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Neuroglialpharmacology: Myelination As A Shared Mechanism of Action of Psychotropic Treatments

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Abstract

Current psychiatric diagnostic schema segregate symptom clusters into discrete entities, however, large proportions of patients suffer from comorbid conditions that fit neither diagnostic nor therapeutic schema. Similarly, psychotropic treatments ranging from lithium and antipsychotics to serotonin reuptake inhibitors (SSRIs) and acetylcholinesterase inhibitors have been shown to be efficacious in a wide spectrum of psychiatric disorders ranging from autism, schizophrenia (SZ), depression, and bipolar disorder (BD) to Alzheimer's disease (AD). This apparent lack of specificity suggests that psychiatric symptoms as well as treatments may share aspects of pathophysiology and mechanisms of action that defy current symptom-based diagnostic and neuron-based therapeutic schema.

A myelin-centered model of human brain function can help integrate these incongruities and provide novel insights into disease etiologies and treatment mechanisms. Available data are integrated herein to suggest that widely used psychotropic treatments ranging from antipsychotics and antidepressants to lithium and electroconvulsive therapy share complex signaling pathways such as Akt and glycogen synthase kinase-3 (GSK3) that affect myelination, its plasticity, and repair. These signaling pathways respond to neurotransmitters, neurotrophins, hormones, and nutrition, underlie intricate neuroglial communications, and may substantially contribute to the mechanisms of action and wide spectra of efficacy of current therapeutics by promoting myelination. Imaging and genetic technologies make it possible to safely and noninvasively test these hypotheses directly in humans and can help guide clinical trial efforts designed to correct myelination abnormalities. Such efforts may provide insights into novel avenues for treatment and prevention of some of the most prevalent and devastating human diseases.

Pervasive brain myelination underlies neural network synchrony and our distinctiveness as a species. Psychiatric diagnoses may share deficits in myelin development, plasticity, or repair.

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Treatments act on neuroglial signaling pathways such as Akt and GSK3 that improve myelination. Treatment efficacy may derive from myelination-driven improved neural network synchronization. “Neuroglialpharmacology” encapsulates a paradigm shift in medication development strategy.

Keywords

White matter; oligodendrocyte; intracortical myelin; medication; MRI; NG2 cells; neuregulin; ErbB; DISC1; IGF1; Reelin; Cdk; MAPK; mTOR; Leptin

1. Introduction

The diagnostic schema embodied in the Diagnostic and Statistical Manual of Mental Disorders (DSM) is symptom-based and largely disconnected from disease etiologies or a biologic model of healthy human brain function. Useful models of brain function, as well as the dysfunctions that manifest in psychopathology, must by necessity incorporate testable hypotheses that help explain both the mode of action of psychotropic medications as well as their wide spectrum of efficacy (e.g., ability to treat multiple diagnoses). With notable exceptions (e.g., lithium, electroconvulsive treatments, and nutritional interventions), much of current clinical pharmacology is believed to act primarily at neuronal synapses that are largely confined to gray matter. This has focused clinical and research attention on neurons and synapses residing therein. This narrow focus has contributed to the under-appreciation of glia and especially oligodendrocytes and the myelin sheaths they produce in optimizing the timing and synchrony of action potentials on which optimal function of neuronal networks depends. Timing is a key metric to all cortical operations (Klausberger and Somogyi, 2008) and it is primarily dependent on the production, maintenance, and repair of myelin (reviewed in Bartzokis et al., 2011d).

The human brain is exceptionally myelinated compared to other species (Smaers et al., 2011) (reviewed in Bartzokis et al., 2011d). This extensive myelination has imposed exceptionally high metabolic demands and is associated with vulnerabilities that make the human species highly susceptible to distinctive and highly prevalent brain disorders throughout its lifespan (reviewed in Bartzokis, 2002, 2004, 2011a; Bartzokis et al., 2011d). While most think of myelin as a component of white matter, in humans, gray matter is also extensively myelinated (Figure 1), and the key role of this intracortical myelin (ICM) component in optimizing brain function have generally been overlooked.

This report will focus on two important aspects of brain function and dysfunction from the perspective of myelin. First, the importance of intracortical myelin to the plasticity required to continually optimize the timing of action potentials and network oscillations on which learning, cognitive performance, and behavior depend (sections 2–4). Second, the shared mechanisms of action of psychotropic treatments on brain myelin and its continual optimization and repair (sections 5 and 6). These underappreciated aspects of myelination may help explain the efficacy that different classes of pharmaceuticals have on the same sets of symptoms as well as the wide spectrum of efficacy of certain classes of medications on multiple diagnoses/symptom clusters. The emphasis herein on a myelin perspective is not meant to deny the important role of synaptic activity in psychiatric disease and its treatment, rather, the aim is to balance and integrate that neuronal perspective with the key role of glia and myelin in particular in normal and abnormal brain function.

2. Myelin and the Human Brain

The brain is classically divided into gray matter (defined as the regions containing neuronal cell bodies and almost all synaptic connections) and white matter (composed primarily of the very long neuronal appendage (axon) that acts as a "wire" connecting widely dispersed neurons, plus the oligodendrocytes that produce the axon's "insulating" myelin sheaths). The roughly 100 billion neurons in the human brain are actually a small minority of brain cells (10%) while glia, which are present in both gray and white matter, account for the rest: astrocytes (45%), oligodendrocytes (35%), microglia (5%), and progenitor (NG2) cells (5%, the vast majority of which differentiate into oligodendrocytes). The human brain consumes 20% of our total energy expenditure compared to 13% in monkeys and 2-8% in other vertebrates. This striking shift in resource use was made possible by important evolutionary adaptations in lipid and energy metabolism. Compared to other species, these adaptations made it possible to devote a greater proportion (approximately 25%) of our brain's mass to myelin and thus achieve the information processing capacity that defines the human species (reviewed in Bartzokis, 2011b).

Human brain myelination has a quadratic-like (inverted "U") trajectory across the lifespan with increasing myelin content that peaks in middle–age (Figure 1). The "connectivity" provided by myelination consists of increased action potential transmission speed (over 100-fold) and decreased refractory time (34-fold) which increases the number of action potentials that can be transmitted per unit time (in Internet terminology this would represent expanded "bandwidth"). Myelination thus potentially increases the information processing capacity of our brain's "Internet" by over 3,000 fold, making human myelination indispensable for developing our species' elaborate cognitive functions (reviewed in Bartzokis et al., 2011d). Human cognitive functions are also highly dependent on *later*-myelinating oligodendrocytes. These cells myelinate the circuitry of our neural networks all the way to the neuron bodies located in gray matter structures such as the cortex (Figure 1). The extensive intracortical myelination process occurs later (after childhood) and basically "upgrades" neural networks with immediate response capacity such that they are essentially "on line" and process information much more quickly and precisely (reviewed in Bartzokis, 2011b) (see section 3.1).

Although the brain is routinely conceptualized as a singular entity, it is composed of a myriad of interacting neural networks that have highly "plastic" and dynamic developmental and degenerative trajectories. As Figure 1 demonstrates, even at the gross lobar level, the different trajectories reach peak myelination at different ages. These different trajectories are supported by oligodendrocytes that become increasingly more complex the later in life they differentiate. They range from robust oligodendrocytes that myelinate a single axon segment with over 100 wraps of myelin membrane in the early-myelinating motor and sensory regions/networks to more vulnerable oligodendrocytes that myelinate as many as 50 axon segments with less than 10 wraps in late-myelinating intracortical regions (Figure 1) (reviewed in Butt and Berry, 2000). The structurally more complex and metabolically overextended later-myelinating oligodendrocytes and their myelin are especially vulnerable during both developmental (Stark et al., 2004; Uranova et al., 2004; Vostrikov and Uranova, 2011; Vostrikov et al., 2007) as well as degenerative phases (Bartzokis et al., 2004; Marner et al., 2003) of the myelination trajectories over the lifespan (reviewed in Bartzokis, 2011b).

From the perspective of the exceptionally myelinated human species, the development and maintenance/repair of myelin's functional integrity may be the single most important and vulnerable element for acquiring and maintaining optimal cognitive and behavioral function. In short, myelin may arguably represent the "weakest link" of both brain development as well as age-related degeneration and thus contribute to many of the normal as well disease-

causing changes in brain function over the entire human lifespan. Including glia and myelin in a "model" of the human brain can help explain normal brain function, clinical and pathologic phenomenology of multiple diseases, as well as their shared responsiveness to pharmaceutical and other (e.g., nutritional) interventions (section 5 and 6).

3. Function of the Brain's Biologic "Internet" is Directly Dependent on Myelin

3.1 Normal/Optimal Brain Function Depends on Synchrony of Oscillations

Brain regions communicate through synchronized firing of populations of neurons in networks whose activity is reflected in the extracellular field potential as brain oscillations. Oscillations can be measured through techniques such as electroencephalography (Williams and Boksa, 2010). Oscillation-based synchrony is the most energy-efficient physical mechanism for temporal coordination. Mammalian cortical neurons form behavior-dependent oscillating networks that span a very wide frequency spectrum (from 0.05 to 500 Hz) creating tremendous information processing potential. These networks vary in size, are phylogenetically conserved, and oscillation-based functions they support can be highly heritable (Hong et al., 2008; Linkenkaer-Hansen et al., 2007) (reviewed in Buzsaki and Draguhn, 2004). Synchronized oscillations may also establish the precise action potential timing needed for use-dependent synaptic plasticity (e.g., long term potentiation) to occur (Rutishauser et al., 2010) (reviewed in Uhlhaas and Singer, 2010). Conversely, *asynchronous* arrival of action potentials has been shown to contribute to synaptic loss/pruning (Purves and Lichtman, 1980).

The first step towards network synchronization is achieved in childhood by myelinating the *subcortical* white matter portion of axons connecting widely distributed brain regions into functional networks (Figure 2). This initial subcortical myelination can be initiated/directed by neuronal signals themselves (Fields and Burnstock, 2006; Ziskin et al., 2007) (reviewed in Butt, 2011) and results in the remarkably faster conduction (>100 times faster than unmyelinated axon) between widely separated gray matter regions such as thalamus and the many cortical regions with which it interacts. Once subcortical myelination is achieved, the total conduction time between these highly dispersed regions becomes primarily dependent on the much longer time (roughly 10 times) action potentials spend traversing the short but *unmyelinated* portion of axons within cortex. This *intracortical* distance to a *specific* neuronal layer is roughly *constant*. The constant intracortical distance to layer III (which receives most of the cortico-cortical input), together with the slow intracortical signal propagation, establishes the initial roughly synchronous arrival of action potentials to all cortical regions that are at different distances (Kimura and Itami, 2009; Salami et al., 2003). The rough network synchrony achieved by this process underlines the vast repertoire of cognitive and behavioral abilities that can be achieved in childhood albeit few of these functions or their integration are "perfected"/optimized at that early stage of life (Bartzokis, 2011b).

3.2 Intracortical Myelin (ICM) Optimizes Network Oscillations and Brain Function

As described above, the short *intracortical* portion of axonal propagation (that is largely unmyelinated in childhood) exerts a markedly disproportionate influence on synchronicity of action potential arrival across functional networks and their vast numbers of neurons and synapses. Beyond childhood, even faster transmission as well as exquisitely more precisely synchronized timing can be achieved by adding the appropriate amounts of myelin to the intracortical portion of fibers. As Figure 1 suggests, cortical oligodendrogenesis occurs primarily in adulthood (O'Kusky and Colonnier, 1982) and underlies the acceleration and "fine grained" synchronization of cognitive and behavioral networks that continue to be

refined over the entire first six decades of life. This later-differentiating intracortical subgroup of oligodendrocytes seems to differ in subtle ways from their subcortical counterparts (Kessaris et al., 2006; Noble et al., 2003; Power et al., 2002), as may the composition of the myelin they produce (Hartman et al., 1982) (reviewed in Butt and Berry, 2000). Cortical myelination underlies a key mechanism of brain plasticity and its disturbance could have important consequences for disease pathophysiology as well as efficacy of psychotropic treatments (Bartzokis, 2011b; Bartzokis et al., 2009) (see section 4, and 5).

Myelin-based network plasticity is dependent on continued oligogenesis (Figure 1). Life-long oligogenesis is a distinctive oligodendrocyte feature that is central to brain development and plasticity throughout life. Unlike neurons, whose numbers are essentially established at birth, in healthy primates, vast numbers of progenitor (NG2) cells are produced to support the decades-long processes of postnatal myelination and repair/remyelination (Levine et al., 2001). The NG2 cells comprise approximately 5% of total adult brain cells and continue to divide, increasing the number of differentiated oligodendrocytes by as much as 50% during adulthood (O'Kusky and Colonnier, 1982; Peters and Sethares, 2004; Peters et al., 2008; Vostrikov and Uranova, 2011; Vostrikov et al., 2007). By dividing and differentiating into oligodendrocytes, NG2 cells can support both continued myelination of additional axons or portions thereof (e.g., intracortical) as well as remyelinate damaged or lost myelin sheaths (Peters and Sethares, 2003; Peters et al., 2008). The plasticity of *intracortical* myelin (ICM) could also compensate for network synchrony disruptions brought by changes in transmission speeds anywhere in the circuitry, including those resulting from subcortical myelin repair processes that can alter transmission speed by decreasing myelin thickness (Smith and Koles, 1970) (reviewed in Bartzokis, 2011b) (Figure 2).

Although there are multiple possible causes for pathologic changes in circuit oscillations, the importance of ICM in compensating for subcortical transmission delays and optimizing brain function is supported by observations from multiple sclerosis (MS), a canonical myelin disease, and Alzheimer's disease (AD), usually considered a canonical "cortical" disease. Until recently myelin-destroying intracortical MS lesions, which postmortem data show represent as much as 60% of MS lesions, were under-appreciated due in part to difficulty in detecting them on MRI (reviewed in Simon et al., 2010). Prospective studies show that absence of such cortical lesions is associated with a favorable clinical and cognitive outcome independent of deep white matter lesion accumulation (Calabrese et al., 2009). Conversely, the presence and progression of intracortical lesions in MS are most clearly associated with cognitive decline (including processing speed and memory) (Roosendaal et al., 2009). These phenomena can be parsimoniously explained by the plasticity of ICM and its ability to compensate for subcortical delays in transmission and re-establishing network synchrony. Thus, only when the optimizing role of ICM is lost to intracortical demyelination would subcortical delays fully manifest as degraded network synchrony and function and thus become observable as clinical symptoms. Similar focal losses of intracortical myelin associated with amyloid beta (Aβ) plaques were recently documented in AD (Mitew et al., 2010) and may similarly contribute to declines in cognitive and behavioral functions observed in that disease, although this possibility has only recently begun to be directly investigated in vivo (Bartzokis et al, unpublished data).

4. Dysregulated Myelination in Schizophrenia (SZ) and Bipolar Disorder (BD)

Over the last decade the importance of myelin pathology in SZ and BD has become widely recognized (reviewed in Andreasen et al., 2011; Bartzokis, 2002, 2011b; Brambilla et al.,

2009; Corfas et al., 2004; Davis et al., 2003; Dwork et al., 2007; McIntosh et al., 2009). Although white matter abnormalities are present in both diseases, the patterns of abnormalities are not identical (Bartzokis, 2011b).

In chronic SZ, post-mortem gene expression, cytology, and myelin stain studies provide converging evidence to support the view of a deficient trajectory of frontal lobe ICM. Imaging studies that assessed white matter volume provided converging evidence of a deficient myelination trajectory that, unlike in healthy individuals (Figure 1), ceases its development during early adulthood. Similar oligodendrocyte reductions and myelin gene expression deficits are also observed in chronic BD and may even occur in chronic severe unipolar depression (reviewed in Bartzokis, 2011b).

The data on disease-related changes in earlier-myelinating *subcortical* white matter is more complex and may differ in SZ and BD. In SZ, the bulk of post mortem studies suggest that *subcortical* myelin deficits are absent or not as prominent as cortical myelin/oligodendrocyte defects and imaging studies examining subcortical white matter of younger groups of SZ subjects (mean age 26 years or younger) using DTI also suggest that abnormalities are not present at disease onset but rather develop as the disease progresses (Friedman et al., 2008; White et al., 2011) (reviewed in Bartzokis, 2011b). A recent post mortem study supports this apparent progression of subcortical white matter involvement with disease durations. It showed that subcortical myelin defects are observed almost exclusively in brains of older SZ subjects, are associated with longer durations of illness, and are limited to earlier-myelinating large and medium size fibers (Uranova et al., 2011). A trajectory of progressive subcortical myelin/white matter disruption may also be reflected in DTI data from studies that assessed *older-onset* first-episode SZ subjects (mean onset age >26 years), which generally reported significant deficits in white matter integrity (reviewed in Bartzokis, 2011b). These differences may be influenced by a greater repair potential of subcortical white matter (Power et al., 2002) and by age-related reductions in myelin repair potential (Shen et al., 2008).

The thinner myelin produced by remyelination (Peters, 2009) slows conduction (Smith and Koles, 1970) and may thus contribute to degradation of network synchrony. The *intracortical* myelination processes observed in healthy controls (Figure 1) seems to be deficient in *chronic* SZ as well as BD (Bartzokis et al., 2011b; Vostrikov and Uranova, 2011) and therefore, compensating for subcortical changes in conduction velocity may be inadequate or fail altogether (Bartzokis, 2011b). Inadequate control of intracortical myelination could eventually degrade the synchrony of neural network oscillations (see section 3.2) and result in cognitive and behavioral inefficiencies and disorganization that are part of the clinical manifestations of several psychiatric disorders (Bartzokis, 2011b).

Compared to SZ, in BD *subcortical* myelin deficits can be more prominent (Regenold et al., 2007) and on MRI, focal regions of subcortical myelin damage (manifest as increased signal intensity in white matter) is consistently reported in BD (Altshuler et al., 1995) (reviewed in Brambilla et al., 2009; Kempton et al., 2008). Thus, in contrast to SZ where initially ICM deficits may be most prominent, in BP disorder increased vulnerability of earlier-myelinating subcortical fibers may be more pronounced at disease onset. More efficient repair mechanisms of subcortical myelin (Power et al., 2002) would permit the reestablishment of network synchrony and recovery of function, and may be aided by treatments such as lithium (Brambilla et al., 2009; van der Schot et al., 2009). This suggests that in BD adequate ICM plasticity may initially be able to compensate for subcortical transmission delays in BD to a greater extent than in SZ. Nevertheless, post-mortem data suggest that as BD progresses into its *chronic* phases, significant *intracortical* oligodendrocyte deficits develop in BD as they do in SZ (Rajkowska et al., 2001; Uranova et

al., 2004; Vostrikov and Uranova, 2011). These ICM deficits may help account for the eventual appearance of cognitive deficits and functional decline in chronic BD (Burdick et al., 2011; Sole et al., 2011) despite cognitive abilities in youth that may be above average, in contrast to SZ where cognitive deficits are present at onset (Koenen et al., 2009; Zanelli et al., 2010).

5. Psychotropic Treatments Influence Glia and Myelination

Activity-dependent neuroglial communication can be supported through neuronal ATP release as well as its metabolite adenosine. ATP activates purinergic receptors that modulate intracellular calcium and cyclic AMP and have multiple effects on glia, oligodendrocytes, and myelination (Butt, 2011; Fields and Burnstock, 2006). In addition, all the major neurotransmitter systems on which the bulk of currently available psychotropic medications act (dopamine, serotonin, norepinephrine, acetylcholine, GABA, and glutamate) may have important roles in myelination. Neurotransmitter-based neuroglial communication can influence/direct myelination and is supported by at least three mechanisms that will be reviewed next: synaptic, extra-synaptic, and non-synaptic. Their influence on myelination/repair processes may be especially important in synapse-rich cortical and other gray matter regions where all these neurotransmitter-based mechanisms can operate jointly (Bartzokis, 2007; Belachew et al., 1999; Butt, 2006; Karadottir and Attwell, 2007).

5.1 Synaptic, Extra-Synaptic, and Non-Synaptic Neurotransmitter Effects on Glia

Neuronal glutaminergic and GABAergic synapses onto oligodendrocyte progenitors (NG2 cells) have been demonstrated in both the developing brain and in white matter undergoing remyelination following experimental myelin damage (Etxeberria et al., 2010; Velez-Fort et al., 2010) (reviewed in Kolodziejczyk et al., 2010; Mangin and Gallo, 2011). Such direct neurotransmitter-based neuroglial communication mechanisms may have functional importance in oligodendrocyte differentiation and myelin repair as indicated by in vitro work showing an influence of both AMPA type glutamate receptors and GABA-A receptors on migration and differentiation (Gudz et al., 2006; Tong et al., 2009; Yuan et al., 1998).

In addition to direct synapses, neuroglial signaling may also occur through extra-synaptic transmission (also called volume transmission) due to “spillover” of neurotransmitters from synapses or nodes of Ranvier. This neuroglial signaling mechanism may be especially significant during high-frequency discharges and oscillations that release larger volumes of neurotransmitters. The direct synapses that GABA interneurons form onto NG2 cells in development seem to be converted into this kind of extra-synaptic GABA-oligodendrocyte transmission during later maturation (Velez-Fort et al., 2010). Thus, extra-synaptic neuroglial communication mechanisms may be especially important for the plasticity needed to optimize the oscillation synchrony and timing of highfrequency networks that are best supported by myelinated axons (Bartzokis et al., 2010) (see section 3).

Multiple classes of existing psychotropic treatments (e.g., antipsychotics, antidepressants) target neurotransmission and have substantial yet underappreciated neuroglial signaling roles. A very large proportion of cholinergic transmission (up to 90%) both in the developing and adult brain is non-synaptic (e.g., absence of post-synaptic neuronal button), with acetylcholine being released from cholinergic varicosities directly into the extracellular space (reviewed in Bartzokis, 2007). In addition to acetylcholine, catecholamines (primarily dopamine, serotonin, and norepinephrine) are also largely (>50–80%) non-synaptically released (Descarries et al., 1996; Parent et al., 2010; Smiley et al., 1994; Umbriaco et al., 1995) (reviewed in Fuxe and Agnati, 1991). These non-synaptic and extra-synaptic neuroglial communications can impact oligodendrocyte differentiation and myelination (reviewed in Bartzokis, 2007, 2011b).

It is of interest to note that glia may also influence neurotransmitter-based extra- and non-synaptic signaling through secretion of most of the extracellular matrix components such as reelin (see section 5.2.1) and chondroitin sulfate proteoglycans. This extracellular matrix differs from healthy controls in SZ but not BD and could contribute to some of the differences in clinical manifestations (reviewed in Berretta, 2011) despite shared myelination deficits between diseases (see section 4). Such glial-dependent influences would add another level of control as well as complexity to neuroglial communication through diffusible signaling molecules such as neurotransmitters. The following sections will integrate therapeutic as well as countertherapeutic (from drugs of abuse) influences on myelin plasticity from dopaminergic, serotinergic, GABAergic, glutaminergic, and cholinergic signaling (section 5.2.2 and 5.2.3), as well as growth factor, neurotrophic, hormonal (section 6.2), and nutritional factors (section 6.3).

5.2 Multiple Psychotropic Medications Inhibit Glycogen Synthase Kinase 3 (GSK3) and May Promote Myelination

The human species' exceptional myelination is supported by very recent evolutionary changes involving apolipoprotein E, lactate dehydrogenase, and peroxisome organelle function. These adaptations may have evolved in part to support the extremely metabolically "expensive" processes of creating and maintaining a highly myelinated CNS (Rinholm et al., 2011). Thus, metabolic derangements that would have relatively subtle sequelae peripherally, may produce significant dysfunction in brain. It is thus not surprising that metabolic abnormalities such as insulin resistance and brain lipidation seem to increase AD risk, predate the onset of psychiatric disease such as schizophrenia and bipolar disorder, and are associated with worse outcomes (reviewed in Bartzokis, 2011b). Given the very recent evolution of myelinating oligodendrocytes (in vertebrates), myelination's exceptional metabolic requirements had to be integrated with the many metabolic and developmental processes that predated its evolution.

Glycogen synthetase kinase 3 (GSK3) (and other kinases that have similar/overlapping functions (see section 6.1)) is highly conserved from sponges, through insects and vertebrates (Adamska et al., 2011). By the time myelin evolved, many processes were already modulated by GSK3 through its >40 substrates that include metabolic and signaling proteins, structural proteins, and transcription factors in different cellular compartments such as within cytoplasm, and also in nucleus and mitochondria where GSK3 is highly active. The integration of these other functions with GSK3 effects on myelination (see next section) may have further increased the complexity of GSK3 actions and contributed to the plethora of pharmacologic and non-pharmacologic interventions that may impact the myelination process (Figure 3) (Jope and Johnson, 2004; Sutherland, 2011). As will be reviewed below, neurotransmitter-based as well as non-neurotransmitter-based effects on myelination include many different classes of psychotropic treatments ranging from lithium and other mood stabilizers, to antipsychotics, acetylcholinesterase inhibitors, serotonin reuptake inhibitors (SSRIs), and electroconvulsive treatments (ECT). It is therefore proposed that the efficacy of much of the current clinical pharmacology and therapeutics may be due, at least in part, to treatment-induced changes in glia and in particular oligodendrocytes and their myelin (section 2 and 3). This concept gave rise to and is embodied in the term neuro*glial* pharmacology (reviewed in Bartzokis, 2011b). The remaining subsections (5.2.1 – 5.2.3) and section 7 will review some of the signaling mechanisms influencing myelination.

5.2.1 The Akt/GSK3 Myelination Signaling Pathway—Many important classes of psychotropic medications seem to share a mechanism involving Akt (also known as protein kinase B) and GSK3 that are at the core of a signaling cascade with multiple inputs as well as downstream effects (Figure 3). Akt is a serine/threonine kinase regulated through

phosphatidylinositol 3- kinase (PI3K)-mediated signaling that is conserved in vertebrates (Souza et al., 2011). Akt exists in three isoforms (Akt1 – ubiquitously expressed, Akt2 – predominantly expressed in insulin target tissues, and Akt3 – predominant isoform in brain) that show strong homology but are coded by different genes. Akt can phosphorylate GSK3β at the serine-9 position and GSK3α at the serine-21 position and thus inhibit their activity (reviewed in Sutherland, 2011). Historically, GSK3 was associated with glycogen synthesis in response to insulin. It also exists in two closely related isoforms (α and β) coded on different genes (Figure 3).

GSK3 is an unusual serine/threonine kinase that is *constitutively active* and is primarily *controlled by inhibition*. Furthermore, GSK3 preferentially (by 100–1000 fold) phosphorylates pre-primed (pre-phosphorylated) substrates (Thomas et al., 1999) and has over 40 substrates ranging from metabolic and signaling proteins to structural proteins and transcription factors. Other kinases can thus influence GSK3 signaling directly of indirectly, by pre-phosphorylating its substrates (see section 6.1). GSK3 is thus a point of convergence and acceleration (for pre-phosphorylated substrates) for multiple signaling pathways (reviewed in Beaulieu and Gainetdinov, 2011; Jope and Johnson, 2004; Sutherland, 2011; Wang et al., 2011b). The GSK3 isoforms (α and β) have overlapping but not identical substrates as illustrated by the apparent specificity of GSK3a activation in promoting amyloid beta (Aβ) protein production while GSK3β activation promotes tau protein phosphorylation (reviewed in Zhao and Townsend, 2009). For many substrates however, the amount of overlap in activity between GSK3α and β isoforms has not been fully elucidated (Polter et al., 2010).

In addition to its other functions in energy production, inflammation, and apoptosis (Sutherland, 2011), GSK3β has been shown to be a powerful *negative* regulator of oligodendrocyte differentiation and myelination (Figure 3) that can override the effects of other pathways such as Wnt signaling by controlling multiple regulators (Azim and Butt, 2011). Active GSK3β retards the repopulation of demyelinated axons while *its inhibition promotes myelination*. At doses achieved in vivo, lithium as well as several other endogenous and exogenous compounds inhibits GSK3β and enhances oligodendrocyte differentiation and myelination without apparent impact on neurons, axons, or astrocytes (Azim and Butt, 2011). Since Akt activation inhibits GSK3 (Figure 3), activators of Akt also have promyelinating effects (Flores et al., 2008; Narayanan et al., 2009) while Akt deficiency can impair prefrontal cortex function and expression of myelin genes (Lai et al., 2006).

The promyelinating effects of the Akt/GSK3 signaling pathway on brain can be substantial. When Akt is driven to be constitutively active, hypermyelination without increasing oligodendrocyte numbers is specifically observed in CNS but not in PNS (Flores et al., 2008; Yu et al., 2011). Conversely, over-expression of GSK3β reduces myelination (Azim and Butt, 2011), brain size, and cortical thickness without a decline in neuron number and thus results in *increased neuronal density* (Spittaels et al., 2002). This neuronal density increase is similar to increases observed in SZ (Selemon et al., 1995, 1998) that have been suggested to be due, at least in part, to deficient intracortical myelination (Bartzokis, 2002; Bartzokis and Altshuler, 2005). Additional supporting evidence for the role of GSK3 in myelination comes from up-regulating insulin growth factor-1 (IGF1), which also ultimately inhibits GSK3 (Frederick et al., 2007; Ye et al., 2010) (Figure 3) and promotes myelination (Carson et al., 1993; D'Ercole and Ye, 2008; Freude et al., 2008) (see sections 6.1 and 6.2). Conversely, IGF1 *deficiency* impedes myelination and produces a pattern similar to the ones seen in GSK3 over-expression and SZ consisting of brain atrophy, reduced myelination and cortical thickness, and increased neuronal density without a change in neuronal number (reviewed in Spittaels et al., 2002).

Reelin is another key signaling glycoprotein that is secreted into extracellular matrix, interacts with some of the same receptors as apolipoprotein E, and helps coordinate embryonic and adult brain development and repair (Barr et al., 2007). Reelin interacts with the same signaling pathways as dopamine-2 receptors (DR2 - see next section 5.2.2) and can indirectly inhibit GSK3 (Fatemi et al., 2009) and could thus promote myelination (Figure 3). Conversely, inhibition of reelin should reduce myelination and has been shown to impair cognitive functions (Beffert et al., 2005; Brosda et al., 2011; Stranahan et al., 2011; Wedenoja et al., 2010). Reelin *deficits* are consistently observed in developmental disorders such as SZ, BD, major depression, and autism (Fatemi et al., 2005a; Fatemi et al., 2005b; Impagnatiello et al., 1998; Torrey et al., 2005) and such deficits could contribute to the myelination deficits observed in these disorders (section 4). Conversely, reelin overexpression seems to prevent behavioral phenotypes related to SZ and BD in animal models (Teixeira et al., 2011). Reelin is secreted by oligodendrocytes and their precursors (Siebert and Osterhout, 2011) and after childhood, it is also secreted by GABAergic interneurons throughout cortical layers II-VI and hippocampus, and may help account for the co-occurrence of reelin and GABA deficits (as well as myelin – see section 4) in psychiatric diseases (Fatemi et al., 2005b; Guidotti et al., 2011; Shen et al., 2008; Torrey et al., 2005).

In striking contrast to *developmental* disorders associated with reelin deficits, *increased* reelin is observed in trisomy 21 (Downs) subjects (who all eventually develop degenerative AD pathology) as well as in cognitively normal individuals that nevertheless had AD pathology at post-mortem (Botella-Lopez et al., 2010; Kramer et al., 2011). Conversely, in transgenic mouse models of AD, reduced reelin levels result in accelerated AD pathology (Kocherhans et al., 2010). These observations suggest that in individuals *without* developmental psychiatric disorders such as SZ and BD, as myelin repair needs increase due to age-related and/or genetic degenerative processes, homeostatic up-regulation of reelin occurs that may inhibit GSK3 and thus promote compensatory remyelination/repair (Bartzokis, 2011a; Kramer et al., 2011). This compensatory up-regulation of reelin seems to be deficient/absent in developmental psychiatric disorders (Fatemi et al., 2005a; Fatemi et al., 2005b; Impagnatiello et al., 1998; Torrey et al., 2005) possibly through epigenetic mechanisms (Guidotti et al., 2011) (see section 6.1) and may help explain the need for *exogenous* GSK3 inhibition that seems to be provided by so many current therapeutic interventions (Figure 3) (see next section, 5.2.2).

5.2.2 Promyelinating Potential of Major Classes of Psychotropic Medications

—Lithium, an inorganic element administered as a salt for the treatment of BD, is a powerful inhibitor of GSK3β. Lithium can inhibit GSK3β directly via competition with magnesium and indirectly by increasing inhibitory serine-phosphorylation of GSK3 through Akt (Li et al., 2010b) (reviewed in Beaulieu and Gainetdinov, 2011; Polter et al., 2010) (Figure 3). Together, these GSK3 inhibitory mechanisms likely mediate the behavioral effects of lithium (Beaulieu et al., 2004) and it is thus possible that myelination is involved in its mechanism of action (Azim and Butt, 2011) (reviewed in Bartzokis, 2011b) (Figure 3). This proposition is indirectly supported by reports that that bipolar susceptibility genes are associated with white matter volume deficits that may be mitigated by treatment with lithium (van der Schot et al., 2009) as well as decreased Akt activity and increased GSK3β activity in the brain of depressed subjects at post-mortem (Karege et al., 2011; Karege et al., 2007) (reviewed in Pan et al., 2011; Polter et al., 2010). Furthermore, lithium treatment seems to up-regulate several myelin proteins including the long isoform of myelin basic protein (McQuillin et al., 2007), and lithium was useful in the treatment, prevention, and reduced recurrence of myelin damage in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS) (De Sarno et al., 2008). Notably however, even though continuous lithium treatment provided long-lasting (90 day) protection from EAE

symptoms, withdrawal of lithium resulted in a rapid recurrence of symptoms (De Sarno et al., 2008). This is consistent with the suggestion that *continuous inhibition of the constitutively active GSK3*β is important for optimal therapeutic effects. In addition, valproic acid, a medication developed for treating seizures that has proven effective in treating BD, also directly inhibits GSB3β (Kim et al., 2005; Miller et al., 2009) (Figure 3) and has promyelinating effects (Fei et al., 2011). The shared GSK3 inhibition of lithium and valproic acid may help explain their shared efficacy in treating BD despite strikingly different molecular structures. The efficacy of typical and atypical antipsychotics in the treatment of BD (reflected in recent FDA approvals of several antipsychotics for BD treatment) may also act through GSK3 inhibition (Figure 3).

As mentioned previously, GSK3β can be inactivated by phosphorylation of a single serine-9 residue by Akt (as well as other kinases – see section 6.1) or indirectly through many activators of Akt (Figure 3). Dopamine 2 receptor (D2R) signaling, is indirectly mediated through a β-arresting 2 (βArr2)/protein phosphatase 2A (PP2A) signaling complex resulting in *inactivation* of Akt and subsequent *activation* of GSK3 (Beaulieu et al., 2005). Dopaminergic transmission could thus ultimately inhibit myelination (Figure 3). The long-standing hypothesis that SZ is associated with a *hyper* dopaminergic state predating the onset of psychosis (Howes et al., 2011; Seeman, 2010) is thus consistent with a dopamine-driven GSK3 activation resulting in the myelination deficits observed in SZ (see section 4). Supporting this possibility are observations that several polymorphisms of enzymes involved in dopaminergic transmission including dopamine metabolism through catechol-Omethyltransferase (COMT), D2R, and Akt are associated with increased risk for psychiatric diseases and/or BD (Blasi et al., 2011) (reviewed in Beaulieu and Gainetdinov, 2011) (Figure 3). Dopamine-induced GSK activation can be overcome by D2R blockade, a property shared by all antipsychotics (Seeman, 2010). Early in treatment, antipsychotics have been shown to promote oligodendrocyte differentiation and myelin repair in rodent models (Wang et al., 2010; Xu et al., 2010), increase cortical glial numbers in primates (Selemon et al., 1999), and increase intracortical myelin in SZ (Bartzokis et al., 2009). These initial effects may contribute to the high levels of symptom remission that are especially striking within the first year of SZ treatment (ranging from 70 to 87%) (Emsley et al., 2007; Lieberman et al., 1993; Nuechterlein et al., 2006; Robinson et al., 2004; Saravanan et al., 2010).

Antipsychotic-induced GSK3 inhibition is short lived however (Li et al., 2007) and medication non-adherence is a well-known problem in psychiatric populations (Tiihonen et al., 2011). Long-acting intramuscular injection (depo) formulations for antipsychotics mitigate adherence problems (Keith, 2009) and have been associated with improved clinical outcomes (Subotnik et al., 2011; Tiihonen et al., 2011) (reviewed in Keith, 2009) possibly by providing continuous inhibition of the constitutively active GSK3. Furthermore, some animal studies suggest that lower doses of antipsychotics may inhibit GSK3 best (Li et al., 2007) and therefore, the troughs and peaks in antipsychotic blood levels associated with the kinetics of *oral* administration may not be optimal for achieving continuous GSK3 inhibition, as well as possibly increasing risks of untoward side effects. Long-term (> 1 year) treatment with *oral* antipsychotics has been shown to reduce cortical glial numbers in monkeys (Konopaske et al., 2008). In humans, loss of intracortical oligodendrocytes and myelin is clearly observed at post mortem in SZ subjects after many years of treatment with oral antipsychotics (see section 4) and imaging studies of SZ subjects confirm intracortical myelin deficits in patients chronically treated with oral antipsychotics (Bartzokis et al., 2011b). Whether the decline in intracortical myelin is due to poor adherence, pharmacokinetic factors, the disease process itself, or a combination of these factors remains unclear. Nevertheless, a recent randomized study suggests that, early in the disease course, the trajectory of decline in ICM may be modifiable by continuous treatment with injectable

long-acting antipsychotics (Bartzokis et al., 2011a) (Bartzokis et al, unpublished data). The above reports are thus consistent with a recent large study of first-break SZ subjects reporting gray as well as white matter volume losses that were attributed to chronic treatment with *oral* antipsychotics (Ho et al., 2011) and that white matter (but not gray matter) volume losses were associated with cognitive deterioration (Andreasen et al., 2011), one of the best correlates of clinical outcomes. Thus the poor adherence that often follows remission from the initial SZ episode, could result in dysinhibition of GSK3 and may help explain the decreased myelination and lower white matter volumes as well as the associated cognitive and clinical deterioration that occurs after the first year of treatment (Bartzokis et al., 2011a; Bartzokis et al., 2011b) (reviewed in Bartzokis, 2011b).

As is the case with D2R, activation of D1R and D3R seem to also activate GSK3 (Lebel et al., 2009; Miller et al., 2010; Niu et al., 2010) (reviewed in Beaulieu and Gainetdinov, 2011) and as such, could contribute to myelination deficits observed in SZ and BD (see section 4). This would suggest that blockade of multiple subtypes of dopamine receptors may have promyelinating effects (Figure 3). All antipsychotic medications (typical and atypical) share dopamine receptor blockade however, a*typical* antipsychotics can also inhibit GSK3 independently of Akt. Atypical antipsychotics differ from typical ones in part by their strong antagonism of serotonin (5HT2A) receptor (5HT2AR). Since 5HT2AR activates GSK3, blocking 5HT2AR would inhibit GSK3 and potentiate the promyelinating effect of D2R blockade (Xu et al., 2010) (reviewed in Li and Jope, 2010) (Figure 3). This additional potential promyelinating effect present only in atypical antipsychotics could help explain a recent observation on antipsychotic-related ICM increases in early stages of treatment. Although both typical and atypical antipsychotics seemed to increase ICM in SZ patients, the atypical one did so to a significantly greater extent (Bartzokis et al., 2009).

Unlike the apparent similar GSK3-activating effects of dopamine acting through several of its receptors, serotonin 5HT2AR and 5HT1AR have opposite effects on GSK3 activity. As reviewed in the prior paragraph, *antagonism* of 5HT2AR inhibits GSK3 (and thus would increase myelination) while 5HT1AR *agonism* does the same (Figure 3). Some atypical antipsychotics synergistically combine both these effects (not depicted in Figure 3) and have been reported to especially benefit cognitive function (Meltzer and Massey, 2011). Changes in overall level of brain serotonin can also have significant effects on GSK3 activity. Increased serotonin availability with selective serotonin uptake inhibitors (SSRIs), monoamine oxidase inhibitors, and tricyclic antidepressants have been shown to increase GSK3β inhibition in frontal cortex, hippocampus, and striatum of normal mice and may therefore have promyelinating effects in these brain regions. Conversely, *reduced* serotonin (in mutants that lack the ability to synthesize it) results in a two-fold *increase* in GSK3 activity (reviewed in Beaulieu and Gainetdinov, 2011) and would be expected to impair myelination (Azim and Butt, 2011). Interestingly, animal models have shown that *additive* effects on GSK3 inhibition can be achieved by combining D2R and 5HT2AR blockade (using the atypical antipsychotic risperidone) with monoamine reuptake inhibition (using the SSRI fluoxetine) (Li et al., 2007). This would inhibit GSK3 through D2R *plus* 5HT2A blockade by risperidone and combine it with additional GSK3 inhibition due to fluoxetine-induced 5HT2 increases that would provide 5HT21AR agonist activity (Figure 3).

The possibility that reduced intracortical myelin in SZ (see section 4) is due to impaired Akt/GSK3 signaling pathway is supported by post-mortem data on SZ frontal cortex showing reduced levels of Akt protein, Akt mRNA, and phosphorylated (inactive) GSK3β (Balu et al., 2010; Emamian et al., 2004; Thiselton et al., 2008; Zhao et al., 2006). Similar findings are reported for mood disorders (Karege et al., 2011; Karege et al., 2007) (reviewed in Polter et al., 2010) and genetic associations between Akt/GSK3 signaling pathway have been reported for both SZ and BD (Karege et al., 2010). Furthermore, cell models and brain

structural network function assessed with brain imaging in SZ as well as healthy control subjects demonstrated gene-gene interactions (epistasis) between Akt, PI3K, D2R, and COMT polymorphisms (Blasi et al., 2011; Jagannathan et al., 2010; Nicodemus et al., 2011; Sei et al., 2010) that would be expected from the mechanisms depicted in Figure 3.

In addition to the serotinergic and dopaminergic neurotransmitter effects summarized above, cholinergic stimulation could also influence myelination (Bartzokis, 2007). The mechanism may involve nicotinic α7 receptors that have been shown to inhibit GSK3 (Bitner et al., 2010; Rehani et al., 2008) (Figure 3) and/or muscarinic receptors that indirectly inhibit GSK3 by activating Pi3K/Akt and increase oligodendrocyte precursor survival (Cui et al., 2006) (not depicted in Figure 3). Acetylcholinesterase inhibitors, the current mainstay of AD treatment, reduce acetylcholine breakdown. The resulting increase in acetylcholine levels can stimulate both nicotinic and muscarinic receptors resulting in GSK3 inhibition (De Sarno et al., 2006). These treatments have also been shown to increase IGF-1 levels (Gomez, 2008; Narimatsu et al., 2009; Obermayr et al., 2005) that could indirectly inhibit GSK3 acting through Akt (Figure 3), and may increase white matter volume (Venneri and Lane, 2009). Nicotine and its metabolite cotinine can also stimulate nicotinic α7 receptors and, in addition to possible promyelinating effects, may have anti-inflammatory effects (reviewed in Wang et al., 2011b).

5.2.3 ECT and Adjunctive Treatments May Also Inhibit GSK3 and Promote Myelination—Thyrotropin-releasing hormone (TRH) is a small neuropeptide involved in the hypothalamic-pituitary control of thyroid and other hormones (Wallis, 2010). In addition to canonical effects on gene expression TRH can have more direct and immediate non-genomic effects (Pekary et al., 2006). TRH is widely distributed throughout the brain and has been shown to inhibit GSK3β gene expression (Luo and Stopa, 2004), while GSK3β inhibitors in turn can modulate TRH and TRH-like peptide release (Pekary et al., 2010). Although TRH levels decrease in the hypothalamus in aging rats (Pekary et al., 1984), the levels seem to be preserved in healthy aging humans (Mazzoccoli et al., 2010) however, reduced levels are reported in AD (Luo et al., 2002). TRH can alter cognitive and emotional function (Bennett et al., 1997) and is prominently increased after electroconvulsive treatment (ECT) a widely used clinical intervention that is especially efficacious for severe melancholic and/or psychotic depression (Pekary et al., 1999) (reviewed in Sattin, 1999). ECT may also acutely inhibit GSK3 through the canonical mechanism of Akt activation (Kang et al., 2004; Roh et al., 2003) (Figure 3). ECT has been reported to increase oligogenesis (Wennstrom et al., 2003; Wennstrom et al., 2004), an effect that has also been recently reported with antipsychotics (Niu et al., 2010; Xu et al., 2010) (see section 5.2.2).

Triiodothyronine (T3), the biologically active form of thyroid hormone commonly used as an adjunct in the treatment of depression (Bauer et al., 2005) (reviewed in Bauer et al., 2008), may also inactivate GSK3β by activating the PI3K/Akt cascade (Cao et al., 2009) (Figure 3) and has been shown to regulate oligodendrocyte accumulation in rat white matter tracks (Schoonover et al., 2004). Further support for the promyelinating effects of thyroid hormones comes from the prominent myelination deficits that occur when thyroid deficiency is experienced in development (resulting in cretinism) (Barradas et al., 2001; Pinazo-Duran et al., 2011) as well as deficits in myelin repair efficiency in adulthood (Harsan et al., 2008).

In light of the proposed role for myelin in the pathophysiology of multiple psychiatric disorders and common comorbid manifestations of these disorders (reviewed in Altamura et al., 2011; Bartzokis, 2004, 2005), it should not be surprising that treatment with T3, its pro-hormone T4, or TRH itself have been reported to have antidepressant properties (Bauer et al., 2008; Szuba et al., 2005). Furthermore, several reports suggest that heavily myelinated *subcortical* fibers are most clearly susceptible to thyroid deficiencies (Barradas et al., 2001;

Harsan et al., 2008; Pinazo-Duran et al., 2011). This distribution may help explain the relative specificity of these interventions to mood disorders since subcortical white matter abnormalities seem to be most clearly associated with mood disorders (see section 4) (reviewed in Bartzokis, 2011b).

5.2.4 Drugs of Abuse May Dysregulate Myelination and Result in Psychiatric Symptoms—The prior sections suggests that a major mechanism of action for multiple classes of psychiatric treatments may involve, at least in part, the release of oligodendrocytes and myelination from the negative control of GSK3 (Azim and Butt, 2011). Conversely, increased extracellular dopamine, whether produced by genetic variants that increase risk of psychiatric disease or drugs of abuse such as amphetamine and cocaine, results in GSK3 activation (reviewed in Beaulieu and Gainetdinov, 2011). Elevated extracellular dopamine (in dopamine transporter knock out animal models or administration of amphetamine, methamphetamine or the dopamine agonist apomorphine) has been reported to inhibit Akt and thus activate GSK3 (Bourque et al., 2011) (reviewed in Beaulieu and Gainetdinov, 2011). As expected by the signaling pathways depicted in Figure 3, psychostimulant use has been shown to reduce oligodendrocytes and myelination in susceptible late-myelinating regions such as frontal cortex (Bartzokis et al., 2002; Yang et al., 2011) (reviewed in Tobias et al., 2010). Thus *indiscriminate* increase of neurotransmitters (e.g., not directly associated with physiologic neurotransmission) caused by drugs of abuse could degrade homeostatic physiologic mechanisms through which neural networks adjust ICM and reestablish network synchrony (see section 5.1). This could undermine the compensatory ICM changes that restore precise timing of action potentials on which optimal function depends. The resulting degradation in network function could secondarily contribute to the cognitive deficits and thought and mood disturbance-inducing effects associated with these drugs of abuse (reviewed in Bartzokis, 2005, 2011b).

Another class of drugs of abuse, N-methyl-D-aspartic acid (NMDA) receptor antagonists such as phencyclidine (PCP) and dizocilpine (MK-801), are also well-known psychosis–inducing (psychotogenic) compounds. They also activate GSK3β by decreasing the phosphorylation/inhibition of Akt (Luo et al., 2003; Xi et al., 2011) (Figure 3). Anticholinergic drugs could have similar deleterious clinical effects (reviewed in Bartzokis, 2011b) by reducing cholinergic inhibition of GSK3 (Figure 3). Thus, different classes of drugs of abuse, acting through different mechanisms (Solowij et al., 2011) yet sharing deleterious effects on cognition and thought and mood control, may share indiscriminate activation of GSK3 as a possible mechanism of action. Conversely, medications that inhibit GSK3, such as D2R and 5HT2A receptor blockers, seem to have therapeutic effects in psychotic disorders whether secondary to drugs of abuse or due to psychiatric disorders.

6.0 Non-Akt/GSK3 Mechanisms Involved in Myelination

Given the complexity, metabolic cost, and functional importance of myelination (Sections 2 and 3), the existence of parallel/redundant mechanisms to control myelination should not be unexpected. Such redundant signaling pathways considerably increase the complexity of phenotypes, however, they also make it possible to integrate/coordinate myelination with the metabolic and hormonal environments as well as neuronal function. Thus, although focused on oligodendrocytes, this article is not meant to suggest that oligodendrocytes are the only target of successful treatments. It does however propose that the production and maintenance of myelin may be the “weakest link” of the human CNS and may represent a common pathophysiology shared amongst multiple neuropsychiatric disorders. The differential involvement of myelin subtypes with different vulnerabilities (e.g. subcortical versus intracortical – see Section 3) may result in different phenotypes despite sharing a common myelin substrate (see Section 4) (Bartzokis, 2011b). This possibility is indirectly

supported by the observation that many of the current treatment interventions (e.g., antipsychotics, SSRIs, etc.) have a wide spectrum of efficacy and encompass many disease categories as currently defined in the DSM. This wide spectrum of efficacy suggests that multiple pharmacologic as well as non-pharmacologic interventions may act on a shared myelin vulnerability that, given the exceptionally extensive myelination of the human brain, manifests most distinctly in our species (Bartzokis, 2011b). The existence of a common biological substrate could also explain the complexity of phenotypes and frequent co-existence (comorbidity) of more than one disorder within the same individual (Altamura et al., 2011; Bartzokis, 2004, 2005). The next section will briefly review three additional kinase-based signaling pathways that impact the myelination process and act through overlapping but not identical mechanisms.

6.1 Parallel and/or Redundant Signaling Pathways that Modulate Myelination

Another evolutionarily conserved serine/threonine protein kinase initially identified as a target of the immunosuppressant rapamycin thus named mammalian target of rapamycin (mTOR) can also inhibit GSK3. Mammals have two mTOR complexes, one sensing energy/nutrient status and cellular stress while the other senses primarily growth factors, hormones and cytokines (reviewed in Zoncu et al., 2011). This enzyme may have thus further helped integrate the considerable energy and nutritional needs of oligodendrocytes (see section 2) with the complex signaling (including growth factors) that controls the multiple myelination steps (not all interactions shown in Figure 3). Major roles of mTOR have been established for aging, autophagy (including debris clearance necessary for remyelination), degenerative brain diseases (Garelick and Kennedy, 2011; Spilman et al., 2010) (reviewed in Zoncu et al., 2011), inflammation (Wang et al., 2011a), and myelination (Goebbels et al., 2010; Tyler et al., 2009). It also has complex interactions (crosstalk) with Akt/GSK3 (Garelick and Kennedy, 2011; Wang et al., 2011a; Zoncu et al., 2011) and other signaling pathways (see below). Inhibiting mTOR has been shown to extend lifespan in middle age as well as old rodents (Harrison et al., 2009) and, in transgenic models of AD (a strikingly age-related disease), it seems to decrease cognitive deficits as well as its Aβ and tau pathology (Caccamo et al., 2010). Given some of the multiple interactions between signaling pathways (Figure 3) specific effects are difficult to disentangle (Ma et al., 2010; Spilman et al., 2010) however, increased oligodendrocyte differentiation has been reported with mTOR inhibition (Tyler et al., 2009). In addition to integrating myelination with nutrient and energy status described above, some neurotransmitter signaling mechanisms with antidepressant effects may act through mTOR-dependent mechanisms to integrate myelination with synaptogenesis (Duman et al., 2012; Li et al., 2010a).

Inhibition of GSK3β can also be achieved through two mitogen-activated protein kinase (MAPK) signaling pathways: p38 MAPK and the extracellular signal-regulated kinases 1 and 2 (ERK1/2) (Figure 3). P38 MAPK is activated primarily through cellular stress and cytokines and, unlike Akt, inactivates GSK3β by phosphorylating its C terminus. This parallel pathway is relatively specific to brain, may be specific for activating a cell survival pathway, which is not targeted by the Akt/GSK3 pathway (Fragoso et al., 2007; Thornton et al., 2008), and may be involved in epigenetic modifications of DNA (Day and Sweatt, 2011). The ERK1/2 and p38 pathways have been implicated in peripheral myelination (Fei et al., 2011; Newbern et al., 2011) and CNS oligodendrocyte survival (Althaus and Kloppner, 2006; Du et al., 2006; Kumar et al., 1998), myelination (Haines et al., 2010), and timing of myelination especially in late-myelinating regions (Fyffe-Maricich et al., 2011; Haines et al., 2010; Raff et al., 1988). The MAPK pathways can be triggered by multiple growth factors such as platelet–derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), nerve growth factor (NGF) (Du et al., 2006), and IGF1 (Bibollet-Bahena and Almazan, 2009) as well as neurotrophins such as brain derived neurotrophic factor (BDNF)

and neurotropin-3 (Du et al., 2006; Van't Veer et al., 2009) (reviewed in Althaus et al., 2008; Fyffe-Maricich et al., 2011). These same triggers can *also* activate the PI3K/Akt pathway (Bibollet-Bahena and Almazan, 2009; Coelho et al., 2009) (Figure 3) and some triggers, such as IGF1, may impact multiple control points in oligodendrocyte survival, proliferation, and differentiation (Bibollet-Bahena and Almazan, 2009) and is thus depicted in Figure 3 by itself as well as subsumed under “growth factors”.

In addition to GSK3, MAPK, and mTOR, a fourth family of protein kinases, cyclin-dependant kinase (Cdk), can impact myelination. Endogenous CNS-specific modifiers of Cdk5 function are altered in SZ brain (Engmann et al., 2011) and can influence myelination (Miyamoto et al., 2007; Tamura et al., 2005). Cdk5 can have dynamic (age-dependent) crosstalk with kinases such as GSK3 (Engmann and Giese, 2009) mediated in part by neuregulin (Wen et al., 2008) and could thus contribute to the age-related decline in myelin repair/remyelination efficiency (Shen et al., 2008) (reviewed in Bartzokis, 2011a). Due to the complexity of Cdk influences (see below) only this aging-dependent influence depicted in Figure 3. The Cdk family is evolutionarily conserved (Hsu et al., 2011) and with the exception of Cdk5 (that in addition to other functions primes GSK3 substrates (Medina and Wandosell, 2011) – see section 5.2.1), several members such as Cdk1, Cdk2, and Cdk4 are involved cell cycle progression. Given that NG2 cells differentiate into oligodendrocytes throughout the lifespan (section 2), it is not surprising that the Cdk family is also directly involved in regulating several aspects of myelination with each member being influenced by different sets of endogenous modifiers (Atanasoski et al., 2008; Caillava et al., 2011; Hsu et al., 2011; Miyamoto et al., 2007). Cdk2 in particular has 45% homology with GSK3 (Lesuisse et al., 2010) and, as is the case with GSK3, *inhibition* of Cdk2 has recently been shown to accelerate oligodendrocyte precursor differentiation and remyelination in the adult CNS (Caillava et al., 2011). Furthermore, up-regulation of an endogenous Cdk2 inhibitor promotes oligodendrocyte differentiation (Larocque et al., 2005), a process that can be promoted by antidepressants through activation of glucocorticoid receptors (Anacker et al., 2011). Psychotropic medications may thus impact myelination through multiple parallel mechanisms as well as crosstalk between the multiple protein kinases involved in metabolic pathways (Figure 3) that underlie cell cycle progression and differentiation (Frederick and Wood, 2004; Kerns et al., 2010).

6.2 Hormones and Neurotrophins

Akt can inhibit both GSK3α and β in response to multiple hormones and growth factors including BDNF, leptin, IGF1, and insulin itself (Greco et al., 2009, Marwarha et al., 2010) (reviewed in Beaulieu and Gainetdinov, 2011; Polter et al., 2010). The same growth factors can act through parallel pathways involving MAPK and mTOR (see section 6.1) (Figure 3). Thus, at least part of the mechanism of action of these hormones on myelin could be based on reducing the activity of GSK3.

Interactions between the pharmacologic mechanisms reviewed above (section 5.2.2) and the individual’s hormonal state (section 6.1) are also important to consider. Such interactions are suggested by reports that response to acetylcholinesterase inhibitors used in the treatment of AD may be more robust in individuals with higher peripheral levels of IGF1 (Tei et al., 2008), which is normally taken up by the brain from the periphery at rates that surpass those of insulin (Bondy and Cheng, 2004). In addition, treatment interventions themselves may act in part through peripheral mechanisms. For example, antipsychotics have been shown to increase peripheral IGF1 when given to drug-naïve SZ subjects (Venkatasubramanian et al., 2010). Similarly, by increasing peripheral IGF-1 that is taken up by the brain, physical exercise may help improve cognition and mood (Llorens-Martin et al., 2010; Simon et al., 2011; Trivedi et al., 2011) (reviewed in Bartzokis, 2011a). Some oral GSK3 inhibitors have been shown to increase IGF1 transport into brain by interacting with

megalin, a major multicargo transport protein that ferries proteins across the blood brain barrier and choroid plexus (Bolos et al., 2011) (Figure 3). The above reports are consistent with studies showing that peripherally infused IGF-1 (and insulin) enter the brain (Aberg et al., 2007; Anderson et al., 2002) through active transport (Yu et al., 2006) and increase cortical oligodendrocytes (Aberg et al., 2007).

6.3 Nutritional Modifiers

Certain nutrients, such as vitamins B12 and folate, seem to have GSK3 inhibitory effects. Conversely, vitamin B12 deficits or resulting hyperhomocysteinemia have also been shown to *decrease* GSK3 phosphorylation/inhibition (Nicolia et al., 2011; Zhuo et al., 2011) (Figure 3) and could thus impair myelination (Azim and Butt, 2011). This may help explain the epidemiologic (Clarke et al., 1998; Kim et al., 2008) and animal model (Chan and Shea, 2007; Zhuo et al., 2011) studies that report associations between these nutritional deficiencies and increased AD risk as well as white matter deficits (de Lau et al., 2009; Graber et al., 2011) (reviewed in Bartzokis, 2011a).

Omega-3 fatty acids (especially DHA) and iron are also essential nutrients for myelination. Nutritional interventions with these myelin building blocks on oligodendrocytes were reviewed in a prior publication (Bartzokis, 2011b). A subsequent report suggests that a genetic defect in the peroxisome-dependent enzyme that catalyzes the last step of DHA synthesis may put affected individuals at risk for DHA deficiency (Astarita et al., 2010). Individuals with such mutations should be especially helped by DHA supplementation to prevent and possibly treat diseases such as schizophrenia, MDD, autism, and AD where DHA deficits have been reported (reviewed in Bartzokis, 2011b). The contribution of such genetic variants of metabolism to the pathophysiology of these disorders remains to be fully elucidated however (Amminger et al., 2010).

7. Conclusions and Future Directions in Neuroglialpharmacology

For optimal brain function, no class of cells is dispensable. Despite the focus on oligodendrocytes, the goal of this report was to provide a “scaffold” for integrating the largely neuron-centric research efforts with the key roles of glia and especially to the complexity of neuroglial interactions (summarized in section 5 and 6 and Figure 3). In order to help dissipate the historic artificial divide between neurons and glia and encourage an integrated perspective of brain therapeutics, a more inclusive nomenclature (e.g., neuroglialpharmacology) may better serve both clinical and research enterprises. This nomenclature not only enlarges the focus of inquiry to include glia, it also suggests that direct and indirect effects on glia may represent a substantial portion of the efficacy provided by pharmaco- and other therapies (Figure 3).

The hypotheses delineated above are testable through in vivo imaging technologies that provide biomarkers for assessing the trajectory of human myelin development and its subsequent breakdown (Bartzokis et al., 2003; Bartzokis et al., 2004; Hendry et al., 2006; Salat et al., 2005), as well as receptor changes in both gray and white matter (Ding et al., 2004; Pimlott et al., 2004; Vaupel et al., 2005). These technologies, together with genetic as well as clinical and cognitive measures makes it possible to directly test in humans the practical utility of a myelin-focused model of the brain to accelerate medication development. Imaging evidence of promyelination effects of diverse therapeutic interventions in several human psychiatric disorders has recently begun to be measured (Bartzokis et al., 2011a; Bartzokis et al., 2011c; Bartzokis et al., 2009; van der Schot et al., 2009; Venneri and Lane, 2009). Quantifying pharmacologic effects on the brain’s vulnerable oligodendrocyte populations have the potential to elucidate underlying disease processes,

mechanisms of action of treatments, and help uncover opportunities for treatment and prevention of both developmental and degenerative brain disorders.

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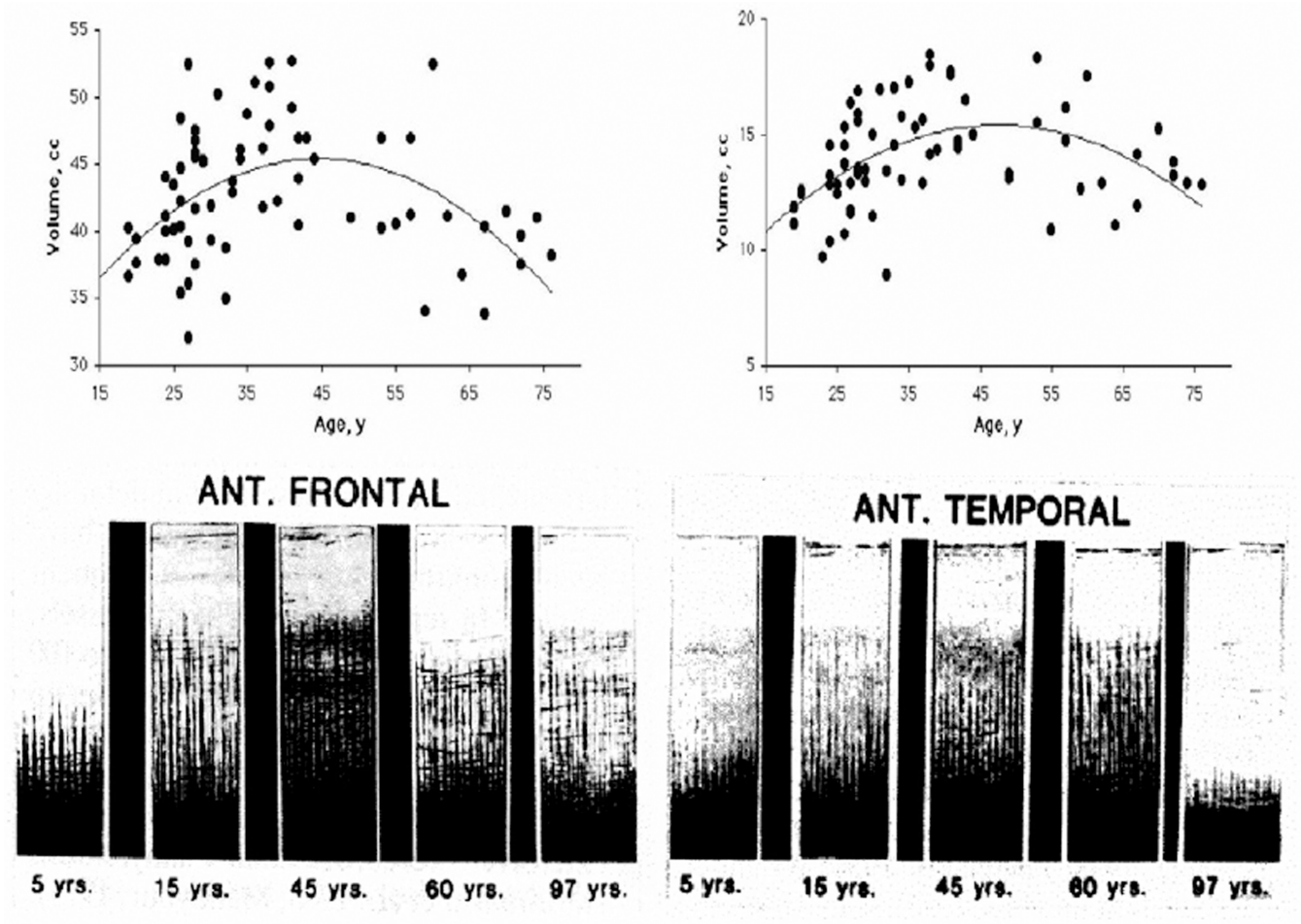

Figure 1. Quadratic (inverted "U") Myelination Trajectories of Human Brain Over the Lifespan

Human brain myelination (Y axis) across the age span (X axis). Frontal and temporal lobes (depicted on left and right figures respectively). Top figures are in vivo MRI data (from Bartzokis et al., 2001) showing significant quadratic relationships ($p<.001$) of myelinated white matter volumes (a measure that includes highly myelinated lower cortical layers). Intracortical myelin stain data are depicted in the lower figures (from Kaes, 1907) (adapted and reproduced in Kemper, 1994). Used with permission. The in vivo (top panels) and post-mortem (lower panels) samples of normal individuals show remarkably similar myelination trajectories demonstrating a dynamic myelin "plasticity" that does not peak until middle age. Note: even though the regions are similar, as is the case with these two late-myelinating association regions, myelination trajectories differ and peak at significantly different ages ($p<.01$) (Bartzokis et al., 2001).

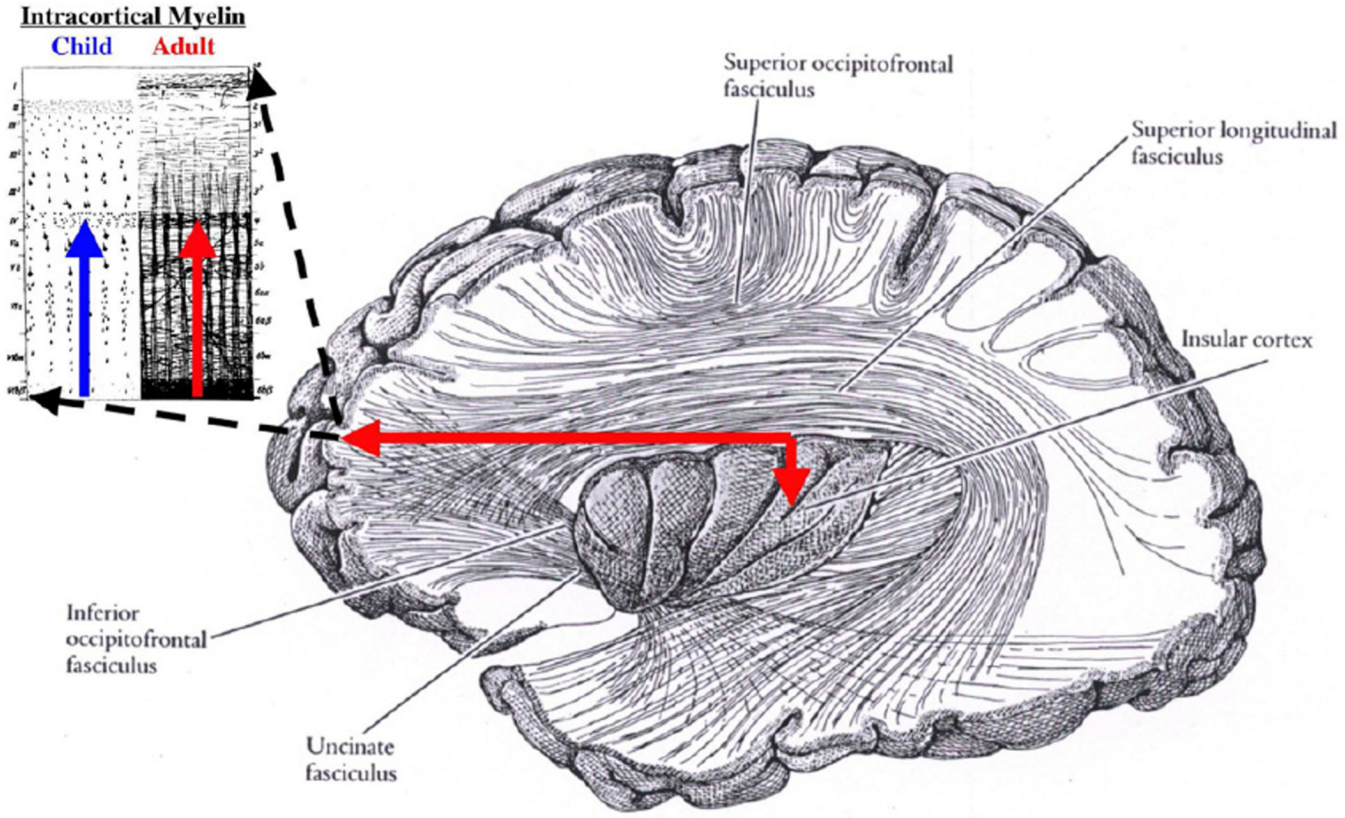

Figure 2. The Human Brain "Internet" Establishes Synchronous Activity in Childhood Through Subcortical Myelination and Perfects it in Adulthood Through Intracortical Myelin (ICM)

Red arrows stand in for myelinated axons with fast transmission (more than 100 fold faster than unmyelinated axons). Insert depicts cortex of child (on left, unmyelinated) and adult (on right, myelinated). Subcortical myelination (accomplished in childhood) makes action potential transmission in circuits of markedly different lengths such as thalamo-frontal (long horizontal red arrow) and thalamoinsular (short down-pointing red arrow) very fast. Once the fast subcortical portion of a circuit is myelinated, the intracortical transmission of the action potential through unmyelinated axons (insert: blue arrow on left panel) takes much longer (10 fold longer than subcortical transmission). Thus, once subcortical myelination is established in childhood, the constant intracortical distance to layer III establishes a roughly synchronous arrival of action potentials to all layer III pyramidal neurons. Later in development and throughout adulthood, appropriate and region-specific myelination of the cortical portion of the axons (insert: red arrow on right panel) continually optimizes the synchrony of action potential arrival and thus optimizes cognitive and behavioral functions (see text for further details).

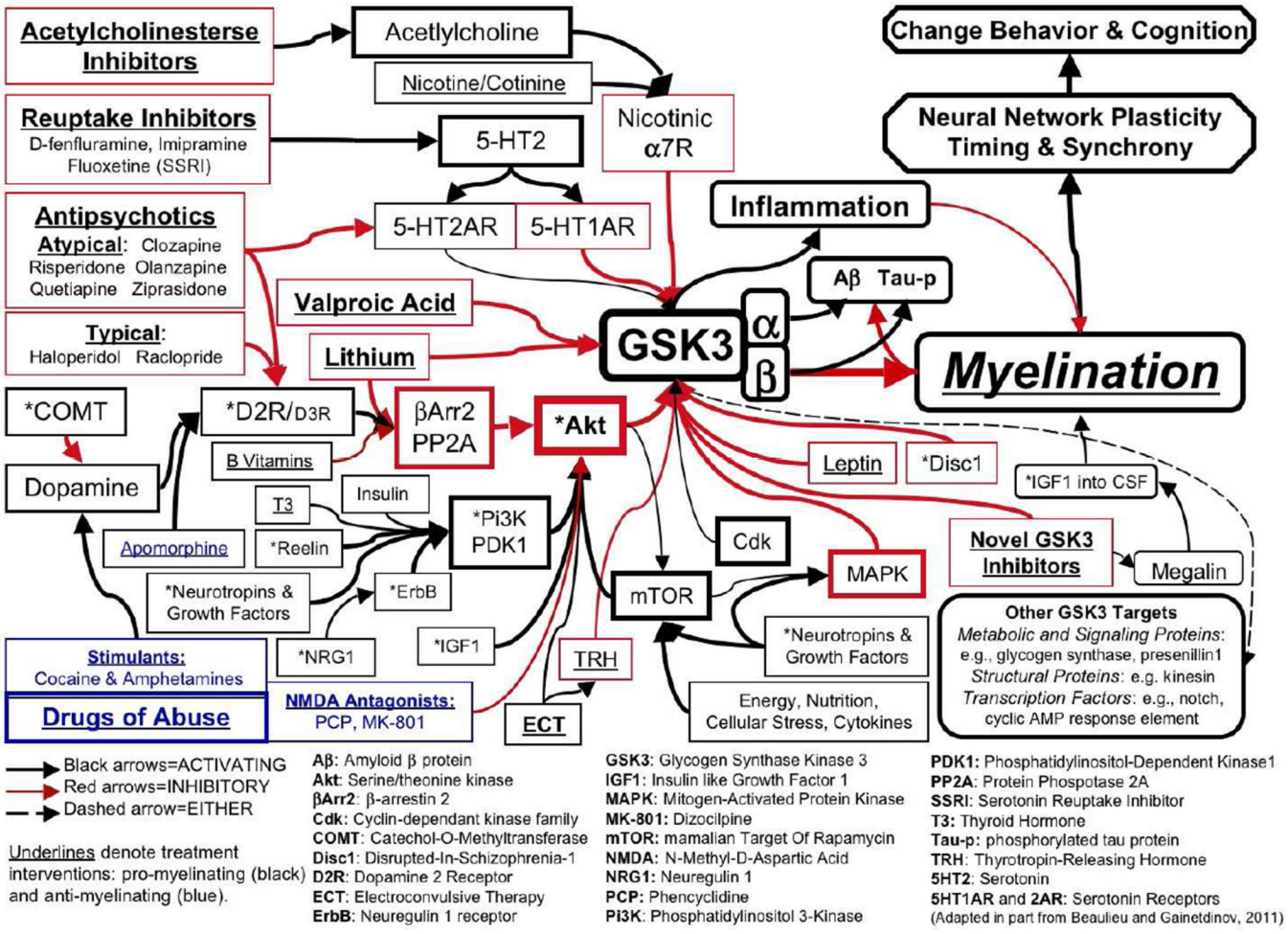

Figure 3. Neuroglialpharmacology of Psychiatric Treatments, Hormones, and Neurotrophins

Major classes of currently available psychotropic medications, other pharmacologic agents, and ECT (underlined) seem to share direct or indirect inhibition of GSK3 as a common mechanism of action. Many but not all GSK3 effects are shared by its α and β isoforms, however in many instances, specific isoform effects remain to be clarified. Indirect (through Akt activation) and direct GSK3β inhibition promotes myelination by releasing the negative control GSK3β has on myelination. Some neurotrophins (NRG & BDNF), hormones (IGF1, T3, TRH), and cytokines (leptin) also seem to inhibit GSK3. Conversely, some drugs of abuse with known cognitive and behavioral toxicities (cocaine, methamphetamine, PCP) seem to have the opposite (GSK3 activation) effect and would be expected to share *inhibition* of myelination as a potential detrimental effect on brain function. Some GSK3-dependent myelin interactions of the dopaminergic, serotinergic, glutaminergic, and cholinergic system are depicted in this figure, however the GABAergic ones are not (see text for details). An asterisk denotes genes known to be associated with increased risk for schizophrenia (SZ) and/or bipolar disorder (BD).

Note: as a schematic focused on the key role of GSK3 on myelination, this figure does not depict many additional relationships such as the ones between GSK3 and other kinases (mTOR, MAPK, Cdk), genes, nutrition, metabolism, environment, and epigenetic changes and the interdependence of all CNS cell types and their specialized structures such as synapses. For further details on these topics please refer to the text and reference list.