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Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments

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1. ABSTRACT

Psychotropic treatments such as second generation or "atypical" antipsychotics are efficacious in a wide spectrum of psychiatric disorders ranging from schizophrenia to depression, bipolar disorder, and autism. These treatments are associated with peripheral metabolic derangements that are often also present in drug-naïve patients. Furthermore, altering lipid composition/levels (with omega 3 fatty acids) and ameliorating oxidative toxicities may treat/prevent disease. The above observations are reexamined from the perspective of a myelin-centered model of the human brain. The model proposes that the human brain's extensive myelination required higher metabolic resources that caused evolutionary adaptations resulting in our quadratic (inverted U) myelination trajectory that peaks in the sixth decade of life. It further proposes that optimal brain function depends on exquisite action potential synchronization that myelin makes possible and that myelin's exceptional vulnerability to subtle metabolic/oxidative abnormalities may promote both developmental and degenerative diseases. Available data are integrated herein to suggest that widely used psychotropic treatments have under-appreciated CNS metabolic and neurotransmitter effects on myelination, its plasticity, and repair that may substantially contribute to their mechanisms of action.

2. INTRODUCTION TO NEUROGLIALPHARMACOLOGY

The scientific and clinical emphasis on "neurons" reflected in our very nomenclature of "neuroscience" and "neuropharmacology" reinforces the widely held belief that the efficacy of pharmacologic treatment of psychiatric disorders is due exclusively or in large part to neuronal synaptic effects. The field has been focused on effects of medications on neurotransmitters (especially dopamine, norepinephrine, serotonin, acetylcholine, glutamate) as the principal way to develop treatments as well as conceptualize their mechanisms of action. This approach has nearly completely overshadowed

alternative explanations for mechanisms of action such as *non*-neuronal effects of neurotransmitters on the brain's glial cells that, by and large, are the cells most prominently involved in brain metabolism and especially lipid metabolism (see section 4). The absence of this metabolic/glial perspective has also helped overshadow alternative ways to conceptualize the peripheral metabolic effects of psychotropics, which are currently almost entirely thought of as detrimental side effects. This narrow interpretation largely overlooks higher than normal rates of such metabolic abnormalities in first break patients that have yet to receive medications (1-4) (reviewed in 5) and the possibility that in the high-metabolism lipid-rich *brain*, these "side effects" may be beneficial and represent an under-appreciated aspect of their mechanism of action (6-8).

This report is not intended to refute the evidence that the vast majority of psychotropic medications affect synaptic neurotransmission nor their detrimental peripheral metabolic effects. Rather, its purpose is to promote scientific inquiry by encompassing a broader perspective on the mechanisms of the action of major classes of existing psychotropic medications that include metabolism and glial effects of neurotransmitters (reviewed in sections 5-7 and 9). It suggests that targeting metabolism, lipids, and neurotransmitter effects on myelination may provide novel and largely unexplored opportunities for treatment and prevention of neuropsychiatric disease across all life stages (6, 7, 9). Ultimately, the report will attempt to rebalance the overwhelming focus on neurons by fostering a greater appreciation for neuron-glial interactions and hopefully help usher in a wider conceptual framework embodied in the term "neuro*glial*pharmacology".

By necessity this report will also examine the often ignored, but ultimately inescapable, role of evolution. Evolution has shaped the human brain through the use of pre-existing genes and their protein products for multiple roles and functions (10). This multiplicity of roles results in the dazzling complexity and redundancy on which normal brain function is based. Evolution has disproportionately increased glial numbers 50-fold more than neuronal numbers that in humans make up only 10% of brain cells (reviewed in 9). All glial cells serve indispensable and interrelated functions that to a very rough approximation can be broken down into energy and lipid production (astrocytes and oligodendrocytes), debris removal and substrate recycling (e.g., lipids, iron, etc) functions (microglia and astrocytes), and maximizing efficiency of our brain "Internet" information transmission (see section 3.1.) and its use of energy and space (the myelin produced by oligodendrocytes) (reviewed in 9, 11). Myelin, a relatively recent evolutionary development of the first vertebrates (fish) (12), made the complex connectivity of the human brain possible. The vast metabolic requirements of myelin may have also helped alter our central and peripheral physiology (see section 4.1.). This wider evolutionary prospective serves to counterbalance the prevailing focus on neurons and their neurotransmitters, that are largely identical in all mammals, as the core pathology of the major neuropsychiatric diseases. After all, many neuropsychiatric diseases ranging from schizophrenia (SZ), bipolar disorder (BD), and Alzheimer's disease (AD) are basically distinctively human disorders (reviewed in 9, 13).

This report will attempt to created a "scaffold" that binds the various levels of research endeavors from molecular genetics through mechanism, cells, circuits, networks, clinical symptoms, and epidemiology in the context of their largely hidden evolutionary connections. It will focus on oligodendrocytes and the myelin they produce not because these structures are the basic unit of our CNS, the neurons, despite their meager proportions, form our brain circuits and are this basic unit. Rather, the case will be made herein that myelin is an indispensable component of brain neuronal circuitry and the exquisite timing of its action potentials on which *optimal function* depends (reviewed in sections 3.2-3.4 and 9). In short, in the cognitive and behavioral spheres, our extensive myelination may arguably be "what makes us human". Equally important however, myelin is the most difficult to produce, protect, and maintain component of brain circuitry. As the last evolved component of the CNS and our species' exceptional dependence on it, myelin may also represent our "weakest link" in the chain of interdependent cells and processes that blossom over many decades into our complex cognition and behavior (9).

2.1. Genetics of myelination

The genes involved in controlling brain myelination have only recently begun to be identified. The regulation of myelin thickness through neuregulin 1 (neuregulin) signaling to the ErbB receptor family (14, 15) (reviewed in 16) influences transmission speed and refractory time (reviewed in 17) and is therefore of specific interest to the synchrony neuronal network function depends on (see section 3). Myelination involves cleavage of neuregulin and its ErbB receptors by the alpha-, beta-, and gamma-secretase complexes (15, 18) (reviewed in 16, 19), the same enzymes involved in the production of beta amyloid, the hallmark of AD (9). The principal gene associated with late onset AD (apolipoprotein E4) as well as the genes associated with early onset or familial forms of this disease (such as gamma-secretase mutations), are significantly associated with myelin repair efficiency, age-related cognitive decline, and several degenerative disorders of old age (20-22) (reviewed in 9).

Several *substrates* of alpha-, beta-, and gamma-secretases are also directly involved in myelination, could contribute to the myelination deficits observed in SZ and BD (see section 8), and have been identified as possible susceptibility genes for these disorders (23, 24) (reviewed in 25, 26). These substrates include neuregulin (27, 28) and its ErbB family of receptors (29, 30) as well as nardilysin (a modulator of neuregulin cleavage (31, 32)) and disrupted in schizophrenia 1 (DISC1) (33, 34). Furthermore, myelin gene variants have also been associated with risk of developing psychotic symptoms in individuals with AD (35, 36).

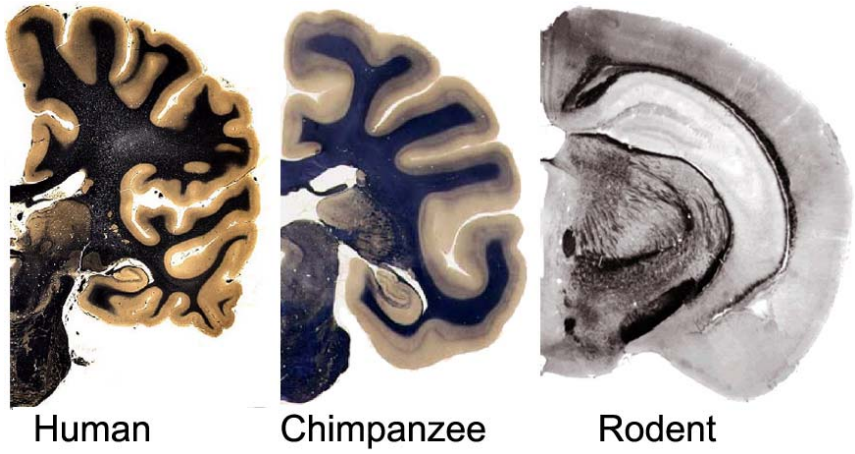

Figure 1. Myelin Stains of Human, Chimpanzee, and Rodent Brains. Brains are not to scale: rodent and chimpanzee brains are enlarged to approximate human brain size in order to more easily demonstrate the striking differences in the *proportion* of myelin (stained black) in each brain. Human brain has approximately 20% more white matter than the chimpanzee (37, 38).

In the case of AD, these genetic defects as well as the epidemiologic, clinical, and treatment data have been considered from the perspective of influencing the myelination and/or myelin repair process in a prior report (9). Herein we will primarily consider the best-studied major psychiatric diseases (SZ and BD) from the same perspective (7, 13). As a prelude to examining these complex relationships a review of the distinctive *functions* oligodendrocytes and their myelin fulfill will follow next.

3. THE BRAIN "INTERNET" DEPENDS ON THE SPEED AND SYNCHRONY PROVIDED BY MYELIN

3.1. The myelin model of the human brain

The human brain is distinguished, even among primates (38), in its extensive and pervasive myelination process that supports its high-capacity information processing (11) (Figure 1). The lifelong trajectory of brain myelination has a quadratic-like (inverted "U") shape with increasing myelin content that peaks in middle–age and subsequently breaks down and declines in older age (39) (Figure 2). The "connectivity" provided by myelination increases speed over 100-fold and, by also decreasing refractory time 34-fold, myelination increases the number of action potentials that can be transmitted per unit time (in Internet terminology this would represent expanded "bandwidth") (7, 13). Myelination thus increases the processing capacity of our brain's "Internet" approximately 3,000 fold and is indispensable for developing our exceptionally elaborate higher cognitive functions. These cognitive functions are especially dependent on later-myelinating oligodendrocytes. These cells myelinate axons all the way to their neuron bodies located in gray matter structures such as the cortex (Figure 2). This extensive myelination process can thus "upgrade" networks of neuronal circuits with immediate response capacity that are essentially "on line" to process information quickly, precisely, and continually (7). Finally, continued myelination allows networks to remain "plastic" (e.g., adapt) (40, 41) in order to optimally synchronize action potentials across the many neuronal networks connecting disparate brain regions and thus optimize function during learning (42, 43) (next two sections).

The model reframes the human lifespan in terms of seamless quadratic-like (inverted U) myelination trajectories of the many spatially distributed neural networks that underlie cognition and behavior (Figure 2). This perspective redefines human brain "development" as roughly the first *six decades* of life (Figure 2). It proposes that dysregulations occurring during the increasingly complex stages of the myelination process contribute to several early-life neuropsychiatric disorders defined by overlapping (comorbid) cognitive and behavioral symptom clusters (reviewed in 6, 7). The model helps to "cut" across current symptom-based classifications of neuropsychiatric diseases and helps explain why the entire cadre of symptoms that define the classic psychiatric disorders embodied in the DSM (psychosis, depression, obsessions, compulsions, poor impulse control, etc.) can reappear in the dementias of old age (9). This perspective suggests that both developmental deficits in myelination of neural networks (contributing to early-life psychiatric disorders), as well as degenerative breakdown and loss of myelin of the *same* networks occurring in the dementias of old age, can result in similar behavioral and cognitive symptoms despite entirely different etiologies (9, 11, 13).

As Figure 2 demonstrates, different cortical regions myelinate at different rates and ages. Oligodendrocytes are increasingly more complex the later in life they differentiate (see section 4.6). The structurally more complex later-myelinating oligodendrocytes and their myelin are especially vulnerable during both developmental (44) as well as degenerative phases (39, 45) of the lifelong myelination trajectory. From the prospective of the model, the development and maintenance/repair of myelin's functional integrity over our lifespan is the single most important element for acquiring and maintaining normal human cognition and behavior. In short, myelin may also

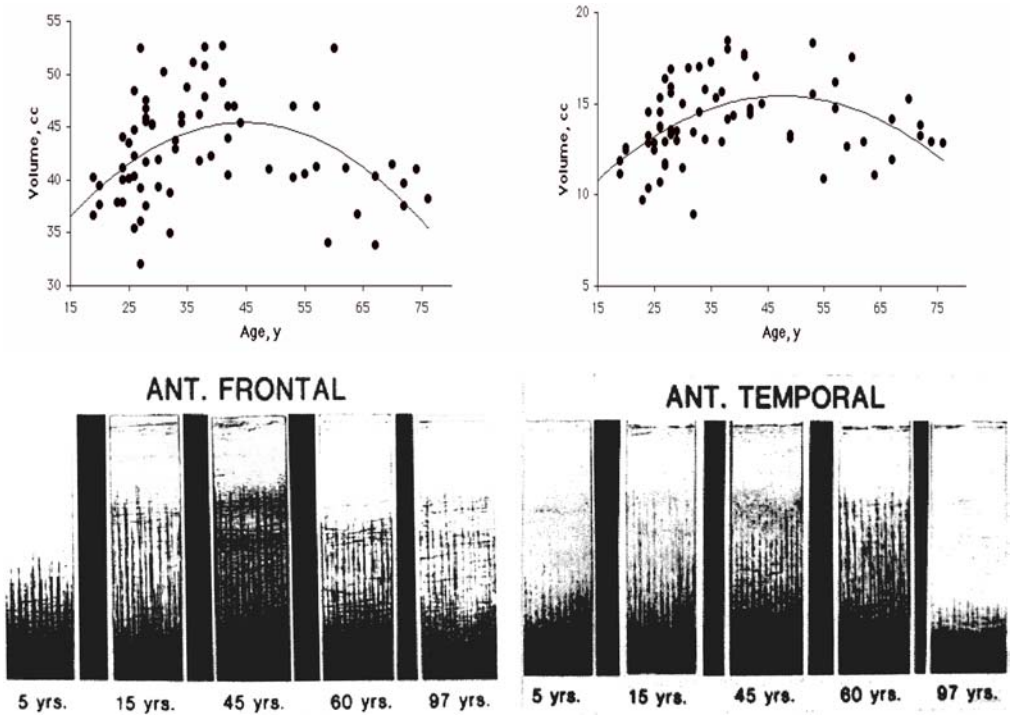

Figure 2. Quadratic (inverted "U") Myelination Trajectories of Human Brain Over the Lifespan. Myelination (Y axis) versus age (X axis) in frontal and temporal lobes (figures on left and right respectively) of normal individuals. Top figures are *in vivo* MRI data (from 63) showing significant quadratic relationships ($p<.001$) of myelinated white matter volumes (a measure that includes highly myelinated lower cortical layers – also see Figure 3) for frontal and temporal lobes which peak at significantly different ages ($p<.01$). Lower figures are post-mortem intracortical myelin stain data (from 64) (adapted and reproduced in 65). Used with permission. The data depicted were acquired 100 years apart yet the two samples of normal individuals show remarkably similar myelination trajectories in the two regions. Note that different brain regions have significantly different myelination trajectories even when the regions are similar as is the case with these two late-myelinating association regions (63). Frontal lobe peak myelination is reached at age 45 but is reached even later in the temporal lobe.

arguably represent the "weakest link" of both brain development as well as age-related degeneration and underlies many of the normal changes as well disease-causing pathophysiologies over the entire human lifespan. By including glia and myelin, this perspective can help explain normal brain function, phenomenology of multiple diseases, as well as their shared responsiveness to pharmaceutical and nutritional interventions (reviewed in sections 4,8, and 9).

3.2. Functional networks depend on synchrony and timing 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 measured through techniques such as electroencephalography (46). 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 0.0.5 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 (47, 48) (reviewed in 49). Synchronized oscillations may also establish the precise action potential timing needed for use-dependent synaptic plasticity (long term potentiation) to occur (reviewed in 50).

Higher-frequency (30-100Hz) Gamma oscillations have been especially studied, as they seem to underlie higher cognitive functions (51). Gamma is an important oscillations frequency between different cortical regions (52) and may define thalamus-frontal lobe oscillations, while different frequencies may predominate in thalamus connections to other cortical regions (53). Abnormal oscillations have been clearly demonstrated in SZ (reviewed in 46, 50) as well as BD and depression (54), autism (55, 56) and the earliest stages of cognitive decline into AD (57, 58).

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. This initial subcortical myelination can be initiated/directed by neuronal signals themselves (59, 60) and results in the very fast (>100 times faster than unmyelinated axon) conduction between widely separated gray matter regions such as thalamus and various

cortical regions it interacts with. Once subcortical myelination is achieved, the total conduction time between these 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, together with the slow signal propagation, establishes the initial roughly synchronous arrival of action potentials to all cortical regions that are at different distances from thalamus (61, 62). Thus, the short intracortical portion of axonal propagation exerts a markedly disproportionate influence on synchronicity of action potential arrival across functional networks and their vast numbers of neurons and synapses.

3.3. Intracortical myelin optimizes network oscillations and brain function

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 2 suggests, this *later-developed* acceleration and "fine grain" synchronization of cognitive and behavioral networks may continue to be refined over the entire first six decades of life. This later-myelination may serve as a powerful mechanism of brain plasticity and its disturbance could have important consequences for disease pathophysiology as well as efficacy of antipsychotic treatment (66).

Primate data suggests that during adult aging, repair and plasticity processes result in oligodendrocyte numbers increasing substantially more in the cortex (50%) than in white matter tracks (<25%) and in addition, the strongest associations between myelin damage and cognitive function is also strongest in cortex (67). These results support the suggestion that *intracortical* myelin plasticity 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 reduce transmission speed. This possibility is consistent with recent human data suggesting that early in the disease, antipsychotics increase intracortical myelin (66) and that in never-medicated SZ subjects, as little as six-weeks of atypical antipsychotic treatment results in increased regional synchronization of neural activity (68).

The importance of intracortical myelin in compensating for subcortical transmission delays and optimizing brain function is further supported by observations from multiple sclerosis (MS), a classic myelin disease. Until recently myelin-destroying intracortical lesions, which post-mortem data show represent as much as 60% of multiple sclerosis lesions and are associated with brain atrophy, were under-appreciated due to difficulty in detecting them on MRI (69, 70) (reviewed in 71). Prospective studies show that absence of such cortical lesions is associated with a favorable clinical and cognitive outcome independent of the well-known deep white matter lesion accumulation (72). Conversely, presence and progression of cortical lesions are most clearly associated with cognitive decline (including processing speed and memory) (73).

Processing speed seems to be more heritable that other cognitive measures (74) and is believed to be the most sensitive measure of cognitive decline over time in MS (75, 76). SZ and BD share cortical myelin deficits with multiple sclerosis except that unlike the focal deficits seen in MS, in these common psychiatric disorders the deficits are less focal and most apparent in later myelinating cortical regions (see section 8). As in MS, slowed cognitive processes are also critical in SZ and BD where such deficits are consistently and positively associated with clinical outcome (77-82). Other speed-related similarities are evident in decreased responses to stimuli as assessed by event-related potentials in MS (83) and are also evident in SZ and BD (84-86). Imaging data support the proposition that the biologic underpinnings of cognitive processing speed may be myelin integrity (21, 87-90).

3.3.1. Measuring intracortical myelin (ICM) *in vivo* with MRI

Intracortical myelination (Figure 2) can have a differential impact on MRI measures of cortical thickness by shifting the gray/white matter border detected by MRI (91). This shift may be dependent on the type of imaging sequence used (Figure 3). The effect of intracortical myelin on MRI measures has remained underappreciated and may have contributed to ambiguities in interpreting imaging data. Recent reviews of MRI literature on antipsychotic effects on brain structure are striking in the absence of a clear pattern of cortical changes (92-95). Key controversies remain regarding separation of medication and disease effects (96-98) and the potential detrimental medication effects on the progressive brain atrophy most often observed in subgroups with poor outcome (92). These controversies are fueled by the difficulties in interpreting differences in cortical volumes (99, 100).

Until recently, an *in vivo* measure to confirm the post-mortem evidence of an intracortical myelination deficit in SZ (see section 8) has not been available (66). Based on observations derived from assessing intracortical myelin (Figure 3), the inconsistencies in the literature can be explained as partially due to an under-appreciation of several key factors: (1) the extensive myelination of the human brain compared to other species and the exceptionally high cholesterol content of myelin (9, 91), (2) the effect of intracortical myelin (ICM) on the separation of gray and white matter in MRI images and the differential ability of imaging sequences to detect intracortical myelin (Figure 3) (66, 91), (3) the quadratic (non-linear) lifespan trajectory of human brain myelination in healthy subjects (Figure 2) (63, 101), (4) the dysregulation of this developmental trajectory in SZ (102-105), (4) the impact of medications on this trajectory (66, 106), and (5) the under-appreciation of medication adherence effects on structural brain changes and clinical outcomes (107).

We have previously postulated that reduced ICM may account for the finding of increased neuronal density in SZ (108, 109) and proposed that psychotropic

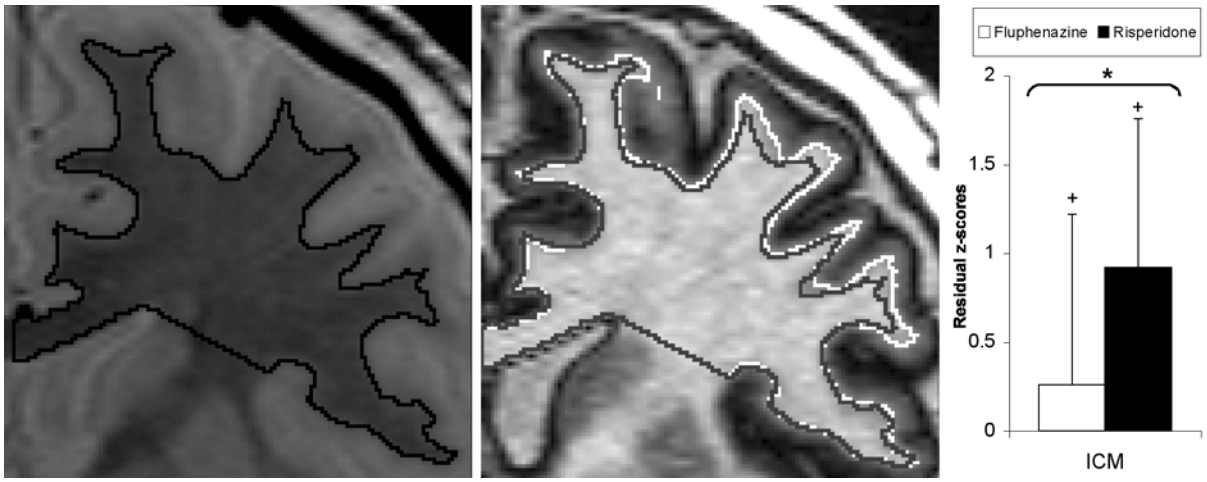

Figure 3. *In vivo* Measure of Intracortical Myelin (ICM) Volume of Frontal Lobe. Left: Proton density (PD) image that is insensitive to the cholesterol in myelin. The black line depicts the border between the gray and white matter. This same gray/white separation line is depicted on the image on the right as the gray line inside the white line. Middle: Inversion recovery (IR) Image of the same slice of brain as in the PD image on the left (both images obtained sequentially in the same imaging session). The IR image optimally detects the high cholesterol in myelin and is used to obtain the "myelinated white matter volume" that includes heavily myelinated parts of the deeper portions of gray matter (see Figure 1 for post-mortem depiction of ICM and its detection by IR images). The white line separates myelinated and unmyelinated portion of gray matter. The difference between the gray and white lines is the measure of ICM. Right: Residual z-scores of frontal lobe ICM volume in male subjects with schizophrenia receiving either an atypical or typical antipsychotic medication during the initial treatment. Between group tests (risperidone vs. fluphenazine): *$p<0.05$. Within group tests (schizophrenic vs. healthy controls, standardized to mean = 0 and SD = 1): +$p < 0.05$. From (66).

medications may be changing ICM (see sections 3.4. and 9) (6, 110). The development of a method to estimate ICM (Figure 3) may be useful in examining this possibility *in vivo* (66) as well as understanding the clinical significance of accumulating post-mortem evidence showing ICM deficits in SZ and BD (see section 8).

3.4. Neurotransmitters can trigger oscillations and may also refine intracortical myelination

The glutamate and GABA (gamma-aminobutyric acid) neurotransmitter systems, and particularly the parvalbumin-expressing fast spiking GABA interneurons (GABApv), seem to be most directly involved in triggering oscillations (50, 51). Oscillations can also be manipulated with drugs such as ketamine, which may act in part by damaging white matter (111) and GABApv interneurons (112) (see section 7), and can induce correlated changes in oscillations and psychiatric symptom measures (113).

Abnormal neuregulin-ErbB signaling changes myelination and is believed to be involved in multiple psychiatric disorders such as SZ and BD (see sections 2.1. and 8). Not surprisingly, altering neuron-glial communication through the neuregulin-ErbB system has also been shown to alter Gamma oscillations (114). Deficits in optimizing synchronization may degrade practice-based learning and result in poor skill acquisition in schizophrenic subjects (115, 116). This deficit may respond to treatment with atypical antipsychotics more than with typical (117) (reviewed in 118) and impact clinical outcome (119, 120). Medication adherence can also impact clinical outcomes (107) yet it is not often assessed in pharmacological literature and may contribute to the uncertainty surrounding the issue of medication effects on cognition and learning (118).

Herein a deceptively simple proposal is made: the fact that the vast majority of efficacious pharmacologic interventions alter neurotransmission within gray matter is not a coincidence. It is within gray matter structures such as the cortex that neurotransmitters themselves can mediate neuron-glial interactions (see section 9). In gray matter neuronal networks themselves can provide a direct layer of control on intracortical myelination through neurotransmitter release. By directly influencing intracortical myelination (66, 121) neurotransmitters may further refine speed and synchrony of action potentials on which optimal cognition and behavior depend (see section 3.3.). In order to understand the key role of oligodendrocytes and their myelin in multiple disease states, a review on the exceptional attributes and *vulnerabilities* that makes them "the weakest link" will follow next.

4. DISTINCTIVE ATTRIBUTES OF OLIGODENDROCYTES AND THEIR MYELIN

4.1. High metabolic requirements

Key evolutionary changes in metabolism and structure occurred to make oligodendrocytes exceptional in several important ways that are directly pertinent to the model (reviewed in 9). First, the production and maintenance of the myelin sheath(s) that is up to 600x the surface area of oligodendrocyte soma membrane and 100x

the weight of the soma (122, 123) makes the energy requirements of oligodendrocytes 2-3 fold higher than other brain cells (124, 125). Oligodendrocytes use of lactate to synthesize lipids at a 6-fold greater rate than neurons and astrocytes while their use of glucose for this purpose is 2-fold greater (125). Since approximately 2-3% of the oxygen consumed in normal mitochondrial respiration is obligatorily transformed into free radicals (126, 127), cells with high metabolism such as oligodendrocytes and neurons (at synapses primarily) may be at risk due to their elevated levels of damaging oxidative reactions. This metabolic stress makes oligodendrocyte most vulnerable to a variety of insults ranging from hypoperfusion, toxic products of activated microglia and inflammation, other free radicals, to heavy metals and excitotoxicity (for review see 13, 128). The metabolic demands are even higher for precursors and oligodendrocytes that are actively myelinating axon segments. Their differentiation induces a marked increase in mitochondrial and cholesterol metabolism enzyme transcripts. Not surprisingly mitochondrial disease often manifests with dysmyelination (129) and mitochondrial variants have been described in psychiatric disorders (130). Oligodendrocyte precursors produce three times their own weight in membrane lipids each day (123) and are even more exquisitely vulnerable than mature cells (131-134) (reviewed in 11). Not surprisingly, oxidative stress has been consistently observed in SZ and BD both peripherally (135-137) and in brain tissue (138-141), as well as in disorders of older age such as AD (142) (reviewed in 9). Several treatments may help address this problem (see section 7).

Humans devote 20% of their total energy to the brain compared to 13% in non-human primates and 2-8% in other vertebrates (143). In order to meet the extraordinary demands for energy and lipid production, important evolutionary adaptations may have occurred to make the development of our highly myelinated brain possible. An evolutionary switch occurred among primates changing lactate dehydrogenase function from supporting primarily anaerobic to oxidative metabolism (144). Thus in brain, astrocytes produce lactate to supply metabolic needs of neurons (145) and especially oligodendrocytes which consume the bulk (>80%) of this supply (125). Lactate concentrations seem to be elevated in the CSF of subjects with BD and SZ (146) and such increases have been observed in prodromal phases of the diseases (147). These observations are consistent with dysregulated myelination (6, 104, 105) (see section 8) and possible underutilization of this trophic factor by oligodendrocytes.

During brain evolution, the vulnerability of oligodendrocytes and their myelin to insults and especially oxidative damage and its associated inflammatory reactions was mitigated by several additional adaptive compensations (148-150). Oligodendrocytes are especially enriched in peroxisomes, organelles that help detoxify reactive oxygen species, and their peroxisomes may be superior to other brain cells at performing this function (148, 151). Peroxisomes also produce plasmalogens (Pls) and myelin is especially enriched in Pls and the omega 3 fatty acids ((O3FAs) - especially docosahexaenoic acid (DHA)) they contain (150). Pls are unique phospholipids characterized by the presence of vinyl-ether bond at the sn-1 position of the glycerol backbone while the sn-2 bond is occupied by polyunsaturated fatty acids such as DHA (152-154). The vinyl-ether bond acts as an endogenous antioxidant protecting DHA (155, 156) from oxidative damage (155, 157). Peroxisome function and Pl production is thus essential for adequate myelination (149, 152). Given these properties it is not surprising that Pls seem most enriched in myelin (150). Brain myelin content appears to drive Pl concentrations that peak in mid-life (158-160) following a similar quadratic lifespan trajectory as myelin (Figure 1) (63, 65, 161) from very low levels at birth (162).

As much as 20-30% of all brain lipids are either arachadonic acid (AA, an omega 6 fatty acid (O6FA)) or DHA, by far the most abundant O3FA (163, 164) (see section 5). In addition to structural role in membranes these FAs and their metabolites have important secondary functions related to inflammation as well as recovery, repair, and CNS protection (163, 165). Phospholipases A2 are an enzyme superfamily with over 20 isoforms that specifically hydrolyze FAs from the sn-2 position of plasmalogens to release free FAs such as AA and DHA and lypophospholipid (166). The effects of phospholipases can be quite drastic and many powerful snake venoms contain such enzymes (163). Once released, AA can be oxidized to eicosanoids and platelet activating factor that *promote* inflammation. Conversely, released DHA can be metabolized to docosanoids and several anti-inflammatory/protective species such as resolvin, protectin D1, and neuroprotectin D1 (163, 165). DHA may also promote repair by inducing the rate-limiting enzymes in Pl synthesis pathway (167) and lipid transport (168). Furthermore, it may induce powerful *transcription factors that control lipid metabolism* (retinoic acid receptors, retinoid X receptors, and peroxisome proliferator-activated receptors). These transcription factors decline with age and are involved in many cellular processes including maintenance of cognitive functions (169). It thus seems that higher brain DHA levels may be protective and direct treatment with such lipids may have substantial therapeutic benefits (see section 5) (170, 171).

4.2. High cholesterol content and requirements

Brain cholesterol is synthesized almost exclusively *de novo* by glia (primarily oligodendrocytes and astrocytes) (125, 172, 173) and peripheral cholesterol does not enter the brain (174). The human brain, which is approximately 2% of the body by weight, contains approximately 25% of the body's membrane cholesterol (172, 175) and up to 80% of brain cholesterol is in myelin (176). Cholesterol does not bind as much water as the polar phospholipids in membrane bilayers. Thus, cholesterol enrichment in the outer myelin membrane bilayers reduces water binding and allows the juxtaposition and tight membrane packing achieved in myelin sheaths. Cholesterol is thus indispensable for myelination (173, 177). With the aid of apolipoproteins such as E, D, and J, (ApoE, ApoD, and ApoJ) cholesterol (and other lipids) is transported and can be “exported” to neurons (178, 179) and contribute to a variety of brain processes, including synaptogenesis, that

are dependent on this essential membrane ingredient (180, 181). Cholesterol is metabolically expensive to synthesize and it is extensively recycled from broken down myelin (182) for use in repair/production of new myelin and other membranes (20, 21, 174). This recycling depends on interactions between apolipoproteins (especially ApoE), ATP-binding cassette transporter A1 that lipidates ApoE, low-density lipoproteins (LDL) with which ApoE associates, and LDL receptors (see sections 5-7). The efficiency of this recycling gives human brain cholesterol a half-life measured in years (183) (summarized in Figure 4).

4.3. High iron content and requirements

Oligodendrocytes have the highest iron content of all brain cell types (124, 184, 185) (reviewed in 186) and as much as 70% of brain iron may be associated with myelin (187, 188) The high iron level is consistent with the iron requirement of cholesterol and lipid-synthesizing enzymes (189) including synthesis of endogenously produced steroids or "neurosteroids" (190-192) that may themselves be involved in promoting myelin repair (193, 194). High iron is also consistent with increased metabolic/mitochondrial needs for the respiratory chain and recent data shows oligodendrocyte differentiation cannot proceed without this induction of mitochondrial genes (195). Mitochondrial defects would thus be expected to and do influence the pathophysiology of SZ, BD, and AD (130, 196-198). Thus, an increase in intracellular iron is essential for oligodendrocyte differentiation (199). Inadequate dietary iron during early development can result in poor myelination and associated mental deficiencies in human infants (124, 200) and young adults (201).

Brain iron levels increase with age (202, 203) and are abnormally elevated in and contribute to the pathophysiology of degenerative diseases of old age such as AD (188, 204, 205). Elevated iron can promote the production of free radicals and their associated oxidative damage (133) compromising a variety of essential functions such as DNA repair (206), phagocytosis, and lysosomal activity (207). Post mortem human data suggests that SZ and BD as well as degenerative diseases such as Alzheimer's are all associated with increased oxidative damage (see sections 4.5. and 7).

4.4. Continued development and proliferation throughout the lifespan

Another distinctive oligodendrocyte feature is especially important to postnatal as well as adult brain development. Unlike neurons, whose numbers are essentially established at birth, in healthy primates, vast numbers of oligodendrocyte *progenitors* are produced to support the decades-long and diverse process of postnatal myelination and repair/remyelination (208, 209). Progenitor cells comprise 5% of total adult brain cells and they continue to divide and increase the numbers of adult oligodendrocytes across the lifespan by as much as 50% (210-212) (reviewed in 213) while building, repairing, and remyelinating damaged or lost sheaths (212, 214). Large numbers of "reserve" progenitor oligodendrocytes (5-8% of brain glia) exist in this undifferentiated form (208, 209).

The continual capacity of oligodendrocytes to proliferate and repair holds the promise of function restoration as well as the danger of increased vulnerability and toxicity as increased oligodendrocyte numbers are associated with increased iron levels (205, 215) (section 4.3.). Oligodendrocytes may be critical to uptake of iron as recent observations show that 50% of hippocampal oligodendrocytes are juxtaposed directly on blood vessels where they may be able to acquire iron directly (209). Increased numbers of oligodendrocytes and iron levels have been associated with aging (202, 203, 210-212) and degenerative diseases such as Huntington's disease (216-218) (reviewed in 215), Parkinson's and AD (188, 204, 205), as well as *presymptomatic* cases of AD (219, 220). The age-related increase brain iron may contribute to the development of an increasingly oxidation-prone brain environment (205) that could be further exacerbated by mitochondrial deficits observed in SZ, BD, and AD (130, 196-198) (see sections 5, 7, and 10) (summarized in Figure 4).

4.5. Developmentally-determined heterogeneity and vulnerability continuum

Oligodendrocytes are markedly heterogeneous based on when, during the protracted process of human brain development, they differentiated into myelin producing cells. At birth, each oligodendrocyte myelinates a single segment of the largest axons that form our primary motor and sensory circuits. Throughout subsequent development however, each oligodendrocyte continually increases the number of segments it myelinates such that by middle age, in association cortical regions for example (Figure 2), each myelinates upwards of 50 axon segments (209, 221). Oligodendrocytes can thus achieve remarkable complexity and undergo specific differentiation for specific circuitry (209). Later-differentiating oligodendrocytes have different lipid properties, myelin turnover, and reduced capacity for myelin repair than earlier differentiating cells (209, 222-225). Compared to earlier-myelinating oligodendrocytes later-myelinating cells support thinner myelin sheaths (226, 227) with shorter internodal length (213). Overall, the later-myelinating regions are more vulnerable to a variety of insults including aging as manifested by higher levels of myelin damage (67, 228) and loss (45) that correlate with cognitive declines (reviewed in 9, 67, 205).

4.6. Epigenetic modifications of oligodendrocytes throughout the lifespan

The continued oligogenesis, myelination, and repair processes have additional consequences that may be unique to myelin. These processes remove the debris from broken down myelin and may "mask" the role of myelin damage and repair in normal function as well as disease states (reviewed in 9). Thus, the principal evidence for these processes is indirect and consists of thinner myelin with shorter segments characteristic of repaired segments, and the age-related increase in oligodendrocytes numbers needed to support repair (reviewed in 213). These lifelong developmental processes produce a spectrum of cells

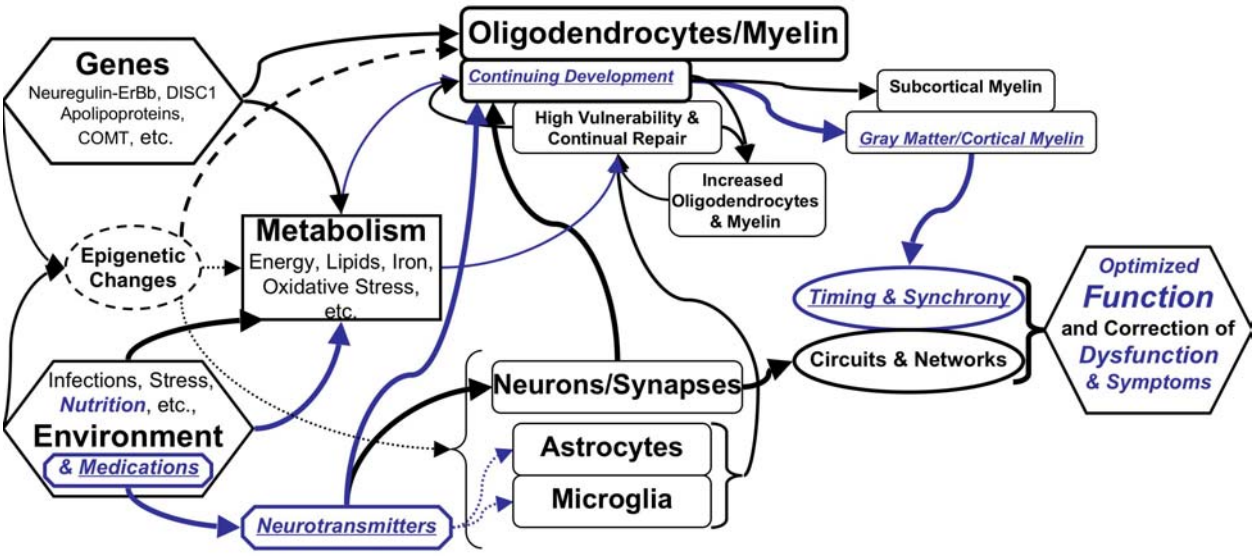

Figure 4. Neuroglialpharmacology and Optimized Brain Function: A Schematic Depiction of Key Interrelated Processes Described in the Text. Continual dynamic processes are denoted by arrows whose thickness attempts to represent both the level of description of these processes (provided in the text) and the novelty of their contributions to the myelination process. Blue arrows and boxes as well as italics summarize currently available modes of interventions at the pharmacotherapeutic and nutritional levels described in the text. Note: as a schematic focused on the key yet underappreciated role of oligodendrocytes and myelin this figure does not depict a myriad of additional relationships such as the ones between genes, environment, epigenetic changes, and metabolism and all four interdependent CNS cell types and their specialized structures such as synapses. For further details please refer to the text and reference list.

ranging from precursors to differentiated oligodendrocytes and create opportunities for environmental-genetic interactions through epigenetic modifications of gene expression (summarized in Figure 4).

Epigenetic modifications of gene expression result from environmental effects that alter nuclear chromatin through methylation and demethylation reactions and histone modifications. These modifications alter gene expression of cells as they differentiate and thus affect cell function far into their future (229-234). Environmental insults (defined as deviations from optimal conditions including brain and peripheral diseases and malnutrition) that occur in earlier stages of development can thus have both immediate as well as long-term effects on developmental/repair processes through epigenetic changes of gene expression.

In a continually dividing and differentiating cell line such as oligodendrocytes, epigenetic modifications on gene expression can be introduced in each subsequent generation of differentiating cells and thus reflect environmental conditions at different stages of the lifespan. Furthermore, myelination itself drives age-related brain structure change (Figure 2) (reviewed in 9, 91). Thus, later-differentiating generations of oligodendrocytes myelinate increasing numbers of axon segments (section 4.4.) and are exposed to increased brain iron levels (section 4 .3.), increasing metabolic demands on individual cells (section 4.1.). For oligodendrocytes, "developmental" requirements (e.g., nutrition, metabolism – see sections 4.1.-4.3) do not stop in infancy and may continue or increase well into adult years. These requirements may actually increase as repair-associated needs increase into old age (9) while concomitantly, epigenetic effects may contribute to the degradation of myelin repair efficiency (234). Without adequate interventions this decline in repair ability may make age-related cognitive decline and dementia almost inevitable for the vast proportion of the population (reviewed in 9).

Since myelination continues into middle age and beyond, repeated episodes of diseases such as SZ and BD may also have both immediate as well as delayed destructive effects through epigenetic modifications of myelination and repair. In postnatal brain, most if not all progenitor cells receive direct excitatory and inhibitory synaptic input (235-237) (see section 9.1.). The neuronal input is likely dramatically disturbed during illness episodes (as well as during episodes of illicit drug use (see section 9.1.)) and could potentially result in a multitude of immediate and long-term changes in progenitors. Psychotic, affective, or illicit drug use episodes could for example prematurely trigger epigenetic effects and accelerate the decline in myelin repair efficiency that is observed in old age (234). Consistent with such a possibility, severe psychotic (positive) symptoms of SZ seem to have similar detrimental effects on clinical outcomes whether they occur at first admission or during later episode (238, 239). A reduction in intracortical myelin may contribute to this illness-related deterioration and the associated deterioration in response to antipsychotics commonly dubbed "treatment resistance" (110). Promyelinating effects of medications may be able to

partially counteract such epigenetic process (66, 240) (see section 9) (summarized in Figure 4) especially when initiated early in the disease process (241).

Similar destructive processes may occur in mood disorders where repeated episodes seem to increase severity of subsequent episodes (242), accelerate cognitive decline (243-245), increase the risk of old-age dementia (246-248), and also result in increasing treatment resistance (reviewed in 249). Conversely, continuous treatment with lithium or antidepressants seems to be associated with reduced risk of dementia (250-252). As in SZ, some reports suggest that antipsychotic treatment may also increases white matter volume in BD (240, 253) (see section 9).

Other nutritional and pharmaceutical interventions that could directly influence epigenetic modifications are also worth considering. Valproic acid for example a branched chain fatty acid that is effective for treatment of seizures and BD may directly impact epigenetic modifications. Valproic acid inhibits histone deacetylases that are crucial to epigenetic processes (234, 254-256). Direct alterations/reversal of epigenetic changes may thus be possible through such interventions. Consistent with this possibility, this medication also affects multiple important transcription factors that are lipid metabolism "control points" including PPARd (254, 255, 257), PPARg (257, 258), and PPARa (259) activators. Furthermore, it may block gene expression of adiponectin (produced by adipocytes and controls insulin sensitivity and glucose homeostasis) that is reduced in overweight, diabetic individuals, and patients receiving it (260-262). It is thus not surprisingly that in addition to beneficial effects on brain, valproic acid also causes obesity and insulin resistance (261, 262).

Specific nutrients such as folate can also influence the methylation reactions and may thus affect the epigenetic processes (263). Furthermore, availability of nutrients such as O3FA (see section 5) that are essential building blocks of myelin and hormones such as VitD may mediate other environmental interactions related to climate (see section 6) (summarized in Figure 4).

5. ESSENTIAL LIPIDS: OMEGA 3 AND 6 FATTY ACIDS (O3FA AND O6FA) AND THEIR METABOLITES

Essential fatty acids cannot be synthesized by humans and must be obtained from diet. Human brain may be especially susceptible to DHA deficits due to inadequate dietary intake and/or accelerated degradation from oxidative and inflammatory processes (see sections 4.1.-4.3., 7, and 8). A major reason for such deficits may be that DHA synthesis from O3FA precursors is very low in omnivorous primates (264). In humans this deficit is especially pronounced in men (265) while in women, higher estrogen levels seem to upregulate DHA formations from O3FA precursors to a modest degree (169, 266). Providing DHA itself in the diet is much more efficient (over seven-fold) in increasing brain DHA levels than providing precursors (267). Unfortunately, most recommendations for daily intake/supplementation with O3FA refer to alpha-linoleic acid requirements (a DHA precursor) as opposed to DHA requirements (reviewed in 268, 269). To increase US intake levels (which are around 100 mg per day in adults) and reach the same levels as a fish-consuming country like Japan, a daily intake of 700-1000 mg may be required for the average US adult (269, 270). The results of such supplementation efforts can be substantially influenced by genetic variants (271, 272) as well as gender/estrogen. Hormonal and genetic effects may have important clinical consequences such as contributing to milder and later onset of SZ in women and may help resolve epidemiologic observations regarding associations between genetic variants, climate, nutrition, and brain disease (see section 6).

As described above, essential fatty acids are especially enriched in myelin but are also important for many other brain membranes. The principal brain O3FA is DHA (22:6n-3), and it comprises 15% of total FA while the principal O6FA, arachadonic acid (AA, 20:4n-6), comprises another 10% (273). In healthy individuals these levels decline with age during adulthood although the mRNA for lipogenic enzymes involved in their synthesis have a quadratic age trajectory peaking in middle age (similar to intracortical myelination – Figure 2) suggesting compensatory responses that crest in middle age (274).

Significantly reduced peripheral levels of O3FA have been consistently reported in never-medicated first episode schizophrenic subjects (275-279). Frontal cortex O3FA levels are also reduced in SZ (280), major depressive disorder (281, 282), BD (283, 284), as well as degenerative disorders of old age such as AD (285-288). It is not clear whether these reductions are due to decreased uptake from diet, increased metabolic breakdown of these fatty acids from processes such as oxidation (see just below), or both. Many damaging processes (such as oxidation, inflammation, and toxins) can directly cause myelin breakdown (289, 290) (section 7).

The above evidence of lipid deficits has been fundamental to the suggestion that abnormalities in brain lipids may have an etiologic role in SZ (170). Further support for this possibility has come from O3FA supplementation trials. A recent study carried out in high-risk subjects with prodromal symptoms reported a significant reduction in the number of subjects who went on to develop SZ as well as reducing their symptom burden (171). In subjects with chronic disease the results of such supplementation are less clear. Although many trials showed that adding O3FA supplementation to psychotropic medications may improve outcome in SZ, BD, and major depressive disorder, the results of meta analyses remain inconclusive and produced consistent calls for larger more definitive studies (291-295).

The apparent dichotomy between first break/prodromal studies and chronic studies may be multifactorial. O3FA deficits may be *ameliorated* somewhat by antipsychotic treatment (atypical>typical) (273, 296) making effects of supplementation harder to

detect in medicated subjects. In addition, myelination deficits seem to increase with the chronicity of disease, a phenomenon most clearly documented in SZ (102, 104, 105, 297) (reviewed in 6, 298). These increasing deficits suggest that the underlying etiology, together with the brain's adaptive/homeostatic responses and epigenetic effects (section 4.6.) could undermine treatment responsiveness to both psychotropic medications as well as nutritional supplementation (e.g., development of "treatment resistance" (110)).

6. PSYCHIATRIC EPIDEMIOLOGY: CROSSROADS OF GENES, LIPID METABOLISM, AND NUTRITION

As described above, the extensive myelination of the human brain requires massive amounts of energy, iron, and lipids. Not surprisingly, epidemiologic data consistently suggests that starvation and malnutrition (of both iron as well as lipids) increase SZ risk (299-301) (302, 303) (reviewed in 304). Interactions between lipid metabolism genes such as Apolipoprotein E (ApoE) and malnutrition have also been reported (305). In SZ and BD increased levels of ApoE have been observed in frontal lobes (306, 307) and CSF (308) suggesting upregulated lipid metabolism in both disorders (see below).

ApoE is a secreted glycoprotein that associates with lipoproteins such as chylomicrons and very low density lipoproteins (VLDL) and mediates uptake of these lipid-rich particles into cells via receptor-mediated endocytosis (309). The polymorphisms of ApoE (with three common alleles designated E2, E3, E4) have important effects on lipid absorption, metabolism, and repair of membranes such as myelin and manifest with very different consequences peripherally versus centrally.

Peripherally, ApoE4 (and 3) are substantially better than ApoE2 at clearing lipids from the circulation due to a better interaction with receptors on target organs such as liver (310, 311) while ApoE2 delays this lipid clearance. Thus, ApoE alleles may impact disposition of small lipid particles such as chylomicrons (produced during intestinal absorption of lipids) and Low Density Lipoprotein (LDL, a key lipid transport in the bloodstream) (312, 313). ApoE genotype may therefore also influence the absorption of several nutrients such as VitD (reviewed in 314), and essential fatty acids (EFA) such as omega 3 and 6 fatty acids (O3FA and O6FA) (271, 272). It thus appears that overall clearance and deposition of food/lipid nutrients into cells is best with ApoE4 alleles and may be advantageous for survival in a resource-poor environment such as northern latitudes or hunter-gatherer as opposed to agrarian societies. Increased resistance to infection in ApoE4 carriers (315) may also be related to this advantage in nutrient absorption.

The superior nutrient absorption (including vitamins such as Vitamins D and K from food sources) may help explain ApoE epidemiology. The ancestral (primate) ApoE4 allele increases in frequency as one moves north in latitude in Europe, Japan (reviewed by 316), and China (317). This observation gave rise to hypotheses that ApoE4 alleles may interact with environmental factors such as sunlight exposure (which can produce VitD in skin) (316) and nutrition (305, 318) since both nutritional abundance and sunlight may be reduced at higher/colder latitudes.

The higher endocytosis of ApoE4 may contribute to the observation of *fewer* circulating ApoE molecules compared to those without an ApoE4 allele (319-322) (reviewed in 323). A similar quantitative gradient (ApoE2>ApoE3>ApoE4) is observed in CSF of transgenic mice that had human ApoE alleles knocked in (324-326). In brain however, fewer circulating ApoE molecules may have detrimental effects.

In brain, ApoE is the primary transporter of *endogenously produced brain lipids* such as cholesterol and sulfatide (327-332) that are essential for membrane and especially myelin production, function, and integrity (173, 177, 331-333). The poor interaction of ApoE2 with endocytosis receptors may in part explain the higher number of ApoE2 containing lipoprotein particles, and may also increase the distance these particles diffuse before being endocytosed. The higher levels and further diffusion could make ApoE2 advantageous for the process of clearing lipid debris created by breakdown of myelin and recycling these lipids to wherever they would be most needed (9). This wider dispersal may be especially important for toxic or inflammatory debris such as sulfatide (9) and toxic proteins (334).

In human brain, the tremendous lipid needs (see section 4.2.) combined with a generalized and accelerating age-related myelin breakdown process (161, 335, 336) (Figure 2) would put a premium on the capacity to mobilize lipids such as cholesterol and recycle them for myelin repair. Thus, ApoE4+ carriers may be at a critical disadvantage in a variety of diseases where repair is important such as AD (9, 21) and this allele is by far the strongest genetic risk factor for late onset form of this disease (337).

7. MYELOTOXICITY AND TREATMENT EFFECTS

Post mortem human data suggests that SZ and BD as well as AD are all associated with increased oxidative damage (136-140) (141, 338, 339). This damage is not likely to be caused by medications since they are observed in unmedicated individuals (139, 338) and some medications have antioxidant properties (see below). Oligodendrocytes and their myelin are distinctively vulnerable to many toxins and especially oxidative damage (section 4.5.). Oxidative damage is likely the most prevalent myelotoxin and is associated with the oxidative peroxidation byproduct lipofuscin (340-342), monotonic increase of brain iron (203) (section 4.3.), as well as compensatory upregulation of repair mechanisms involving ApoE and ApoD (306, 307, 343, 344).

Multiple toxins that may contribute to the development of psychosis may share dysregulations in oxidative pathways (345). One important immunotoxin is

interleukin 6 (IL6), a proinflammatory cytokine that can enter the brain (346). In humans and animal models elevated *peripheral* IL6 has been consistently associated with lower global and regional brain gray and white matter volumes (346-349) as well as functional measures of frailty in older individuals (350, 351). IL6-induced oxidative stress may also be a final common pathway to several insults that trigger inflammatory reactions including psychotogenic pharmaceuticals such as ketamine and methamphetamine, which can be especially toxic to fast-spiking GABApv interneurons (112, 352). Some of these interneurons have especially heavily myelinated axons (353, 354) and, if their myelin becomes dysfunctional, they may be susceptible to compensatory feedback overstimulation from their excitatory efferent inputs (e.g., excitotoxicity) (355). Supporting evidence for white matter damage related to abuse of these drugs has recently been published (111, 356). An excitotoxic mechanism could help explain significant reductions of GABApv interneurons in SZ (357, 358, reviewed in 359) and the psychotogenic effects produced by abuse of these drugs (360-362).

Recent data suggests that antipsychotics may promote myelination although they may have different myelination effects (8, 66, 240, 363-365). Multiple mechanisms could promote myelination and contribute to differences amongst treatments. For example, some but not all antipsychotics may have antioxidant properties (364). Greater increase in cortical DHA has been reported with atypical versus typical antipsychotic medications (273, 296). This possibility is supported by animal data showing that treatment with antipsychotics can increase O3FA (366) although this increase is not seen with clozaril and haldol (367, 368). Given that both typical and atypical antipsychotics are effective in reducing clinical symptoms, these data suggests that medications may achieve similar pro-lipidation/myelination effects through different mechanisms (106, 121, 273, 363, 364) although in *healthy* animals treatment-related decreases in oligodendrocyte markers have been reported (369, 370).

Cell culture models reveal that several antipsychotic and antidepressant medications increase lipid biosynthesis by upregulating Sterol Regulatory Binding Element-Binding Protein (SREBP) (371-373) although, since substantial differences exist between medications (374), once again different mechanisms may be at work. The effects of medications may also be altered by SREBP gene polymorphisms that have been associated with susceptibility to SZ (375) as well as metabolic side-effects (376). Compensatory reparative increases in apolipoproteins (ApoD and ApoE (306, 307, 343, 344)) and other enzymes involved in lipid metabolism have also been observed, suggesting that medications may impact "master regulator" transcription factors such as Liver X receptor and sterol regulatory element transcription factor (375, 377). The possibility that antipsychotic and antidepressant medications have metabolic effects in common may underlie their shared antidepressant and antimanic properties (378). The wide spectrum of efficacy of atypical antipsychotics in treating affective symptoms has recently led to the drastic expansion of their FDA-approved indications and support the suggestion that lipid and myelin abnormalities may be shared by several psychiatric disorders (see sections 3, 4, 8 and 9).

The suggestion that antipsychotics may also act on lipidation and specifically ameliorate myelin toxicity is supported by several recent studies of cuprizone, a myelin-specific toxin whose effects depend at least in part on increased cytokine production and oxidative stress (379) (reviewed in 364, 380). Antipsychotics promote myelin repair in the cuprizone animal model (364, 381, 382). Protecting intracortical myelin seems to be more difficult however as only the combination of haldol and clozapine was able to attenuate demyelination in prefrontal cortex while in caudate, putamen, and hippocampus both quetiapine and clozapine did so but haldol did not (364). The ameliorative effects of antipsychotic medications on cuprizone-induced toxicity (364, 381, 382) support the suggestion that antipsychotic treatments could be directly supporting myelination as part of their mechanism of action (6, 66, 102, 240) (see section 9). This is consistent with human studies that reveal a deficient myelination process in SZ (102, 104, 105) (section 8) and significant beneficial effects in cortex lipidation (66, 139) (section 9). Although both typical (fluphenazine) and atypical (risperidone) antipsychotics may increase prefrontal cortex myelination, risperidone may increase myelination significantly more (Figure 3) (66). A superior promyelinating effects of atypicals on intracortical myelin may also help explain the apparently wider spectrum of efficacy observed with this class of medications and their expanding FDA indications. The combined animal and human data could be interpreted to suggest that, in disorders involving abnormal myelination and/or myelin damage, cortical myelination may be mediating antipsychotic efficacy however, much additional research is needed to clarify neuronal and/or glial mechanisms of action and their interactions (section 9).

Given the increasing evidence of oxidative damage or deficient myelination in psychiatric disorders, it is not surprising that several clinical trials of an antioxidant intervention have shown efficacy in several disorders. N-acetyl cysteine (NAC) supplementation is well tolerated and helps replenish the rate-limiting supply of cysteine for glutathione (a tripeptide that is arguably the principal brain antioxidant) (reviewed in 383) (249, 384) and is decreased in the brain of psychiatric subjects (141). NAC penetrates the blood-brain-barrier (385) and has been shown to protect oligodendrocytes from oxidative damage and a variety of toxins (134, 386-391). Protective effects of NAC treatment have been observed in animal models of several myelin diseases (389, 392, 393) and animal models of psychiatric disease caused by toxic effects of drugs of abuse such as methamphetamine, cocaine, and phencyclidine (394-397). Furthermore, this treatment has shown promising results in a senescent-accelerated mouse that develops premature memory deficits (385). This mouse strain also shows the major elements of oxidative stress and myelin breakdown including increased pro-inflammatory cytokines such as IL6 (398), loss of hippocampus oligodendrocytes (399),

and premature age-related degeneration of myelin (400). Most importantly, placebo-controlled human clinical trials have shown significant symptom reduction in SZ, BD, trichotillomania, and AD (401-404) as well as improved cognitive performance (405).

8. DYSREGULATED MYELINATION IN SCHIZOPHRENIA (SZ) AND BIPOLAR DISORDER (BD)

In the last decade the importance of myelin pathology in SZ (reviewed in 6, 406, 407) and BD (408, 409) has become widely recognized. This section will summarize the evidence that myelin pathology contributes to these diseases. Twin studies suggest that in both diseases, white matter reductions are related to the genetic risk of developing the disease while the cortical gray matter changes seem related to environmental factors (410-412).

Although the white matter abnormalities are present in both diseases and they may share myelination abnormalities, the patterns are not identical (413). In SZ, imaging studies that assessed white matter volume (102-105); (reviewed in 6) and post-mortem studies (44, 414-422) provide converging evidence to support the view of a deficient frontal lobe *cortical* myelination trajectory. Further, post mortem studies suggest that *subcortical* myelin deficits are absent or not as prominent as cortical myelin reductions (423-426). DTI studies examining subcortical white matter of younger-onset groups of subjects (mean age <26) suggest that abnormalities are *not* present at disease onset but rather develop as the disease progresses (427, 428) while DTI studies that assessed older-onset (mean age >28) first-episode subjects found significant deficits in white matter integrity (429-433). In first-brake studies of similarly older-onset individuals (mean age >28) the location of subcortical white matter integrity deficits has varied widely. For example, reduced fractional anisotropy was observed in the splenium but not genu of corpus callosum in one study (433) and vice versa in another (432).

The apparent absence of subcortical oligodendrocyte and myelin fiber deficits in post-mortem studies (425, 426) suggest that if present, subcortical myelin deficits may be patchy and initially more amenable to repair and become most pronounced later in the disease and/or in later-onset disease. Such a pattern is consistent with a *dynamic* process of continual repair of subcortical myelin that would result in reduced myelin thickness (213) without loss of myelinated fibers or oligodendrocytes (425, 426). The totality of the data would thus suggests that the myelination deficit associated with SZ may be limited to and/or more severe in late-myelinating structures such as the cortex and adjacent white matter (66, 414, 434) while subcortical myelin may have better reparative abilities.

In contrast to consistent reports of white matter *deficits* in SZ (435), several DTI reports suggest *increased* white matter integrity in BD (436-440). Other DTI studies suggest *reduced* white matter integrity (441) including reductions in early-myelinating regions such as the internal capsule (409). In BD, disease state (e.g., depressed versus manic) may be contributing to these apparently contradictory observations. Thus one could speculate that hyperactivity/increased verbal output, that is often observed clinically in association with elevated mood states, could be related to increased myelination and cognitive processing speed of some circuits (e.g., excitatory) and/or decreased myelination in others (e.g., inhibitory circuits). Supporting this possibility is recently published data suggesting beneficial effects of the myelotoxic agent ketamine in treatment-resistant BD (111, 442, 443) as well as myelination-reducing effects of lithium (444).

Other factors could also contribute to contradictory imaging DTI findings. Differences in exposure to neuroleptic treatment that have been reported to change DTI parameters (445) just as they seem to change volumetric parameters (66, 240, 253). A third possible contribution may be genetic differences in NRG1-ErbB signaling which, in addition to altering myelination, may also alter cellular migration to final locations (33, 446, 447). Altered neuronal migrations could result in altered fiber organization and this possibility must be kept in mind in interpreting DTI measures that can be influenced by fiber orientation/crossing (448). Furthermore, many other gene variants and environmental effects may alter brain homeostasis and influence both the development of these disorders as well as imaging findings (Figure 4).

Human brain cytology data confirm a *cortical* glial deficit of patients with SZ that is primarily due to lower numbers of oligodendrocytes (44, 414-417). Staining data confirms an *intracortical* myelin (ICM) deficit (418-421) that seems to be particularly prominent in frontal lobes (44, 415, 417, 420). The ICM deficit is consistent with decreased expression of myelin genes revealed in proteome and transcriptome analyses (449-451) (reviewed in 452) and the prominence of myelin and myelination signaling genes as candidates for genetic components of this disease (27) (reviewed in 25, 26).

The oligodendrocyte reductions and myelin gene expression deficits are also observed in BD (44, 453, 454) (reviewed in 409) and may even occur in severe unipolar depression (44). Furthermore, genetic susceptibility risks alleles such as the ones for neuregulin and its ErbB family of receptors, that have crucial roles in myelination (see section 2.1.), seem to be shared by SZ and BD (23, 24). The cortical localization of myelination deficits is less clear in BD than in SZ however. Furthermore, in BD subcortical myelin deficits may be more prominent (455) and on MRI, focal regions of subcortical myelin damage manifested as increased signal intensity in white matter is consistently reported (456) (reviewed in 457).

9. PSYCHOTROPIC MEDICATIONS INFLUENCE GLIA AND MYELINATION: A KEY MECHANISM OF ACTION?

9.1. Synaptic and non-synaptic neurotransmitter effects on glia

Treatment interventions with O3FA, antioxidants, and some psychotropic medications that may have epigenetic effects (e.g., valproic acid) have been reviewed above (sections 4.6., 5, and 7). These

interventions have a wide spectrum of efficacy and reinforce the hypothesis that the production and maintenance of myelin may be the "weakest link" of the human CNS and may represent shared pathophysiology amongst multiple neuropsychiatric disorders (sections 2, 3, 8). Pharmacotherapy using antipsychotics remains the best established, efficacious, and widely used clinical intervention for SZ. Antipsychotics have also established a much wider spectrum of efficacy that includes affective disorders and multiple disorders that are "treatment-resistant" to approved/accepted first line pharmacotherapy. Any model of psychopathology must by necessity incorporate testable hypotheses that help explain the mode of action and wide spectrum of efficacy of antipsychotics.

Much of current clinical psychopharmacology (including antipsychotics) acts at synapses that are primarily confined to gray matter. This has helped focus clinical and research attention on synapses, neurons, and gray matter and likely contributed to the under-appreciation of the contribution of glial and especially oligodendrocytes and their myelin in optimizing neuronal network function. As reviewed in sections 3.2. and 3.4. however, it is in cortical gray matter that myelin may have some of the most powerful "plastic" synchronizing effects on neural network function. In this context, it is crucial to reconsider the widely accepted dogma that all or even most neurotransmission is synaptic and contemplate the alternative possibility that many neurotransmitters also directly affect glia through a variety of neurotransmitter receptors (458) (reviewed in 121, 235, 459) (summarized in Figure 4).

Active glutaminergic neuronal synapses on oligodendrocyte progenitors that directly affect their differentiation have been demonstrated (460, 461). Neurotransmitters effects on glia can also occur in deep white matter (59, 60, 462), have been shown to have functional importance in oligodendrocyte differentiation and myelin repair (460, 461), and to be functionally integrated with and responsive to excitatory and inhibitory input from neuronal networks in gray matter regions such as hippocampus (237, 463). Activity-dependant neuron-glial communication can also be supported through neuronal ATP release. ATP activates purinergic receptors that modulate intracellular calcium and cyclic AMP and have multiple effects on glia, oligodendrocytes, and myelination (60).

The neurotransmitter targets of major classes of existing pharmacologic treatments of psychiatric disorders also have substantial neuron-glial 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 (464-466). In addition to acetylcholine, catecholamines (primarily dopamine, serotonin, and norepinephrine) are also largely (>50%) non-synaptically released (467, 468). All these neurotransmitters can impact oligodendrocyte differentiation and myelination (30, 458, 469-472) (reviewed in 121). It is thus apparent that neurons have a multitude of neurotransmitter mechanisms to communicate with oligodendrocytes and influence/direct myelination and repair processes in cortex (reviewed in 121, 459, 470). These multiple neurotransmitter effects range from dopamine, which is shared by all antipsychotics (362), to serotonin, norepinephrine, acetylcholine, etc. which are present in varying portions amongst the antipsychotics and may help explain their differential effects (e.g., typical versus atypical (Figure 3) (66)). It is therefore proposed that the efficacy of current pharmacology may be due, at least in part, to changes induced in glia and in particular oligodendrocytes and their myelin (66, 240) (section 3.3. and 3.4.). The supporting evidence for two key neurotransmitter systems targeted by existing pharmacology (acetylcholine and dopamine) will be reviewed next.

9.2. The cholinergic system and myelination

A considerable portion of brain cholinergic receptors is associated with non-excitable cells such as oligodendrocytes and their progenitors (reviewed in 121). These non-neuronal receptors may be involved in mammalian brain development (473-477) and the especially protracted, extensive, and "plastic" nature of the lifelong myelination process in human brain (see sections 3.3. and 3.4.) (Figure 2).

Cholinergic treatments are the mainstay of treatment for AD and have been shown to improve both cognition (and in particular processing speed (478)), as well as the vast array of behavioral syndromes (including psychoses) associated with this disease (479). The substantial proportion of patients with Alzheimer's that develop psychosis may be especially benefited from such treatments (480). Conversely, *anti*cholinergic drugs are well known to be capable of inducing psychotic symptoms and cognitive deficits in both young (481) and elderly individuals (482, 483).

Cholinergic treatments have been hypothesized to have promyelinating effects (reviewed in 121). The cognitive impairments and psychosis-inducing potential of anticholinergic drugs can also be considered from the prospective of myelin. It is proposed that anticholinergics interfere with cholinergic stimulation of oligodendrocytes, compromise myelin, and thus degrade myelin-dependent network synchronicity on which optimal brain function depends (section 3.3. and 3.4.). The psychotic symptoms produced by anticholinergic drugs (481-483) can thus reconceptualized to be the result, at least in part, of interference with myelination, its maintenance and/or repair rather than an exclusive neuronal cholinergic receptor effect. Conversely, the beneficial effects of cholinergic stimulation in AD (480, 484, 485) can also be considered from the perspective of promoting myelination. In this context, it is not surprising that beneficial effects have also been observed in SZ (486) (reviewed in 121).

9.3. The dopaminergic system and myelination

Catecholamines can affect oligodendrocytes and their progenitors (470-472). Myelin-specific toxins such as

cuprizone are associated with dopamine disturbance and antipsychotic medications mitigate this damage (364) (see section 7). Knock out mouse models also support a strong relationship between dopamine and myelin (30). NRG1-erbB signaling is important for oligodendrocyte development and both NRG1 and its ErbB4 receptor are genetically linked with susceptibility to SZ and BD (see section 2.1. and 8). Transgenic mice in which ErbB signaling is specifically blocked *only* in oligodendrocytes leads to changes in oligodendrocyte number and morphology, reduced myelin thickness, and slower conduction velocity in specific regions such as corpus callosum and basal ganglia that suggest primary effects on earlier-myelinating circuits. Importantly, these mice also manifested increased dopamine receptor and transporter levels and behavioral alterations consistent with neuropsychiatric disorders (30). In primates and humans however, even an apparently "limited" effect on oligodendrocyte progenitors may have far reaching consequences since progenitors continue to differentiate and myelinate into middle age and beyond (section 4.4.). Thus a wide spectrum of early- to late-myelination as well as remyelination of damaged/lost segments may be mediated through effects on progenitor cells (reviewed in 9, 121) (section 4.6.).

Strikingly, all currently available antipsychotic medications share dopamine receptor blockade as a principal if not only known *shared* effect, and their dopamine-2 receptor affinity is highly correlated with their clinically effective dose (362). Furthermore, dopamine receptor agonists may have protective effects on oligodendrocytes (472) and antipsychotics have shown effectiveness in multiple disorders that do not necessarily involve psychotic symptoms (see section 8). Dopamine receptor blockers such as haldol promote oligodendrocyte precursors proliferation but may actually inhibit their differentiation into myelinating cells (365). On the other hand, dopaminergic treatments may promote myelination (471) and protect oligodendrocytes from metabolic and excitotoxic insults (472) while *excess* dopamine, caused by drugs of abuse such as methamphetamine and cocaine for example, may damage myelin (487), arrest myelination (488, 133), and cause or exacerbate psychotic symptoms (reviewed in 362). Dopamine receptor blockade can produce secondary upregulation of dopamine receptors that is associated with extrapyramidal side effects and loss of efficacy (489) however the effect of such blockade on oligodendrocytes remains unexplored.

A striking dichotomy of dopamine metabolism exists in different brain regions. In subcortical structures such as the basal ganglia and nucleus accumbens, dopamine transporters clear the vast majority of released dopamine (490, 491). In the prefrontal cortex however, dopamine transporters are sparse (492) and reuptake of dopamine is primarily dependent on norepinephrine transporters and catecol-O-methyltransferase (COMT) (493) which catalyses the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to catecholic compounds (494, 495) and is responsible for approximately half the dopamine metabolism (493). The most common COMT single nucleotide polymorphism (G -> A transition at codon 158 (rs4680)) is associated with a greater than two-fold decreases in enzyme activity and increased dopamine levels especially in prefrontal cortex (496, 497). Most COMT is associated with glia and especially oligodendrocytes (498, 499) and its polymorphisms have been associated with a variety of neuropsychiatric diseases (500, 501), cognitive function (502), and treatment responsiveness (503-507). Although evidence of interactions between COMT and neuregulin and GABA polymorphisms exist (495, 508), no data that pertain to oligodendrocytes has been published. Nevertheless, COMT alleles have been associated with brain volume changes (509-511) and associations between intelligence and white matter integrity measures (512, 513).

Furthermore, although the dopamine blockade occurs within minutes, the therapeutic effects of antipsychotics can take days to weeks. We postulate that both the therapeutic effects of antipsychotics (see below) and the counter therapeutic/toxic effects of drugs of abuse (section 7) may act, at least in part, through changes in the myelination process. The delay in the therapeutic effects suggests an indirect mechanism. The common dopamine receptor blockade triggers a homeostatic response on the part of neurons to increase dopamine release in specific cortical regions and layers (514). The dopamine from non-synaptic neuronal buttons could create/reinforce the "normal" *neuronal circuit-directed stimulus* for myelination. This *directed* signaling may increase myelination of *appropriate* axons, improve network synchrony and function, and thus eventually manifest in decreased clinical symptoms and improved cognition. On the other hand, *indiscriminate* drug-induced dopamine increase could also promote myelination in a "random" fashion that is not responsive/directed by neuronal circuits to specific regions and/or cortical layers. This could degrade rather than optimize network synchrony and function and thus worsen or produce de-novo clinical symptoms. Furthermore, stimulants such as methamphetamine and cocaine could be directly toxic by markedly increasing extracellular levels of dopamine whose oxidative metabolism can cause secondary toxicity to oligodendrocytes and precursors (133, 515). These effects may contribute to the consistently observed "U" shape relationships between dopamine and measures of brain structure and function (502, 511, 512, 516) that suggest an optimal amount of dopamine is flanked by suboptimal low and high amounts.

Consistent with clinical observations, the euphoric effects of drugs of abuse would be immediate (e.g., synaptic), accounting for their highly reinforcing properties. Their ability to trigger rapid psychotic symptoms would depend on whether the network circuitry of drug users is already dysfunctional, as would be the case with psychiatric patients that abuse these drugs. Conversely, healthy individuals who would be presumably further from the "brink" of brain dysfunction (e.g., "recreational" users) would be less likely to suffer immediate psychotogenic effects but may experience such symptoms after substantial cumulative/toxic exposure (362).

10. CONCLUSIONS ON NEUROGLIALPHARMACOLOGY

For optimal brain function, no class of cells is dispensable. Despite the focus on oligodendrocytes, the goal of this work was to redirect a greater proportion of research attention to the role of glia in general and the importance and complexity of neuron-glial interactions (summarized in Figure 4). In order to help dissipate the historic artificial divide between neurons and glia, a more appropriate nomenclature (e.g., neuroglialpharmacology) may better serve both clinical and research enterprises.

Vertebrate brain function and especially the very recently evolved capabilities of human brain are dependent on our species' pervasive and dynamic process of myelination. The tremendous post-natal elaboration of myelin and its key role in synchronizing neuronal networks and optimizing cognitive and behavioral functions have arguably earned oligodendrocytes the status of "the cells that make us human" and raises the prospect that, in the cognitive and behavioral spheres, humans may be best described as "myelin beings". The tremendous success of homo sapiens is a testament to the amazing power of this adaptation. Our specie's very recent evolution however has denied this most recent brain elaboration the time needed for continued improvement and may be contributing to common occurrence of myelin deficits during its development as well as age-related deficits in its maintenance and repair. This has earned oligodendrocytes and the myelin they produce the status of the "weakest link" of the human brain and may help explain the tremendous burden of psychiatric disease our species suffers from during all life stages.

A century of neuron-centric under-appreciation of the importance, vulnerability, and dynamic lifelong elaboration of our brain's myelination have unfortunately also helped undermine progress in clinical and research endeavors into both normal brain function and disease-related abnormalities. Herein an attempt is made to show that both clinical treatment and research endeavors may be converging onto glia and oligodendrocytes in particular as the indispensable key for understanding function as well as dysfunction of the human brain (summarized in Figure 4). The wide spectrum of efficacy of several classes of existing medications, the shared metabolic effects of pharmacotherapy, and beneficial effects nutritional supplements such as O3FA and NAC supports the possibility that treatment efficacy may well be primarily associated with protecting (section 7), nurturing (section 5 and 6), and promoting maturation (section 8 and 9) of glia and especially oligodendrocytes and myelin. The myelin model of the brain may also help dismantle artificial barriers created by the clinical symptom clusters on which disease classification is currently based and may provide more parsimonious explanations for substantial portions of symptomatology, pharmacology, and pathology of several common diseases. Thus, decrements in the timing of action potentials and synchronous interaction of neuronal networks may result in behavioral and cognitive dysfunctions that secondarily result in clinical symptom clusters despite different etiologies.

Current clinical categorizations such as the DSM do not "fit" either the wide spectrum of efficacy of available treatments nor the preexisting metabolic abnormalities associated with some psychiatric diseases. Furthermore, metabolic abnormalities and weight increases associated with pharmacologic treatments also do not segregate neatly into our clinical diagnostic classifications. The totality of the data seems to suggests that several mechanisms (e.g., metabolic, toxic, developmental, maintenance, and repair-related) may be shared between diseases in various proportions and imply that perpetuating the historic and imperfect artificial divide between diseases into discrete categories based on symptoms may have become counterproductive.

A better understanding of the human condition cannot easily occur without an increased appreciation of the continual and interrelated dynamic changes that influence trajectories of change. For example, repair of subcortical myelin produces shorter myelin segments altering transmission speed and thus triggers compensatory changes in intracortical myelin (ICM) for optimal function to be restored (section 3.3 and Figure 4). The under-appreciation of dynamic brain changes that occur throughout the lifespan has likely contributed to the myriad of contradictory findings in the literature. This is much worse that the parable of three blind men touching different parts of an elephant and coming to widely differing conclusions. The difficulty in arriving at the correct conclusion is greatly amplified if, in addition to different body parts, they are examining a mixture of newborns, adolescents, and adult elephants. Since the timeline/trajectory of myelination differs amongst networks, the clinical and research community has an even more complex problem to overcome.

The hypotheses delineated above are testable through *in vivo* imaging technologies that provide new avenues of assessing the trajectory of human myelin development and its subsequent breakdown (39, 161, 517, 518), as well as receptor changes in both gray and white matter (519-521). These technologies, together with genetic as well as clinical and cognitive measures make it possible to directly test in humans the practical utility of the myelin-centered model to accelerate medication development. The lifespan trajectory framework together with these new technologies can be imbedded into clinical trials to help foster the development of novel treatments, as well as assessing the efficacy of currently available treatments (9, 121). It is possible that much of the wide spectrum of efficacy of available treatments is due to improved oligodendrocyte protection, and promotion of myelination and myelin repair. Such effects on the brain's vulnerable oligodendrocyte populations may offer exciting opportunities for treatment as well as primary prevention of both developmental and degenerative brain disorders and deserve much closer scrutiny (7, 9).

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