Neuroinflammation and Disrupted Synaptic Plasticity, the Main Pathological Processes in Multiple Sclerosis and Obsessive-Compulsive Disorder: An Enrichment Analysis

Ali Sepehrinezhad
Iran University of Medical Sciences
Ali Bozorgmehr
Iran Psychiatric Hospital
Sajad Sahab Negah
Mashhad University of Medical Sciences
Minoo Karimi
Tehran University of Medical Sciences
Ali Shahbazi (shahbazi.a@iums.ac.ir)
Iran University of Medical Sciences https://orcid.org/0000-0001-5222-4792

Research

Keywords: Multiple sclerosis, obsessive-compulsive disorder, enrichment analysis, neuroinflammation, synaptic plasticity

Posted Date: May 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27604/v1

Abstract

Background: Multiple sclerosis (MS) is an autoimmune, inflammatory demyelinating, and disabling disorder of the central nervous system (CNS) with various clinical symptoms. Approximately 30% of the patients experience a variety of psychiatric problems during their disease course. Obsessive-compulsive disorder (OCD) is correlated with MS, but little is known about common molecular mechanisms of two diseases.

Methods: In this study, after a comprehensive review of the existing literature, we collected almost all the genes involved in MS and OCD, and then analyzed the common genes between MS and OCD. Next, the connections and functional interactions between these three gene sets were investigated in the STRING database and analyzed in 3 separate networks by Cytoscape software. Eventually, after a multi-part enrichment analysis, we found the main molecular and cellular pathways, biological processes, brain areas, and, more importantly, cells/tissue related to the shared genes between MS and OCD.

Results: Three genes of brain-derived neurotrophic factor (*BDNF*), tumor necrosis factor-alpha (*TNFα*), and neurexin-1 (*NRXN1*) are the major genes that were common between MS and OCD. Also, the deficit in synaptogenesis and neurotransmitter release in the nervous system are the most common complications of MS and OCD. Signaling receptor activity and estrogen receptor activity are the most important signaling pathways that are disturbed. Moreover, the presynaptic membrane, membrane raft, and growth cone are the main microenvironments that are affected in MS and OCD.

Conclusions: In addition to an enrichment analysis that showed physical and functional interactions of genes related to MS and OCD, we demonstrated and predicted some new genes and microRNAs that can be promising biomarkers/targets for future experimental studies. Also, our finding indicated that neuroinflammation and synaptic plasticity are two significant pathological processes that are affected in MS and OCD.

1. Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory and debilitating disease of the central nervous system. In the MS patients, changes in mobility, balance, sensation, vision, and cognition are obvious. The disease is categorized according to the initial disease course into relapsing-remitting and progressive primary types [1]. The relapsing-remitting form of the disease is the most common type and occurs in 90%-85% of MS patients [2]. Also, this type of MS affects young adults more and is three times more likely to occur in women than men [3]. In addition to various clinical signs and symptoms, psychiatric manifestations such as depression, euphoria, anxiety, mania, emotional lability, and psychosis may also be seen in these patients [4–6]. About 30% of MS patients experience psychiatric disorders during their illnesses [4]. Research on psychiatric manifestations of MS focuses more on depression, anxiety[6], and psychosis [7]. The rate of anxiety disorder in patients with MS has been reported by the National Comorbidity Survey as 25% [8]. In some studies, anxiety disorders, including

general anxiety disorder, obsessive-compulsive disorder (OCD), and panic disorder, have been reported in MS patients[9].

OCD is a neuropsychiatric disorder that is associated with intrusive thoughts and or repetitive behaviors that are created in response to obsessions and usually to reduce distress [10]. An early indication of this disorder is anxiety that can reveal itself as panic, phobic avoidance, intrusive experiences, excessive worry, and or difficulty controlling worry. Therefore, OCD may cause severe turmoil in everyday life and social relationships [11]. The global prevalence of OCD is about 2%-3%, and the World Health Organization has placed this disorder as one of the ten debilitating diseases [12–14].

The relationship between MS with symptoms of generalized anxiety disorder, panic attacks [15–17], and OCD [18] has already been mentioned. Also, the frequency of anxiety symptoms according to neuropsychiatry inventory was reported 37% in 44 patients with MS [15]. Research studies on psychiatric disorders in MS patients mainly focus on depression, anxiety [6], and psychosis [7]. Anxiety lifespan rate in patients with MS has been reported as 25% by the National Comorbidity Survey [8]. Several studies have reported that the onset of OCD was seen in MS patients[4, 9, 18–23]. The association between OCD-like behavior and MS in experimental autoimmune encephalomyelitis mice also has been reported [24].

In recent decades, the interference and role of genes have been investigated in many studies on mental disorders and inflammatory diseases, especially MS. For example, it has been reported that the genes such as *YP27B1*[25], *VDR* [26], *MOG* [27], *IL1RA* [28], *HLA-C* [29], *TGF-β2* [30], *MANBA*, *CXCR5*, *SOX8* [31], *CNTF* [32], *IFNAR1* [33], *IL10* [34] and a large number of other genes are significantly involved in the development of MS. Besides, it has been shown that variations in such genes as *SLC6A4* [35], *GRIK*2 [36], *MAOA* [37], *DRD4* [38], *COMT* [39], *BDNF* [40], and so on are associated with the risk of OCD in different populations.

Despite many studies done on OCD and MS, there is still little information on the pathogenesis of OCD and MS. In this regard, we assume that the comorbidity of MS and OCD may reflect the common pathophysiological mechanisms between these two disorders. Therefore, our study aimed to find and create two functional networks for MS-associated and OCD-associated genes separately and then reconstruct a new network for their shared genes. Afterward, we complete the study by analyzing each network in terms of topological and physical interaction, such as degree and betweenness centrality. Then, we investigate the most important biological processes, cellular components, and molecular functions that are distrusted in MS and OCD. Finally, our study demonstrates the most significant chromosomal regions, brain areas, cell lines, and pathways related to shared genes between MS and OCD. Also, the current study predicts some new genes that are probably involved in the pathophysiology of MS and OCD.

2. Materials And Methods

In this study, almost all genes involved in MS and OCD were manually collected in the first phase. Then, y into the STRING database to investigate and predict gene-

gene connections. Finally, Cytoscape was used to interpret and analyze the physical and functional interactions between genes and access to topological parameters related to each gene set. In other words, we use Cytoscape to visualize complicated networks.

2.1. Software and hardware requirements

The system requirements for Cytoscape depends on the size of the network (number of nodes and edges) that is loaded into the software. A system with at least 512 MB of memory and 1 GHz of the processor is required to run Cytoscape. Also, it requires a 64-bit Java runtime environment to work better and improve its running. Cytoscape is easily and freely downloadable at the following address: https://cytoscape.org/.

2.2. Searching resource for finding MS-association and OCD-association genes

We found and collected MS-related and OCD-related genes through a comprehensive literature review. We surveyed genetic association studies, linkage studies, genomewide association studies, and systematic reviews, by applying some keywords in PubMed and Google Scholar databases. The key terms were "multiple sclerosis," "MS," "Disseminated," "Obsessive-compulsive," "Obsessive-compulsive disorder," and "OCD." GWAS meta-analysis papers and animal studies also were excluded from the study. After a detailed evaluation, we found almost all of the genes associated with MS and OCD structurally, and then we analyzed the shared genes between them separately.

2.3. Genetic network creation and analysis

To form gene networks for MS-related and OCD-related genes, as well as shared genes between them, we loaded the genes found from the literature review to the STRING database (https://string-db.org/). The STRING database is a very outstanding base for integrating protein-protein interactions/associations, such as direct (physical) and indirect (functional) associations [41–43]. Finally, all of the genes and their interactions were uploaded to Cytoscape version 3.7.0 as three separate files. Cytoscape is open-source and free software for visualizing, integrating, and analyzing molecular connections, and genetic interaction networks [44, 45]. Afterward, for each gene set, some physical parameters and topological features of each network, such as diameter, centralization, the average number of neighbors, density, and clustering coefficient, were evaluated. Furthermore, to evaluate the significance of each gene in each network, we calculated the degree (number of connections) and the betweenness centrality. We used Network Analyzer Toolkit for visualizing each node/gene.

For a vertex $v \in V(G)$,

$$C_B(v) = \sum_{s \neq v \neq t \in V(G)} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

,

where σ_{st} is the total number of shortest paths from node s to node t. Also, $\sigma_{st}(v)$ is the number of those paths that pass through v [46]. Betweenness centrality (C_B) indicates how much each node is involved in passing information in the genetic networks. It is a great indicator for integrating and visualizing the data. The size and color of each node were matched to characterize degree and betweenness centrality, respectively.

2.4. Geneontology enrichment analysis

Gene set enrichment analysis is a statistical approach to identify classes of genes that are over-represented in a large set of genes and may have an association with disease phenotypes [47]. Gene ontology (GO) Consortium database (http://www.geneontology.org/) and a functional enrichment analysis web tool (WEB-based Gene SeT AnaLysis Toolkit) (http://www.webgestalt.org/) were used for enrichment analysis. Then the statistically significant molecular functions, biological processes, and cellular components associated with each gene set were extracted. GO calculates the probability or chance of seeing at least x number of genes out of the total n genes in the list annotated to a particular GO term, given the proportion of genes in the whole genome that are annotated to that GO term [48]. According to Google Analytics, WebGestalt (http://www.webgestalt.org/) has, on average, 26000 users from 144 countries and territories per year. WebGestalt is a popular and widespread database for the interpretation of gene sets derived from large scale- omics studies. In the last update, WebGestalt supports 12 organisms, 354 gene identifiers from numerous databases, and 321,251 functional categories from public databases and computational analyses. [49]

2.5. Cytogenetic band enrichment analysis

We used Enrichr (http://amp.pharm.mssm.edu/Enrichr/) for finding chromosomal locations related to shared genes between MS and OCD. Enrichr currently contains 302225 annotated gene set from 153 gene set libraries for analysis.

2.6. Tissue/cell specific expression analysis

Using Enrichr (http://amp.pharm.mssm.edu/Enrichr/), tissue-specific expression analysis was carried out to find the most prominent brain regions associated with genes shared between MS and OCD. Afterward, we use the Genotype-Tissue Expression (GTEx) project (https://gtexportal.org/) for demonstrating brain expression regions of most important genes (genes that have more connections and more centrality) between MS and OCD.

2.7. miRNA family prediction

NetworkTrail (https://networktrail.bioinf.uni-sb.de/) offers different analysis tools for each gene network. Using this web based analysis we predicted some microRNAs (miRNAs) in relation to target genes.

3. Results

3.1. Searching resources and finding genes

By searching the available resources and closely reviewing almost 2100 articles, we found 363 MS-associated genes (Supplementary Table 1) and 130 genes associated with OCD (Supplementary Table 2). According to the determined criteria, 12 genes were shared between the two disorders (Table 1).

Table 1
Shared genes between MS and OCD

Index	Official Symbol	Official Full Name	Ensembl ID
1	BDNF	Brain-derived neurotrophic factor	ENSG00000176697
2	CNR1	Cannabinoid receptor 1	ENSG00000118432
3	EAAT2	Glutamate transporter/solute carrier family 1 member 2	ENSG00000110436
4	EFNB1	Ephrin B1	ENSG00000090776
5	ESR1	Estrogen receptor 1	ENSG00000091831
6	ESR2	Estrogen receptor 2	ENSG00000140009
7	HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	ENSG00000196126
8	MOG	Myelin oligodendrocyte glycoprotein	ENSG00000204655
9	NRXN1	Neurexin 1	ENSG00000179915
10	PCDH10	Protocadherin 10	ENSG00000138650
11	TNFA	Tumor necrosis factor	ENSG00000232810
12	UCP2	Uncoupling protein 2	ENSG00000175567

3.2. Genetic network reconstruction and analysis

Among the genes associated with MS and OCD, we found no interaction for 19 and 22 genes. The MS network included 363 genes and 4401 interactions (Supplementary Fig. 1). Given the one topological feature, betweenness centrality, tumor protein p53 (*TP53*), interleukin 6 (*IL-6*), tumor necrosis factor (*TNF*), epidermal growth factor receptor (*EGFR*), mitogen-activated protein kinase 1 (*MAPK1*), brain-derived neurotrophic factor (*BDNF*) and interleukin 2 (*IL-2*) were the most determinant nodes in this network, in the order of importance. The OCD network included 130 genes and 661 interactions (Supplementary Fig. 2). *BDNF*, discs large MAGUK scaffold protein 4 (*DLG4*), Fos proto-oncogene (*FOS*), and DLG associated protein 1 (*DLGAP1*) were the most outstanding genes, in the order of prominence.

MS-OCD shared network included 12 genes and 16 edges (Fig. 1). Simple parameters of this network were diameter = 4; centralization = 0.691; average number of neighbors = 2.667; density = 0.242; and clustering coefficient = 0.423. In this network, *BDNF* was the most connected and central gene (Fig. 1). [illegible] a, we found *RIPK1, TRAF2, TRADD, IKBKG, IKBKB, TAB2,*

MAP3K7, TNFRSF1B, TNFRSF1A, and *NTRK2* as the most relevant novel genes to the network, in the order of relevance (Fig. 2).

3.3. Geneontology enrichment analysis

Biological process enrichment analysis for MS-associated genes indicated that this disorder develops mainly due to disturbance in the cell-surface receptor-signaling pathway, immune system process, cell communication, and response to cytokine (Supplementary Table 3). Also, enrichment analysis for OCD-associated genes showed that OCD progress was mainly due to a disruption of trans-synaptic signaling, regulation of neurotransmitter levels, chemical synaptic transmission, and cell-cell signaling (Supplementary Table 4). Biological process enrichment analysis showed that 168 processes are associated with genes shared between MS and OCD (Table 2). In summary, the regulation of inflammatory response to antigenic stimulus and axon development besides response to external stimulus could be considered the disrupted key processes (Table 2). Enrichment analysis of the gene shared set indicated three main deficient activities, signaling receptor binding (*BDNF, EFNB1, ESR1, ESR2, HLA-DRB1, NRXN1*, and *TNF*), signaling receptor activity (*CNR1, ESR1, ESR2, HLA-DRB1*, and *NRXN1*), and estrogen receptor activity (*ESR1* and *ESR2*), inside cells or cell membrane. Further analysis demonstrated that defects in an integral component of the plasma membrane, membrane raft, and axon part are the most significant cellular component associated with genes involved in both MS and OCD (Table 2). KEGG pathway enrichment analysis indicated that 23 pathways/diseases/disorders significantly enriched. Type I diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis, amyotrophic lateral sclerosis, endocrine resistance, influenza A, and herpes simplex infection were the most crucial diseases/disorders that involved in MS and OCD (Table 3).

Table 3
KEGG pathway enrichment analysis for shared genes between MS and OCD

Enrichment analysis	False discovery rate
Endocrine resistance	0.0122
Antigen processing and presentation	0.0122
Hematopoietic cell lineage	0.0122
Prolactin signaling pathway	0.0122
Type I diabetes mellitus	0.0122
Amyotrophic lateral sclerosis (ALS)	0.0122
Leishmaniosis	0.0122
Toxoplasmosis	0.0122
Asthma	0.0122
Inflammatory bowel disease (IBD)	0.0122
Systemic lupus erythematosus	0.0122
Rheumatoid arthritis	0.0122
Allograft rejection	0.0122
Graft-versus-host disease	0.0122
Estrogen signaling pathway	0.0163
Cell adhesion molecules (CAMs)	0.0166
Breast cancer	0.0174
Tuberculosis	0.0213
Influenza A	0.0213

Table 2
Geneontology enrichment analysis results (biological processes, cellular component, and molecular functions) for shared genes between MS and OCD

Enrichment analysis	False discovery rate
Biological processes	
regulation of insulin secretion	6.15E-05
regulation of inflammatory response to antigenic stimulus	0.00013
regulation of hormone levels	0.00013
cell-cell signaling	0.00023
response to external stimulus	0.00048
cell communication	0.00071
regulation of monooxygenase activity	0.00071
regulation of insulin secretion involved in cellular response to glucose stimulus	0.00071
regulation of protein localization	0.00078
response to chemical	0.00081
negative regulation of response to stimulus	0.00081
system development	0.00081
positive regulation of fever generation	0.001
regulation of neurotransmitter levels	0.0016
positive regulation of inflammatory response to antigenic stimulus	0.0016
regulation of inflammatory response	0.002
regulation of response to external stimulus	0.0022
response to organic substance	0.0024
signaling	0.0024
regulation of cellular localization	0.0024
axon development	0.0025
response to lipid	0.0032
inflammatory response to antigenic stimulus	0.0035
cell adhesion	0.0035
	0.0035

Enrichment analysis	False discovery rate
intracellular estrogen receptor signaling pathway	0.0035
Cellular components	
integral component of plasma membrane	0.0019
integral component of membrane	0.0033
plasma membrane	0.0146
cell surface	0.0146
axon part	0.0146
presynaptic membrane	0.0146
membrane raft	0.0146
growth cone	0.0423
Molecular functions	
signaling receptor binding	0.00075
estrogen receptor activity	0.00075
estrogen response element binding	0.00075
nuclear receptor activity	0.0164
virus receptor activity	0.0205
steroid binding	0.0205
signaling receptor activity	0.0205
receptor regulator activity	0.0344
molecular function regulator	0.0344

3.4. Cytogenetic band enrichment analysis

Cytogenetic band enrichment analysis represented 7 chromosomal regions associated significantly with the MS-OCD shared genes. However, the significance of chromosomes X, 11, and 2 was remarkable (Table 4).

Table 4
Cytogenetic band enrichment analysis results (chromosomal regions) for shared genes between MS and OCD

Index	Chromosome no.	Cytoband	P-value	Adjusted P-value
1.	2	p14	0.031931816	0.066280226
2.	4	q28	0.038320724	0.066280226
3.	6	q14	0.03600197	0.066280226
4.	6	q24	0.043519238	0.066280226
5.	11	p14	0.023744211	0.066280226
6.	14	q21	0.046396158	0.066280226
7.	X	q12	0.017857111	0.066280226

3.5. Tissue/cell specific expression analysis

Tissue/cell-specific expression analysis using the Enrichr online tool showed that five brain regions of the dorsal striatum, cerebral cortex, cingulate gyrus, prefrontal cortex, and the superior frontal gyrus besides two cell lines of astrocytes and $CD19^+$ B cells are significantly associated with MS-OCD shared genes (Table 5). Specific analysis of 3 important genes (*BDNF, TNF*, and *NRXN1*) using GTEx, showed exact brain expression regions of them (Fig. 3).

Table 5
Tissue/cell specific expression analysis results (brain regions and cells line) for shared genes between MS and OCD

Index	Brain area/cell lines	P-value	Adjusted P-value
1.	Dorsal striatum	0.008142308	0.348173914
2.	Cerebral cortex	0.041367198	0.348173914
3.	Cingulate gyrus	0.041367198	0.348173914
4.	Prefrontal cortex	0.041367198	0.348173914
5.	Superior frontal gyrus	0.041367198	0.348173914
6.	Astrocyte	0.041367198	0.348173914
7.	$CD19^+$ B cells	0.041367198	0.348173914

3.6. miRNA prediction analysis

miRNAs prediction analysis using NetworkTrail provided four miRNAs of *miR-410*, *miR-344de*, *miR-344b-1-3p*, and *miR-221* were more significantly associated with MS-OCD shared genes (Fig. 4).

4. Discussion

In this study, we found 12 common genes between MS and OCD with a wide-ranging and targeted overview of available resources. Furthermore, network analysis showed that among the 12 common genes, three genes of *BDNF*, *TNFα*, and *NRXN1*, were the most central genes, in the order of centrality.

BDNF is a member of the neurotrophin family, which plays essential roles in many neural processes such as synaptic plasticity, neuronal development, and cell survival [50, 51]. This protein promotes ensheathing the neurites with myelin by maturating oligodendrocyte precursor cells to oligodendrocytes and increasing myelin synthesis via tropomyosin-related kinase B signaling in them [52]. It has been shown that the level of *BDNF* in patients with relapsing-remitting MS (RRMS) is reduced [53], and this decrease can contribute to the progression of axonal loss and demyelinating disease in MS patients [54]. It has also reported that Sequence Variants in the *BDNF* gene are related to OCD [40, 55]. Other studies have also shown that the Val66Met *BDNF* gene variant is associated with OCD development [56, 57].

TNFα is a cytokine released from various types of cells, such as macrophages, lymphocytes, neutrophils, and brain astrocytes [58]. This cytokine has many functions in immunity, inflammation, and cell death [59]. Various studies have shown that TNFα levels in the brain and cerebrospinal fluid of MS patients rise, and an increase in this pro-inflammatory cytokine is associated with the development of MS [60–62]. The presence of this gene in the regenerated gene network represents the involvement of the immune system and inflammatory processes in these disorders. Also, the role of TNFα and inflammatory reactions have been shown in the progression of OCD, and it has been shown that polymorphisms in the TNFα gene are related to OCD [63]. Besides, the plasma levels of this pro-inflammatory cytokine are related to the progress of OCD [64].

Neurexins are a family of proteins that are essential as cell adhesion molecules in the development and establishment of the nervous system synapses [65]. Reduced synaptic density in the hippocampus and cerebral cortex of MS patients and impaired function of the neural circuits in the OCD has already been documented [66–68]. Besides, the dysregulation of *NRXN1* leads to neurodegeneration in MS patients [69]. Noh et al. study also showed that *NRXN1* is a strongly linked gene with OCD [70]. Because BDNF/TrkB signaling plays an important role in regulating synaptic strength and transmission [50], the involvement of *BDNF* and *NRXN1* genes in MS and OCD can explain the synaptic disruption in these two disorders.

Among the new genes that entered the network, *TNFRSF1A* and *MAP3K7* genes had the highest degree of centrality and degree of difference and importance. The Tumor Necrosis Factor Receptor superfamily member 1A (*TNFRSF1A*) gene encodes a variety of TNFα receptors (TNFR1), which results in many inflammatory processes, apoptosis, and cell survival [71]. Studies have shown that variation in the *TNFRSF1A* gene can contribute to the progression of MS [72]. Simsek et al. suggested that low levels of TNFα through the *TNFRSF1A* may cause OCD or worsen it [73]. Although further studies on the changes in this gene in OCD can be valuable.

Mitogen-activated protein kinase 7 is an upstream activator of Jun N-terminal kinases (JNKs), which is activated in response to various stimuli such as growth factors, pro-inflammatory cytokines, hormones, and environmental stress and plays an important role in the development of the nervous system [74]. MAP3K7 has been reported as a new autoantigen in MS patients [75]. Future studies on the possible role of the *MAP3K7* gene in MS and OCD can be helpful.

The results of enrichment analysis on common genes between MS and OCD show the regulation of the inflammatory response to antigenic stimuli (*CNR1, HLA-DRB1, TNF*), response to external stimulus (*BDNF, CNR1, EFNB1, HLA-DRB1, NRXN1, SLC1A2, TNF, UCP2*) and axon development (*BDNF, CNR1, EFNB1, NRXN1*) are the most important processes affected by these two disorders. It is believed that cannabinoid receptor 1 (CNR1) exists on peripheral immune cells, and is strongly expressed in active T cells [76]. Class II major histocompatibility complex (*MHC*) genes are molecules expressed by various types of immune system cells, including B cells, activated T cells, macrophages, dendritic cells, and thymus epithelial cells. They play a central role in the immune system by presenting peptides derived from extracellular proteins [77]. BDNF is a factor that is essential for the growth and development of axons [78], and studies have shown that the expression of BDNF in the inflammation conditions is significantly reduced [79, 80]. Neurexins play a significant role in synaptogenesis, and neurotransmitter releases [65, 81]. The findings indicate that CNR1 is essential for the normal growth of axons [82], and the rate of expression of these receptors on peripheral blood mononuclear cells increases in inflammatory conditions by inflammatory cytokines [83]. It has also been shown that defect in *EFNB1* gene leads to malformation of the corpus callosum [84]. The results also showed that estrogen receptor activity and estrogen response element-binding are other processes associated with MS and OCD common genes. It shows that estrogen may also play a role in the pathogenesis of these disorders. It has been shown that the use of the ER1 and ER2 ligands has protective effects in the animal model of MS, namely, experimental autoimmune encephalomyelitis (EAE) [85, 86].

Further analyses of MS and OCD common genes indicate that the integral component of the plasma membrane, membrane raft, and growth cone are the most important areas affected by the disorders. Membrane rafts play a significant role in the adhesion and motility of growth cone, and therefore their normal function is essential for axon guidance [87].

Tissue/cell specific expression analysis showed that five major brain regions and two cell lines are associated with MS and OCD. The relationship between dorsal striatum, prefrontal cortex, cingulate cortex, and cerebral cortex with MS in neuroimaging studies has been proven in patients [88, 89]. Astrocytes are the most important glial cells in the CNS. In the animal model of EAE, they have neuroprotective and anti-inflammatory effects by the expression of ER1 and the production of neurosteroids such as estrogen [90]. The reactive form of these cells is critical in the development of brain lesions and the production of scars in MS by producing pro-inflammatory cytokines and movement of innate immune cells (chemotaxis) into the brain tissue [91]. The role of $CD19^{+}$ B-cell in the pathogenesis of MS has also been proven [92]. Besides, dysfunction of structures such as the striatum, ate cortex in OCD has also been reported [93]. At the cellular

level, recent studies have also shown the involvement of brain astrocytes in repetitive and compulsive behaviors [94, 95].

MicroRNAs are small noncoding RNA molecule that are involved in the regulation of gene expression through silencing their target mRNAs and inhibit their translation [96]. Each miRNA can regulate the expression of a large number of target genes. Recent experiments have strongly focused on these molecules. For instance *miR-410* has neuroprotective effects and can regulate neurogenesis [97, 98]. Also, *miR-344-3p* is crucial for development of nervous system and morphogenesis [99]. Interestingly, *miR-221* could stimulate Schwann cell proliferation [100] and also, decrease inflammatory responses and cell death in neuronal cells [101].

5. Conclusions

In summary, we concluded that the three genes of *BDNF*, *TNFα*, and *NRXN1* are the major genes involved in the pathogenesis of MS and OCD and deficit in synaptogenesis and neurotransmitter release in the nervous system are the most common complications of MS and OCD. Also, disruption of signaling receptor and estrogen receptor activity are the most important signaling pathways that are disturbed and, the presynaptic membrane, membrane raft, and growth cone are the main areas that are affected in MS and OCD. On the other hand, we predicted ten new genes, seven chromosomal regions, five brain areas, ten miRNAs, and two cell lines that are common between MS and OCD. Finally, our study showed that the commonality between MS and OCD is related to the dysfunction of genes involved in synaptogenesis, plasticity, and neuroinflammation in some brain regions, especially in the dorsal striatum, cerebral cortex, cingulate gyrus, and prefrontal cortex. Also, it seems that astrocytes are among the cells target responsible for the neuropathological change in MS and OCD. We suggest that experimental studies in the future confirm some of these findings and our predicted miRNAs can be a therapeutic target for MS and OCD.

Abbreviations

BDNF
Brain-derived neurotrophic factor; **CNR1**:Cannabinoid receptor 1; **CNS**:Central nervous system; **DLGAP1**:DLG associated protein 1; **DLG4**:Discs large MAGUK scaffold protein 4; **EFNB1**:Ephrin B1; **EGFR**:Epidermal growth factor receptor; **FOS**:Fos proto-oncogene; **GO**:Gene ontology; **IL-2**:Interleukin 2; **IL-6**:Interleukin 6; **JNKs**:Jun N-terminal kinases; **miRNAs**:microRNAs; **MAPK1**:Mitogen-activated protein kinase 1; **MS**:Multiple sclerosis; **NRXN1**:Neurexin-1; **OCD**:Obsessive-compulsive disorder; **RRMS**:relapsing-remitting MS; **TNFα**:Tumor necrosis factor-alpha; **TNFRSF1A**:Tumor Necrosis Factor Receptor superfamily member 1A; **TP53**:Tumor protein p53

Declarations

Acknowledgments

Not applicable.

Funding

Funding information is not applicable / No funding was received.

Authors' contributions

Ali Sepehrinezhad, Ali Bozorgmehr, and Ali Shahbazi designed the study, carried out the literature review, and drafted the manuscript. Ali Shahbazi, Sajad Sahab Negah and Minoo Karimi carried out the literature review and participated in drafting the manuscript. Also, Ali Shahbazi and Sajad Sahab Negah critically edited the manuscript and corrected grammatical errors in the revised manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interest's policy

The authors declare that they have no competing interests.

References

1. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet. 2017;389:1336–46.
2. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292–302.
3. Hirst C, Ingram G, Pickersgill T, Swingler R, Compston DA, Robertson NP. Increasing prevalence and incidence of multiple sclerosis in South East Wales. J Neurol Neurosurg Psychiatry. 2009;80:386–91.
4. Wilken JA, Sullivan C. Recognizing and treating common psychiatric disorders in multiple sclerosis. Neurologist. 2007;13:343–54.

5. Bal MAA, Vázquez-Barquero JL, Peña C, Miro J, Berciano JA. Psychiatric aspects of multiple sclerosis. Acta Psychiatr Scand. 1991;83:292–6.
6. Feinstein A. Multiple sclerosis and depression. Mult Scler. 2011;17:1276–81.
7. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. Neurology. 2005;65:1123–5.
8. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51:8–19.
9. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler. 2007;13:67–72.
10. Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian J Psychiatry. 2013;55:220–3.
11. Bartz JA, Hollander E. Is obsessive-compulsive disorder an anxiety disorder? Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:338–52.
12. Murray CJ, Lopez AD. Evidence-based health policy–lessons from the Global Burden of Disease Study. Science. 1996;274:740–3.
13. Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, Rossler W. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. Eur Arch Psychiatry Clin Neurosci. 2004;254:156–64.
14. Murphy DL, Moya PR, Fox MA, Rubenstein LM, Wendland JR, Timpano KR. Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive-compulsive disorder as an example of overlapping clinical and genetic heterogeneity. Philos Trans R Soc Lond B Biol Sci. 2013;368:20120435.
15. Politte LC, Huffman JC, Stern TA. Neuropsychiatric manifestations of multiple sclerosis. Prim Care Companion J Clin Psychiatry. 2008;10:318–24.
16. Zorzon M, de Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G, Bratina A, Zivadinov R. Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. J Neurol. 2001;248:416–21.
17. Janssens AC, van Doorn PA, de Boer JB, van der Meche FG, Passchier J, Hintzen RQ. Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression, and disease-related distress. J Clin Epidemiol. 2004;57:180–6.
18. Shabani A, Nikravesh S, Panaghi L. Obsessive-compulsive Disorder: Is it Common in Multiple Sclerosis? Iranian Journal of Psychiatry Clinical Psychology. 2006;12:209–15.
19. Shabani A, Attari Moghadam J, Panaghi L, Seddigh A: **Anxiety disorders in multiple sclerosis**: **significance of obsessive-compulsive disorder comorbidity**. 2007 2007, **12**:6.
20. Foroughipour M, Behdani F, Hebrani P, Marvast MN, Esmatinia F, Akhavanrezayat A. Frequency of obsessive-compulsive disorder in patients with multiple sclerosis: A cross-sectional study. J Res Med

Sci. 2012;17:248–53.

21. George MS, Kellner CH, Fossey MD. Obsessive-compulsive symptoms in a patient with multiple sclerosis. J Nerv Ment Dis. 1989;177:304–5.
22. **Obsessive-compulsive disorder in patients with multiple sclerosis**. *The Journal of Neuropsychiatry and Clinical Neurosciences* 1995, 7:507–510.
23. Tinelli E, Francia A, Quartuccio EM, Morreale M, Contessa GM, Pascucci S, Sbardella E, Pozzilli C, Pantano P. Structural brain MR imaging changes associated with obsessive-compulsive disorder in patients with multiple sclerosis. AJNR Am J Neuroradiol. 2013;34:305–9.
24. Kant R, Pasi S, Surolia A. Auto-Reactive Th17-Cells Trigger Obsessive-Compulsive-Disorder Like Behavior in Mice With Experimental Autoimmune Encephalomyelitis. Front Immunol. 2018;9:2508.
25. Sundqvist E, Baarnhielm M, Alfredsson L, Hillert J, Olsson T, Kockum I. Confirmation of association between multiple sclerosis and CYP27B1. Eur J Hum Genet. 2010;18:1349–52.
26. Fukazawa T, Yabe I, Kikuchi S, Sasaki H, Hamada T, Miyasaka K, Tashiro K. Association of vitamin D receptor gene polymorphism with multiple sclerosis in Japanese. J Neurol Sci. 1999;166:47–52.
27. Burfoot RK, Jensen CJ, Field J, Stankovich J, Varney MD, Johnson LJ, Butzkueven H, Booth D, Bahlo M, Tait BD, et al. SNP mapping and candidate gene sequencing in the class I region of the HLA complex: searching for multiple sclerosis susceptibility genes in Tasmanians. Tissue Antigens. 2008;71:42–50.
28. Schrijver HM, Crusius JBA, Uitdehaag BMJ, García González MA, Kostense PJ, Polman CH, Peña AS: **Association of interleukin-1 < strong > β and interleukin-1 receptor antagonist genes with disease severity in MS**. *Neurology* 1999, **52**:595–595.
29. Yeo TW, De Jager PL, Gregory SG, Barcellos LF, Walton A, Goris A, Fenoglio C, Ban M, Taylor CJ, Goodman RS, et al. A second major histocompatibility complex susceptibility locus for multiple sclerosis. Ann Neurol. 2007;61:228–36.
30. He B, Xu C, Yang B, Landtblom A-M, Fredrikson S, Hillert J. Linkage and association analysis of genes encoding cytokines and myelin proteins in multiple sclerosis. J Neuroimmunol. 1998;86:13–9.
31. Lill CM, Schjeide BM, Graetz C, Ban M, Alcina A, Ortiz MA, Perez J, Damotte V, Booth D, Lopez de Lapuente A, et al. MANBA, CXCR5, SOX8, RPS6KB1 and ZBTB46 are genetic risk loci for multiple sclerosis. Brain. 2013;136:1778–82.
32. Giess R, Maurer M, Linker R, Gold R, Warmuth-Metz M, Toyka KV, Sendtner M, Rieckmann P. Association of a null mutation in the CNTF gene with early onset of multiple sclerosis. Arch Neurol. 2002;59:407–9.
33. Leyva L, Fernandez O, Fedetz M, Blanco E, Fernandez VE, Oliver B, Leon A, Pinto-Medel MJ, Mayorga C, Guerrero M, et al. IFNAR1 and IFNAR2 polymorphisms confer susceptibility to multiple sclerosis but not to interferon-beta treatment response. J Neuroimmunol. 2005;163:165–71.
34. Almeras L, Meresse B, Seze J, De Lefranc D, Dubucquoi S, Fajardy I, Vermersch P, Prin L. Interleukin-10 promoter polymorphism in multiple sclerosis: association with disease progression. Eur Cytokine

35. Kinnear CJ, Niehaus DJ, Moolman-Smook JC, du Toit PL, van Kradenberg J, Weyers JB, Potgieter A, Marais V, Emsley RA, Knowles JA, et al. Obsessive-compulsive disorder and the promoter region polymorphism (5-HTTLPR) in the serotonin transporter gene (SLC6A4): a negative association study in the Afrikaner population. Int J Neuropsychopharmacol. 2000;3:327–31.
36. Delorme R, Krebs MO, Chabane N, Roy I, Millet B, Mouren-Simeoni MC, Maier W, Bourgeron T, Leboyer M. Frequency and transmission of glutamate receptors GRIK2 and GRIK3 polymorphisms in patients with obsessive compulsive disorder. Neuroreport. 2004;15:699–702.
37. Camarena B, Rinetti G, Cruz C, Gomez A, de La Fuente JR, Nicolini H. Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive-compulsive disorder. Am J Med Genet. 2001;105:279–82.
38. Cruz C, Camarena B, King N, Paez F, Sidenberg D, de la Fuente JR, Nicolini H. Increased prevalence of the seven-repeat variant of the dopamine D4 receptor gene in patients with obsessive-compulsive disorder with tics. Neurosci Lett. 1997;231:1–4.
39. Karayiorgou M, Sobin C, Blundell ML, Galke BL, Malinova L, Goldberg P, Ott J, Gogos JA. Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive-compulsive disorder. Biol Psychiatry. 1999;45:1178–89.
40. Hall D, Dhilla A, Charalambous A, Gogos JA, Karayiorgou M. Sequence variants of the brain-derived neurotrophic factor (BDNF) gene are strongly associated with obsessive-compulsive disorder. Am J Hum Genet. 2003;73:370–6.
41. Franceschini A, Szklarczyk D, Frankild S, Kuhn M, Simonovic M, Roth A, Lin J, Minguez P, Bork P, von Mering C, Jensen LJ. STRING v9.1: protein-protein interaction networks, with increased coverage and integration. Nucleic Acids Res. 2013;41:D808–15.
42. Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M, Santos A, Doncheva NT, Roth A, Bork P, et al. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res. 2017;45:D362-d368.
43. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, et al. STRING v10: protein–protein interaction networks, integrated over the tree of life. Nucleic Acids Res. 2014;43:D447–52.
44. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003;13:2498–504.
45. Cline MS, Smoot M, Cerami E, Kuchinsky A, Landys N, Workman C, Christmas R, Avila-Campilo I, Creech M, Gross B, et al. Integration of biological networks and gene expression data using Cytoscape. Nat Protoc. 2007;2:2366.
46. Freeman LC. A Set of Measures of Centrality Based on Betweenness. Sociometry. 1977;40:35–41.
47. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP. Gene set enrichment analysis: a knowledge-based approach for [illegible] ofiles. Proc Natl Acad Sci U S A. 2005;102:15545–50.

48. **Gene Ontology Consortium**. : going forward. Nucleic Acids Res. 2015;43:D1049–56.
49. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. **WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs**. *Nucleic Acids Research* 2019.
50. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24:677–736.
51. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci. 2003;4:299–309.
52. Fletcher JL, Murray SS, Xiao J. **Brain-Derived Neurotrophic Factor in Central Nervous System Myelination: A New Mechanism to Promote Myelin Plasticity and Repair**. *Int J Mol Sci* 2018, 19.
53. Wens I, Keytsman C, Deckx N, Cools N, Dalgas U, Eijnde BO. Brain derived neurotrophic factor in multiple sclerosis: effect of 24 weeks endurance and resistance training. Eur J Neurol. 2016;23:1028–35.
54. Sarchielli P, Greco L, Stipa A, Floridi A, Gallai V. Brain-derived neurotrophic factor in patients with multiple sclerosis. J Neuroimmunol. 2002;132:180–8.
55. Alonso P, Gratacos M, Menchon JM, Saiz-Ruiz J, Segalas C, Baca-Garcia E, Labad J, Fernandez-Piqueras J, Real E, Vaquero C, et al. Extensive genotyping of the BDNF and NTRK2 genes define protective haplotypes against obsessive-compulsive disorder. Biol Psychiatry. 2008;63:619–28.
56. Hemmings SM, Kinnear CJ, Van der Merwe L, Lochner C, Corfield VA, Moolman-Smook JC, Stein DJ. Investigating the role of the brain-derived neurotrophic factor (BDNF) val66met variant in obsessive-compulsive disorder (OCD). World J Biol Psychiatry. 2008;9:126–34.
57. Katerberg H, Lochner C, Cath DC, de Jonge P, Bochdanovits Z, Moolman-Smook JC, Hemmings SM, Carey PD, Stein DJ, Sondervan D, et al: **The role of the brain-derived neurotrophic factor (BDNF) val66met variant in the phenotypic expression of obsessive-compulsive disorder (OCD)**. *Am J Med Genet B Neuropsychiatr Genet* 2009, **150b**:1050–1062.
58. Cammack R, Atwood T, Campbell P, Parish H, Smith A, Vella F, Stirling J: *Oxford Dictionary of Biochemistry and Molecular Biology.* Oxford University Press; 2008.
59. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood. 2012;119:651–65.
60. Olesen MN, Soelberg K, Debrabant B, Nilsson AC, Lillevang ST, Grauslund J, Brandslund I, Madsen JS, Paul F, Smith TJ, et al. Cerebrospinal fluid biomarkers for predicting development of multiple sclerosis in acute optic neuritis: a population-based prospective cohort study. Journal of Neuroinflammation. 2019;16:59.
61. Rossi S, Motta C, Studer V, Barbieri F, Buttari F, Bergami A, Sancesario G, Bernardini S, De Angelis G, Martino G, et al. Tumor necrosis factor is elevated in progressive multiple sclerosis and causes excitotoxic neurodegeneration. Mult Scler. 2014;20:304–12.
62. Hofman FM, Hinton DR, Johnson K, Merrill JE. Tumor necrosis factor identified in multiple sclerosis brain. J Exp Med. 1989;170:607–12.

63. Hounie AG, Cappi C, Cordeiro Q, Sampaio AS, Moraes I, Rosario MC, Palacios SA, Goldberg AC, Vallada HP, Machado-Lima A, et al. TNF-alpha polymorphisms are associated with obsessive-compulsive disorder. Neurosci Lett. 2008;442:86–90.
64. Konuk N, Tekin IO, Ozturk U, Atik L, Atasoy N, Bektas S, Erdogan A. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. Mediators Inflamm. 2007;2007:65704.
65. Craig AM, Kang Y. Neurexin-neuroligin signaling in synapse development. Curr Opin Neurobiol. 2007;17:43–52.
66. Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, Young EA, Fox RJ, Staugaitis SM, Trapp BD. Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. Ann Neurol. 2011;69:445–54.
67. Wegner C, Esiri MM, Chance SA, Palace J, Matthews PM. Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. Neurology. 2006;67:960–7.
68. Simmler LD, Ozawa T. Neural circuits in goal-directed and habitual behavior: Implications for circuit dysfunction in obsessive-compulsive disorder. Neurochem Int. 2019;129:104464.
69. Kattimani Y, Veerappa AM. Dysregulation of NRXN1 by mutant MIR8485 leads to calcium overload in pre-synapses inducing neurodegeneration in Multiple sclerosis. Mult Scler Relat Disord. 2018;22:153–6.
70. Noh HJ, Tang R, Flannick J, O'Dushlaine C, Swofford R, Howrigan D, Genereux DP, Johnson J, van Grootheest G, Grünblatt E, et al. Integrating evolutionary and regulatory information with a multispecies approach implicates genes and pathways in obsessive-compulsive disorder. Nat Commun. 2017;8:774.
71. Greco E, Aita A, Galozzi P, Gava A, Sfriso P, Negm OH, Tighe P, Caso F, Navaglia F, Dazzo E, et al. The novel S59P mutation in the TNFRSF1A gene identified in an adult onset TNF receptor associated periodic syndrome (TRAPS) constitutively activates NF-kappaB pathway. Arthritis Res Ther. 2015;17:93.
72. **The genetic association of variants in CD6, TNFRSF1A and IRF8 to multiple sclerosis: a multicenter case-control study**. *PLoS One* 2011, 6:e18813.
73. Şimşek Ş, Yüksel T, Çim A, Kaya S. **Serum Cytokine Profiles of Children with Obsessive-Compulsive Disorder Shows the Evidence of Autoimmunity**. *Int J Neuropsychopharmacol* 2016, 19.
74. Chang L, Karin M. Mammalian MAP kinase signalling cascades. Nature. 2001;410:37–40.
75. Zandian A, Forsström B, Häggmark-Månberg A, Schwenk JM, Uhlén M, Nilsson P, Ayoglu B. Whole-Proteome Peptide Microarrays for Profiling Autoantibody Repertoires within Multiple Sclerosis and Narcolepsy. J Proteome Res. 2017;16:1300–14.
76. Borner C, Hollt V, Kraus J. Activation of human T cells induces upregulation of cannabinoid receptor type 1 transcription. Neuroimmunomodulation. 2007;14:281–6.
77. Klein J, Sato A. The HLA system. First of two parts. N Engl J Med. 2000;343:702–9.

78. Liao GY, Bouyer K, Kamitakahara A, Sahibzada N, Wang CH, Rutlin M, Simerly RB, Xu B. Brain-derived neurotrophic factor is required for axonal growth of selective groups of neurons in the arcuate nucleus. Mol Metab. 2015;4:471–82.
79. Guan Z, Fang J. Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. Brain Behav Immun. 2006;20:64–71.
80. Schnydrig S, Korner L, Landweer S, Ernst B, Walker G, Otten U, Kunz D. Peripheral lipopolysaccharide administration transiently affects expression of brain-derived neurotrophic factor, corticotropin and proopiomelanocortin in mouse brain. Neurosci Lett. 2007;429:69–73.
81. Ahmad M, Missler M: **Neurexins**. In *Encyclopedia of Neuroscience*. Edited by Squire LR. Oxford: Academic Press; 2009: 261–267.
82. Watson S, Chambers D, Hobbs C, Doherty P, Graham A. The endocannabinoid receptor, CB1, is required for normal axonal growth and fasciculation. Mol Cell Neurosci. 2008;38:89–97.
83. Jean-Gilles L, Braitch M, Latif ML, Aram J, Fahey AJ, Edwards LJ, Robins RA, Tanasescu R, Tighe PJ, Gran B, et al. Effects of pro-inflammatory cytokines on cannabinoid CB1 and CB2 receptors in immune cells. Acta Physiol (Oxf). 2015;214:63–74.
84. Bush JO, Soriano P. Ephrin-B1 regulates axon guidance by reverse signaling through a PDZ-dependent mechanism. Genes Dev. 2009;23:1586–99.
85. Morales LBJ, Loo KK, Liu H-b, Peterson C, Tiwari-Woodruff S, Voskuhl RR. Treatment with an Estrogen Receptor α Ligand Is Neuroprotective in Experimental Autoimmune Encephalomyelitis. The Journal of Neuroscience. 2006;26:6823–33.
86. Wisdom AJ, Cao Y, Itoh N, Spence RD, Voskuhl RR. Estrogen receptor-β ligand treatment after disease onset is neuroprotective in the multiple sclerosis model. J Neurosci Res. 2013;91:901–8.
87. Guirland C, Zheng JQ. Membrane lipid rafts and their role in axon guidance. Adv Exp Med Biol. 2007;621:144–55.
88. Cui F, Zhou L, Wang Z, Lang C, Park J, Tan Z, Yu Y, Sun C, Gao Y, Kong J. Altered Functional Connectivity of Striatal Subregions in Patients with Multiple Sclerosis. Front Neurol. 2017;8:129.
89. Calabrese M, Filippi M, Gallo P. Cortical lesions in multiple sclerosis. Nat Rev Neurol. 2010;6:438–44.
90. Spence RD, Wisdom AJ, Cao Y, Hill HM, Mongerson CR, Stapornkul B, Itoh N, Sofroniew MV, Voskuhl RR. Estrogen mediates neuroprotection and anti-inflammatory effects during EAE through ERalpha signaling on astrocytes but not through ERbeta signaling on astrocytes or neurons. J Neurosci. 2013;33:10924–33.
91. Ponath G, Park C, Pitt D. The Role of Astrocytes in Multiple Sclerosis. Front Immunol. 2018;9:217.
92. Ellrichmann G, Bolz J, Peschke M, Duscha A, Hellwig K, Lee DH, Linker RA, Gold R, Haghikia A. Peripheral CD19(+) B-cell counts and infusion intervals as a surrogate for long-term B-cell depleting therapy in multiple sclerosis and neuromyelitis optica/neuromyelitis optica spectrum disorders. J Neurol. 2019;266:57–67.

93. Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, et al. Global Resting-State Functional Magnetic Resonance Imaging Analysis Identifies Frontal Cortex, Striatal, and Cerebellar Dysconnectivity in Obsessive-Compulsive Disorder. Biol Psychiat. 2014;75:595–605.
94. Liston C. Astrocyte dysfunction and compulsive behavior. Sci Transl Med. 2018;10:eaav3882.
95. Yu X, Taylor AMW, Nagai J, Golshani P, Evans CJ, Coppola G, Khakh BS. Reducing Astrocyte Calcium Signaling In Vivo Alters Striatal Microcircuits and Causes Repetitive Behavior. Neuron. 2018;99:1170–87.e1179.
96. Hammond SM. An overview of microRNAs. Adv Drug Deliv Rev. 2015;87:3–14.
97. Tsan YC, Morell MH, O'Shea KS. miR-410 controls adult SVZ neurogenesis by targeting neurogenic genes. Stem Cell Res. 2016;17:238–47.
98. Su R, Sun P, Zhang D, Xiao W, Feng C, Zhong L. Neuroprotective effect of miR-410-3p against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway via targeting C-X-C motif chemokine receptor 5. Genes Genomics. 2019;41:1223–31.
99. Liu Q, He H, Zeng T, Huang Z, Fan T, Wu Q. Neural-specific expression of miR-344-3p during mouse embryonic development. J Mol Histol. 2014;45:363–72.
100. Yu B, Zhou S, Wang Y, Qian T, Ding G, Ding F, Gu X. miR-221 and miR-222 promote Schwann cell proliferation and migration by targeting LASS2 after sciatic nerve injury. J Cell Sci. 2012;125:2675–83.
101. Zhao D, Deng SC, Ma Y, Hao YH, Jia ZH. miR-221 alleviates the inflammatory response and cell apoptosis of neuronal cell through targeting TNFAIP2 in spinal cord ischemia-reperfusion. Neuroreport. 2018;29:655–60.

Figures

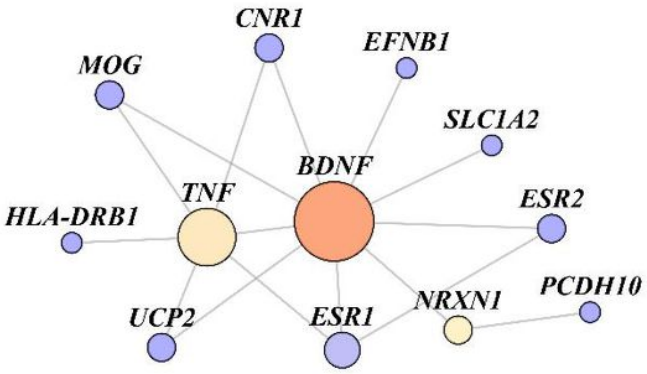

Figure 1

This genetic network represents interactions between shared genes in MS and OCD. This network consists of 12 nodes and 16 edges. The larger nodes indicate a higher degree and more connections, while darker orange color means greater betweenness centrality.

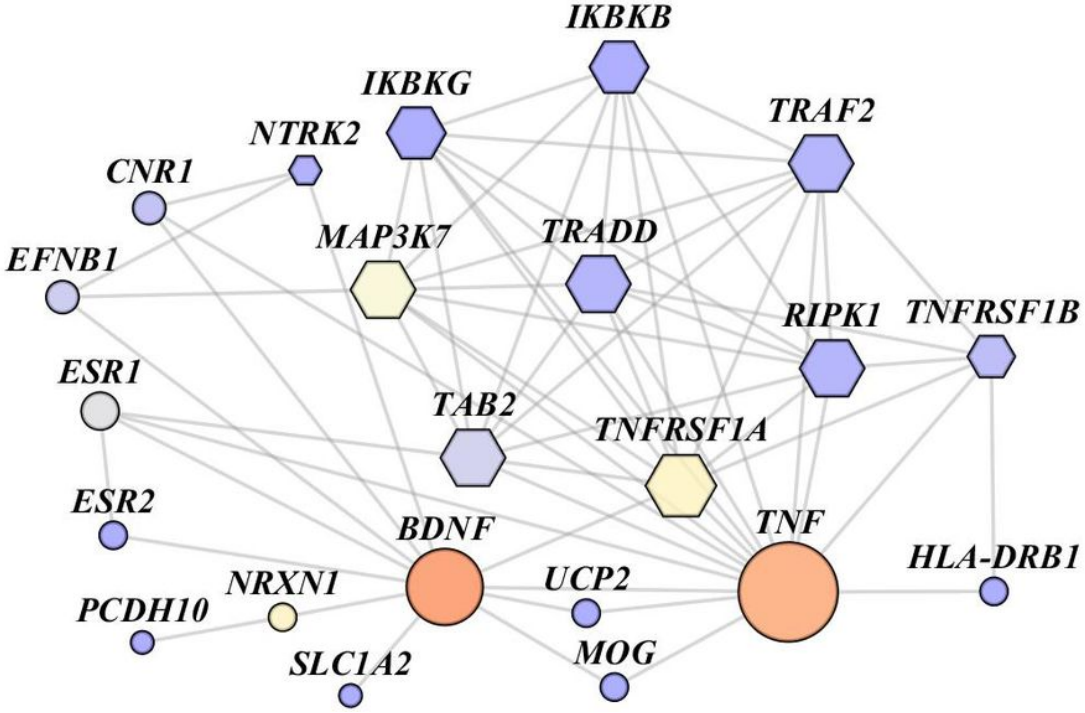

Figure 2

This genetic network represents interactions between MS- OCD shared genes and novel genes that are added. The current network comprised 22 nodes and 65 edges. Circular nodes indicate common genes between MS and OCD based on the literature review, while hexagonal nodes represent novel genes that are added based on the interaction data. The larger nodes indicate a higher degree and more connections, while darker orange color means greater betweenness centrality.

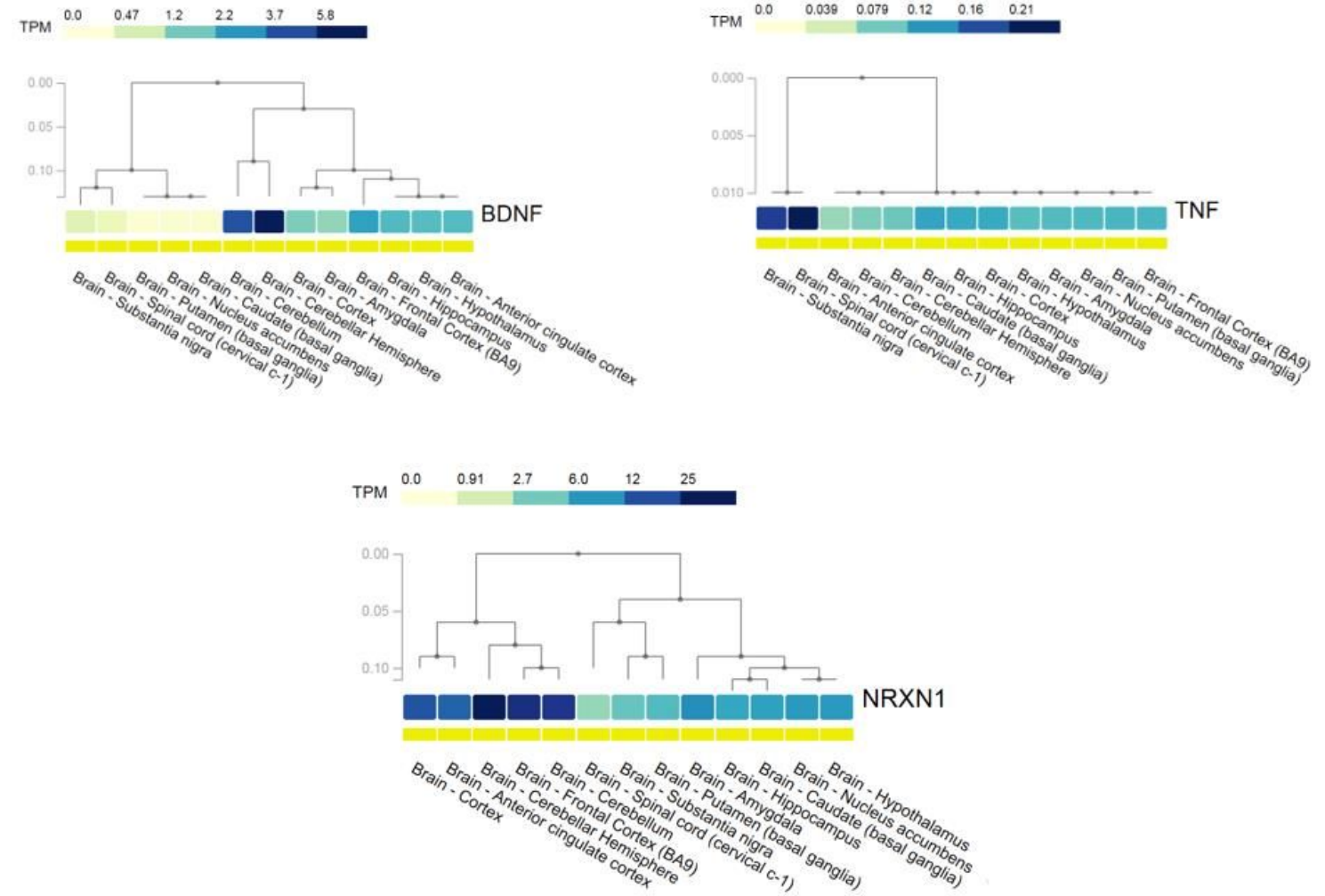

Figure 3

Genotype-Tissue expression analysis results for BDNF, TNF, and NRXN1. Expression value for each gene displayed in TPM (Transcripts Per Million). Darker color indicates more expression in that area.

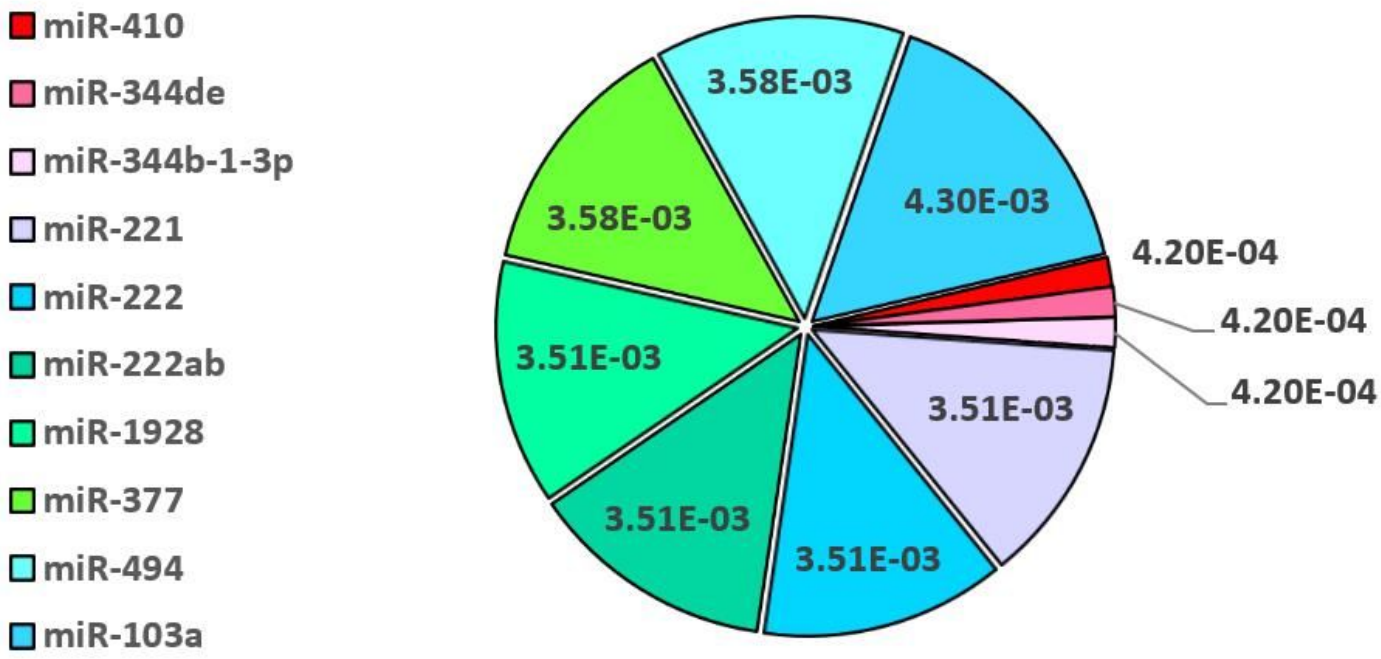

Figure 4

Predicted microRNAs families in MS- OCD shared genes. Each miRNA family adjusted with p-value (Benjamini and Hochberg).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfiles.docx