Obrela JOURNAL Dialogues in Clinical Neuroscience & Mental Health

Volume 2, issue 2, 2019

Special Issue in Demyelinating Diseases

Safety of the newer disease-modifying agents for multiple sclerosis: disproportionality analysis in the FDA Adverse Events Reporting System database.
Vasiliki Nikolopoulou, Spyridon Siafis, Antonios Milonas, Dimitrios Kouvelas, Georgios Papazisis, DOI: 10.26386/obrela.v2i2.114

Randomized Controlled Trials: The case of Multiple Sclerosis - Refining the constraints of a treasure, a short outline
Theodoros S. Constantinidis, DOI: 10.26386/obrela.v2i2.115

Is there a therapeutic potential for repetitive Transcranial Magnetic Stimulation (rTMS) in the management of cognitive impairment in Multiple Sclerosis?
Grigorios Nasios and Lambros Messinis, DOI: 10.26386/obrela.v2i2.116

Does multiple sclerosis cause progressive and widespread cognitive decline?
Marina Katsari, Dimitrios Kasselimis, Georgios Koutsis, and Constantin Potagas, DOI: 10.26386/obrela.v2i2.117

Is psychosis, at least in part, an immune-related dysmyelination disease?

Orestis Giotakos, DOI: 10.26386/obrela.v2i2.118

Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.114 ISSN 2585-2795

Safety of the newer disease-modifying agents for multiple sclerosis: disproportionality analysis in the FDA Adverse Events Reporting System database.

Vasiliki Nikolopoulou, Spyridon Siafis, Antonios Milonas, Dimitrios Kouvelas, Georgios Papazisis
Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Greece.

Abstract

Purpose: Aim of the present study was to identify potential safety signals for the six newer disease-modifying therapies (DMTs) for multiple sclerosis using the FDA Adverse Events Reporting System (FAERS) database.

Methods: A case/non-case study was conducted with data from spontaneous reports submitted in FAERS between 2004 and 2018, using the OpenVigil2.1-MedDRA. Daclizumab, natalizumab integrin, alemtuzumab dimethyl fumarate, fingolimod, teriflunomide were examined. Adverse events were selected by the Summary Product Characteristics of the products, including all frequency levels. The reporting odds ratio (ROR) was used to express the association between DMTs and reporting adverse events.

Results: Currently approved DMTs share some common side effects such as increased risk for infections (especially progressive multifocal leukoencephalopathy and herpes virus infections), risk for neoplasms (basal and squamous cell carcinoma, kaposi's sarcoma) and blood disorders (lymphopenia, leukopenia, pure red cell aplasia) which were confirmed by our analysis.

Conclusion: This disproportionality analysis strengthens the already knowledge about the safety of DMTs for multiple sclerosis and emerges some new potential safety signals.

Keywords: multiple sclerosis, drug safety, disease-modifying therapies, FDA Adverse Events Reporting System

Special Issue in Demyelinating Diseases

Corresponding Author: Georgios Papazisis, Psychiatrist, Associate Professor of Clinical Pharmacology, Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Tel and Fax: +30 2310 999323, e-mail: papazisg@auth.gr

DOI: 10.26386/obrela.v2i2.114 ISSN 2585-2795

Introduction

Multiple sclerosis (MS) is a chronic disabling disorder of the central nervous system with autoimmune demyelinating and neurodegenerative components. Disease course is highly variable but it can be classified as relapse-remitting (in about 85% of the new-onset MS) and primary or secondary progressive [1]. Recent advances in understanding the pathogenetic mechanisms led to the development of treatment options aiming to modify and improve disease progression rather than simply ameliorating symptoms; these treatments are usually called disease-modifying therapies (DMTs) [1]. Evolution of DMTs started in early 2000s with the introduction IFN-β1b and was later expanded with the introduction of natalizumab, but available DMTS are mainly effective on the relapse-remitting pattern of MS [1]. A considerable number of DMTs with different efficacy and tolerability patterns is available, yet their mechanism of actions is not clearly understood. Drug choice should consider the benefit-risk ratio for each individual. Therefore, DMTs are usually classified as first-line (moderately effective, favorable safety profile) and second-line (highly effective, risk of more severe side effects) [2]. Accordingly, a recent network meta-analysis found that there are differences in the efficacy of DMTs; alemtuzumab, natalizumab and ocrelizumab were the most efficacious [3]. Older DMTs have a long list of possible adverse effects in the Summary of Product Characteristics (SPC), in contrast to newer DMTs with not well-studied long-term safety [2]. Long-term safety of a DMTs cannot be studied with RCTs, and as a result post-marketing studies are needed. Herein, safety signals for the six DMTs for multiple sclerosis were evaluated using the FDA Adverse Events Reporting System (FAERS) database.

Methods

Examined DMTs and adverse events

The Six newer DMTs were examined in this study, three monoclonal antibodies (daclizumab, natalizumab integrin, alemtuzumab) and three oral agents (dimethyl fumarate, fingolimod, teriflunomide). The very recently approved DMTs ocrelizumab and cladribrine, were not included, because their data were not accessible with OpenVigil, the software used to analyze FAERS data [4]. Adverse events of the DMTs were selected by the Summary Product Characteristics of the products, including all frequency levels. A long list of adverse events was investigated (Table 1).

Table 1. Investigated adverse events selected from SPC of DMTs. Preferred terms (PT) according to MedDRA version 17 were used whenever available, otherwise higher level terms were used.

System Organ Classes	Adverse events
infections and infestations	influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, sepsis, herpes viral infection, tinea versicolor, pneumonia, progressive multifocal leukoencephalopathy, cryptococcal infections, nasopharyngitis, conjunctivitis, cellulitis, herpes zoster
neoplasms	basal cell carcinoma, malignant melanoma, lymphoma, squamous cell carcinoma, kaposi's sarcoma, merkel cell carcinoma, lymphoproliferative disorders
blood and lymphatic system disorders	lymphopenia, leuckopenia, neutropenia, anemia, thrombocytopenia, peripheral oedema, red blood cell analyses abnormal, leukocytosis, coagulopathies, pancytopenia, thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy, pure red cell aplasia, agranulocytosis, haemolytic anaemia
endocrine disorders	hirsutism
immune system disorders	rash, anaphylaxis, angioedema, urticaria, hypersensitivity
psychiatric disorders	anxiety, depression, insomnia, confusion and disorientation, hallucination, mental disorders, nightmare, psychotic disorder
nervous system disorders	headache, paraesthesia, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, dizziness, migraine, posterior reversible encephalopathy syndrome-PRES, tremor, seizures, encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, paralysis and paresis, amnesia, hypertonia, burning sensation, flushing
eye disorders	vision blurred, macular oedema, photophobia, cataract, blindness, optic neuropathy
ear and labyrinth disorders	tinnitus, hypoacusis, deafness neurosensory
cardiac disorders	palpitations, bradycardia, atrioventricular block, T-wave inversion, myocardial infraction, tachycardia, heart failures, ventricular arrhythmias, cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ventricular hypertrophy, pericardial effusion, torsades de pointes
vascular disorders	hypertension, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders, venous thrombosis, shock
respiratory thoracic and mediastinal disorders	interstitial lung disease, cough, dyspnea, pleural effusion, nasal congestion and inflammations, respiratory failures, asthma, acute respiratory distress syndrome, hypoxia
gastrointestinal disorders	diarrhoea, nausea, abdominal pain upper, vomiting, toothache, pancreatitis, stomatitis, abdominal pain, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, acute and chronic pancreatitis, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying, pancreatic pseudocyst, subileus, gastroenteritis, gastritis
hepatobiliary disorders	alanine aminotransferase increase, gamma-glutamyltransferase increase, aspartate aminotransferase increase, acute hepatitis, bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice, venoocclusive liver disease, hepatic artery thrombosis, hepatic failure, drug-induced liver injury

metabolism and nutrition disorders	dyslipidemia, diabetes mellitus, hyperglycaemic conditions, hyperkalaemia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia, dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia
skin and subcutaneous tissue disorders	alopecia, acne, severe skin disorders, nail disorders, eczema, pruritus, dermatitis, photosensitivity, toxic epidermal necrolysis-Lyell's syndrome, Stevens Johnson syndrome, erythema
musculoskeletal and connective tissue disorders	musculoskeletal pain, myalgia, arthralgia, back pain, muscle spasms, pain in extremity, mobility decreased
renal and urinary disorders	pollakiuria, renal impairment, nephropathy-BK virus, renal failure, nephropathy toxic, renal tubular necrosis, oliguria, haemolytic uraemic syndrome, anuria, cystitis haemorrhagic
reproductive system and breast disorders	menorrhagia, dysmenorrhea, uterine bleeding
general disorders and administration site conditions	pyrexia, pain and discomfort, asthenic conditions, oedema, influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, temperature intolerance, fall, ulcer, thirst, fat tissue increased
Investigations	weight decrease, neutrophil count decrease, white blood cell count decrease, neutrophil count decreased, blood creatine phosphokinase increased, blood triglycerides increased, liver function tests abnormal, weight increased, amylase increased, blood lactate dehydrogenase increased, echocardiogram abnormal, electrocardiogram QT prolonged, blood immunoglobulin M decreased, Blood immunoglobulin G decreased, albumin urine present
injury, poisoning and procedural complications	post-traumatic pain, infusion-related reactions

Case/non-case study

A case/non-case study was conducted with data from spontaneous reports submitted in FAERS between 2004 and 2018, using the OpenVigil2.1-MedDRA, an open pharmacovigilance data mining and analysis tool [4]. FAERS is consisting of individual safety reports mainly by consumers and health professionals from the United States, including administrative information, patient demographics, adverse events, information about drug therapy, patient outcomes and type of reporter [5]. In FAERS, adverse events are coded using the MedDRA ontology (version 17 is implemented in OpenVigil2.1-MedDRA). As cases adverse events were evaluated and they were primarily identified by Preferred Terms (PT), and if not available a higher level term was used. Reports with one or more of DMTs as suspected, interacting or concomitant were used to define exposure. In each analysis, all the other events were defined as non-cases and all other drugs as non-exposure. OpenVigil2.1-MedDRA operates only on cleaned FDA data, that is to say deleting most duplicates or reports with missing data [4].

Disproportionality analysis

The reporting odds ratio (ROR) was used to express the association between DMTs and reporting adverse events. ROR estimates the frequency of the examined adverse event co-reported with DMTs compared with all other drugs in the database. Disproportionality or safety signals were defined when the lower boundary of the 95% CI of ROR was greater than one and the number of reports was higher than three [5].

Results

The dataset contained 5791772 reports submitted in FAERS

between 2014 and 2018. Alemtuzumab (FDA approved 2001) was included in 4992, daclizumab (FDA approved 2016) in 1784, natalizumab (FDA approved 2004) in 103387, dimethyl fumarate (FDA approved 2013) in 53621, fingolimod (FDA approved 2010) in 21077 and teriflunomide (FDA approved 2012) in 12122 reports. Disproportionality signals are reported in Table 2.

Table 2. Safety signals identified for the association between co-reporting of a DMT and an adverse event. PML: progressive multifocal leuckoencephalopathy, BCC: basal cell carcinoma, SCC: squamous cell carcinoma , ARDS: acute respiratory distress syndrome, TTP: thrombotic thrombocytopenic purpura

Drug	Adverse event (ROR; 95% CI)
Alemtuzumab	Infections: PML (21.64; 15.87-29.5), herpes zoster (10.54; 8.74-12.71), herpes simplex (9; 5.58-14.51), sepsis (5.57; 4.67-6.64), urinary tract infection (3.25; 2.66-3.98), oral herpes (2.57; 1.38-4.79), pharyngitis (2.29; 1.03-5.11), cystitis (2.3; 1.41-3.76), viral gastroenteritis (2.11; 1-4.43), pneumonia (2.66; 2.27-3.11), conjunctivitis (3.38; 1.76-6.52), Neoplasms: lymphoproliferative disorder (20; 11.78-33.93), BCC (13.19; 9.53-18.26), SCC (13.47; 9.27-19.57), neuroendocrine carcinoma (10.59; 2.63-42.63), melanoma (6.45; 4.28-9.73), Kaposi's sarcoma (5.68; 2.13-15.17), lymphoma (4.32; 2.69-6.97), Blood: lymphopenia (48.66; 39.95-59.27), pure red cell aplasia (20.84; 13.38-32.45), TTP (17.67; 11.59-26.95), leukopenia (11.66; 9.66-14.06), neutropenia (7.84; 6.74-9.12), anaemia (1.88; 1.49-2.37), thrombocytopenia (7.2; 6.15-8.44), coagulopathy (2.79; 1.58-4.92), pancytopenia (11.14; 9.32-13.32), thrombotic microangiopathy (12.67; 8.05-19.93), agranulocytosis (4.37; 2.53-7.54), haemolytic anaemia (14.19; 10-20.13) Immune: rash (2.09; 1.8-2.43) Psychiatric and neurologic: PRES (8.39; 5.4-13.04), headache (1.73; 1.52-1.97), encephalopathy (2.43; 1.41-4.18), paresis (4.85; 1.56-15.09) Cardiac: bradycardia (5.61; 4.43-7.11), tachycardia (3.06; 2.38-3.93), pericardial effusion (3.25; 1.99-5.32)

	Respiratory: ARDS (6.65; 4.55-9.72), respiratory failure (5.21; 4.23-6.42), pleural effusion (4.85; 3.8-6.2), intersistital lung disease (3.28; 2.27-4.72), cough (1.71; 1.37-2.13), dyspnea (1.27; 1.08-1.49), hypoxia (4.06; 2.78-5.93) Gastrointestinal and hepatobiliary disorders: venoocclusive liver disease (30.6; 21.27-44.02), hepatic artery thrombosis (13.97; 1.94-100.36), ascites (8.45; 6.43-11.12), ulcer (4.59; 1.48-14.27), gastroenteritis (4.06; 2.3-7.17) , ALT increased (4.51; 3.56-5.71), AST increased (2.76; 2-3.8), GGT increased (2.26; 1.28-3.98), acute hepatitis (2.73; 1.02-7.28), cholestasis (3.67; 2.03-6.64), jaundice (2.05; 1.56-3.36), hepatic failure (4.41; 3.19-6.1) Metabolic: fluid overload (4.37; 2.58-7.38), hyperglycaemia (2.05; 1.27-3.31), Skin: eczema (2.39; 1.24-4.6), erythema (1.37; 1.02-1.83) Renal: BK-virus infection (120.21; 86.36-167.35), cystitis haemorrhagic (27.38; 17.56-42.7), tubular necrosis (5.29; 2.84-9.86), renal impairment (2.25; 1.61-3.13), renal failure (2.52; 2.02-3.14), anuria (3.6; 1.8-7.22), General: pyrexia (5.91; 5.33-6.55), temperature intolerance (2.51; 1.04-6.03), neutrophil count decrease (4.91; 3.46-6.95), LDH decrease (4.85; 3.09-7.62), infusion related reaction (4.79; 3.51-6.55), liver function test abnormal (2.12; 1.41-3.2),
Daclizumab	Infections: urinary tract infection (7.3; 5.8-9.19), pharyngitis (3.21; 1.03-9.96), herpes zoster (4.35; 2.7-7.01), influenza (2.64; 1.66-4.21), upper tract infection (2.18; 1.04-4.59), cystitis (2.41; 1.08-5.38), herpes simplex (4.41; 1.42-13.7), sepsis (6.91; 5.31-9.01), pneumonia (1.73; 1.26-2.39),
	Neoplasms: lymphoproliferative disorder (11.82; 3.8-36.76), BCC (4.92; 2.04-11.84), SCC (12.02; 6.24-23.17), Kaposi's sarcoma (15.92; 5.96-42.58), Blood: pure red cell aplasia (40.77; 24.02-69.21), TTP (4.42; 1.1-17.71), lymphopenia (3.67; 1.18-11.4), leukopenia (3.38; 1.92-5.97), pancytopenia (3.65; 2.2-6.07), agranulocytosis (3.75; 1.41-10.02) Psychiatric and neurologic: optic neuropathy (15.55; 5-48.4), confusional state (2.49; 1.78-3.48), amnesia (2.28; 1.4-3.74), Vascular: hypertension (1.64; 1.12-2.4) Respiratory: ARDS (4.11; 1.84-9.17) Gastrointestinal and hepatobillary disorders: obstructive bile duct disorders (excluding neoplasms; 5.04; 1.62-15.67), impaired gastric emptying (5.76; 1.85-17.9), diarrhea (1.52; 1.18-1.94), ascites (3.15; 1.5-6.61), gastroenteritis (6.64; 3.16-13.95), ALT increased (2.5; 1.48-4.23), AST increased (3.05; 1.83-5.06), GGT increased (2.63; 1.09-6.34), Metabolic: fluid overload (6.99; 3.49-14), metabolic acidosis (4.36; 2.41-7.89), hyperglycaemia (3.04; 1.58-5.86), dehydration (2.5; 1.69-3.72) Skin: eczema (6.71; 3.48-12.93), photosensitivity reaction (6.22; 3.23-11.98), dermatitis (4.74; 1.97-11.41), Muscle: mobility decreased (5.13; 3.48-7.56) Renal: BK-infection (63.61; 31.55-128.25), tubular necrosis (19.39; 11.22-33.52), HUS (12.22; 3.93-38.01), toxic nephropathy (7.9; 3.54-17.62), anuria (5.04; 1.89-13.45) renal impairment (2.15; 1.22-3.8),

	General: temperature intolerance (5.62; 2.1-15), liver function test abnormal (4.94; 3.14-7.77), influenza-like illness (2.83; 1.91-4.2), LDH increased (2.85; 1.07-7.59), fall (1.5; 1.08-2.09), pyrexia (1.61; 1.18-2.19)
Natalizumab	Infections: influenza (3.14; 2.96-3.33), upper tract infection (2.7; 2.46-2.95), urinary tract infection (6.36; 6.14-6.59), bronchitis (2.79; 2.61-2.99), sinusitis (3.56; 3.37-3.76), pharyngitis (1.54; 1.24-1.92), cystitis (6.96; 6.49-7.46), viral gastroenteritis (4.23; 3.74-4.78), oral herpes (2.11; 1.81-2.47), tooth infection (3.24; 2.75-3.81), laryngitis (2.19; 1.8-2.66), tinea pedis (2.42; 1.51-3.87), PML (29.6; 27.13-32.28), nasopharyngitis (196.04; 191.6-200.58), cellulitis (1.52; 1.36-1.69), herpes zoster (4.35; 4.07-4.65) Neoplasms: BCC (1.61; 1.31-1.97), melanoma (1.81; 1.53-2.15) Immune: hypersensitivity (1.94; 1.85-2.04) Psychiatric and neurologic: migraine (2.89; 2.71-3.07), headache (2.25; 2.19-2.31), amnesia (2.06; 1.92-2.21), depression (1.39; 1.33-1.45), confusional state (1.43; 1.35-1.52), paraesthesia (1.92; 1.83-2.02), sciatica (1.78; 1.43-2.21), carpal tunnel syndrome (1.38; 1.43-2.21), hyperesthesia (1.7; 1.35-2.14), neuralgia (1.7; 1.35-2.14), tremor (1.77; 1.68-1.86), seizures (1.15; 1.09-1.22), paralysis (1.29; 1.07-1.56), burning sensation (1.51; 1.38-1.64) Eye: vision blurred (1.5; 1.4-1.59), blindness (1.31; 1.16-1.48) Ear: hypoacusis (1.48; 1.32-1.66) Gastrointestinal and hepatobillary disorders: toothache (1.62; 1.36-1.93)
	Muscle: mobility decreased (8.71; 8.32-9.11)musculoskeletal pain (1.3; 1.18-1.44), arthralgia (1.16; 1.1-1.21), back pain (1.52; 1.45-1.6), pain in extremity (2.24; 2.16-2.33), Renal: pollakiuria (1.18; 11.04-1.35) General: temperature intolerance (16.26; 14.75-17.92), fall (3.35; 3.25-3.46), infusion-related reaction (3.27; 3-3.57), post-traumatic pain (2.75; 1.01-7.51), discomfort (2.05; 1.87-2.24), influenza-like illness (1.91; 1.79-2.04), pain (1.27; 1.23-1.32), feeling abnormal (1.23; 1.17-1.29), pyrexia (1.12; 1.06-1.17),

Dimethyl fumarate	Infections: viral gastroenteritis (2.5; 2.02-3.09), herpes zoster (2.41; 2.14-2.71), urinary tract infection (2.04; 1.89-2.21), influenza (1.89; 1.71-2.09), cystitis (1.87; 1.58-2.2), PML (1.74; 1.25-2.41), nasopharyngitis (1.76; 1.63-1.9), Blood: lymphopenia (5.24; 4.38-6.28) Immune: rash (1.08; 1.01-1.15), hypersensitivity (1.26; 1.16-1.37) Psychiatric and neurologic: flushing (31; 30.16-31.88), burning sensation (4.18; 3.89-4.49), paraesthesia (2.29; 2.14-2.43), neuralgia (2.09; 1.72-2.54), amnesia (1.89; 1.71-2.09), confusional state (1.69; 1.57-1.82), headache (1.32; 1.26-1.38), migraine (1.68; 1.51-1.87), Eye: blindness (2.06; 1.8-2.36) Ear: hypoacusis (2.07; 1.81-2.37) Gastrointestinal and hepatobillary disorders: abdominal pain upper (5.18; 4.96-5.41), diarrhea (2.71; 2.62-2.81), nausea (2; 1.93-2.07), vomiting (2.15; 2.06-2.24), abdominal pain (1.56; 1.46-1.67), dyspepsia (2.45; 2.25-2.65), flatulence (2.69; 2.42-2.98), constipation (1.49; 1.38-1.62), GERD (1.25; 1.1-1.42)
	Metabolic: dehydration (1.3; 1.17-1.44) Skin: pruritus (2.9; 2.77-3.04), erythema (2.68; 2.51-2.86), alopecia (2.3; 2.17-2.45), Muscle: mobility decreased (4.74; 4.39-5.12) General: temperature introlerance (4.63; 3.77-5.68), influenza-like illness (1.8; 1.65-1.97), feeling abnormal (1.17; 1.09-1.26), fall (1.6; 1.51-1.7)
Fingolimod	Infections: herpes zoster (6.93; 6.18-7.76), PML (6.86; 5.25-8.97), nasopharyngitis (2.92; 2.65-3.22), urinary tract infection (2.49; 2.3-2.79), influenza (2.03; 1.74-2.37), upper tract infection (2.58; 2.11-3.15), oral herpes (2.02; 1.43-2.84), herpes simplex (2.12; 1.31-3.42), laryngitis (2.13; 1.39-3.27), bronchitis (1.98; 1.66-2.36), sinusitis (1.87; 1.59-2.2), cystitis (2.05; 1.59-2.64), viral gastroenteritis (1.86; 1.26-2.73), conjunctivitis (1.69; 1.08-2.66), Neoplasms: BCC (7.15; 5.76-8.88), melanoma (4.21; 3.28-5.4), SCC (2.37; 1.54-3.64) Blood: lymphopenia (21.01; 18.1-24.38), leukopenia (2.51; 2.07-3.04) Psychiatric and neurologic: paresis (8.64; 5.65-13.21), migraine (2.88; 2.52-3.29), headache (2.38; 2.25-2.51), paraesthesia (2.48; 2.26-2.74), depression (1.39; 1.26-1.54), confusional state (1.73; 1.54-1.94), neuralgia (3.49; 2.74-4.44), dizziness (2.08; 1.95-2.22), tremor (1.31; 1.16-1.49), seizures (1.53; 1.37-1.71), paralysis (1.6; 1.11-2.33), amnesia (1.67; 1.41-1.97), hypertonia (1.87; 1.2-2.9), burning sensation (1.32; 1.08-1.61) Eye: macular oedema (46.58; 40.81-53.15), vision blurred (4.25; 3.91-4.63), photobia (3.44; 2.63-4.5), blindness (2.29; 1.87-2.8), cataract (1.31; 1.01-1.71),

	Cardiac: T wave inversion (9; 6.14-13.21), bradycardia (5.08; 4.49-5.74), atrioventricular block (2.8; 1.87-4.18), palpitations (2.32; 2.07-2.61), Vascular: hypertension (1.2; 1.05-1.36) Respiratory: cough (1.97; 1.78-2.17), dyspnea (1.26; 1.16-1.36) Gastrointestinal and hepatobillary disorders: γ-GT increased (4.38; 3.58-5.36) ALT increased (2.68; 2.31-3.11), AST increased (1.99; 1.66-2.39), nausea (1.15; 1.07-1.23), Skin: alopecia (1.46; 1.29-1.64) Muscle: back pain (2.55; 2.34-2.78), musculosketal pain (1.25; 1-1.56), pain in extremity (1.52; 1.39-1.67), mobility decreased (1.89; 1.57-2.27) Renal: pollakiuria (1.68; 1.32-2.14) General: temperature intolerance (6.17; 4.67-8.15), blood IgG decreased (5.5; 2.45-12.33), QT prolonged (2.28; 1.84-2.83), feeling abnormal (2.03; 1.86-2.22), fall (2.09; 1.93-2.27), influenza-like illness (1.95; 1.7-2.24), liver function test abnormal (2.2; 1.8-2.67), pain (1.09; 1-1.18), discomfort (1.48; 1.18-1.86), pyrexia (1.38; 1.25-1.52),
Teriflunomide	Infections: cystitis (3.7; 2.88-4.75), urinary tract infection (3.35; 2.95-3.81), viral gastroenteritis (2.61; 1.7-4.01), bronchitis (2.08; 1.66-2.6), laryngitis (2.11; 1.2-3.72), nasopharyngitis (2.06; 1.77-2.39), influenza (1.94; 1.58-2.39), herpes zoster (1.95; 1.48-2.56), sinusitis (1.46; 1.15-1.85) Blood: lymphopenia (3.98; 2.62-6.06) Immune: rash (1.65; 1.49-1.84)

	Psychiatric and neurologic: paraesthesia (7.11; 6.57-7.69), neuralgia (4.62; 3.5-6.09), burning sensation (3.77; 3.22-4.4), carpal tunnel syndrome (2.75; 1.75-4.31), peripheral neuropathy (2.66; 2.21-3.19), paralysis (2.29; 1.52-3.46),headache (2.23; 2.07-2.4), sciatica (2.12; 1.2-3.74), dizziness (1.18; 1.06-1.31), migraine (1.94; 1.57-2.4), depression (2.18; 1.96-2.43), insomnia (1.16; 1-1.33), Eye: blindness (1.69; 1.24-2.3)vision blurred (1.54; 1.29-1.84), Respiratory: cough (1.33; 1.14-1.56) Gastrointestinal and hepatobillary disorders: diarrhea (5.26; 4.97-5.56), abdominal pain upper (1.94; 1.69-2.23), nausea (1.89; 1.76-2.03), pancreatitis (1.99; 1.61-2.47), flatulence (1.47; 1.1-1.96), ALT increased (1.79; 1.41-2.27), hepatocellular injury (1.73; 1.02-2.93) Metabolic: decreased appetite (1.46; 1.25-1.7) Skin: mobility decreased (4.34; 3.69-5.11) back pain (1.72; 1.5-1.96), alopecia (1.35; 1.02-1.78), pain in extremity (2.13; 1.92-2.37), Renal: pollakiuria (2.7; 2.1-3.48) General: temperature abnormal (8.18; 5.96-11.23), fall (3.87; 3.57-4.2), pain (1.58; 1.44-1.72), influenza-like illness (2.08; 1.74-2.48), weight decreased τ(2.1; 1.87-2.37), liver function test abnormal (1.9; 1.44-2.51), feeling abnormal (1.57; 1.38-1.79), discomfort (1.46; 1.08-1.97)

Interestingly, although alemtuzumab was included in a smaller number of reports compared to the most of the other agents our analysis revealed significantly more safety signals with a higher ROR (>5). Particularly, alemtuzumab was significantly associated with various types of infections, with the strongest signal identified for bk polyomavirus infection (ROR 120.21; 95% CI 86.36-167.35), progressive multifocal leukoencephalopathy and herpes virus infections. Potential safety signals also emerged for blood disorders (lymphopenia, pure red cell aplasia, thrombotic thrombocytopenic purpura, haemolytic anaemia, leukopenia) but also neoplasms (lymphoproliferative disorder, basal cell carcinoma, squamous cell carcinoma. Venoocclusive liver disease and cystitis haemorrhagic were also significantly associated with alemtuzumab. Similar to alemtuzumab, the statistically strongest signal for daclizumab emerged for bk polyomavirus infections (ROR 63.61; 95% CI 31.55-128.25). Potential signals from the renal system included tubular necrosis and urinary tract infection. Further, the analyses showed significant association between daclizumab exposure and neoplasms (squamous cell carcinoma and Kaposi's sarcoma). Pure red cell aplasia was also strongly associated with daclizumab use. According to the analysis, the most probable safety signal for natalizumab was for nasopharyngitis (ROR 196.04; 95% CI 191.6-200.58). Progressive multifocal leukoencephalopathy, cystitis, urinary tract infection and herpes zoster infection were also identified as potential safety signals.

Dimethyl fumarate revealed a different adverse event profile since potential safety signals emerged for flushing, upper abdominal pain, decreased muscle mobility, lymphopenia, burning sensation and temperature intolerance. The most significant association for fingolimod was found for eye macular oedema (ROR 46.58; 40.81-53.15), followed by lymphopenia and herpes zoster infection. Electrocardiogram t wave inversion, basal cell carcinoma and progressive multifocal leukoencephalopathy were also significantly associated with fin-

golimod use. Finally, teriflunamide exposure was significantly associated with alopecia, nervous system paraesthesia, temperature intolerance and diarrhea.

Discussion

The safety profile of DMTs for multiple sclerosis has been evaluated using disproportionality analysis in the large pharmacovigilance database of FDA. Currently approved DMTs have different mechanisms of actions on targeting the immune system, therefore, they have different side effect profiles [6]. However, they share some common side effects such as increased risk for infections (e.g progressive multifocal leukoencephalopathy, herpes virus infections), risk for neoplasms (basal and squamous cell carcinoma, kaposi's sarcoma) and blood disorders (e.g lymphopenia, leukopenia, pure red cell aplasia, haemolytic anaemia) which were confirmed by our analysis.

The first disease-modifying treatment approved were IFN beta and glatiramer acetate, while the first approved newer agent with a different mechanism of action was natalizumab in 2004. Natalizumab, an anti-4alpha integrin monoclonal antibody, was temporarily suspended in 2005 after the reporting of 3 cases with progressive multifocal leucoencephalopathy in clinical trials. After the implementation of TOUCH safety recording system, for the early detection of PML, natalizumab was re-approved in 2006. Globally recording systems were developed by the marketing authorization holder to follow up infections, malignancies, melanoma and other adverse events occurring under natalizumab treatment (Tysabri Global Observational Program in Safety [TYGRIS], Tysabri Observational Protocol [TOP]) [7-9]. Our analysis confirmed the safety signal for PML and other infections, especially cystitis, urinary tract infection and herpes zoster infection. The strongest association for natalizumab use was found for nasopharyngitis.

Alemtuzumab is a humanized monoclonal antibody which binds to CD52, expressed by T and B lymphocytes, monocytes, macrophages, and eosinophils. It has the longest lasting effect on immune system among drugs used for MS. Our disproportionality analysis showed significant associations between alemtuzumab exposure and various types of infections, with the strongest signal identified for bk polyomavirus infection, progressive multifocal leukoencephalopathy and herpes virus infections. Potential safety signals also emerged for blood disorders (lymphopenia, pure red cell aplasia, thrombotic thrombocytopenic purpura, haemolytic anaemia, leukopenia) but also neoplasms (lymphoproliferative disorder, basal cell carcinoma, squamous cell carcinoma. Our findings strengthen the results of previous alemtuzumab trials that recorded mainly mild infections, but also serious opportunistic infections such as listeria meningitis or CMV activation. Secondary autoimmunity. have also been reported, including thyroid related disorders, immune mediated thrombocytopenia and rare cases of autoimmune nephropathies [10]. Those findings led to the development of a safety vigilance program to monitor any autoimmune disorders, renal, thyroid and hematological functions are screened regularly for the first 48 months after treatment [11].

Daclizumab is an anti-IL-2 monoclonal antibody, which received warning about hepatic injury and immune-mediated disorders. In addition the SPC warned about hypersensitivity reactions, depression, infections (such as upper respiratory tract infections and nasopharyngitis) [12]. To our results, statistically safety signal emerged for bk polyomavirus infections, pure red cell aplasia tubular necrosis, urinary tract and neoplasms (squamous cell carcinoma and kaposi's sarcoma). However, in March 2018, the drug was immediately suspended from the market after 12 reports of serious inflammatory brain encephalitis and meningoencephalitis with three of the cases being fatal [13].

The first oral agent approved for MS was fingolimod in 2010, a sphingosine 1 phosphate (S1P) analogue. In our analysis the most significant association for fingolimod was found for eye macular oedema followed by lymphopenia, herpes zoster infection, electrocardiogram t wave inversion, basal cell carcinoma and progressive multifocal leukoencephalopathy. Secondary macular edema due to retinal S1P receptor modulation leading to increased vascular permeability, has been reported in 0.5% of patients receiving 0.5 mg fingolimod in the clinical trials. Regulators require ophthalmological exam before initi-

ation of fingolimod treatment and because macular edema is most prevalent in the first 3–4 months after treatment onset, ophthalmological examination should be repeated at that time. Fingolimod should be stopped in the case of macular edema [14].

Teriflunomide is the second oral medication approved by FDA for the treatment of MS in 2012. In the clinical trials, most common side effects were headache, liver enzyme abnormalities, diarrhea, alopecia and nausea. Alopecia is usually mild and usually recovers after the first months [15]. Our results confirmed that, the most significant association for teriflunamide exposure was for alopecia, followed by nervous system paraesthesia, temperature intolerance and diarrhea.

Finally, the third oral drug approved 2013 for MS is dimethyl fumarate. It is a first-line drug with immunomodulatory and cytoprotective effects. According to the pre-marketing trial the most common adverse effects included flushing, abdominal pain, diarrhea, nausea, vomiting, pruritus and papular eruption [16]. In accordance, our analysis revealed potential safety signals for flushing, upper abdominal pain, decreased muscle mobility, lymphopenia, burning sensation and temperature intolerance.

The strengths of our analysis are the large number of reports and the comprehensive list of adverse events. However, it has certain limitations. First, the older disease-modifying agents IFN-β and glatiramer acetate were not investigated, yet they have quite well-known safety profile. Second, pharmacovigilance databases suffer from under-reporting, temporal patterns of reporting, notoriety of the adverse event and suboptimal quality of reports [5]. In addition, all other drugs in FAERs were used as reference in the disproportionality analysis as well as indication bias could have infiltrated the results. Finally, disproportionality analysis is a statistical method that measures co-reporting of adverse events and drugs, without being able to confirm causality.

Concluding, this disproportionality analysis strengthens the already knowledge about the safety of DMTs for multiple sclerosis and emerges some new potential safety signals. Considering the limitations of pharmacovigilance databases and statistical analysis, an appropriate causality assessment is needed to validate these signals, while further research is warranted to elucidate the comparative safety profile of DMTs in MS.

References

1. Ransohoff, R.M., D.A. Hafler, and C.F. Lucchinetti, Multiple sclerosis-a quiet revolution. Nature reviews. Neurology, 2015. 11(3): p. 134-142. doi: 10.1038/nrneurol.2015.14.

2. Soelberg Sorensen, P., Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol Scand, 2017. 136(3): p. 168-186. doi: 10.1111/ane.12712.

3. Lucchetta, R.C., et al., Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis: A Network Meta-Analysis. CNS Drugs, 2018. 32(9): p. 813-826. doi: 10.1007/s40263-018-0541-5

4. Böhm, R., et al., OpenVigil FDA – Inspection of U.S. American Adverse Drug Events Pharmacovigilance Data and Novel Clinical Applications. PLOS ONE, 2016. 11(6): p. e0157753. doi.org/10.1371/journal.pone.0157753

5. Sakaeda, T., et al., Data mining of the public version of the FDA Adverse Event Reporting System. Int J Med Sci, 2013. 10(7): p. 796-803. doi: 10.7150/ijms.6048

6. TaŞKapilioĞLu, Ö., Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis. Noro psikiyatri arsivi, 2018. 55(Suppl 1): p. S15-S20. doi: 10.29399/npa.23402

7. Selewski, D.T., et al., Natalizumab (Tysabri). American Journal of Neuroradiology, 2010. 31(9): p. 1588. DOI: https://doi.org/10.3174/ajnr.A2226

8. Sabol, R.A., et al., Melanoma complicating treatment with natalizumab for multiple sclerosis: A report from the Southern Network on Adverse Reactions (SONAR). Cancer Med, 2017. 6(7): p. 1541-1551. doi: 10.1002/cam4.1098

9. FDA, TYSABRI® (natalizumab) Injection FULL PRESCRIBING INFORMATION 2018.

10. Guarnera, C., P. Bramanti, and E. Mazzon, Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. Ther Clin Risk Manag, 2017. 13: p. 871-879. doi: 10.2147/TCRM

11. Devonshire, V., et al., Monitoring and management of autoimmunity in multiple sclerosis patients treated with alemtuzumab: practical recommendations. J Neurol, 2018. 265(11): p. 2494-2505. DOI: 10.1007/s00415-018-8822-y

12. FDA, ZINBRYTA (daclizumab) injection, for subcutaneous use 2017.

13. EMA. EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta. 2018 [cited 2018 07/03/2018]; Available from: https://www.ema.europa.eu/en/news/ema-recommends-immediate-suspension-recall-multiple-sclerosis-medicine-zinbryta.

14. Eckstein, C. and M.T. Bhatti, Currently approved and emerging oral therapies in multiple sclerosis: An update for the ophthalmologist. Surv Ophthalmol, 2016. 61(3): p. 318-32. DOI: 10.1016/j.survophthal.2015.12.001

15. Confavreux, C., et al., Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol, 2014. 13(3): p. 247-56. DOI:

10.1016/S1474-4422(13)70308-9

16. Fox, R.J., et al., Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med, 2012. 367(12): p. 1087-97. DOI: 10.1056/NEJMoa1206328

Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.115 ISSN 2585-2795

Randomized Controlled Trials: The case of Multiple Sclerosis - Refining the constraints of a treasure, a short outline

Theodoros S. Constantinidis

Abstract

Randomized controlled trials (RCTs) are the most valid methodological tool for establishing causal relationships. Nevertheless, their validity is constrained by various methodological details concerning their design, conduction and implementation. Failure of successful randomization, absence of correction for multiple comparisons, use of noisy scales for measuring a disease parameter, are a few of these constraints. Furthermore, there are constraints inherent in the scientific research methodology, like the use of the p-value as a threshold of statistical significance and in succession of inferential reasoning, as a threshold of truth. In this work, the examples of RCTs illustrating these limitations are drawn from the field of multiple sclerosis (MS). In general, RCTs in MS mostly are well designed, adequately powered, and well conducted. Nevertheless, sometimes there are exceptions, leading to false conclusions and steering clinical practice toward wrong choices.

Keywords: Clinical trials, multiple sclerosis, methodology, disability, p-value, replication.

Special Issue in Demyelinating Diseases

Corresponding author: Theodoros S. Constantinidis MD, PhD, Private Consultant Neurologist, 31 Ermou str, Korinthos 20131,t.constantinidis@gmail.com

DOI: 10.26386/obrela.v2i2.115 ISSN 2585-2795

Introduction

Multiple Sclerosis is a chronic autoimmune disease of the central nervous system (CNS), implicating both inflammatory and neurodegenerative pathogenic mechanisms (1). The main clinical phenotype is the relapsing-remitting type of the disease (RRMS). In the majority of cases it is characterized by acute exacerbations and subsequent various degrees of recovery (2). The typical course of RRMS, after several years of relapses and remissions, is the gradual and continuous (perhaps fluctuating) worsening of disability, marking the transition to the secondary progressive subtype of the disease (SPMS) (3). In a minority of patients, this gradual and continuous worsening of disability begins from the disease onset. This is the defining clinical feature of the primary progressive subtype of MS (PPMS). Both SPMS and PPMS subtypes belong to the spectrum of progressive type of MS (3).

European Medicines Agency (EMA) has already approved 16 drugs for MS (4), which aim to either prevent relapses or treat symptoms (Table 1). In Greece, 14 of these drugs are already being reimbursed from social security services while the other two (Cladribine and Ocrelizumab) will be integrated in the forthcoming months. It should be noted that Ocrelizumab has been approved by EMA for the early stages of PPMS (4). It is the first drug approved with this indication.

TABLE 1

Active Substance	Year of Approval	Administration	Indication
Interferon β 1-b	1995	Injectable SC	RRMS
Interferon β 1-a EM	1997	Injectable SC	RRMS
Interferon β 1-a SC	1998	Injectable SC	RRMS
Mitoxantrone	1998	Injectable IV	RRMS
Glatiramer Acetate	2002	Injectable SC	RRMS
Natalizumab	2006	Injectable IV	RRMS
Fingolimod	2011	Per os	RRMS
Fampridine	2011	Per os	Walking Disability
Cannabidiol / δ-9-tetrahydrocannabinol	2011	Oromucosal Spray	Spasticity
Chronic Pain			
Teriflunomide	2013	Per os	RRMS
Alemtuzumab	2013	Injectable IV	RRMS
Dimethylfumarate	2014	Per os	RRMS
Peginterferon β-1a	2014	Injectable SC	RRMS
Daclizumab	2016 | Withdrawn	Injectable IV	RRMS
Cladribine	2018	Per os	RRMS
Ocrelizumab	2018	Injectable IV	RRMS | PPMS

Randomized Controlled Trials

A prerequisite for drug approval by the authorities is the design and implementation of large scale, multicenter, multinational, double blind, RCTs. The randomization procedure is considered as the most valid and reliable method for balancing all the baseline confounders (effect modifiers), both known (table 2a and 2b) and unknown, between the groups under comparison e.g. novel therapy vs placebo. This is why in the framework of evidence-based medicine, RCTs are graded with the highest level of validity among other types of studies, namely cohort or case control observational studies (5).

TABLE 2a

Effect modifiers usually checked for balancing between groups, after randomization	
NOVEL THERAPY	PLACEBO
Age	Age
Sex (Usually % of females)	Sex (Usually % of females)
Duration from disease onset	Duration from disease onset
No of Relapses the Last 1 or 2 years or ARR*	No of Relapses the Last 1 or 2 years or ARR*
Disability-EDSS** score	EDSS** score
MRI‡- No or volume of T2 hyperintense lesions	MRI‡ - No or volume of T2 hyperintense lesions
MRI‡ – No of Contrast enhancing T1 lesions	MRI‡ – No of Contrast enhancing T1 lesions
Previous use of DMT§	Previous use of DMT§

TABLE 2b

Effect modifiers usually not-checked for balancing between groups, after randomization	
CSF†	CSF†
Cognitive Status	Cognitive Status
Total Brain Volume or Grey or White Matter Volume	Total Brain Volume or Grey or White Matter Volume
Nfl$ in CSF or Blood	Nfl$ in CSF or Blood

*ARR: Annualized Relapse Rate **EDSS: Expanded Disability Status Scale

‡MRI: Magnetic Resonance Imaging §DMT: Disease Modifying Therapy

†CSF: Cerebrospinal Fluid $Neurofilaments (Light Chain)

Does Randomization always succeed?

In the majority of clinical trials randomization works as expected. Nevertheless, sometimes it may result in imbalances, due to mostly unidentified reasons. An example is the pivotal clinical trial of glatiramer acetate 20mg (GA), published on 1995 (6). The randomization was implemented using the SAS statistical package. The baseline EDSS score, after randomization, was 2.8±1.2 (mean± standard deviation) for the GA group and 2.4±1.3 for placebo (6). This difference is imbalanced since a t-test results in t=2.5, p<0.02 (7). The effect of GA on disability progression, as measured by the EDSS change (increase) for 3 or 6 consecutive months, was not significantly different from the effect of placebo. The final conclusion was that GA does not inhibit disability deterioration more significantly than placebo. In addition, for the calculation of the relapse rate, the authors employed a multiple regression statistical technique, using the EDSS change as a covariate in order to adjust for the EDDS imbalance. This adjustment resulted in a significant difference in relapse rate between GA and placebo, with a p-value=0.007. The Food and Drug Administration (FDA) did not accept this statistical adjustment because it was not pre-planned. In its own report only the unadjusted comparisons of relapse rate with a p-value=0.055 are mentioned (8). This pivotal RCT of GA was the only one for several years. As a result, a systematic review of disease modifying therapies (DMTs) in MS, including only double blind RCTs, reported (21) the efficacy of GA as simi-lar to the efficacy of placebo under several outcome measures, without any mention to the EDSS imbalance in the baseline of GA's pivotal RCT (9). For a whole decade after this RCT of GA, there was a growing bibliographic trend of suggesting that GA is as effective as placebo. This trend changed after the publica-tion of two open label, randomized, head-to-head trials, com-paring GA to interferon β-1b (BEYOND) (10) and subcutaneous interferon β-1a (REGARD) (11). According to their conclusion, the efficacy of GA was equivalent to that of the two other inter-ferons-β in all outcome measures.

Multiple Comparisons

All pivotal clinical trials in MS aim to establish a statistically significant outcome of a primary endpoint. This may be a single outcome measure e.g. annualized relapse rate (12) (13). Alternatively, multiple primary endpoints (e.g. multiple dosing schemas) may be investigated. Furthermore, the endpoint may be composite. For example, in the context of time to failure, failure is defined either as the first occurrence of a relapse or the permanent discontinuation of treatment due to any cause

(14). In addition to these primary endpoints several other secondary ones are also included in the trial's list of endpoints, e.g. disability progression, magnetic resonance imaging (MRI) lesion burden, adverse events etc. All these endpoints have to be investigated through a vast number of comparisons. However, increasing the number of comparisons leads to a higher probability of getting falsely lower p-values (at the significance threshold 0.05). In turn, this may lead to a higher number of false positive results (15). In order to tackle the inflation of false positives due to multiple comparisons, several statistical procedures have been developed. The Bonferroni test is the most traditional. Roughly, it divides the p-value by 2 for every successive comparison. Nevertheless, this correction may be dramatic and has been criticized for overcorrection (15). Other more modest corrective procedures are used more frequently, like Hochberg, Benjamini-Hochberg, Hommel, Dunnet etc. The pivotal RCTs in MS include prespecified statistical procedures for controlling false positives due to multiple comparisons, since the regulatory agencies, namely FDA (16) and EMA (17), demand adherence to their guidelines on controlling multiplicity issues. Nevertheless, after the approval of a DMT by the authorities, several post-hoc group comparisons are published in order to assess various aspects of the treatment profile of DMT based on the original data of the pivotal RCT. All these comparisons should be embedded in the succession of comparisons of the initial RCT and should be corrected for multiplicity in order to avoid type I error inflation.

The latest example is the ORATORIO trial of ocrelizumab for PPMS (18). In this trial a prespecified exploratory endpoint (among several others, both primary and secondary) was a 20% confirmed progression in the time of Nine-Hole Peg Test (9-HPT) in all patients with PPMS in order to examine upper extremity function separately. One year after the initial publication of ORATORIO trial in the New England Journal of Medicine, a paper dedicated to the upper extremity function in PPMS patients was published in Multiple Sclerosis (19). This paper is a re-analysis of the ORATORIO upper extremity data. But this time, several more groups of patients were investigated, each with different confirmed progression thresholds in 9-HPT: 25%, 30% and 35%, during three different time periods: 12, 24 and 120 weeks. In addition, confirmed improvement (instead of progression) was used as a grouping factor in order to compare the two groups (improvement versus no improvement) according to two different thresholds of 9-HPT: 15% and 20% (19). All these comparisons were carried out for the total number of patients, and additionally the authors examined two more groups: patients with EDSS ≥ 6 and EDSS < 6. All these post-hoc comparisons were carried out without any multiplicity correction resulting in inflation of type I error. For example, the time to ≥ 25% confirmed progression in 24 weeks was significantly less than the corresponding time for placebo with a p-value 0.027 for both hands and 0.033 for the better hand. These p-values are close to the significance threshold of 0.05 and should be rather insignificant if corrected (at least according to the Bonferroni correction). In spite of the authors of this paper declaring these analyses as exploratory (19), multiplicity testing should be rigorously performed even in exploratory tri-als (15).

Estimation of disability with EDSS score

Permanent, irreversible disability, of any severity, is the greatest concern of all MS patients and the most important outcome measure of RCTs. Relapses cause temporary disability and, if absolutely remitted, cause only a dysfunction for few days or weeks. On the contrary, permanent disability affects decisively all aspects of the patients' daily life, their present and future. All the outcome measures of RCTs, like the relapse rate, the MRI lesion burden or the degree of short-term disability sustained over 3 or 6 months, are surrogate measures of permanent disability.

The EDSS scale is the gold standard tool for the assessment of disability in MS. Besides that, many RCTs also used EDSS for the confirmation of relapse. This is defined by an increase of 0.5 points in EDSS score or 2 points in one functional system or by 1 point in two functional systems of EDSS. To estimate the improvement or the worsening of permanent disability, the threshold for the EDSS score change is 1 point or more, except from the patients with baseline EDSS score 0 and >5.5, for whom a change of 1.5 and 0.5 has to be confirmed, respec-

tively. But the most important parameter for the confirmation of disability as (permanent) progression is the period of time. The vast majority of RCTs use the 3 or/and 6 months period of sustained EDSS score change to define disability progression or improvement. Is this time period sufficient to confirm any EDSS score change as irreversible? A study published in Brain on 2015 (20), investigated the events of EDSS score progression, as defined by the persistence of this score over 3, 6, 12 and 24 months, and calculated the proportion of events sustained over the following five years. The number of patients included in the study was 16.636, extracted from the international MSBASE registry. The proportion of events persisted over 5 years was 70%, 74%, 80% and 89%, for the 3, 6, 12, 24 months of confirmed disability progression (CDP), respectively. That is, the 3 months confirmation for the estimation of permanent disability progression is false in 30% of events, the 6 months estimation in 26% of events, the 12 months estimation in 20% of events and even the 24 months estimation is false in 11% of events. More commonly the restored progression confirmations were recorded in younger patients, those with relapsing-remitting course of MS, small changes in EDSS score and more frequent visits. The prominence of false permanent progression in these subpopulations of patients probably highlights the implication of measurement errors in low EDSS scores. This is in accordance with the finding of Ebers et al (21), who examined the placebo arms of 31 RCTs and concluded that the EDSS score as a surrogate marker of disability progression is totally unreliable in RRMS. Furthermore, a baseline EDSS score < 4, reflects measurement errors, random variations and remitting relapses (21). In contrast, baseline EDSS score > 4, which is usually the case of SPMS, is significantly more reliable and less noisy.

Taking in mind these findings, we may estimate that many disability progression events recorded in RCTs eventually proved to be relapses with delayed remittance. In addition, high potency DMTs (Natalizumab, Alemtuzumab, Ocrelizumab, Cladribine), which were thought to significantly affect the disability status (either higher rate of inhibition of disease worsening or higher rates of disability improvement), may simply act by their potent anti-inflammatory mechanism of action (remitting of relapses) and not against neurodegenerative pathophysiological mechanisms. Besides this disadvantage of EDSS, we have to mention the absence of a cognitive functional system assessment, as well as the absence of fatigue estimation. Both are important sources of disability of MS patients, affecting seriously their activities of daily living and subsequently their quality of life.

No Evidence of Disease Activity (NEDA)

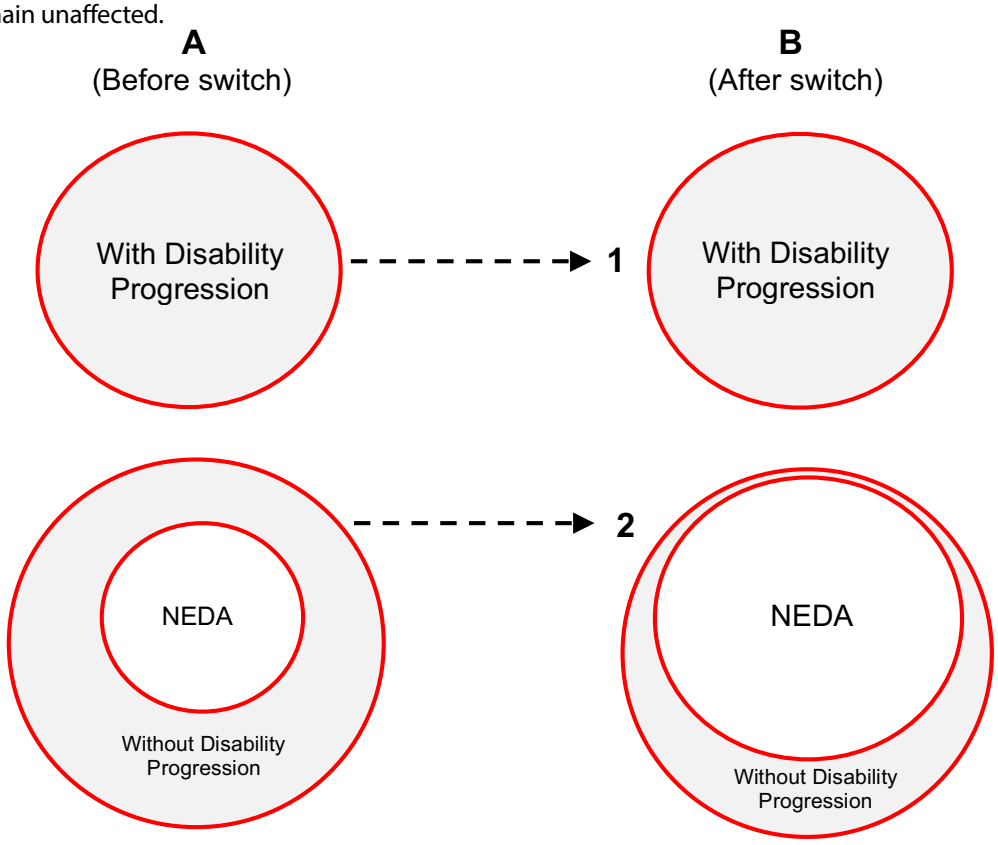
NEDA is a recently proposed treatment target for MS (22) and denotes the absence of any disease activity concerning relapses, disability progression and MRI lesion burden. A NEDA-4 treatment target has also been proposed (23), incorporating the brain volume loss as measured by MRI, as well as NEDA-5, adding to the NEDA-4 the light chain neurofilament levels in cerebrospinal fluid. Among all these proposed treatment targets only NEDA has been widely adopted by the MS community.

In a 7-years longitudinal cohort, 46% of the patients fulfilled NEDA at 1 year, while only 7.9% after 7 years (24). Another similar 10-years cohort found that only 9% of the patients fulfilled NEDA at the 10th year. (25) Thus, it is clear that NEDA could not be maintained in the long-run. It is an acceptable treatment goal but too ambitious at present time, under the current pharmacological armamentarium in MS. The extension of TRANSFORMS trial presents special interest, since it compares two DMTs using NEDA as an outcome measure, and may provide some insights. The TRANFORMS trial compared fingolimod with intramuscular interferon β-1a for one year. At the end of first year, all patients on interferon β-1a switched to fingolimod and followed up over the next 3.5 years (26). At the end of first year, the proportion of patients with NEDA was 44.3% for interferon β-1a and 63.4% for fingolimod. At the end of second year (one year after the switch to fingolimod), the interferon β-1a group showed a statistically significant increase in the proportion of patients with NEDA to 66% (i.e. 21.7% increase). On the contrary, for the fingolimod group, the continuation of the same drug resulted in an insignificant increase, to 69%. Hence, by relying on NEDA as an outcome measure, it seemed that there was a striking difference in the therapeutic

effect between the two DMTs, in favor of fingolimod. However, there is a point demanding special attention: the disability progression. Both criteria of disability confirmation, i.e. persistence over 3 or 6 months, showed statistically insignificant differences between groups throughout the whole period of study. More specifically, after the switch, the proportion of patients with 3 months CDP was 21% for interferon β-1a and 22% for fingolimod. Similarly, with 6 months CPD the proportions were 15% and 17% respectively (26). Therefore, there is a striking discrepancy between NEDA and disability progression. But the latter is included in the former and subsequently NEDA should have been affected by the proportion of patients with disability progression, resulting in a non-significant difference for NEDA as well. In order to clarify this point we propose an alternative interpretation of these findings of the study, as illustrated in figure 1. In short, after exposition to a DMT improving NEDA, the patients with the better course (without disability progression) of their disease continue to improve even more (as estimated by NEDA proportion), while those with the worse course remain unaffected.

Figure 1

Column A represents the patients in the group of interferon β-1a, before switching (at first year of study) and column B after switching (at the second year of study). The patients in column A were divided in two sets: 1. With disability progression, 2. Without disability progression. Group 1, in the first row, remained unchanged (i.e. the proportion of patients with disability progression was equal to fingolimod during first year. After switching, during the second year, the equality was sustained). Group 2, in the second row, includes a subset of patients with NEDA. This subset, during the first year of the study, was already significantly smaller in interferon β-1a group than fingolimod. This subset increased in favour of fingolimod after switching during the second year. That is, the patients with the better course of the disease from the beginning (without disability progression, group A, 2) improved even more.



P-value per se
The meaning of the p-value (the threshold 0.05).

The conceptual definition (without mathematical formulation) of the p-value may be the following. It is the value of probability of the data under examination, or even smaller values, provided the null hypothesis is true (27). This definition may be further divided in two conceptual steps:

1. The observed data may correspond to a probability value (p-value or less) in the tails of probability distribution, given the null hypothesis.

2. There are two hypotheses for testing, before any experimentation: the null hypothesis and the alternative hypothesis. After the calculation of type I (α) and type II (β) error, and using both of them, we define the critical region and accordingly accept/reject the null or alternative hypothesis (28).

The first step was introduced by Ronald A. Fisher and the second by Jersey Neyman and Egon Pearson. Among them, there was a conceptual and methodological-philosophical gap. Nevertheless, the concept of p-value used after them and up to this day is a hybrid of the two conceptual steps. None of the founders intended this interpretation of the p-value (28). According to Steven Goodman, the most pernicious misconception around the p-value is believing that a 0.05 value represents a 5% chance of the null hypothesis to be true (27). This misconception and the definition of the p-value in the beginning of the paragraph differ at the point that the definition considers as given that the null hypothesis is true and does not attribute any probability of being true to either the null or the alternative hypothesis. Nevertheless, the p-value deviated from its original meaning and is used in every day scientific research practice as a threshold of truth.

An extension of the misconception around the p-value is that it denotes the false positives of the null hypothesis. Nevertheless, a method employing Bayes theorem and the likelihood ratio (Bayes factor) has been proposed by Colquhoun (29) in order to calculate more precisely the false positive risk, which is the complementary of positive predictive value. He points out that if you get a p=0.05 from your analyzed data, then the probability of being wrong is at least 30%, and even higher if the study is underpowered (30). Colquhoun constructed a free access web page for the calculation of false positive risk, requiring the user to provide the sample sizes, the level of p-value, the prior probability and the standardized effect size: http://fpr-calc.ucl.ac.uk/.

Replication crisis

During the last twenty years, there has been a growing body of evidence questioning the validity of research findings (31), culminating in a 2005 publication by Ioannidis (32). Ioannidis mentioned that the increased number of false positives due to the use of the p-value threshold is an important factor contributing to the replication crisis. One corrective proposal concerning the p-value was signed by 72 renowned statisticians and epidemiologists (33). Its authors proposed lowering the p-value threshold to 0.005, which is 10 times lower than its current value. With the use of Bayesian statistics, it was shown that the number of false positives decreases down to 5% if the p-value threshold is set to 0.005. In addition, on March 20, 2019, the American Statistician journal dedicated a whole supplement to the subject: "Statistical Inference in the 21st Century: A World Beyond $p < 0.05$" (34). On the same day, a plea was published in Nature to "retire statistical significance" (35). The plea was signed by more than 800 statisticians and epidemiologists around the globe. This indicates a significant consensus on the role of the p-value threshold on the depreciation of the validity of research findings.

Significance tests are used in every scientific field and of course in RCTs. Hence a number of comparisons should be false positives, especially those with marginal significance. We would like to mention two large RCTs, for two different DMTs, that did not replicate their own previous results. The FREEDOMS trial of fingolimod showed a significant effect on the disability progression, 30% greater than placebo (HR=70%) (36). Nevertheless, the FREEDOMS II trial failed to reveal any significant effect on the disability progression in comparison to placebo (37). Exactly the same failure of duplicating the dis-

ability progression effect occurred between DEFINE (38) and CONFIRM (39) trials of dimethyfumarate (DMF). The disability progression effect of the twice daily DMF in DEFINE trial was 38% better than placebo, while in CONFIRM trial, the same two comparisons were equally effective. Do these discrepancies represent the noisy EDSS score mentioned above? Or rather the false positive results of the first trial of the couple of trials (FREEDOMS, DEFINE)? Or even the false negative of the second trial of the couples (FREEDOMS II, CONFIRM)? The questions could not be answered. The fact is the absence of replication.

Long-term DMT use and ethical issues

In general, the majority of RCTs in MS, are well designed, adequately powered, well conducted and of long enough duration (usually about 2 years).

The long-term extensions of RCTs in MS, concerning the first line injectables, have shown convincingly, that 15 years after randomization, there was a substantial decrease in the ac-cumulation of disability (EDSS≥4 or ≥6) for the patients taking the injectable DMT (subcutaneous interferon β-1a) consistently (high cumulative dose drug exposure), in comparison to those with intermittent use of DMT (low cumulative dose drug exposure) (40). The patients in the placebo arm were part of the last group of low dose drug exposure. In addition, the stron-gest predictor of the long-term disability accumulation was the EDSS change during the first two years after randomization (40). This change was equivalent to 30% benefit for the DMT group versus placebo (40). Besides that, 21 years after random-ization, a significant number of the patients assigned to sub-cutaneous interferon β-1b showed a considerable reduction in all-cause mortality. In terms of hazard rate, this reduction cor-responded to a 46.8%, in the proportion of deaths among DMT patients compared to placebo.

The majority of RCTs used a placebo arm for comparison to the novel therapy. According to the above-mentioned long-term disability accumulation and survival rates, every RCT designed with a placebo arm condemns the patients in this arm to long-term disability progression and decreased survival. Of course, this is a serious ethical issue.

This article is intended to be only a very short outline of several major methodological and statistical issues, concerning the design, conduct and analysis of RCTs, drawing examples from the field of MS. It aims only to highlight several points of interest in order to facilitate the critical reading from the viewpoint of the clinicians.

Disclosures: The author declares no conflicts of interest relevant to the present article.

References

1. Lassmann H. Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. Front. Immunol. 2019, 9:3116. Doi:10.3389/fimmu.2018.03116

2. Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr Opin Neurol. 2015, 28:193-205. Doi: 10.1097/WCO.0000000000000206

3. Lublin F. New Multiple Sclerosis Phenotypic Classification. Eur Neurol 2014;72(suppl 1):1-5. Doi:10.1159%2F000367614

4. European Medicines Agency. Ocrevus. Accessed March 25, 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/ocrevus

5. Guyatt G, Rennie D, Meade MO, Cook DJ. Users' Guides to the Medical Literature. Essentials of Evidence Based Clinical Practice. McGraw Hill-JAMA Network. 3rd Edition, pages 31-33, 2015. ISBN: 978-0-07-180872-9.

6. Johnson K.P., Brooks B.R., Cohen J.A., Ford C.C., Goldstein J., Lisak R.P. et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 1995;45:1268-1276. Doi: 10.1212/WNL.45.7.1268.

7. Goodin D.S. Disease-modifying therapy in MS: a critical review of the literature. Part I: Analysis of clinical trial errors. J. Neurol. 2004;251:Suppl 5:V/3-V/11. Doi: 10.1007/s00415-004-1503-z.

8. Food and Drug Administration. Copaxone. Accessed March 27, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/020622_S015_COPAXONE_INJECTION_AP.pdf

9. Freedman M.S, Hughes B, Mikol D.D, Bennett R, Cuffel B, Divan V, et al. Efficacy of Disease-Modifying Therapies in Relapsing Remitting Multiple Sclerosis: A Systematic Comparison. Eur Neurol 2008;60:1–11. Doi:10.1159/000127972.

10. Paul O'Connor, Massimo Filippi*, Barry Arnason, Giancarlo Comi, Stuart Cook, Douglas Goodin, Hans-Peter Hartung, Douglas Jeffery, Ludwig Kappos, Francis Boateng, Vitali Filippov, Maria Groth, Volker Knappertz, Christian Kraus, Rupert Sandbrink, Christoph Pohl, Timon Bogumil,for the BEYOND Study Group. 250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol 2009; 8:889–97. Doi:10.1016/S1474-4422(09)70226-1.

11. Mikol D.D, Barkhof F, Chang P, Coyle P.K, Jeffery D.R, Schwid S.R, et al, on behalf of the REGARD study group. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis. Lancet Neurol 2008; 7: 903–14. Doi:10.1016/S1474-4422(08)70200-X.

12. O'Connor P, Wolinsky J, Confavreux C,Comi G, Kappos L, Olsson T, for the TEMSO trial group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365:1293-303. Doi:10.1056/NEJMoa1014656.

13. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al, for the TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo controlled, phase 3 trial. Lancet Neurol 2014;13:247-256. Doi:10.1016/ S1474-4422(13)70308-9.

14. Vermersch P, Czlonkowska A, Grimaldi LME, Confavreux C, Comi G, Kappos L, et al, for the TENERE trial group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler 2014;20:6:705-716. Doi: 10.1177/1352458513507821.

15. Dmitrienko A, D'Agostino RB. Multiplicity Considerations in Clinical Trials. N Engl J Med 2018;378:2115-22. Doi: 10.1056/NEJMra1709701.

16. Food and Drug Administration. Multiple endpoints in clinical trials. Guidance for industry. January 2017. Accessed March 30, 2019. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf

17. European Medicines Agency. Guideline on multiplicity issues in clinical trials. 15 Dec 2016. Accessed March 30, 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf

18. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus placebo in progressive multiple sclerosis. N Engl J Med 2017;376:3:209-220. Doi:10.1056/NEJMoa1606468.

19. Fox EJ, Markowitz C, Applebee A, Montalban X, Wolinsky JS, Belachew S, et al. Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: Findings from the phase III randomized ORATORIO trial. Mult Scler. 2018;24(14):1862-1870. doi: 10.1177/1352458518808189.

20. Defining reliable disability outcomes in multiple sclerosis. Brain 2015;138:3287–3298. Doi:10.1093/brain/awv258.

21. Ebers CG, Heigenhauser L, Daumer M, Noseworthy JH. Disability as an outcome in MS clinical trials. Neurology 2008;71:624-631. Doi: 10.1212/01.wnl.0000313034.46883.

22. Banwell B, Giovannoni G, Hawkes C, Lublin F. Editors' welcome and a working definition for a multiple sclerosis cure. Mult. Scler. Relat. Disord. 2013;2:65-67. Doi:10.1016/j.msard.2017.07.011.

23. Kappos L, Radu EW, Freedman MS, Cree BA, Radue EW, Sprenger T, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. Mult. Scler. 2016;22:10:1297-1305. Doi:10.1177/1352458515616701.

24. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol. 2015;72:152–158. Doi:10.1001/jamaneurol.2014.3537.

25. De Stefano N, Stromillo ML, Giorgio A, Battaglini M, Bartolozzi ML, Amato MP, et al. Long-term assessment of no evidence of disease activity in relapsing-remitting MS. Neurology 2015;85:19:1722-1723. Doi:10.1212/WNL.0000000000002105

26. Cohen JA, Khatri B, Barkhof F, Comi G, Hartung HP, Montalban X, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. J Neurol Neurosurg Psychiatry 2016;87:5:468-475. Doi:10.1136/jnnp-2015-310597.

27. Goodman S. A dirty dozen: twelve p-value misconceptions. Semin. Hematol. 2008;45:135-140. Doi:10.1053/j.seminhematol.2008.04.003.

28. Goodman S. Toward evidence-based medical statistics. 1: the p-value fallacy. Ann. Int. Med. 1999;130:995-1004. Doi:10.7326/0003-4819-130-12-199906150-00008.

29. Colquhoun D. The false positive risk: a proposal concerning what to do with p-values. The American Statistician, 2019;73:sup1:192-201, Doi:10.1080/00031305.2018.1529622.

30. Colquhoun D. An investigation of the false discovery rate and the misinterpretation of p-values. R. Soc Open Sci, 2014;1:3:140216. Doi:10.1098/rsos.140216

31. Loken E, Andrew Gelman A. Measurement error and the replication crisis. Science 2017;355:6325:584-585. Doi:10.1126/science.aal3618.

32. Ioannidis J. Why Most Published Research Findings Are False. PLoS Med 2005;2:8 e124. Doi:10.1371/journal.pmed.0020124.

33. Benjamin DJ, Berger JO, Johannesson M, Nosek BA, Wagenmakers E-J, Berk R, et al. Redefine statistical significance. Nature Human Behavior 2017;2:6-10. Doi: 10.1038/s41562-017-0189-z.

34. Statistical Inference in the 21st Century: A World Beyond p < 0.05. American Statistician 2019;73:1-401. https://www.tandfonline.com/toc/utas20/73/sup1?nav=tocList

35. Amrhein V, Greenland S, McShane and more than 800 signatories. Retire statistical significane. Nature 2019; 567:305-307. Doi:10.1038/d41586-019-00857-9.

36. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al.

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. N Engl J Med 2010; 362:387-401. Doi:10.1056/NEJMoa0909494.

37. Calabresi A, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13: 545–56. Doi:10.1016/S1474-4422(14)70049-3.

38. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. for the DEFINE investigators. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. N Engl J Med 2012;367:1098-107. Doi:10.1056/NEJMoa1114287.

39. Fox RJ, Miller DH, Phillips TJ, Hutchinson M, Havrdova E, Kita M, et al. for the CONFIRM investigators. Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis. J Neurol Neurosurg Psychiatry 2012; 367:1087-1097. Doi:10.1056/NEJMoa1206328.

40. Kappos L, Kuhle J, Multanen J, Kremenchutzky M, Verdun di Cantogno E, Cornelisse P, et al. Factors influencing long-term outcomes in relapsing–remitting multiple sclerosis: PRISMS-15. J Neurol Neurosurg Psychiatry 2015;86:1202-1207. Doi:10.1136/jnnp-2014-310024.

41. Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J, et al. Survival in MS. A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurology 2012;78:1315–1322. Doi:10.1212/WNL.0b013e3182535cf6.

Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.116 ISSN 2585-2795

Is there a therapeutic potential for repetitive Transcranial Magnetic Stimulation (rTMS) in the management of cognitive impairment in Multiple Sclerosis?

Grigorios Nasios [1] and Lambros Messinis [2]

[1] Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina

[2] Neuropsychology Section, Departments of Neurology and Psychiatry, University Hospital of Patras and University of Patras Medical School

Abstract

Multiple sclerosis (MS) is an autoimmune central nervous system disease, with inflammatory and degenerative components, affecting mostly young individuals, and resulting in accumulation of motor and cognitive dysfunction. Even from its insidious, subclinical phase, and through the entire course, cognitive impairment is frequently present, although often undiagnosed, and almost always untreated. Cognitive impairment is important, due to its impact on patients' quality of life and everyday functioning capacacity as current pharmaceutical interventions have not provided sufficient therapeutic efficacy. One reason why cognitive impairment remains hidden for long periods is the brains functional reorganization, in other words its capacity to recruiting reserve networks in order to compensate for damaged ones, retaining "normal" functioning. In the era of neuromodulation, techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) can serve as a non-pharmacological therapeutic option, enhancing neuroplasticity changes, and maintaining or improving cognitive functioning. In this short review we discuss the therapeutic potential of rTMS in the management of cognitive impairment in MS patients.

Key-words: multiple sclerosis, cognitive impairment, transcranial magnetic stimulation

Special Issue in Demyelinating Diseases

Corresponding author: Grigorios Nasios, Professor, Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, e-mail: grigoriosnasios@gmail.com

DOI: 10.26386/obrela.v2i2.116 ISSN 2585-2795

Transcranial magnetic stimulation and neuroplasticity

Multiple sclerosis (MS) is considered the most common non traumatic neurological disorder. Although the etiology of the disease is still unknown, MS is considered an autoimmune, chronic, central nervous system disease. Its major neuropathological characteristics are an ongoing demyelinating, inflammatory and degenerative process, that affects both the white and grey matter of the brain and the spinal cord. As a result there is an accumulation of disabling motor and cognitive dysfunction over time. These symptoms have a significant impact on functional capacity, psychosocial and professional status and overall quality of life [1, 2, 3].

Although Charcot firstly described the cognitive and mood aspects of MS almost 150 years ago, it was only more recently that these symptoms were considered an important aspect of the disease. Evidence now exists that deterioration of cognitive performance can be detected many years before formal diagnosis [4,5]. Of significant interest is that even in the so-called “benign” form of the disease, where the disability status (EDDS) score remains up to 3, at least 15 years after the diagnosis, cognitive impairment can be diagnosed in at least 50 % of these patients [6].

The therapeutic impact of disease modifying medications on patients’ cognitive capacity, has not reached the desired outcomes [7], although they do provide protection by delaying the accumulation of brain tissue damage and brain volume loss. Even in the small proportion of patients achieving the desired NEDA status (no evidence of disease activity) over time, cognitive dysfunction was not precluded [8]. The lack of sufficient evidence from the pharmacological arena to treat cognitive deficits in MS has provided the ground for non pharmacological neurobehavioral treatments to emerge with relatively positive outcomes [9, 10]. Various other non pharmaceutical interventions have also been introduced in ameliorating the physical and cognitive aspects of the disease [11]. Among these interventions repetitive transcranial magnetic stimulation (rTMS) appears to have both the scientific-theoretical support and evidence from experimental models of the disease and trials in MS patients. [12,13,14,15]

Transcranial magnetic stimulation (TMS) is a neurostimulatory and neuromodulatory technique, based on the principle of electromagnetic induction of an electric field in the brain [12]. This technology has become a method of choice for noninvasive stimulation of the brain in conscious human subjects in the last two decades in order to study the excitability of different cortical areas and to map the connectivity of neuronal pathways [16,17]. When TMS pulses are applied repetitively they can modulate cortical excitability, either decreasing or increasing it, depending on the parameters of stimulation. Repetitive Transcranial Magnetic Stimulation (rTMS) has local and remote effects on neural function either of an excitatory or inhibitory nature [18]. The direction, magnitude, and duration of conditioning rTMS effects depends on the stimulation site, frequency, intensity, and the duration of the rTMS training. Evidence from experimental animal models of MS (experimental autoimmune encephalomyelitis) has shown that rTMS modifies astrocytosis, cell density and lipopolysaccharide levels, implying that it could be a promising treatment for neuroinflammatory conditions such as multiple sclerosis [19].

Of significant interest supported by accumulating evidence towards this is that we can impact cognitive functioning in healthy humans by utilizing rTMS. In an interesting systematic review, Guse et al., reported that high-frequency rTMS (10–20 Hz) is most likely to cause significant cognitive improvement when applied over the left (dorsolateral) prefrontal cortex, within a range of 10–15 successive sessions and an individual motor threshold between 80 and 110% [14]. In another study, Li et al., noted that high-frequency rTMS over the left DLPFC not only recruits more neural resources from the prefrontal cortex by inducing an electrophysiologic excitatory effect but also enhances efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing in healthy young people [15]. Moreover, Wan-Yu Hsu et al., in a systematic review and meta-analysis of the literature involv-

ing the period from (1990 to 2014) evaluating the effects of non-invasive brain stimulation (rTMS and tDCS) on cognitive function in healthy older adults and patients with Alzheimer's disease (AD), concluded that non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging [20].

An important characteristic of the brain that modulates the potential of cognitive therapeutic interventions is neuroplasticity, which is studied as altered brain functional connectivity both at rest (resting state functional connectivity, rs-FC) and during tasks. Hyper-connectivity or hypo-connectivity can be detected, depending on the severity and extension of structural brain damage, the nature of disease process and its time course. These alterations may be adaptive, or maladaptive. A far as multiple sclerosis is concerned, several reports have noted that early stage patients activate additional brain areas adjacent to those primarily involved during task performance, allowing them to perform normally prior to cognitive deficits being detectable on formal neuropsychological assessment [21]. This additional activation serves as a compensatory mechanism through which the patient is able to maintain relatively intact cognitive capacity for a period of time, functionally compensating for damage related to disease progression, thus masking the defects [22,23]. In one such study, Mainero et al., found that RRMS patients exhibit altered patterns of activation during tasks exploring sustained attention, information processing and episodic memory. Specifically, fMRI activity was greater in MS patients with better cognitive function. The authors concluded that functional changes in specific brain areas increase with increasing tissue damage suggesting that they may also represent adaptive mechanisms that reflect underlying neural disorganization or disinhibition, possibly associated with MS [24]. In contrast to task-based fMRI, resting state functional connectivity (rs-FC) examines the communication between different brain regions within neural networks at "rest." Increased connectivity during rs-FC is thought to serve as a compensatory mechanism for cognitive deficits early in the MS disease process [9,25,26], but later in the disease process, extra connections are associated with worse cognitive performance [9,27].

Is there a therapeutic potential for utilizing rTMS in MS?

Owing to the absence of effective pharmacological treatments, the combination of rTMS with medications has been used with efficacy mainly for the improvement of spasticity [28,29,30], fatigue and depression [11], lower urinary tract dysfunction [31], gait [32] and hand dexterity [33] in MS. The majority of these studies, however, have methodological limitations, including small number of participants, and low to moderate level of efficacy, indicating the emerging need for more studies in the future. Considering the management of cognition in MS, we are of the opinion that a therapeutic potential may exist for utilizing rTMS, for several reasons that we will expand on. First of all, pharmaceutical interventions have not provided sufficient evidence regarding their efficacy in treating cognitive dysfunction in MS. Perhaps, as we stated above, they have an indirect positive influence on cognitive performance by delaying the accumulation of brain tissue damage and brain volume loss, but they failed to show effectiveness directly on cognition. Secondly, accumulating empirical research has provided evidence that MS patients' brains undergo functional reorganization even from the initial disease phases, by altering functional connectivity in various regions, therefore acting as a compensatory mechanism. A third important point is that no major safety or adverse event considerations have been raised in a large and fast growing number of MS patients which are exposed to rTMS protocols for various symptoms. Finally, and more importantly, rTMS has shown beneficial effects on cognitive performance in healthy persons and in patients with other neurological diseases, by enhancing the brain's functional capacity (evoking neuroplasticity changes). We have further evidence that cognitive performance in MS patients can be positively influenced by higher cognitive reserve [34] and cognitive rehabilitation interventions [35,36], and this is possible through neuroplasticity changes [9,34,37].

Despite this favorable theoretical background, clinical trials using rTMS to target cognitive deficits in patients with MS are absent. To our knowledge, only Hulst and colleagues investigated the therapeutic use of rTMS on cognition in MS patients [38]. In their recent study, they studied the effects of high-frequency rTMS of the right dorsolateral prefrontal cortex (DLPFC) on working memory performance in patients with MS, while measuring task-related brain activation and task-related brain connectivity. They reported improvement in task accuracy only in patients and interpreted these results as an rTMS-induced change in network efficiency in MS patients, implicating the potential role for rTMS in cognitive rehabilitation in MS. With the limitation of the small sample of participants (17 MS patients and 11 HCs), the results of this study are very promising, and undoubtedly call for more trials, in order to provide robust evidence of r-TMS therapeutic effects in cognitively impaired MS patients.

One could, therefore, consider using, and even combining, the available non-pharmacological, non-invasive interventions to enhance functional reorganization in MS patients' brains in order to compensate for continuous brain damage. Ideally these interventions should be utilized early in the disease course, in order to maximize benefits, by maintaining patient activity in all aspects of their lives.

References

1. Janardhan V and Bakshi R. Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis. Arch Neurol, 2000, 57(10):1485-91. PMID: 11030802

2. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008, 7(12):1139-51. doi: 10.1016/S1474-4422(08)70259-X

3. Lunde HMB, Assmus J, Myhr KM1, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry 2017, 88(8):621-625. DOI: 10.1136/jnnp-2016-315238

4. Sinay V, Perez Akly M, Zanga G, Ciardi C, Racosta JM. (2014) School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis. Mult Scler, 2014, 21(7):945-52. doi: 10.1177/1352458514554054

5. Cortese M, Riise T, Bjørnevik K, Bhan A, Farbu E et al. Preclinical disease activity in multiple sclerosis: A prospective study of cognitive performance prior to first symptom. Ann Neurol 2016, 80(4):616-24. doi: 10.1002/ana.24769

6. Correale J, Ysrraelit MC & Fiol MP. Benign multiple sclerosis: does it exist? Curr Neurol Neurosci Rep 2012, 12(5):601-9. doi: 10.1007/s11910-012-0292-5

7. Roy S, Benedict RH, Drake AS, Weinstock-Guttman B. Impact of Pharmacotherapy on Cognitive Dysfunction in Patients with Multiple Sclerosis. CNS Drugs 2016, 30(3):209-25. doi: 10.1007/s40263-016-0319-6

8. Damasceno A, Damasceno BP, Cendes F. No evidence of disease activity in multiple sclerosis: Implications on cognition and brain atrophy. Mult Scler 2016, 22(1):64-72. DOI: 10.1177/1352458515604383

9. Chiaravalloti ND, Genova HM. and DeLuca J. Cognitive rehabilitation in multiple sclerosis: the role of plasticity. Front. Neurol 2015, 6:67. doi: 10.3389/fneur.2015.00067

10. Messinis L, Nasios G, Kosmidis MH, Zampakis P, Malefaki S, Ntoskou K, Nousia A, Bakirtzis C, Grigoriadis N, Gourzis P, and Papathanasopoulos P. Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial. Behavioural Neurology 2017, 2017:5919841. doi: 10.1155/2017/5919841

11. Palm U, Ayache SS, Padberg F, Lefaucheur JP. Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimul 2014, 7(6):849-54. doi: 10.1016/j.brs.2014.09.014

12. Rossi S, Hallett M, Rossini PM., Pascual-Leone A,

and The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009, 120(12): 2008–2039. doi: 10.1016/j.clinph.2009.08.016

13. Sherafat MA, Heibatollahi M, Mongabadi S, Moradi F, Javan M, Ahmadiani A. Electromagnetic field stimulation potentiates endogenous myelin repair by recruiting subventricular neural stem cells in an experimental model of white matter demyelination. J Mol Neurosci 2012, 48(1):144-53. DOI: 10.1007/s12031-012-9791-8

14. Guse B, Falkai P, and Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J Neural Transm 2010, 117(1): 105–122. DOI: 10.1007/s00702-009-0333-7

15. Li Y, Wang L, Jia M, Guo J, Wang H, Wang M. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. PLoS One 2017, 12(6):e0179430. doi: 10.1371/journal.pone.0179430

16. Rothwell JC. Physiological studies of electric and magnetic stimulation of the human brain. Electroencephalogr Clin Neurophysiol Suppl 1991;43:29-35.

17. Civardi C, Cantello R, Asselman P, Rothwell J C. Transcranial Magnetic Stimulation Can Be Used to Test Connections to Primary Motor Areas From Frontal and Medial Cortex in Humans. Neuroimage 2001, 14 (6), 1444-1453. DOI: 10.1006/nimg.2001.0918

18. Fox P, Ingham R, George MS, Mayberg H, Ingham J, et al. Imaging human intra-cerebral connectivity by PET during TMS. Neuroreport 1997, 8(12):2787-91. PMID: 9295118

19. Medina-Fernández FJ, Luque E, Aguilar-Luque M, Agüera E, Feijóo M, et al. Transcranial magnetic stimulation modifies astrocytosis, cell density and lipopolysaccharide levels in experimental autoimmune encephalomyelitis. Life Sci 2017, 169:20-26. DOI: 10.1016/j.lfs.2016.11.011

20. Hsu WY, Ku Y, Zanto TP, Gazzaley A. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging 2015, 36(8):2348-59. DOI: 10.1016/j.neurobiolaging.2015.04.016

21. Audoin B, Ibarrola D, Ranjeva JP, Confort-Gouny S, Malikova I, et al. Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. Hum Brain Mapp 2003, 20(2):51-8. DOI: 10.1002/hbm.10128

22. Forn C, Barros-Loscertales A, Escudero J, Belloch V, Campos S, et al. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. Neuroimage 2006, 31(2):686-91. DOI: 10.1016/j.neuroimage.2005.12.030

23. Forn C, Barros-Loscertales A, Escudero J, Benlloch V, Campos S, et al. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. Hum Brain Mapp 2007;28(5):424-30. DOI: 10.1002/hbm.20284

24. Mainero C, Caramia F, Pozzilli C, Pisani A, Pestalozza I, et al. fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. Neuroimage 2004, 21(3):858-67. DOI: 10.1016/j.neuroimage.2003.10.004

25. Bonnet MC, Allard M, Dilharreguy B, Deloire M, Petry KG, Brochet B. Cognitive compensation failure in multiple sclerosis. Neurology 2010, 75(14):1241-8. doi: 10.1212/WNL.0b013e3181f612e3

26. Cader S, Cifelli A, Abu-Omar Y, Palace J, Matthews PM. Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. Brain 2006, 129(Pt 2):527-37. DOI: 10.1093/brain/awh670

27. Leavitt VM, Wylie G, Genova HM, Chiaravalloti ND, DeLuca J. Altered effective connectivity during performance of an information processing speed task in

multiple sclerosis. Mult Scler 2012, 18(4):409-17. doi: 10.1177/1352458511423651

28. Centonze D, Koch G, Versace V, Mori F, Rossi S, et al. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology 2007, 27;68(13):1045-50. DOI: 10.1212/01.wnl.0000257818.16952.62

29. Mori F, Codecà C, Kusayanagi H, Monteleone F, Boffa L, Rimano A, Bernardi G, Koch G, Centonze D. Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis. Eur J Neurol. 2010, 17(2):295-300. doi: 10.1111/j.1468-1331.2009.02806.x

30. Amatya B, Khan F, La Mantia L, Demetrios M, Wade DT. Non-pharmacological interventions for spasticity in multiple sclerosis. Cochrane Database Syst Rev 2013, 28;(2):CD009974. doi: 10.1002/14651858.

31. Centonze D, Petta F, Versace V, Rossi S, Torelli F, et al. Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. Mult Scler 2007, 13(2):269-71. DOI: 10.1177/1352458506070729

32. Burhan AM, Subramanian P, Pallaveshi L, Barnes B, Montero-Odasso M (2015). Modulation of the Left Prefrontal Cortex with High Frequency Repetitive Transcranial Magnetic Stimulation Facilitates Gait n Multiple Sclerosis. Case Rep Neurol Med. 2015, 251829. doi:10.1155/2015/251829.

33. Koch G, Rossi S, Prosperetti C, Codecà C, Monteleone F, Petrosini L, Bernardi G, Centonze D. Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment. Mult Scler 2008, 14(7):995-8. doi: 10.1177/1352458508088710

34. James F. Sumowski, Glenn R. Wylie, John DeLuca, and Nancy Chiaravalloti Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. Brain 2010, 133(2): 362–374. doi: 10.1093/brain/awp307

35. Bonavita, S., Sacco, R., Della Corte, M., et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. Journal of Neurology 2015, 262, 91-100. doi: 10.1007/s00415-014-7528-z

36. Mitolo, M., Venneri, A., Wilkinson, I.D., & Sharrack, B. Cognitive Rehabilitation in multiple sclerosis: A systematic review. J Neurol Sci. 2015, 15;354(1-2):1-9. doi: 10.1016/j.jns.2015.05.004

37. De Giglio L, Tona F, De Luca F, Petsas N, Prosperini L, Bianchi V, Pozzilli C, Pantano P. Multiple Sclerosis: Changes in Thalamic Resting-State Functional Connectivity Induced by a Home-based Cognitive Rehabilitation Program. Radiology. 2016, 280(1):202-11. doi: 10.1148/radiol.2016150710

38. Hulst HE, Goldschmidt T, Nitsche MA, de Wit SJ, van den Heuvel OA, et al. rTMS affects working memory performance, brain activation and functional connectivity in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2017, 88(5):386-394. DOI: 10.1136/jnnp-2016-314224

Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.117 ISSN 2585-2795

Does multiple sclerosis cause progressive and widespread cognitive decline?

Marina Katsari[1], Dimitrios Kasselimis[1,2], Georgios Koutsis[3], and Constantin Potagas[1]

[1]Neuropsychology and Language Disorders Unit, 1st Department of Neurology, Eginition Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece

[2]Division of Psychiatry and Behavioral Sciences, School of Medicine, University of Crete, Heraklion, Greece.

[3]Neurogenetics Unit, 1st Department of Neurology, Eginition Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece

Abstract

The existence of cognitive deficits in Multiple Sclerosis (MS) can be supported by clinical observation and assessment or large-scale research studies. The fact that part of the MS patient population does demonstrate some type of cognitive impairment may be unequivocal, although a crucial question remains: Is this impairment in the context of a progressive decline? The literature provides inconclusive evidence. Nevertheless, the notion of "MS dementia" seems to be gaining popularity during the last decade. In this short review, we present the findings of the main longitudinal studies on cognitive course of MS patients in an attempt to reveal the vulnerabilities of that particular view. Overall, we corroborate the idea that MS does not inevitably result in cognitive decline with advancing age, and further argue that researchers and clinicians should take the emerging trend of "MS Dementia" with a grain of salt.

Keywords: Multiple Sclerosis; longitudinal studies; cognitive decline; dementia

Funding: This opinion essay, is part of a study, concerning cognition in MS. This research is co-financed by Greece and the European Union (European Social Fund- ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning» in the context of the project "Strengthening Human Resources Research Potential via Doctorate Research" (MIS-5000432), implemented by the State Scholarships Foundation (IKY).

Special Issue in Demyelinating Diseases

Corresponding author: Constantin Potagas, National and Kapodistrian University of Athens, Eginition Hospital, 74 Vas. Sofias Av., 11528, Athens, Greece. Tel: +302107289307, Fax: +302107216474, Email: cpotagas@otenet.gr

DOI: 10.26386/obrela.v2i2.117 ISSN 2585-2795

The cognitive deficits in MS, and their progression over time

Multiple Sclerosis (MS) is a chronic, immune-mediated neurological disease of the central nervous system, which typically causes damage to myelin sheaths and secondary axonal loss. In time, accumulating widespread lesions in the central nervous system may cause problems associated with motor control and sensation, as well as fatigue, depression, and cognitive deficits. [1]. The reported prevalence of cognitive deficits in MS patients ranges from 20 to 65% [2]. This rather wide range could be attributed to several methodological factors, since most relevant studies differ in terms of the definition of cognitive impairment, the inclusion criteria, and the neuropsychological tests used. This limitation notwithstanding, one can clearly see a trend emerging from these studies: information processing speed [3-5], complex attention [6,7], and long-term memory [8-10] seem to be the cognitive functions most affected in MS.

Regarding the cognitive course of MS, it has been argued that progression of the disease parallels a continuously deteriorating cognitive status, characterized as "subcortical dementia" [10],or "white matter dementia" [11]. However, the term "dementia" implies that the nature of the observed deficits is progressive, therefore suggesting a decline rather than an isolated impairment in specific cognitive domains. Mahler and Benson [12] (cited in Rao, 1990, pp. 95-96), in their attempt to resolve this issue, proposed that the term cognitive dysfunction might be used when deficits involve only one or two areas; more extensive dysfunction deserving the term dementia It should be noted, however, that the aforementioned definition, does not take into account one of the most crucial criteria for dementia, namely every-day living functionality. Benedict& Bobholz [13], in a study investigating this topic, indicated that only 22% of their sample truly met the criteria for dementia, according to DSM (American Psychiatric Association,V) [14] or ICD10 [15]. Moreover, a detailed examination of longitudinal studies focusing on the cognitive course of MS patients, reveals that cognitive deterioration, far from being the norm, is usually restricted to specific domains [3,11,16-29].More specifically, deterioration is shown in only a small proportion (and is usually restricted to specific cognitive domains) in most longitudinal studies of cognition in MS. Additionally, such findings are often contradictory, and therefore a definitive conclusion about which cognitive domains tend to decline over time cannot yet be drawn. The interpretation of such studies is further complicated, by the as-yet obscure effect of MS-related clinical factors on cognition. For example, physical disability, as measured by the Expanded Disability Status Scale (EDSS) appears to be associated with the severity of cognitive deficits in some studies [2,17,19,30]. In contrast, other studies show that only EDSS scores indicating severe disability (>4,5), are actually correlated with cognitive variables [3, 31,32]. As far as duration of illness is concerned, a recent cross-sectional study [2] showed that most patients started experiencing cognitive difficulties from the fifth year post onset. The subtype of MS has also been shown to affect cognition. In particular, patients with secondary progressive MS (SPMS) have significantly worse cognitive performance than patients with relapsing-remitting MS (RRMS) or primary progressive MS (PPMS), even when controlling for physical disability [33,29]. In the following section, we provide a brief, critical presentation of longitudinal studies that focus on cognitive course of different MS subtypes.

Longitudinal studies focusing on different MS subtypes

Most longitudinal studies on RRMS patients have relatively short time intervals (≤5 years) between initial and final assessment [e.g. 11, 16-18,20,24,25,28,31-34], while only few have longer time intervals between two assessments (7 to 20 years) [2,3,19,21,22, 27]. The results from these studies are inconclusive: Many of them demonstrate cognitive deterioration in processing speed [3,19,28,29], some in visual learning and memory [19,22,28,35], and others in verbal learning and memory [19-21]. Almost all of the aforementioned studies indicate selective decline, i.e. deterioration in specific cognitive domains. It is also noteworthy that that four of them did not show any significant cognitive deterioration over time [16,24,34,36].

Overall, only three of the above studies have fairly long time periods between the initial assessment and follow up (from 10

to 20 years) [19, 27,29], thus providing more robust findings. Two of them (10 and 18 years follow up, respectively), have partly converging results: Schwid et al.[27] found mild deterioration only in processing speed, and a small increase (5%) in the proportion of cognitively impaired patients over time. Strober et al. [29] found, in addition to a mild deterioration in processing speed, deteriorations in simple and complex auditory attention span, visual construction and episodic memory. In this study, the proportional increase in cognitively impaired patients over time was higher (18%). Interestingly, Schwid and colleagues [27] noted that patients with better baseline performance demonstrated greatest decline over time than patients cognitively impaired at baseline, while Strober et al. [29] suggested the same schema only for the SDMT test. Amato and colleagues [19] found significant decline in almost all cognitive domains between baseline and follow-up assessment (ten years interval). At baseline, the patient group showed impaired mean performance on verbal memory and abstract reasoning. Four years later, working memory difficulties emerged, and, after an additional period of 6 years, short term verbal and spatial memory impairments were evident. Furthermore, of the initially 37 cognitively unimpaired patients, only 20 remained as such, while the proportion of patients who became cognitively impaired at follow up, rose up to 56% (from 26%, at initial assessment). Nevertheless, there are some issues concerning this study, which should be addressed. Firstly, disease duration at baseline assessment was very short (mean: 1.5 years). Short disease duration at baseline assessment indicates that most patients may not yet have demonstrated cognitive dysfunction. As previously noted [2], cognitive decline is usually most clearly demonstrated beyond the fifth year of disease duration. . Furthermore, a more detailed examination of the cognitive grouping utilized, reveals an interesting observation. The proportion of mildly cognitive impaired patients is 8% at the 1st assessment, becomes 33% at 1st follow-up, and remains stable (34%) at the 2nd follow-up. The proportion of moderately cognitively impaired patients shows small fluctuations over time (18% , 16%, and 22% at first, second and third assessment respectively). The above percentages indicate that the number of mildly cognitive impaired patients may have increased 4 years post onset, however remained stable during the following 6 years. Furthermore, the proportion of the moderately impaired patients did not show significant increase, from onset to final assessment (4%). In sum, it seems that the number of patients who initially demonstrate cognitive deficits does not increase at a constant rate over time.

In the two longitudinal studies on PPMS patients [23,26], the time intervals are very short (two and three years respectively). Camp et al.[23] failed to find generalized cognitive decline. In particular, they found that, of the 73 patients that completed the Brief Repeatable Battery of Neuopsychological tests , 52 were intact at baseline (mean disease duration at baseline was 10, 4 years), and only 4 of them became impaired (using the definition of at least 3 tests scores below 1,5 SD). Patients who were mildly impaired at baseline (n=6) scored within normal range at follow-up, while 15 patients who were moderately to severely impaired at baseline remained stable. In this study, different versions of the neuropsychological battery were used, in order to avoid learning effects. Denney et al. [26] found that decline was restricted to processing speed, regardless of the initial cognitive status of the patients. It must be noted that the sample in this study was quite small, consisting of only 24 patients. A somewhat unexpected finding was that verbal memory showed significant improvement at follow up assessment for the whole sample. Due to the small time interval between the two assessments, this improvement could be attributed to learning effects, since, in contrast to the processing speed task, the verbal memory task is sensitive to learning effects. Finally, there is one study by Kujala et al.[18], which included a sample of mixed MS subtypes (relapsing-remitting and progressive) and implemented a quite short interval between assessments (3 years). The authors argue that 50% of the patients (22 out of 45) showed cognitive impairment already at baseline. This specific subgroup showed significant deterioration after 3 years, in verbal learning and memory, visuomotor performance, and processing speed. The rest of the patients remained cognitively intact at follow-up. In summary, the above short review does not support the notion of a definite, progressive, and widespread cognitive decline over time in MS.

Clinical and research implications

Dementia is a highly emotionally-charged word, which can have serious psychological implications on patients, who are usually young people, during the most productive period of their life, attending to be efficient in their job, and possibly trying to raise young children. Consequently, a clinician should be very cautious when interpreting the results of these studies, before he/she explicitly uses the term "dementia", when treating an MS patient. It should be however made clear that the need for scepticism is not solely based on humanitarian reasons and the psychological status of the patient. It is rather a matter of a clinical consensus based on research evidence. We must acknowledge that results regarding the cognitive course of MS are still inconclusive and therefore the notion of "MS dementia" should be thoroughly scrutinized before becoming common ground. Otherwise, the belief of MS resulting in progressive cognitive decline, could lead to confirmation bias in future studies. We will briefly speculate on the reasons behind the above described blurry image and possible misconceptions, which could be attributed to methodological issues. First, the intervals adopted by different longitudinal studies vary dramatically, and are often too short. Judging from the available findings, we suggest that the time period between baseline and follow up, should be no less than 5 years, in order for possible cognitive changes to be detectable. Another methodological constraint of such longitudinal studies, is dropouts. Even though clinical, behavioural, and demographic variables (as measured at baseline) may not differ between the drop-out group and the patient subsample assessed at follow-up in some studies, the fact that only part of the initial sample is re-assessed, may lead to distorted results. For example, it is possible patients with prominent mobility difficulties, who reportedly demonstrate greater cognitive impairment [3,31,32], may not visit the clinic for reassessment. If this limitation is not taken into consideration, any longitudinal study may be highly susceptible to statistical fallacies. It should be however noted that, by acknowledging this limitation, we do not suggest that the general outline emerging form the available findings can be attributed to statistical negligence or methodological misconduct. Another issue is the definition of impairment. The available studies may have different approaches with regard to characterization of a patient as cognitively impaired, and may also use different psychometric tools for assessment. Finally, one should take into consideration possible differences stemming from the type of MS. For example, the prevalence of cognitive deficits is shown to be higher in secondary progressive MS subtype [30,33]. In addition, the course of the disease may manifest as a continuum with overlaps between types with advancing age (e.g. RRMS evolving into SPMS).

Conclusion

Cognitive course in MS is a rather complicated phenomenon, influenced by several factors, such as disability status, disease duration, MS subtype, type of assessment, time interval between assessments, manifestation of depression, and fatigue, among many others. Some of these factors are difficult to be controlled, in order to acquire clear and comprehensive results. Contradictory findings reported in the literature make clear that additional longitudinal studies are needed in order to elucidate the issue at hand. Thus far, there is no robust evidence allowing us to corroborate the idea of MS resulting in inevitable cognitive decline with advancing age. Therefore, we must remain sceptical against the emerging trend of "MS Dementia".

References t

1. Snyder, P. J., Nussbaum, P. D., & Robins, D. L. (2006). Clinical neuropsychology: A pocket handbook for assessment. American Psychological Association.

2. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie M, Bercovich E, Polliack M, Doniger GM, Stern Y, Khilkevich O, Menascu S, Hararai G, Gurevich M, Barak Y. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PloSone 2013, 8(8), e71058

3. Bergendal, G., Fredrikson, S., & Almkvist, O. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. European Neurology 2007, 57(4), 193-202. doi.org/10.1159/000099158

4. DeLuca J, Chelune GJ, Tulsky DS, Lengenfelder J, Chiaravalloti ND. Is speed of processing or working memory the primary information processing defi cit in multiple sclerosis? J Clin Exp Neuropsychol 2004; 26: 550–62. DOI: 10.1080/13803390490496641

5. Janculjak D, Mubrin A, Brinar V, Spilich G. Changes of attention and memory in a group of patients with multiple sclerosis. Clin Neurol Neurosurg 2002; 104: 221–27. PMID: 12127658

6. Winkelmann, A., Engel, C., Apel, A., and Zettl, U.K. Cognitive impairment in multiple sclerosis. J. Neurol. 2007, 254(Suppl. 2),II35–II42. DOI: 10.1007/s00415-007-2010-9

7. Guimarães, J. and Sá, M.J. Cognitive dysfunction in multiple sclerosis. Front. Neurol. 2012, 3, 74. DOI: 10.3389/fneur.2012.00074

8. Brassington JC, Marsh NV. Neuropsychological aspects of multiple sclerosis. Neuropsychol Rev 1998; 8: 43–77. PMID: 9658410

9. DeLuca J, Barbieri-Berger S, Johnson SK. The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. J Clin Exp Neuropsychol 1994; 16: 183–89. DOI: 10.1080/01688639408402629

10. Schwid, S. R., Goodman, A. D., Weinstein, A., McDermott, M. P., & Johnson, K. P. Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. Journal of the neurological sciences 2007, 255(1), 57-63. doi.org/10.1016/j.jns.2007.01.070

11. Filley, C. M. White matter dementia. Therapeutic advances in neurological disorders 2012, 5(5), 267-277. doi: 10.1177/1756285612454323

12. Mahler and Benson. Cognitive Dysfunction in Multiple Sclerosis, a Subcortical dementia? In: Rao, S. M. (Ed.) (1990). Neurobehavioral aspects of multiple sclerosis. Oxford University Press, USA.

13. Benedict RH, Bobholz JH.Multiple sclerosis. Semin Neurol. 2007, 27(1):78-85. DOI: 10.1055/s-2006-956758

14. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

15. World Health Organization. (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.

16. Jennekens-Schinkel, A., Lanser, J. B. K., Van der Velde, E. A., & Sanders, E. A. C. M. Performances of multiple sclerosis patients in tasks requiring language and visuoconstruction: Assessment of outpatients in quiescent disease stages. Journal of the neurological sciences, 1990, 95(1), 89-103. DOI: 10.1016/0022-510X(90)90119-8

17. Amato, M. P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., &Amaducci, L. Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. Archives of Neurology 1995, 52(2), 168-172.

18. Kujala, P., Portin, R., & Ruutiainen, J. The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. Brain: a journal of neurology 1997, 120(2), 289-297.

19. Amato, M. P., Ponziani, G., Siracusa, G., &Sorbi, S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Archives of neurology 2001, 58(10), 1602-1606. DOI: 10.1001/archneur.58.10.1602

20. Zivadinov, R., Sepcic, J., Nasuelli, D., De Masi, R., Bragadin, L. M., Tommasi, M. A., &Pozzi-Mucelli, R. S. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2001, 70(6), 773-780. PMCID: PMC1737379

21. Piras MR, Magnano I, Canu E D G Paulus , K S, Satta W M , Soddu A , Conti M, Achene A , Solinas G, Aiello I. Longitudinal study of cognitive dysfunction in multiple sclerosis: neuropsychological, neuroradiological, and neurophysiologi-

cal findings. Journal of Neurology, Neurosurgery & Psychiatry 2003, 74(7), 878-885. doi.org/10.1136/jnnp.74.7.878

22. Haase, C. G., Tinnefeld, M., Daum, I., Ganz, R. E., Haupts, M., & Faustmann, P. M. Cognitive, but not mood dysfunction develops in multiple sclerosis during 7 years of follow-up. European neurology 2004, 52(2), 92-95. DOI: 10.1159/000079937

23. Camp, S. J., Stevenson, V. L., Thompson, A. J., Ingle, G. T., et al. A longitudinal study of cognition in primary progressive multiple sclerosis. Brain 2005, 128(12), 2891-2898. DOI: 10.1093/brain/awh602

24. Jønsson, A., Andresen, J., Storr, L., Tscherning, T., Sørensen, P. S., & Ravnborg, M. Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. Journal of the neurological sciences 2006, 245(1), 77-85.

25. Amato, M P, Portaccio E, Goretti B, Zipoli V, Battaglini M, Letizia M. B, Stromillo M L, Guidi L; Siracusa G, Sorbi S, Federico A, De Stefano N. Association of Neocortical Volume Changes With Cognitive Deterioration in Relapsing-Remitting Multiple Sclerosis. Arch Neurol. 2007 ;64(8):1157-1161

26. Denney, D. R., Lynch, S. G., & Parmenter, B. A. A 3-year longitudinal study of cognitive impairment in patients with primary progressive multiple sclerosis: speed matters. Journal of the neurological sciences 2008, 267(1-2), 129-136.

27. Schwid, S. R., Goodman, A. D., Weinstein, A., McDermott, M. P., & Johnson, K. P. (2007). Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. Journal of the neurological sciences, 255(1), 57-63. doi.org/10.1016/j.jns.2007.01.070

28. Glanz, B. I., Healy, B. C., Hviid, L. E., Chitnis, T., & Weiner, H. L. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. Journal of Neurology, Neurosurgery & Psychiatry 2012, 83(1), 38-43. DOI: 10.1136/jnnp.2010.237834

29. Strober Lauren B., Rao Stephen M.,Lee Jar-Chi, Fischer Elizabeth, Rudick Richard Elizabeth Fischerc, Richard Rudickc (2014). Cognitive impairment in multiple sclerosis: An 18year follow-up study. Multiple Sclerosis and Related Disorders 2014, 3, 473–481 doi.org/10.1016/j.msard.2014.03.004

30. Potagas, C., Giogkaraki, E., Koutsis, G., Mandellos, D., Tsirempolou, E., Sfagos, C., & Vassilopoulos, D.Cognitive impairment in different MS subtypes and clinically isolated syndromes. Journal of the neurological sciences 2008, 267(1), 100-106.

31. Bsteh, G., Ehling, R., Lutterotti, A., Hegen, H., Di Pauli, F., Auer, M., ... & Berger, T. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis: insights from a 10-year observational study. PloS one 2016, 11(7), e0158978. doi.org/10.1371/journal.pone.0158978

32. Drew, M., Tippett, L. J., Starkey, N. J., & Isler, R. B. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. Archives of Clinical Neuropsychology2008, 23(1), 1-19. DOI: 10.1016/j.acn.2007.09.005

33. Huijbregts, S. C., Kalkers, N. F., de Sonneville, L. M., de Groot, V., & Polman, C. H. Cognitive impairment and decline in different MS subtypes. Journal of the neurological sciences 2006, 245(1-2), 187-194. DOI: 10.1016/j.jns.2005.07.018

34. Patti, F., Failla, G., Ciancio, M. R., L'Episcopo, M. R., & Reggio, A. Neuropsychological, neuroradiological and clinical findings in multiple sclerosis. A 3 year follow-up study. European journal of neurology 1998, 5(3), 283-286.

35. Feinstein, A., Kartsounis, L. D., Miller, D. H., Youl, B. D., & Ron, M. A. Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. Journal of Neurology, Neurosurgery & Psychiatry 1992, 55(10), 869-876. PMID: 1431949

36. Sperling, R. A., Guttmann, C. R., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., &Kikinis, R. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. Archives of neurology 2001, 58(1), 115-121. PMID: 11176944

Dialogues in Clinical Neuroscience & Mental Health

DOI: 10.26386/obrela.v2i2.118 ISSN 2585-2795

Is psychosis, at least in part, an immune-related dysmyelination disease?

Orestis Giotakos

Abstract

Epidemiological studies have borne out the association between psychotic disorders and autoimmune disease, while the immunogenetic contribution in psychosis is largely dominated by the major histocompatibility complex genetic diversity. On the other hand, demyelinating diseases, like multiple sclerosis, are characterized by a large array of invading immune cells that degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. Schizophrenia has been proposed to be a dysconnectivity syndrome, and numerous lines of evidence implicate myelin and oligodendrocyte function as critical processes that could affect neuronal connectivity. Disruption in myelination and dysmyelination-induced delays in information processing can produce phenocopies of psychosis similar to schizophrenia. Rethinking the clinical and pathophysiological similarities between de- or dysmyelination diseases and psychosis, we may consider that the dysconnectivity syndrome of psychosis represents the phenomenological and behavioral result of a multiple-faces dysmyelination disorder, which is based on a lifelong immunogenetic dysregulation process.

Key-words: psychosis, schizophrenia, multiple sclerosis, myelin, demyelination, dysmyelination, dysconnectivity syndrome

Special Issue in Demyelinating Diseases

Correspondence: Orestis Giotakos, MD, MSc, PhD, Founder, the npo obrela, Imittou 112, Athens, Greece, www.obrela.gr, info@obrela.gr

DOI: 10.26386/obrela.v2i2.118 ISSN 2585-2795

Myelin

Myelin, the lipid membrane that ensheathes axons, is essential for the efficient conduction of action potentials, which supports the integrity of axons. In terms of evolution of the nervous system, the myelin sheath is the most recent of nature's structural inventions. The first myelin-like ensheathed axons may have appeared about 400 million years ago. The number of glial cells increases during evolution and they constitute 25% of total cells in the Drosophila, 65% in rodents, and 90% in the human brain. Glial cells may well constitute 50%–90% of the cells in the human and rodent CNS. Myelination begins after 30 weeks gestation, occurs mainly in the post-natal period and is largely complete by young adulthood, although fine tuning of the pathways may continue as myelin internodes continue to be created into adulthood. PNS myelinated fibers are separated from each other by an extracellular compartment, the endoneurium, whereas the CNS myelinated fibers are in close contact. Some of the components of PNS myelin, lipids, and proteins are different **1, 2**.

High-speed conduction, fidelity of transfer signaling on long distances, and space economy are the three major advantages conferred to the vertebrate nervous system by the myelin sheath. In the invertebrate nervous system rapid conduction is accompanied by increased axonal calibers. The conduction velocity in a myelinated fiber is linearly correlated with diameter and at a given diameter, but there is a particular myelin thickness that maximizes conduction velocity. There is a myelin gradient, with the axons of the deeper cortical layers to be more uniformly myelinated and intermittent unmyelinated axonal segments in superficial layers of the cortex interspersed with myelinated internodes **3**.

Oligodendrocytes is the myelin-forming cells of the central nervous system. Glutamate is involving in the shaping of the oligodendrocyte population. The main ionotropic glutamate receptors expressed by oligodendrocytes belong to the dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate classes. It has been shown that non-NMDA glutamate receptor agonists are able to inhibit oligodendrocytes progenitor proliferation in cell cultures. Oligodendrocytes express opioid receptors, μ-receptors are apparent at the earliest stages of oligodendrocyte development, while κ-receptors are detected later. There is also a proliferative response to μ-receptor stimulation **1**.

Microglial cells share certain characteristics with macrophages and contribute to immune-surveillance in the central nervous system. M1 polarized microglia can produce pro-inflammatory cytokines, while M2 polarized microglia express cytokines and receptors that are implicated in inhibiting inflammation and restoring homeostasis. Based on these aspects, Nakagawa & Chiba (2014) **4** propose a possibility that M1 and M2 microglia are related to relapse and remission, respectively in psychiatric disorders, such as major depressive disorder and bipolar disorder **5**.

Multiple Sclerosis (MS) is characterized by a large array of invading immune cells that attack and degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. These lesion sites develop with time and initially result in clinically benign symptoms but can progress in to profound disabilities. Suggesting the concept of an autoimmune predisposition there have been reports hypothesizing shared risk and increased statistical susceptibility for people with one of autoimmune disorder to develop another. There has been an extensive research for pathophysiological mechanisms that may underlie autoimmunity resulting in the frequent co-occurrence of autoimmune disorders, such as MS and Hashimoto's thyroiditis among others. Given that MS currently remains incurable and the immunomodulatory therapies do not completely prevent disease progression in most patients, the final option for managing patients who do not respond to immunomodulatory treatment is to use a chemotherapeutic agent. Azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, mitoxantrone, cyclophosphamide and rituximab are the most utilized agents **6**.

Neurogliobiology or the myelin-neuron interaction

The term "neurogliobiology" refers to the concept that neurons and glia (including microglia) in the nervous system are

inseparable partners **1**. Neurons and glia cooperate to build a complex network during development. Numerous studies have demonstrated an interdependent relationship of oligodendrocytes and the axons they myelinate **7**. The reciprocal communication between neurons and oligodendrocytes is essential for the generation of myelin, a multilamellar insulating membrane that ensheathes the axons. Neuron-derived signalling molecules regulate the proliferation, differentiation and survival of oligodendrocytes. Moreover, signals from oligodendrocytes to neurons direct the assembly of specific subdomains in neurons at the node of Ranvier. Heterogeneous neuronal populations may have differential signaling patterns modulating localized oligodendrocyte myelination. The interaction of these neurons and oligodendrocytes may regulate plasticity in the adult brain **8**. Moreover, not only does the thickness of the myelin coating on axons affect conductance speed but synaptic activity influences the activity and replacement of oligodendrocytes in the brain throughout life **9** .

New myelin is being generated in the healthy adult brain, and adding new myelin internodes in areas of discontinuous myelination may be a mechanism for local plasticity **10**. Altered or inadequate myelination in the adult could also be a component in some of the psychiatric or neurodegenerative disorders that involve white matter **11**. Oligodendrocytes provide essential trophic support to axons. Aerobic glycolysis in oligodendrocytes is sufficient to maintain the myelin itself and the structure and function of the myelinated axons. The lactate produced by these cells is rapidly utilized by the axons, except when neuronal function is reduced as under anesthesia, at which point lactate accumulates in the tissue **12**.

Adaptive myelination implies that neuronal electrical excitability modifies myelin plasticity and that myelin plasticity in turn feeds back to modulate neural activity and behavior **11**. Some studies suggest a critical period in which neuronal function impacts myelination, either during early or late development. Neural activity, either in the medial prefrontal cortex or the barrel cortex of the somatosensory cortex, impacts myelination. Social isolation for as little as 2 weeks in the early post-weaning period has a dramatic effect reducing myelination in the prefrontal cortex, although motor activity is unaffected. Reintroduction of mice to a social environment at the end of the two weeks does not improve myelination. In these studies, 30 days social isolation in the adult has little impact on myelin content. Moreover, it was myelination per se that is reduced, since the number of oligodendrocytes themselves was normal in these tissues **13, 14**.

Dysfunction of neurotransmitters is one of the primary aetiologies of schizophrenia, while antagonists or selective-agonists of dopamine, serotonin and/or glutamate receptors were developed and used as major antipsychotic drugs. Concerning the action of antipsychotic drugs on white matter, a recent neuroimaging study using diffusion tensor imaging (DTI) assessed the myelin integrity among normal control and acutely psychotic, drug-free schizophrenics, before and after antipsychotic drugs treatment. It was found that a decrease of myelin integrity was partially restored in drug-responding schizophrenic individuals, whereas the poorly responsive schizophrenics did not appear to be related to a disordered myelin **15**. Moreover, it seems that haloperidol and olanzapine stimulate proliferation but inhibit differentiation of oligodendrocytes via different molecular mechanisms. Quetiapine, however, is diametrically opposed to the above processes, although it targets the similar receptors as does olanzapine. Therefore, Ren et al (2013) **16** proposed that the improvement of myelin/oligodendrocyte dysfunction by antipsychotic drugs may not rely on canonical neurotransmitters but rather that cross-communication may exist through different molecular mechanisms.

Demyelinating diseases

There are many causes of demyelination in human diseases. The main causes of primary demyelination are genetic, immune mediated, viral such as HIV, and toxic; they may also be secondary to neuronal dysfunction. Some genetic diseases may give rise to leukoencephalopathies in which demyelination is secondary to vascular, mitochondrial, or neuronal alterations or may be linked to a metabolic disease. Demyelination, breakdown of myelin, is characteristic of metabolic leukodystrophies, such as Krabbe's disease, metachromatic leukodystro-

phy, ALD, Canavan disease, Alexander disease, orthochromatic leukodystrophy, or mitochondrial disorders. Dysmyelination and hypomyelination are failure to myelinate occurring during fetal life or early infancy, as observed in different forms of Pelizaeus-Merzbacher disease **1**.

Multiple sclerosis (MS) is a chronic and inflammatory demyelinating disease. In MS, there is a loss of myelin in defined areas (lesion sites) in the brain and spinal cord. Current evidence shows that the etiology of MS and other demyelinating diseases may involve a combination of viral and autoimmune factors. MS is an autoimmune disorder that is characterized by muscle weakness and numbness as well as problems with vision and bladder control. There is a profound heterogeneity of pathology and immunopathogenesis of the lesions. There is a high interindividual but a low intraindividual variety of MS lesions. It is caused by the immune system attacking the nerve-insulating myelin sheath, which disrupts the communication between brain and peripheral parts of the body **6**.

In chronic MS lesions, oligodendrocyte precursor cells are present; however, they appear to be quiescent, not expressing a nuclear proliferation antigen. In MS, remyelination occurs, but it is incomplete and poorly sustained. After a demyelinating lesion, remyelinated myelin never regains its normal thickness, and the normal linear relationship between axon and sheath thickness is also never regained. It is not clear whether the mechanism of remyelination is identical to myelination. Normal appearing white matter in MS tissue often has reduced axonal density, which is generally attributed to inflammation. This normal appearing white matter may well have dysfunctional myelin that cannot provide the necessary trophic and metabolic support for axons. This suggests that altered myelin and oligodendrocyte function in human brain could be just as important as myelin loss in neurodegeneration **11**.

In addition to the well-known demyelinating and dysmyelinating diseases such as MS, neuromyelitis optica, and the leukodystrophies, myelin deficits resulting from altered glial structure/function and or glial/neuronal interactions are seen in human psychiatric disorders and developmental disorders including autism spectral disorder (ASD), sensory processing delay disorder, and attention deficit hyperactivity disorder **17, 18, 19**.

Clemastine, a Food and Drug Administration-approved antimuscarinic compound that has been shown to enhance myelination under demyelinating conditions, successfully reversed social avoidance behavior in adult socially isolated mice. This was associated with enhanced myelination and oligodendrocyte differentiation in the prefrontal cortex through epigenetic regulation. Thus, enhancing myelination may be a potential means of reversing depressive-like social behavior **20**. Clemastine also have been suggested as a potential therapy for hypoxic brain injuries associated with white matter injury and oligodendrocyte precursor cell maturation arrest **21**.

Multiple Sclerosis vs psychosis

MS and schizophrenia have numerous similarities in terms of the onset and cause. SCZ affects the same age distribution as MS; however, it has a 10- to 100-fold higher estimated prevalence rate **22**. Both schizophrenia and MS are substantially more widespread in the northern and temperate regions of the world than in the tropics **23**. Concordance rates in identical twins range from 30 to 80% for MS and approximately 50 to 60% for schizophrenia. Moreover, dizygotic twins exhibit approximately 5–10% concordance rate only **24**.

MS and schizophrenia may be present together in the same patient. In a recent review, 91 cases were identified in the literature in which both MS and psychotic disorders or mood disorders with psychotic features were present in the same patient. In most cases (> 60%), frontotemporal lesions were present and, in 26 cases, corticosteroids were successfully used for therapy **25**. The inflammatory process that occurs in MS patients is directly associated with human leukocyte antigen (HLA) class I and II loci The major histocompatibility complex (MHC) is responsible for the genetic overlap in both MS and SCZ, since a GWAS noted the involvement of similar HLA alleles in MS and SCZ **26**.

The pathophysiologies of MS and schizophrenia are similar but not identical. MS is more prevalent in females than males,

whereas the incidence of schizophrenia is equal in males and females. For MS, the pathophysiology appears to lie in an autoimmune reaction directed against the myelin sheaths of the nerves, which disrupt the transmission of information. On the other hand, only in a subgroup of patients with schizophrenia, autoantibodies cause the disease, which are directed against receptors on the perikarya of the nerve cells (NMDA receptors) **27**. Additionally, the HLA genes involved appear to be the same; however, alleles or mutations within these genes appear to have opposite effects in MS and schizophrenia **25**.

Genetics

The etiological significance of genetic factors in psychotic disorders is substantial: the heritability of schizophrenia spectrum and bipolar disorders is around 65–85%. Numerous studies have correlated variants in schizophrenia candidate genes with phenotypic features, sometimes also with outcome measures. However, recent genetic studies have questioned the validity of previously suggested schizophrenia candidate genes **28, 29** .

A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours **30, 31**. Genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms **32**. The candidate marker for schizophrenia Neuregulin-1 is possibly related to oligodendrocyte dysfunction and defective myelination **33**, while several other myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia **34** .

Neuregulin 1 (NRG1) risk genotypes or haplotypes have been associated with schizophrenia **35**. The potential pathophysiologic role of NRG1 is further supported by its diverse neurobiological functions, including neuro-glial trophic effects and myelination **36**. Genetic evidence also supports ERBB4 – the NRG1 receptor – as a candidate susceptibility gene and suggests positive epistatic interactions between NRG1 and ERBB4 in schizophrenia **37**. Disrupted-in-schizophrenia 1 (DISC1) is a strong candidate gene for schizophrenia **38** followed by additional genetic evidence for association with sporadic cases of schizophrenia **39**. The DISC1 SNPs is also associated with white matter integrity as measured by DTI **40**. Reticulon 4 receptor (RTN4R) is a myelin-associated protein that inhibits the outgrowth of neurites and nerve terminals and is upregulated in the brains of patients with schizophrenia **41**. Genetic association analysis of oligodendrocyte lineage transcription factor 2 (OLIG2), which encodes a transcription factor central to oligodendrocyte development, is associated with schizophrenia, having also an epistatic effect with 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) and ERBB4 **42**. No OMR genetic association reached genome-wide significance; however, a handful of OMR genes (ANK3, ERBB4, and NRG1) show suggestive association **43**. The above observations suggest that genetic alterations underlying oligodendroglial and myelin related cell type functions increase susceptibility to schizophrenia and provide evidence that the "neuron-centric" hypothesis of schizophrenia should be extended to include a role for glia in the etiopathogenesis of the disease. The oligodendroglial and myelin related gene and protein expression abnormalities can hamper saltatory conduction by affecting node of Ranvier integrity, which may results in failures of saltatory conduction, disconnection of higher-order association areas, and finally to the disconnectivity syndrome **7**.

Patients with a deletion at chromosome 22q11.2 (22q11DS) have 30% lifetime risk of developing a psychosis. People fulfilling clinical criteria for ultra-high risk (UHR) for psychosis have 30% risk of developing a psychosis within 2 years. Both high-risk groups show white-matter abnormalities in microstructure and volume compared to healthy controls, which have been related to psychotic symptoms. Bakker et al (2916) **44** found that UHR and 22q11DS patients were characterized by distinct patterns of withe matter alterations, in relation to healthy controls. Interestingly, while UHR patients were typified by signs suggestive of aberrant myelination, 22q11DS subjects showed signs suggestive of lower axonal integrity.

Dysregulated immune response and psychosis

The association of a dysregulated immune response and

psychosis is well-established. Several pro-inflammatory cytokines are elevated in first episode psychosis (FEP) patients. The changes are similar in the cerebrospinal fluid (CSF) and blood, and they occur across severe mental disorders **45**. While meta-analyses initially suggested that antipsychotic medication might decrease pro-inflammatory activation, a later meta-analysis did not find a significant medication effect **46**. C-reactive protein (CRP) has been the most commonly used measure of inflammation. CRP levels are increased in both drug-naïve and unmedicated patients, as well as after the onset of psychosis, although it has been studied and suggested as a biomarker for numerous acute and chronic diseases **47**. The question remains open regarding to what extent inflammation might be secondary to metabolic changes, or vice versa **48**.

Autoimmune disorders occur after the failure of self-recognition processes with consequent production of pathogenic autoantibodies directed against specific or multiple organs. They are heterogeneous disorders, representing more than 80 different diseases. The "immunogenetic" contribution is largely dominated by the major histocompatibility complex (MHC) genetic diversity and, at a lesser extent, by mutational events affecting cytokines encoding genes **49** . Several genome-wide association studies (GWAS) confirmed an association between the MHC region (chromosome 6) and psychosis **50, 51**.

Autoantibodies, specifically against the central nervous system, have been found in schizophrenic patients. These patients have a higher prevalence of circulating antibodies against hippocampus and hypothalamus as compared to healthy control **52**. A systematic review demonstrated that among patients with established schizophrenia, 20 autoantibodies (including antinuclear antibody [ANA], anti-cardiolipin, anti-N-methyl-d-aspartate receptor [NMDAR], and anti-serotonin) were present at higher rates than among controls. Rates of anticardiolipin and anti-NMDAR antibodies were also present in patients with first-episode psychosis **53**.

Schizophrenic patients are three times more likely to have high levels of anti-glutamate receptor antibodies, N-methyl-d-aspartic acid receptor (NMDAR), compared to controls (Pearlman et al, 2014). In at least a subgroup of schizophrenic patients, led us to propose the concept of "autoimmune psychosis" **54**. The anti-N-methyl-D-aspartate-type glutamate receptor (anti-NMDAR) encephalitis can in some cases present with prominent psychotic symptoms. The identification of encephalitis in patients with early psychosis is crucial, as over 75% of patients with classic anti-NMDAR encephalitis have substantial recovery with specific treatments, while antipsychotic treatment is not effective. Other than anti-NMDAR antibodies, autoantibodies detected in autoimmune encephalitis seem to remain negative in patients with isolated early psychotic symptoms **55**.

Peripheral monoamines and their metabolites have been studied as candidate biomarkers for treatment response in FEP. Tryptophan metabolite kynurenine acid (KYNA) has been studied extensively in recent years. A meta-analysis found that KYNA levels are elevated in CSF, but not in plasma, in patients with schizophrenia, and KYNA elevation is linked to proinflammatory activation **56**.

An immunohistochemical study revealed that a marked activation of microglia and astrocytes in the middle frontal and anterior cingulate gyri and cerebellum is obtained at autopsy from Autism spectrum disorder (ASD) subjects **57**. Similarly, microglial cells are markedly activated in the dorsolateral prefrontal cortex of ASD individuals **58**. Risperidone in combination with a cyclooxygenase-2 inhibitor, celecoxib, showed a superior efficacy as compared with monotherapy of risperidone in a randomized double-blind placebo-controlled clinical study in ASD children **59**. Neuroinflammation mediated by M1 microglia appears to be associated with ASD and schizophrenia and a drug that selectively suppresses polarization of M1 microglia may provide a beneficial therapy these disorders **5, 60**.

Is psychosis an immune-dysregulation dysmyelination disorder?

Environmental stressors are of major importance for the onset of autoimmunity. The occurrence of infections by pathogens such as, influenza, herpes simplex type 2, cytomegalovirus, and Toxoplasma gondii and/or increased C-reactive protein plas-

ma levels during pregnancy are known to be associated with an increased risk of developing schizophrenia in adulthood **61**. Childhood autoimmune diseases as well as inflammatory diseases, such as asthma, are known to be associated with an increased number of psychotic experiences in adolescence. Epidemiological studies have borne out the association between psychotic disorders and autoimmune disease. Rates of autoimmune disorders such as celiac disease, Graves' disease, systemic lupus erythematosus, multiple sclerosis, autoimmune hepatitis, and psoriasis are higher in those with schizophrenia **62, 63**. Moreover, in patients with autoimmune conditions, the risk to develop schizophrenia increases linearly with the number of severe infectious episodes **64**. Recent research also have been suggested that neuroinflammation plays a role in the with matter processes associated with catatonia **65**.

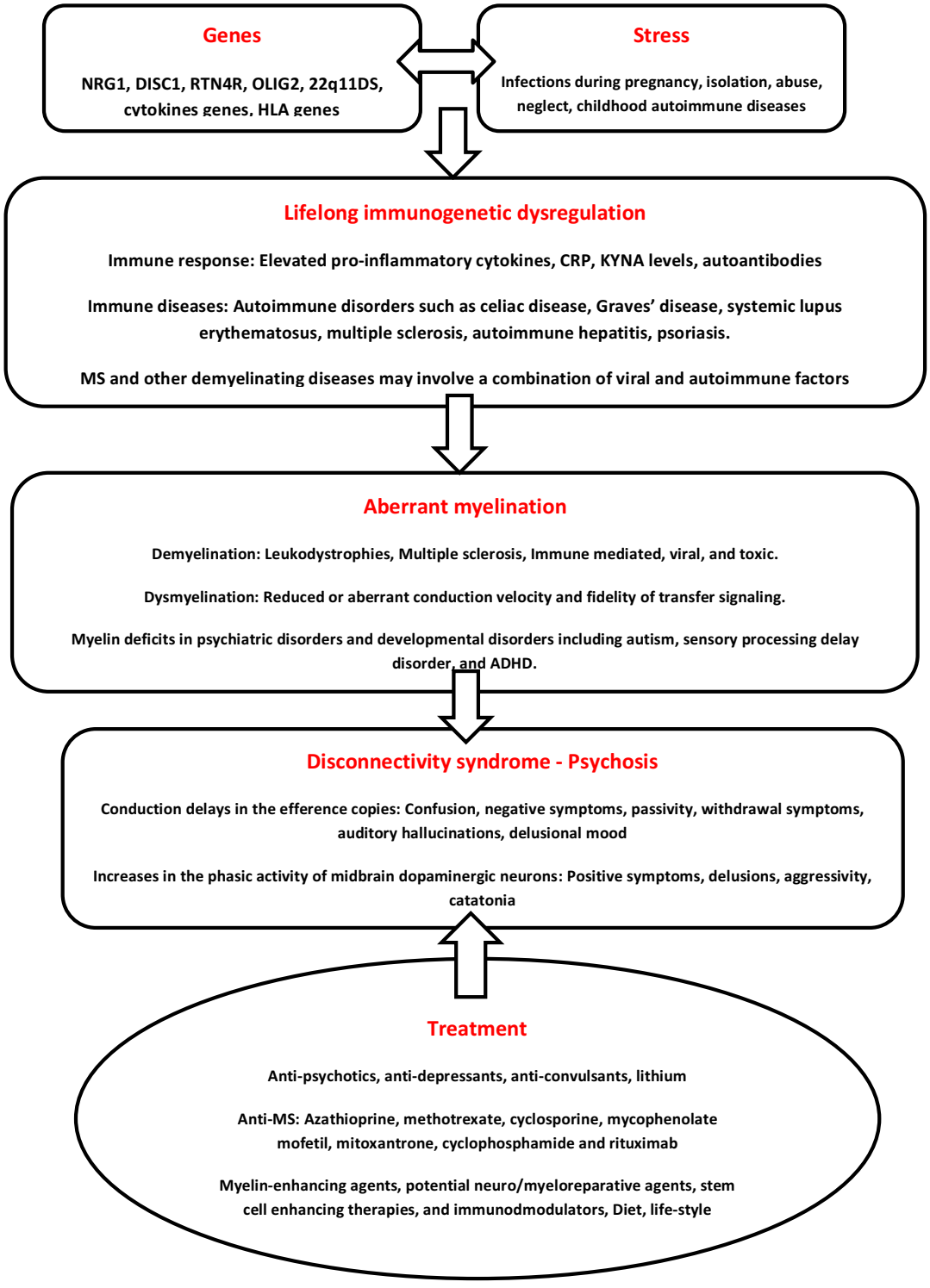
Dizocilpine (also known as MK-801), an N-methyl-d-aspartate receptor [NMDAr] antagonist and pharmacological model of schizophrenia seem to affects the metabolic processes of oligodendrocytes rather than neurons in vitro **66**. Interestingly, clozapine counters the metabolic effects of MK-801 and promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes **67, 68**. A number of putative myelinenhancing therapies would be potential candidates for large-scale clinical trials in schizophrenia. These include myelin-enhancing agents such as n-3 PUFA, minocycline, clemastine, polyphenols, and potential neuro/myeloreparative agents such as sulfasalazine, nano-curcumin, stem cell enhancing therapies such as Gli-1 inhibitors, and immunodmodulators, such as fingolimod **69**.

The neurodevelopmental hypothesis for schizophrenia posits that mis-wiring the cortex including the with matter connections is the underlying pathology of schizophrenia **70**. Several studies have suggested that some prediction aspects are impaired in psychotic patients **71, 72, 73, 74**. They manifest confusion at the initiation of the actions, and hence passivity experiences in the case of willed motor actions, and auditory hallucinations in the case of willed cognitions. Research suggests that changes in white matter integrity occur in schizophrenia and these may be more associated with cognition and even negative symptomology. Some studies have been shown that the dysmyelination-induced delays may cause a discrepancy in sensory feedback mechanisms, which may represent a prediction error and a phenomenological and neurophysiological salient event **75**. Extending this aspect, Whitford et al (2012) **76** suggested that passivity or negative symptoms and auditory hallucinations could arise initially because of dysmyelination-induced conduction delays in the efference copies. The resultant increases in the phasic activity of midbrain dopaminergic neurons could amplify these symptoms and concurrently trigger additional psychotic symptoms. The authors concluded that on a phenomenological level, these prediction errors cause confusion, giving rise to passivity experiences and auditory hallucinations. On a neurophysiological level, these prediction errors give rise to a second cause of psychotic symptoms, by increasing the phasic activity of midbrain dopaminergic neurons **76, 77** (Fig 1).

Summarizing, while not clear if white matter changes are a cause or an effect of underlying pathology, it is clear that white matter integrity is affected in schizophrenia. The pathophysiologies of MS and schizophrenia show some similarities. MS is characterized by a large array of invading immune cells that attack and degrade the myelin sheath, the myelin producing oligodendrocytes and the nerve itself. On the other hand, schizophrenia has been proposed to be a dysconnectivity syndrome. Disturbance in neuronal connectivity between different brain regions, rather than abnormalities restricted to individual brain regions, may be responsible for the clinical symptoms and cognitive dysfunctions observed in psychosis. In addition, the association of a dysregulated immune response and psychosis is well-established, and autoantibodies, specifically against the central nervous system, have been found in schizophrenic patients. Myelin and oligodendrocyte dysfunction affect neuronal connectivity, which has been implicated as a central abnormality in schizophrenia, resulting in prediction errors and dysconnectivity. Clinical and neuropathological studies have shown that disruption in myelination and dysmyelination-induced delays in information process can produce a high fidelity phenocopy of psychosis similar to schizophrenia **78, 79, 80, 81, 82, 83, 84, 85, 86**.

Recently, Boyle et al (2017) **87** found that disease risk is driven mostly by genes with no direct relevance to disease, but which act as modifiers of more fundamental biologic processes, perhaps related to individual genetic backgrounds and environmental experience. Based on these findings, Weinberger (2017) **88** reported: "This proposal echoes the question of whether psychiatric disorders are really "diseases" rather than varying states of brain development that have a particular way of expressing difficulties in particular environmental contexts, based on genomic background, development and experience". Rethinking the relative research findings and suggestions on psychosis, we may further suggest that the above described dysconnectivity syndrome in psychosis represents the phenomenological and behavioral result of a multiple faces dysmyelination disorder, which is based obviously on a lifelong immunogenetic dysregulation process.

Fig 1. Factors implicating in the immune-related dysmyelination process of psychosis


Genes
NRG1, DISC1, RTN4R, OLIG2, 22q11DS, cytokines genes, HLA genes
Stress
Infections during pregnancy, isolation, abuse, neglect, childhood autoimmune diseases
Lifelong immunogenetic dysregulation
Immune response: Elevated pro-inflammatory cytokines, CRP, KYNA levels, autoantibodies
Immune diseases: Autoimmune disorders such as celiac disease, Graves' disease, systemic lupus erythematosus, multiple sclerosis, autoimmune hepatitis, psoriasis.
MS and other demyelinating diseases may involve a combination of viral and autoimmune factors
Aberrant myelination
Demyelination: Leukodystrophies, Multiple sclerosis, Immune mediated, viral, and toxic.
Dysmyelination: Reduced or aberrant conduction velocity and fidelity of transfer signaling.
Myelin deficits in psychiatric disorders and developmental disorders including autism, sensory processing delay disorder, and ADHD.
Disconnectivity syndrome - Psychosis
Conduction delays in the efference copies: Confusion, negative symptoms, passivity, withdrawal symptoms, auditory hallucinations, delusional mood
Increases in the phasic activity of midbrain dopaminergic neurons: Positive symptoms, delusions, aggressivity, catatonia
Treatment
Anti-psychotics, anti-depressants, anti-convulsants, lithium
Anti-MS: Azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, mitoxantrone, cyclophosphamide and rituximab
Myelin-enhancing agents, potential neuro/myeloreparative agents, stem cell enhancing therapies, and immunodmodulators, Diet, life-style

References

1.Baumann N & Pham-Dinh D. Biology of Oligodendrocyte and Myelin in the Mammalian Central Nervous System. Physiological Review 2001, doi.org/10.1152/physrev.2001.81.2.871

2.Snaidero, N., and Simons, M. The logistics of myelin biogenesis in the central nervous system. Glia 2017, 65:1021–1031. doi: 10.1002/glia.23116

3.Tomassy G.S., Berger D.R., Chen H.H., Kasthuri N. et al. Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex. Science. 2014; 344: 319-324 doi: 10.1126/science.1249766

4.Nakagawa Y and Chiba K. Involvement of Neuroinflammation during Brain Development in Social Cognitive Deficits in Autism Spectrum Disorder and Schizophrenia. Journal of Pharmacology and Experimental Therapeutics 2016, 358: 504-515; DOI: https://doi.org/10.1124/jpet.116.234476

5.Nakagawa Y and Chiba K. Diversity and plasticity of microglial cells in psychiatric and neurological disorders. Pharmacol Ther 2015, 154:21–35. doi: 10.1016/j.pharmthera.2015.06.010

6.Perga S, Martire S, Montarolo F, et al, The Footprints of Poly-Autoimmunity: Evidence for Common Biological Factors Involved in Multiple Sclerosis and Hashimoto's Thyroiditis. Front Immunol. 2018, 9:311. doi: 10.3389/fimmu.2018.00311

7.Nave K. A. Myelination and support of axonal integrity by glia. Nature 2010, 468: 244–252 10.1038/nature09614

8.Simons M, Trajkovic K. Neuron-glia communication in the control of oligodendrocyte function and myelin biogenesis. J Cell Sci. 2006, 1;119(Pt 21):4381-9. DOI: 10.1242/jcs.03242

9.Almeida, R. G., and Lyons, D. A. On myelinated axon plasticity and neuronal circuit formation and function. J. Neurosci. 2017, 37:10023–10034. doi: 10.1523/JNEUROSCI.3185-16.2017

10.Young K.M., Psachoulia K., Tripathi R.B., Dunn S.J., Cossell L., Attwell D., Tohyama K., Richardson W.D. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. Neuron. 2013, 77: 873-885 doi: 10.1016/j.neuron.2013.01.006

11.Bercury KK, Macklin WB. Dynamics and mechanisms of CNS myelination. Developmental cell 2015, 32:4 447-458 doi org/10.1016/j.devcel.2015.01.016

12.Frühbeis C., Fröhlich D., Kuo W.P. et al. Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. PLoS Biol. 2013; 11: e1001604

13.Makinodan M., Rosen K.M., Ito S., Corfas G. A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science. 2012; 337: 1357-1360. doi: 10.1126/science.1220845

14.Barrera K., Chu P., Abramowitz J., Steger R., Ramos R.L., Brumberg J.C. Organization of myelin in the mouse somatosensory barrel cortex and the effects of sensory deprivation. Dev. Neurobiol. 2013; 73: 297-314. doi: 10.1002/dneu.22060.

15.Garver D, Holcomb J, Christensen J. Compromised myelin integrity during psychosis with repair during remission in drug-responding schizophrenia. Int J Neuropsychopharmacol. 2008, 11:49–61. DOI: 10.1017/S1461145707007730

16.Ren Y Wang H, Xiao X. Improving myelin/oligodendrocyte-related dysfunction: a new mechanism of antipsychotics in the treatment of schizophrenia? International Journal of Neuropsychopharmacology, 2013, 16:691–700, https://doi.org/10.1017/S1461145712001095

17.Haroutunian V. Katsel P. Roussos P. Davis K.L. Altshuler L.L. Bartzokis G. Myelination, oligodendrocytes, and serious mental illness. Glia. 2014, 62: 1856-1877. doi: 10.1002/glia.22716

18.Owen J.P. Marco E.J., Desai S., Fourie E., Harris J., Hill S.S., Arnett A.B., Mukherjee P. Abnormal white matter microstructure in children with sensory processing disorders. Neuroimage Clin. 2013, 2: 844-853. doi: 10.1016/j.nicl.2013.06.009

19.Li Q., Sun J., Guo L., Zang Y., Feng Z., Huang X., Yang H., Lv Y., Huang M., Gong Q. Increased fractional anisotropy in white matter of the right frontal region in children with attention-deficit/hyperactivity disorder: a diffusion tensor imaging study.

Neuroendocrinol. Lett. 2010, 31: 747-753. PMID: 21196923

20.Liu J, Dupree JL, Gacias M, Frawley R, Sikder T, Naik P, Casaccia P. Clemastine Enhances Myelination in the Prefrontal Cortex and Rescues Behavioral Changes in Socially Isolated Mice. J Neurosci. 2016, 20:36:957-62. doi: 10.1523/JNEUROSCI.3608-15.2016.

21.Cree BAC, Niu J, Hoi KK et al, Clemastine rescues myelination defects and promotes functional recovery in hypoxic brain injury. Brain. 2018, 1:141:85-98. doi: 10.1093/brain/awx312.

22.Stevens J.R. Schizophrenia and multiple sclerosis. Schizophr. Bull. 1988, 14:231–241. doi: 10.1093/schbul/14.2.231.

23.Sartorius N., Jablensky A., Korten A., Ernberg G., Anker M., Cooper J.E., Day R. Early manifestations and first-contact incidence of schizophrenia in different cultures: A preliminary report on the initial evaluation phase of the, WHO Collaborative Study on Determinants of Outcome of Severe Mental Disorders. Psychol. Med. 1986, 16:909–928. doi: 10.1017/S0033291700011910.

24.McGuffin P., Farmer A.E., Gottesman I.I., Murray R.M., Reveley A.M. Twin concordance for operationally defined schizophrenia: Confirmation of familiality and heritability. Arch. Gen. Psychiatry 1984, 41:541–545. doi: 10.1001/archpsyc.1984.01790170015002

25.Camara-Lemarroy CR, Ibarra-Yruegas BE, Rodriguez-Gutierrez R, Berrios-Morales I, Ionete C, Riskind P. The varieties of psychosis in multiple sclerosis: A systematic review of cases. Mult Scler Relat Disord. 2017, 12:9-14. doi: 10.1016/j.msard.2016.12.012

26.Bush W.S., Moore J.H. Genome-wide association studies. PLoS Comput. Biol. 2012, 8:e1002822 doi: 10.1371/journal.pcbi.1002822.

27.Dev KK, O'Connell KE. The immune and metabolic factors of schizophrenia. J J Psych Behav Sci. 2014, 1(1):004.

28.Farrell MS, Werge T, Sklar P, Owen MJ, Ophoff RA, O'Donovan MC, et al. Evaluating historical candidate genes for schizophrenia. Mol Psychiatry 2015, 20:555–62. doi: 10.1038/mp.2015.16

29.Johnson EC, Border R, Melroy-Greif WE, de Leeuw CA, Ehringer MA, Keller MC. No evidence that schizophrenia candidate genes are more associated with schizophrenia than noncandidate genes. Biol Psychiatry 2017, 82:702–8. doi: 10.1016/j.biopsych.2017.06.033

30.Savonenko AV, Melnikova T, Laird FM, et al. Alteration of BACE1-dependent NRG1/ErbB4 signaling and schizophrenia-like phenotypes in BACE1-null mice. Proc Natl Acad Sci U S A. 2008, 105:5585–90

31.Dries DR, Zhu Y, Brooks MM, et al. Loss of nicastrin from oligodendrocytes results in hypomyelination and schizophrenia with compulsive behavior. J Biol Chem. 2016, 291(22):11647-56. doi: 10.1074/jbc.M116.715078

32.Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011, 43:969–76. doi: 10.1038/ng.940

33.Roy K, Murtie JC, El-Khodor BF, et al. Loss of erbB signaling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders. Proc Natl Acad Sci U S A. 2007, 104:8131–6. DOI: 10.1073/pnas.0702157104

34.Takahashi N, Sakurai T, Davis KL, et al. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Prog Neurobiol. 2011, 93:13–24. doi: 10.1016/j.pneurobio.2010.09.004.

35.Stefansson H., Sigurdsson E., Steinthorsdottir V., Bjornsdottir S., Sigmundsson T., Ghosh S., et al. (2002). Neuregulin 1 and susceptibility to schizophrenia. Am. J. Hum. Genet. 2002, 71: 877–892 DOI: 10.1086/342734

36.Harrison P. J., Law A. J. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. Biol. Psychiatry 2006, 60:132–140 10.1016/j.biopsych.2005.11.002

37.Norton N., Moskvina V., Morris D. W., Bray N. J., Zammit S., Williams N. M., et al. (2006). Evidence that interaction between neuregulin 1 and its receptor erbB4 increases susceptibility to schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2006, 5:141B(1):96-101. DOI: 10.1002/ajmg.b.30236

38.Millar J. K., Wilson-Annan J. C., Anderson S., Christie S., Taylor M. S., Semple C. A., et al. (2000). Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum. Mol. Genet. 2000, 9:1415–1423 10.1093/hmg/9.9.1415

39.Chubb J. E., Bradshaw N. J., Soares D. C., Porteous D. J., Millar J. K. The DISC locus in psychiatric illness. Mol. Psychiatry 2008, 13 36–64 10.1038/sj.mp.4002106

40.Sprooten E., Sussmann J. E., Moorhead T. W., Whalley H. C., Ffrench-Constant C., Blumberg H. P., et al. (2011). Association of white matter integrity with genetic variation in an exonic DISC1 SNP.Mol. Psychiatry 2011, 16685:688–689 10.1038/mp.2011.15

41.Novak G., Kim D., Seeman P., Tallerico T. Schizophrenia and Nogo: elevated mRNA in cortex, and high prevalence of a homozygous CAA insert. Brain Res. Mol. Brain Res. 2002, 107 183–189 10.1016/S0169-328X(02)00492-8

42.Georgieva L., Moskvina V., Peirce T., Norton N., Bray N. J., Jones L., et al. Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. Proc. Natl. Acad. Sci. U.S.A. 2006, 103:12469–12474 10.1073/pnas.0603029103

43.Roussos P, Haroutunian V. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Front Cell Neurosci. 2014, 8:5. doi: 10.3389/fncel.2014.00005. eCollection 2014.

44.Bakker G, Caan MW, Schluter RS, et al. Distinct white-matter aberrations in 22q11.2 deletion syndrome and patients at ultra-high risk for psychosis. Psychol Med. 2016, 46:2299-311. doi: 10.1017/S0033291716000970.

45.Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. Schizophr Bull. 2018, 44:75–83. doi: 10.1093/schbul/sbx035

46.Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res. 2014, 155:101–8. doi: 10.1016/j.schres.2014.03.005

47.Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry 2016, 21:554–64. doi: 10.1038/mp.2015.87

48.Suvisaari J, Mantere Q, Keinänen J, Mäntylä T, Rikandi E, Lindgren M, Kieseppä T, Raij TT. Is It Possible to Predict the Future in First-Episode Psychosis? Front. Psychiatry, 2018 doi.org/10.3389/fpsyt.2018.00580

49.Gutierrez-Arcelus M, Rich SS, Raychaudhuri S. Autoimmune diseases – connecting risk alleles with molecular traits of the immune system. Nat Rev Genet 2016, 17:160–74.10.1038/nrg.2015.33

50.Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 2009, 460(7256):753–7.10.1038/nature08192

51.Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. Common variants conferring risk of schizophrenia. Nature 2009, 460(7256):744–7.10.1038/nature08186

52.Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, et al. Altering the course of schizophrenia: progress and perspectives. Nat Rev Drug Discov 2016, 15:485–515.10.1038/nrd.2016.28

53.Ezeoke A, Mellor A, Buckley P, Miller B. A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophr Res. 2013,150:245–251. doi: 10.1016/j.schres.2013.07.029

54.Ellul P, Groc L, Tamouza R, Leboyer M, The Clinical Challenge of Autoimmune Psychosis: Learning from Anti-NMDA

Receptor Autoantibodies, Front Psychiatry. 2017, 8: 54, doi: 10.3389/fpsyt.2017.00054

55.Mantere O, Saarela M, Kieseppä T, Raij T, Mäntylä T, Lindgren M, et al. Anti-neuronal anti-bodies in patients with early psychosis. Schizophr Res. 2018, 192:404–7. doi: 10.1016/j.schres.2017.04.027

56.Erhardt S, Schwieler L, Imbeault S, Engberg G. The kynurenine pathway in schizophrenia and bipolar disorder. Neuropharmacology 2017, 112(Pt B):297–306. doi: 10.1016/j.neuropharm.2016.05.020

57.Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 2005, 57:67–81. DOI: 10.1002/ana.20315

58.Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, Courchesne E, Everall IP. (2010) Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biol Psychiatry 2010, 68:368–376. doi: 10.1016/j.biopsych.2010.05.024.

59.Asadabadi M, Mohammadi M-R, Ghanizadeh A, Modabbernia A, Ashrafi M, Hassanzadeh E, Forghani S, Akhondzadeh S. Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. Psychopharmacology 2013, 225:51–59. Doi 10.1007/s00213-012-2796-8.

60.Nakagawa Y, Chiba K. Role of microglial m1/m2 polarization in relapse and remission of psychiatric disorders and diseases. Pharmaceuticals (Basel). 2014, 25;7:1028-48. doi: 10.3390/ph7121028.

61.Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med 2013, 43:239–57.10.1017/S0033291712000736

62.Benros ME, Eaton WW, Mortensen PB. The epidemiologic evidence linking autoimmune diseases and psychosis. Biol Psychiatry 2014, 75:300–306. doi: 10.1016/j.biopsych.2013.09.023.

63.Benros ME, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. Ann N Y Acad Sci. 2012, 1262:56–66. doi: 10.1111/j.1749-6632.2012.06638.x

64.Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry 2011), 168:1303–10.10.1176/appi.ajp.2011.11030516

65.Janova, H., Arinrad, S., Balmuth, E., Mitjans, M., Hertel, J., Habes, M., et al. Microglia ablation alleviates myelin-associated catatonic signs in mice. J. Clin. Invest. 2018, 128: 734–745. doi: 10.1172/JCI97032

66.Guest PC, Iwata K, Kato TA, et al. MK-801 treatment affects glycolysis in oligodendrocytes more than in astrocytes and neuronal cells: insights for schizophrenia. Front Cell Neurosci. 2015:12:180. doi: 10.3389/fncel.2015.00180. eCollection 2015.

67.Cassoli JS, Iwata K, Steiner J, et al. Effect of MK-801 and clozapine on the proteome of cultured human oligodendrocytes. Front Cell Neurosci. 2016,10:52. doi: 10.3389/fncel.2016.00052

68.Steiner J, Martins-de-Souza D, Schiltz K, et al. Clozapine promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes. Front Cell Neurosci. 2014, 8:384. doi: 10.3389/fncel.2014.00384. eCollection 2014.

69.Crocker CE & Tibbo PG. Confused Connections? Targeting White Matter to Address Treatment Resistant Schizophrenia. Front. Pharmacol., 2018 doi.org/10.3389/fphar.2018.01172

70.Fatemi SH, Folsom TD, Reutiman TJ, et al. Abnormal expression of myelination genes and white matter volume abnormalities following prenatal viral influenza infection at E16 in mice. Schizophr Res. 2009, 112:46–53. doi: 10.1016/j.schres.2009.04.014

71.Ford J.M., Palzes V.A., Roach B.J., Mathalon D.H. Did I do that? Abnormal predictive processes in schizophrenia when button pressing to deliver a tone. Schizophr. Bull. 2014, 40:804–812. doi: 10.1016/j.schres.2009.04.014

72.Franck N., Farrer C., Georgieff N. Defective recognition of one's own actions in patients with schizophrenia. Am. J. Psychiatry 2001, 158:454–459. DOI: 10.1176/appi.ajp.158.3.454

73.Frith CD. 1992, The Cognitive Neuropsychology of Schizophrenia. Hove, UK: Lawrence Erlbaum Associates.

74.Frith C. The neural basis of hallucinations and delusions. C.R. Biol. 2005;328(2):169–175. PMID: 15771003

75.Whitford TJ, Grieve SM, Farrow TF, et al. Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. Am J Psychiatry 2007, 164:1082–1089. DOI: 10.1176/ajp.2007.164.7.1082

76.Whitford TJ, Ford JM, Mathalon DH, Kubicki M, , Shenton ME. Schizophrenia, Myelination, and Delayed Corollary Discharges: A Hypothesis. Schizophr Bull. 2012, 38: 486–494. doi: 10.1093/schbul/sbq105

77.Bartholomeusz, C. F. et al. Structural neuroimaging across early-stage psychosis: Aberrations in neurobiological trajectories and implications for the staging model. Aust. N. Z. J. Psychiatry 2017, 51: 455–476. doi: 10.1177/0004867416670522

78.Catts VS, Fung SJ, Long LE, Joshi D. et al. Rethinking schizophrenia in the context of normal neurodevelopment. Front Cell Neurosci. 2013, 15:7:60. doi: 10.3389/fncel.2013.00060. eCollection 2013.

79.Dukart J, Smieskova R, Harrisberger F, et al. Age-related brain structural alterations as an intermediate phenotype of psychosis. Psychiatry Neurosci. 2017, 42:307-319. PMCID: PMC5573573

80.Friston K. Schizophrenia and the disconnection hypothesis. Acta Psychiatr Scand Suppl. 1999;395:68–79. PMID: 10225335

81.Griffa A, Baumann PS, Klauser P, Mullier E, et al. Brain connectivity alterations in early psychosis: from clinical to neuroimaging staging. Translational Psychiatry, 2019, 9, Article number: 62 doi.org/10.1038/s41398-019-0392-y

82.Kochunov P, Coyle TR, Rowland LM, Jahanshad N, et al. Association of White Matter With Core Cognitive Deficits in Patients With Schizophrenia. JAMA Psychiatry. 2017, 1;74(9):958-966. doi: 10.1001/jamapsychiatry.2017.2228.

83.Mighdoll MI, Tao R, Kleinman JE, Hyde TM. Myelin, myelin-related disorders, and psychosis. Schizophr Res. 2015, 161:85-93. doi: 10.1016/j.schres.2014.09.040. Epub 2014 Oct 23.

84.Peters, B. D. & Karlsgodt, K. H. White matter development in the early stages of psychosis. Schizophr. Res. 2014, 161:61–69 . doi: 10.1016/j.schres.2014.05.021

85.Sánchez, P. et al. Predictors of longitudinal changes in schizophrenia: the role of processing speed. J. Clin. Psychiatry 2009, 70: 888–896. doi.org/10.4088/JCP.08m04294

86. Giotakos O. Poor insight in psychosis and meta-representation models, Dialogues in Clinical Neuroscience & Mental Health 2018, 1:12-24. DOI: https://doi.org / 10. 26386/obrela.v1i1.5

87.Boyle EA, Li YI, Pritchard JK. An Expanded View of Complex Traits: From Polygenic to Omnigenic . Cell 2017, 169:15,1177-1186. doi: 10.1016/j.cell.2017.05.038

88.Weinberger DR, The neurodevelopmental origins of schizophrenia in the penumbra of genomic medicine, World Psychiatry 2017, 225-226. doi: 10.1002/wps.20474