Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Personalized Medicine

PON1 polymorphisms can predict generalized anxiety and depressed mood in patients with multiple chemical sensitivity

Alessio Mosca[‡,1], Antonio Del Casale*[,‡,2,3], Marina Borro[1,4], Giovanna Gentile[1,4], Leda Marina Pomes[1,4], Alessio Padovano[1,3], Federica Fiaschè[1,3], Vito Pinzone[1,3], Chiara Rapinesi[1], Teodolinda Zoppi[1,3], Roberto Brugnoli[1,3], Gabriele Sani[5], Georgios Demetrios Kotzalidis[1], Paolo Girardi[1,3], Stefano Ferracuti[6], Maurizio Simmaco[1,4] & Maurizio Pompili[1,3]

[1]Department of Neuroscience, Mental Health, & Sensory Organs (NESMOS), Faculty of Medicine & Psychology, Sapienza University, Rome, Italy

[2]Department of Clinical & Dynamic Psychology, Faculty of Medicine & Psychology, Sapienza University, Rome, Italy

[3]Unit of Psychiatry, 'Sant'Andrea' University Hospital, Rome, Italy

[4]Unit of Laboratory & Advanced Molecular Diagnostics, 'Sant'Andrea' University Hospital, Rome, Italy

[5]Institute of Psychiatry & Psychology, Department of Geriatrics, Neuroscience & Orthopedics, Fondazione Policlinico Universitario IRCCS "A. Gemelli", Università Cattolica del Sacro Cuore, Rome, Italy

[6]Department of Human Neuroscience, Sapienza University; Unit of Risk Management, 'Sant'Andrea' University Hospital, Rome, Italy

*Author for correspondence: Tel.: +390633777774; antonio.delcasale@uniroma1.it

[‡]Authors contributed equally

Background: Multiple chemical sensitivity (MCS) is a chronic condition with somatic, cognitive and affective symptoms that follow contact with chemical agents at usually non toxic concentrations. We aimed to assess the role of genetic polymorphisms involved in oxidative stress on anxiety and depression in MCS. **Materials & methods:** Our study investigated the *CAT* rs1001179, *MPO* rs2333227, *PON1* rs662 and *PON1* rs705379 polymorphisms in MCS. **Results:** The AG genotype of the *PON1* rs662 and the TT and CT genotypes of the *PON1* rs705379 were involved in anxiety and depression. **Discussion:** These results are in line with existing evidence of *PON1* involvement in MCS and suggest a further role of this gene in the exhibition of anxiety and depression in this disease.

First draft submitted: 18 November 2019; Accepted for publication: 28 January 2021; Published online: TBC

Keywords: anxiety • depression • genomics • hyperosmia • multiple chemical sensitivity • oxidative stress • paraoxonase

Multiple chemical sensitivity (MCS) is a chronic syndrome characterized by different somatic, cognitive and affective symptoms occurring after exposure to chemical agents at concentrations that are not usually associated with toxic reactions in the general population [1,2]. MCS etiology and pathogenesis are not clarified, with no laboratory abnormality being consistently associated with it. It mainly affects women between 40 and 50 years [3,4], without differences in ethnicity, education and economic status [5]; its prevalence is not well defined since it is not a universally accepted diagnosis [6–8]. Common symptoms include weakness, lethargy, sore throat, hyperosmia, dyspnea, dizziness, headache, confusion and difficulty concentrating [1].

The Cullen Criteria were extended by Lacour [9], according to whom MCS is a chronic condition that causes significant lifestyle or functional impairments for at least 6 months (a); CNS recurrently symptoms are related to self-reported odor hypersensitivity (b); at least one CNS symptom is associated to at least one symptom of another organ/system (c); symptoms are related to the exposure to low levels (d) of multiple unrelated chemicals (e) and improve or are resolved when exposure is avoided (f).

Table 1. Genes possibly involved in the manifestation of psychological symptoms in multiple chemical sensitivity.

Gene	Name	Function	Mechanisms involved	Ref.
PON1	Paraoxonase-1	Antioxidant activity of HDL and protection of LDL from oxidative modification Biodegradation of organophosphates and oxidized phospholipids. Hydrolysis of pesticides and nerve gases	Increase of lipid peroxidation, oxidative stress and hydroperoxide lipids. Differences in the regulation of enzymatic activity, expression and polymorphisms have been reported in most psychiatric disorders	[16–20]
CAT	Catalase	Converts hydrogen peroxide into water and oxygen. Clearance of reactive oxygen species (ROS)	Increased ROS and oxidative stress. Differences in the regulation of enzymatic activity have been reported in patients with GAD and depression	[21–23]
MPO	Myeloperoxidase	Peroxidase enzyme expressed in neutrophil granulocytes produces hypohalous acids to carry out their antimicrobial activity. Involved in inflammation regulation and oxidative stress.	The increase in activity is associated with a rise of oxidative stress, inflammation and mood disorders	[24–29]
SOD2	Manganese-dependent superoxide dismutase	Clear mitochondrial ROS	Increased ROS and oxidative stress. Differences in the regulation of enzymatic activity have been reported in patients with anxiety and depression	[21–23]
GSTM1, GSTT1, GSTP1	Glutathione S-transferase	A family of isozymes involved in the detoxification of xenobiotics by catalyzing the nucleophilic attack by GSH	Increased oxidative stress and inflammatory processes. Differences in the regulation of enzymatic activity and polymorphisms have been reported in mood disorders	[30]

Anxiety and depression have been attributed to the social and work hardships related to the disease, and frustration of being affected by medically unexplained conditions [10]. Besides this, some authors argued that MCS diagnosis is a misdiagnosis of an unrecognized psychiatric disorder [11,12] or a 'psychosomatic' illness [13,14]. These theses are supported by a remarkable overlap between the diagnostic criteria of somatoform disorders and MCS symptoms [15]. Furthermore, anxiety and depression may also constitute a principal component between MCS symptoms, even relatively to genomic correlates (Table 1), although no somatic origins of these symptoms have been demonstrated.

Individual responses to chemicals are so varied that over time a very wide range of nosological terms and entities have been used to describe sensitivity to environmental factors and chemical intolerances, including 'chemical intolerance', 'environmental sensitivities' [10], 'ecological illness', 'environmental illness' and 'idiopathic environmental intolerances' (IEI), a term coined by the WHO in 1996, which also refers to hypersensitivity to electromagnetic fields, radio signals, loud noise and intolerance to odors [14]. Today, considering that symptoms do not always occur in response to a chemical, MCS is viewed as an aspect of the IEI, and in the scientific literature, the terms MCS and IEI are mostly interchangeable [13,14].

Patients with MCS have an increased likelihood of having a history of a psychiatric disorder [31] and a very high rate of psychiatric comorbidity. MCS patients significantly showed higher rates of depression and anxiety than the general population, with more frequent lifetime diagnoses of major depressive disorder and/or generalized anxiety disorder [12,32,33]. Other reported frequent psychiatric comorbidities were histrionic personality disorder [15,34], panic attacks [32], as well as trauma and childhood abuse [13,35].

MCS has different biological correlates. Alterations of the nitric oxide/peroxynitrite ($NO/ONOO^-$) cycle were related to the formation of peroxynitrite, and subsequent neuronal sensitization and neuroinflammation involved in MCS [36]. Oxidative stress has been implicated in the etiopathogenesis of both MCS and other psychiatric disorders [16,17,37], in which the SOD2 [21–23] and GSTM1 [30] genes were involved. Furthermore, oxidative stress has been related to mitochondrial dysfunction [38,39] and changes in neuroplasticity [40,41].

Genes with a role in oxidative stress, including paraoxonase1 (*PON1*) [42,43], catalase (*CAT*) [21–23,40,4144,45] and myeloperoxidase (*MPO*) [46,47] were consistently involved in the pathophysiology of anxiety and depression. Changes in the activity of paraoxonase have been considered possible pathophysiological correlates of MCS [48].

The *PON1* gene is located on the chromosome 7 long arm (7q21.3-22.1) [49] and encodes paraoxonase, a calcium-dependent glycoprotein synthesized in the liver and secreted in the blood. It bounds the HDL, and is responsible for most of their antioxidant activity, protecting the LDL from oxidative modification, and counteracting the formation of atherosclerotic plaques. *PON1* plays a key role in the biodegradation of various organophosphates (OPs) and oxidized phospholipids and participates in hydrolysis of pesticides and nerve gases [50]. *PON1* A-575G polymorphism has been related to the magnitude of paraoxonase activity [51], while the C-108T polymorphism to variation in the amount of its activity [52]. Different antidepressants (i.e. mirtazapine and escitalopram), displayed a potential inhibitory effect on PON1 activity *in vitro* [53], as well as on 6-phosphogluconate dehydrogenase and

glucose-6-phosphate dehydrogenase enzymes [54]. Also, other drugs, including some sulfonamides, antihypertensives, antineoplastics, some quinones, benzenesulfonamide derivatives and usnic and carnosic acids showed potential inhibitory effects on PON1 [55–60].

PON1 A-575G heterozygotes are more likely to present neurological symptoms, which were more common in Gulf War Syndrome veterans [61–63]; a lower mean activity of the *PON1* enzyme has been reported in post-traumatic stress and attention deficit and hyperactivity disorders [64]. Some biological correlates of post-traumatic stress could be shared with MCS, fibromyalgia and chronic fatigue syndrome [65,66].

Patients with bipolar disorder showed diminished *PON1* activity correlated with A-575G polymorphism, which suggested that these polymorphisms may play a role in the pathophysiology of bipolar disorder, type I, due to the decreased ability to cope with stress oxidative [18]. Furthermore, A-575G polymorphism was significantly associated with depressive symptoms in women [38]. *PON1* polymorphisms, activity and expression have been correlated with the diagnosis of schizophrenia [67–69], first-episode psychosis [19] and mood disorders [20,42,70].

MPO (myeloperoxidase) is a heme enzyme expressed in brain cells [71] and immune cells; it is involved in inflammation regulation and oxidative stress [72]. Its activation is correlated to hypochlorous acid and other toxic oxidants production, with subsequent antimicrobial function [24,25,73]. Low *MPO* levels correlated with reduced risk of inflammatory states [26] and depression [74–77]. *MPO* deficiency also attenuates cytokine production [27]. *MPO* has been associated with oxidative stress and inflammation and involved in recurrent MDD and related cognitive dysfunction [28,29], and in bipolar I disorder [78].

CAT (Catalase) is one of the primary antioxidant enzymes against superoxide. It catalyzes the decomposition of hydrogen peroxide to oxygen and water and plays an important role in reactive oxygen clearance [79]. Different studies have described CAT polymorphisms and activities with various pathophysiological states and diseases [80], including major depressive [44] and bipolar [81] disorders, and schizophrenia [82].

Our main hypothesis was that *PON1*, *CAT* and *MPO* polymorphisms might have a role in the pathophysiology of anxiety and depressive symptoms in patients with MCS. The main objective of this study was to identify gene polymorphisms that constitute predictors of anxiety and depressive symptoms in patients with MCS.

Materials & methods

This was a single-center observational study conducted at the Centre of Personalised Medicine, "Sant'Andrea" University Hospital, Rome, Italy, during the years 2014–2015. All admitted patients required a medical consult and a pharmacogenomics assessment for previous and proven drug treatment resistance. All those who manifested their interest in participating were considered possible candidates.

Inclusion criteria were a manifestation of MCS syndrome according to the Cullen [1] and Nethercott *et al.* [83] criteria for MCS extended by Lacour (see description above) [9]; age $\geq$18 years; and ability to provide valid informed consent. Exclusion criteria included pregnancy, recent brain injury, severe medical illness, DSM-5 [84] diagnoses of schizophrenia-spectrum disorder, substance use disorder, other acute psychiatric disorders, and inability to provide informed consent. Based on our inclusion and exclusion criteria, the final sample included 129 of 173 assessed patients.

During the medical consult, the physician investigated the presence of MCS symptoms through the compilation of a checklist of symptoms as described in another study of our group [85]. Participants underwent venous blood sampling for functional biochemical analyses. All patients were fully informed about the observational nature of the study, and each provided written informed consent.

Genetic analyses

Genomic DNA was isolated from peripheral blood samples using the X-tractor Gene system (Corbett Life Science, Australia), according to the manufacturer's protocol. We studied the following polymorphisms: *CAT* C-262T (rs1001179), *MPO* G-463A (rs2333227), *PON1* A-575G (rs662) and *PON* C-108T (rs705379). We performed genotyping with the MassARRAY system, in other words, a MALDI-TOF mass spectrometry platform by the iPLEX chemistry (Agena Bioscience, CA, USA). We used the Agena Bioscience Assay Design 4.0 software to design the locus-specific amplification and extension SNP primers (Table 2), considering a success rate of 97.9–100% for the genotype call of each SNP.

Table 2. Amplification and extension primers used in the multiplex genotyping assay.

Gene name	Polymorphism		Oligonucleotides (F: forward; R: reverse; E: extension)
CAT C-262T	rs1001179	F	ACGTTGGATGAGCAATTGGAGAGCCTCGC
		R	ACGTTGGATGAGGATGCTGATAACCGGGAG
		E	AGCCCCGCCCTGGGTTCGGCTAT
MPO G-463A	rs2333227	F	ACGTTGGATGCTCTAGCCACATCATCAAT
		R	ACGTTGGATGGGCTGGTAGTGCTAAATTC
		E	CTTTGGGAGGCTGAGGC
PON1 A575G	rs662	F	ACGTTGGATGTAGACAACATACGACCACGC
		R	ACGTTGGATGGATCACTATTTTCTTGACCC
		E	TTTCTTGACCCCTACTTAC
PON C-108T	rs705379	F	ACGTTGGATGCTTCTGTGCACCTGGTCGG
		R	ACGTTGGATGTGCTGGGGCAGCGCCGATT
		E	CGCCGATTGGCCCGCCCC

Statistical analyses

We used the IBM SPSS® Statistics 24.0 (Armonk, NY, USA: IBM Corp. 1989, 2016) for all analyses, except for the Hardy–Weinberg equilibrium deviation test, for which we used an online calculator based on the methods of Rodriguez *et al.* [86,87].

We performed descriptive statistics with a one-way analysis of variance for the continuous variables and the *Chi*-square (χ^2) test for categorical variables. We performed a binary logistic regression with the 'Enter' method, using the presence/absence of both generalized anxiety and depressed mood as the dependent variable, and the polymorphisms of genes involved in cellular oxidative stress (*PON1* A575G, *PON1* C-108T, *CAT* C-262T and *MPO* G-463A) as the independent, categorical variables. We set the cut off for statistical significance at (two-tailed) $p < .05$.

Results

Study participants were 129 MCS patients (112 women and 17 men) with a mean age of 51.58 years (SD = 11.34). The group of women did not differ significantly from the group of men in age ($F = 0.603$; $p = 0.439$). The sample showed significant prevalence of women ($\chi^2 = 69.961$; $p < .001$). Patients most frequently showed hyperosmia (96.8%), asthenia (82.4%) and dyspnea (81.6%). We reported the main clinical characteristics of this sample in another study on MCS [85]. Considering the whole sample, 70 patients (54.26%) had comorbid anxiety and depression (63 women, 7 men; mean age = 51.75 years, SD = 10.07); 7 patients showed generalized anxiety but not depressed mood; one patient had depressed mood but not anxiety; the other 51 patients did not show generalized anxiety nor depressed mood. We summarized the sociodemographic and clinical characteristics of the study sample in Table 3.

The analyzed SNPs were in Hardy–Weinberg equilibrium. Logistic regression showed that our model was significant for a good predictability of comorbid anxiety and depressive symptoms (Omnibus Tests of Model Coefficients $\chi^2 = 22.263$; $p = 0.004$) and explained over 25% of the variance (Nagelkerke $R^2 = 0.253$). Overall, this logistic regression model proved to be useful, with good positive predictive value (66.4%). *PON1* A575G and *PON1* C-108T polymorphisms were significant predictors of comorbid anxiety and depressed mood. The odds ratio (OR) for *PON1* A575G AG versus GG was 10.403 (unstandardized coefficient B = 2.342; $p = 0.011$; 95% CI: 1.71–63.43), while that of AG versus AA was 4.04 (B = 1.397; $p = 0.008$; 95% CI: 1.44–11.36). The overall effect of *PON1* A-575G polymorphism on anxiety and depressive symptoms was significant (Wald = 9.646; df: 2; $p = 0.008$). The OR for *PON1* C-108T CT versus CC was 5.559 (B = 1.715; $p = 0.006$; 95% CI: 1.63–19), and for TT versus CC was 4.814 (B = 1.571; $p = 0.019$; 95% CI: 1.3–17.86). The overall effect of *PON1* C-108T polymorphism on anxiety and depressive symptoms was significant (Wald = 7.925; df: 2; $p = 0.019$). The logistic regression showed that *CAT* C-262T and *MPO* G-463A polymorphisms did not predict comorbid anxiety and depressed mood (Table 4).

Discussion

Our results showed that two polymorphisms of the PON1 gene, which is involved in cellular detoxification, predict comorbid anxiety and depressed mood in patients with MCS. Our sample was mainly composed of women, in line with many reports of the high prevalence of MCS in middle-aged women in the USA, Europe and Japan [88–90].

Table 3. Demographic and clinical characteristics of the study sample.

Sample	Men	Women	Test	p-value
Number	17	112	$\chi^2 = 69.961$	<0.001
Age (standard deviation)	49.59 (10.67)	51.89 (11.46)	*1-way ANOVA F = 0.603*	0.439
Symptom	**Absent (%)**	**Present (%)**	χ^2	***p-value***
Hyperosmia	3.2	96.8	109.512	<0.001
Asthenia	17.6	82.4	52.488	<0.001
Dyspoea	18.4	81.6	49.928	<0.001
Cough	26.4	73.6	27.848	<0.001
Cephalalgia (headache)	28	72	24.2	<0.001
Tachypnea	28.8	71.2	22.472	<0.001
Attention deficit	30.4	69.6	19.208	<0.001
Sense of confusion	33.6	66.4	13.448	<0.001
Nausea	35.2	64.8	10.952	0.001
Sense of obnubilation	36.8	63.2	8.712	0.003
Sense of suffocation/choking	41.6	58.4	3.528	0.06
Dyspepsia	41.6	58.4	3.528	0.06
Sleep disturbance	42.4	57.6	2.888	0.089
Paresthesia	44	56	1.8	0.18
Generalized anxiety	44.8	55.2	1.352	0.245
Decision-making deficit	46.4	53.6	0.648	0.421
Arthromyalgia	47.2	52.8	0.392	0.531
Gastric pyrosis	48.8	51.2	0.072	0.788
Pruritus	49.6	50.4	0.008	0.929
Depressed mood	49.6	50.4	0.008	0.929
Dizziness	53.6	46.4	0.648	0.421
Rash	54.4	45.6	0.968	0.325
Fibromyalgia	55.2	44.8	1.352	0.245
Working memory deficit	55.2	44.8	1.352	0.245
Erythema	55.2	44.8	1.352	0.245
Diarrhea	57.6	42.4	2.888	0.089
Meteorism	57.6	42.4	2.888	0.089
Motor incoordination	58.4	41.6	3.528	0.06
Palpitations	58.4	41.6	3.528	0.06
Chest tightness	64	36	9.8	0.002
Vomiting	64	36	9.8	0.002
Hyporexia	66.4	33.6	13.448	<0.001
Trembling	70.4	29.6	20.808	<0.001
Pressure peaks	70.4	29.6	20.808	<0.001
Gastro-esophageal reflux	72	28	24.2	<0.001
Cystitis	73.6	26.4	27.848	<0.001
Recurrent fever	76	24	33.8	<0.001

The AG genotype of the A-575G polymorphism of the *PON1* gene has about tenfold probability of manifestation of anxiety and depression compared with the GG genotype. The TT genotype of the C-108T polymorphism of the *PON1* gene also showed higher (4.5) probability of depressed mood and anxiety compared with the CC genotype, and the CT versus CC also showed a risk higher than 5.5-fold.

This is in-line with the existing evidence of involvement of *PON1* in the manifestation of MCS [48], although there are some inconsistent findings in this regard [91–93]. However, our results suggest an additional and specific role for both the *PON1* A-575G and C-108T polymorphisms in the exhibition of anxiety comorbid with depressed mood in MCS.

Table 4. Logistic regression model for predictors of comorbid generalized anxiety and depressed mood.

Variables in the equation		B	SE	Wald	df	p-value	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1 Contrast 1	*CAT* C262T (CC)			2.736	2.000	0.255			
	CAT C262T (CT)	0.304	0.464	0.429	1.000	0.512	1.355	0.546	3.366
	CAT C262T (TT)	−1.926	1.345	2.051	1.000	0.152	0.146	0.010	2.034
	PON1 A575G (AA)			9.646	2.000	***0.008***			
	PON1 A575G (AG)	1.397	0.527	7.027	1.000	***0.008***	4.043	1.439	11.356
	PON1 A575G (GG)	−0.945	0.861	1.204	1.000	0.272	0.389	0.072	2.102
	PON1 C108T (CC)			7.925	2.000	***0.019***			
	PON1 C108T (CT)	1.715	0.627	7.487	1.000	***0.006***	5.559	1.627	18.996
	PON1 C108T (TT)	1.571	0.669	5.516	1.000	***0.019***	4.814	1.297	17.864
	MPO G463A (AA)			2.876	2.000	0.237			
	MPO G463A (AG)	−0.381	1.340	0.081	1.000	0.776	0.683	0.049	9.448
	MPO G463A (GG)	0.412	1.336	0.095	1.000	0.758	1.509	0.110	20.703
	Constant	−1.530	1.462	1.096	1.000	0.295	0.217		
Step 1 Contrast 2	*CAT* C262T (TT)			2.736	2.000	0.255			
	CAT C262T (CT)	2.230	1.370	2.647	1.000	0.104	9.298	0.634	136.423
	PON1 A575G (GG)			9.646	2.000	***0.008***			
	PON1 A575G (AG)	2.342	0.922	6.447	1.000	***0.011***	10.403	1.706	63.427
	PON1 C108T (TT)			7.925	2.000	***0.019***			
	PON1 C108T (CT)	0.144	0.519	0.077	1.000	0.781	1.155	0.418	3.193
	MPO G463A (GG)			2.876	2.000	0.237			
	MPO G463A (AG)	−0.793	0.468	2.875	1.000	0.090	0.453	0.181	1.132
	Constant	−2.418	1.597	2.294	1.000	0.130	0.089		

	Omnibus tests of model coefficients			Model summary			Hosmer and Lemeshow Test		
	Chi-square	df	p-value	- 2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square	Chi-square	df	p-value
Step 1	22.263	8	***0.004***	123.358	0.188	0.253	1.193	8	0.997

Classification

Observed			Predicted, selected cases		
			Comorbid AD		Percentage correct
			No	Yes	
Step 1	Comorbid AD	No	25	20	55.6
		Yes	16	46	74.2
	Overall percentage				66.4

Dependent variable: Comorbid generalized anxiety and depressed mood. Independent variables entered on Step 1: *CAT* C262T, *MPO* G463A, *PON1* A575G and *PON1* C108T polymorphisms. Step 1 contrast 1: Contrast reference categories are: *CAT* C262T (CT vs CC; TT vs CC); *PON1* A575G (AG vs AA; GG vs AA); *PON1* C108T (CT vs CC; TT vs CC) and *MPO* G463A (AG vs AA; GG vs AA). Step 1 Contrast 2: Contrast reference categories are: *CAT* C262T (CT vs TT); *PON1* A575G (AG vs GG); *PON1* C108T (CT vs TT) and *MPO* G463A (AG vs GG). Bold italic font denotes p-values significant for less than 0.05.
AD: Anxiety and depressed mood; B: Unstandardized coefficient; df: Degree of freedom; Exp(B)**:** Odds ratio; SE.**:** Standard error.

In particular, the condition of heterozygosity of the A-575G polymorphism of *PON1* (rs622) and the presence of the T allele in the genotype of the C-108T polymorphism (rs705379) are more frequently correlated with the manifestation of anxiety and depression in subjects with MCS. Why the heterozygous condition of the rs622 can be more at risk for anxiety/depression in MCS should be the subject of further studies. A possible hypothesis is that phenomena due to linkage disequilibrium may be involved. Another aspect concerns the protective role of the C allele in the rs705379 genotype on the manifestation of anxiety and depression in MCS, which is also worthy of further scientific studies.

A deficit in detoxifying OPs has been hypothesized in the etiopathogenesis of MCS; this has been confirmed by data showing an association between *PON1* polymorphisms, MCS [48], and outcome of OP poisoning [94].

Low *PON1* activity in patients with anxiety correlated with high levels of lipid peroxidation, oxidative stress and hydroperoxide lipids, and has been involved in the etiopathogenesis of generalized anxiety [43]. Cholinergic hyperactivation has been implicated in the pathophysiology of anxiety and depression, and response to antidepressant treatment [95]. OPs act as cholinesterase inhibitors and subacute intoxication with OP insecticides induce anxiogenic effects [96]. *PON1* protects from oxidative stress by detoxifying OPs that are potential cholinesterase inhibitors in the peripheral and CNS [97,98]. When the enzyme is inhibited, it may not hydrolyze acetylcholine, leading to the accumulation of the neurotransmitter, which would, in turn, increase macrophage release of proinflammatory cytokines involved in anxious mechanisms [99]. The toxic effects involve parasympathetic, sympathetic, motor and CNSs [100]. These data are in-line with inverse correlations between acetylcholinesterase and anxiety, as well as with *PON1* activity, whereby subjects with low *PON1* activity may be at greater risk of severe state anxiety [43]. Furthermore, polymorphisms of *PON1* and *ACHE* genes, which are adjacent in the locus 7q21-22 and influence reciprocal expression in an allelic dependent manner [97] may play a role in susceptibility to chronic organophosphorus intoxication [100].

Recent studies showed the role of neuroinflammation in the pathogenesis of mood and anxiety disorders [101–105]. Neuroinflammation and oxidative stress have also been correlated with anxiety disorders, and sleep deprivation and anxiety [106–108]. Oxidative stress and diminished capacity in detoxifying organophosphates have been involved in the pathophysiology of MCS [36]. This evidence is in line with the involvement of oxidative stress in the pathophysiology of mental disorders, based on the vulnerability of the CNS to free radicals. These could damage the structure of the neuronal cell, reacting with the membrane lipids, proteins and nucleic acids [106,109–111].

Furthermore, limbic hyperactivation has been correlated to sensitization caused by neurogenic inflammation [112]. Another important aspect regards the odor processing in MCS patients. Some neuroimaging studies showed that exposure to odorants in MCS correlated to dysfunctions in the hippocampus, amygdala and thalamus [113]. MCS patients also showed hyperactivation of the anterior cingulate cortex and cuneus-precuneus related to exposure to odors, but without signs of neuronal sensitization [114].

The functionality of the frontal cortex in MCS subjects must be further investigated, as there is evidence of both increased and reduced metabolism during exposure to odors. MCS patients showed increased metabolism than controls in the prefrontal cortex during olfactory stimulation, and for about 20–30 s in the orbitofrontal cortex after stimulation, at the recognition threshold or usually perceived level [115]. These functional neural changes have been related to cognitive and memory processing adaptations during past exposure to unsafe chemicals [115]. Another study showed frontal cortex hypoactivation, with possible active recruitment of the left inferior temporal cortex during olfactory stimulation [116].

These data suggest that patients with MCS process odors differently from the healthy population, pointing to the need for further investigation on the relationships between anxiety-depressive symptoms, oxidative stress and odor processing in MCS.

Further investigations are needed with the aim of clarifying the factors related to the expression levels and activity of the paraoxonase enzyme, which is influenced not only by its related genetic polymorphisms but also by environmental factors and/or substances that can increase or decrease its expression and consequently its activity. In fact, it has been shown that cigarette smoking, a high-fat diet and several drugs, including antidepressants, antihypertensives, antiepileptics, cardiovascular, antineoplastics, some quinones, benzenesulfonamide derivatives, usnic and carnosic acids, and sulfonamides can decrease the activity of paraoxonase [52–60], which in turn can influence the levels of atherosclerosis and risk of the onset of cardiovascular, neurological and psychiatric diseases [20,51,56].

This evidence showed that the regulation of paraoxonase is very complex, and it is still necessary to shed light on how these factors interact with each other to define its activity levels. This point to the need of further studies aimed to research other mechanisms underlying the *PON1* activity and the pathophysiological correlates that can be associated with different organic and psychiatric conditions, including atherosclerosis, hypertension, other cardiovascular illnesses and anxiety, and depression.

Limitations

The results of this study must be considered with caution because of their preliminary nature and considering the following limitations. First, the sample size we obtained was not large enough to yield definite results, especially in the light of the fact that peculiarity of the population. Second, results are not corrected for multiple comparisons; however, this was related to the exploratory nature of the study. Third, the lack of use of assessment scales for anxiety and depression constitutes a significant limitation, for which the results of this study should be taken with

caution and need to be replicated. However, the compilation of a checklist by a physician allowed an adequate categorical assessment of symptoms. Furthermore, the lack of a control sample from the general population made our results not applicable to other than this population, the existence of which has still to gain consensus.

Future perspective

Due to the serious state of suffering of some affected subjects, understanding the etiopathogenesis of MCS and finding optimal therapy represents an invariable challenge for medicine. In the next few years, new studies that include neuroimaging data and correlations with psychological and psychopathological dimensions are necessary to understand the nature of this pathology. A growing body of evidence seems to demonstrate the close link between cellular detoxification, oxidative stress, psychiatric disorders and MCS; then new therapies could be developed to prevent brain damage from free radicals, such as the use of antioxidant agents, anti-inflammatory drugs, dietary recommendations and nutritional interventions [117,118]. Oxidation-reduction mechanisms could be a novel target for pharmacological intervention in MCS, also considering that pharmacogenomics will support the choice of targeted therapies in the field of precision medicine [119]. The recognition of specific polymorphisms that may be related to the efficacy of the pharmacological response may direct the clinician in the best choice of treatments that can be undertaken in this category of patients, also for the treatment of anxiety-depressive symptoms.

Conclusion

In this study, we showed *PON1* polymorphisms to predict anxiety and depressive symptoms in an MCS population. The *PON1* AG versus GG genotype of the A575G polymorphism increased the likelihood of reporting depressive or anxiety symptoms by more than ten-times, and *PON1* C-108T also appears to be significantly involved in the manifestation of comorbid generalized anxiety and depressed mood in MCS. These results apply to an MCS sample and have to be tested in the general and other populations.

Author contributions

A Mosca, A Del Casale, M Borro and GD Kotzalidis wrote the first draft of the manuscript and performed the statistical analyses. M Simmaco, M Borro, G Gentile and LM Pomes performed laboratory analyses, sample inclusion, and created the database. A Del Casale, A Mosca, A Padovano, F Fiaschè, V Pinzone, C Rapinesi, T Zoppi, R Brugnoli and G Sani did the literature search. GD Kotzalidis, P Girardi, S Ferracuti, M Simmaco and M Pompili supervised the study. Each author participated in manuscript writing and approved the final version.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

This work received no funding. No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Cullen MR. The worker with multiple chemical sensitivities: an overview. *Occup. Med.* 2(4), 655–661 (1987).

•• **This was a first important paper focused on multiple chemical sensitivity symptoms.**

2. Dantoft TM, Skovbjerg S, Andersson L *et al.* Inflammatory mediator profiling of n-butanol exposed upper airways in individuals with multiple chemical sensitivity. *PLoS ONE* 10(11), e0143534 (2015).

3. Dupas D, Dagorne MA. Multiple chemical sensitivity: a diagnosis not to be missed. *Rev. Mal. Respir.* 30(2), 99–104 (2013).

4. Eis D, Helm D, Mühlinghaus T *et al.* The German Multicentre Study on multiple chemical sensitivity (MCS). *Int. J. Hyg. Environ. Health.* 211(5-6), 658–681 (2008).

5. Caress SM, Steinemann AC. A review of a two-phase population study of multiple chemical sensitivities. *Environ. Health Perspect.* 111(12), 1490–1497 (2003).

6. Donnay AH. On the recognition of multiple chemical sensitivity in medical literature and government policy. *Int. J. Toxicol.* 18, 383–392 (1999).
7. Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am. J. Epidemiol.* 150(1), 1–12 (1999).
8. Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? *J. Psychosom. Res.* 51(4), 549–557 (2001).
9. Lacour M, Zunder T, Schmidtke K, Vaith P, Scheidt C. Multiple chemical sensitivity syndrome (MCS)–suggestions for an extension of the U.S. MCS-case definition. *Int. J. Hyg. Environ. Health.* 208(3), 141–151 (2005).

• **Provides an important extension of multiple chemical sensitivity criteria.**

10. Driesen L, Patton R, John M. The impact of multiple chemical sensitivity on people's social and occupational functioning; a systematic review of qualitative research studies. *J. Psychosom. Res.* 132, 109964 (2020).
11. Brodsky CM. 'Allergic to everything': a medical subculture. *Psychosomatics* 24(8), 731–2 734–736 740–742 (1983).
12. Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. A controlled study. *Ann. Intern. Med.* 119(2), 97–103 (1993).
13. Staudenmayer H. Clinical consequences of the EI/MCS "diagnosis": two paths. *Regul. Toxicol. Pharmacol.* 24(1 Pt 2), S96–S110 (1996).
14. Staudenmayer H. Idiopathic environmental intolerances (IEI): myth and reality. *Toxicol. Lett.* 120(1-3), 333–342 (2001).
15. Bornschein S, Hausteiner C, Zilker T, Bickel H, Förstl H. Psychiatric and somatic morbidity of patients with suspected multiple chemical sensitivity syndrome (MCS). *Nervenarzt.* 71(9), 737–744 (2000).
16. Herken H, Akyol O, Yilmaz HR *et al.* Nitric oxide, adenosine deaminase, xanthine oxidase and superoxide dismutase in patients with panic disorder: alterations by antidepressant treatment. *Hum. Psychopharmacol.* 21(1), 53–59 (2006).
17. Herken H, Gurel A, Selek S *et al.* Adenosine deaminase, nitric oxide, superoxide dismutase, and xanthine oxidase in patients with major depression: impact of antidepressant treatment. *Arch. Med. Res.* 38(2), 247–252 (2007).
18. Ezzaher A, Mouhamed DH, Mechri A *et al.* Association between bipolar I disorder and the L55M and Q192R polymorphisms of the paraoxonase 1 (PON1) gene. *J. Affect. Disord.* 139(1), 12–17 (2012).

•• **Shows correlations between PON1 and bipolar disorder symptoms.**

19. Brinholi FF, Noto C, Maes M *et al.* Lowered paraoxonase 1 (PON1) activity is associated with increased cytokine levels in drug naïve first episode psychosis. *Schizophr. Res.* 166(1-3), 225–230 (2015).
20. Bortolasci CC, Vargas HO, Souza-Nogueira A *et al.* Lowered plasma paraoxonase (PON)1 activity is a trait marker of major depression and PON1 Q192R gene polymorphism-smoking interactions differentially predict the odds of major depression and bipolar disorder. *J. Affect. Disord.* 159, 23–30 (2014).
21. Fındıklı E, Camkurt MA, İzci F *et al.* The diagnostic value of malondialdehyde, superoxide dismutase and catalase activity in drug naïve, first episode, non-smoker generalized anxiety disorder patients. *Clin. Psychopharmacol. Neurosci.* 16(1), 88–94 (2018).
22. Szuster-Ciesielska A, Słotwińska M, Stachura A *et al.* Accelerated apoptosis of blood leukocytes and oxidative stress in blood of patients with major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32(3), 686–694 (2008).
23. Wigner P, Czarny P, Synowiec E *et al.* Variation of genes involved in oxidative and nitrosative stresses in depression. *Eur. Psychiatry* 48, 38–48 (2018).
24. Heinecke JW. Mechanisms of oxidative damage by myeloperoxidase in atherosclerosis and other inflammatory disorders. *J. Lab. Clin. Med.* 133(4), 321–325 (1999)
25. Podrez EA, Abu-Soud HM, Hazen SL. Myeloperoxidase-generated oxidants and atherosclerosis. *Free Radic. Biol. Med.* 28(12), 1717–1725 (2000)
26. Carr AC, Frei B. The nitric oxide congener nitrite inhibits myeloperoxidase/H2O2/ Cl- -mediated modification of low density lipoprotein. *J. Biol. Chem.* 276(3), 1822–1828 (2001).
27. Haegens A, Heeringa P, van Suylen RJ *et al.* Myeloperoxidase deficiency attenuates lipopolysaccharide-induced acute lung inflammation and subsequent cytokine and chemokine production. *J. Immunol.* 182(12), 7990–7996 (2009).
28. Talarowska M, Orzechowska A, Szemraj J, Su KP, Maes M, Gałecki P. Manganese superoxide dismutase gene expression and cognitive functions in recurrent depressive disorder. *Neuropsychobiology* 70(1), 23–28 (2014).
29. Talarowska M, Szemraj J, Gałecki P. Myeloperoxidase gene expression and cognitive functions in depression. *Adv. Med. Sci.* 60(1), 1–5 (2015).
30. Odebrecht Vargas Nunes S, Pizzo de Castro MR, Ehara Watanabe MA *et al.* Genetic polymorphisms in glutathione-S-transferases are associated with anxiety and mood disorders in nicotine dependence. *Psychiatr. Genet.* 24(3), 87–93 (2014).
31. Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. *Psychosom. Med.* 58(1), 38–49 (1996).

32. Bell IR, Peterson JM, Schwartz GE. Medical histories and psychological profiles of middle-aged women with and without self-reported illness from environmental chemicals. *J. Clin. Psychiatry* 56(4), 151–160 (1995).
33. Katerndahl DA, Bell IR, Palmer RF, Miller CS. Chemical intolerance in primary care settings: prevalence, comorbidity, and outcomes. *Ann. Fam. Med.* 10(4), 357–365 (2012).
34. Rosenberg SJ, Freedman MR, Schmaling KB, Rose C. Personality styles of patients asserting environmental illness. *J. Occup. Med.* 32(8), 678–681 (1990).
35. Bell IR, Baldwin CM, Fernandez M, Schwartz GE. Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. *Toxicol. Ind. Health.* 15(3-4), 295–304 (1999).
36. Pall ML. Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: central role of N-methyl-D-aspartate receptors in the sensitivity mechanism. *Environ. Health Perspect.* 111(12), 1461–1464 (2003).
37. Steckert AV, Valvassori SS, Moretti M, Dal-Pizzol F, Quevedo J. Role of oxidative stress in the pathophysiology of bipolar disorder. *Neurochem. Res.* 35(9), 1295–1301 (2010).
38. Gao X, Zheng CY, Qin GW, Tang XC, Zhang HY. S-52, a novel nootropic compound, protects against β-amyloid induced neuronal injury by attenuating mitochondrial dysfunction. *J. Neurosci. Res.* 90(10), 1981–1988 (2012).
39. Hayashi M, Miyata R, Tanuma N. Oxidative stress in developmental brain disorders. *Adv. Exp. Med. Biol.* 724, 278–290 (2012).
40. Brocardo PS, Boehme F, Patten A, Cox A, Gil-Mohapel J, Christie BR. Anxiety-and depression-like behaviors are accompanied by an increase in oxidative stress in a rat model of fetal alcohol spectrum disorders: protective effects of voluntary physical exercise. *Neuropharmacology* 62(4), 1607–1618 (2012).
41. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci. Biobehav. Rev.* 36(2), 764–785 (2012).
42. Herken DA, Day IN, Gaunt TR *et al.* The association of the paraoxonase (PON1) Q192R polymorphism with depression in older women: findings from the British Women's Heart and Health Study. *J. Epidemiol. Community Health* 61(1), 85–87 (2007).
43. Sklan EH, Lowenthal A, Korner M *et al.* Acetylcholinesterase/paraoxonase genotype and expression predict anxiety scores in health, risk factors, exercise training, and genetics study. *Proc. Natl Acad. Sci. USA* 101(15), 5512–5517 (2004).
44. Wigner P, Czarny P, Synowiec E *et al.* Variation of genes involved in oxidative and nitrosative stresses in depression. *Eur. Psychiatry* 48, 38–48 (2018).
45. Olsen RH, Johnson LA, Zuloaga DG, Limoli CL, Raber J. Enhanced hippocampus-dependent memory and reduced anxiety in mice over-expressing human catalase in mitochondria. *J. Neurochem.* 125(2), 303–313 (2013).
46. Gałecki P, Gałecka E, Maes M, Chamielec M, Orzechowska A, Bobińska K *et al.* The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder. *J. Affect. Disord.* 138(3), 360–366 (2012).
47. Liang S, Li X, Huang W, Gong H. Change of serum myeloperoxidase and lipoxin A4 level in coronary heart disease patients with anxiety and/or depression. *Zhong Nan Da Xue Xue Bao Yi Xue Ban J Central South University. Med. Sci.* 38(4), 370–375 (2013).
48. McKeown-Eyssen G, Baines C, Cole DE *et al.* Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *Int. J. Epidemiol.* 33(5), 971–978 (2004).
49. La Du BN, Aviram M, Billecke S *et al.* On the physiological role(s) of the paraoxonases. *Chem. Biol. Interact.* 119-120, 379–388 (1999).
50. Richter RJ, Jarvik GP, Furlong CE. Paraoxonase 1 (PON1) status and substrate hydrolysis. *Toxicol. Appl. Pharmacol.* 235(1), 1–9 (2009).
51. Fridman O, Gariglio L, Riviere S, Porcile R, Fuchs A, Potenzoni M. Paraoxonase 1 gene polymorphisms and enzyme activities in coronary artery disease and its relationship to serum lipids and glycemia. *Arch. Cardiol. Mex.* Oct - Dec; 86(4), 350–357 (2016).
52. Brophy VH, Jampsa RL, Clendenning JB, McKinstry LA, Jarvik GP, Furlong CE. Effects of 5′ regulatory-region polymorphisms on paraoxonase-gene (PON1) expression. *Am. J. Hum. Genet.* 68(6), 1428–1436 (2001).
53. Demir Y, Balcı N, Gürbüz M. Differential effects of selective serotonin reuptake inhibitors on paraoxonase-1 enzyme activity: an *in vitro* study. *Comp. Biochem. Physiol. C. Toxicol. Pharmacol.* 226, 108608 (2019).
54. Özaslan MS, Balcı N, Demir Y, Gürbüz M, Küfrevioğlu Öİ. Inhibition effects of some antidepressant drugs on pentose phosphate pathway enzymes. *Environ. Toxicol. Pharmacol.* 72, 103244 (2019).
55. Demir Y, Köksal Z. The inhibition effects of some sulfonamides on human serum paraoxonase-1 (hPON1). *Pharmacol. Rep.* 71(3), 545–549 (2019).
56. Demir Y. The behaviour of some antihypertension drugs on human serum paraoxonase-1: an important protector enzyme against atherosclerosis. *J. Pharm. Pharmacol.* 71(10), 1576–1583 (2019).
57. Demir Y, Türkeş C, Beydemir Ş. Molecular docking studies and inhibition properties of some antineoplastic agents against paraoxonase-I. *Anticancer Agents Med. Chem.* 20(7), 887–896 (2020).
58. Demir Y. Naphthoquinones, benzoquinones, and anthraquinones: molecular docking, ADME and inhibition studies on human serum paraoxonase-1 associated with cardiovascular diseases. *Drug Dev. Res.* 81(5), 628–636 (2020).

59. Işık M, Beydemir Ş, Demir Y, *et al.* Benzenesulfonamide derivatives containing imine and amine groups: inhibition on human paraoxonase and molecular docking studies. *Int. J. Biol. Macromol.* 146, 1111–1123 (2020).

60. Ceylan H, Demir Y, Beydemir Ş. Inhibitory effects of usnic and carnosic acid on some metabolic enzymes: an *In vitro* Study. *Protein Pept. Lett.* 26(5), 364–370 (2019).

61. Haley RW, Billecke S, La Du BN. Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. *Toxicol. Appl. Pharmacol.* 157(3), 227–233 (1999).

62. Hotopf M, Mackness MI, Nikolaou V *et al.* Paraoxonase in Persian Gulf War veterans. *J. Occup. Environ. Med.* 45(7), 668–675 (2003).

63. Thomas HV, Stimpson NJ, Weightman AL, Dunstan F, Lewis G. Systematic review of multi-symptom conditions in Gulf War veterans. *Psychol. Med.* 36(6), 735–747 (2003).

64. Ceylan MF, Sener S, Bayraktar AC, Kavutcu M. Changes in oxidative stress and cellular immunity serum markers in attention-deficit/hyperactivity disorder. *Psychiatry Clin. Neurosci.* 66(3), 220–226 (2012).

65. Eisen SA, Kang HK, Murphy FM *et al.* Gulf War Study Participating Investigators. Gulf War veterans' health: medical evaluation of a U.S. cohort. *Ann. Intern. Med.* 142(11), 881–890 (2005).

66. Ismail K, Lewis G. Multi-symptom illnesses unexplained illness and Gulf War Syndrome. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 361(1468), 543–551 (2006).

67. Güneş M, Camkurt MA, Bulut M *et al.* Evaluation of paraoxonase, arylesterase and malondialdehyde levels in schizophrenia patients taking typical, atypical and combined antipsychotic treatment. *Clin. Psychopharmacol. Neurosci.* 14(4), 345–350 (2016).

68. Matsumoto C, Ohmori O, Hori H, Shinkai T, Nakamura J. Analysis of association between the Gln192Arg polymorphism of the paraoxonase gene and schizophrenia in humans. *Neurosci. Lett.* 321(3), 165–168 (2002).

69. Păvăl D, Nemeş B, Rusu RL, Dronca E. Genotype-phenotype analysis of paraoxonase 1 in Schizophrenic patients treated with atypical antipsychotics. *Clin. Psychopharmacol. Neurosci.* 16(1), 32–38 (2018).

70. Moreira EG, Correia DG, Bonifácio KL *et al.* Lowered PON1 activities are strongly associated with depression and bipolar disorder, recurrence of (hypo)mania and depression, increased disability and lowered quality of life. *World J. Biol. Psychiatry* 20(5), 368–380 (2019).

•• **Shows correlations between PON1 activity and mood symptoms.**

71. Jolivalt C, Leininger-Muller B, Drozdz R, Naskalski JW, Siest G. Apolipoprotein E is highly susceptible to oxidation by myeloperoxidase, an enzyme present in the brain. *Neurosci. Lett.* 210(1), 61–64 (1996).

72. Hansson M, Olsson I, Nauseef WM. Biosynthesis, processing, and sorting of human myeloperoxidase. *Arch. Biochem. Biophys.* 445(2), 214–224 (2006)

73. Winterbourn CC. Biological reactivity and biomarkers of the neutrophil oxidant, hypochlorous acid. *Toxicology* 181-182, 223–227 (2002)

74. McCaffery JM, Frasure-Smith N, Dubé MP *et al.* Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. *Psychosom. Med.* 68(2), 187–200 (2006).

75. Maes M, Bonifacio KL, Morelli NR *et al.* Generalized anxiety disorder (GAD) and comorbid major depression with GAD are characterized by enhanced nitro-oxidative stress, increased lipid peroxidation, and lowered lipid-associated antioxidant defenses. *Neurotox. Res.* 34(3), 489–510 (2018).

76. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro. Endocrinol. Lett.* 32(1), 7–24 (2011).

77. Gałecki P. Peripheral markers of inflammation, oxidative & nitrosative stress pathways and memory functions as a new target of pharmacotherapy in depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 80(Pt C), 167 (2018).

78. Selek S, Altindag A, Saracoglu G, Aksoy N. Oxidative markers of Myeloperoxidase and Catalase and their diagnostic performance in bipolar disorder. *J. Affect. Disord.* 181, 92–95 (2015).

79. Ogata M. Acatalasemia. *Hum. Genet.* 86(4), 331–340 (1991).

80. Kodydková J, Vávrová L, Kocík M, Žák A. Human catalase, its polymorphisms, regulation and changes of its activity in different diseases. *Folia Biol. (Praha)* 60(4), 153–167 (2014).

81. de Sousa RT, Zarate CA Jr, Zanetti MV *et al.* Oxidative stress in early stage bipolar disorder and the association with response to lithium. *J. Psychiatr. Res.* 50, 36–41 (2014).

82. Bošković M, Vovk T, Saje M *et al.* Association of SOD2, GPX1, CAT, and TNF genetic polymorphisms with oxidative stress, neurochemistry, psychopathology, and extrapyramidal symptoms in schizophrenia. *Neurochem. Res.* 38(2), 433–442 (2013).

83. Nethercott JR, Davidoff LL, Curbow B, Abbey H. Multiple chemical sensitivities syndrome: toward a working case definition. *Arch. Environ. Health* 48(1), 19–26 (1993).

84. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th Edition. American Psychiatric Association, Arlington, VA (2013).

85. Del Casale A, Ferracuti S, Mosca A *et al.* Multiple chemical sensitivity syndrome: a principal component analysis of symptoms. *Int. J. Environ. Res. Public Health* 17(18), 6551 (2020).
86. Biocompute.org. Hardy-Weinberg equilibrium calculator including analysis for ascertainment bias. http://apps.biocompute.org.uk/hwe-mr-calc.html
87. Rodriguez S, Gaunt TR, Day IN. Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. *Am. J. Epidemiol.* 169(4), 505–514 (2009).
88. Steinemann A. National prevalence and effects of multiple chemical sensitivities. *J. Occup. Environ. Med.* 60(3), e152–e156 (2018).
89. Eis D, Helm D, Mühlinghaus T *et al.* The German Multicentre Study on multiple chemical sensitivity (MCS). *Int. J. Hyg. Environ. Health* 211(5-6), 658–681 (2008).
90. Hojo S, Ishikawa S, Kumano H, Miyata M, Sakabe K. Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan. *Int. J. Hyg. Environ. Health* 211(5-6), 682–689 (2008).
91. Berg ND, Rasmussen HB, Linneberg A, *et al.* Genetic susceptibility factors for multiple chemical sensitivity revisited. *Int. J. Hyg. Environ. Health* 213(2), 131–139 (2010).
92. Fujimori S, Hiura M, Yi CX, Xi L, Katoh T. Factors in genetic susceptibility in a chemical sensitive population using QEESI. *Environ. Health. Prev. Med.* 17(5), 357–363 (2012).
93. Wiesmüller GA, Niggemann H, Weissbach W, *et al.* Sequence variations in subjects with self-reported multiple chemical sensitivity (sMCS): a case-control study. *J. Toxicol. Environ. Health A.* 71(11-12), 786–794 (2008).
94. Lee BW, London L, Paulauskis J, Myers J, Christiani DC. Association between human paraoxonase gene polymorphism and chronic symptoms in pesticide-exposed workers. *J. Occup. Environ. Med.* 45(2), 118–122 (2003).

- **Shows the PON1 involvement in the manifestation of symptoms in patients exposed to pesticides.**

95. Dazzi L, Vacca G, Ladu S, Pisu MG, Serra M, Biggio G. Long-term treatment with antidepressant drugs reduces the sensitivity of cortical cholinergic neurons to the activating actions of stress and the anxiogenic drug FG 7142. *Neuropharmacology* 41(2), 229–237 (2001).
96. Sánchez-Amate MC, Flores P, Sánchez-Santed F. Effects of chlorpyrifos in the plus-maze model of anxiety. *Behav. Pharmacol.* 12(4), 285–292 (2001).
97. Bryk B, BenMoyal-Segal L, Podoly E *et al.* Inherited and acquired interactions between ACHE and PON1 polymorphisms modulate plasma acetylcholinesterase and paraoxonase activities. *J. Neurochem.* 92(5), 1216–1227 (2005).
98. Chia SE, Mohamed Ali S, Yap PH, Gan L, Ong YB, Chia KS. Distribution of PON1 polymorphisms PON1Q192R and PON1L55M among Chinese, Malay and Indian males in Singapore and possible susceptibility to organophosphate exposure. *Neurotoxicology* 30(2), 214–219 (2009).
99. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann. Med.* 35(1), 2–11 (2003).
100. Kamanyire R, Karalliedde L. Organophosphate toxicity and occupational exposure. *Occup. Med. (Lond).* 54(2), 69–75 (2004).
101. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. *Psychiatry Res.* 229(1-2), 27–36 (2015).
102. Kotzalidis GD, Ambrosi E, Simonetti A *et al.* Neuroinflammation in bipolar disorders. *Neuroimmunol. Neuroinflamm.* 2, 252–262 (2015).
103. Jeon SW, Kim YK. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness? *World J. Psychiatry* 6(3), 283–293 (2016).
104. Jeon SW, Kim YK. The role of neuroinflammation and neurovascular dysfunction in major depressive disorder. *J. Inflamm. Res.* 11, 179–192 (2018).
105. Bouayed J, Rammal H, Soulimani R. Oxidative stress and anxiety: relationship and cellular pathways. *Oxid. Med. Cell. Longev.* 2(2), 63–67 (2009).
106. Kim YK, Jeon SW. Neuroinflammation and the immune-kynurenine pathway in anxiety disorders. *Curr. Neuropharmacol.* 16(5), 574–582 (2018).
107. Chanana P, Kumar A. GABA-BZD receptor modulating mechanism of panax quinquefolius against 72-h sleep deprivation induced anxiety like behavior: possible roles of oxidative stress, mitochondrial dysfunction and neuroinflammation. *Front. Neurosci.* 10, 84 (2016).
108. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.* 11(6), 851–876 (2008).
109. Rammal H, Bouayed J, Younos C, Soulimani R. Evidence that oxidative stress is linked to anxiety-related behaviour in mice. *Brain Behav. Immun.* 22(8), 1156–1159 (2008).
110. Hovatta I, Juhila J, Donner J. Oxidative stress in anxiety and comorbid disorders. *Neurosci. Res.* 68(4), 261–275 (2010).
111. Wang C, Liu L, Zhang L, Peng Y, Zhou F. Redox reactions of the α-synuclein-Cu(2+) complex and their effects on neuronal cell viability. *Biochemistry* 49(37), 8134–8142 (2010).
112. Alessandrini M, Micarelli A, Chiaravalloti A *et al.* Involvement of subcortical brain structures during olfactory stimulation in multiple chemical sensitivity. *Brain Topogr.* 29, 243–252 (2016).

113. Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity. *J. Neurol. Sci.* 287, 72–78 (2009).

114. Hillert L, Musabasic V, Berglund H, Ciumas C, Savic I. Odor processing in multiple chemical sensitivity. *Hum. Brain Mapp.* 28(3), 172–182 (2007).

•• **This PET study demonstrates abnormal regional cerebral blood flow patterns in response to odor signals, suggesting that MCS has changes in odor processing, but without neuronal sensitization.**

115. Azuma K, Uchiyama I, Tanigawa M *et al.* Association of odor thresholds and responses in cerebral blood flow of the prefrontal area during olfactory stimulation in patients with multiple chemical sensitivity. *PLoS ONE* 11(12), e0168006 (2016).

116. Chiaravalloti A, Pagani M, Micarelli A *et al.* Cortical activity during olfactory stimulation in multiple chemical sensitivity: a (18)F-FDG PET/CT study. *Eur. J. Nucl. Med. Mol. Imaging* 42, 733–740 (2015).

117. Giacobbe J, Benoiton B, Zunszain P, Pariante CM, Borsini A. The anti-inflammatory role of omega-3 polyunsaturated fatty acids metabolites in pre-clinical models of psychiatric, neurodegenerative, and neurological disorders. *Front. Psychiatry* 11, 122 (2020).

118. Rhie SJ, Jung EY, Shim I. The role of neuroinflammation on pathogenesis of affective disorders. *J. Exerc. Rehabil.* 16(1), 2–9 (2020).

119. Shin C, Han C, Pae CU, Patkar AA. Precision medicine for psychopharmacology: a general introduction. *Expert Rev. Neurother.* 16(7), 831–839 (2016).