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REVIEW

White matter pathways as both a target and mediator of health behaviors

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Health behaviors arise from the dynamics of highly interconnected networks in the brain and variability in these networks drives individual differences in behavior. In this review, we show how many factors that predict the physical health of the body also correlate with variability of the myelinated fascicles, called white matter, that connect brain regions together. The general pattern present in the literature is that as predictors of physical health decline, there is often a coincident reduction in the integrity of major white matter pathways. We also highlight a plausible mechanism, inflammatory pathways, whereby health-related activation of the immune system can impact the myelin sheath, a protective tissue that facilitates long range communication in the brain. The growing body of evidence supports the hypothesis that degrading health in the periphery may disrupt the communication efficiency of the macroscopic neural circuits that mediate complex behaviors, which can in turn contribute to poorer physical health.

Keywords: health; white matter; myelin; diffusion tensor imaging; inflammation

Introduction

Complex forms of human cognition, such as motivation, attention, decision making, and reward perception, all rely on the effective communication between billions of neurons that operate as immensely interconnected networks in the brain.[1,2] Variability in these forms of high-level cognition also associate with individual differences in behaviors such as eating habits, smoking, and engaging in physical activities that can directly impact the peripheral health of the body.[3–9] This means that individual differences in health behaviors may be driven, at least in part, by differences in the connectivity of macroscopic brain networks.

The function of brain networks is constrained by the structural connectivity between brain regions. Long-range communication in the brain, across distances of centimeters, relies on dense bundles of axons that are known as white matter.[10] These fiber bundles are supported by the myelin sheath, a tissue composed of nonneuronal glial cells that facilitate the conduction of action potentials across long cellular distances. The myelin sheath is thought to be critical for synchronizing information transmission between distal brain areas, thereby fostering the ability of these networks to adapt over time.[11,12] Demyelination or disruption of the myelin sheath thus impairs the ability of brain networks to function properly,[13] affecting those high-level cognitive abilities that are critical for health behaviors.

When discussing the underlying mechanisms of health behaviors, there is often the implicit assumption that inherent differences in neural architecture drive individual differences in behavior. However, a variety of socially and behaviorally mediated processes can directly or indirectly impact the brain, including the myelin sheath. This means that it is possible for the outcomes of health behaviors in the peripheral body to contribute to reduced communication efficiency in the central nervous system. Here, we review the emerging evidence that health in the periphery associates with the architecture of white matter pathways. We begin by providing a brief review of the primary measurement method

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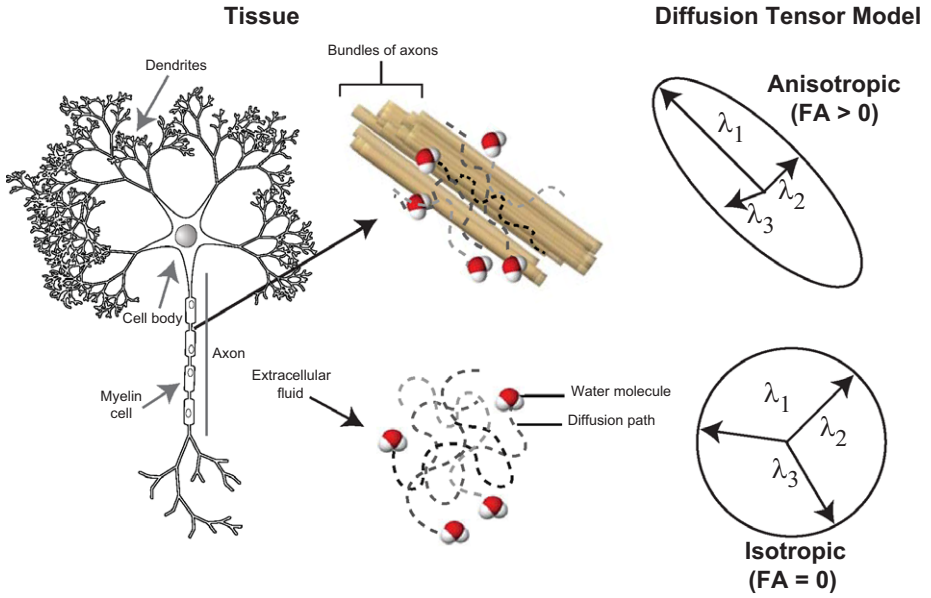

Figure 1. The origin of the DWI signal. On the left is a representation of a myelinated neuron. Cellular features such as microtubules within axons and cellular walls form a barrier that restricts the diffusion of water molecules within the cell. The diffusion properties of these water molecules are fundamentally different from that of unconstrained water that exists outside of the cell. Individual DWI images are sensitive to the speed and density of water diffusion in a given direction. The DTI approach to DWI reconstructs the speed of water diffusion within a voxel by fitting the collection of DWI images in many directions to a tensor model. This produces three orthogonal vectors ($\boldsymbol{\lambda}_1$, $\boldsymbol{\lambda}_2$, $\boldsymbol{\lambda}_3$) that show the most variance across the set of DWI images. Restriction of water molecules within an axon would result in an anisotropy of the three vectors (i.e., $\boldsymbol{\lambda}_1 > \boldsymbol{\lambda}_2 + \boldsymbol{\lambda}_3$), producing a high FA value, whereas without cellular barriers the diffusion of water molecules occurs in any direction equally (i.e., $\boldsymbol{\lambda}_1 = \boldsymbol{\lambda}_2 = \boldsymbol{\lambda}_3$), resulting in an FA value near zero.

of *in vivo* white matter, called diffusion-weighted imaging (DWI). We then review evidence of associations between measures of health in the peripheral body and structural connections in macroscopic brain networks, including the emerging evidence that white matter serves as an indirect pathway linking health outcomes in the body to cognitive function. We end by identifying one plausible physiological mechanism, inflammatory pathways, whereby behaviorally induced changes in the body could impact cellular pathways in the central nervous system. Taken together, the evidence suggests that the brain, behavior, and the body are reciprocally related such that behaviorally driven changes in peripheral health could impact the structural connectivity of neural circuits that, in turn, give rise to behaviors that impact the health of the body.[3]

Measuring white matter *in vivo*

The most commonly used noninvasive method for measuring white matter pathways in the living brain is DWI. DWI is a magnetic resonance imaging approach that takes advantage of the fact that cellular walls form a barrier that restricts the diffusion of water molecules within the cell (Fig. 1). Since axons are shaped like tubes, the diffusion of water molecules within axons is highly restricted along one dimension (i.e., it is anisotropic), with greater diffusion speed and density along the direction of the axon itself. Thus, DWI is able to indirectly quantify the structure of the large white matter pathways by calculating the direction and restriction of water molecules within axons. Analysis of white matter microstructure is estimated based on whether or not water is moving freely (isotropic) or restricted (anisotropic) within brain tissue in a volumetric pixel (known as a voxel), usually spanning a few millimeters in size. DWI assumes that stronger directional patterns in the estimated water diffusion patterns reflect underlying axon bundle density and orientation. Because DWI is sensitive to tissue properties within a couple millimeters of space, we will use the term "microstructure" to refer to the

underlying characteristics of tissues that contribute to the DWI signal.

One of the most commonly used DWI techniques is a method called diffusion tensor imaging (DTI).[14–18] DTI is a model-based approach that reconstructs the speed of water diffusion in any given direction within a voxel by fitting the DWI data to a tensor model. This produces three orthogonal vectors (right side of Fig. 1), each reflecting both the direction and degree of water diffusivity, that show the most variance across DWI samples. These three vectors are used to produce several metrics of the underlying tissue within a voxel. Fractional anisotropy (FA) is the most commonly used metric in DTI studies.[19] FA reflects the orientation of water diffusion, with an FA value of 1 suggesting that water is moving in a perfect linear direction, consistent with all water molecules within a voxel being constrained by axons or other cell structures.[20,21] An FA value of zero would indicate that water diffusion appears perfectly spherical, suggesting no cell walls are present and water is moving in any direction at an equivalent rate. Axial diffusivity (AD) corresponds to water diffusivity of the major axis (λ_1 in Fig. 1) parallel to the largest bundle of axons and approximates both fiber coherence and axonal integrity. Radial diffusivity (RD) measures diffusivity along the orthogonal plane to λ_1 ($\lambda_2 + \lambda_3$ in Fig. 1), describing the degree to which water diffusivity is perpendicular to the major axis (i.e., AD) and is thought to reflect the diameter of fiber bundles and possibly the integrity of the myelin sheath (see next paragraph). Finally, mean diffusivity (MD) reflects the average magnitude of diffusion, independent of the shape of diffusivity pattern. While these diffusivity measures are the most commonly used DWI metrics, other nondiffusivity measures using model-free reconstruction approaches (e.g., see Refs. 22 and 23) have also grown in popularity over the last 10 years; however, to date, DTI remains the most popular DWI method, particularly for health neuroscience researchers.

One useful aspect of DWI is that it appears to be sensitive to both developmental[24] and experience-dependent[25,26] plasticity in white matter pathways. The time scale of these changes is relatively slow, occurring over weeks, months, or even years. Recent work in our lab estimated that local architecture of all macroscopic white matter pathways in the brain changes at a rate of 13% every 100 days, meaning that two DWI images of an individual's white matter pathways would be only 87% similar after 14 weeks.[27] While one study found that experience-dependent plasticity detected in the DWI signal was coincident with increased myelination,[28] suggesting a relatively long-term reconfiguration of neural connectivity with learning, the extent to which this longitudinal variability reflects permanent structural changes or temporary changes in white matter pathways has yet to be conclusively determined.

The extent to which the DWI signal generally reflects meaningful patterns in underlying cellular systems remains largely elusive. Animal models of demyelination disorders have suggested that decreases in AD strongly coincide with direct axonal damage[29–31] and increases in RD to coincide with demyelination.[32–34] A more recent study integrating DTI with Clear Lipid-exchanged, Anatomically Rigid, Imaging/immunostaining compatible, Tissue hYdrogel (CLARITY), a tissue staining technique that allows for the visualization of target proteins in the whole intact postmortem brain in rodents, found that variability in FA across most white matter pathways is predominantly associated with myelin content, specifically levels of myelin basic protein (MBP) within a voxel, whereas RD only associated with myelin in a subset of pathways.[35] This suggests that differences in FA largely reflect aspects of myelin systems, rather than axon properties themselves. However, the strict link between white matter integrity and DTI-based diffusivity measures is not always so straightforward given the complex tissue structures within a voxel (e.g., see Refs. 36–38). Therefore, some caution must be applied when inferring how variation in the tensor properties of the DWI signal relates to the underlying white matter microstructure.

Associations between peripheral health and white matter

Over the last decade, a growing body of research using DWI has shown a consistent relationship between direct and indirect predictors of peripheral health and estimates of white matter microstructure. In most cases, these observations rely on correlating cross-sectional variability in a health predictor with a particular DWI-based metric, either at the voxel, region of interest, or fascicular (i.e., large white matter bundle) level. Table 1 presents a summary of all the DWI studies mentioned in this section.

Table 1. A summary of significant associations between health predictors and DWI measures

	N (%M)	Age (years)	Health predictor	FA	AD	RD	Other
Marks *et al.*[a,b]	15 (53%)	60–72	BMI	−−			
Mueller *et al.*[c]	49 (53%)	20–31	BMI	−− (Females only)	−−	++ (Females only)	
Stanek *et al.*[c]	103 (55%)	21–86	BMI	−−			
Verstynen *et al.*[d]	28 (39%)	18–69	BMI	−−	−−	++	
Xu *et al.*[c]	51 (58%)	18–40	BMI	−−	−−	++	MD: ++
Karlsson *et al.*[d]	45 (27%)	40–50	BMI	−−			MD: −−
			BFP				
Gianaros *et al.*[a,c]	155 (50%)	30–50	WC	−−			
Verstynen *et al.*[d]	155 (50%)	30–50	BMI	−−		++	
			WC				
Ryan *et al.*[b]	94 (0%)	52–92	BMI	−−	−−	++	
Alosco *et al.*[c]	120 (58%)	6–18	BMI				
Yau *et al.*[d]	140	14–21	BMI	−−			
			WC				
He *et al.*[c]	336 (42%)	18–24	BMI	−−			
Bolzenius *et al.*[e]	62 (32%)	51–81	BMI	−−			
Spieker *et al.*[c]	761 (42%)	18–81	BMI	−−			
			WC				
Shott *et al.*[d]	42	27–36		−−			
Van Bloemendaal *et al.*[c]	48 (50%)	55–63	BMI		−−		
Figley *et al.*[d]	32 (50%)	18–60	BMI	+/−			MD: ++
			BFP				
Yeh *et al.*[e]	60 (46%)	18–45	BMI				QA: −−
Chen *et al.*[c]	36 (0%)	18–23	BMI	−−			
			BFP				
Papageorgiou *et al.*[c]	268 (43%)	30–62	BMI	−−			
Birdsill *et al.*[c]	168 (43%)	40–62	BMI	++	−−	−−	MD: −−
			WC				
Zhang *et al.*[c]	1255 (50%)	19–80	BMI	−−			
			WHR				
Marks *et al.*[b]	28	21–74	VO_2	++			
Marks *et al.*[a,b]	15 (53%)	60–72	VO_2	++			MD: −−
Johnson *et al.*[c]	26 (46%)	60–69	VO_2	++		−−	
Voss *et al.*[c,f]	70 (35%)	55–80	VO_2	++			
Schaeffer *et al.*[b,f]	18	8–11	VO_2	++		−−	
Chaddock-Heyman[c]	12 (66%)	9–11	VO_2	++			
Hayes *et al.*[c]	59 (45%)	18–82	VO_2	++			
Oberlin *et al.*[a,c]	113 (36%)	60–81	VO_2	++			
Oberlin *et al.*[a,c]	154 (31%)	60–80	VO_2	++			
Jacobsen *et al.*[d]	67 (38%)	13–18	CS-E	++			
Phil *et al.*[b]	20 (50%)	26–50	FTND	+/−			
Zhang *et al.*[c]	96 (50%)	23–39	FTND	−−			
Liao *et al.*[c]	88 (79%)	19–39	CS	++			
Gons *et al.*[d]	499 (57%)	57–73	CS-C	−−			MD: −−
Hudkins *et al.*[b]	36 (52%)	26–40	CS	+/−			
Lin *et al.*[c]	68 (80%)	33–58	FTND	−−	−−	++	
Gianaros *et al.*[a,c]	155 (50%)	30–50	CS-R	−−			
Savjani *et al.*[c]	62 (50%)	22–50	CS	−−	−−	++	MD: ++

Continued

Table 1. *Continued*

	N (%M)	Age (years)	Health predictor	FA	AD	RD	Other
Huang *et al.*[c,f]	97 (100%)	26–56	CS-C	+/– (Relapse)			
				– – (Quitters)			
				– – (Smokers)			
Chiang *et al.*[d]	705 (41%)	12–25	SEI	++			
Jednoróg *et al.*[c]	23 (43%)	8–10	Educ-MP				
			CP				
Gianaros *et al.*[a,c]	155 (50%)	30–50	Income	++			
			Educ				
			cSEP				
Noble *et al.*[c]	47 (44%)	17–23	Educ	++			
Molesworth *et al.*[c]	155 (50%)	30–50	SND	++		– –	
Ursache *et al.*[c]	1082 (52%)	3–21	Income-P	++			
			Educ-P				
Eluvathingal *et al.*[c]	7 (28%)	6–11	SD	– –			
Bick *et al.*[c,f]	69	8–11	SD	– –		++	MD: ++

Note: ++, Increased health predictor, overall positive association with DWI measure. – –, Increased health predictor, overall negative association with DWI measure. +/–, Generally mixed results.

[a]Study is cross-referenced under another health predictor.

[b]Manually traced region of interest analysis.

[c]Tract-based spatial statistics (TBSS), voxelwise analysis used to make comparisons on major white matter tracts common across subjects.

[d]Volexwise analysis, a univariate analysis correcting for multiple comparisons.

[e]Streamline analysis produces three-dimensional space curves from a seed point through the tensor field; the curve follows the orientation of the principle eigenvector across voxels.

[f]Intervention-based study.

BMI, body mass index; BFP, body fat percentage; WC, waist circumference; WHR, waist-to-hip ratio; VO_2, maximum volume of oxygen output; CS, cigarette smoking; CS-E, prenatal cigarette smoking exposure; CS-C, cigarette smoking cessation study; CS-R, rate of cigarette intake; FTND, Fagerström test for nicotine dependence; Educ, education; Educ-P, parental education; Educ-MP, maternal parent education; CSEP, community-level socioeconomic position; Income-P, parental income; SEI, socioeconomic index; CP, current profession; SND, social network diversity; SD, socioemotional deprivation; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity; QA, quantitative anisotropy.

One of the most consistent associations between a predictor of peripheral health in the body and white matter is obesity. Sena *et al.* initially found that mutant mice who were genetically predisposed to obesity had significantly lower levels of myelin throughout the brain, compared to nonmutant control mice.[39] This drop in myelin was not associated with reductions in other fatty and enzymatic tissues, suggesting a specific impact on myelin itself. More recent DWI studies have found a similar pattern in humans. Human studies typically measure obesity, or adiposity, using either body mass index (BMI), waist circumference, or direct measures of fatty tissues (e.g., dual-energy X-ray absorptiometry; DXA). In general, these obesity measures largely correlate with lower DWI-based estimates of white matter microstructure. Most studies in the literature use cross-sectional analysis and observe a distributed negative link between obesity and FA throughout the brain.[40–56] For example, work by our group found that 24 of the 27 white matter regions of interest tested were significantly associated with BMI, such that individuals with higher BMI had lower FA.[40] In some cases, the association between obesity and lower FA coincides with a trend for lower AD and higher RD as well.[40,42,46,48,49] Yet, there are some exceptions to this general pattern. Mueller *et al.* found that while both men and women demonstrated the expected negative correlation between BMI and AD, only women expressed a positive association between BMI and RD.[46] In other cases, the negative correlation between obesity

and FA is more mixed, with a subset of white matter pathways showing a positive relationship.[44,49,57] One potential reason for this inconsistency is that age may play a moderating role in the relationship between obesity and white matter, with at least one study failing to find an association between BMI and FA in a large sample of children and adolescents.[58] Of course, some of these inconsistencies may result from the limitations of diffusivity-based measures in quantifying white matter microstructure in voxels with multiple, crossing fiber pathways (e.g., see Refs. 36 and 37). Indeed, work in our lab using non-diffusivity measures of the DWI signal that are not as sensitive to the crossing fiber problem also shows a largely negative association between obesity and white matter signal.[21]

Of course, the associations between obesity and DWI estimates of the white matter architecture may simply be epiphenomenal in nature and have little relation to the well-established association between obesity and cognitive function. Yet, emerging evidence suggests that the microstructural characteristics of white matter may serve as a critical mediator between obesity and cognition. Zhang *et al.* recently reported the results of a statistical mediation analysis looking at obesity, white matter, and cognition links in a large sample of 1255 adults from the Leipzig Research Center for Civilization Diseases (LIFE-Adult) cohort.[54] Consistent with the general pattern of associations reported in Table 1, they observed a distributed negative correlation between measures of obesity (BMI and waist-to-hip ratio) and FA in association with white matter pathways (i.e., fascicles that connect association areas of cortex), including the superior longitudinal fasciculus, inferior longitudinal fasciculus, anterior thalamic radiations, and corpus callosum. FA in these same pathways was positively associated with neuropsychological measures of executive function and processing speed. Most importantly, FA in the association pathways provided an indirect pathway linking individual differences in obesity to individual differences in executive control and processing speed. In most cases, these indirect effects persisted even after controlling for age, gender, education, APOE status, and other health comorbidities. These effects of white matter structure serving as an indirect link between measures of obesity and cognitive function largely agree with patterns reported elsewhere.[42] Although these studies are cross-sectional designs, they provide confirmatory evidence that obesity–white matter associations may impact cognitive function.

The peripheral health associations with white matter are not limited to body fat composition. Cardiorespiratory fitness, measured as maximum volume of oxygen ($VO_{2\,max}$) consumption, also associates with white matter microstructure. In particular, individuals with higher $VO_{2\,max}$ output also have higher FA throughout the brain.[53,59–63] Several studies have also found that $VO_{2\,max}$-related variance in FA coincides with reductions in RD, but not AD.[63,64] Thus, cardiorespiratory associations with white matter may be tied specifically to variability of the myelin sheath.

This link between cardiorespiratory fitness and white matter also appears to have implications for cognitive function. Using a statistical mediation analysis on two large cross-sectional cohorts of healthy older adults, Oberlin *et al.* found that FA in a distributed network of white matter pathways, including anterior corona radiata, anterior internal capsule, fornix, cingulum, and corpus callosum, served as an indirect pathway linking $VO_{2\,max}$ to spatial working memory function.[60] This cross-sectional analysis suggests that individuals with greater cardiorespiratory fitness had better spatial working memory abilities due, in part, to greater microstructural integrity of white matter pathways.

One important advantage of cardiorespiratory health is that it is effectively modulated by aerobic exercise interventions, allowing for experimental interventions that directly manipulate the cardiorespiratory fitness and white matter association. Indeed, aerobic exercise interventions have been reported to lead to a global increase in FA.[64,65] For example, Schaeffer *et al.* found that after just 8 months of aerobic exercise, children and adolescents who underwent a moderate exercise intervention exhibited increased FA in the bilateral uncinate fasciculus and decreased RD in the left uncinate fasciculus, consistent with improving myelin integrity of a pathway important for emotional and behavioral regulation.[64] This pattern of exercise-related changes in the DWI signal corresponds with similar observations in rodents. For example, adult mice given the option of exercising on a running wheel show reduced swelling in glial cells and enhanced myelin content after 6 weeks of exercise, compared to control mice not provided access to a

running wheel.[66] Thus, while the available literature on aerobic exercise interventions and white matter integrity is limited, it does suggest a direct causal relationship whereby improvements in cardiorespiratory fitness lead to improved estimates of microstructural integrity of white matter pathways.

A related cardiovascular health predictor with links to white matter pathways is smoking. Smoking exposure, duration, and intake are all associated with variability in DWI measures, albeit in somewhat mixed ways. For example, exposure to smoking in early adolescence associates with higher FA, particularly in pathways that connect cortical association areas, like the cingulum bundle.[67] While some studies interpret this higher FA in adolescent smokers as reflecting an early rise and later fall in FA into adulthood,[68] the analysis of adult smokers is somewhat inconsistent with this model. For instance, studies measuring chronic smokers saw region-specific increases in FA[68–72] while other studies have shown smoking to be associated with globally lower FA.[68,72–76] Smoking cessation studies show higher regional FA in right cerebellum and white matter pathways near the right postcentral gyrus, while lower FA in white matter pathways projecting to the orbitofrontal cortex, among those who relapsed compared to quitters,[72] leading to the argument that smoking contributes to long-term alterations in these pathways that bolster addictive behaviors. This interpretation is complicated by the observation that 24-hour abstinent smokers appear to have decreased FA and AD, along with increased RD in corpus callosum compared to those who have never smoked.[76] Even smokers who remain abstinent for over 20 years appear to have decreased FA and MD in regions that match those who have never smoked.[70]

The inconsistencies found at the fascicular level with regard to smoking–white matter associations in human neuroimaging studies also appear at the cellular level in rodent studies. For example, Cao *et al.* examined gestational nicotine intake in Sprague–Dawley rats, revealing mixed results in terms of age and sex on smoking–myelin associations, noting increased measures of myelin gene expression in prefrontal cortex and the striatum for adolescent males that normalized by adulthood, while females exhibited decreases in prefrontal and nucleus accumbens myelin in adolescence that normalized by adulthood with decreased expression in the striatum.[77] Yet, mouse models of cigarette smoke exposure in adulthood suggest that it broadly reduces myelin synthesis and maintenance that could not be reversed by short-term withdrawal.[78] These largely mixed results on the direction of the link between smoking and white matter architecture suggest a more complex relationship compared to obesity or cardiorespiratory fitness; however, the emerging findings do make it clear that smoking does have a strong association with the integrity of the underlying white matter systems.

Obesity, cardiorespiratory fitness, and smoking all largely reflect aspects of peripheral health that are specific to the individual. Yet, it is known that environmental and social factors also predict health outcomes of the individual.[79] Many of these social and environmental predictors of health in the periphery have also been associated with white matter microstructure. For example, socioeconomic status (SES) indicators, such as income, education, or markers of the general SES of an individual's neighborhood,[80,81] positively correlate with white matter, such that higher SES indicators associate with stronger FA.[75,82–84] In our collaborative work with colleagues, we found that multiple indicators of SES positively associated with FA throughout the brain and that this relationship was statistically mediated by health behaviors such as smoking and central adiposity (i.e., waist circumference).[75] This lead us to infer that the SES–brain associations were largely driven by the influence that access to resources has on determining health behaviors. Although, it is worth pointing out that the association between SES indicators and DWI-based measures of white matter microstructure is not always consistent in the literature. For example, Jednoróg *et al.* found that while parental SES correlates positively with the morphology of gray matter regions in children, there was no reliable association between parental SES and FA present.[85] This suggests that the general relationship between SES indicators and white matter may be moderated by other factors, such as age.

Emerging evidence suggests that the observed SES–white matter association may play a role in indirectly associating SES indicators with cognitive control. Noble *et al.* applied a cross-sectional statistical mediation analysis, with white matter measures serving as an indirect pathway linking educational attainment to cognitive control, to a

subset of 47 healthy individuals ranging from 17 to 23 years old.[82] Consistent with the general pattern of associations reported in Table 1, the authors found a positive correlation between measures of educational attainment and FA in the superior longitudinal fasciculus. More importantly, this positive education–FA association served as an indirect pathway linking more education with greater cognitive control abilities, even after adjusting for age effects. While this finding presents positive evidence that white matter mediates a health-related SES indicator (education) to high levels of cognition, this pattern is not consistently observed in the SES literature. For example, a recent study by Ursache and Noble found that white matter failed to mediate a relationship between parental education levels and inhibitory control of their offspring.[84] Although, the inconsistencies in the literature may be attributed to the complexity of quantifying SES via generalized metrics. For example, education is composed of many underlying components that may differentially relate to both white matter pathways and cognition.

Social isolation is another factor that both predicts health outcomes in the periphery[86,87] and associates with white matter microstructure.[88,89] Studies on orphaned Romanian children who were isolated during a critical period of development (<2 years old) reveal lower FA in the left uncinate fasciculus compared to controls.[88] Remarkably, early life intervention through the Bucharest Early Intervention Project revealed higher FA after 6 years of foster care.[89] Yet when compared to children raised in family settings, foster care children still exhibited lower FA and higher RD and MD in the corpus callosum. Even natural variation in social contact appears to relate to white matter architecture. For example, we used a measure of social network structure, that had previously been shown to be predictive of susceptibility to illness,[90] to look at how social network structure correlates with white matter microstructure in a large sample of community-dwelling adults.[91] In this experiment, we found that social network diversity, reflecting the number of high contact social roles that a person has, positively correlates with FA, and negatively correlates with RD, in several prefrontal white matter pathways, including the cingulum, corpus callosum, and corticostriatal pathways. More importantly, we found that individual variability in FA statistically mediates an indirect relationship between social network diversity and resting state functional connectivity within corticostriatal pathways that project to the rostral striatum, suggesting that the structural variability impacts the functional dynamics in brain circuits that play a critical role in action selection and value-based decision making.

The link between social experiences and white matter in humans mirrors closely what is observed during direct social interventions in other species. For example, socially isolated mice have decreased maturation of oligodendrocytes, one of the two types of myelin cells, compared to nonisolated controls.[92–94] This reduction in myelin integrity due to immediate postnatal social isolation does not recover after reintroduction to a social environment, suggesting a long-term alteration of the structural integrity of these white matter pathways.[93] However, this permanency may be due to the timing of the isolation during early development. Adult mice exposed to 8 weeks of isolation, followed by social reintegration for 4 weeks, show a recovery of myelin to control levels in the prefrontal cortex.[92] This impact of social isolation on the myelin sheath in rodents is consistent with the pattern of socially associated variability in the DWI signal observed in humans, providing supportive evidence that the DWI signal is picking up on real underlying variability in the myelin sheath itself.

The collective evidence from both individual level and social health predictors paints a relatively consistent picture of the relationship between peripheral health of the body and the architecture of white matter pathways in the central nervous system. In general, more negative predictors of peripheral health coincide with lower levels of FA throughout the brain, sometimes associated with a greater RD or lower AD. This specific pattern is what would be predicted if the DWI signal were picking up on impacts to the myelin sheath, as opposed to destruction of axons themselves.[32–34] In the following section, we explore a possible mechanism that could provide a direct link between the health of the body and integrity of myelin.

Inflammation as a link between peripheral health and myelin integrity

Almost all of the negative health predictors that associate with white matter architecture, including obesity,[95–97] smoking,[98,99] social isolation,[80,100–103]

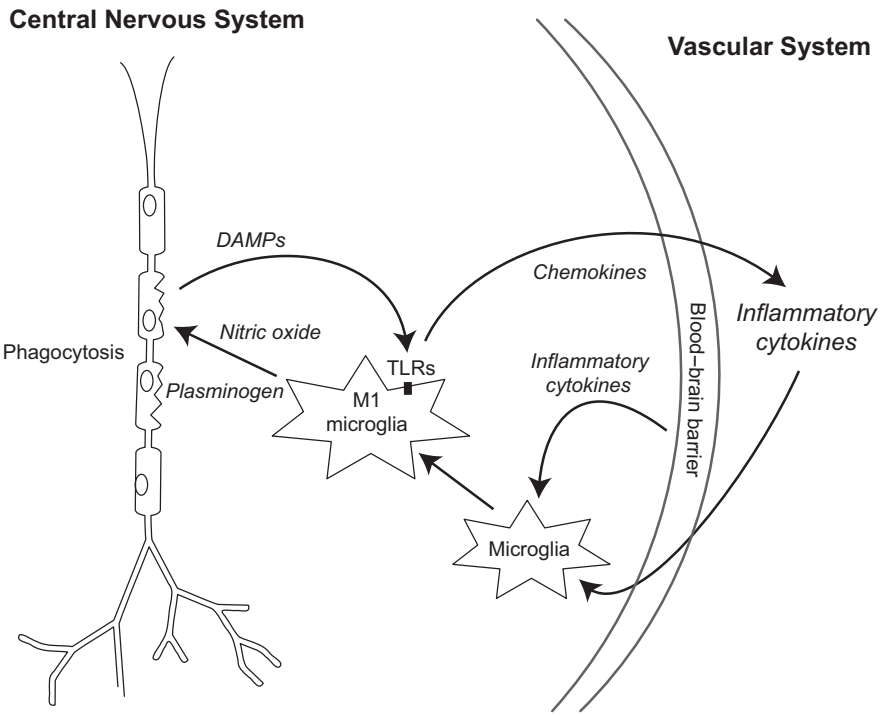

Figure 2. **Central feedback loop and cellular mechanisms of inflammatory demyelination. Inflammatory cytokines produced in the periphery enter the brain through the blood–brain barrier. Additional cytokines are generated by endothelial cells of the blood–brain barrier in response to peripheral cytokines. Microglia are also activated by the influx of cytokines, converting them into the M1 phenotype. M1 microglia produce plasminogen activator and nitric oxide that damage the wall of the myelin cell. In response, damage-associated molecular pattern molecules (DAMPs) bind to Toll-like receptors (TLRs) on the surface of microglia, signaling the recruitment of more monocytes, and even T cells from the periphery. This cycle repeats and results in demyelination in response to systemic inflammation in the periphery.**

and smaller social network structure[104,105] coincide with an increase in chronic systemic inflammation.[106] In contrast, improved cardiorespiratory fitness[107–111] and higher SES indicators[80,101] are associated with decreased systemic inflammation. This link with inflammation is informative because many demyelination disorders that damage white matter pathways, such as amyotrophic lateral sclerosis or multiple sclerosis (MS), arise from dysregulation of the body's inflammatory response. Indeed, even acute, subclinical increases in inflammation coincide with altered cognitive[112,113] and emotional regulation,[100,114] suggesting that subclinical activation of inflammatory pathways in the periphery may immediately impact the function of brain networks. In this section, we illustrate how chronic inflammation in the periphery can directly impact the microstructure of white matter pathways in the central nervous system.

The inflammatory response begins as a reaction to the presence of foreign entities or damaged cells that need to be removed. These factors are generally known as pathogen-associated molecular pattern molecules (PAMPs) and damage-associated molecular pattern molecules (DAMPs), both of which trigger an immune response to clear waste or potential pathogens.[115] Within the central nervous system, PAMPs and DAMPs compose part of a feedback loop designed to clear waste from neurons, preventing further damage, and possibly rebuild tissue.[116] In the instance of chronic inflammation, where the cytokine levels in the bloodstream are sustained at elevated levels, this loop cycles back on itself and can result in the targeting and damage of myelin cells (Fig. 2). This cycle starts in the periphery with the generation of inflammatory cytokines, including interleukin (IL)-6, IL-1β, IL-1, and tumor necrosis factor (TNF)-α, among others. These

inflammatory cytokines are also expressed by central adipose tissue, particularly white adipose tissue,[117–123] that is a critical reason why chronic inflammation increases with obesity. These inflammatory cytokines pass the blood–brain barrier in a variety of ways, including through saturable passive transport systems, active transport, and by triggering cells in the blood–brain barrier to release additional cytokines directly into the central nervous system.[124–127] The result is a local inflammatory response in the central nervous system that originates from inflammatory activity in the periphery. Once behind the blood–brain barrier, inflammatory cytokines signal the activation of microglia. Microglia are monocytes that change to M1 microglia when activated. These activated microglia then search for a foreign invader or waste to consume and remove from the environment, as well as releasing more cytokines that, in turn, recruit more microglia.

While this process is meant to remove waste and pathogens, there are many ways in which the activated microglia can also mistakenly damage healthy cells, including the myelin sheath. One such mechanism is by signaling something known as a plasminogen activator, which activates the transport of the protein plasmin.[128,129] Plasminogen cleaves MBP and breaks down the extracellular matrix of the cell wall itself, resulting in damage and cell death.[130,131] Interestingly, plasminogen may also increase permeability of the blood–brain barrier to other immune agents, including leukocytes and inflammatory cytokines,[132–134] thereby accelerating a feedback loop between the central nervous system and periphery that increases inflammatory activity.

This plasminogen pathway is not the only route by which activated microglia can damage the myelin sheath. Microglia also release nitric oxide, which at certain levels can result in cell death.[135–137] Interestingly, obesity and poor dietary habits correlate with higher levels of nitric oxide, oxidative stress, and neuronal death.[138] Thus, when inflammatory pathways activate microglia, there may be multiple mechanisms that result in subsequent myelin damage.

As if to accelerate this process, damage to myelin can result in further activation of local inflammatory pathways. For example, in response to damage, myelin releases DAMPs that bind to receptors on the microglia called Toll-like receptors (TLRs).[115] TLRs signal to local microglia that cells are threatened and damaged, requiring removal (phagocytosis). This then initiates the cycle again, as the microglia begin to locally produce inflammatory cytokines, thereby activating more microglia. Finally, as if to add further complexity to this process, the locally produced inflammatory cytokines can pass back across the blood–brain barrier and potentially trigger a secondary inflammatory response in the periphery.[124,139,140] In fact, research suggests that active microglia recruit lymphocytes from the periphery back across the blood–brain barrier and into the brain again.[141,142]

The role of inflammation as a mediator between the health of the peripheral body and white matter systems in the brain is supported by evidence in the neuroimaging literature as well. For example, work in our lab has shown that levels of IL-6 and C-reactive protein (CRP) in the bloodstream associated with lower FA throughout the brain and these inflammatory levels statistically mediated a relationship between obesity and FA.[49] In a similar analysis on the same cohort of subjects, we found that levels of CRP in the bloodstream indirectly linked socioeconomic inequality to global FA through health behaviors such as obesity and smoking.[75] Finally, our analysis of social network structure found that the FA in segments of white matter pathways that correlated with social network diversity also correlated with circulating levels of IL-6.[91] Thus, the neuroimaging evidence is consistent with the hypothesis that inflammatory pathways are a central mechanism linking health in the periphery with white matter microstructural integrity.

It is important to point out that any impact that chronic inflammation has on myelin appears to be predominantly expressed at subclinical ranges. Thus, while local damage to myelin tissue may be occurring, it does not appear to reach levels associated with demyelinating diseases or axon damage. This is important since it provides hope for recovery if improvements in health reduce the levels of circulating inflammatory cytokines. For example, at the cellular level, plasminogen activator inhibitors have successfully stopped the progression of demyelination in rodent models of MS.[143] Therefore, any interventions that can result in the reduction of plasminogen activator signaling could potentially attenuate any progressive effects on white matter tissue.

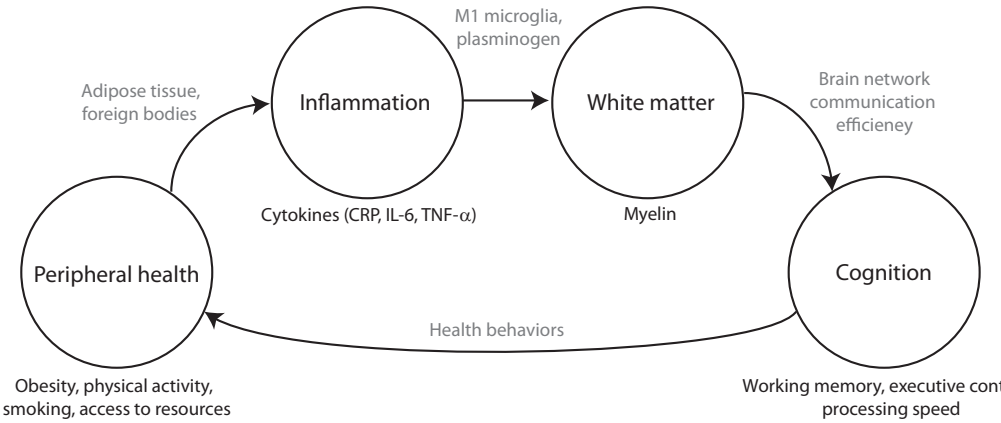

Figure 3. **A model from physical health to the brain and back again. The existing data suggest a model whereby reduced health in the periphery triggers inflammation, particularly the secretion of inflammatory cytokines that cross the blood–brain barrier and activate microglia that can damage myelin tissue in turn. Over time, this can impact those cognitive abilities that rely on these long-distance connections. This influence on cognitive function may then alter health behaviors and contribute to further reductions in peripheral health. Light gray terms shown in the figure refer to hypothetical mechanisms, while all other terms are based on reports in the current literature.**

While it is not clear yet whether targeting plasminogen activator through nonpharmaceutical interventions can effectively reduce the levels of plasminogen in the brain, studies have effectively targeted and manipulated nitric oxide levels through behavioral interventions. For example, a 3-week diet and exercise intervention significantly decreased nitric oxide levels in the urine of middle-aged obese adults.[144] More recently, a 16-week exercise intervention successfully lowered nitric oxide levels in individuals with obesity and type 2 diabetes.[145] Unfortunately, despite changes in nitric oxide, circulating inflammatory cytokines (i.e., IL-6, TNF-α) did not significantly decrease, nor was any assessment done to see how the white matter signal changes with lowered nitric oxide levels. Exercise also holds promise as an effective preventative therapy for inflammatory demyelination (for a review, see Ref. 146). Pryor *et al.* demonstrated that exercise attenuated demyelination in mice, a finding confirmed by subsequent studies.[147,148] These findings illustrate the potential for behavioral interventions that reduce plasminogen activator signaling during some of the critical stages in the pathways that lead to myelin damage.

In addition to prevention, myelin repair also appears to be possible. Remyelination is a commonly occurring process in the central nervous system and has the ability to be induced even in disease states.[149] Several rodent models have begun to tackle the possibility of initiating remyelination through exercise. Recently, Jensen and Yong presented findings that voluntary exercise increased remyelination of the spinal cord in mice after demyelination, with a 30% increase in oligodendrocyte population after 14 days and nearly a threefold increase in number of myelinated axons.[150] Similarly, Alvarez-Saavedra *et al.* found that voluntary exercise increased myelination in mice after 50 days.[151] Along with exercise, diet has also been examined as a possible facilitator of remyelination. Specifically, vitamin D supplementations have been shown to increase oligodendrocyte proliferation in rodents.[152,153] Thus, improvements in peripheral health, in particular cardiorespiratory health, appear to promote healing of myelin tissue. While there remain many open questions as to the nature and mechanisms of normal remyelination, it does suggest that improvements in health that reduce central inflammation may not only stop further myelin damage but may also allow for natural recovery of subclinical white matter damage over time.

Conclusions

A growing body of evidence suggests that the structural connectivity of macroscopic brain networks associates with the overall physical health of the body. Across a range of predictors of peripheral physical health, including both individualized

factors (e.g., obesity and cardiorespiratory fitness) and social factors (e.g., social isolation and SES), a general pattern emerges such that lower indicators of physical health correlate with reduced microstructural integrity of white matter tissue. We also highlight a plausible mechanism, inflammatory pathways, by which health-related changes in the periphery may directly target the integrity of white matter, in particular the myelin sheath. Based on the dynamics by which peripheral inflammation can impact myelin integrity, the evidence suggests a causal direction whereby degradation of health in the periphery leads to subsequent changes in communication across macroscopic brain networks, through inflammatory mechanisms that cross the blood–brain barrier and impact the myelin sheath, thereby influencing the complex behaviors that contribute to physical health. This model is outlined in Figure 3.

The possible role for inflammatory processes as a mechanism for linking changes in peripheral health to central white matter provides critical insights for potential interventions to alleviate health-related impacts on white matter. There are several pharmaceutical approaches for reducing inflammation, including many that target mild chronic inflammation. In addition, behavioral interventions such as aerobic exercise can lead to reductions in the levels of circulating inflammatory cytokines.[154] We have already shown how exercise can improve the white matter signal measured by DTI,[64,65] suggesting that these interventions are robust enough to improve white matter integrity. Yet, it remains unknown whether a reduction in inflammation mediates the recovery of the white matter signal as predicted here and whether these systems together mediate health–cognition relationships. If inflammation is mediating the health–white matter relationship and white matter mediates the health–cognition relationship, then recovery of white matter signal, and subsequent improvements in cognitive function, should be amplified through a combination of behavioral exercise interventions and regimens of anti-inflammatory medications. This leaves an ample number of open questions for longitudinal intervention studies to explore.

Here, we have advanced a specific model whereby the effects of poor health behaviors on the peripheral body are the primary mechanisms that increase chronic inflammation and lead to subclinical damage to myelin tissue. Yet there are in fact many mechanisms that both increase peripheral inflammation and associate with physical health outcomes. For example, psychological factors such as depression, stress, and anxiety are associated with elevated levels of inflammatory cytokines (for reviews, see Refs. 155 and 156), altered white matter pathways,[157–159] and poor health outcomes.[4] In addition, a large portion of the inflammatory response is genetically mediated. Expression of certain inflammation-related genes are also coincident with several mental and physical health outcomes such as depression[160] and obesity.[161] This link between genetics, inflammation, and health outcomes is likely bidirectional in nature, since interventions like diet-induced weight loss have been shown to regulate the expression of inflammation-related genes in adipose tissue.[162] The specific contribution of psychological and genetic factors to the pathways that we have outlined in this review should also be a focus of future work so as to provide a holistic understanding of health–brain–body relationships.

While we tried to highlight where the DWI findings overlap with observations in rodent models of myelin integrity, it is important to point out that studying health–white matter associations with DWI is particularly tricky due to the fact that many of the health predictors presented here also contribute to artifacts that lower DWI signal-to-noise.[163,164] This could lead to many spurious associations that do not directly relate to underlying white matter architecture, but instead reflect secondary artifacts in the DWI signal. Any study looking at health-related associations with white matter needs to take into account as many sources of noise as possible, as well as keep up to date on current denoising or artifact-identification procedures. In addition, this limitation points to a greater need to integrate health neuroscience work being done at the human level with animal models that allow for direct validation of underlying cellular integrity.

Despite these limitations and unanswered questions, the emerging evidence in the literature is clear. White matter pathways can serve as both a mediator of health behaviors, by facilitating the efficiency of cognition, and as a target of health behaviors, through sensitivity to chronic inflammation and its effects on myelin integrity. Explicating the precise roles that health-related changes in white matter

architecture contribute to health behaviors should be a major focus of future work.

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Competing interests

The authors declare no competing interests.

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