether and how alterations in glial functions during early development could associate with psychiatric conditions later in life like MDD and ANX.

3. Glia – lost and confused in depression

Glial status in individuals with MDD has been mainly assessed in post-mortem samples by counting different types of cells, visualizing cell morphology or measuring glia-related substances. Despite limitations of such studies including small sample sizes, different post-mortem time periods and life histories that might introduce heterogeneity within and between studies, a number of glia-related alterations have been reported that are reviewed here.

3.1. Human brain – glial number

Magnetic Resonance Imaging (MRI) studies have shown smaller brain volumes, including in the frontal cortex and hippocampus, in living MDD patients in comparison to control groups (Bremner et al., 2000; Lorenzetti et al., 2009; MacQueen et al., 2008). Investigations of post-mortem brains of MDD patients have not given consistent results regarding whether there might be a change in neuronal number (Bielau et al., 2007; Hercher et al., 2009; Maciag et al., 2010; Rajkowska et al., 2005; Rajkowska et al., 2007; Smiley et al., 2015; Steiner et al., 2008), however a number of post-mortem studies of individuals with MDD found decreased glial number or density (Hercher et al., 2009; Rajkowska and Stockmeier, 2013) in amygdala (Altshuler et al., 2010; Bowley et al., 2002), prefrontal cortex (PFC) (Cotter et al., 2002; Ongur et al., 1998; Rajkowska et al., 1999), anterior cingulate cortex (ACC) (Cotter et al., 2001) and hippocampus (Cobb et al., 2013; Gos et al., 2013; Muller et al., 2001) as compared to age-matched controls. Using specific markers to identify affected glial subtypes, reduction in oligodendrocytes was shown in post-mortem amygdala (Hamidi et al., 2004) and PFC (Honer et al., 1999; Regenold et al., 2007; Tham et al., 2011; Uranova et al., 2004), reduction of NG2 glia was found in post-mortem frontal cortices (Birey et al., 2015) while decrease in an astrocyte marker glial fibrillary acidic protein (GFAP) was reported in post-mortem hippocampus (Muller et al., 2001) and amygdala of MDD patients (Altshuler et al., 2010). GFAP levels in PFC may be linked to age, as in post-mortem PFC samples from groups of MDD patients of over 45 years (Miguel-Hidalgo et al., 2000) or over 60 years of age (Davis et al., 2002; Si et al., 2004) GFAP was found increased compared to age-matched controls. The respective younger MDD patient groups in these studies demonstrated a decrease in post-mortem PFC GFAP as compared to the age-matched controls (Miguel-Hidalgo et al., 2000; Si et al., 2004). This suggests a possible interplay between aging processes and MDD.

In a subset of depressed suicide victims, GFAP was found to be downregulated in mediodorsal thalamus, caudate nucleus and with a number of other astrocyte-enriched genes in PFC (Nagy et al., 2015; Torres-Platas et al., 2016). Microglia, on the other hand, were more numerous in brains of individuals with MDD that had committed suicide than in control post-mortem brains (Schnieder et al., 2014; Steiner et al., 2008). However, in these studies of depressed suicides, the control group was not depressed and did not die by suicide, leaving a possibility that these cellular changes were suicide- rather than MDD-related.

In conclusion, smaller brain volumes of MDD sufferers may be attributable to alterations in glial number, rather than in neuronal number.

3.2. Human brain – glial morphology

Examination of MDD patients' brain on a microscopic level has revealed alterations in glial morphology and function. Oligodendrocyte soma size was reported to be decreased and myelin-related gene expression dysregulated in gyral white matter of the MDD group (Rajkowska et al., 2015), which corroborates reported white matter hypoplasia and microstructural abnormalities in MDD brains (Alexopoulos et al., 2002; Nobuhara et al., 2006; Peterson and Weissman, 2011). Compared to the control group, fibrous astrocytes of the ACC white matter of depressed suicide victims' post-mortem brain samples were found to have longer, more ramified processes and larger cell bodies (Torres-Platas et al., 2011). Functional consequences of such hypertrophy are unclear, but due to the increase in activated microglia in the same brain area, it was suggested to reflect local inflammation (Torres-Platas et al., 2014). Despite this possible expansion of astrocyte size reported in one study, in another post-mortem study of individuals with MDD, coverage of PFC vasculature with astrocyte processes (stained for aquaporin-4 marker) was found to be only around 50% of that of the control group. Notably, comparing GFAP-positive astrocyte coverage did not reveal a difference between groups in this study (Rajkowska et al., 2013). Such results could mean significant malfunction of the BBB, which has elsewhere been suggested to constitute an underlying pathology in depression (Shalev et al., 2009).

3.3. Inflammation

BBB leakage would enable entrance of peripheral inflammatory substances and macrophages that would further contribute to the excess inflammatory condition in the CNS (McNally et al., 2008). Whether due to altered BBB or not, activation of pro-inflammatory pathways in MDD has been observed relatively frequently (Haapakoski et al., 2016; Miller and Raison, 2016; Raison et al., 2006). Microglia are a major source of inflammatory substances (including cytokines, nitric oxide and reactive oxygen species) in the CNS (Lisboa et al., 2016; Prinz and Priller, 2014). However, the microglial pro-inflammatory "activated" state has not been found as consistently present in MDD post-mortem samples as in neurological conditions like Parkinson's disease, epilepsy and multiple sclerosis (Bhattacharya and Drevets, 2016). Depression phenotypes have in different studies been associated with both microglial pro-inflammatory over-activation and senescence processes (Yirmiya et al., 2015).

3.4. Neurotrophins

Decreased expression of the brain-derived neurotrophic factor (BDNF) (Castren and Kojima, 2016; Polyakova et al., 2015; Satomura et al., 2011; Wolkowitz et al., 2011) and misregulation of other trophic factors like fibroblast growth factor (FGF) (Evans et al., 2004; Turner et al., 2012) have been detected in MDD patients' post-mortem brains as well as serum and plasma (Boku et al., 2013; Duman and Monteggia, 2006; Sharma et al., 2016). Glia are an important source of neurotrophins (Bessis et al., 2007; Riley et al., 2004; Taylor et al., 2003). Furthermore, BDNF release from astrocytes and microglia is necessary for some learning-induced plasticity processes (Jean et al., 2008; Parkhurst et al., 2013; Sun et al., 2016). Inflammation may disturb glial neurotrophin release through interactions with glucocorticoid receptors (GR) (Cai et al., 2015) the expression of which was found to be two-fold higher in MDD post-mortem amygdala astrocytes as compared to controls (Wang et al., 2014).

More research is needed to determine whether neurotrophin level alterations observed in MDD originate primarily from changes in glial functions.

3.5. Glucocorticoids and glutamate

The hypothalamic-pituitary-adrenal (HPA) axis hyperactivity has long been implicated as a feature of the MDD (Pariante and Lightman, 2008) and glucocorticoids are important mediators of the HPA axis that can act in a harmful or protective way, depending of the context (Anacker et al., 2011). Glucocorticoid receptor (GR) expression level was found significantly higher in post-mortem amygdala astrocytes from patients with MDD as compared to the controls (Wang et al., 2014). The *in vivo* implications are not clear (Jauregui-Huerta et al., 2010). *In vitro*, glucocorticoids inhibit astroglial capacity to transport glucose and uptake glutamate (Virgin et al., 1991). In possibly related observations, glial glutamate transporters Glutamate Aspartate Transporter (GLAST) and Glutamate Transporter 1 (GLT-1) were noted to be downregulated in MDD post-mortem cerebral cortices (Choudary et al., 2005). Glutamate levels in the cortex, plasma and cerebrospinal fluid of the individuals with MDD have mostly found to be elevated relative to the controls, together with increased glutamine (Auer et al., 2000; Hashimoto et al., 2007; Kim et al., 1982; Levine et al., 2000; Mathis et al., 1988; Sanacora et al., 2004). Prolonged high glutamate levels could contribute to the loss of synapses (Kang et al., 2012) (Gilabert-Juan et al., 2012), dendritic cytoarchitecture (Hercher et al., 2010; Rosoklija et al., 2000) and PFC, hippocampus and amygdala gray matter observed in MDD patients (Sacher et al., 2012; Stockmeier et al., 2004; Zhao et al., 2014). The role of hyperglutaminergia in MDD was further supported by a study with 19 treatment-resistant depressed patients, all of whom showed significant improvement after treatment with Riluzole – a compound thought to increase astrocytic glutamate uptake (Zarate et al., 2004).

In summary, macroscopic and microscopic glial alterations are prevalent in the brains of individuals with MDD. Due to the mostly cross-sectional study designs, it remains unclear whether such glial alterations constitute a genuine risk factor or are a consequence of MDD.

4. Rodent models of adult depression

Chronic stress is the most common paradigm used to create a depression-like state in rodents, recapitulating some features of depression like anhedonia and helplessness, often accompanied by increased anxiety (Krishnan and Nestler, 2011). However, rodent and human glia may be morphologically and functionally different (Han et al., 2013; Oberheim et al., 2009; Torres-Platas et al., 2011). Hence, results from rodent studies need to be interpreted with caution.

4.1. Astrocytes

Chronic social or unpredictable stress (CUS) brings about a number of glial changes in rodents, for example a decrease in levels of the astrocyte marker GFAP in hippocampus (Araya-Callis et al., 2012; Czeh et al., 2006; Liu et al., 2011) and PFC (Banasr and Duman, 2008) where it was also correlated with diminished glial cell metabolism (Banasr et al., 2010). Altered expression of glial glutamate transporters and elevated glutamatergic transmission were reported in rodent depression models (Banasr et al., 2010; Gomez-Galan et al., 2013; Reagan et al., 2004). Conversely, pharmacologically blocking the glial glutamate transporter, even only in central nucleus of the amygdala, elicited anxiety- and depression-like symptoms in rats (John et al., 2015). Riluzole, a drug thought to decrease glutamate release and enhance astrocytic glutamate uptake, reversed chronic stress-induced behavioural alterations in sucrose preference and active avoidance and normalized glial acetate metabolism and GFAP mRNA expression (Banasr et al., 2010). Another drug stimulating astrocytic glutamate uptake, Ceftriaxone, had antidepressant effects on mice even without stress exposure, reducing immobility and freezing in the forced swim and tail suspension tests (Mineur et al., 2007). Additionally, the glia-regulated co-agonist of glutamatergic neurotransmission, D- serine (Van Horn et al., 2013), and the glial and neuronal signaling molecule adenosine triphosphate (ATP) (Fields and Stevens, 2000) were found to have lower than normal levels in rodent depression model brains (Cao et al., 2013; Gomez-Galan et al., 2013). Blocking astroglial ATP release was sufficient to cause depressive-like behaviours in mice that could in turn be rescued with ATP administration (Cao et al., 2013). Exact targets of astroglial ATP in preventing the development of depressive-like symptoms are yet unclear, but likely to include neurons and other types of glia (Fields and Stevens, 2000; Rial et al., 2015).

4.2. NG2 glia

Genetically ablating over 25% of NG2 glia from the cerebral cortex and hippocampus resulted in depressive-like behaviours in mice, producing increased anxiety, anhedonia and social avoidance (Birey et al., 2015). NG2 glia depletion also correlated with reduced astrocytic glutamate uptake in the PFC and hippocampus, indicating that NG2 glia may regulate astrocytes (Birey et al., 2015). NG2 glia repopulation rescued all the phenotypes that were shown to be mediated by NG2 glial release of trophic factor FGF2 (fibroblast growth factor 2) (Birey et al., 2015). Interestingly, 8 days of social defeat stress decreased NG2 glia density in rodent hippocampus (CA1) and PFC, but only in a subgroup of mice (around 60%) that responded to the stress with depression-like behavioural alterations and were thus deemed “susceptible”. The remaining mice did not respond to the stress paradigm with behavioural changes and were termed “resilient”. This demonstrates glial implications in the interindividual variations in stress vulnerability (Birey et al., 2015). Further investigation is still needed to clarify if causes for such variations between individuals lie within glia themselves or in other systems interacting with glia. Emerging data points to the importance of epigenetic regulation as a source for individual differential responses to stress (Zovkic et al., 2013).

The decrease in NG2 cells could lead to a decline in mature oligodendrocyte number as reported in the cortex of the chronic stress animal models (Banasr et al., 2007). At the same time, NG2 cells might disappear due to differentiation into oligodendrocytes. It has been found that chronic stress induces oligodendrogenesis in the hippocampus, possibly forming a cellular and structural basis for stress-related disorders vulnerability (Chetty et al., 2014). Chronic stress-related morphological changes of NG2 cells (excess arborisation) have also been reported (Miyata et al., 2011). However, despite potentially larger oligodendrocyte branch arbours, axon wrapping in the corpus callosum of similarly chronically stressed mice was shown to be defective (Miyata et al., 2016). Interestingly, changes in myelination can also be induced by signals from other non-myelinating glia, namely astrocytes or microglia (Domingues et al., 2016). For instance, pro-inflammatory microglia, suggested to be present in MDD, caused myelin damage in mixed cell culture (di Penta et al., 2013).

Thus, despite it still being early days in the research concerning NG2 glia in MDD and ANX, it can already be concluded that NG2 glia quickly respond to stress and may have promising roles in the prevention of the development of depressive-like phenotypes.

4.3. Microglia

Several types of chronic stress have been found to induce microglial proliferation (Nair and Bonneau, 2006) or pro-inflammatory activation (Chabry et al., 2015; Wohleb et al., 2011) in brains of rodents, together with depressive-like behavioral phenotypes. On the other hand, treatment with minocycline, an antibiotic known to suppress microglial pro-inflammatory activation (Kobayashi et al., 2013), was shown to prevent chronic stress-induced memory impairment (Hinwood et al., 2012; Liu et al., 2015) and learned helplessness (Arakawa et al., 2012; Iwata et al., 2016).

Although inflammation-activated microglia are usually considered

to have an ameoboidal morphology, microglia with excessively branched processes have been observed in some rodent depression model studies. Such hyper-ramification can be reversed with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Hellwig et al., 2016) and minocycline (Hinwood et al., 2013). The consequences of excessive microglial branching are not clear, but a similar phenomenon has been noticed in the normal human aging process (Streit and Sparks, 1997; Streit et al., 1999).

Thus, chronic stress in rodents elicits glia-related changes resembling those seen in human MDD: decrease in glial markers, aberrations in glutamatergic transmission, alterations in glial factor release and inflammation. Furthermore, animal studies have revealed intricate signaling systems not only between glia and neurons, but between different types of glia.

5. Glia in anxiety disorders

Surprisingly little is known about the roles of glia in ANX. High comorbidity of ANX and MDD in patients and common co-occurrence of depression- and anxiety-like phenotypes in chronic stress animal models challenge separation of the disorders. It has been postulated that ANX and MDD share some disease mechanisms (Gorwood, 2004). Thus, some (glial) pathologies in ANX may resemble those of MDD.

Similarly to MDD, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to be efficient in the treatment of ANX in many patients (Ballenger, 1999; Lee and Keltner, 2006). Serotonin induces calcium transients in cultured rat astrocytes and human enteric glia (Boesmans et al., 2013; Hansson et al., 2008; Munsch and Deitmer, 1992) that may indicate similar interaction with other glia. Calcium transients may signify glial structural plasticity, cytogenesis and/or the release of glial factors (Arpin-Bott et al., 2006; Bernardinelli et al., 2014; Metea and Newman, 2006). D-serine, ATP and trophic factors FGF2 and BDNF are among factors that are released by glia and have been repeatedly shown to have anxiolytic and anti-depressant effects (Birey et al., 2015; Cao et al., 2013; Elsayed et al., 2012; Malkesman et al., 2012; Perez et al., 2009; Quesseveur et al., 2013; Ressler et al., 2004; Xia et al., 2013). Concordantly, FGF2 expression levels were found to be lower in the hippocampus of rats selectively bred for high anxiety as compared to the low-anxiety rats of the same breed (Perez et al., 2009), whereas injection of FGF2 decreased anxiety behaviour of a Post-Traumatic Stress Disorder (PTSD) rodent model compared to the control injection group. Interestingly, PTSD-like rats that received FGF2 exhibited normal expression levels of hippocampal astrocytic GFAP that was otherwise found to be downregulated in the PTSD-like rats that received only control injection (Xia et al., 2013).

In addition to astrocytes themselves (Kirby et al., 2013), NG2 glia were shown to be a major source of FGF2. Loss of FGF2 secretion from NG2 glia in mouse PFC induced anxiety-like behaviour and social avoidance. As ablation of NG2 glia in the same study distorted astrocytic glutamate uptake, it was suggested that behavioural phenotypes depend at least partially on NG2-glial FGF2 release-mediated glutamate homeostasis (Birey et al., 2015). Consistent with these findings, injection of glial glutamate transporter inhibitor dihydrokainic acid (DHK) into the amygdala resulted in anxiety-like behaviours in mice (John et al., 2015) and the astrocytic glutamate uptake enhancer riluzole improved the condition of generalized anxiety disorder patients (Mathew et al., 2005). Hence, despite studies of glia in ANX are preliminary, accumulating evidence hints that glial regulation of trophic factors and glutamate homeostasis are likely processes to be altered in the ANX.

Also similarly to MDD (Nobuhara et al., 2006), brain imaging studies have revealed differences in white matter and connectivity between controls and individuals with ANX (Atmaca et al., 2010; Ayling et al., 2012; Etkin et al., 2009) These findings may reflect alterations in oligodendrocyte properties in ANX relative to controls. Systemic reduction of oligodendrocyte number/myelin by treatment with the toxin cuprizone elicted anxiety-like behaviour in rats in the open field and elevated plus maze tests as compared to the controls. However, cuprizone also induced inflammation (Serra-de-Oliveira et al., 2015) that may partially explain behavioural changes. Inflammation has been associated with ANX (Hoge et al., 2009; Vogelzangs et al., 2013). Interestingly, benzodiazepines (Ballenger, 1999) have been found to reduce microglial pro-inflammatory state and cytokine tumor necrosis factor α (TNFα) release (Lokensgard et al., 1998). Astrocytes and oligodendrocytes appear to also possess peripheral benzodiazepine receptors (PBR) (Ji et al., 2008; Lokensgard et al., 1998; Zlobina et al., 1982) but how benzodiazepines regulate their function, remains yet to be investigated.

In conclusion, based on the emerging data on glial state in MDD, ANX and respective animal models, there is an overlap in which glial functions may be altered in MDD and ANX. Glia-related processes that may be affected in both disorders include (but are not limited to) inflammation, trophic support, and glutamate homeostasis. Furthermore, animal studies point to the importance of glia-glia crosstalk in prevention of depressive- and anxiety-like phenotypes.

6. Impact of early adversity on glia

Prenatal or early life adversity is a significant risk factor for psychiatric disorders later in life (Benjet et al., 2010; Heim and Nemeroff, 2001; Kessler et al., 2010; Scott et al., 2012; Weinstock, 2008). Patients with MDD who have experienced trauma early in life are less likely to achieve completely depression-free state (Fuller-Thomson et al., 2016). Knowing that CNS glia appear very early in prenatal development (Barry et al., 2014; Gotz and Huttner, 2005), and that glia are among other functions required for correct assembly and maintenance of the neural circuits and vasculature (Attwell et al., 2010; Rakic, 1972; Sild et al., 2016; Silver et al., 1982; Verkhratsky and Nedergaard, 2014) and responsive to stress (Jauregui-Huerta et al., 2010), it is important to investigate if and how early life adversity can maladaptively change glial properties and whether such changes are permanent.

6.1. Prenatal adversity

Rodent prenatal stress paradigms have been used to probe later-life consequences on glia. Several pro-inflammatory glial phenotypes have been reported in association with pre-natal stress. Maternal treatment with bisphenol A (BPA; organic synthetic compound widely used in plastic household products (Srivastava et al., 2015)) induced microglia and astrocyte activation in the PFC of female juvenile offspring together with anxiety-like behaviour. BPA concentration in dam blood was estimated to be similar to usual human exposure. Males were not analyzed in this study (Luo et al., 2014). Alterations in neurotrophin and pro-inflammatory cytokine production were reported for cultured microglia from male adult offspring of rats who had been chronically stressed with bright light exposure during second half of the pregnancy. Compared to the age-matched controls, prenatally stressed males exhibited increased anhedonia and helplessness as adults (Slusarczyk et al., 2015). Increased number of hippocampal Iba-1 microglia and exaggerated inflammatory response to bacterial lipopolysaccharide (LPS) administration were detected in adult (female ovariectomized) offspring of dams that underwent restraint stress during pregnancy (Diz-Chaves et al., 2012). Prenatal restraint stress has also been associated with astrocyte hypertrophy (Barros et al., 2006). Further analysis of how inflammation interacts with depression- or anxiety-like phenotypes is necessary.

On the other hand, a decrease in the astrocyte marker glial fibrillary acidic protein (GFAP), the myelin basic protein (MBP) (Bennett et al., 2015) and a reduction in glial number (Behan et al., 2011) have been reported in hippocampus of rodents who were exposed to prenatal stress (Behan et al., 2011; Bennett et al., 2015). In one of these studies,

pregnant guinea pigs were stressed with repeated strobe light. Their juvenile offspring exhibited increased anxiety-like and neophobic behaviour compared to controls (Bennett et al., 2015). In the second study where restraint stress was applied to pregnant mice, glial loss and anhedonia were reported only for the female offspring whereas offspring of both sexes demonstrated memory impairment (Behan et al., 2011).

Intriguingly, a depression-like state of the dams can extend an influence over the offspring even if chronic stress stimuli have ended before pregnancy. Female mice that had undergone a 6-week chronic mild stress protocol before conceiving gave rise to offspring that as adults exhibited 29% less GFAP-positive cells in the hippocampus compared to the controls, as well as increased anxiousness and lower exploratory behaviour. Interestingly, the significant decline in GFAP-astrocytes became obvious only in adult stages (Gong et al., 2012).

Conversely, some early-life rodent stress experiences with alcohol or LPS exposure have been reported to have an anxiolytic effect in later life (Brolese et al., 2014; Wang et al., 2013). This is not necessarily beneficial, since prenatal LPS treatment was also associated with activated microglia, hippocampal axonal defects and learning disabilities in later life of the female pups (males not studied) (Wang et al., 2013) whereas prenatal moderate alcohol exposure altered levels of astrocyte marker GFAP and astrocyte/oligodendrocyte marker S100b in male offspring (females not studied) (Brolese et al., 2014). In another study, heavy alcohol consumption in adolescence increased anxiety in female adult rats (males not studied) together with a loss of hippocampal astrocytes, neurons and microglia (Oliveira et al., 2015). Thus, the effects of toxins or stress are likely age-, dose-, and brain area-specific. Sex-specific differences in glial alterations in response to prenatal stress are possible as well (Behan et al., 2011), but this needs more exploration as in current studies there is generally no comparison between sexes or only one sex is included.

6.2. Post-natal adversity

The brain remains sensitive to stress during post-natal development (Heim and Nemeroff, 1999, 2001). Maternal deprivation is a commonly used rodent early life stress paradigm, and has been correlated with decreased GFAP-immunoreactive astrocyte density in adult rat PFC, hippocampus and amygdala (Leventopoulos et al., 2007). Maternal deprivation was associated with increased process motility of somatosensory cortex microglia in adult mice. The level of glial process motility correlates with changes in neuronal function (nociceptive threshold level). It has been suggested that microglia may respond to the 4-fold higher level of glutamate that has been detected in the maternal deprivation group cortex (Takatsuru et al., 2015), which may be due to dysregulation of astroglial glutamate transport, as was observed in the hypothalamus of pre-pubertal rats who had experienced suboptimal maternal care (Gunn et al., 2013). Astroglial glutamate transporter GLT-1 was found to be downregulated in the hippocampus of adult rats who had experienced juvenile uncontrollable stress relative to non-stressed age-matched controls (Albrecht et al., 2016). A different type of early life experimental stressor − excess noise − reduced cingulate cortex astrocyte number, cytogenesis and capacity to re-learn a task in adult rats. Curiously, in infra- and prelimbic areas, noise group astrocytes appeared to have a more complex ramified morphology (Ruvalcaba-Delgadillo et al., 2015) which may constitute an attempt to compensate for the functions of locally lost glia cells, for example by interacting with more synapses that would otherwise have been serviced by other astrocytes.

Effects of early life adversity may manifest in a different way during adulthood as compared to the juvenile stages (Gong et al., 2012). More studies are needed to assess how early life stress shapes glial functions through lifespan and whether different types of stressors can lead to distinct consequences.

6.3. Possible epigenetic changes

Epigenetic processes have been shown to mediate some early trauma-related physiological changes (Reus et al., 2013; Weaver et al., 2004). Whether and which epigenetic modifications occur specifically in glia in response to early adversity has not yet been investigated *in vivo*. However, use of a known mood stabilizer and histone deacetylase inhibitor (HDACi) valproic acid in rat astrocyte culture enhanced histone H4 acetylation at glial glutamate transporter GLT1 promoter and increased transcription of GLT1 (Perisic et al., 2010). That can lead to more efficient glial glutamate uptake (Perisic et al., 2010). In another study, three different HDACi-s were shown to upregulate neurotrophins GDNF and BDNF expression in astrocytes, through GDNF promoter histone acetylation, leading to protective effect on dopamine neurons in the same culture (Wu et al., 2008). Glial differentiation (including GFAP expression) and neurogenesis are also epigenetically controlled (Hsieh and Eisch, 2010; Takizawa et al., 2001). Furthermore, although little is currently known regarding epigenetic modifications in glia in the context of MDD and ANX, studies with a subgroup of depressed suicide victims (selected for decreased astrocyte markers) suggested that such downregulation of astrocyte genes might at least partially occur due to epigenetic mechanisms like DNA and histone methylation (Nagy et al., 2015; Nagy et al., 2016). Thus, expression of glial genes relevant in MDD and ANX may be epigenetically regulated and is likely to be (reversibly) modified by early-life environmental conditions.

7. Glia in treatment strategies

7.1. Antidepressants

Antidepressant (AD) medications are used for treatment of both MDD and ANX. ADs interact with glia in various ways. It has even been suggested, that certain ADs primarily target glia and that effects on neurons are secondary (Iwata et al., 2011; Tanasic et al., 2016). For example, treatment with fluorocitrate [a toxin preferentially disrupting glial metabolism] blocked AD effects of imipramine in a rodent learnt helplessness paradigm (Iwata et al., 2011).

ADs have been found to change expression pattern of glia-specific genes like GFAP, vimentin, aquaporin (Czeh and Di Benedetto, 2013; Manev et al., 2003) and affect glial cell numbers. In rodents, treatment with the SSRI fluoxetine counteracted chronic stress-induced loss of hippocampal astrocytes and PFC NG2-cells (Czeh et al., 2007; Czeh et al., 2006; Elsayed et al., 2012). Glia can respond to 5-hydroxytryptamine (5-HT or serotonin) directly, since at least human and rat astrocytes express serotonin transporters (Inazu et al., 2001; Kubota et al., 2001) and the 5HT1A receptor (Deecher et al., 1993). Elevated 5-HT levels due to SSRI-s have been suggested to induce glial differentiation and trophic factor release (Morita et al., 2006; Morita and Her, 2008). 5-HT effects on neurons *in vitro* (such as neurite outgrowth) have been found to be more evident in the presence of glia (Liu and Lauder, 1992), which implies that glia can moderate neuronal response to 5-HT. However, it has also been reported that certain AD effects on glia like increased glucose uptake, lactate release and neurotrophin production may occur independently of 5-HT (Allaman et al., 2011).

Different ADs have been shown to induce expression of glial neurotrophic factors. The SSRIs fluoxetine and paroxetine were found to increase BDNF, vascular endothelial growth factor (VEGF), VGF nerve growth factor inducible (VGF) expression and boost glucose metabolism in murine cortical astrocytes. In this study, tricyclic ADs had no effect on neurotrophin expression nor on glial glucose metabolism (Allaman et al., 2011). However, in other studies, a tricyclic AD amitriptyline was found to increase glial cell line-derived neurotrophic factor (GDNF) expression in the C6 glial cell line (Hisaoka et al., 2007) and FGF-2, BDNF, VEGF and GDNF expression in rat cortical astrocyte culture (Kajitani et al., 2012).

It is possible that SSRIs directly induce release of glial factors, since

an *in vitro* study demonstrated that medial prefrontal cortex (mPFC) astrocytes respond to 5-HT and SSRI administration with a specific calcium transient pattern, even when neuronal activity was inhibited (Schipke et al., 2011). Glial calcium transients are thought to be linked to release of glial factors, structural plasticity or cytogenesis (Arpin-Bott et al., 2006; Bernardinelli et al., 2014; Metea and Newman, 2006). Importantly, in the same study, exposure of astrocytes to excess glutamate eliminated glial calcium responses to 5-HT, indicating that the hyperglutaminergic condition, thought to occur in MDD, can interfere with glial interaction with 5-HT (Schipke et al., 2011).

Interestingly, microglia may react to ADs in an opposite way compared to astrocytes, as SSRIs paroxetine and sertraline inhibited interferon-γ-induced calcium transients in a mouse microglial cell line, with a subsequent decreased release of tumor necrosis factor-α and nitric oxide (Horikawa et al., 2010). Amitriptyline was reported to reduce bacterial lipopolysaccharide (LPS)-stimulated interleukin-1beta release in rat microglial culture (Obuchowicz et al., 2006). Imipramine suppressed stress-induced hippocampal microglial activation *in vivo* (Iwata et al., 2016). Furthermore, inhibiting microglial activation with fluoxetine was shown to promote the survival of oligodendrocytes and better preservation of myelin and axons in a rodent injury model (Lee et al., 2015). Thus, ADs may promote astrocyte neurotrophic activities while suppressing microglial detrimental pro-inflammatory state.

Finally, there are some reports of glial implications in the negative side effects of ADs. For example, with regard to memory impairment, one of the most common side effects of antidepressants (Nagane et al., 2014), it was revealed that a tricyclic AD desipramine can hinder hippocampal synaptic potentiation through inhibiting astrocytic mitogen-activated protein kinase (MAPK) signalling. This is thought to result in abnormal astrocyte morphology that may impede astrocyte-synapse interactions (Tanasic et al., 2016). Two SSRI-s citalopram and fluoxetine were separately found to induce microglial activation in rat substantia nigra after long-term (28 days) treatment (MacGillivray et al., 2011). The same treatment resulted in a significant decrease in neurons expressing tyrosine hydroxylase [TH; rate-limiting enzyme for dopamine biosynthesis], which may be a consequence of microglial pro-inflammatory activity (MacGillivray et al., 2011). Decrease in TH neurons may lead to SSRI side effects like dystonia, dyskinesia, akathisia and parkinsonism (MacGillivray et al., 2011).

7.2. Electroconvulsive therapy, transcranial magnetic stimulation, and transcranial direct current stimulation

Electroconvulsive therapy (ECT) has emerged as a treatment for drug treatment-resistant depression (Kellner et al., 2012). Among theories of how ECT may convey its beneficial effects, it has been suggested that slightly "shocking" glia may result in minor modifications in glial morphology and function promoting glial neurotrophic agent release and increased glutamate transport (Jansson et al., 2009; Wennstrom, 2006). Similar speculations concerning glial roles, but based on a smaller number of studies, have been brought forward for non-invasive transcranial magnetic stimulation (TMS) (Cullen and Young, 2016) and transcranial direct current stimulation (tDCS) (Gellner et al., 2016). In cell culture, a prolonged exposure to a low-intensity direct current electric field causes astrocyte and microglia-like cells to extend protrusions and align themselves with the electric field (Alexander et al., 2006; Pelletier et al., 2014). Even 10–30 min DCS of 0.3 mV/cm was shown to boost glucose metabolism in mouse astrocyte culture by 30% (Huang et al., 1997), thus resulting in a significantly increased energy supply for neurons in the form of lactate released by astrocytes. Furthermore, an *in vivo* study with transcranial imaging of cellular activity in mice demonstrated that tDCS elicited large astrocytic intracellular calcium waves in living cortex, whereas no neuronal activation was detected during the time of the stimulation. However, after the tDCS, cortical neuronal responsiveness to visual stimuli was enhanced (Monai et al., 2016). Such tDCS-induced metaplastic changes (increased neuronal excitability after anodal stimulation) had been noted before in human and animal studies (Liebetanz et al., 2002) while the major involvement of glia was a novel find. Some of the effects of ECT, tDCS and TMS may be due to an increase in glial number, since at least ECT has been shown to induce proliferation of glial cells expressing NG2 or oligodendrocyte markers in rat PFC (Madsen et al., 2005; Ongur et al., 2007), and NG2 or OX-42 microglial markers in amygdala (Wennstrom et al., 2004) and hippocampus (Wennstrom et al., 2003). However, cellular proliferation does not necessarily guarantee long-term survival of the new cells, which also depends on environmental factors.

7.3. Lifestyle factors: exercise, environmental enrichment, diet, sleep

One of the most investigated lifestyle factors in the context of MDD and ANX is exercise that has in some studies been found to have antidepressant effects comparable to medications (Blumenthal et al., 2007; Bocco et al., 2016; SIGN, 2010). A widely postulated hypothesis for how exercise affects mood links it to adult neurogenesis (Ernst et al., 2006). Interestingly, voluntary exercise was also found to induce cortical gliogenesis, and to a significantly larger extent than neurogenesis (Mandyam et al., 2007). Animal studies have shown that voluntary exercise (*i.e.*, free access to running wheels) enhances generation of astrocytes, microglia and NG2 cells in rodent cortex (Barton et al., 2016; Ehninger and Kempermann, 2003; Mandyam et al., 2007). In rodent amygdala, voluntary exercise decreased microgliogenesis (Ehninger et al., 2011; Hall et al., 2014). Intense involuntary exercise, however, may have distinct effects that are not necessarily beneficial but more resemble those of stress (*i.e.*, decrease in hippocampal astrocyte glutamate uptake was observed in rodents that were subjected to repeated forced swimming) (Borsoi et al., 2015; Lloyd et al., 2017).

Astrocytes in the globus pallidus of mice who had free access to a running wheel for 3 weeks were found to develop much more complex arborisation compared to the "sedentary" mouse group. However, if the mice discontinued exercise for 3 weeks after their initial regimen, the morphology of astrocytes reverted back to the simple arborisation levels observed in the control group (Tatsumi et al., 2016). Increased astrocytic process ramification was also reported in the hippocampus of rats subjected to 4 weeks of involuntary light exercise (Saur et al., 2014). It is now known that glial processes are in dynamic interaction with synapses, regulating their number, maturation and plasticity (Bernardinelli et al., 2014; Haber et al., 2006; Procko and Shaham, 2010; Sild et al., 2016), thus more complex glial process arbours would likely mean more efficient support and fine-tuning of the network. Since atrophy of dendritic arbours in areas like hippocampus and cortex has been observed in MDD and ANX (Hercher et al., 2010; Rosoklija et al., 2000; Soetanto et al., 2010), exercise may exert some of its therapeutic effect through glia-mediated restoration of these neural components (Procko and Shaham, 2010), for example by targeted release of glial factors or contact-mediated signaling.

An interesting experimental condition that shares features with the effects of exercise is environmental enrichment (EE), which also has been shown to relieve anxiety and depression symptoms in rodents (Benaroya-Milshtein et al., 2004; Grippo et al., 2014). In case of rodents, EE is usually implemented using larger, more elaborate cages with more elements that inspire moving and exploring, thus some of the effects may be partially attributable to increased voluntary exercise. However, attempts have been made to separate environmental complexity from general physical exercise (for example by removing the running wheel from the cage) (Ehninger and Kempermann, 2003; Ehninger et al., 2011). EE has been reported to increase the number of astrocytes in hippocampus (Kronenberg et al., 2007; Perez et al., 2009), cortex (Ehninger and Kempermann, 2003), decrease microglia number in amygdala (Ehninger et al., 2011) and reduce microglia pro-inflammatory activation in the hippocampus and hypothalamus of rodents (Chabry et al., 2015). In a study using rats selectively bred for

high-anxiety behaviour, EE was shown to especially benefit the anxious animals by re-inducing hippocampal production of FGF2 which in turn re-established normal astrocyte and neuron number in the hippocampus (Perez et al., 2009). Exercise has also been shown to boost FGF2 expression specifically in hippocampus, with its source likely being glia (Gomez-Pinilla et al., 1997; Gomez-Pinilla et al., 1995). It has been suggested that whereas exercise induces cell proliferation, EE promotes glial and neuronal survival (Fabel et al., 2009; Perez et al., 2009).

There are some indications that dietary factors interact with glia. *In vitro*, compounds derived from rosemary induced production of neurotrophins by glial cell lines and decreased activation of a microglial cell line (de Oliveira, 2016). LPS-induced microglial inflammatory activity was reversed by omega-3 polyunsaturated fatty acid administration in hippocampal slices (Chang et al., 2015). These studies would benefit from *in vivo* validation, since most compounds do not pass through the BBB. That was also evident in the attempts to develop specifically CNS glia-targeting drugs, where several agents that were promising *in vitro* did not cross the BBB *in vivo* (Madhusudanan et al., 2016; Moller and Boddeke, 2016).

Intriguingly, it may turn out that not every compound has to enter the CNS, since the digestive system also contains glia and there is accumulating evidence that gut conditions, such as the composition of its microbiota, are linked to the cognitive and affective functions of the CNS, through the so-called “gut-brain axis” (Anderson et al., 2016; Carabotti et al., 2015). Furthermore, gut composition was linked to anxiety and depression phenotypes (De Palma et al., 2015; Evrensel and Ceylan, 2015; Messaoudi et al., 2011). Glia in the gut, referred to as “enteric glia”, have some common properties with astrocytes, including signalling by calcium transients and responding to neurotransmitters that are also present in the gut (Boesmans et al., 2013; Lyte, 2011). The mechanisms underlying gut-CNS interactions are yet unknown, but likely to involve enteric glia, the roles of which in the context of mental disorders and as a target for probiotics or drugs, remain to be fully explored.

Finally, another non-pharmacological and at least transiently efficient therapy to treat depression, sleep deprivation (Svendsen, 1976), has been directly linked to the function of astrocytes (Haydon, 2017). Blocking astrocyte-specific ATP release induces depressive-like behaviours in mice, whereas enhancing ATP release by PFC astrocytes produces AD-like effects (Cao et al., 2013). It appears that the same pathway is crucial for modulating sleep homeostasis − sleep deprivon leads to the accumulation of astrocyte-released ATP that builds the pressure to sleep and at the same time mediates the antidepressant effects (Hines et al., 2013). The adenosine A1 receptor agonist 2-chloro−N6-cyclopentyladenosine (CCPA) has been tested successfully in mice as a chemical alternative for the beneficial effects of sleep deprivation (Hines and Haydon, 2014; Hines et al., 2013).

8. Monitoring glia in disease and treatment

Since glia carry out numerous important roles in the CNS, several tools already used in imaging of the living human brain largely reflect the status of glia (Garden and Campbell, 2016). Brain imaging techniques that can be used to assess myelin (diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET)) report on oligodendrocyte condition (Alonso-Ortiz et al., 2015; Garden and Campbell, 2016; Madden et al., 2012). Hemodynamic functional magnetic resonance imaging (fMRI) methods are based on blood flow that in large part changes due to astrocytic regulation of the vasculature (Figley and Stroman, 2011; Rosenegger et al., 2015; Schummers et al., 2008). A common method to assess brain metabolism using PET imaging visualizing radioactive fluorodeoxyglucose uptake (FDG-PET), substantially reports astroglial glucose metabolism (Magistretti and Pellerin, 1996; Zimmer et al., 2017).

In addition, ligands that detect glial activation have been developed. 18 kDa translocator protein (TSPO) expression is upregulated in pro-inflammatory activated microglia (Rupprecht et al., 2010) and activated astrocytes (Lavisse et al., 2012). A PET study with a new-generation TSPO ligand [^{18}F]FEPPA revealed over 25% increase in TSPO binding in the ACC, insula and PFC of MDD patients as compared to controls (Setiawan et al., 2015). As a binding partner for some benzodiazepines and a part of the neurosteroid biosynthesis pathway, TSPO has additionally been found to be a promising anti-anxiety drug target (Nothdurfter et al., 2012).

In addition to brain imaging methods, peripheral markers can be potentially useful to assess the state of CNS glia. TSPO and S100beta are CNS-glia related proteins and found also in peripheral blood. Despite interesting associations with ANX and MDD (Ambree et al., 2015; Arolt et al., 2003; Schroeter et al., 2008) (Gavish et al., 1996; Johnson et al., 1998; Nakamura et al., 2002; Nudmamud et al., 2000; Rocca et al., 1998; Weizman et al., 1995), the extent to which peripheral TSPO and S100beta levels reflect CNS glia function remains to be further validated, as these proteins also appear to be produced by other cell types outside the CNS (Batarseh and Papadopoulos, 2010; Zimmer and Van Eldik, 1987).

Peripheral leukocyte telomeres have been found to be significantly shorter in individuals with MDD and ANX than in matched controls (Lindqvist et al., 2015; Simon et al., 2006; Verhoeven et al., 2015). This observation has led to an interesting hypothesis that MDD and ANX may represent a form of “accelerated aging” (Heuser, 2002; Verhoeven et al., 2015; Verhoeven et al., 2014). In a post-mortem study of patients with MDD, MDD group oligodendrocytes were found to have significantly shorter telomeres compared to matched controls, whereas astrocyte telomere length was unaffected (Szebeni et al., 2014). More studies would be needed to assess how MDD and ANX affect glial telomere length, what is the relevance of that and whether CNS glial telomere length is correlated with peripheral measures.

Finally, epigenetic measures of peripheral cell DNA have emerged as potential indicators of neural susceptibility to MDD and ANX (Frodl et al., 2015; Nikolova and Hariri, 2015; Wang et al., 2012; Won et al., 2016). Future research may reveal suitable peripheral epigenetic markers for specifically assessing glial status.

9. Discussion

Advances in understanding the roles of CNS glia in MDD and ANX are very promising and may lead to development of new therapeutic strategies. However, due to the relative newness of the field, many observations need to be solidified with replication studies, especially with regard to the influences of early life adversity, exercise and environmental/lifestyle factors on glia. Moreover, defining patient groups with similar nature of the disease is a challenge, as MDD and ANX are highly heterogeneous conditions. Additionally, measuring glial number and activation are still developing techniques. For example, it is still under speculation whether GFAP, the most commonly used astrocyte marker, constitutes a marker for normal, activated or a special subgroup of astrocytes (Bushong et al., 2002). Despite the popularity of GFAP, other markers with potentially more consistent astrocyte-specific expression have been proposed (Cahoy et al., 2008). Similar problems arise for microglia, which are now understood to have different pro- or anti-inflammatory activation states, and are more accurately described as representing a continuum of activation states (Cherry et al., 2014).

Despite these technical challenges, a multitude of studies indicate that MDD, ANX and chronic stress in animals reduce astrocyte, NG2 glia and oligodendrocyte number and trophic functions, whereas microglial number and pro-inflammatory activation may increase. Such changes have been most often reported for the hippocampus and PFC, which are the most studied brain regions in this context. Interestingly, both pharmacological treatments and beneficial non-pharmacological approaches appear to increase astrocyte, NG2 glia and oligodendrocyte number and/or survival, while generally decreasing pro-inflammatory state of microglia.

Elucidating the mechanisms of glial responses to non-pharmacological approaches/lifestyle factors is likely to help improve pharmacological treatments (as non-pharmacological treatments have much less detrimental side effects). An example of such strategy is mimicking the antidepressant effects of sleep deprivation with the adenosine A1 receptor agonist CCPA (Hines et al., 2013). Further investigations of the effects of exercise or environmental enrichment on glia could provide exciting possibilities of new antidepressant and anti-anxiety drugs, for instance especially useful in cases where individuals are not capable of participating in athletic activites. Another promising avenue is the exploration of epigenetic mechanisms in glia, especially epigenetic modifications that may be retained as a result of early life adversity and may be reversible with later-life treatments like HDACi administration.

In addition to alterations in glial number, animal models as well as studies in patients with MDD and ANX demonstrate differences in glial functionality as compared to the controls. A newly emerged aspect of glial function is their highly plastic morphological state, meaning changes in the shape or process number of glial cells in response to environmental factors. Examples of morphological responses by glia include astrocyte process atrophy in MDD, as a result of chronic stress or as a consequence of early adversity (Gunn et al., 2013; Rajkowska et al., 2013; Tynan et al., 2013), glial process re-growth in response to ADs (Di Benedetto et al., 2016) or reversible elaboration of glial arbour processes in response to exercise (Saur et al., 2014; Tatsumi et al., 2016). Such morphological modifications may have significant implications, as it is now known that glial dynamic processes are required for maintenance of the BBB (Cabezas et al., 2014; Rajkowska et al., 2013) and for synapse development and maturation (Sild et al., 2016). Better understanding of the involved signaling pathways may help to develop interventions to “boost” the functions of glia cells and maybe even compensate for some loss in glial number that may occur in MDD and ANX.

In conclusion, glia have emerged as a crucial component in the maintenance of mental health and as important mediators of the effects of interventions, stress, and lifestyle factors. Much remains to be investigated, including how glial properties may contribute to MDD and ANX susceptibility, heterogeneity and whether neuroimaging or peripheral epigenetic measures may enable assessing glial characteristics even before the disease onset. Further research about glial function and malfunction in psychiatric disorders and in relation to early life adversity is likely to yield novel insights into the etiology of MDD and ANX and prospects for better treatments.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Dr Florence Pomares for helpful discussion. This work was facilitated by the Concordia University Horizon Postdoctoral Fellowship and Estonian Üliõpilaste Teadustööde Riiklik Konkurss Ist Prize awarded to Dr Mari Sild. Dr Linda Booij was supported by a New Investigator Award from the Canadian Institutes of Health Research. Dr. Edward Ruthazer holds a Research Chair from the Fonds de Recherche du Québec – Santé. The funding sources had no involvement in the preparation of the manuscript.

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