Received: 4 March 2020 | Revised: 19 May 2020 | Accepted: 22 May 2020

DOI: 10.1002/glia.23868

GLIA

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REVIEW ARTICLE

White matter alterations in Williams syndrome related to behavioral and motor impairments

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Funding information
Fritz Thyssen Stiftung; SPARK Tel Aviv; BrainBoost by Sagol School of Neuroscience, Tel Aviv University

Abstract

Myelin is the electrical insulator surrounding the neuronal axon that makes up the white matter (WM) of the brain. It helps increase axonal conduction velocity (CV) by inducing saltatory conduction. Damage to the myelin sheath and WM is associated with many neurological and psychiatric disorders. Decreasing myelin deficits, and thus improving axonal conduction, has the potential to serve as a therapeutic mechanism for reducing the severity of some of these disorders. Myelin deficits have been previously linked to abnormalities in social behavior, suggesting an interplay between brain connectivity and sociability. This review focuses on Williams syndrome (WS), a genetic disorder characterized by neurocognitive characteristics and motor abnormalities, mainly known for its hypersociability characteristic. We discuss fundamental aspects of WM in WS and how its alterations can affect motor abilities and social behavior. Overall, findings regarding changes in myelin genes and alterations in WM structure in WS suggest new targets for drug therapy aimed at improving conduction properties and altering brain-activity synchronization in this disorder.

KEYWORDS

clemastine, motor abilities, myelin, neuron–glia interaction, social behavior, white matter, Williams syndrome

1 | INTRODUCTION TO WILLIAMS SYNDROME (WS)

WS is a neurodevelopmental genetic disorder caused by the hemizygous deletion of approximately 25 genes on the long arm of chromosome 7 (7q11.23) (Korenberg et al., 2000). The deleted genes are part of the WS Chromosomal Region (WSCR). WS prevalence has been reported as approximately 1 in 7,500 (Stromme, Bjornstad, & Ramstad, 2002) and 1 in 20,000 individuals (Barak & Feng, 2016; Pober, 2010). WS is characterized by social abnormalities, such as hypersociability and the inability to inhibit social behavior, with a conflict of some individuals described as socially isolated, sharing many of the autistic characteristics (Laws & Bishop, 2004; Pober, 2010).

WS individuals usually have weak visuospatial skills (Mervis, Robinson, & Pani, 1999), increased musical interest and emotional reactivity to music (Dykens, Rosner, Ly, & Sagun, 2005), and elevated non-social anxiety derived from fear and specific phobias (Dykens, 2003; Green et al., 2012; Zarchi et al., 2014). A less discussed impairment often seen in WS is a motor impairment (Greer, Brown, Pai, Choudry, & Klein, 1997; Preus, 1984). WS individuals repeatedly hold some motor abnormalities in oromotor skills, gait, hyperreflexia, balance, coordination, fine motor, gross motor, and hypotonia (Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Chapman, du Plessis, & Pober, 1996; Greer et al., 1997; Trauner, Bellugi, & Chase, 1989). The gait and coordination difficulties persist among adulthood, but tone abnormalities vary with age, as young WS individuals suffer from decreased tone and older individuals from increased tone (Chapman et al., 1996). Additionally, early motor skills development is often delayed in WS (Pober, 2010; Trauner et al., 1989).

Aside from the motor, social, and emotional abnormalities, individuals with WS also have cognitive impairments. Most WS individuals rank in the "mild to moderately intellectually disabled" range, with

global standard scores on IQ tests ranging from 40 to 100 and a mean of around 60 (Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Magnusson, 1997). Furthermore, individuals with WS are characterized as having connective tissue abnormalities, cardiovascular disease, and facial dysmorphology (Barak & Feng, 2016; Martin, Snodgrass, & Cohen, 1984; Morris, Demsey, Leonard, Dilts, & Blackburn, 1988). The gene microdeletion in WS allows for a better understanding of the relationship between genotype and WS-specific phenotypes, such as social abnormalities and specific motor impairments.

2 | WS BEHAVIORAL PHENOTYPE

WS individuals possess a special and complex behavioral phenotype. The main and most forward characteristic is their friendly social personality, which includes increased interest in approaching strangers, and increased empathy when interacting with others (Gosch & Pankau, 1994, 1997; Klein-Tasman & Mervis, 2003). WS individuals were proposed to be lively and to openly engage in social interactions, pay great attention to others' faces and be seemingly overly responsive to facial cues (Bellugi, Wang, & Jernigan, 1994; Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006; Skwerer, Verbalis, Schofield, Faja, & Tager-Flusberg, 2006; Tager-Flusberg, Boshart, & Baron-Cohen, 1998). Therefore, they are referred to as overly friendly and hypersocial. However, some of the WS individuals show characteristics of autistic behavior, and experience difficulties with social interaction and social communication (Klein-Tasman, Phillips, Lord, Mervis, & Gallo, 2009; Laws & Bishop, 2004). Many parents report that the children possess poor social skills and have difficulties in establishing friendships (Klein-Tasman et al., 2009). In a parental questionnaire study from 1998, it was suggested that WS group compared to control is less emotionally stable and show less openness and more irritability (van Lieshout, De Meyer, Curfs, & Fryns, 1998). Additionally, 50–90% of adolescents and adults with WS are described by experts to meet the criteria of psychiatric disorders including anxiety, phobic disorder, attention deficit-hyperactivity disorder, or a combination of them (Pober, 2010). By parental reports, more than 80% of WS adults are anxious, irritable and have obsessions (Davies, Udwin, & Howlin, 1998).

One of the hypersocial phenotypes recognized in WS is social evaluative language, which refers to lexically conveyed affect and sociability, or language that reflects the narrator's attitude or perspective (Bellugi et al., 2007; Losh, Reilly, & Anderson, 2000; Reilly, Losh, Bellugi, & Wulfeck, 2004). It has been suggested that WS is associated with strong verbal and language skills (Fishman, Yam, Bellugi, & Mills, 2011), and their expressive language abilities are preserved in comparison to other genetic disorders with intellectual disabilities, such as Down syndrome (Reilly et al., 2004). However, their language abilities do not match chronological age (Mervis & Becerra, 2007), and there are contradictory findings to the matter of their good language skills. One such finding is reported in a study from 2003, which claimed that WS individuals have pragmatic language impairments and are producing significantly less coherent narratives and dialogs than controls, resembling more to the Down syndrome group (Laws & Bishop, 2004).

All these findings suggest a very complex behavioral phenotype in WS, even though the genotype is similar in most individuals, as the typical deletion in WS is similar in ~95% of the individuals. To fully understand these contrasts in social phenotype, it is important to examine social-related brain networks and related brain mechanisms. Interestingly, studies have shown a correlation between abnormalities in the brain's white matter (WM) and deficits in social behavior (Eluvathingal et al., 2006; Hibbits, Pannu, Wu, & Armstrong, 2009; Phan et al., 2009; Sanchez, Hearn, Do, Rilling, & Herndon, 1998), as myelin participates in optimizing the transfer of electrical signals through saltatory conduction (Fields, 2008b, 2015). Thus, lack of synchronicity between social behavior-related brain networks, as a result of myelination deficits and signal leakage, can potentially lead to abnormal social behavior.

3 | WM AND MYELIN FORMATION

The WM is the part of the brain connecting gray matter regions in complex neural networks and is composed of axons coated with lipid-rich substance essential for electrical insulation, called myelin. In myelination, the axons are wrapped in myelin to help increase the efficiency of an electrical signal's transfer down a neuron, as well as providing metabolic support to the axons (see reviews (Nave, 2010b; Saab, Tzvetanova, & Nave, 2013)), and reducing the energy consumption of the myelinated neuron by restricting ion currents and action potentials (Nave, 2010a). In addition, myelinating glia's are promoting axonal survival (Sherman & Brophy, 2005). In the central nervous system, the process of myelination begins when the oligodendrocyte cells (OLs), a type of glial cell that produces the fatty membrane, detect and adhere to the specified axon (Fields & Stevens-Graham, 2002; Hildebrand, Remahl, Persson, & Bjartmar, 1993; Simons & Trajkovic, 2006). This is followed by the synthesis and transport of myelin compounds that encircle segments of the axon (up to 100 layers), wrapping around the axon in a lateral motion, and ultimately creating the myelin sheath (Fields, 2014; Simons & Trajkovic, 2006). This process influences the regulation and synchronization of signal transduction traveling through cortical regions and affecting brain connectivity (Fields, 2008a, 2008b), and continues throughout development (Fields, 2008a; Yeung et al., 2014).

3.1 | Myelination is a developmental process

Myelination is a continuous developmental process. In humans, myelination in the cortex begins in utero and continues throughout early adulthood, plateauing in around the fourth decade of life (Davison & Dobbing, 1966; Fields, 2008b; Kinney, Karthigasan, Borenshteyn, Flax, & Kirschner, 1994; Shonkoff et al., 2000; Yeung et al., 2014). During this extended period of myelination in humans, the cerebral

cortex is simultaneously undergoing alterations in synaptic connections as a result of external experiences (Fields, 2008b). This is consistent with mouse studies, which indicated that OL formation in the cortex proceeds throughout the mouse's lifetime, with OLs doubling in number from 4 to 10 months of age (Hughes, Orthmann-Murphy, Langseth, & Bergles, 2018).

In humans, the process of myelination develops in stages (Abraham et al., 2010), beginning from the back of the cerebral cortex and continuing to the front as we mature (Fields, 2008b; Leipsic, 1901). In 2019, Grydeland et al. (2019) demonstrated that different regions of the brain undergo myelination in different phases, concluding that areas of the brain associated with primary motor and sensory responses develop earlier than areas associated with limbic and insular regions (Grydeland et al., 2019). The last area of the brain in which myelination occurs is the frontal lobe (Fields, 2008b; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999), which is responsible for higher-level functioning, including reasoning, planning and judgment (Chayer & Freedman, 2001), skills that are influenced by new experiences. This goes hand in hand with the fact that myelination in the cerebral cortex can be modified by interactions and experiences through the production of new OLs (Hughes et al., 2018); it also raises the possibility of myelin's participation in optimizing information processing through environment and experience (Fields, 2008b, 2015; Zatorre, Fields, & Johansen-Berg, 2012), as well as other factors.

3.2 | Environment and experience-dependent myelination

Individual responses to experience and environmental stimuli influence the development of WM and myelin formation in both humans (Als et al., 2004; Bengtsson et al., 2005; Kaller, Lazari, Blanco-Duque, Sampaio-Baptista, & Johansen-Berg, 2017; Long & Corfas, 2014; Scholz, Klein, Behrens, & Johansen-Berg, 2009) and rodents (Kaller et al., 2017; McKenzie et al., 2014; Sampaio-Baptista et al., 2013; Wiggins & Gottesfeld, 1986), by affecting electrical impulses, ATP release, and neuron–glia interactions (Fields, 2008b; Ishibashi et al., 2006). For example, in 2004, Teicher et al. (2004) discovered that children suffering from severe childhood neglect have a 17% reduction in the size of their corpus callosum (CC), a WM tract that plays an important role in the transfer and integration of information (Bloom & Hynd, 2005). Similarly, in rats, an enriched environment increased the number of myelinated axons in the CC and the number of OLs (Bennett, Diamond, Krech, & Rosenzweig, 1964; Sirevaag & Greenough, 1987; Szeligo & Leblond, 1977), suggesting positive interplay between the environment and the process of myelination.

4 | WM AND SOCIAL BEHAVIOR

Early social neglect or isolation can result in behavioral dysfunctions that are related to altered WM and brain connectivity (Eluvathingal et al., 2006). A study demonstrating this idea compared magnetic resonance imaging (MRI) scans of a group of orphans who were adopted, and a control normal group. The orphan group was termed "early socioemotional deprivation group" (Eluvathingal et al., 2006). This study found that the neglected group presented significantly reduced fractional anisotropy (FA) values, a measure of WM microstructure (Assaf & Pasternak, 2008), in the left uncinate fasciculus (UF), a structure connecting the temporo–amygdalo–orbitofrontal network (Ameis & Catani, 2015; Catani, Howard, Pajevic, & Jones, 2002; Kier, Staib, Davis, & Bronen, 2004). In addition, lower FA values, albeit not significantly so, were found in limbic fiber tracts and the corticospinal tract in the socially neglected group. This study suggested that social experiences during early childhood, a critical period for the formation of social capabilities, are correlated with WM tracts' development and functionality in the human brain; in this case, social deprivation may lead to hypoconnectivity. Interestingly, the neglected group was characterized by relatively mild specific cognitive deficiency and impulsivity, as well as a significant relative divergence between verbal and nonverbal intellectual functioning (Eluvathingal et al., 2006). An additional study found the UF to be associated with social behavior (Elison et al., 2013). That study suggested that this specific tract is essential for social development, as its structure predicts an infant's response to joint attention. Increased FA values in the right UF (at 6 months of age) were correlated with higher levels of performance in responding to joint attention 3 months later (at 9 months of age) (Elison et al., 2013).

Similar results were seen in animal studies. A study of infant rhesus monkeys raised under different levels of nurturing suggested that CC size was greater in animals raised in large groups, compared to individually raised monkeys (Sanchez et al., 1998). In addition, the large group monkeys had better cognitive abilities (Sanchez et al., 1998). Mouse studies demonstrated similar findings, as social isolation in mice was found to affect OLs in the prefrontal cortex (PFC) (Liu et al., 2012; 2016), including ultrastructural changes in OLs, downregulated OLs transcripts' expression and defective heterochromatin formation in OLs compared to control mice (Liu et al., 2012). Further, in a study that isolated mice for 2 weeks, myelin deficits in the PFC were found, presenting a reduction in receptors of the OL ErbB3, along with reduced expression of the ErbB3 ligand neuregulin-1 (Makinodan, Rosen, Ito, & Corfas, 2012) (Figure 1). Myelin deficits and deficient brain connectivity following social isolation were also found in a study from 2016 (Liu et al., 2012), which isolated adult mice; it was eventually suggested that PFC myelination is regulated by social experience. The mouse CC was also found to be related to social interaction performance, as alterations in social interaction correlated with CC demyelination by cuprizone (Hibbits et al., 2009): a higher number of social interactions in a resident–intruder assay were measured in mice with demyelinated CC compared to control mice (Hibbits et al., 2009).

A study suggesting that deficiency in myelin is associated with poor social abilities showed a correlation between myelin features and impaired social interaction following social isolation (Makinodan et al., 2017). The isolated mice in this study showed thinner myelin in the medial PFC compared to their controls (measured by *g*-ratio,

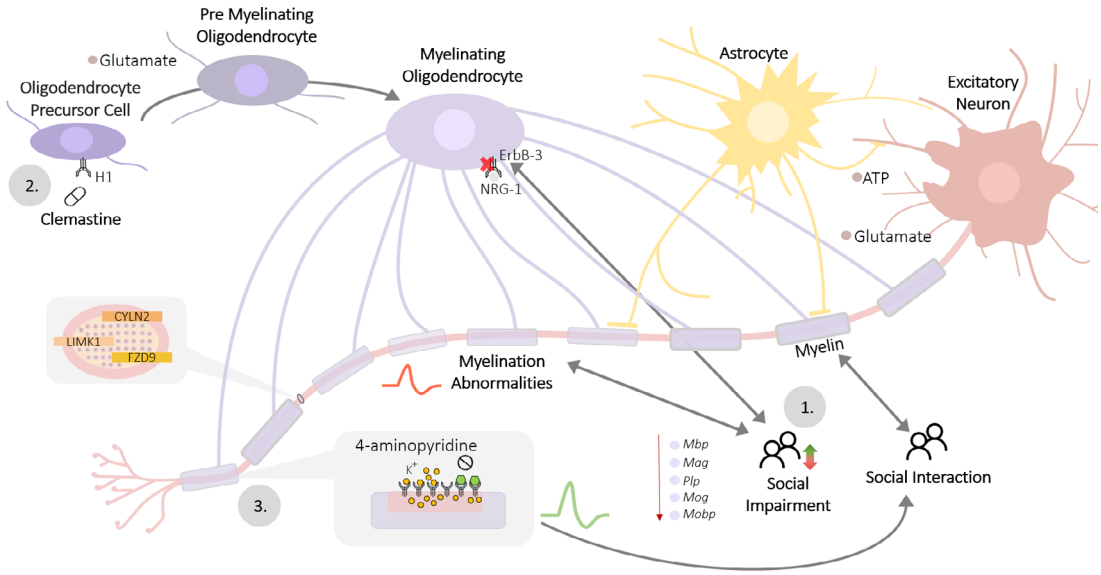

FIGURE 1 The interplay between OLs differentiation, pharmacology, social interaction and myelination. (1) Social interaction interplay with myelination. As a result of social isolation, OLs in mice show reduced ErbB3 receptors expression, along with a reduced ErbB3 ligand NRG-1 expression and myelin deficits. In addition, social isolation of adult mice leads to a downregulation of myelin-related genes expression (*Mbp*, *Mag*, *Plp*, *Mog*, *Mobp*). Mutations in the genes that regulate neuronal cytoskeletal dynamics in WS, such as *LIMK1*, *CYLN2*, and *FZD9*, can lead to abnormal WM tracks. (2) Clemastine targets H1 receptors and can stimulate OPC differentiation and maturation. As a result of Clemastine treatment, social behavior was normalized in a WS mouse model. (3) 4-aminopyridine is a potassium channel blocker, which was found to increase the amplitude and duration of action potentials. As a result of 4-aminopyridine treatment, social behavior was normalized in a WS mouse model. OLs, oligodendrocyte cells; OPC, OL precursor cell; WM, white matter; WS, Williams syndrome

which serves as an index of axonal myelination (Chomiak & Hu, 2009)). Later on, mice were socialized again (i.e., isolated mice were housed together with other isolated mice from the same litter or with group-housed mice), resulting in normalization of the myelin thickness in the medial PFC, comparable to normal control mice (Makinodan et al., 2017). Interestingly, this effect was found only in mice that underwent socialization with group-housed mice. These results suggest that myelination in the medial PFC is sensitive to social isolation and social behaviors.

In addition to social abnormalities related to myelin and signal conduction, motor deficits are also known to be related to this matter, in both humans (Bengtsson et al., 2005; Scholz et al., 2009) and rodents (McKenzie et al., 2014; Sampaio-Baptista et al., 2013).

Taken together, these studies suggest a correlation between myelination abnormalities and deficient motor and social behavior, most likely caused by abnormal conduction velocity (CV).

4.1 | WM deficits in WS may alter signal conduction

Individuals with WS were found to have less average gray and WM volume in several brain regions, as well as some areas with significant volume increase (Figure 2) (Campbell et al., 2009; Green et al., 2016).

It was suggested that the significant volume reduction in WS individuals' brains is in the WM, not the gray matter (Reiss et al., 2000). In 2007, Marenco et al. (2007) suggested that due to some mutations in the genes that regulate neuron cytoskeletal dynamics in WS, such as *LIMK1*, *CYLN2*, and *FZD9*, WS individuals have abnormal WM tracts (Figure 1). They claimed that these irregularities might result from a lack of intact growth cone regulation that occurs during early development (Marenco et al., 2007). They performed a diffusion tensor imaging (DTI) study in which they concluded that modifications to WM tissue are indeed present in individuals with WS, including differences in organization and fiber orientation (Marenco et al., 2007). These WM abnormalities can lead to CV delays, which may influence neuronal activity and neural oscillators (Pajevic, Basser, & Fields, 2014). Studies show that even minor changes, such as in spike arrival time or the frequency and coupling of oscillators, could drastically influence neuronal network functions (Pajevic et al., 2014). In addition, the abnormal fiber organization described, can have an impact on the speed of information processing (Bells et al., 2017; Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006).

In a WS mouse model in which *Dnajc30* had been knocked out, significantly reduced *g*-ratio values, a less complex dendritic architecture and reduced CC thickness were found in the knockout mice compared to control mice (Tebbenkamp et al., 2018). These findings of abnormal *g*-ratio values, may lead to multiple deficits, as for CV to function at optimal levels, the thickness of the myelin sheath must be proportional to the diameter of the axon it envelops (Chomiak & Hu, 2009; Pajevic et al., 2014; Seidl, 2014). Myelin sheaths that are thicker or thinner than the theoretical optimal *g*-ratio will have a direct influence on CV performance (Pajevic et al., 2014; Rushton, 1951). Thus, when myelination is compromised, axonal CV may be hindered,

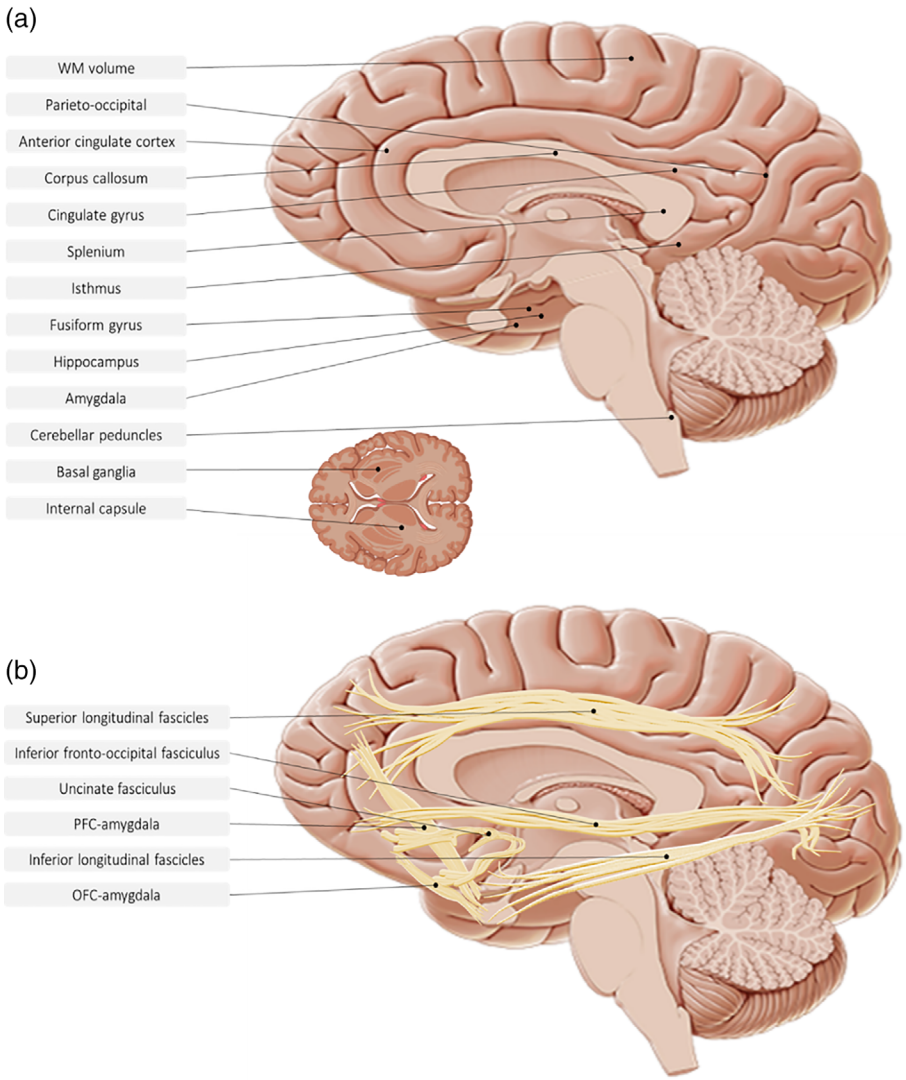

FIGURE 2 Altered WM regions and tracts in WS. Presented are estimated locations of neuroanatomical regions and neural circuits with WM abnormalities in WS. (a) WM altered regions in WS individuals compared to typically developed individuals. (b) WM tracts and pathways presenting aberrations in WS individuals compared to typically developed individuals. OFC, orbitofrontal cortex; PFC, prefrontal cortex; WM, white matter; WS, Williams syndrome

affecting brain function as a result of lack of optimal synchrony of spike arrival time (Fields, 2008a, 2015).

4.2 | WM deficits in WS may lead to cognitive, social, and motor impairments

An MRI study conducted on individuals with WS revealed that the CC in WS individuals is more convex than that in the controls, and the overall volume is significantly reduced (Figure 2) (Tomaiuolo et al., 2002). Other findings have shown that the total area of the midsagittal CC is significantly reduced, additional to a reduction in splenium and isthmus size, beyond the total reduction of the CC (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001) (Figure 2). These CC irregularities may be the cause of some of the cognitive deficits observed in individuals with WS, as the CC is important for transfer and integration of information, and agenesis of the CC in humans leads to cognitive delays, especially in language ability (Paul et al., 2007). Gothelf et al. (2008) performed a study showing a link between neuroanatomical irregularities and abnormal social behavior in individuals with WS. They indicated that the ventral anterior PFC and bending angle of the CC are related to social evaluative language, and distinguish individuals with WS from typically developing (TD) controls (Gothelf et al., 2008).

Furthermore, myelination abnormalities in prefrontal–amygdala pathways were measured in individuals with WS (Figure 2) (Avery, Thornton-Wells, Anderson, & Blackford, 2012). In WS, an analysis of the connectivity between the PFC and amygdala revealed that the pathway between the orbitofrontal cortex (OFC) and the amygdala is abnormal. This pathway in WS had lower FA values compared to TD individuals who demonstrated a strong negative interaction between the two regions (Avery et al., 2012) (Figure 2). The reduced inhibition of OFC to the amygdala in WS individuals may be a result of structural and functional deficiencies in the OFC, which may influence the lack of social inhibition demonstrated in WS (Meyer-Lindenberg, Mervis, & Berman, 2006). In addition, the discrepancies in the structural integrity of prefrontal–amygdala pathways might induce increased activity in the amygdala, which may contribute to the extreme fear of WS

individuals in non-social situations (Avery et al., 2012). This is supported by a study conducted by Meyer-Lindenberg et al. (2005) in which WS individuals demonstrated increased activation in the amygdala when presented to threatening scenes, although their response to threatening faces was dampened. Thus, abnormal connectivity between the OFC and amygdala is a possible neural basis for dysregulated social behavior in WS.

Recently, we revealed several WM abnormalities in a WS mouse model in which *Gtf2i* had been knocked out specifically in the forebrain excitatory neurons (Barak et al., 2019). Surprisingly, abnormalities included downregulation of myelination-related genes, reduced number of myelinating OLs, disrupted myelin ultrastructure, and impaired axonal conductivity (Figure 3). Similarly, transcriptome analysis of the human frontal cortex of WS individuals revealed significant downregulation of myelination-related genes. Our study demonstrates the importance of neuron–glia interaction for myelination, as was also seen in previous studies, describing the proliferation, differentiation and survival of OLs often regulated by neuron-derived signaling molecules (Barres & Raff, 1999). In addition, it is now known that electrical activity in neurons contributes to the secretion of promyelinating factors (Demerens et al., 1996; Fields & Stevens, 2000; Long & Corfas, 2014; Stevens, Porta, Haak, Gallo, & Fields, 2002; Wake, Lee, & Fields, 2011). These ideas were emphasized in a study by Zhan et al. (Zhan et al., 2014) who manipulated mice to be deficient in neuron–microglia signaling, resulting in decreased functional brain connectivity. This study also showed abnormal social behavior, as well as increased repetitive behavior, as a result of the impaired neuron–glia interaction (Zhan et al., 2014), supporting the idea of myelin properties and behavior interplay.

A DTI study from 2014 examined WM pathways which are known to be involved in social cognition in WS children (inferior fronto-occipital fasciculus [IFOF] and UF) and associated brain regions (fusiform gyrus, amygdala, hippocampus, and medial orbitofrontal gyrus) (Haas et al., 2014). They found that in comparison to TD children, WM pathways were altered in WS children, with higher FA and axial diffusivity values, and lower radial diffusivity and apparent diffusion coefficient values (Haas et al., 2014). Another DTI study that showed high FA values in WS individuals suggested a correlation between FA values in the right superior longitudinal fasciculus (SLF) and poor visuospatial abilities (Hoeft et al., 2007) (Figure 2).

An MRI study from 2018 suggested that there are some posterior brain regions characterized by hyperconnectivity in WS, leading to altered wiring of the brain, in addition to disrupted connectivity in anterior areas (Gagliardi et al., 2018). DTI analysis in this study, as well as others, discovered altered FA values in superior and inferior longitudinal fascicles, the posterior limbs of the internal capsules, middle and superior cerebellar peduncles, splenium of the CC, subcortical WM of the parieto-occipital regions and in the UF (Gagliardi et al., 2018; Hoeft et al., 2007). Some of these areas have been linked to motor abilities before (Arlinghaus, Thornton-Wells, Dykens, & Anderson, 2011), suggesting a possible explanation for the motor deficits presented in WS (Pober, 2010). WM in correlation with motor abilities was suggested in DTI studies in humans which detected changes in the structure of WM in people who trained in complex sensorimotor tasks such as playing the piano, which induced WM plasticity, (Bengtsson et al., 2005) and in visuo-motor skill training such as juggling, which resulted in increased FA values (Scholz et al., 2009). In rodents, a rat study from 2013 suggested that WM pathways changes and myelination is increasing as a result of learning

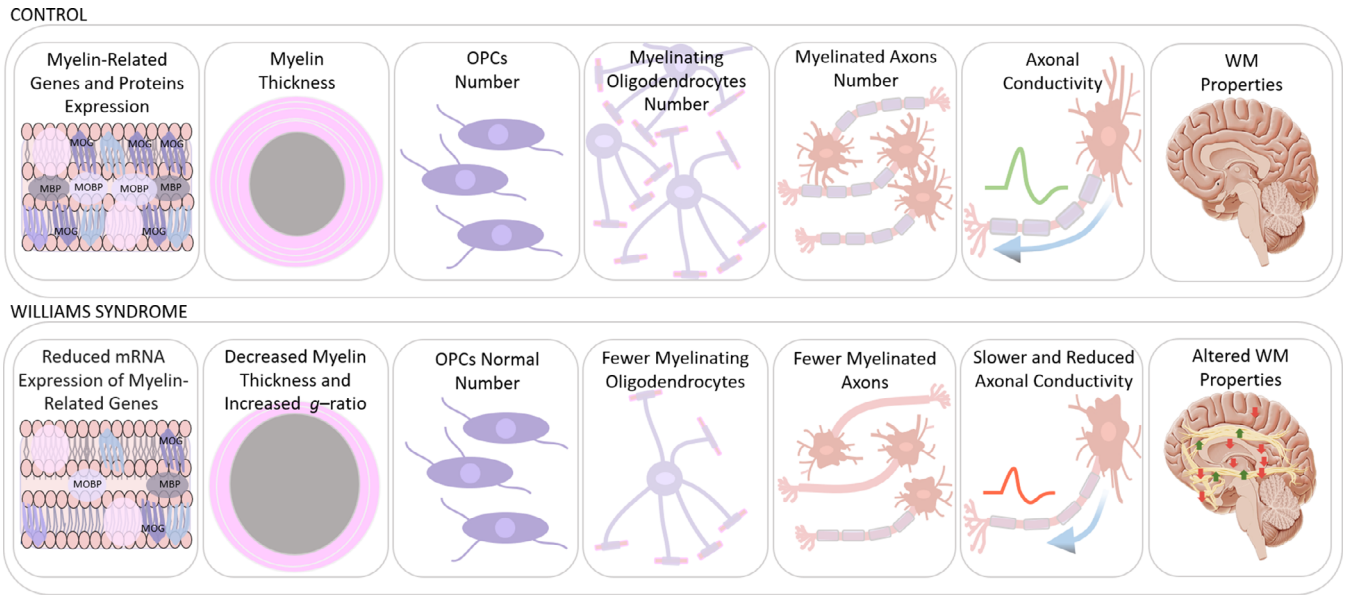

FIGURE 3 A schematic summary of myelination and WM abnormalities known in mouse models for WS and human individuals. Top row presents normal properties in control mice and TD individuals. Bottom row presents known defects in myelination and WM properties in mouse models and human individuals with WS. WM, white matter; WS, Williams syndrome

TABLE 1 Optional pharmacological treatments for myelin deficits (clinical and preclinical)

Drug	Dosage forms	General functions	Myelin related functions	Clinical status	References
OLs and OPCs differentiation					
Clemastine	Tablets or syrup	Antihistamine/anticholinergic compound blocking histamine H1 receptor	Enhance maturation of OLs	FDA approved	Mei et al. (2014)
Miconazole	Cream, solution, lotion, powder, gel, spray or lacquer	Antifungal agent interfering with ergosterol synthesis	Enhances OPCs differentiation through mitogen-activated protein kinase and activation of ERK1/2	FDA approved	Najm et al. (2015)
Clobetasol	Cream, gel, ointment, lotion, foam, or spray	Topical corticosteroid with anti-inflammatory, anti-pruritic, and vasoconstrictive properties	Enhances OPC differentiation through activation of the glucocorticoid receptor signaling axis	FDA approved	Najm et al. (2015)
Prostacyclin/ Epoprostenol	Oral	Inhibits platelet aggregation	Promotes OPC recruitment and migration via a protein kinase A (PKA)-dependent mechanism	FDA approved	Takahashi, Muramatsu, Fujimura, Mochizuki, and Yamashita (2013)
Copaxon/Glatiramer acetate	Injection	Anti-inflammatory and immunomodulatory activities. Used to treat relapsing–remitting multiple sclerosis (MS)	Promotes oligodendrogenesis and remyelination through mechanisms that involve the elevation of growth factors conducive for repair	FDA approved	Skihar et al. (2009)
NSAID—Non steroidal anti-inflammatory drug	Tablets	Reduce pain, decrease fever, prevent blood clots, decrease inflammation	Promotes differentiation of primary OLs through inhibition of the Wnt/ β-catenin pathway	FDA approved	Preisner et al. (2015)
Progesterone	Injection or capsules	Acts on the uterus, the mammary glands, and the brain. It is required in embryo implantation, pregnancy maintenance, and the development of mammary tissue for milk production	Increases the density of $NG2^+$ OPC and $CA\ II^+$ mature OLs and enhances the formation of myelin basic protein (MBP) and proteolipid protein (PLP)	FDA approved	El-Etr et al. (2015)
Diosgenin	Oral	Precursor of various synthetic steroidal drugs. Traditionally used for hormone replacement in menopausal women, and in the treatment of diabetes, hypercholesterolemia, and gastrointestinal ailments	Promotes OPCs differentiation through estrogen receptor-mediated ERK1/2 activation	FDA approved	Xiao et al. (2012)
Citicoline (CDP-choline)	Oral or IV	Used for Alzheimer's disease and other types of dementia, head trauma, cerebrovascular disease such as stroke, age-related memory loss, Parkinson's disease, attention deficit-hyperactive disorder and glaucoma	Enhances OPC proliferation	FDA approved	Skripuletz et al. (2015)
Solifenacin/Vesicare	Oral	Solifenacin is a urinary antispasmodic of the anticholinergic class. Muscarinic receptor antagonist	Enhances maturation of OLs	FDA approved	Abiraman et al. (2015)
Benztropine	Oral	Antimuscarinic agent used as an adjunct in the treatment of Parkinson's disease	Enhances OPCs differentiation by blocking notch signaling	FDA approved	Deshmukh et al. (2013)

(Continues)

TABLE 1 (Continued)

Drug	Dosage forms	General functions	Myelin related functions	Clinical status	References
Thyroid hormone	Oral	Hormone produced and released by the thyroid gland	Enhances OPCs differentiation through thyroid hormones receptor β	FDA approved	Franco, Silvestroff, Soto, and Pasquini (2008), Harsan et al. (2008)
Tamoxifen	Oral	Selective estrogen receptor modulator	Enhances OPCs differentiation through estrogen receptors ERα, ERβ, and GPR30	FDA approved	Gonzalez et al. (2016)
Quetiapine fumarate	Oral	Antipsychotic agent that targets the serotonin 5-HT2 receptor; histamine H1 receptor, adrenergic alpha1 and alpha2 receptors, as well as the dopamine D1 and D2 receptors. It is used in the treatment of schizophrenia; bipolar disorder and depression	Enhances maturation of OLs	FDA approved, phase 2 study in MS	Bi et al. (2012), Zhornitsky et al. (2013)
GSK239512	Oral	Histamine H3 receptor antagonist	Enhances OPCs differentiation through H3 receptor	Phase 2 in MS	Saligrama, Case, del Rio, Noubade, and Teuscher (2013), Schwartzbach et al. (2017)
BIIB033 (opicinumab) anti-LINGO-1 monoclonal antibody BIIB033	IV infusion or subcutaneous injection	Human monoclonal antibody that binds LINGO-1 with high affinity and specificity and is being developed as an investigational product to lead to remyelination and axonal protection and/or repair in patients with MS	Enhances maturation of OLs by LINGO-1 binding	Phase 2 clinical trial failed	Tran et al. (2014)
Olesoxime	Oral	Promotes the function and survival of neurons and other cell types under disease-relevant stress conditions through interactions with the mitochondrial permeability transition pore (mPTP)	OLs maturation and myelination enhancement	Phase 2 clinical trial failed	Magalon et al. (2012)
VX15/2503	Intravenous administration	VX15/2503 is a humanized monoclonal antibody that binds to the semaphorin 4D (SEMA4D; CD100) antigen	Enhances OPC differentiation	Phase 1 in MS	Smith et al. (2015)
IRX4204	Oral	RXR receptors are involved in remyelination. IRX4204 is a RXR receptor agonist	Enhances OLs differentiation	Preclinical in MS	Huang et al. (2011)
GANT61	—	A small molecule inhibitor of Gli1	Promotes the generation of OLs from adult neural stem cells	—	Samanta et al. (2015)
Tocopherol derivative TFA-12	—	Synthetic compound belonging to tocopherol long-chain fatty alcohols. Vitamin E analogue	Enhances OPCs differentiation through the inhibition of the notch/Jagged1 signaling pathway	—	Blanchard et al. (2013)

TABLE 1 (Continued)

Drug	Dosage forms	General functions	Myelin related functions	Clinical status	References
Signal transduction or myelin synthesis					
4-Aminopyridine	Oral	Potassium channel blocker. Used in MS	Overcomes conduction failure in demyelinated nerve fibers	FDA approved	Sherratt, Bostock, and Sears (1980)
Diarylpropionitrile	Powder	Selective agonist of ERβ receptor	Enhances OLs survival and axon myelination through ERβ and the phosphatidylinositol 3-kinase (PI3K)/serine–threonine-specific protein kinase (Akt)/mammalian target of rapamycin (mTOR) signaling pathway	FDA approved	Kumar et al. (2013)
rHigM22	IV infusion	Recombinant human antibody binding to vitronectin/fibronectin receptor αvβ3	Promotes the synthesis of new myelin in animal models by reduction of OLs apoptosis	Phase 1 in MS	Watzlawik, Warrington, and Rodriguez (2013)

Abbreviations: OLs, oligodendrocyte cells; OPCs, OL precursor cells.

a novel motor skill (Sampaio-Baptista et al., 2013). Another study manipulated and blocked OLs production in adult mice and showed that active myelination is necessary for learning new motor skills. Additionally, this study showed the other way around—OLs production is increased as a result of learning a new motor skill (McKenzie et al., 2014).

4.3 | Drug therapy for myelin deficits may normalize social abnormalities

It can be concluded that myelination adapts to social experience in a circuit-specific manner, suggesting altered myelination in WS as a possible mechanism for social abnormalities in this syndrome; in turn, social abnormalities can lead to impaired myelination (Figure 1). Therefore, drug therapy that improves myelination properties and axonal conduction could potentially lead to a reduction in social behavior deficiencies in WS, as well as in other disorders. This idea was emphasized in a study from 2016, in which clemastine, an FDA-approved antimuscarinic compound that promotes OL precursor cells (OPCs) differentiation, thereby enhancing the myelination process (Cree et al., 2018; Mei et al., 2014), improved social interactions in previously isolated adult mice, reversing their social-avoidance behavior (Liu et al., 2016). The improved social behavior was suggested to be correlated with improved myelination and differentiation of PFC OLs (Figure 1). Thus, the possibility of enhanced myelination and signal conduction leading to improvements in social interactions was raised (Barak et al., 2019; Liu et al., 2016). In addition, 4-aminopyridine, an FDA-approved drug that increases amplitude and duration of action potentials in axons with disrupted myelination (Bostock, Sears, & Sherratt, 1981), normalized social deficits in a WS mouse model (Barak et al., 2019) (Figure 1). Moreover, chronic oral gavage of clemastine normalized hypersociability in those mice, associated with normalization of myelination properties (Barak et al., 2019) .

Addition of drug therapy can improve myelination in many aspects in the brain, for example, by enhancing OPCs' and OLs' maturation, and by improving axonal conductivity or myelin synthesis (see Table 1). Moreover, there is no specific time frame for this type of treatment, as drug treatments for myelination deficits can be relevant at postnatal stages, as seen in our recent study (Barak et al., 2019), and can therefore also be given in adulthood.

5 | DISCUSSION

Many psychiatric disorders are characterized by WM abnormalities such as hyper- or hypomyelination, but it is not clear whether these abnormalities are the main cause for the neurological symptoms, or rather a process or side effect of the disorder. Myelin abnormalities occurring in WS can lead to social impairments, as discussed in this review, but there is also the possibility that the social impairments in WS impact myelination. In addition, the motor abnormalities presented in WS could possibly be a result also of poor WM functioning and abnormalities.

The studies discussed in this review indicate that myelination can adapt to social experiences and is impaired as a direct cause of social isolation, suggesting a brain mechanism and possible future therapeutic mechanism. Indeed, drug treatment for hypersocial WS mice normalized their social behavior in parallel to improving myelination properties (Barak et al., 2019), suggesting a possible therapeutically relevant interplay between myelin and sociability.

The idea of myelin and social behavior going hand in hand is of great importance as it suggests new pharmacological treatments for social symptoms through enhancement of signal conduction and improvement of brain network synchronization for WS.

Psychiatric and neurological disorders such as dyslexia (Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010), attention deficit hyperactivity disorder (Hamilton et al., 2008), depression (Regenold et al., 2007), bipolar disorder (Chambers & Perrone-Bizzozero, 2004; Regenold et al., 2007), language disorders (Herbert et al., 2004), obsessive–compulsive disorder (Zai et al., 2004), post-traumatic stress disorder (Villarreal et al., 2002), cognitive decline in aging (Gootjes et al., 2004), Alzheimer's disease (Gootjes et al., 2004; Rose et al., 2000), Tourette syndrome (Neuner et al., 2010), schizophrenia (Chambers & Perrone-Bizzozero, 2004; Fields, 2008a; Regenold et al., 2007; Sokolov, 2007), and autism spectrum disorder (Herbert et al., 2004; Koul, 2005) were found to have WM alterations. The variation in WM in these disorders differs, but includes mainly impairments in gene expression and axonal conductivity, as well as loss of axons and myelin sheaths. For example, a postmortem examination of brain tissue from individuals with schizophrenia, major depression and bipolar disorder showed a reduction in the expression of myelin-related genes and in those that regulate the differentiation and survival of OLs (Aston, Jiang, & Sokolov, 2005; Katsel, Davis, & Haroutunian, 2005; Tkachev et al., 2003). Further research is necessary to determine whether changes in myelin-related genes' expression and WM organization are sufficient to cause psychiatric disorders directly, or alternatively, a side effect of abnormal development of WM and brain function. Nevertheless, some disorders can be linked to, or even result from slowed or desynchronized impulse conduction between cortical regions.

To conclude, this review examines WM deficits in WS and shows a clear correlation between social as well as motor symptoms, and brain connectivity and synchronicity deficits in this disorder. Future research should include clinical trials for pharmacological drugs to help enhance conduction in WS individuals.

ACKNOWLEDGMENTS

The authors gratefully acknowledge K. Falk, S. Trangle, E. Bar, G. Levy, M. Grad, and M. Recanati for insightful comments on the manuscript. This work was funded by funds from Brainboost innovation center by Sagol School of Neuroscience at Tel Aviv University, SPARK Tel Aviv, and Fritz Thyssen Stiftung.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Nir A, Barak B. White matter alterations in Williams syndrome related to behavioral and motor impairments. *Glia*. 2021;69:5–19. https://doi.org/10.1002/glia.23868