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Behavioral experiences as drivers of oligodendrocyte lineage dynamics and myelin plasticity

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Abstract

Many behavioral experiences are known to promote hippocampal neurogenesis. In contrast, the ability of behavioral experiences to influence the production of oligodendrocytes and myelin sheath formation remains relatively unknown. However, several recent studies indicate that voluntary exercise and environmental enrichment can positively influence both oligodendrogenesis and myelination, and that, in contrast, social isolation can negatively influence myelination. In this review we summarize studies addressing the influence of behavioral experiences on oligodendrocyte lineage cells and myelin, and highlight potential mechanisms including experience-dependent neuronal activity, metabolites, and stress effectors, as well as both local and systemic secreted factors. Although more study is required to better understand the underlying mechanisms by which behavioral experiences regulate oligodendrocyte lineage cells, this exciting and newly emerging field has already revealed that oligodendrocytes and their progenitors are highly responsive to behavioral experiences and suggest the existence of a complex network of reciprocal interactions among oligodendrocyte lineage development, behavioral experiences, and brain function. Achieving a better understanding of these relationships may have profound implications for human health, and in particular, for our understanding of changes in brain function that occur in response to experiences.

Keywords

Oligodendrocyte; OPC; Myelin; Exercise; Enriched environment; Social isolation

1. Introduction

What is the biological basis (“nature”) by which our experiences (“nurture”) generate long-term changes in brain function? The molecular underpinnings of how experiences affect the brain in a lasting way remain poorly understood. The prevailing view suggests that major structures, i.e., the cells and circuits of the brain, are relatively fixed, but that more malleable structures, such as synapses, are strengthened or weakened in response to experiences, thus altering nerve transmission. However the pioneering efforts of Fred Gage, Henriette van Praag and many others have led to a recognition that the cellular components of brain circuitry are not entirely fixed, with the production of newborn cells contributing to

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experience-dependent brain plasticity. In particular, behavioral experiences including physical activity, social interaction, and environmental enrichment have been found to influence neurogenesis within the hippocampus, which houses a germinal niche critical for learning and memory in the adult brain (Brown et al., 2003; Stranahan et al., 2006; van Praag et al., 1999).

While exercise and environmental enrichment have been found to promote neurogenesis in the hippocampus (Brown et al., 2003; van Praag et al., 1999; van Praag et al., 2005), social isolation has been found to attenuate neurogenesis, at least in certain contexts (Leasure and Decker, 2009; Stranahan et al., 2006). In contrast, the other major neural stem cell niche in the adult brain, the Subventricular Zone (SVZ), has received only limited investigation as being potentially responsive to behavioral experiences, with some studies concluding that behavioral experiences, including exercise, do not affect SVZ neurogenesis under normal physiological conditions (Brown et al., 2003). A similarly limited set of investigations have examined behaviorally-induced cell proliferative responses in areas outside of neurogenic niches (Ehninger and Kempermann, 2003), with some studies reporting that behavioral experiences such as exercise and environmental enrichment have either no or minor effects on glia, a population that comprises an expansive and diverse group of brain cell types (Brown et al., 2003; Ehninger and Kempermann, 2003; Steiner et al., 2004). However in some studies Glial Fibrillary Acidic Protein (GFAP) has been used as a generic marker for “glia” (Hattori et al., 2007; Trejo et al., 2001), and thus these studies may have missed effects on other glial cell types such as oligodendrocyte lineage cells. Another confounding factor is that common techniques used to assess neurogenesis may have clouded assessments of glial responses to behavioral experiences. For example, Bromodeoxyuridine (BrdU), a compound widely used to birth-date newly born cells, has a relatively short half-life, approximately 8–11 min in plasma (Taupin, 2007), and when injected, may not be sensitive enough to appropriately label large populations of slowly-dividing oligodendrocyte precursor cells (Cifuentes et al., 2011; Simon et al., 2011). To circumvent the short half-life often multiple injections of BrdU are used, however this is stressful and leads to upregulation of corticosterone pathways that can inhibit cell proliferation (Stranahan et al., 2006).

On the other hand, a growing number of human imaging studies have concluded that behavioral experiences including juggling, abacus training and extensive piano practice can result in increases in fractional anisotropy in a number of white matter regions (Bengtsson et al., 2005; Hu et al., 2011; Scholz et al., 2009), which have been speculated upon as reflective of changes in myelination (Fields, 2008). Until recently, however, only a handful of investigations in animal models attempted to link behavioral experiences to changes in myelin itself, or to potential alterations in the oligodendrocyte lineage. However, given the profound responsiveness of oligodendrocyte lineage cells to local cues, for example, in response to injury, some investigators have begun to take a fresh look at the potential for behavioral experiences to regulate oligodendrocyte lineage cells.

Oligodendrocyte precursor cells (OPCs) comprise one of the most prevalent cell types in the adult brain. OPCs constitute 2–3% of the total population of cells in the cortex and 8–9% in white matter (Dawson, 2003), and, as suggested by the name, OPCs can differentiate into

oligodendrocytes as a normal part of development and homeostasis, as well as in response to injury. OPCs can be identified by the expression of Neuron-Glial antigen 2 (NG2), Platelet derived growth factor receptor alpha (PDGFR α), and/or the transcription factor, Olig2 (however, the latter is also expressed in oligodendrocytes). Cycling OPCs in the adult cerebral cortex are a dynamic population of cells that actively survey local environments with motile filopodia, establish exclusion domains based on self-repulsion, and maintain their density through local self-renewal (Hughes et al., 2013). At rest, OPCs exhibit a long dividing time of approximately 37 days (Simon et al., 2011; Young et al., 2013). Thus, it is possible that studies examining cell proliferation in response to behavioral experiences have neglected the OPC population due to the duration of behavioral manipulations (i.e., too short), as well as use of labeling techniques that are biased for rapidly dividing cells (to be discussed further below).

Although a significant fraction of OPCs remain undifferentiated, particularly in gray matter, many will eventually differentiate to become myelinating oligodendrocytes (Baumann and Pham-Dinh, 2001). Oligodendrocytes are the myelin-producing cells of the CNS, and as such, wrap layers of lipid-dense insulating myelin around axons (Boulanger and Messier, 2014). In a myelinated axon the voltage gated sodium channels are found clustered at short myelin-free segments termed nodes of Ranvier. The propagation of action potentials from node to node, along with the insulation provided along internodes, leads to an increase in nerve conduction speed between 20 and 100 fold in comparison to unmyelinated axons of the same diameter (Nave and Werner, 2014). Mature oligodendrocytes have also been shown to provide metabolic support to axons through transport systems within myelin, which may help prevent neurodegeneration (Lee et al., 2012). Studies in zebrafish and mice have suggested that newly-differentiated oligodendrocytes have a limited temporal window in which to myelinate (Czopka et al., 2013). Intriguingly, a recent study that assessed the turnover of radioactively labeled cells in humans (an accidental “experiment” generated by atomic bomb testing in the 1950s), suggested that mature oligodendrocytes (rather than adult OPCs) may more significantly contribute to ongoing myelin homeostasis during aging (Yeung et al., 2014).

Recent investigations into behavioral experiences have looked closely at regions relevant to oligodendrocyte cell lineage dynamics and myelin plasticity, using approaches more suitable to capture potential changes. The emerging evidence supports a model in which experience regulates both oligodendrogenesis and myelination (Fig. 1). These recent studies may represent a turning point in our emerging understanding of how experiences translate into changes in brain form and function. The aim of the current review is therefore to provide an overview of research that investigates behavioral experience-dependent influences on oligodendrocyte precursor cells, oligodendrocytes, and myelin, and also highlight important unanswered questions in this burgeoning field.

2. Do behavioral experiences regulate the oligodendrocyte lineage?

2.1. Exercise influences oligodendrocyte precursor cell production and maturation

Physical activity promotes a wide array of neurological changes, including the enhancement of learning, memory, and executive function in both children and adults (Hopkins et al.,

2012; Pereira et al., 2007; Voss et al., 2011). Many of these activity-related neurological changes have been primarily associated with changes in neurons (van Praag, 2009). However, there are a number of human neuroimaging studies that report that training in physical skills promotes changes in white matter that are suggestive of alterations in myelin architecture (Bengtsson et al., 2005; Scholz et al., 2009; Voss et al., 2013), with similar findings demonstrated in rodents (Sampaio-Baptista et al., 2013). Voluntary exercise, i.e., giving rodents free access to running wheels, is a common experimental paradigm used to investigate the effects of physical activity on the brain. Voluntary exercise has been demonstrated conclusively to stimulate neurogenesis in the dentate gyrus of the hippocampus (van Praag et al., 1999; van Praag et al., 2005). However, many investigations (of the dentate gyrus and other structures including the SVZ) have suggested that voluntary exercise has either limited or no effect on glia (Brown et al., 2003; van Praag et al., 2005). Furthermore, those studies that have argued for behaviorally-induced glial responses have most frequently implicated astrocytes (Ehninger and Kempermann, 2003; Steiner et al., 2004). In retrospect, however, commonly used investigative approaches may have inadvertently attenuated cell genesis. For instance, housing animals individually, as is typical in exercise studies, has been shown to inhibit neurogenesis, and differences in exercise experimental protocols such as exercise duration and/or forced treadmill running can introduce confounding factors such as stress (Leasure and Jones, 2008; Stranahan et al., 2006).

Alternative cell labeling approaches, including administration of BrdU in drinking water to label slowly dividing cells, and transgenic fluorescent reporter lines, have recently provided insight into the effect of exercise on oligodendrocyte lineage cells. These studies have found that voluntary exercise influences the development of oligodendrocyte lineage cells in a variety of cortical and white matter regions (see Table 1), although the precise nature of the influence is still being resolved (Mandyam et al., 2007; McKenzie et al., 2014; Simon et al., 2011). In the study by Mandyam and colleagues, the effect of methamphetamine administration frequency, in addition to control groups with and without exercise, was assessed on cellular responses in the medial prefrontal cortex (mPFC) (Mandyam et al., 2007). As the prefrontal cortex is involved in drug addiction, myelinates well into adulthood, and plays a role in motor cortical control (Miller et al., 2012; Narayanan and Laubach, 2006; Rhodes et al., 2005; Weinstein et al., 2012), it is an important cortical area to assess cellular changes related to both drug seeking and voluntary exercise. Adult female rats were allowed two weeks of acclimation to a running wheel prior to one BrdU injection, and were subsequently given an additional 28 days of running wheel access. Using immunohistochemistry to assess acutely proliferative Ki67-positive cells as well as “surviving” BrdU positive cells, it was found that the mPFC of exercising rats had a robust increase in Ki67 and BrdU positive cells compared to the mPFC in sedentary counterparts. While there was no significant change in neurogenesis (co-labeled NeuN positive, BrdU positive cells) in the voluntary exercise group, there was a modest increase in BrdU-labeled, GFAP-positive astrocytes and a three-fold increase in the number of BrdU-labeled, NG2-positive OPCs. These data suggested that OPC proliferation is enhanced by voluntary exercise, and that OPCs are the cell type *most* affected by voluntary exercise in the mPFC.

Similarly, a recent study performed by McKenzie and colleagues assessed the effect of voluntary exercise on oligodendrocyte lineage cells by administering ethynyldeoxyuridine (EdU, an analog of BrdU) in drinking water (McKenzie et al., 2014). Two weeks of training on a complex running wheel (a wheel with rungs that are differentially spaced), a challenging physical activity that also promotes motor learning, resulted in increased OPC proliferation and oligodendrocyte production in the corpus callosum. A similar effect on OPC proliferation was demonstrated in mice exposed to a regular wheel, however it remains unclear whether this effect was due to exercise per se or the novelty of the wheel. Importantly, the McKenzie study considered whether motor learning *required* the formation of new myelin by testing a conditional knockout line of mice in which PDGFR α -expressing cells (OPCs but not oligodendrocytes) were induced to lose the expression of Myelin Regulatory Factor (Myrf), a critical transcription factor for oligodendrocyte maturation and myelin production. Therefore, post-induction, new myelination was prevented but existing myelin was preserved. These myelination-impaired mice had poorer performances (lower running speeds and reduced traveling distances) on the complex running wheel compared to controls. This study is groundbreaking in providing the first evidence that changes in oligodendrocyte lineage development are not just *triggered* by a new experience involving motor learning, but are *essential* for optimal motor learning.

In contrast, some have concluded that voluntary exercise may *suppress* OPC proliferation. As adult cortical OPCs have a long cell cycle (Simon et al., 2011; Young et al., 2013), the investigators in one study administered BrdU in the drinking water of adult mice during a two-week period of free access to running wheels. Because of the extended exposure to BrdU, a large percentage of cortical OPCs were labeled. Surprisingly however, exercising mice exhibited *lower* densities of proliferating cells (Ki67-positive) and BrdU-labeled cells (compared to control mice in standard cages) in motor and somatosensory cortices. Phenotypic analyses then revealed that almost all of the BrdU-labeled cells in the control group were NG2-positive (92.8%) while in the exercising group, BrdU-labeled cells were approximately 40% NG2-negative and GST π -positive (i.e., mature oligodendrocytes) and 40% NG2-positive but GST π -negative (i.e., OPCs). In fact, phenotype switching was observed in another investigation, in which mice undergoing voluntary exercise for 4 weeks had fewer BrdU-positive cells in the amygdala compare to in control mice, as well as significant increases in the percentages of newborn (BrdU-labeled) NG2-positive cells that were S100 β -negative, yet had no change in newborn oligodendrocytes (Ehninger et al., 2011). Taken together, these studies suggest that voluntary exercise can in some circumstances lead to decreased OPC proliferation, potentially by triggering early cell cycle exit and subsequent oligodendrocyte differentiation, or, alternatively, by altering the phenotype of existing OPCs.

In summary, although relatively few studies have investigated the effects of exercise on oligodendrogenesis and myelination, there is emerging evidence suggesting that voluntary exercise influences OPC development and increases oligodendrocyte differentiation over the course of a few days to a few weeks. One possibility is that physical activity stimulates oligodendrogenesis through increased neuronal activity. Indeed a recent study using optogenetics to drive motor cortical neuronal activity reported that increased neuronal firing promoted a variety of changes in oligodendrocyte lineage development including circuit-

specific OPC proliferation and increases in myelin sheath thickness (Gibson et al., 2014). From a human health perspective, the cellular dynamics of oligodendrocytes themselves may be somewhat more influential, as recent work has found that OPC turnover in humans is relatively low compared to that in mice, implying that myelin plasticity may be more heavily influenced by the ability (or disability) of existing oligodendrocytes to generate new myelin (Yeung et al., 2014). These observations highlight the need for additional investigations into how exercise influences oligodendrocyte behaviors including survival and myelination.

2.2. Social environment promotes myelination within a critical window

Socialization has long been known to be an important factor in childhood cognitive development. Neuroimaging studies have shown that socially isolated and neglected children have impaired cognition and increased impulsivity, and less activation within the prefrontal cortex (PFC) (Chugani et al., 2001). The PFC is important for both cognition and impulse control, and is known to continue developing myelin at least into the third decade of life (Gogtay et al., 2004). Excitingly, there is an emerging body of literature on the importance of socialization to oligodendrocyte lineage development (see Table 1). Here, a variety of social isolation paradigms have been used to demonstrate that the absence of social stimuli may perturb normal oligodendrocyte development.

By assessing oligodendrocyte-specific reporter mice, recent investigations found that social stimuli is important for the development of oligodendrocytes and myelin in the prefrontal cortex (PFC) in both juvenile and adult mice (Liu et al., 2012; Makinodan et al., 2012). In these investigations, social isolation referred to housing a mouse individually rather than with conspecifics. Similar to the long-term behavioral deficits noted in neglected children, mice that were isolated exhibited decreased performance on measures of sociability. The two investigations furthermore found that mice that underwent social isolation as juveniles had numerous (and long-lasting) changes in oligodendrocytes: morphological deficits, decreased percentages of oligodendrocytes with heterochromatin, lower myelin transcript levels, and thinner myelin sheaths (i.e., higher g-ratios). Interestingly, one study identified a critical period (postnatal days 21–35) for mice that were isolated and subsequently re-introduced into a “normal” social environment (Makinodan et al., 2012), in which both social behavior and myelin transcripts in the PFC failed to return to normal after social reintegration. This was in contrast to slightly older mice, who “bounced back” following a 30 day social isolation period (postnatal days 35–65) that occurred *after* group housing during the critical window (postnatal days 21–35) (Makinodan et al., 2012). In contrast, significant myelin loss and changes to oligodendrocyte chromatin occurred in the PFC of adults exposed to social isolation for longer periods (8 weeks) (Liu et al., 2012). These exciting investigations offer new avenues of research with respect to both critical periods for myelin development and adult myelin plasticity in response to social environment.

2.3. Environmental enrichment influences oligodendrocyte lineage cellular dynamics in multiple brain regions

Environmental enrichment refers to group housing rodents in cages with free access to a variety of novel toys, foods and running wheels (although the inclusion of the latter two

varies depending upon the study). Environmental enrichment is thought to stimulate motor, sensory, and cognitive systems, providing a cognitively rich environment relative to standard housing conditions (Nithianantharajah and Hannan, 2006). Objects such as toys and tunnels are frequently replaced to provide novelty. It is believed that the increase in BrdU-positive cells following environmental enrichment is due, at least in part, to an enhancement of cell survival, as increases in BrdU are not observed immediately, but typically weeks *after* the start of enrichment (Kempermann et al., 1997; Cao et al., 2004; Tashiro et al., 2007). As such, environmental enrichment paradigms provide a promising avenue for investigators to assess the effects of a stimulating environment on the brain both during homeostasis and during recovery from disease states. While environmental enrichment is known to influence hippocampal neurogenesis (reviewed in Nithianantharajah and Hannan, 2006; Van Praag et al., 2000), the scope of the current article is oligodendrocyte lineage cellular dynamics.

Several investigations examining non-hippocampal regions, including the amygdala, substantia nigra and several cortical regions, have concluded that OPCs are responsive to environmental enrichment, due to a relatively large increase in BrdU labeling of OPC populations after enrichment (Ehninger et al., 2011). However, one of the earliest and most extensive studies investigating the effects of environmental enrichment on non-hippocampal regions found little evidence to support behaviorally-induced oligodendrogenesis (Ehninger and Kempermann, 2003). In this study, after a 40-day enrichment paradigm that included BrdU injections during the last 10 days, there was little effect on cell genesis in environmental enrichment groups, with most cortical areas surveyed exhibiting no significant increase in BrdU-positive cells. The few areas that displayed significant changes were further examined using immunohistochemistry to detect astrocytes and microglia (using S100 β and Iba1 antibodies, respectively). These analyses suggested environmental enrichment primarily affected astrogliogenesis in layer 1 of the cingulate and motor cortices. This study was promising as being one of the first to demonstrate that environmental enrichment could have a specific (and localized) effect on a glial subtype. In this study, however, few oligodendrocytes were detected and OPCs were not investigated, leaving open the question of whether environmental enrichment influences oligodendrocyte lineage dynamics. A more recent investigation with a focus on the PFC found no significant differences in oligodendrocyte density, morphology, or levels of myelin transcripts between mice undergoing environmental enrichment and controls (Makinodan et al., 2012). In contrast, however, another recent study on middle-aged and aged male rats found that a four month long exposure to environmental enrichment resulted in increases in myelin sheath volumes (in white matter) compared to those in control counterparts (Yang et al., 2013b). Here, the authors concluded that exposure to environmental enrichment enhanced ongoing myelin repair during aging. This study, and another study from the same group (Zhao et al., 2011), lent support to the hypothesis that environmental enrichment may stimulate oligodendrocytes to produce more myelin, with the cellular basis of this effect at least in part due to increases in the density of CNPase-positive oligodendrocytes. However, whether the changes in myelin sheaths might also be influenced by other factors (e.g., increased myelin wrapping) was not explored.

Analyses of subcortical regions, such as the amygdala, have also uncovered cellular changes in oligodendrocyte lineage cells in response to an enriched environment. Specifically,

environmental enrichment was found to affect the number of newborn OPCs (specifically, S100 β -) in the amygdala (Ehninger et al., 2011). Ehninger and colleagues also reported that mice exposed to environmental enrichment exhibited an overall decrease in the numbers of BrdU-positive cells found in the amygdala, along with specific decreases in the number of newborn astrocytes and microglia (noted by co-labeled S100 β /BrdU or Iba1/BrdU, respectively). However, no changes in CNPase-positive oligodendrocytes were observed. In control mice (i.e., mice in standard housing), a large fraction of newly generated NG2-positive cells in the amygdala were also S100 β -positive. After environmental enrichment, there was an increase in the fraction of BrdU-labeled NG2-positive cells (~90%) that were also S100 β -negative. These results suggest that environmental enrichment could switch (or delay) fates adopted by NG2 cells in the amygdala.

In contrast, environmental enrichment was reported by Okuda and colleagues to *increase* the number of cells labeled by BrdU in the amygdala, with no significant differences in the fraction of the cells within the oligodendrocyte lineage (Olig2+) compared to in sedentary controls. The opposing environmental enrichment related effects on BrdU incorporation in the two studies could be due to the fact that the enriched environment in the Okuda study also contained a running wheel, making it difficult to determine the specific effect of environmental enrichment from that of voluntary exercise. Additionally, the length of environmental enrichment varied in the two studies (1 week in the Okuda study versus 40 days in the Ehninger study), as did the time of BrdU administration (before environmental enrichment in the Okuda study versus during environmental enrichment in the Ehninger study). A further point of difference is that OPC generation has been found to differ depending on gender in C57BL/6 mice (Tatar et al., 2013), and Ehninger and colleagues assessed female mice while Okuda and associates assessed male mice.

Investigations into recovery following neural insults, including stroke, have also offered insights into the effects of environmental enrichment on oligodendrocyte lineage cells. For example, after BrdU administration and a few days post-insult, an increase in BrdU-labeled NG2-positive cells can be found together with increases in microglia and astrocytes (Keiner et al., 2008; Klaissle et al., 2012; Simon et al., 2011). In addition, Komitova and colleagues found that hypertensive rats placed in enriching environments after stroke had increased functional recovery and increased numbers of OPCs in the ipsilateral and contralateral cortical regions, compared to rats given stroke that were housed in standard environments (Komitova et al., 2006). Similar results were found in another investigation, which examined cellular dynamics following stroke in the sensorimotor cortex, with reported environmental enrichment related increases in astrogliogenesis and a transient increase in OPCs (Keiner et al., 2008). Similar increases in OPC production were found in the substantia nigra after dopaminergic lesions in rats given access to enriched environments. Here, Steiner and colleagues performed dopaminergic lesions and found an increase in the number of GFAP-positive cells labeled with BrdU in rats exposed to enriched environments compared to rats in standard housing. However, the largest increase in BrdU incorporation was found in NG2-positive cells (several times higher than in lesioned rats without environmental enrichment) (Steiner et al., 2006). This later result was confirmed by Klaissle and colleagues (Klaissle et al., 2012). However, despite the levodopa-induced increase in NG2-positive cell

density, which was accompanied by functional recovery, there was no significant increase in CNPase-positive oligodendrocytes.

Overall the results suggest that OPCs are highly responsive to environmental enrichment, particularly after insults such as stroke. However, in many of these studies the newly-generated OPCs do not seem to differentiate into oligodendrocytes, at least during the time frame of several weeks to a month. Further studies will be necessary to better understand the molecular mechanisms that underlie this enhanced production of OPCs in response to environmental enrichment, as well as determine the function of the newly-generated OPCs in the recovery process.

3. Potential mechanisms

3.1. Stress: the intermediate effector

The behavioral experiences mentioned above are also known to play a role in modulating stress (Morley-fletcher et al., 2003; Stranahan et al., 2008). While environmental enrichment and voluntary exercise are generally thought to attenuate the negative effects of stress, social isolation has been shown to increase the negative effects of stress, in particular through the hypothalamus-pituitary-adrenal axis and through the release of stress hormones including corticosterone and other glucocorticoids (Stranahan et al., 2008). However exercise itself is a mild physiological stressor, and as such initially stimulates canonical stress related systems, but differs from stress-responses evoked by aversive stimuli by using mechanisms that include reducing binding affinities of corticosterone receptors (Droste et al., 2003). This is relevant as fully-activated corticosterone pathways (in the absence of modulators such as exercise) have been shown to inhibit both endothelial cell genesis and neurogenesis in the PFC and hippocampus (Ekstrand et al., 2008; Stranahan et al., 2006). To date, it remains unclear how mild stressors such as exercise may influence oligodendrocyte development and aversive stressors such as social isolation can inhibit oligodendrocyte development. Interestingly, OPCs and oligodendrocytes are known to express some of the same stress receptors as neural stem cells, such as glucocorticoid receptors (Matsusue et al., 2014), and many studies have shown that stress hormones negatively impact oligodendrocyte lineage development. For example, corticosteroids have been shown to decrease OPC proliferation and decrease myelin production (Chari et al., 2006; Clarner et al., 2011). It has also been suggested that differing interactions among stress-responsive cells in different brain areas could result in regional effects on oligodendrocyte lineage cells, for instance in the PFC, which is highly responsive to behaviorally-induced stress but continues to generate significant numbers of oligodendrocytes well into adulthood (Caudal et al., 2014; Liu et al., 2012; Makinodan et al., 2012). Clearly, more work is needed to understand how stress responses are integrated at the cellular and molecular levels to result in both positive and negative effects on oligodendrocyte lineage cellular dynamics.

3.2. Neural activity

Changes in neuronal activity could underlie a great deal of the interplay between behavioral experiences and changes in oligodendrocyte lineage cells, as studies have shown that neuronal activity can drive oligodendrogenesis and even myelination itself (Ishibashi et al.,

2006; Gibson et al., 2014). As this topic is examined in-depth in a review in this same issue (Purger et al., 2015), what follows here is a general summary of some of the highlights of the potential relationship between behavioral experiences and neuronal activity-induced changes in the oligodendrocyte lineage.

Neural activity has been a leading contender for many years to explain how experiences influence oligodendrocyte lineage development. For instance, investigations in the visual system revealed a number of intriguing findings using neurotoxins to manipulate electrical activity and assess the resulting effects on OPCs and myelination. Injection of tetrodotoxin (a blocker of sodium channels used to eliminate electrical activity) resulted in an 80% decrease in the number of newly-generated OPCs in the optic nerve, and a decrease in myelination (Barres and Raff, 1993). Conversely, injection of alpha scorpion-toxin (a sodium channel inactivation inhibitor used to *stimulate* electrical activity) increased myelination (Demerens et al., 1996). Additionally, myelination of cultured dorsal root ganglia can be inhibited by administering low frequency stimulation via electrodes (Stevens et al., 1998), whereas studies using high frequency stimulation have demonstrated *increases* in OPC proliferation and differentiation (Li et al., 2010). Other investigations have identified potential intermediaries of neural activity (purinergic signaling) and myelination (Ishibashi et al., 2006), and OPC differentiation (Stevens et al., 2002). However, in some cases it has been suggested that activity-dependent effects were only apparent when action potentials were stimulated during a narrow developmental period (Demerens et al., 1996), pointing to the potential for critical periods in which neural activity is instructive. For instance, deprivation of sensory experiences by removing whiskers at critical periods in early postnatal development was shown to drastically increase OPC proliferation and alter OPC distribution, as well as lead to decreased innervation of OPCs by thalamocortical neurons (Mangin et al., 2012). Through the use of in vivo imaging of the somatosensory cortex after whisker removal, Hill and colleagues demonstrated a slight increase in OPC proliferation coupled with a reduction in oligodendrocyte production (Hill et al., 2014). Although, precise results from the various investigations differed, the studies all pointed to the labile nature of oligodendrocyte lineage cells during sensory experiences, particularly during critical periods. It will be interesting to determine the degree to which changes in neural activity contribute to the effect of social isolation on myelination (Liu et al., 2012; Makinodan et al., 2012), where a critical period has also been demonstrated.

More recent work using optogenetic approaches has now provided direct evidence for circuit-specific neuronal activity in regulating oligodendrocyte lineage development (Gibson et al., 2014). Here, neurons in the premotor cortex (layer V) were stimulated at a physiologically mimetic frequency of 20 Hz after which the mice displayed complex ambulatory motor behavior (turning in unidirectional circles). This neuronal activity resulted in changes to local oligodendrocyte lineage cells including: OPC proliferation, differentiation into mature oligodendrocytes, and increased myelin sheath thickness. Intriguingly, these activity-induced changes were dependent on epigenetic changes known to regulate oligodendrocyte differentiation (i.e., histone deacetylation). Additionally, some changes were circuit-specific, particularly OPC proliferation, which was noted in the association fiber limb but not in the corticofugal limb of the premotor circuit.

In addition, a recent study of myelination in Zebrafish has revealed that oligodendrocytes decide which axons to myelinate depending on axonal activity (Hines et al., 2015). Using an elegant approach in which they both silenced individual axons and imaged individual oligodendrocytes and their processes during myelination onset, Hines and colleagues were able to determine that initial contacts between oligodendrocyte processes and axons were activity-independent, while the retraction of oligodendrocyte processes from axons was activity-dependent. In other words, oligodendrocytes indiscriminately contacted both electrically active and inactive axons but were far less likely to retract from the active axons, the net result being that active axons were preferentially myelinated.

Together these studies highlight the potential for neural activity to play a role in driving behavioral experience-related responses within oligodendrocyte lineage cells. Although much of how experience-dependent neural activity translates into changes in myelin remain unknown, the recent ground-breaking optogenetic study clearly shows great promise for this approach to help dissect out the underlying effectors responsible for the influence of behavioral experiences on oligodendrocyte cell lineage development.

3.3. Neurotransmitters

Neurotransmitters are good candidates to contribute to experience-dependent changes in oligodendrocyte lineage cells. OPCs express functional glutamate (AMPA and NMDA) and GABA receptors, as well as receptors for other transmitter types (Boulanger and Messier, 2014; Dawson, 2003; De Biase et al., 2011; Káradóttir and Attwell, 2007) including purinergic receptors (Othman et al., 2003; Stevens et al., 2002; Zonouzi et al., 2011). Several investigations have suggested that increases in particular neurotransmitters may have region-specific effects on oligodendrogenesis. For instance, treatments with levodopa have been shown to increase the number of newly-born NG2-positive cells in the substantia nigra following dopaminergic lesions, where environmental enrichment is known to ameliorate damage (Klaissle et al., 2012). CNPase-positive oligodendrocytes also express dopamine receptors, and D2 and D3 agonists have been found to prevent oligodendrocyte injury caused by glutamate oxidative stress or glucose/oxygen deprivation in culture models (Rosin et al., 2005).

Additionally, glutamate transmission may also be important in driving behavioral experience-dependent effects on oligodendrocyte lineage cellular development. In line with this idea, mice lacking a critical NMDA receptor subunit do not exhibit exercise-related increases in neurogenesis within the hippocampus (Kitamura et al., 2003). Removing whiskers during the critical period led to a reduction in the innervation of glutamatergic thalamocortical neurons in the barrel cortex, which was also detected concurrently with an increase in OPC proliferation and an abnormally uniform OPC distribution in the barrel cortex (Mangin et al., 2012), suggesting that experiences can affect the development of OPC-to-neuron signaling. This is intriguing considering reports suggesting an increase in glutamate receptor levels (GluR3 and GluR4) in OPCs and immature oligodendrocytes (Itoh et al., 2002) and the finding that increased activation of AMPA receptors may promote OPC migration to myelination sites (Gudz et al., 2006). Despite this, experiments using mice with a conditional knockout for an essential NMDA subunit have suggested that NMDA signaling

may not be essential for the development of OPCs and myelination (De Biase et al., 2011). However, while not being required to generate myelin per se, several studies suggest that glutamate signaling is an important regulator of myelination in response to neuronal activity (Wake et al., 2011; Lundgaard et al., 2013; Wake et al., 2015). For instance it has been suggested that growth factors (neuregulin or BDNF) can drive a switch from developmental to activity-dependent myelination through NMDA receptors (Lundgaard et al., 2013). This finding is also relevant in terms of myelination critical windows, as the activity-dependent switch may contribute to the critical window for behavioral experiences (e.g., socialization) and could explain the oligodendrocyte and myelination deficits noted in absence of socializing (between P21-35) (Liu et al., 2012; Makinodan et al., 2012). In other words, socialization may provide an essential environmental stimulus to drive neurotransmission during the switch from developmental to activity-dependent myelination programs, and thus promote oligodendrocyte lineage cell development. In addition, several studies have linked local glutamate signaling to the ability of MBP to undergo local translation, providing a mechanism to spatially target optimal myelin production (Wake et al., 2011, 2015).

3.4. Growth factors

Although many growth factors have been implicated in contributing to how behavioral experiences influence neurogenesis, this review will focus on growth factors that are likely to contribute to experience-dependent effects within the oligodendrocyte lineage.

Recent evidence has implicated Insulin-like Growth Factor 1 (IGF1) as a contributing factor to brain cellular changes following behavioral experiences. IGF1 is produced by the liver and passed into circulation, where it can cross the blood brain barrier when bound to accessory IGF binding proteins, however it is important to note that it is also produced locally by a variety of brain cell types (Puche and Castilla-Cortázar, 2012). IGF1 has trophic effects on cells in a wide range of tissues. Within the brain many cells express the IGF receptor (IGFR), including neural stem cells and oligodendrocytes (Mason et al., 2000; Puche and Castilla-Cortázar, 2012). IGF1 overexpression leads to increases in myelination (Luzi et al., 2004), while IGF1 knockout leads to decreases in myelination (Zeger et al., 2007), and IGF1 is important for the development and survival of OPCs and oligodendrocytes (see review D'Ercole and Ye, 2008). For instance, preventing IGF1R expression specifically in early OPCs using Olig1-Cre mice results in an approximately 60% decrease in the number of OPCs, which leads to half the number of mature oligodendrocytes (Zeger et al., 2007). This decrease in OPC and oligodendrocyte densities was driven by both a decrease in OPC proliferation and an increase in apoptosis. Other studies have also suggested that IGF1 primarily influences myelination by promoting oligodendrocyte lineage survival (Lagarde et al., 2007; Mason et al., 2003).

Strikingly, several studies have found that exercise in adult rodents leads to increases in IGF1 levels in the brain, where it is produced locally by astrocytes (D'Ercole and Ye, 2008). In addition, circulating IGF1 can cross the blood-brain barrier, and this distally-produced IGF1 is also required for exercise-induced increases in stem cell proliferation and differentiation in the brain, as blocking IGF1 with an anti-IGF antiserum during exercise

eradicates the effect of exercise on neurogenesis (Trejo et al., 2001). This suggests that behavioral experience-related effects on brain cells can be driven by IGF1.

Recent evidence also suggests that neuregulin-1, a member of the epidermal growth factor family, may play a role in mediating the effects of socialization on myelination. Mice with an oligodendrocyte lineage specific knockout of ErbB3, a neuregulin receptor subunit, undergo a socialization-related enhancement of myelination during a critical period (postnatal days 21–35) (Makinodan et al., 2012). In other words, mice with oligodendrocytes that were less responsive to neuregulin-1 no longer benefited from group housing, and instead mirrored the myelination patterns seen in socially-isolated mice. In line with this idea, recent work has linked neuregulin to activity-dependent myelination (Lundgaard et al., 2013). Here, in the absence of neuregulin, oligodendrocytes from the forebrain co-cultured with dorsal root ganglia neurons underwent myelination in a manner independent of glutamate and neural activity. However, in the *presence* of neuregulin, myelination was both enhanced and accelerated, an effect that was NMDA receptor-dependent. In this study it remained unclear whether the effect of added neuregulin was via oligodendrocyte or neuronal neuregulin receptors (or both), however the study provides an important link between neuregulin and activity-dependent modulation of myelination. Intriguingly, the loss of neuregulin signaling in oligodendrocytes *in vivo* did not affect developmental myelination (Brinkmann et al., 2008), suggesting that other growth factors such as Brain-Derived Neurotrophic Factor (BDNF) may compensate for the loss of neuregulin signaling, and, additionally, may also be able to mediate a switch from developmental to activity-dependent myelination. However, the perturbation of neuregulin signaling mid-way during development using inducible means (either by removing ErbB3 in oligodendroglia or expressing a dominant-negative ErbB4) *does* impact myelination, further suggesting that signals via neuregulin, and possibly other growth factors, play critical roles in the regulation of myelination in a way that is highly dependent on the developmental time window (Makinodan et al., 2012).

Overall BDNF has been heavily implicated in modulating cellular responses to behavioral experiences such as environmental enrichment and voluntary exercise. For example, BDNF mRNA and protein levels increase in the hippocampus after both environmental enrichment and voluntary exercise (Olson et al., 2006). Trophic signaling cascades via TrkB and other receptors then exert the behaviorally-dependent effects of BDNF on LTP and neurogenesis, resulting in enhanced learning and memory (Lista and Sorrentino, 2010; Olson et al., 2006; Scaccianoce et al., 2006; Vaynman et al., 2004). The actions of BDNF on neurons have been extensively characterized, however, it is clear from both cell culture and *in vivo* studies that OPC proliferation, differentiation and oligodendrocyte myelin production can increase in response to BDNF (Du et al., 2003; McTigue et al., 1998; Vondran et al., 2010). Thus it is likely that increases in BDNF, stimulated by behavioral experiences, affect OPCs and oligodendrocytes, however this idea has not yet been tested directly.

Oligodendrocyte lineage cells may also be influenced by experience-dependent angiogenesis, as increased angiogenesis could lead to an enhanced delivery of circulating growth factors, as has been suggested for neurogenesis in the hippocampus (Cao et al., 2004; Kleim et al., 2002; Llorens-Martín et al., 2010; Pereira et al., 2007; Trejo et al., 2001). It is

also possible that growth factors could act as intermediaries downstream of changes in neural activity. For example, activity dependent transmission of ATP from neurons can stimulate the release of Leukemia Inhibitory Factor (LIF) from nearby astrocytes, and in turn promote oligodendrocyte myelination (Ishibashi et al., 2006). An activity-to-growth factor mechanism would be nicely positioned to dictate, or modulate, which specific circuits (those stimulated by behavioral experiences) become myelinated. This hierarchy may be particularly relevant in the PFC, where experience dependent myelin plasticity in response to socialization has been observed (Liu et al., 2012; Makinodan et al., 2012). Here, epigenetic changes may also play a role, potentially as an underlying effector downstream of growth factors, as significant changes in heterochromatin and histone deacetylases in response to socialization deficit were reported (Liu et al., 2012). More work is required to explore the potential for the activity-to-growth factor axis in triggering the effects of behavioral experiences on oligodendrocyte lineage cells.

3.5. Exosomes

In addition to growth factors, other secreted constituents in the periphery are poised to influence behavioral experience-related oligodendrocyte lineage responses. One class of potential effectors are exosomes. Exosomes are microvesicles (approximately 30–120 nm in diameter) that are formed as a byproduct of the invagination of larger endosomes and are subsequently secreted into the extracellular space (Théry et al., 2009, 2002). Exosomes exert their effects by transporting a select array of proteins and microRNAs to other cells. These microvesicles have been implicated in antigen presentation within the immune system (Bobrie et al., 2011) as well as in modulating cell function in a number of diseases and biological processes (Korkut et al., 2013; Théry et al., 2009).

The potential role of exosomes in facilitating the effects of behavioral experiences on the brain remains relatively unexplored. However it was recently demonstrated through parabiosis (surgical union of blood circulation between two organisms) that the blood milieu from young mice could ameliorate the poorer recovery typically seen in older mice following lysolecithin-induced demyelination (Ruckh et al., 2012). Although the authors concluded that youthful macrophages contributed to successful remyelination, this conclusion did not exclude the contribution of circulating factors such as exosomes. Another recent investigation demonstrated that the beneficial effects of environmental enrichment on oligodendrocytes may be partly mediated through exosomes carrying miRNA219, which suppresses neuronal lineage genes within oligodendrocyte lineage cells as well as genes that inhibit OPC differentiation and oligodendrocyte myelination (Pusic and Kraig, 2014). Exosomes from rats exposed to environmental enrichment added to cultured hippocampal tissue sections from 12-month old rats resulted in increased proliferation of OPCs and enhanced myelination, relative to exosomes from non-enriched rats. To demonstrate the potential relevance of this mechanism in vivo, the investigators administered exosomes collected from environmentally-enriched rats into sedentary rats through nasal administration; this resulted in increased MBP immunoreactivity within the motor cortex. These data suggested that behavioral experiences could trigger in the periphery, a specific release of exosomes infused with miRNAs that direct the growth and development of OPCs and oligodendrocytes.

3.6. Metabolism

Oligodendrocytes produce substantial amounts of myelin, which by some estimates is approximately 100 times the weight of the cell body (Connor and Menzies, 1996; McTigue and Tripathi, 2008). This highlights the high metabolic demand myelination exerts on the cell, which makes oligodendrocytes particularly responsive to metabolic effectors and stressors. Certain behavioral experiences, particularly physical activity (Agudelo et al., 2014; Rowe et al., 2014; Zhuravliova et al., 2009), have profound influences on cellular metabolism. As such, global and/or region-specific modulation of metabolites could play a critical role in the exercise-dependent effects on oligodendrocyte lineage cells.

As brain energy metabolism relies on glia-dependent interactions (Allaman et al., 2011; Hirrlinger and Nave, 2014), the metabolic changes that occur as a result of exercise may be particularly well suited to influence oligodendrocyte lineage cells. For instance, a recent investigation has shed light on how exercise can influence mood elevation via alteration of metabolites produced by muscles (Agudelo et al., 2014). PGC-1 α (also known as PGC-1 α 1) is a transcriptional coactivator important for many of the skeletal muscle adaptations to exercise (Rowe et al., 2014; Ruas et al., 2012). Recently, PGC-1 α 1 was shown to promote the upregulation of kynurenine aminotransferase (KAT), an enzyme that converts the stress-induced metabolite kynurenine into kynurenic acid, which cannot cross the blood brain barrier (Schwarcz et al., 2012). Interestingly, mice with muscle-specific overexpression of PGC-1 α 1 were resistant to the depressive-like effects of a chronic mild stress procedure, while wild type mice were not. Furthermore, exercising wild type mice exhibited increases in PGC-1 α 1 mRNA and KAT mRNA in muscle, possibly explaining how exercise prevents peripheral kynurenine from crossing the blood brain barrier to exert negative effects on the brain. If kynurenine does cross into the brain, it is then metabolized to kynurenic acid by astrocytes and into other metabolites in microglia and macrophages (Schwarcz et al., 2012). Since kynurenic acid is a competitive inhibitor of AMPA, kainate and NMDA receptors (Hartai et al., 2005; Hilmas et al., 2001; Prescott et al., 2006), all three of which are expressed in OPCs (De Biase et al., 2011; Yang et al., 2013a), kynurenic acid is poised to influence OPC development. In addition, as oligodendrocytes are *also* thought to produce kynurenic acid (Lim et al., 2007; Wejksza et al., 2005), the promotion of kynurenine-to-kynurenic acid conversion in the periphery by exercise may prevent potential blocking of communication between OPCs and neurons at non-classical synapses (Yang et al., 2013a). Similar results have been noted in studies with adiponectin, suggesting that it may be an effector of exercise that acts in alleviating depression and increasing cell genesis (Yau et al., 2014).

As is often the case, the underlying mechanisms that result in oligodendrocyte lineage cellular changes in response to behavioral experiences are likely multiple and complex, and not necessarily mutually exclusive. Further investigations will be required to fully understand the mechanisms underlying the effects of behavioral experiences on oligodendrocyte lineage cells.

4. Common effectors? The potential for intersecting mechanisms downstream of behavioral experiences and diet

In addition to the behavioral experiences discussed in this article, many other lifestyle “inputs” such as diet, sleep (recently reviewed in Bellesi, 2015), and exposure to toxins, have also been shown to influence oligodendrocyte lineage cells and myelination. Diet in particular has been studied in the context of developmental myelination, where polyunsaturated fatty acids (PUFAs) have been linked to increased myelin gene expression and protection against white matter injury, with PUFA administration during maternal gestation leading to accelerated myelination and early development of behavioral reflexes (Confaloni et al., 1993; Gozzo et al., 1982; Salvati et al., 1996, 2002; Tian et al., 2011; Tuzun et al., 2012). PUFAs are integral components of cell membranes including myelin membranes (Yurlova et al., 2011). Omega-3 fatty acids appear to play a protective role during demyelination, resulting in increased oligodendrocyte survival and preserved integrity of the myelin sheath (Lim et al., 2013; Pu et al., 2013; Salvati et al., 2013). During remyelination, omega-3 fatty acid administration was found to result in increased CNPase expression (a marker of oligodendrocyte differentiation) and increased levels of myelin gene mRNAs (Salvati et al., 2008).

In some studies, diets rich in PUFAs have been found to increase cognitive performance. Here, age may be a primary factor in determining effectiveness, with infants being the most, or, potentially, only, receptive population to PUFAs in terms of improved cognition (Bondi et al., 2014; Boucher et al., 2011; He et al., 2009; Jackson et al., 2012; Karr et al., 2012; Liu et al., 2014; Muldoon et al., 2010; van de Rest et al., 2009; Vinot et al., 2011). Cognitive performance studies have also reported that omega-3 fatty acids promote BDNF signaling, and thus have the potential to interact with, or synergize with, the exercise-mediated effects of BDNF (Vaynman et al., 2004; Wu et al., 2008). Additionally, the activation and expression of key synaptic plasticity signaling effectors such as CREB, CamKII, syntaxin-3 and synapsin I, may be stimulated by omega-3 fatty acids (Bhatia et al., 2011; Chytrova et al., 2010; Vaynman et al., 2003, 2004). PUFAs have additionally been shown to stimulate synaptic plasticity at least in part by changing vesicular transport dynamics and altering neurogenesis (Cutuli et al., 2014; Gedalya et al., 2009; Janssen et al., 2015; Kudas et al., 2002; Lesa et al., 2003; Marza et al., 2008; Wurtman et al., 2006; Zimmer et al., 2000). Conversely, omega-3 fatty acid deficiency is associated with neurodevelopmental deficits, neurodegenerative disorders, and attenuated cognitive performance (Bhatia et al., 2011; Sable et al., 2013; Saugstad, 2006). It remains to be determined whether PUFA-modulated signaling pathways influence the molecular responses in oligodendrocyte lineage cells in response to behavioral experiences, so additional studies are needed to understand if, and how, these “inputs” may converge at the molecular level. However, abnormalities in the composition of PUFAs have been identified in the frontopolar cortex of bipolar and major disorder patients (Tatebayashi et al., 2012). Analysis of PUFA content in erythrocytes and diffusion tensor imaging performed in patients with psychotic disorders established a correlation of decreased PUFAs and fractional anisotropy, a measurement of water movement correlated with white matter integrity (Peters et al., 2013). Lower PUFA levels

are also correlated with cognitive decline in aging (Bowman et al., 2013), where decreases in white matter integrity occur concomitantly.

On the other hand, some fatty acids may be detrimental to brain structure/function, as diets high in saturated fats have a deleterious impact on white matter integrity, cognitive function, neuronal plasticity, neurotrophic signaling and activation of the stress-related hypothalamic-pituitary-adrenal axis (Auvinen et al., 2012; Bruce-Keller et al., 2009; Freeman et al., 2014; White et al., 2009). High fat diets have been found to reduce BDNF signaling in the hippocampus, attenuating cognitive responses and functions, yet exercise can restore BDNF regulated neuronal plasticity even under a high fat diet, suggesting that physical activity may help retain normal neurotrophic signaling (Vaynman et al., 2006; Wu et al., 2004). Given the influence of BDNF on developmental myelination, BDNF represents a potential point of convergence downstream of both diet and exercise in regulating myelin homeostasis.

Vitamins may also be highly influential on cellular targets associated with behavioral experiences. For example, vitamins D and E have been found to be beneficial during demyelination, by stimulating oxidative stress responses that may play a protective role in mitochondrial function and maintenance of energy generation (Chabas et al., 2013; Goudarzvand et al., 2010; Wergeland et al., 2011). These vitamin-mediated effects share many commonalities with exercise-related reductions of oxidative stress responses and regulation of mitochondrial biogenesis (St-Pierre et al., 2006; Rowe et al., 2014). Vitamin D receptors are found throughout the brain in many cell types, including oligodendrocytes (Eyles et al., 2005; Harms et al., 2011), and vitamin D receptor signaling engages in cross-talk with many signaling pathways known to influence oligodendrocyte lineage biology, including MAPK signaling (Deeb et al., 2007). Conversely, vitamin *deficiencies* have been correlated with demyelination and susceptibility to mood disorders, including schizophrenia, post-traumatic stress disorder, and dementia (De Lau et al., 2009; Malouf and Areosa Sastre, 2003; Miller et al., 2005; Mitchell et al., 2014). Here, vitamin supplementation may enhance or preserve cognitive performance, particularly learning and memory, by stimulating calcium related signaling, G protein functions, synaptic transmission, or even clearance of amyloid plaques (Adlard et al., 2005; Ding et al., 2006; Farmer et al., 2004; Soni et al., 2012; Vaynman et al., 2003; Yu et al., 2011). Additionally, vitamins have also been linked to the stimulation of adult hippocampal neurogenesis, although whether vitamins directly influence oligodendrogenesis remains unknown (Hall et al., 2014; Stangl and Thuret, 2009). However vitamins, including vitamin D and vitamin B12, are known to influence developmental myelination (Black, 2008; Chabas et al., 2013).

Caloric restriction (CR), involving a 30–40% reduction in total calorie intake, increases lifespan in certain animal models (Arslan-Ergul et al., 2013). CR also has significant positive effects on memory and neurogenesis (Witte et al., 2009; Lee et al., 2002; Wu et al., 2003), and increases the survival of neural progenitors in old age in a manner similar to environmental enrichment (Bondolfi et al., 2004; Lee et al., 2001). It remains to be determined if CR influences the survival of oligodendrocytes or OPCs in the aging brain. However CR induces hormonal and cytokine changes that are consistent with an anti-inflammatory and neuroprotective profile during Experimental Autoimmune Encephalomyelitis, an inflammatory-demyelinating mouse model (Piccio et al., 2008).

Furthermore, at least in peripheral nerves, CR appears to attenuate myelin degeneration associated with aging (Amer et al., 2014; Rangaraju et al., 2009).

Malnutrition, on the other hand, has a profoundly negative impact on myelination. Malnutrition can result in damaged myelin, impaired myelin sheath packing, and alterations in the lipid composition at the myelin membrane, all resulting in white matter abnormalities that are somewhat irreversible and last through adulthood (Almeida et al., 2005; Pacagnella et al., 2013; Vargas et al., 2000). Malnutrition is furthermore linked to activation of the stress response via the hypothalamic-pituitary-adrenal axis (Nanri et al., 2014; Soares et al., 2013).

Overall, the emerging evidence suggests that the quality, and quantity, of dietary intake influences brain functioning in ways that intersect with cellular responses modulated by behavioral experiences, and that myelin plasticity may be one such intersection point.

5. The chicken or the egg? How behavioral experiences may contribute to changes in oligodendrocyte lineage cells in neuropsychiatric diseases

Glial dysfunction has increasingly been linked to neuropsychiatric diseases, including major depressive disorder, bipolar disorder, and schizophrenia (Mighdoll et al., 2015). For example, decreased densities of OPCs and/or mature oligodendrocytes, reduced proliferation of oligodendrocyte progenitors, and decreased expression of myelin-specific genes (e.g., MOG, MBP) have been reported in a variety of neuropsychiatric diseases (Edgar and Sibille, 2012). Diffusion tensor imaging studies on patients with neuropsychiatric diseases have furthermore revealed decreased white matter tract connectivity as well as regional decreases in white matter volume (Takahashi et al., 2011). While it remains unclear in many instances whether changes to oligodendrocyte lineage cells seen in neuropsychiatric diseases are correlative or causative to disease progression, the majority of the neuroscience community has long assumed that these changes are the result of underlying neuronal dysfunction. An exciting counterpoint has emerged from several recent investigations, in which disturbances in oligodendrocyte lineage cell function have been found to directly contribute to disturbances in mood during neuropsychiatric diseases, in the absence of pre-existing neuronal dysfunction (Yu et al., 2014). In support of a model in which oligodendroglial deficits are an underlying risk factor for the development of neuropsychiatric diseases, patients with neuropsychiatric diseases have been found to have mutations in genes that encode oligodendrocyte lineage proteins. However, studies examining the role of behavioral experiences in modulating oligodendrocyte lineage cells raise another, albeit not mutually exclusive, possibility: inappropriate behavior itself could be causing oligodendrocyte lineage cell loss and/or dysfunction, as well as changes in myelin plasticity during the course of neuropsychiatric disease. For example, the lack of social interaction engaged in by patients suffering from major depression could in turn negatively influence oligodendrocyte development and myelin plasticity, generating a feed-forward change that contributes to further oligodendrocyte lineage cellular dysfunction.

Also relevant to the role of behavioral experiences as effectors of oligodendrocyte lineage cells and myelin are studies linking positive effectors of myelination to improved outcomes in mood disorders. For instance, electroconvulsive therapy (ECT) treatment, which can be

beneficial to patients with refractory major depressive disorder, leads to increased fractional anisotropy in humans (Nobuhara et al., 2004), suggesting a possible role for myelin plasticity in promoting recovery from mood disorders. In support of this idea, ECT-like treatment in rats leads to increased OPC proliferation (Ongür et al., 2007). Conversely, negative effectors of mood, such as chronic stress, have been shown to negatively impact OPC proliferation and oligodendrocyte density (as discussed above). Disorders involving the destruction of oligodendrocyte lineage cells and myelin exhibit a strong comorbidity with depression. This is true in Multiple Sclerosis, in which the cellular pathology is (at least in early phases) believed to be selective towards oligodendrocytes, or in Alzheimer's disease, in which neuronal degeneration is coupled quite strongly with the loss of myelin. Again, it remains unclear the extent to which oligodendrocyte/myelin loss is causative in the development of depression in these disorders.

More study is therefore needed to distinguish cause and correlation when it comes to understanding the relationship between oligodendrocyte lineage cells and emotional “outputs” such as mood. Intriguingly, some studies do point to oligodendrocyte lineage cell dysfunction as being causative. For example, the genetic manipulation of CNP1 or PLP levels in oligodendrocytes leads to changes in mood (e.g., anxiety responses to social isolation) that appear many months prior to evidence of neurodegeneration (Edgar et al., 2011; Tanaka et al., 2009). Taken together, many of the studies summarized in the current review suggest a two way street in which altered behavioral experiences during psychiatric disease may have profound impacts on ongoing oligodendroglial homeostasis and myelin plasticity. These effects may be most damaging in younger patients, when developmental myelination is still ongoing.

6. Conclusions

There is growing evidence that behavioral experiences including exercise, socialization and environmental enrichment induce significant changes in oligodendrocyte lineage cells, altering proliferation, differentiation and myelination. More work is needed to answer a number of compelling questions including: how oligodendrocyte lineage cells in different states, e.g. OPCs versus oligodendrocytes, as well as newly-generated versus mature cells, may be differentially affected, what regional differences in oligodendrocyte lineage dynamics exist and their basis, and how oligodendrocyte lineage cellular responses change during aging and in response to other environmental influences (e.g., diet, sleep). There are a number of plausible molecular mechanisms that may regulate oligodendrocyte lineage cellular responses to behavioral experiences. Many have been suggested by investigations with a focus on behavioral-experience dependent hippocampal neurogenesis. However, explorations of the mechanistic links between behavioral experiences and changes in oligodendrocyte lineage cells are in their infancy, achieving limited consensus as of yet. Interestingly, as all of the behavioral experiences discussed here influence stress effectors, stress-induced modifications of cellular signaling pathways and/or epigenetic modulators are particularly promising candidates to be central mediators translating behavioral experiences into the molecular changes that drive oligodendrocyte lineage cellular dynamics. Additionally, neuronal activity and subsequent neurotransmitter release, as well as growth factor modulations, likely play roles in dictating which brain structures, circuits and

oligodendrocyte lineage cells undergo experience-dependent changes. Oligodendrocytes, given their relatively high metabolic demand, may be particularly affected by exercise-regulated metabolites. Although more studies are required to better understand the underlying process by which behavioral experiences regulate glia, recent studies suggest this emerging and exciting field may uncover a complex network of reciprocal interactions among oligodendrocyte lineage development, behavioral experiences and brain function.

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Fig. 1.

Behavioral experiences influence oligodendrocyte lineage cellular development. Several behavioral experiences have been found to promote various stages of oligodendrocyte lineage development including myelination: exercise, social interactions, and environmental stimulation including exposure to novel objects. In contrast, other behavioral experiences have been found to suppress or lessen oligodendrocyte lineage development and myelination; these include a sedentary lifestyle, social isolation, and environmental deprivation. While the cellular and molecular changes involved are not yet completely characterized, several stages in oligodendroglial development are likely affected: (1) the generation of new oligodendrocyte precursor cells (OPCs) from neural stem and intermediate progenitor cells, (2) the proliferation of OPCs, (3) the transition from OPC to oligodendrocyte, (4) oligodendrocyte maturation, and (5) myelination. In addition, OPC interactions at synapses and oligodendroglial interactions with axons are potential regulation points.

Table 1

Summary of behavioral experiences and their effects on oligodendroglia development.

Behavioral experience: EE, SI or VE	Brain area	Disorder	Cellular effects	Molecular effects	Behavioral effects	References
SI	Prefrontal Cortex	None	<ul style="list-style-type: none"> • Abnormal oligodendrocyte morphology • Decreased myelin thickness (increased G-ratios) • Decreased heterochromatin 	<ul style="list-style-type: none"> • Decreased myelin gene transcripts (MBP, MAG, Mobp) • Decrease levels of enzymes regulating histone acetylation transcripts • Decrease in neuregulin 1-III transcripts 	<ul style="list-style-type: none"> • Deficits in Social interaction • Deficits in working memory 	(Liu et al., 2012; Makinodan et al., 2012)
VE	Prefrontal Cortex	None	<ul style="list-style-type: none"> • Increased proliferation (Ki67+) • Increase in BrdU labeled astrocytes • Increase in BrdU labeled OPCs 			(Mandyam et al., 2007)
VE	Cingulate Cortex	None	<ul style="list-style-type: none"> • Increase in BrdU labeled microglia 			(Ehninger and Kempermann, 2003)
VE/Motor Learning	Corpus Callosum	None	<ul style="list-style-type: none"> • Increase in EdU labeled OPCs • Increase in OPC density • Increase in EdU labeled Oligodendrocytes 	<ul style="list-style-type: none"> • Myrf activation • Increase in active myelination 	<ul style="list-style-type: none"> • Motor learning (dependent on new myelination) 	(McKenzie et al., 2014)
VE	Motor/ Somatosensory Cortex	None	<ul style="list-style-type: none"> • Decreased proliferation (Ki67+) • Increased oligodendrocyte production • Increase in BrdU labeled microglia (Mtx) • Increase in BrdU labeled astrocytes (Mtx) 			(Ehninger et al., 2011; Simon et al., 2011)
VE	Amygdala	None	<ul style="list-style-type: none"> • Decrease in BrdU labeled cells • Increase in BrdU labeled OPCs (NG2+S100β-BrdU+) • Decrease in BrdU labeled astrocytes (S100β+BrdU+) • Decrease in BrdU labeled microglia 			(Ehninger et al., 2011)
VE	Visual Cortex	None	<ul style="list-style-type: none"> • Increase in BrdU labeled cells • Increase in BrdU labeled OPCs (NG2+S100β-BrdU+) • Increase in BrdU labeled microglia 			(Ehninger and Kempermann, 2003; Ehninger et al., 2011)
EE	Prefrontal Cortex	None	<ul style="list-style-type: none"> • No significant differences in oligodendrocyte density or morphology 	<ul style="list-style-type: none"> • No significant differences in myelin transcript levels 	<ul style="list-style-type: none"> • No significant differences in social exploration 	(Makinodan et al., 2012)
EE	Cingulate Cortex	None	<ul style="list-style-type: none"> • Increase in BrdU labeled astrocytes (S100β+BrdU+) 			(Ehninger and Kempermann, 2003)
EE	Corpus Callosum	None	<ul style="list-style-type: none"> • Increase in oligodendrocyte number 		<ul style="list-style-type: none"> • Improvements in Morris Water Maze Task 	(Zhao et al., 2011)

Behavioral experience: EE, SI or VE	Brain area	Disorder	Cellular effects	Molecular effects	Behavioral effects	References
EE	Motor Cortex	None	<ul style="list-style-type: none"> • Increase in BrdU labeled astrocytes (S100β+BrdU+) 			(Ehninger and Kempermann, 2003)
EE	Amygdala	None	<ul style="list-style-type: none"> • Increase in BrdU labeled cells • Increase in BrdU labeled OPCs (NG2+S100β-; Olig2+) • No change in BrdU labeled OPCs (Okuda) • Decrease in BrdU labeled microglia • Increase in BrdU labeled astrocytes 			(Ehninger et al., 2011; Okuda et al., 2009)
EE	Visual Cortex	None	<ul style="list-style-type: none"> • Increase in BrdU labeled cells • Increase in BrdU labeled microglia 			(Ehninger and Kempermann, 2003)
EE	Sensorimotor Cortex	Stroke	<ul style="list-style-type: none"> • Increase in BrdU labeled OPCs • Decrease in BrdU labeled astrocytes (GFAP+S100β+)) 		<ul style="list-style-type: none"> • Improved sensorimotor capabilities of impaired contralateral forelimb 	(Keiner et al., 2008; Komitova et al., 2006)

OPC = Oligodendrocyte Precursor Cells; VE= Voluntary Exercise, SI = Social Isolation, EE = Environmental Enrichment; BrdU = Bromodeoxyuridine; EdU = EthynylDeoxyuridine.