MYELINATION HYPOTHESIS IN SCHIZOPHRENIA: ROLE OF THYROID HORMONES FROM PRECLINICAL EVIDENCE TO THERAPY SUGGESTIONS

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Abstract

Objective: Several lines of evidence converge on the fact that myelination might be a possible molecular mechanism underlying those intracerebral misconnectivity probably involved in schizophrenia. Thyroid hormones may play a role within this paradigm. A critical review of evidence supporting this possibility has been performed, starting from preclinical findings to possible therapy suggestions.

Method: Data from PubMed search and references from relevant reviews on this topic have been extensively analyzed.

Results: After early histological analyses of post mortem tissues and neuroimaging studies supporting a possible role of myelin abnormalities in schizophrenia, now also genetic findings are claiming a possible role of myelin-related proteins in abnormal oligodendrocyte development. The expression of some genes involved in this process is regulated by thyroid hormones and a symptomatologic overlap of cognitive aspects is found between hypothyroidism and negative symptoms of schizophrenia, suggesting a possible clinical and therapeutic involvement of thyroid hormones in schizophrenia research.

Conclusions: Present evidence suggests a possible thyroid hormones involvement in the myelination pathogenesis of schizophrenia, leading to possible future therapeutic perspective.

Key Words: schizophrenia, myelination, myelin, thyroid hormones, white matter

Declaration of interest: none

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Introduction

Schizophrenia, one of the most devastating psychiatric disorders, is characterized by hallucinations, delusions, disorganized thoughts, and various cognitive impairments, and affects about 1% of the population worldwide. Among several different etiological theories, growing evidence from histological, genetic, and neuroimaging studies suggests that myelin and oligodendrocyte dysfunction could be involved in its development (Davis et al. 2003).

Myelin is the multilayered compacted cell membrane wrapped around axons by glial cells, oligodendrocytes in the brain, that speeds conduction of nerve impulses through electrical insulation. As result of damage and disease affecting the myelin sheets many neurological disorders has been attested, but recently this kind of defects has also been associated with a wide range of psychiatric disorders through exploring psychiatric phenomena as they appear in white matter (WM) disorders. For example several neuropsychiatric symptoms as depression, mania, psychosis, and euphoria could be all part of multiple sclerosis clinical expression. Thus, potential relevance of WM dysfunction in psychiatric diseases has also been investigated (Schmahmann et al. 2008). Myelin-related abnormalities, due to abnormal development, maintenance or oligodendrocyte death, represent plausible neurobiological substrates of those dis- or misconnectivity among different brain regions that have been postulated to contribute to the central pathophysiology of schizophrenia (Arnold and Trojanowski 1996, Haroutunian and Davis 2000, Raedler et al. 1998, Stewart and Davis 2004, Weinberger and Lipska 1995). The basis for WM involvement consisted basically of gene expression studies, different

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types of brain imaging studies methods and histological analysis of post mortem tissue. Since the first suggestion of a myelin-related pathophysiology underling schizophrenia (Hakak et al. 2001) numerous and extensive reports on this hypothesis (Davis et al. 2003, Dwork et al. 2007, Hoistad et al. 2009, Karoutzou et al. 2008, Segal et al. 2007, Sokolov 2007, Walterfang et al. 2006) have been performed.

The role of thyroid hormone on oligodendroglial ontogenetic development has been extensively studied both in vitro and in vivo and myelination was found as a thyroid hormone-dependant process (Bernal 2002, Darras 2008, Rodriguez-Pena 1999, Zoeller and Rovet 2004).

The aim of this paper is to review actual evidence of thyroid hormones involvement in the myelination pathogenesis of schizophrenia, from preclinical findings to therapy suggestions.

Thyroid hormone and myelination

Thyroid hormones are essential for the proper development of the central nervous system (Maden 2002, Morreale de Escobar et al. 2004) and, among other several processes, myelination and oligodendrocyte maturation have been identified as regulated by thyroid hormones (Rodriguez-Pena 1999). 3,5,39-triiodothyronine (T3) is generally accepted as the active thyroid hormone, whilst thyroxine (T4) is considered a precursor of T3 rather than an active hormone (Leonard and Koehrle 1996). T3 would act as a major regulator of oligodendrocyte precursor cell (OPC) proliferation and differentiation. In cooperation with platelet-derived growth factor (PDGF) TH would trigger OPCs cell cycle exit (Durand et al. 1997, Durand and Raff 2000, Lu et al. 2008) as when OPCs proliferate they become sensitive to T3 after eight cell divisions (or corresponding time), probably because of a cell cycle-dependent expression of Thyroids Receptors (Maruvada et al. 2004) (see below in the text). So at appropriate times T3 could stop cell division and lead to terminal differentiation (Calzà et al. 2010). Moreover THs stimulate the morphological and functional maturation of oligodendrocytes (OLs) (Rodriguez-Pena 1999), by stimulating the expression of various genes, such as myelin basic protein (MBP) and proteolipid protein (PLP) and consistently levels of mRNA for this myelin proteins were found as markedly reduced in the hypothyroid neonatal rat brain (Munoz et al. 1991, Tosic et al. 1992). Gene for MBP would be directly regulated by thyroid hormone: Farsetti and colleagues (Farsetti et al. 1992, Farsetti et al. 1991) demonstrated in preclinical studies a sequence in the promoter of MBP gene effective in the hormonal transactivation. This regard, Younes-Rapozo and collegues (Younes-Rapozo et al. 2006) found a higher number of pre-oligodendrocytes and a lower number of mature oligodendrocytes in T3 deficient cultures and establish a possible impairment in oligodendroglial differentiation under T3 deficiency. Furthermore, membrane sheets in T3 deficient cultures were not as spread as those in control cultures, suggesting a role for thyroid hormone on the later stages of oligodendroglial maturation and myelin formation. In particular T3 deficiency changes the distribution of MBP during oligodendroglial differentiation in vitro and the effects of T3 deficiency and MBP distribution may account for the failures in myelin compaction that are observed in vivo (Younes-Rapozo et al. 2006). Another *in vitro* study (Fernandez et al. 2004) reported the T3 influence on oligodendrocytes' ramification. In fact, cultures derived from hyperthyroid animals showed oligodendrocytes with longer processes, and cultures derived from hypothyroid animals showed oligodendrocytes with shorter processes. Analysis of myelination in hypothyroid and hyperthyroid animals (Jagannathan et al. 1998, Obregon et al. 2007) supports *in vivo* the abundant evidence that THs plays an important part in regulating oligodendrocytes lineage and maturation. Most thyroid-hormone-mediated actions are controlled by transcriptional regulation (Bassett et al. 2003, Yen 2001). Thyroid hormone T3 bind to thyroid hormone receptors (THRs), which function as ligand-activated transcription factors (Palha and Goodman 2006). Two main genes were found to encode THRs, the THRα gene and the THRβ gene. The identification of various receptor isoforms prompted efforts to define the developmental pattern of the appearance of each in the brain. Although it was assumed that T3 binding sites were expressed mainly in neurons, a study showed that oligodendrocytes contain approximately the same number of T3 binding sites as neurons (Yusta et al. 1988). The expression of various THRs isoforms in different life moment and the different actions that this could exert in oligodendrial lineage has been extensively analyzed in literature. TRα1 and TRα2 were found as widely expressed in hybridization studies in the rat fetal brain, while TRβ was found only in restricted regions of the brain (Bradley et al. 1992, Mellstrom et al. 1991). A dramatic 40-fold increase in TRβ1 levels begins at the time of birth and reaches maximal levels by postnatal day 10, when the serum thyroid hormone levels also peak. In contrast, the levels of TRα1 and TRα2 mRNA, already high prenatally subsequently fall to adult levels by postnatal day 15 (Strait et al. 1990). Expression of β1, at the level of both mRNA and protein, increases along with the number of oligodendrocytes in isolated rat glial cells at various age (Carre et al. 1998). The different Thyroid Receptor isoforms could regulate the differential hormonal sensitivity and the transcriptional response to T3 through a cell cycle dependent expression in the different phases of the cell cycle (Maruvada et al. 2004). TRα expression seems to decline as soon as oligodendrocyte precursor cell (OPC) progress toward myelinating oligodendrocyte (OLs), whereas TRβ1 seems to be associated with terminal maturation (Sarlieve et al. 2004).

Schizophrenia and thyroid hormonal imbalance

Thyroid function abnormalities in schizophrenia were reported since early 1960s.

First findings of a supposed reduced thyroid activity in chronic schizophrenic male population was found to be related to a high intake of iodine (Simpson and Cooper 1966, Simpson et al. 1963, Simpson et al.

1964), as lately such differences disappeared with correction of diet (Rosenbaum 1968). Nevertheless several more recent studies have reported thyroid hormone level abnormalities in hospitalized schizophrenic patients, though in most cases not expression of a clinical thyroid disease. These test abnormalities vary into a spectrum from sick euthyroid syndrome, suppressed hypothalamo-pituitary-thyroid axis, subclinical hypothyroidism and thyroid antibodies (Othman et al. 1994). A positive correlation between circulating free thyroxine (fT4) and triiodothyronine (fT3) and severity of schizophrenic disease has been found, where these hormones were significantly higher in patients with mild and major syndrome compared to no syndrome (Sim et al. 2002).

Elevated and normal total T4 levels have been reported in drug naive and acute schizophrenic patients and are described to normalize or decrease, respectively, as a response to treatment with different drugs (Baumgartner et al. 2000, Kelly and Conley 2005, Martinos et al. 1986, Rao et al. 1984, Rinieris et al. 1980). A possible correlation between thyroid hormones level before and after treatment and possible prognosis has been proposed. Baumgartner and colleagues found that the higher T4 and rT3 levels in patients before treatment, the better they respond to neuroleptic medication; and the better the patients responded, the more their T4 levels fell (significant only at the 5% and not after Bonferroni's correction) (Baumgartner et al. 2000). Prediction of outcome has been proposed also on the basis of TSH response to TRH. Although this predictor has been studied mostly in depressive patients, some studies on the treatment of psychosis indicate a better (Langer et al. 1986) and more rapid response (Beasley et al. 1988) to neuroleptics in patients showing blunted TSH response to TRH. Consistently with the findings of Langer et al. another study found a considerably higher percentage of remitter patients who showed a blunted TSH response to TRH compared to non responders after neuroleptical treatment (Yazici et al. 2002), whereas higher total and free T3 levels, a blunted TSH response to TRH may indicate a better response in schizophrenic patients (Yazici et al. 2002).

These clinical findings seem partially disconfirm studies attesting a possible role for deficient THs level in schizophrenia in myelin growth. Nevertheless these hormones seem to exert their role on myelination process early in life and the dosage of their level at the onset of disease or when the disease is already well established could not be adequate to explain their role in pathogenesis. Thus further studies specifically aimed to find possible link between altered thyroid hormone circulation levels in schizophrenia and altered myelination are requested.

Myelin hypothesis on schizophrenia

First appearance of myelin hypothesis in schizophrenia was due to pivotal findings in human post-mortem tissue (Hakak et al. 2001). More in depth, a significantly decreased expression of six myelin-related genes predominantly express in oligodendrocytes, including the myelin-associated glycoprotein (MAG), myelin and lymphocyte protein (MAL), 22 ,32 -cyclic nucleotide 32 -phosphodiestase (CNP), gelsolin, transferrin and HER3 (ErbB3) was found in the dorsolateral prefrontal cortex (DLPFC) in postmortem schizophrenic brains. Subsequent studies (Aberg et al. 2006, Aston et al. 2004, Dracheva et al. 2006, Iwamoto et al. 2005, Katsel et al. 2005a, Katsel et al. 2005b, Sugai et al. 2004, Tkachev et al. 2003) and a microarray study confirmed previous studies that implicate changes in myelin-related genes in the pathology of schizophrenia (Haroutunian et al. 2007). In this study the superior temporal cortex of schizophrenic patient group showed the largest number of altered transcripts, followed by the anterior and posterior cingulate cortices (with almost 50% fewer altered transcripts), and then by the hippocampus. These findings are consistent with post-mortem and neuroimaging studies that have repeatedly shown the susceptibility in schizophrenia of temporal, medial temporal/hippocampal, cingulate and frontal cortical regions of the limbic pathway (Baumann and Bogerts 1999, Benes 2000, Bogerts 1997, Buchsbaum 1990, Harrison and Eastwood 2001, Todtenkopf et al. 2005), the brain regions that showed the greatest number of aberrantly expressed genes in schizophrenia. Moreover, PCR-based studies completed to validate microarray findings. With this regards, mRNA levels for myelin oligodendrocyte glycoprotein (MOG) in the DLPFC (Dean et al. 2007) and myelin-associated protein (MAG), quaking (QK1), transferring and 20,30-cyclic nucleotide 30-phosphodiesterase (CNP) in the anterior cingulate cortex (ACC) were found as decreased in patients with schizophrenia (McCullumsmith et al. 2007), although another study did not confirmed changes in levels of mRNA for MAG or CNP in the DLPFC of schizophrenic patients (Mitkus et al. 2008).

Altered expression of myelin genes could be entailed in those subtle abnormalities in oligodendrocytes involved in abnormal neuron-glia interactions and in a profound decrease in the conduction velocity (CV) (Tanaka et al. 2009). With this regard an interesting study by Tanaka and collegues (Tanaka et al. 2009) attested an abnormal behavior related to schizophrenia in a *plp1* transgenic mouse line where defects in white matter made CV reduced by half. Hence, these results suggested that defects in white matter could cause a decreased CV also in human schizophrenic patients. Although many symptoms of the disorder are difficult to measure in rodents, some measurable behavioral abnormalities in schizophrenia, such as disruption in prepulse inhibition of startle response (PPI) and cognitive deficits, can be also assessed by the tests for rodents that mimic the ones for humans. They observed PPI deficit, decreased working memory, and decreased spatial memory in the *plp1* transgenic mice. PPI provides a measure of sensorimotor gating that can model the preattentive processing deficits that are observed in schizophrenic patients. *Plp1* gene expression is mainly restricted to oligodendrocytes, indicating that a primary abnormality in white matter can lead to cognitive deficits. White matter changes, including an increased cell density in deep white matter (Akbarian et al. 1996, Kirkpatrick et al. 1999) have also been found in schizophrenic patients.

Thus, current data suggest that changes in the expression of myelin-related proteins, and therefore

myelination, may be an important mechanism underlying schizophrenia pathogenesis. The expression of some genes involved in this process are regulated by thyroid hormones so an important task could be deepen the role of their abnormalities in clinical aspects.

Imaging

The majority of studies implicating white-matter alterations in schizophrenia employ in-vivo imaging and the use of magnetic resonance imaging (MRI) has been central to the establishment of these white matter changes. In T2-weighted sequence signal intensity is largely determined by water content and therefore serves as an indicator of demyelination although white-matter hyperintensities were certainly not consistently found in several studies (Brown et al. 1992, Brown et al. 1995, Hulshoff Pol et al. 2000, Keshavan et al. 1996, Lane et al. 1996, Rivkin et al. 2000, Symonds et al. 1997). Thus, newer and more sensitive scanning technologies, namely magnetic transfer imaging (MTI) and diffusion tensor imaging (DTI) has in recent years refined to provide the subtle abnormalities and to increase information to structural white matter findings. Magnetic transfer imaging gives an indirect visualization of protons bound to macromolecules such as myelin and cell membrane and a loss of this macromolecules, such as myelin lipids, results in decreased magnetization transfer ratio (MTR) (Grossman et al. 1994). Significant reductions in MTR were found in inferior frontal, middle frontal, inferior and middle temporal, and superior occipital gyri, particularly in frontal and temporal regions (Foong et al. 2001). Decreased MTR was related to negative symptom severity in left parietal and temporo-occipital areas. Nevertheless, recently abnormalities of white matter were retrieved by diffusion tensor imaging (DTI), which measures the sum of the vectors of water diffusion within axons or myelin sheaths, namely the fractional anisotropy (FA) of the tissue. White matter structures, axons and myelin aligned in the same plane have a higher anisotropy than structures that are found in multiple planes, and hence (Hoistad et al. 2009). Other measure gathered from DTI is the diffusion of water molecules within white matter, a helpful tool to describe the structural integrity of white matter as damaged white matter appears with a greater diffusivity than normal (Rugg-Gunn et al. 2001, Taber et al. 2002, Ulug et al. 1999). Most of at least 39 DTI or MT studies in schizophrenia showed decreased FA somewhere in the white matter without consistent localization of such loss, whilst four were entirely negative (Begre et al. 2003, Foong et al. 2002, Price et al. 2005, Wang et al. 2003) (see (Dwork et al. 2007) for an extensive review). A predominance of ventral abnormalities in prefrontal white matter were found (Ardekani et al. 2003, Buchsbaum et al. 2006a, Buchsbaum et al. 2006b, Buchsbaum et al. 1998, Hao et al. 2006, Kumra et al. 2004), but other studies found generalized decreases that included dorsal prefrontal white matter (Federspiel et al. 2006, Lim et al. 1999, Minami et al. 2003), underlying a cortical region implicated in functional imaging studies of cognition in schizophrenia (Callicott et al. 2003, Weinberger et al. 1986).

Other DTI studies have shown decreases in FA in the cingulum bundle as well as in the overlying cingulate gyrus in patients with schizophrenia (Fujiwara et al. 2007, Kubicki et al. 2003, Kumra et al. 2005, Sun et al. 2003, Wang et al. 2004, White et al. 2008). Although a decrease in anisotropy seen in schizophrenia has not been univocally assessed, it could represent a further support to the possible implication of white matter abnormalities in schizophrenia, creating a functional obstacle to corticocortical and corticosubcortical interaction compatible with some of the symptoms of schizophrenia, particularly the cognitive deficits.

Symptomatologic correlations in white matter pathology

Several evidences suggest the importance of myelination for cognitive functions as cognition, learning and development of skills and memory (Fields 2008). Myelination of different brain regions coincides with the development of specific cognitive functions (Mabbott et al. 2006, Nagy et al. 2004, Yakovlev and Lecours 1967) and also individual difference within normal range in normal cognitive development (Casey et al. 2000, Liston et al. 2006, Walhovd and Fjell 2007), IQ (Miller 1994, Schmithorst et al. 2005), variation in reading skill (Gold et al. 2007, Klingberg et al. 2000, Niogi and McCandliss 2006), and working memory (Gold et al. 2007, Nestor et al. 2007) are correlated with difference in white matter structure. Altered myelination could be involved in a disrupted functional connectivity and lead to impair information processing, clinically expressed as several cognitive symptoms (Fields 2008). Consistently, a wide range of neurological and psychiatric disorders (see (Fields 2008) for a referenced complete list) have been found to be accompanied by changes in white matter structures or abnormalities in myelin genes, e.g. in 40% of multiple sclerosis patients defects in myelin insulation can lead to impaired cognitive function (Kujala et al. 1997).

In schizophrenia cognitive impairment is recognized as a core feature. In young individuals with schizophrenia, cognitive deficits are often detectable on psychological testing (Goldberg and Weinberger 1988, Green et al. 2004). In the majority of elderly individuals with schizophrenia, cognitive impairments are of a severity that would be characterized as dementia in individuals without schizophrenia (Arnold et al. 1995, Davidson et al. 1995, Dwork et al. 1998).

The possible dysfunction in myelin in schizophrenia is attested also by overlapping clinical expression and neuroanatomic topography of lesion with Metachromatic leukodystrophy (MLD), which is characterized by demyelination in the frontal lobes, particularly in the periventricular white matter and in corpus callosum (Davis et al. 2003). The late-onset form (adolescent to young adulthood) of MLD has been characterized by cognitive changes with combined frontal gray and white matter cognitive changes (D'Hooge et al. 2001, Johannsen et al. 2001, Shapiro et al. 1994) that has a great deal of overlap with the cognitive changes seen in schizophrenia.

As above reported, Tanaka and collegues (Tanaka

et al. 2009) attested behavioral abnormalities of schizophrenia in rodent model, such as disruption in prepulse inhibition of startle response (PPI) and cognitive deficits, assessed by the tests for rodents that mimic the ones for humans, in a *plp1* transgenic mouse line where defects in white matter made CV reduced by half.

Thyroid hormone have been directly implicated in the processes of learning and memory (Zoeller and Rovet 2004), particularly working memory (Wietrzych et al. 2005), which is intricately involved in schizophrenia (Mitchell and Crow 2005). Major thyroid hormone deficiency during pregnancy results in cretinism, while mild hypothyroidism is associated with poorer cognitive development. Mice deprived of transthyretin (TTR), a T4 plasma binding protein in circulation, are euthyroid hypothyroxinemic but display increased exploratory activity and reduced signs of depressive like behavior (Sousa et al. 2004). Follow up of thyroid function throughout pregnancy and evaluation of the psychomotor development of the offspring, possibly until adulthood, would clearly be a more relevant indication of a relationship between thyroid hormones and behavior disorders such as schizophrenia.

White matter development and schizophrenia hypothesis

Although initiated prenatally in humans, most tracts and regions become myelinated during the first year of life. White matter expansion then proceeds linearly from 4 to 20 years (Giedd et al. 1999) and myelination continues also into third decade of life (Yakovlev and Lecours 1967). Connections between the cortex and hippocampus have been found to be actively myelinating through childhood, adolescence, and adulthood and a defect in myelination of key corticolimbic pathways could be related to the development of schizophrenia (Benes 1989, Benes et al. 1994). One of the critical brain structures of highly myelinated axons is the corpus callosum, especially in the posterior region connecting the temporal and parietal association cortex (Bagwell et al. 1996). The corpus callosum increases throughout childhood and up to the third decade, and this enlargement has been attributed to the process of myelination (Giedd et al. 1999). A linear relation was demonstrated between age and corpus callosum size in normal young subjects (Pujol et al. 1993), but not in the schizophrenic patients, as reported in a series of 30 patients with previously untreated schizophrenic illness where a reductions in the size of the corpus callosum, especially in the posterior region connecting the temporal and parietal association cortex was found (Bagwell et al. 1996). Nevertheless, myelination processes that occur during late adolescence to early adulthood (the time of peak incidence of onset of schizophrenia) are concentrated in the frontal and temporal lobes. In particular the fact that prefrontal cortex, a region critical in the development of schizophrenia, is the last region of the brain to mature (Fuster 2002) with its myelination not complete until late adolescence (Paus et al. 2001) may be significant for the involvement of myelination in schizophrenia physiopathology (Hoistad et al. 2009). A model in which a deficit of myelin in schizophrenia arises from a partial or complete failure of myelination in late adolescence and early adulthood has been suggested (Dwork et al. 2007). In this model, normal myelination would progress with a normal developmental variability, with differences occurring early in life that remain constant and that contribute to cognitive variability both to individuals who remain healthy and to those who develop schizophrenia. Myelination in individuals who will develop schizophrenia would start off normally, but during late adolescence and several years before the onset of schizophrenia myelination would be interrupted, depriving affected individuals of much of the myelin normally acquired in adulthood. The trajectory of age related white matter volume expansion for schizophrenic patients through middle age deviates from that observed for age-matched normal controls, with schizophrenic patients showing less robust increases in white matter volume (Bartzokis et al. 2001). The onset of clinical disease may follow several years of failing myelination that would not necessarily entail further deficits of myelin. These suggestions claim the postnatal processes of myelination to be altered in schizophrenic patients.

Conclusion and future direction

White matter changes may not be the sole cause for the development of schizophrenic symptoms, but recent evidence is accumulating to indicate that this plays an important role in at least some subset of schizophrenia.

Although previous DTI studies have shown decreases in FA in schizophrenia, these findings have not been univocally assessed and could be somewhat inconsistent due in large part to small subject samples and different methods of identifying particular brain regions of interest (Kubicki et al. 2007). Another important limitation of available results is that the majority of the studies were conducted on chronic patients and not at the onset (or before the onset) of psychosis. With this regards the only study on first episode psychosis (Price et al. 2005) did not find difference between patients and controls. Moreover, even if Segal and collaborators found a significant decrease in the overall grey matter volume in the anterior cingulate gyrus in schizophrenia, patients with recent-onset schizophrenia resulted to have the highest FA in several regions and patients with chronic schizophrenia had the lowest both in grey and white matter (and consequently a supposed higher functional obstacle to possible interaction) (Segal 2008). Thus, findings in chronic patients might just be a consequence of the long duration of the illness or of the effect of medication and not be suggestive of what lead to the onset of schizophrenia. More imaging studies at the onset of schizophrenia are requested to test our hypothesis of a possible involvement since the early phase of the illness. Moreover in a recent anatomo-pathological study no significant differences in the oligodendrocyte distribution or density (specifically in the cingulum bundle) were found between 13 chronic

schizophrenics and 13 age-matched controls, in contrast to earlier data from the prefrontal subcortical white matter (Segal et al. 2009). These results suggest that subtler oligodendrocyte or myelin anomaly may underlie the structural deficits observed by brain imaging in schizophrenia and that more precise techniques could be requested to identify them.

If myelin and myelination deficits represent a major abnormality in the disease, it could be of interest to consider factors that determine this process and that could be involved in clinical symptomathology if dysfunctional. In this perspective, the long-held hypotheses of abnormal dopamine system function could be re-conceptualized within a myelination framework for a possible interaction of the abnormalities in dopamine function with oligodendrocytes proper development and function, as two dopamine receptor, D2 and D3 are expressed on oligondendrocytes and aberrant dopamine action on oligodendrocytes has been suggested as a pathological mechanism for myelin impairment.

Among different regulators, thyroid hormone exerts a critical role in developmental myelination, acting on the production and maturation of oligodendrocyte, and on the expression of genes encoding for myelin protein of oligodendrocytes.

Question about possible therapeutical implication of thyroids hormones in schizophrenia could then arise. An early report by Gornall and colleagues (Gornall et al. 1953) illustrates the successful treatment of a periodic, schizophrenic illness by thyroid administration with a striking effect on the mental health of 2 only cases. They could not assess a reason for this effect, but they hypothesized that thyroid hormone may render the tissue cells less vulnerable to an existing state of hormonal imbalance, which in some cases could be associated with a subnormal oxygen utilization by the tissues. Since remyelination is considered a recapitulation of cellular and molecular events occurring during development a recent preclinical study (Fernandez et al. 2009) tested the possibility of stimulating with 3,5,30-L-triiodothyronine (T3) the oligodendroglial lineage and maturation in neurospheres derived from the subventricular zone of brains both from adult rats non-pathological and pathological (affected by the inflammatory demyelinating disease experimental allergic encephalomyelitis). T3 was found reducing the proliferation rate of neurospheres, shifting towards oligodendroglial lineage, and also favoring oligodendrocyte maturation and authors suggested that T3 might be an important factor in favoring remyelination in demyelinating disorders. Otherwise the hypothesis that typical and atypical medications may differentially impact brain myelination in adults with schizophrenia was assessed (Bartzokis et al. 2009). In two different male cohorts of healthy controls compared to cohorts of subjects with schizophrenia who were treated with either oral risperidone or fluphenazine decanoate an increased white matter volume suggestive of increased myelination was detected in the patient group treated with atypical antipsychotic compared to typical one, both with "classical" and novel MRI method used to estimate intracorticalmyelin (ICM) volume. When compared with healthy controls, the two groups of schizophrenic patients differed in the frontal lobe ICM measure with the risperidone group having significantly higher volume. The data suggest that in adults with schizophrenia antipsychotic treatment choice may be specifically and differentially impacting later-myelinating intracortical circuitry. Although evocative, these later findings report a possible role of T3 and antipsychotics in remyelination but, as expressed above, the suggested deficit of myelin in schizophrenia would arise in late adolescence and early adulthood and a central period for schizophrenia pathogenesis could be early life. So an open question and field of future research remains if the evaluation of a correct thyroid imbalance, with its role in myelination and eventually in the pathogenesis of schizophrenia, might be assessed early in pediatric and adolescence age to prevent with appropriate supplementation those neurotrophic impairment that could reflect in clinical expression in successive years.

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