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Review article

Multiple chemical sensitivity: It's time to catch up to the science

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ABSTRACT

Multiple chemical sensitivity (MCS) is a complex medical condition associated with low dose chemical exposures. MCS is characterized by diverse features and common comorbidities, including fibromyalgia, cough hypersensitivity, asthma, and migraine, and stress/anxiety, with which the syndrome shares numerous neurobiological processes and altered functioning within diverse brain regions. Predictive factors linked to MCS comprise genetic influences, gene-environment interactions, oxidative stress, systemic inflammation, cell dysfunction, and psychosocial influences. The development of MCS may be attributed to the sensitization of transient receptor potential (TRP) receptors, notably TRPV1 and TRPA1. Capsaicin inhalation challenge studies demonstrated that TRPV1 sensitization is manifested in MCS, and functional brain imaging studies revealed that TRPV1 and TRPA1 agonists promote brain-region specific neuronal variations. Unfortunately, MCS has often been inappropriately viewed as stemming exclusively from psychological disturbances, which has fostered patients being stigmatized and ostracized, and often being denied accommodation for their disability. Evidence-based education is essential to provide appropriate support and advocacy. Greater recognition of receptor-mediated biological mechanisms should be incorporated in laws, and regulation of environmental exposures.

1. Chemical exposure overview

Humans are regularly exposed to thousands of chemicals, which are ubiquitous, and in complex and dynamic mixtures (Thornton et al., 2002; Marshall et al., 2002; Li et al., 2019; Hofman et al., 2016; CDC Centers for Disease Control and Prevention, 2019). Long term exposures to pollution contribute to morbidity and mortality; (Cohen et al., 2017) indeed, the World Health Organization declared that pollution is one of the top five major risk factors for developing non-communicable diseases, such as cardiovascular, respiratory, and neurodegenerative disorders (WHO, 2020; Linou et al., 2018). The impact of chemical exposures on health is related to both the level of exposures and the ability to detoxify and eliminate these substances (Moulton and Yang, 2012), making detoxification a fundamental and essential feature of defense mechanisms inherent in every cell. Nutritional deficiencies or being overwhelmed by xenobiotic exposures can contribute to inadequate detoxification, possibly being moderated by genetic or epigenetic factors (Hodges and Minich, 2015). Pollution exposures can induce or increase oxidative stress, which is considered a primary pathway to the development of chronic diseases that are associated with air pollution (Mudway et al., 2020; Ayres et al., 2008).

People spend 90% of their time indoors (Leech et al., 2002). The building envelopes of homes and workplaces may moderate exposures to outdoor air pollution, but this pollution infiltrates and persists indoors (Leung, 2015). With respect to chemical exposures, indoor air is worse than outdoors. Total volatile organic compound (VOC) concentrations are approximately four times higher indoors than outdoors, predominantly originating from indoor sources, with higher VOC concentrations observed in new or renovated buildings (Leung, 2015; US EPA, 2017). Common indoor sources of VOCs include fragrances, scented products (personal care, cleaning and laundry products, "deodorizers" and disinfectants), dry-cleaned clothes, furnishings, and building materials (Molot et al., 2021a). VOCs are the chemicals that patients with multiple chemical sensitivity (MCS) most likely to identify as triggers for their symptoms (Cooper, 2007; Masri et al., 2021).

As yet, no threshold for pollution exposure has been identified below

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which no damage to health is observed (Vedal et al., 2003). Studies examining the effects of air pollution exposure in cell culture, animal models, and human patients repeatedly demonstrate changes in oxidative stress and inflammatory biomarkers (Cheng et al., 2016; Guerra et al., 2013; Morgan et al., 2011). Oxidative stress is the consequence of an imbalance between the generation of oxidant molecules and capabilities of endogenous antioxidant defense mechanisms to reduce potentially damaging impacts (Dato et al., 2013; Cioffi et al., 2019). Responses to oxidative stress and systemic inflammation are central in mediating the hazardous effects of environmental stressors (Mittal et al., 2014; Münzel and Daiber, 2018). It has repeatedly been demonstrated that oxidative stress occurs with exposures to a wide range of ubiquitous indoor and outdoor pollutants (Hong et al., 2009; de Oliveira et al., 2014; Genuis and Kyrillos, 2017; Gao, 2019; Byun and Baccarelli, 2014).

2. The cellular response to pollution

Low dose exposures to xenobiotic chemicals are perceived by living organisms, by early warning detection receptor systems that sense environmental chemicals and regulate the expression of detoxifying genes, promote detoxification, and reduce oxidative stress before the chemicals can cause tissue damage (Suzuki et al., 2020; Suzuki and Yamamoto, 2015; Itoh et al., 1997; Buendia et al., 2016; Vatner et al., 2020; Suzuki et al., 2013; Itoh et al., 1999). To do this well, these receptors must balance a low threshold for sensitivity with high reliability (Zhao et al., 2020). They include xenobiotic receptors (XRs), the aryl hydrocarbon receptor (AhR), the Keap1 (Kelch-like ECH-associated protein 1)-Nrf2 (NF-E2-related factor 2) system and several members of the transient receptor potential (TRP) family of cation channels, in particular the subfamily vanilloid 1 (TRPV1) and subfamily ankyrin 1 (TRPA1) receptors.

XRs and AhRs are intracellular receptors that function as sensors for a diverse array of foreign compounds, including environmental chemicals, and toxic by-products derived from endogenous and exogenous chemical degradation (Suzuki et al., 2020). When activated, these receptors target genes influencing xenobiotic Phase I and Phase II detoxification (Li and Wang, 2010).

Nrf2 and its endogenous inhibitor, Keap1, function together as a ubiquitous, evolutionarily conserved intracellular defense mechanism to counteract oxidative stress (Bellezza et al., 2018). Keap1 regulates Nrf2 activity but also acts as a sensor for oxidative stress (Suzuki and Yamamoto, 2017, 2015). When oxidative stress occurs, Nrf2 detaches from Keap1, translocates to the nucleus and induces the expression of antioxidant and metabolic genes involved in phase I and phase II detoxification, and phase III xenobiotic transporters (Bellezza et al., 2018). Nrf2 also suppresses pro-inflammatory cytokine genes (Suzuki and Yamamoto, 2017, 2015; Itoh et al., 1997). The Keap1-Nrf2 pathway plays a crucial role in determining the sensitivity of mammalian cells to chemical and oxidative insults that have the capacity to provoke cellular harm (Copple, 2012). If the cellular response to pollution is overwhelmed, oxidative stress and systemic inflammation is maintained. The TPRA1 and TRPV1 receptors sense multiple products of oxidative stress and together mediate responses to noxious environmental stimuli (Zhao et al., 2020).

Some individuals have more effective detoxification systems than others and this helps to explain inter-individual variations in disease susceptibility (Shastry, 2005; Polimanti et al., 2013; Manikandan and Nagini, 2018). Inter-individual genetic variation in endogenous detoxification defense systems results in some individuals having lower capacity to metabolize xenobiotics and greater oxidative stress, thereby magnifying the toxic effects of long-term exposure, and potentiating subsequent disease development (Da Costa et al., 2012; Szyf, 2007). Genetic polymorphisms that negatively affect detoxification significantly increase the risk of developing non-communicable diseases linked to the environment (Ward-Caviness, 2019; Heslop et al., 2012; Hirvonen, 2009; Wang et al., 2014; Yang et al., 2008; Jiménez-Jiménez et al., 2016; Wang et al., 2016).

Some genetic detoxification polymorphisms are also more common in people who meet the criteria for MCS (McKeown-Eyssen et al., 2004; Schnakenberg et al., 2007; La Du et al., 2001; Furlong et al., 2005; Caccamo et al., 2013; Cui et al., 2013; D'Attis et al., 2019). Although these findings have not been completely consistent (Berg et al., 2010; Fujimori et al., 2012), a regression analysis published in 2019 reinforces the hypothesis that a genetic risk related to phase I and II liver enzymes involved in xenobiotic detoxification can play a role in the pathophysiological route towards sensitization to VOCs in MCS (Micarelli et al., 2019). This is not the sole reason for MCS; even when no polymorphisms that affect detoxification are identified, greater oxidative stress and systemic inflammation are observed in MCS patients compared to controls (De Luca et al., 2010; Gugliandolo et al., 2016).

3. Introduction to multiple chemical sensitivity

Many individuals observe sensitivity to common chemicals. The odors of perfumes and cleaning products provoke symptoms in up to 60% of asthmatics (Haines et al., 2020) and 70% of migraine patients report that headaches are triggered by the odors of perfume, paints and gasoline (Silva-Néto et al., 2014). Interestingly, migraine headaches and asthma are frequently comorbid (Wang et al., 2021) and one common denominator in this bidirectional association is the sensitivity to chemical odors (Sayyah et al., 2018; Steinemann, 2018a).

Multiple chemical sensitivity (MCS) is the term most frequently used to describe an acquired condition in which the person experiences a range of recurrent non-specific symptoms which they attribute to exposures to commonly tolerated low levels of chemicals (Dantoft et al., 2015). Other names used for this disorder include environmental sensitivities or hypersensitivities, environmental illness, environmental intolerances, idiopathic environmental intolerances, or toxicant-induced loss of tolerance. The most distinguishing feature is intolerance to common, airborne chemical exposures at levels previously tolerated, and tolerated by the healthy population.

3.1. Symptoms

Symptoms may occur in the nervous, respiratory, gastrointestinal, and cardiovascular systems (Magill and Suruda, 1998). They can vary widely (Gibson et al., 2003; Shinohara et al., 2004) and are usually attributed to inhalation of an irritant chemical. Commonly reported symptoms include runny nose, shortness of breath, heart palpitations, headache, burning eyes, sore throat, dizziness, confusion, fatigue, irritability, depression, short-term memory loss, upset stomach, and muscle and joint pain (Cooper, 2007; Bornschein et al., 2001; Winder, 2002). Most common are central nervous system (CNS) symptoms, especially complaints of poor cognition (Lacour et al., 2005; McKeown-Eyssen et al., 2001).

3.2. Definition

In the 1980 s and 1990 s, several case definitions for MCS were proposed with differing characteristics in addition to the one characteristic in common; that symptoms were linked to low levels of chemical exposures (McKeown-Eyssen et al., 2001). The most widely cited case definitions are those by Cullen (1987) and the MCS consensus (1999) (Cullen, 1987; No authors listed, 1999). Cullen defined MCS as an acquired disorder characterized by recurrent symptoms referable to multiple organ systems and occurring in response to exposure to chemically unrelated compounds at doses far below those established in the general population to cause harmful effects (Cullen, 1987).

The MCS consensus definition was based upon previous work by Nethercott et al (Nethercott et al., 1993). It comprises criteria that reflected an internationally consistently observed pattern of symptom presentation, which was agreed upon by 34 North American clinicians

and researchers who collectively had experience with thousands of MCS patients (No authors listed, 1999). Shortly thereafter, these criteria were validated by the Ontario Ministry of Health-funded Environmental Hypersensitivity Research Unit (EHRU) at the University of Toronto (McKeown-Eyssen et al., 2000). The criteria include the following: (McKeown-Eyssen et al., 2001).

1. The symptoms are reproducible with [repeated] chemical exposure;
2. The condition is chronic;
3. Low levels of exposure [lower than previously or commonly tolerated] result in manifestation of the symptoms;
4. The symptoms improve or resolve when the incitants are removed;
5. Responses occur to multiple chemically unrelated substances; and
6. Symptoms involve multiple organ systems

The symptoms which most commonly distinguished patients with MCS from controls involved the CNS, including having a stronger sense of smell than others, difficulty concentrating, feeling dull or groggy and feeling spacey (McKeown-Eyssen et al., 2001). In 2005, Lacour opined that the most comprehensive and well-known case definition, the MCS 1999 consensus, should specify that the CNS is always one of the multiple systems involved (Lacour et al., 2005).

3.3. Epidemiology

Using the term “chemical intolerance,” described as being less tolerant than normal or attributing immediate reactions to chemical exposure, self-report studies found similar prevalence estimates of 9–16% in the USA, Canada, Germany, Sweden, Finland, Australia, Korea and Japan. Lower rates of 0.5–3.9% are reported for doctor-diagnosed MCS (Dantoft et al., 2015; Magill and Suruda, 1998; Bornschein et al., 2001; McKeown-Eyssen et al., 2001; Winder, 2002; Shinohara et al., 2004; Lacour et al., 2005; Gibson et al., 2003; Cooper, 2007). Middle-aged women are most commonly affected (Kreutzer et al., 1999; Park and Gilmour, 2017; Del Casale et al., 2020). The prevalence of self-reported chemical sensitivity and medically diagnosed MCS in the USA was reported in 2018 to have increased in a little over 10 years by more than 200% and 300% respectively, to 26% and 13% (Steinemann, 2018a). Factors that could explain this increase include greater awareness of chemicals and health concerns in the general population, greater knowledge and comfort in making the diagnosis by health care professionals, and a true increase in prevalence.

These numerous studies in multiple countries on four continents attest to the fact that MCS has become a significant public health dilemma. It is indeed an illness, i.e., a subjective state of suffering (Flegel, 2010), and is unique in its attribution to common chemical exposures at levels previously tolerated and tolerated by others. There is overwhelming consensus within the scientific community that patients labelled with MCS are clearly distressed, and that many are functionally disabled (Bolt and Kiesswetter, 2002). What is argued is whether the observed triggering of symptoms by common chemical exposures is “real” (i.e., biological), a false attribution due to psychiatric conditions, or even a conditioned response.

4. MCS etiology: history of contested views

Descriptions of sensitivity to multiple chemicals first appeared in the medical literature in the 1960 s (Randolph, 1961). By the 1990 s, multiple medical bodies had developed positions denying the existence of MCS, stating that the purported phenomenon was not consistent with known pathophysiological mechanisms (Magill and Suruda, 1998). Since then several multinational prevalence studies have been published, some mainstream clinics are developing management strategies (Women’s College Hospital - Environmental Health Clinic Internet, 2021), well established scientific bodies have initiated scent free policies (Canadian Committee on Indoor Air Quality, 2020), hospitals are beginning to offer safer environments for chemically sensitive individuals (Flegel and Martin, 2015), and MCS has been legally recognized as a disability with the right to accommodation (Canadian Human Rights Commission, 2019).

To deny the existence of MCS as a distinct medical condition or syndrome is wrong.

The opinions of the multiple medical bodies denying the existence of MCS are now more than 20 years old. Today the clinical diagnosis is made based on the pattern of symptoms according to published case criteria; (McKeown-Eyssen et al., 2001) there is still no clinical biomarker to aid in the diagnosis (Labarge and McCaffrey, 2000; De Luca et al., 2011). It is still stated by some that there is no agreed-upon definition for MCS (De Luca et al., 2011), but the published criteria reviewed earlier are based on the consensus of experts (No authors listed, 1999; Government of Ontario M of H and LTC, 2018a) and have been validated (McKeown-Eyssen et al., 2000). The six consensus criteria (McKeown-Eyssen et al., 2001) are still unrefuted in the published literature almost two decades after publication, and are commonly used in research studies on MCS. According to a 2018 systematic review of the literature published over the last 17 years, the Cullen criteria and the 1999 consensus criteria are the most commonly used and accepted definitions (Rossi and Pitidis, 2018).

MCS is frequently described as a controversial diagnosis (Hausteiner et al., 2007; Genuis, 2014), disputing whether attribution of symptoms to ambient environmental exposures is false or true. The term "idiopathic environmental intolerance" was proposed to be used instead of MCS more than 20 years ago because “it avoided unsubstantiated assumptions of etiology.” (International Programme on Chemical Safety IPCS, 1996) If the attribution of symptom provocation is truly biologic, there should be significant supportive evidence for a biological, pathophysiological component to the declared sensitivity. The lack of awareness and understanding of the evidence for biological mechanisms perpetuates the perception that the etiology of MCS is psychogenic.

4.1. Low dose exposures and toxicity

The traditional concept of toxicology is based on Paracelsus’ 500 year old dictum, “the dose makes the poison;” i.e., in small doses toxic substances may be harmless and substances considered harmless may be poisonous when over-consumed (No authors listed, 2011). Toxicology includes the study of chemical exposures in the laboratory to characterize the dose response in model systems. Real-life studies are done by epidemiologists, who look for patterns of adverse conditions in the population, associated with acute and chronic exposures. In fact, exposures are multiple and simultaneous, and constantly in flux (Nachman et al., 2011).

We now know that some toxicants may exert different effects with different doses. For example, chemical pollutants known as endocrine disruptors can interfere with hormone actions at tiny doses yet can exhibit different effects at higher doses (Bergman et al., 2013; National Research Council USA, 2014; Xu et al., 2017). As with hormones, it is often not possible to extrapolate low-dose effects from the high-dose effects of EDCs (Bergman et al., 2013). One of the main mechanisms for hormone disruptor chemical pollutants is binding to receptors (Toporova and Balaguer, 2020; Diamanti-Kandarakis et al., 2009; Gore et al., 2015). At low doses, if a xenobiotic chemical has an affinity to bind to a receptor, it can act as an agonist (magnifying receptor response) or antagonist (damping receptor response), and initiate changes in cell signalling and function (Kanno, 2016).

Paracelsus’ dictum is too simple. It is the complex, varying, lifetime mixtures of toxicants, with short- and long-term effects, that are “making the poison.”

5. TRP chemosensitive receptors

The 2021 Nobel Prize in Physiology or Medicine was awarded jointly

to David Julius and Ardem Patapoutian for their identification of the transient receptor potential vanilloid-one (TRPV1) receptor (The Nobel Prize in Physiology or Medicine, 2021). This led to the discovery of a family of TRP receptors, which comprise a group of unique, polymodal ion channels that function as cellular sensors. They can detect a wide spectrum of potentially harmful physical and chemical stimuli, ranging from temperature and mechanical or osmotic stress to chemical compounds, radiofrequency radiation, mediators of inflammation and oxidative stress (Straub, 2014; Clapham, 2003; Ramsey et al., 2006; Zheng, 2013; Ertilav et al., 2018; Çiğ and Nazıroğlu, 2015). Here we focus on two particular TRP receptors: subfamily vanilloid 1 (TRPV1) and subfamily ankyrin 1 (TRPA1), which are fundamentally involved in the molecular physiology of chemical perception and are widely expressed in the nervous system (Vennekens et al., 2012; Bessac and Jordt, 2008). These act as transducers for signals from thermal, chemical, and mechanical stimuli, and so they play a crucial role as sensory receptors in several physiological and pathophysiological processes, including cough, pain sensation, inflammation and the perpetuation of inflammatory and nociceptive pain (Bonvini and Belvisi, 2017; Dai, 2016; Borbély et al., 2019; Giorgi et al., 2019; Weng et al., 2015; Hung and Tan, 2018).

Multiple in vitro and in vivo studies have demonstrated that both TRPA1 and TRPV1 receptors can be activated by pollution (Deering-Rice et al., 2011, 2012; Robertson et al., 2014), oxidative stress (Furuta et al., 2012; Sawada et al., 2008; Chuang and Lin, 2009; Susankova et al., 2006) and systemic inflammation (Kistner et al., 2016; Bujak et al., 2019; Zhang et al., 2005; Breese et al., 2005; Ogawa et al., 2016). Repeated, chronic activation of these receptors can lead to upregulation and sensitization (Giorgi et al., 2019; Chuang and Lin, 2009; Susankova et al., 2006; Miao et al., 2019; Gu et al., 2019; Yoshida et al., 2006; Miller and Zhang, 2011). Upregulation in this context refers to an increase in the number or density of receptors on cell surfaces, which can cause an increase in the cellular response to an activating substance (Medical Definition of UPREGULATION, 2020). Sensitization involves receptor hyperexcitability and the perception of an input as noxious, even if it is at normal or even at a subthreshold level that generally comprises an innocuous stimulus (Schumacher, 2010).

Most significant is that TRPV1 and TRPA1 function as chemosensory receptors (Futamura et al., 2009; Saito et al., 2011; Usuda et al., 2012; Lübbert et al., 2013; Bessac et al., 2009; Lanosa et al., 2010; Talavera et al., 2020). In particular, they respond to low levels of VOCs (Lübbert et al., 2013; Inoue and Bryant, 2005; Martinez and Eling, 2019), which are most abundant in indoor environments (Leung, 2015; US EPA, 2017). These are common chemicals, to which MCS patients generally react most strongly. VOCs sensed by TRPV1 receptors include m-xylene, toluene, styrene, benzene, ethylbenzene, acetone, diethyl ether, hexane, heptane and cyclohexane and formaldehyde (Futamura et al., 2009; Saito et al., 2011; Usuda et al., 2012). The TRPA1 channel is the most broadly-tuned chemosensory channel known. More than 130 different chemicals have been identified as activators of TRPA1 receptors (Talavera et al., 2020), including multiple VOCs (Lübbert et al., 2013; Bessac et al., 2009; Lanosa et al., 2010).

These receptors are also extensively co-localized. TRPA1-positive neurons co-express TRPV1 97% of the time, while 30% of TRPV1-positive neurons co-express TRPA1 (Story et al., 2003). The functional properties, and therefore the pathophysiological roles, of TRPA1 receptors are regulated by their almost universal co-expression with TRPV1 (Talavera et al., 2020). TRPV1 and TRPA1 function together (Fernandes et al., 2012; Lee et al., 2015). Their co-expression results in unique activation profiles that can be distinct from those of cells expressing only TRPA1 or TRPV1 (Sadofsky et al., 2014). Jointly, they modulate sensitivity and they can sensitize each other (Spahn et al., 2014; Gouin et al., 2017). For example, sensitization of TRPA1 receptors via repeated low dose exposures to acrolein can enhance sensitization of TRPV1 receptors to its well known agonist, capsaicin (Allen et al., 2016). In fact, the sensitization of each of these receptors is dependent on co-expression with one another (Patil et al., 2020; Nielsen et al., 2018). When activated simultaneously, the effect can be synergistic (Hsu and Lee, 1985).

When TRPV1 and TRPA1 are both upregulated by shared triggers, they are co-expressed in close proximity (Meng et al., 2016). They can form heterotetramers, which are complex units (TRPA1V1) with properties that are different from the individual channels (Lee et al., 2015). When cells co-expressing these receptors are challenged with chemicals, the TRPA1V1 heterotetramer is more commonly activated than either TRPA1 or TRPV1 alone (Sadofsky et al., 2014). This results in a lower threshold for a cellular response to chemical stimuli (sensitization) and enhances the strength and duration of the reactions (Lee et al., 2015).

Multiple single nucleotide polymorphisms (SNPs) of the TRPV1 genes in humans are associated with neuron excitability, and increases in both the response to capsaicin and the expression of TRPV1 on the cell surface (Mori et al., 2012; Xu et al., 2007; Liviero et al., 2020). There are 11 SNPs related to capsaicin sensitivity (Okamoto et al., 2018). Genetic mutations in TRPV1 and TRPA1 have been found which are associated with increased sensitivity to chemicals (Boukalova et al., 2014; Vanden Abeele et al., 2019; Deering-Rice et al., 2016; Naert et al., 2020; Schütz et al., 2014) as well as an enhanced perception of odorous stimulants (Naert et al., 2020). MCS patients may possibly have TRPV1 and/or TRPA1 polymorphisms that predispose them to develop sensitization to pollutant exposures and odors (Molot et al., 2021a). TRPV1 and TRPA1 polymorphisms contributing to the likelihood of risk or the diagnosis of MCS is a concept that requires further research.

Peripherally, these channels are expressed on ganglia and nerves that innervate visceral organs and tissues throughout the body, and their activation enables crosstalk between neurons, immune cells and epithelial cells (Silverman et al., 2020). Of note is that they are highly expressed in the olfactory and trigeminal nerve endings, which extend within a few microns of the surface of the nasal epithelium, just below the tight junctions, thereby giving lipid soluble chemical stimuli almost direct access (Finger et al., 1990; Zeliger, 2013).

5.1. TRPV1 and TRPA1 in the CNS

TRPV1 and TRPA1 receptors are located on numerous cells of the nervous system, including glia, astrocytes and neurons (Wang et al., 2020), and are widely expressed in the brain (Borbély et al., 2019; Fernandes et al., 2012). Specifically, they have been found in the somatosensory cortex, prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala, hippocampus, dentate gyrus, thalamus, hypothalamus, periaqueductal grey, superior colliculus, locus coeruleus and cerebellar cortex (Borbély et al., 2019; Fernandes et al., 2012; Patin and Pause, 2015; Xiao et al., 2016; Zschenderlein et al., 2011; de Moura et al., 2014; Liu and Zhuo, 2014; Marrone et al., 2017; Peres et al., 2021; Roberts et al., 2004).

It is well documented that activation of TRPV1 can modulate synaptic transmission via both pre- and postsynaptic mechanisms (Storozhuk and Zholos, 2018). When located presynaptically, activation can potentiate the release of excitatory glutamate and adrenaline/noradrenaline (Marinelli et al., 2002; Musella et al., 2009; Bhaskaran and Smith, 2010). Activation of presynaptic TRPA1 channels modulate glutamatergic primary afferent synaptic transmission (Wrigley et al., 2009).

5.2. VOC exposures and the CNS

Several hundred different VOCs have been identified in indoor air by academic researchers and government organizations (Tsai, 2019). A Canadian study measuring 84 VOCs in the indoor air found close to 50 different VOCs in more than 50% of 3800 homes, with higher levels in apartments (Zhu et al., 2013; Li et al., 2019a). VOCs at levels typically found in indoor air can induce oxidative stress (Wang et al., 2013; Bönisch et al., 2012; Mörbt et al., 2011; Mögel et al., 2011). Higher

levels of oxidative stress have been demonstrated in individuals complaining of poor indoor air quality associated with "sick building syndrome" in comparison with occupants in these buildings without complaints (Ruotsalainen et al., 1995; Lu et al., 2007).

Most common VOCs are moderately lipophilic chemicals of small molecular weight and are non-polar (lacking chemical charge). These factors allow them to be rapidly absorbed from the lungs and to diffuse passively through the blood-brain barrier into the brain (Zeliger, 2013; National Research Council US, 2009; Warren et al., 2000; Chmiel et al., 2019). In fact, inhaled VOCs quickly accumulate in the brain after inhalation, producing CNS effects in as little as one to two minutes (Anand et al., 2014). VOCs can have adverse effects on cognition and mood (Allen et al., 2016; van Valen et al., 2009, 2012). Reducing indoor VOC emissions and/or improving ventilation, resulting in lower VOC exposures is associated with improved cognitive function, whether measured in conventional or 'green' office environments (Allen et al., 2016). VOCs encountered indoors are also the most common triggers of reactions in MCS (Lax and Henneberger, 1995).

6. MCS and functional imaging studies

Chemical challenge testing was recommended in the 1990 s to examine whether chemical exposures could provoke a receptor-mediated pathophysiological response in MCS (Workshop on Multiple Chemical Sensitivities, 1996). Even then, there were already questions about methodology and protocols (Selner, 1996). The results of multiple studies using double-blind chemical exposure challenges on MCS patients to demonstrate sensitivity were inconsistent. A 2006 systematic review of these challenge studies failed to validate the existence of MCS (Das-Munshi et al., 2006). This was may have been due to flawed methodologies (Selner, 1996), including the quality of blinding, the masking of odors with other chemicals, and the lack of proper adaptation and wash-out periods (Joffres et al., 2005). These factors were not considered by the authors of that systematic review (Das-Munshi et al., 2006), in the few studies upon which they chose to base their conclusions. Furthermore, the authors acknowledged that they purposely excluded inhalation challenge studies using capsaicin as a provocation, with the explanation that it is not a classic stimulus described by people with MCS.

6.1. Challenge studies using capsaicin

Capsaicin is the pungent ingredient in hot chili peppers that produces the sensation of heat (Caterina et al., 1997). TRPV1 receptors are heat sensitive and show exquisite sensitivity and selectivity for capsaicin (Conway, 2008; Yang and Zheng, 2017). Capsaicin is also a well-known cough-inducing agent when inhaled. It produces this action by stimulating the TRPV1 receptors in the trigeminal nerve (Dicpinigaitis, 2012; Banner et al., 2011) in a safe, reliable and dose-dependent manner (Azuma et al., 2019; Dicpinigaitis, 2003). The more sensitive the receptors are, the more easily coughing can be provoked with capsaicin inhalation (Millqvist, 2015).

The significance of this is that there are multiple challenge studies using capsaicin inhalation that have consistently demonstrated respiratory hyper-reactivity in those who also meet the criteria for MCS, even when asthma has been ruled out by methacholine challenge (Millqvist, 2000; Millqvist et al., 2000; Ternesten-Hasséus et al., 2002; Millqvist et al., 2005; Ternesten-Hasséus et al., 2006; Millqvist et al., 2008; Holst et al., 2010; Nogami et al., 2004). The non-respiratory symptoms identified in the patients in these capsaicin challenge studies included headaches, light-headedness, nausea and/or fatigue. TRPV1 receptors play a role in the sensation of respiratory symptoms, such as dyspnea, breathlessness, and unsatisfied inspiration or air hunger (Fisher, 2009).

MCS patients frequently have respiratory sensory hyper-reactivity, which is likely due to the sensitization of TRPV1 receptors. Follow-up after five and ten years showed no reduction in sensitivity to inhaled capsaicin (Ternesten-Hasséus et al., 2007; Ternesten-Hasséus, 2016). MCS patients consistently demonstrate TRPV1 sensitivity with capsaicin inhalation challenge, which is a reliable clinical research tool with good short- and long-term reproducibility (Dicpinigaitis, 2003). Thus far, there is one published single-blind inhalant challenge study using acrolein that also demonstrated greater cough sensitivity in MCS patients compared to controls (Claeson and Andersson, 2017), suggesting that TRPA1 receptor sensitization may contribute to chemical hypersensitivity as well. Sensitization of TRPV1 and TRPA1 receptors in MCS provides a significant, evidence-based explanation for the multitude of structurally unrelated chemicals to which MCS patients attribute sensitivity reactions following low dose exposures (Miller and Mitzel, 1995).

Capsaicin inhalation challenge has consistently demonstrated cough hypersensitivity in MCS patients when one of the multiple systems involved is the respiratory system. There are, however, no capsaicin challenge studies in MCS patients without respiratory symptoms. Given that the most common system involved is the brain, the question remains whether low dose exposures can provoke effects in the brain that could explain the CNS complaints. These include a heightened sense of smell, cognition complaints, and pain such as headache.

6.2. Challenge studies using functional imaging

Multiple case-control functional imaging MCS studies have been published since 2009 (Hillert et al., 2007; Alessandrini et al., 2016). Their common purpose was to look for changes in the CNS of MCS patients when challenged with odors, which would be consistent with odor hypersensitivity or abnormal odor processing. Unfortunately, these studies had the same problems with experimental design protocols previously noted in the previously published chemical challenge studies (Das-Munshi et al., 2006; Joffres et al., 2005). The studies differed in experimental design such as patient selection criteria, and the type, number, frequency and duration of chemical exposures. The studies also used several different activation imaging techniques, including using different radioactive tracers (15 O-H2O (Hillert et al., 2007) and 18 F-FDG) (Chiaravalloti et al., 2015; Alessandrini et al., 2016) for positron emission tomography (PET). Other tools used in these studies include single photon emission computed tomography (SPECT) (Orriols et al., 2009), near-infrared spectroscopy (NIRS) (Azuma et al., 2013, 2015a, 2016) and magnetic resonance imaging (MRI) (Andersson et al., 2014, 2017). There are strengths and limitations for each method (Kameyama et al., 2016).

The results of these studies are summarized in Table 1. Notably, none of them measured the odor threshold for the sense of smell; however, when assessed, other studies reported no differences in odor detection thresholds (Caccappolo et al., 2000; Doty, 1994; Nordin et al., 2005) or odor identification (Caccappolo et al., 2000; Fiedler et al., 1996; Ojima et al., 2002) in MCS patients compared to controls. Nevertheless, brain responses at the recognition threshold level were stronger (Azuma et al., 2016; Hillert et al., 2007) and perceived intensity and unpleasantness of odors were significantly higher for participants with MCS compared to controls (Alessandrini et al., 2016).

The functioning imaging studies demonstrated increased activity compared to controls in various areas of the brain responsible for motivational, emotional and non-conscious processing of information, such as the amygdala and hippocampus in the limbic system, ACC, cuneus/precuneus, orbitofrontal cortex (OFC) and PFC (Hillert et al., 2007; Orriols et al., 2009; Azuma et al., 2013, 2015a, 2016; Andersson et al., 2014).

Many recent reports, however, highlight difficulties with replication and reliability of research in psychology, neuroscience, and neuroimaging (Nickerson, 2018), and the functional imaging studies demonstrated in Table 1 resulted in different anatomical findings. Nevertheless, these various regions of the brain do play important roles to process top–down and bottom–up sensory stimuli in decision-making, emotion, and cognitive processing of stimuli (Etkin et al., 2011;

Table 1
Summary of functional changes in regions of the brain.

	Increased activity in MCS	Decreased activity in MCS
(Hillert et al., 2007)	ACC and precuneus; ACC slightly at baseline	lower brainstem (incl trigeminal nuclei); cerebral olfactory processing (amygdala + piriform cortex [primary olfactory cortex] and insular cortex)
(Orriols et al., 2009)	increased activation, but **less than controls**, in cingulate cortex, frontal, right parahippocampus, left parietal, left thalamus and right temporal cortex.	stronger deactivation compared to controls in olfactory, left hippocampus, Rolandic area and right thalamus.
(Azuma et al., 2013)	PFC during olfactory stimulation with several different odorants: • both right and left PFC.	
(Azuma et al., 2015a)	Recovery in PFC activation is delayed; activation of OFC during recovery.	
(Azuma et al., 2016)	PFC during olfactory stimulation. OFC after olfactory stimulation. differences persisted approximately 20–30 s after olfactory stimulation.	
(Andersson et al., 2014)	left thalamus and left cerebellum as well as in several areas in the parietal, temporal, and frontal lobes during CO2 exposure	left superior frontal gyrus during one exposure.
(Chiaravalloti et al., 2015)	left temporal and occipital lobe bilaterally.	frontal lobe bilaterally.
(Alessandrini et al., 2016)	metabolism in olfactory cortex during resting state.	
(Andersson et al., 2017)	**Sensitizers:** mid and anterior insula, middle cingulate gyrus, superior parietal lobule, precuneus and olfactory region of the OFC. **Habituaters:** rostral ACC.	

ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; PFC: prefrontal cortex;

Rushworth et al., 2007).

6.3. *Functional imaging and activation of TRP receptors*

The areas of the brain responding in these functional imaging studies of MCS patients exposed to odor challenges express TRPV1 and/or TRPA1 receptors. This is highly significant because the substances used in these studies to provoke the changes in MCS patients are VOCs, which are readily absorbed and quickly enter the brain, and most of them have been identified as agonists for TRPV1 and/or TRPA1 receptors (Table 2).

The functional imaging studies used different protocols for timing and duration of challenges and several different imaging technologies, and they exemplified the protocol difficulties similar to those identified in previous chemical challenge studies. These include insufficient acclimatization and washout periods between challenges and not assessing provocation of symptoms, although some studies assessed valence. Furthermore, studies demonstrated different, heterogenous patterns of brain areas involved (Table 1). These studies also used different substances for challenges, and did not assess substances based on products identified as triggers by the patients. That said, one common denominator is that the majority of the challenge substances used are TRPV1 or TRPA1 agonists (see Table 2).

Despite shortcomings, these studies all demonstrated differences in brain activity in MCS patients compared to controls. The first two published studies showed unexpectedly lower activity in areas of olfaction in MCS participants compared to controls (Hillert et al., 2007; Orriols et al., 2009). In combination with increased activity in areas responsible for anticipation, attention, conditioning, harm avoidance, and perceptual stimulus selection, these results support the perspective of a top-down mechanism, and the authors opined that their data was not supportive of a neuronal sensitization mechanism (Hillert et al., 2007; Orriols et al., 2009). Of note, the first study by Hillert et al (Hillert et al., 2007). has not been repeated using the same procedures, while the second study by Orriols et al. found reduced olfaction only 30 min after exposures. Furthermore, both are inconsistent with two later studies, which showed an increase in activation in areas of olfaction. Although it was concluded that the observed changes related to olfaction were of neurological origin (Chiaravalloti et al., 2015; Alessandrini et al., 2016), the diverse results led to varied postulations regarding etiology.

Two systematic reviews of the functional imaging studies of MCS remarked on discrepancies in results in these brain areas; i.e., activation (Hillert et al., 2007; Orriols et al., 2009) versus deactivation (Alessandrini et al., 2016; Chiaravalloti et al., 2015) and the resulting mismatching theories. It was suggested that chemical odors are processed differently by MCS patients in comparison with healthy matched controls (Viziano et al., 2018; Azuma et al., 2019). Furthermore, although not considered by these authors, the functional imaging studies of MCS patients showed that the changes compared to controls were provoked by exposures to TRPV1 and/or TRPA1 agonists and occurred in brain regions in which these receptors are known to be expressed (see Table 2).

The fact that each study used TRPV1 and/or TRPA1 agonists helps to explain the differences in the responses in the MCS participants compared to controls, and lends support for a biological etiology of MCS, i.e., sensitization of chemosensitive receptors.

7. MCS and odor threshold

What is important to understand is that MCS is at least in part explained by chemosensory receptor sensitization to chemicals (Molot et al., 2021a). Patients attribute their reactions to particular chemical(s) because they can be identified by their distinctive odors. Some MCS researchers consider MCS to be a perceived intolerance to odors because one of the distinguishing symptoms described by MCS patients is having a stronger sense of smell than others (McKeown-Eyssen et al., 2001). Yet, several studies have repeatedly shown that MCS is not characterized by a lower threshold for odor detection or discrimination (Andersson et al., 2020; Caccappolo et al., 2000; Doty et al., 1988; Kärnekull et al., 2011; Papo et al., 2006). This discrepancy appears to invalidate the MCS patients' perception of a heightened sense of smell. As a result, it was argued that attributing symptoms to odors must be psychiatric (Papo et al., 2006).

A key factor that might be responsible for the failure to detect olfactory differences is that the published sensory studies on MCS used absolute detection thresholds for chemical stimuli in comparison to healthy controls. This is based on classical threshold theory, where the threshold is conceptualized as a step-like function producing either signal-present or signal-absent responses; (Andersson et al., 2020) however, this approach does not capture inherent ambiguity of sensation (Andersson et al., 2020). An alternative perspective is provided by signal detection theory (SDT), where the task of the sensory system is described as deciding whether an observation is just a sample of irrelevant noise, or if the signal is of importance amidst this noise (Green and Swets, 1966).

A premise of SDT is that sensory triggers generate noisy inner sensations, which must exceed a certain threshold to be noticed. Sensitivity is how well the stimulus is perceived. Andersson et al. used SDT to explore whether self-reported chemical intolerance is associated with altered sensory sensitivity or response bias, and found that higher self-reported chemical intolerance is associated with a lower (more lenient) sensory criterion (Andersson et al., 2020). He suggested that the

Table 2
Agonists used in imaging studies.

Study	Odorant	TRPV1	TRPA1	Comments
Hillert 2007 (Hillert et al., 2007)	vanillin	✓ (Lübbert et al., 2013)	✓ (Lübbert et al., 2013)	. Considered only an olfactory stimulant in 2007. There is more recent evidence for trigeminal stimulation (Rothermel et al., 2011)
	acetone	?	✓ (Pabbidi and Premkumar, 2017)	Strong trigeminal properties
	cedar oil	?	?	Contains many VOCs, notably thujone which has affinity for cannabinoid receptors and inhibits GABA
	lavender	No (Ohkawara et al., 2010)	✓ (Lindsay and Timperley, 2020)	Contains linalool
	eugenol	✓ (Nkambeu et al., 2021)) (Saunders et al., 2013)		
	butanol	?	✓ (Komatsu et al., 2012)	
(Orriols et al., 2009)	plastic paint	✓ (Talavera et al., 2020)	✓ (Pabbidi and Premkumar, 2017;Talavera et al., 2020)	
	perfume (ethanol and limonene)	No (Silver et al., 2006)	✓ (Kaimoto et al., 2016)	Authors only listed ethanol and limonene. The top 25 selling scented products emit more than one hundred Different VOCs, averaging 17 each (Potera, 2011; Steinemann, 2018a). The International Fragrance Association publishes a "Transparency List" of over 3000 chemicals that might be in a formulation (International Fragrance Association, 2020).
	petrol	✓ (Saunders et al., 2013)	✓ (Norões et al., 2019)	Contains toluene and cyclohexane. Also, benzene, n-heptane and methyl cyclohexane
	glutaraldehyde	?	?	. Glutaraldehyde is a reactive aldehyde (van Birgelen et al., 2000). TRPV1 and TRPA1 sensors respond to reactive aldehydes (Hellenthal et al., 2021)
(Azuma et al., 2013)	mandarin orange			
(Azuma et al., 2015b)	(multiple VOCS – e.g., limonene, linalool, octanol) (Sawamura et al., 2004)	?	✓ (Moulton and Yang, 2012; Riera et al., 2009;Fothergill et al., 2016)	
	Japanese cypress	N/A	N/A	
	Menthol		✓ (Karashima et al., 2007)	
	perfume	No (Silver et al., 2006)	✓ (Kaimoto et al., 2016)	
(Azuma et al., 2016)	γ-undecalactone (fruits, heavy, and sweet)	✓ (Tobita et al., 2021)	?	The olfactory stimulation test was limited to a total of six repetitions (two odorants and three concentrations) every 1.5 min
	skatole (vegetable chips, fecal)	N/A	N/A	
(Alessandrini et al., 2016)	Vanillin	✓ (Marshall et al., 2002)	✓ (Marshall et al., 2002)	
(Chiaravalloti et al., 2015)	Vanillin	✓ (Lübbert et al., 2013)	✓ (Lübbert et al., 2013)	
(Andersson et al., 2017)	Amyl acetate	No (Saunders et al., 2013)	✓ (Richards et al., 2010)	
	CO_2	✓ (Andersson et al., 2009b)	✓ (Wang et al., 2010)	

? unknown; N/A information not available

results could be due to an altered state of sensory nerves – that neurons are in a state of increased excitability, or that signal duration is longer than usual. This can occur with sensitization of TRPV1 and TRPA1 receptors (Molot et al., 2021a). Although cognitive factors are clearly an important determinant of bias, he proposed that at least some changes in bias are due to effects on sensory encoding (Jin and Glickfeld, 2019).

Sensitization has been described as a progressive increase in response to repeated identical stimulus exposures (Overmier, 2002). The most recent fMRI challenge study of MCS aimed to investigate whether sensitization and habituation to odors involve the same brain regions as those that have been implicated in pain modulation, and whether such responses would be associated with self-reported chemical intolerance (Andersson et al., 2017). In this study, 58 women with and without self-reported chemical intolerance underwent fMRI while experiencing 20 consecutive exposures to amyl acetate at levels well below the irritation threshold (Claeson and Nordin, 2011) for 30 s each, and to 13.5% carbon dioxide, using the same exposure pattern (Andersson et al., 2017). These substances were chosen because of their effect on the trigeminal nerve. Carbon dioxide is an odorless gas that stimulates the trigeminal system almost exclusively, and enables isolation of an intranasal trigeminal sensation from an accompanying odor sensation (Albrecht et al., 2010). The intensity of the exposures was rated repeatedly. Participants who rated the invariant exposures as increasing in magnitude over the course of the session were identified as "sensitizers." Participants who rated the exposures as decreasing in magnitude over the course of the session were considered "habituaters."

During the recruitment phase for this study, several weeks before the scanner session, the Chemical Sensitivity Scale (CSS) was filled out by the participants. This validated questionnaire is particularly sensitive to discriminate patients with sensory hyperreactivity from controls (Nordin et al., 2003), and is directly related to capsaicin inhalation sensitivity (Johansson et al., 2006; Nordin et al., 2004). In conjunction with the brain activity changes observed (see Table 1), the sensitizers scored significantly higher than the habituators in the CSS, meaning that they were also more likely to have sensitized TRPV1 receptors. Not surprisingly, the olfactory sensitizers rated the trigeminal targeting exposure as significantly more intense than did the habituaters.

7.1. Attention bias explains perception of heightened sense of smell

Closely related to sensitization is the concept of attention bias (Brosschot, 2002), which is the tendency to prioritize the processing of

certain types of stimuli over others. Attention bias implies facilitated or automatic shifts of attention toward information that is perceived as threatening, and it affects the ability to disengage attention away from that stimulus (MacLeod et al., 1986). In those with an attention bias, the processing of threat-related information is fast and involves limbic areas of the brain (Brosschot, 2002). It has been suggested that persons with MCS have an attention bias to chemical exposures (Sorg, 1999; Van den Bergh et al., 2001; Witthöft et al., 2006), meaning that attention systems in MCS individuals are biased to identify and discriminate chemical odors from background noise and to avoid the chemical exposures, and that such an exposure will have processing priority over other tasks (Andersson et al., 2009b). Evidence for attention bias in MCS has been found by measuring evoked reaction potentials, which indicated that MCS participants do not habituate to the same extent as controls and have difficulties ignoring the chemical exposure (Andersson et al., 2009a). MCS participants also had faster overall reaction times, and the perceived intensities for the chemosomatosensory stimuli did not decrease with time, in comparison to the controls. The significance of this is the relationship with sensitization. This suggests that attention bias, with faster reaction time, perceived increased intensity, awareness and concern, may contribute to the perception of a heightened sense of smell (Andersson et al., 2020). There is also robust evidence that less stimulus input or exposure is required to detect a negative stimulus than a positive one, indicating that negative stimuli are processed faster and more efficiently (Kuhbandner et al., 2016).

8. MCS and comorbidities

Comorbidity is typically considered to be the presence of more than one distinct condition in an individual (Valderas et al., 2009). The term multimorbidity is defined as having at least two chronic medical conditions. Most people with a chronic medical condition are multimorbid, which becomes progressively more common with age (Barnett et al., 2012). Multimorbidity accounts for 78% of all consultations in primary care (Muckelt et al., 2020; Salisbury et al., 2011). It appears that comorbidity becomes the norm rather than the exception for those with chronic disease (Starfield, 2006; Nicholson et al., 2019).

The epidemiological frequency of comorbidity challenges the reductionist single-disease framework by which most health care, medical research, and medical education is designed (Barnett et al., 2012). Medical conditions are more likely to be comorbid in an individual if they share associated risk factors and/or genetic, molecular and cellular pathophysiological mechanisms, which strongly suggests underlying common etiological pathways (Valderas et al., 2009; Ko et al., 2016; Menche et al., 2015; Ko et al., 2016).

A cluster of comorbidities associated with severity of MCS has been identified, including migraine, asthma, allergies, eczema, psoriasis, anxiety and depression (Palmer et al., 2021). Given that comorbid conditions are frequently observed in patients with MCS (Marshall et al., 2011), examining the comorbidity pattern in MCS could enhance the understanding of its underlying molecular disease mechanisms (Ko et al., 2016).

8.1. MCS: comorbidities and the nervous system

The polymodal chemosensitive TRPA1 and TRPV1 receptors that are widely expressed in multiple areas in the CNS (Fernandes et al., 2012) may play an important role in synaptic plasticity and may thereby contribute to an impressive array of dysfunctional behaviors, including anxiety, depression and cognitive functions (Bashiri et al., 2018; Lee et al., 2017). They have been extensively studied in relation to pain and neurogenic inflammation. TRPV1 is co-expressed on the vast majority of TRPA1-expressing sensory nerves and both integrate a variety of noxious stimuli (Fernandes et al., 2012). Their sensitization has been identified in MCS and there is evidence for increased sensory dysfunction other than olfactory.

8.1.1. MCS and chronic pain

Capsaicin induces an increased sensitivity to pain in participants with MCS (Holst et al., 2011), which helps to explain why MCS is often comorbid with fibromyalgia and other chronic pain conditions (Yunus, 2008; Aaron et al., 2000; Dantoft et al., 2017; Jason et al., 2000; Bell et al., 1994). This observation implies overlapping mechanisms. One functional brain imaging study performed on 14 participants with abnormal capsaicin inhalation challenge tests found a lower pain threshold and higher intrinsic functional connectivity of their salience network compared to controls (Heba et al., 2020). The participants were otherwise healthy and had normal lung capacity and immunoglobulin E levels, negative methacholine challenge tests and no past history of psychological disorders.

Functional imaging of MCS participants revealed that sensitizers display elevated pain/saliency detection, but lower activation of the rostral anterior cingulate cortex (rACC), relative to habituators (Andersson et al., 2017). The rACC is also a key area for the inhibition of nociceptive pain (Bingel et al., 2007; Ellerbrock et al., 2015). MCS and chronic pain appear to share a mechanism resulting in an imbalance in excitatory and inhibitory inputs, that contributes to the enhancement of sensory intensity (Cardinal et al., 2019).

8.1.2. Central sensitization

MCS has been described as a disorder of central sensitization (Tran et al., 2013a, 2013b), which is defined as a state in which sensory input from many organ systems, especially pain, becomes amplified by the CNS (Houghton et al., 2019; den Boer et al., 2019; Fleming and Volcheck, 2015; Yunus, 2008). In central sensitization, disruptions in normal functioning occur in neurons of the CNS. Hypersensitized central neurons have lower firing thresholds, expanded receptive areas, prolonged stimulus-independent activity, and potentiated responses compared to typical central neurons (Adams and Turk, 2018). In essence, central sensitization consists of alterations in CNS structure and function which lead to the amplification of sensory signaling (Yunus, 2008). This enhanced response to sensation involves neuronal plasticity that increases sensitivity to future stimulation; (Latremoliere and Woolf, 2009) importantly, TRPV1 receptors play a role in synaptic plasticity in multiple brain regions (Kauer and Gibson, 2009).

One feature of central sensitization that has been explored in the context of chronic overlapping pain associated syndromes is the concept of generalized sensory hypersensitivity (Williams, 2018). For example, individuals with fibromyalgia, chronic migraine, and irritable bowel syndrome (IBS) also tend to report hypersensitivity to other sensory modalities including auditory, olfactory, and visual stimuli (Geisser et al., 2008; Wilbarger and Cook, 2011; Friedman and De ver Dye, 2009; Goadsby et al., 2017; Main et al., 1997; Berman et al., 2002; Blomhoff et al., 2000; Bourke et al., 2015; Ando et al., 2016). Noise sensitivity is a common feature of these disorders (Paulin et al., 2016), that are frequently comorbid with MCS (Park and Gilmour, 2017; Dantoft et al., 2021), which in turn is also associated with noise sensitivity (Viziano et al., 2017; Baliatsas et al., 2016; Nordin et al., 2013).

Generalized sensory hypersensitivity has been associated with activation of a cortical network composed of the anterior and midcingulate, insula, and prefrontal cortices (Pujol et al., 2014). The function of this network is not specific for pain but appears to have the more general function of extracting salient sensory stimuli for subsequent higher order neural processing (Iannetti and Mouraux, 2010; Schmidt-Wilcke et al., 2014). Enhanced activities in this cortical network have been observed in MCS (Andersson et al., 2017). Interestingly, the dorsal ACC has been implicated as a component linked to the perception (or interpretation) of physical pain as well as social pain (e.g., in response to social rejection) (Eisenberger, 2015) (Eisenberger, 2015). Thus, the pain sensitivity apparent in MCS may reflect the conjoint actions of different components of the ACC that integrate noxious physical and psychological information.

Virtually any sensory experience, including nonpainful sensation,

that results in greater-than-anticipated amplitude, duration, and/or spatial extent of sensation potentially reflects central amplification as a result of increased excitation or reduced inhibition (Woolf, 2011).

In chronic pain disorders, central sensitization involves the inhibition of descending inhibitory pain pathway causing an imbalance in excitatory and inhibitory inputs that contribute to the intensity of pain, changes in pain thresholds, and spreading or radiation of pain to uninjured sites (Kwon et al., 2014). This imbalance between facilitation and inhibition found in migraineurs is seen in other chronic pain disorders such as fibromyalgia (Cardinal et al., 2019). There is evidence for this imbalance in MCS as well (Orriols et al., 2009; Andersson et al., 2017).

8.1.3. MCS and fibromyalgia

MCS and pain disorders such as fibromyalgia are similar in that both imply adverse reactions to previously non-problematic stimuli. Furthermore, it is well accepted that both TRPV1 and TRPA1 receptors are significantly involved in the mechanism of pathological pain (Hung and Tan, 2018; Laing and Dhaka, 2016; Bamps et al., 2021). As in MCS, capsaicin is used to study the sensory mechanisms of pain processing because it activates TRPV1 receptors in pain-sensing afferents as well (Heba et al., 2020).

Similar to olfactory stimulation in healthy participants, a common reaction to pain is habituation, i.e., a decrease in pain and pain-related responses with continuous or repetitive painful stimulation. Habituation corresponds to signal increases in the rACC (Bingel et al., 2007; Ellerbrock et al., 2015). In fibromyalgia, which has a substantial comorbidity with MCS, there is a lower activity in the rACC compared to healthy controls (Jensen and Finnerup, 2014; Jensen et al., 2009), which has also been observed in MCS, i.e., in sensitizers compared to habituators (Andersson et al., 2017) as well as in comparison to controls (Orriols et al., 2009).

8.1.4. MCS and chronic migraine

There is evidence that triggering of migraine headaches is associated with elevated ambient outdoor particulate matter and ozone pollution exposures (Lee et al., 2018; Szyszkowicz et al., 2010; Szyszkowicz, 2008; Chiu and Yang, 2015; Li et al., 2019b; Kunkler et al., 2015). The indoor environment is also implicated; over 40% of migraineurs cite odors as a migraine trigger, including the odors of perfume and paints (Silva-Néto et al., 2014; Friedman and De ver Dye, 2009; Scharff et al., 1995; Blau and Solomon, 1985). Prevalence studies have demonstrated a significant association of migraine with MCS (Steinemann, 2018a, 2018a), suggesting an overlap in risk factors and shared pathophysiological mechanisms (Ko et al., 2016).

Both TRPA1 and TRPV1 are upregulated in migraine and activated by physiological stimuli related to attacks (Benemei and Dussor, 2019; Demartini et al., 2017). A number of irritants well known to be migraine triggers are in fact activators of the TRPA1 channel (Dussor et al., 2014). Inhalation of environmental irritants can excite trigeminal neurons via these receptors and subsequently cause trigeminovascular activation leading to headache (Kunkler et al., 2015). Both TRPA1 and TRPV1 are associated with the function of calcitonin gene-related peptide (CGRP) (Shibata and Tang, 2021; Dodick, 2018). The release of CGRP from trigeminal root ganglia neurons plays a key role in pain sensitivity and migraine headaches (Kunkler et al., 2011; Edvinsson, 2019; Benemei et al., 2014). Trigeminovascular sensitization can occur, and is driven and perpetuated by CGRP (Iyengar et al., 2019; Noseda and Burstein, 2013). At least 70% of neurons expressing TRPV1 in the trigeminal ganglion also express CGRP (Martins et al., 2017; Shimizu et al., 2007), and TRPA1 is co-expressed with TRPV1 97% of the time (Story et al., 2003).

Functional MRI studies performed in migraine patients show a distinctive pattern of cortical and subcortical activation and elaboration of pain in response to trigeminal and extracephalic nociceptive stimuli (Demarquay and Mauguière, 2016; de Tommaso et al., 2005). They provide objective evidence of atypical functional connectivity of sensory processing regions (Schwedt and Chong, 2015). The neuronal responses of migraine patients is hyperreactive to sensory stimuli, with lower inhibition in response to sensory stimuli and an absence of habituating responses even between migraine attacks (Schwedt and Chong, 2015). In particular, migraineurs have stronger activation in several pain-facilitating regions, whereas pain-inhibiting regions are hypoactive (Schwedt and Chong, 2015). The abnormal sensory processing in migraineurs includes a lack of physiological habituation to repeated sensory stimulation especially during the intervals between attacks (Marucco et al., 2019; de Tommaso et al., 2014; Meylakh and Henderson, 2022). Abnormal sensory processing with a lack of habituation is also found in MCS, suggesting shared mechanisms (Andersson et al., 2017).

The imbalance of pain facilitation and pain inhibition could contribute to migraineurs being more sensitive to noxious stimuli. It results in hyperalgesia and allodynia, which are more common in chronic migraine (Kitaj and Klink, 2005; Aguggia, 2012), and provides clinical evidence of central sensitization (Louter et al., 2013). This imbalance is also observed in other disorders, including chronic cough (Ando et al., 2016; Singh et al., 2020) and MCS (Orriols et al., 2009; Andersson et al., 2017), providing more evidence for shared mechanisms.

Chronic pain and chronic cough encompass a wide variety of overlapping clinical features, such as hyperalgesia/hypertussivity and allodynia/allotussivity (O'Neill et al., 2013). These both involve TRPA1 and TRPV1 receptors, central sensitization, and inhibition of descending controls, which are the descending neural pathways that play a pivotal role in the modulation of pain and cough signals (O'Neill et al., 2013; Bourke et al., 2015).

Chronic migraine is associated with oxidative stress and systemic inflammation (Aczél et al., 2021; Borkum, 2016) and there is evidence for disruption of blood-brain barrier function (DosSantos et al., 2014), similar to MCS (Molot et al., 2021a). MCS shares several risk factors, pathways and patterns of dysfunction with chronic migraine. Another association shared between chronic migraine and MCS is insulin resistance. Insulin resistance has a well-documented association with chronic migraine (Bhoi et al., 2012; Rainero et al., 2005; Fava et al., 2014). It results in a compensatory increase in beta-cell insulin production and hyperinsulinemia (Freeman and Pennings, 2022). Insulin sensitizes TRPV1 receptors (Thornton et al., 2002), which enhances the release of CGRP from meningeal afferents (Thornton et al., 2002). Insulin resistance is also associated with MCS (Bjerregaard et al., 2021).

Chronic migraine is also associated with low vitamin D levels (Togha et al., 2018; Rebecchi et al., 2021; Iannacchero et al., 2015) and protein kinase activation (Wu et al., 2017). Vitamin D antagonizes the stimulatory effects of TRPV1 agonists such as capsaicin and reduces trigeminal signalling mediated by TRPV1 (Long et al., 2020). Protein kinase activity is activated by oxidative stress and systemic inflammation and can sensitize TRPV1 and TRPA1 receptors (Sikand and Premkumar, 2007; Koda et al., 2016; Ji et al., 2002; Meents et al., 2017). This activity contributes to the central sensitization frequently observed in migraineurs (Wu et al., 2017). Moreover, vitamin D reduces the protein kinase effect on TRPV1 sensitization (Tripathy and Majhi, 2020). Associations between Vitamin D and protein kinase activity have not been tested in MCS (Molot et al., 2021a).

8.1.5. MCS: migraine and neurodegeneration

A systematic review and meta-analysis confirmed that migraineurs had concordant lower grey matter volume in multiple areas, some of which were related to the frequency of headache attack (Jia and Yu, 2017; Borkum, 2016; Valfrè et al., 2008) and, like MCS (Molot et al., 2021a), chronic migraine is comorbid with neurodegenerative disorders (Islamoska et al., 2020; Lee et al., 2021a; Kostev et al., 2019; Lee et al., 2019; Avitan et al., 2021). In a previously published review, we examined the overlapping pathophysiological mechanisms of MCS and neurodegenerative disorders for which there is some evidence for

comorbidity (Molot et al., 2021a). Chronic migraine, neurodegeneration and MCS are comorbid and share risk factors and mechanisms. (See Table 3).

8.2. MCS: comorbidities and the respiratory system

People with MCS frequently attribute upper and lower respiratory symptoms, including rhinitis, dyspnea and cough, to chemical exposures (Del Casale et al., 2020).

8.2.1. MCS and cough hypersensitivity

Cough, which can be provoked by capsaicin inhalation, is one of the most frequent symptoms in MCS (Del Casale et al., 2020) and as reviewed earlier, cough hypersensitivity has been repeatedly demonstrated by capsaicin inhalation challenge in MCS patients with respiratory symptoms, even when asthma has been ruled out by methacholine challenge (Millqvist, 2000; Millqvist et al., 2000; Ternesten-Hasséus et al., 2002; Millqvist et al., 2005; Ternesten-Hasséus et al., 2006; Millqvist et al., 2008; Holst et al., 2010; Nogami et al., 2004).

Cough is a protective reflex controlled at the level of the brainstem, but it also involves higher levels of regulation (Mazzone et al., 2007). There is a perception of irritation that precedes the motor event of coughing, which is known as the urge-to-cough (UTC) (Dicpinigaitis et al., 2012). In healthy participants, functional MRIs demonstrate that the capsaicin-induced UTC sensation is associated with activation of a variety of brain regions, such as limbic and somatosensory cortices (Dicpinigaitis et al., 2012; Farrell and Mazzone, 2014).

The majority of human studies of UTC involve inhaled chemical stimuli (Farrell and Mazzone, 2014). Of major interest is that chemical stimuli capable of activating the capsaicin sensitive TRPV1 receptors do not evoke cough in unconscious or decerebrated animals, in contrast to mechanosensor-evoked reflexive cough (Farrell and Mazzone, 2014). What this demonstrates is that chemosensory stimulation is relayed to higher brain regions, which induces the perception of airway irritation, and the resultant cough response includes descending motor drives from the cortex to respiratory centres in the lower brain (Narula et al., 2014).

8.2.1.1. Overlapping mechanisms of urge-to-cough and pain. Inhalation of capsaicin in healthy humans reliably evokes an UTC with activations in a distributed brain network involving somatosensory, motor, prefrontal and limbic cortices (Narula et al., 2014). These brain regions include the insula cortex, ACC, primary sensory cortex and orbitofrontal cortex (Mazzone et al., 2007; Cho and Turner, 2021), similar to the those activated when pain is elicited by noxious stimulation (Farrell et al., 2012). In participants with cough hypersensitivity demonstrated by capsaicin inhalation, including those who meet the criteria for MCS, there is evidence for an increased UTC at least in part due to peripheral and central neural sensitization, as well as inhibition of signalling in areas normally responsible for cough suppression, including the mid-cingulate cortex, anterior insula and inferior frontal gyrus (Ando et al., 2016; Farrell and Mazzone, 2019; Cho et al., 2019).

Further evidence for overlapping mechanisms for UTC and pain is demonstrated by conditioning pain modulation, a phenomenon whereby painful conditioning stimuli applied to one body site are known to reduce the perception of pain at another site (Willer et al., 1990). This is noteworthy because preconditioning with a moderately painful stimulus (applied pressure to the thumb) is associated with both a diminished UTC and a reduced number of provoked coughs in response to inhaled capsaicin (Abubakar et al., 2021; Hilton et al., 2020). This observation has been further evidenced by functional brain MRI, which demonstrated that the application of painful conditioning stimuli during scanning was associated with widespread decreases in activity in the specific regions of the brain that are associated with capsaicin inhalation, and the magnitude of the reduction was proportional to the degree of change in the UTC. This adds to the evidence that pathways for pain and cough overlap.

Another similarity in pain and UTC mechanisms is the change generated by activated TRPV1 and TRPA1 receptors in the CNS. As we have already indicated, TRPV1 and TRPA1 receptor activation is crucial for the perception of pain (Bonvini and Belvisi, 2017; Dai, 2016; Hung and Tan, 2018; Julius, 2013). Consistent with these observed overlapping mechanisms is the finding that chronic pain disorders and cough are associated with each other (Arinze et al., 2021; Satia et al., 2021; Lee et al., 2021b).

Given the neuroanatomical and phenomenological overlap between UTC and chronic pain, it appears that sensations arising from airway stimulation are influenced by sensitization in ways that mirror hyperalgesia (Farrell and Mazzone, 2019). Furthermore, capsaicin sensitivity, which demonstrates a lower threshold for UTC and pain, has also been well documented in MCS (Millqvist, 2000; Millqvist et al., 2000; Ternesten-Hasséus et al., 2002; Millqvist et al., 2005; Ternesten-Hasséus et al., 2006; Millqvist et al., 2008; Holst et al., 2010; Nogami et al., 2004).

8.2.2. MCS and asthma

Asthma is often comorbid with MCS (Steinemann, 2018a; Caress and Steinemann, 2005; Hojo et al., 2018). It is also associated with pain disorders (Lunardi et al., 2011; Calvo-Lobo et al., 2018) and frequently comorbid with migraine headache (Wang et al., 2021; Steinemann, 2018a). One of the identified shared associations is the sensitivity to chemical odors (Haines et al., 2020; Silva-Néto et al., 2014). Multiple other associations are shared among asthma, chronic migraine and MCS. (Table 4).

8.3. MCS: comorbidities and other organ systems

MCS is by definition a multisystem disorder, and two of the most common organ systems involved are the nervous and respiratory systems (Lacour et al., 2005; McKeown-Eyssen et al., 2001; Del Casale et al., 2020). TRPV1 and TRPA1 receptors are expressed in both systems but are also frequently co-expressed in the conjunctiva and cornea, larynx, urinary bladder, upper and lower gastrointestinal system and the cardiovascular system (Fernandes et al., 2012; Shuba, 2020; Mergler et al., 2012; Lilja et al., 2007; Avelino and Cruz, 2006; Birder et al., 2001; Kechagias et al., 2005; Akbar et al., 2008; Holzer, 2008; Hamamoto et al., 2009; Takemura et al., 2008; Steinritz et al., 2018; Wang et al.,

Table 3
Shared associations: chronic migraine, neurodegeneration and MCS (reproduced with permission (Molot et al., 2021a)]).

	Chronic migraine	Neurodegeneration	MCS
Air pollution exposure	✓	✓	✓
Genotype for detoxification	No	✓	✓
Oxidative stress	✓	✓	✓
Systemic inflammation	✓	✓	✓
Disruption of BBB	✓	✓	✓
Chronic pain	✓	✓	✓
Central sensitization	✓	✓	✓
Decreased cognition	✓	✓	✓
TRPV1 upregulation	✓	✓	✓
TRPA1 upregulation	✓	✓	✓
Loss of brain mass	✓	✓	None
Olfactory dysfunction	✓	Loss of function	✓
Olfactory threshold	Normal	Raised	Normal
Trigeminal dysfunction	✓	None	✓
TRPV1 chemical sensitivity	✓	None	✓
TRPA1 chemical sensitivity	✓	None	✓
Onset with chemical exposure	No	Insidious	✓
Symptoms triggered by chemical exposure	> 40%	No	100%
Low vitamin D	✓	✓	Unknown
Protein kinase activity	✓	✓	Unknown

Table 4
Shared associations: chronic migraine, asthma and MCS.

	Chronic migraine	Asthma	MCS
Air pollution exposure	✓	✓ (Lin et al., 2021; Guarnieri and Balmes, 2014)	✓
Genotype for detoxification	No	✓ (Wang et al., 2014; Schroer et al., 2009;Su et al., 2020)	✓
Triggered by chemical exposures	> 40%	70%	100%
Oxidative stress	✓	✓ (Mishra et al., 2018)	✓
Systemic inflammation	✓	✓ (Mishra et al., 2018)	✓
Chronic pain	✓	✓	✓
Central sensitization	✓	✓ (Calvo-Lobo et al., 2018;Rodríguez-Torres et al., 2021)	✓
Impaired cognition	✓ (Vuralli et al., 2018; Martins, 2020)	✓ (Irani et al., 2017)	✓
TRPV1 upregulation	✓	✓ (Dumitrache et al., 2021)	✓
TRPA1 upregulation	✓	✓ (Kim, 2018;Yang and Li, 2016)	✓
Low vitamin D	✓	✓ (Bener et al., 2014;Liu et al., 2019)	Unknown
Protein kinase activity	✓	✓ (Vachier et al., 1997)	Unknown
Mast cell activation	✓	✓	✓
Associated psychiatric disorders	✓	✓ (Jiang et al., 2014; Katon et al., 2004; Cooley et al., 2020)	✓
Associated with neurodegenerative disorders	✓	✓ (Rosenkranz et al., 2021)	✓

2019; Manneck et al., 2021). These receptors are involved in a plethora of physiological and pathophysiological functions related to the urinary, cardiovascular, gastrointestinal, and respiratory systems (Du et al., 2019). For example, sensitization of TRPV1 is involved in functional dyspepsia (Choi et al., 2016) and IBS (Blackshaw et al., 2010; Szymaszkiewicz et al., 2020; Wouters et al., 2016; Scalera and Loguercio, 2012), both of which are frequently comorbid with MCS (Marshall et al., 2011). Allergic disease is also frequently comorbid with MCS (D'Attis et al., 2019; Hojo et al., 2008; Katerndahl et al., 2012; Jeong et al., 2014).

8.3.1. *The observed activation of mast cells*

We have been aware for decades that mast cells have been implicated in the pathogenesis of asthma and allergy (Méndez-Enríquez and Hallgren, 2019), but they also function as intermediaries between the nervous and immune systems (Forsythe, 2019). Mast cells are activated by several neurotransmitters and neuropeptides, enabling neural control of innate and adaptive immunity. Conversely, mast cells also secrete mediators including neurotransmitters and neurotrophic factors that directly affect neuronal functioning, causing acute activation and/or long-lasting changes in excitability and phenotype (Forsythe, 2019). Mast cells exist in the brain, generally present adjacent to blood vessels, glial cells, and neurons in the CNS, and participate in cross-talk which can result in the release of several inflammatory mediators (Kempuraj et al., 2018). Mast cells are also important cellular regulators of physiological and pathological pain pathways (Chatterjea and Martinov, 2015). Notably, they play fundamental roles in migraine pathophysiology (Koyuncu Irmak et al., 2019; Levy et al., 2007) and their activation suggests a shared mechanism that helps to explain further the recognized comorbidity between migraine and asthma (Wang et al., 2021).

Mast cells often lie in close association with enteric neurons (Philpott et al., 2011) and their activation appears to be involved in gastrointestinal dysmotility and IBS (Zhang et al., 2016). In fact, IBS and mast cell hyperactivity are frequently associated (Kurin et al., 2021). These cells are the major producer of histamine (Thangam et al., 2018), which can sensitize TRPV1 receptors and contribute to visceral hypersensitivity and abdominal pain in IBS (Wouters et al., 2016). Both TRPV1 and TRPA1 receptors are expressed on mast cells and are involved with their activation and degranulation (Freichel et al., 2012; Naert et al., 2021). Sensitization of these receptors may help explain why those with mast cell activation syndrome report increased chemical intolerances, similar to those observed in MCS (Miller et al., 2021).

There is also a bidirectional association between asthma and IBS (Shen et al., 2016). One of the shared mechanisms appears to be mast cell dysfunction. TRPV1 and TRPA1 receptors are mechanistically involved in both conditions and MCS is comorbid with asthma, allergies, dyspepsia and IBS (Aaron and Buchwald, 2003; Steinemann, 2018b). The evidence for a biological cause for MCS is robust when one takes into account the function of TRPV1 and TRPA1 receptors. Among other things, these receptors exhibit numerous features associated with MCS, including sensitivity to multiple unrelated chemicals; a propensity to be sensitized; sensitization in MCS; locations where they are expressed; distinct functional imaging results using TRPV1 and TRPA1 agonists; biological risk factors; and pathophysiological mechanisms, that MCS shares with comorbid conditions.

8.4. *MCS and psychiatric conditions*

Data gleaned from 21,977 adults in the 2012 Canadian Community Health Survey found that in individuals with MCS the odds of mood disorders and of being severely distressed were markedly elevated (Johnson and Colman, 2017). There are multiple studies which report associations of MCS with panic disorder (Binkley and Kutcher, 1997; Binkley et al., 2001), somatoform spectrum disorder (Fiedler et al., 1996; Bailer et al., 2008; Staudenmayer, 2000; Das-Munshi et al., 2007), anxiety, and major depression (Bell et al., 1995b; Black et al., 2000; Lax and Henneberger, 1995, 2001).

Seven studies have reported higher rates of a lifetime history of psychiatric conditions in MCS patients, compared to controls (Black et al., 2000; Caccappolo-van Vliet et al., 2002; Black et al., 1990; Simon et al., 1993; Hausteiner et al., 2006; Eis et al., 2008; Simon et al., 1990). Two of these studies reported that 80% had a longstanding psychiatric history (Black et al., 2000; Eis et al., 2008). Three studies demonstrated a lifetime history of approximately 50% (Caccappolo-van Vliet et al., 2002; Black et al., 1990; Simon et al., 1993), which also means that 50% of MCS patients did not have this history. Finally, two studies reported that more than 70% of MCS patients did not have a history of a psychiatric condition (Fiedler et al., 1996, 1992).

Critically, none of these papers considered that the MCS symptoms could be explained by a biological response to low dose chemical exposures. How many patients expressed worry about their future or sadness at the loss of quality of life, but were misdiagnosed as anxious or depressed, or with a somatoform disorder because their symptoms were "not fully explained by a general medical condition or by the direct effects of a substance"? This was the prevailing definition of somatoform disorders at that time (Lieb et al., 2002). Doctors' ratings that symptoms are "medically unexplained" is highly problematic (Rief and Rojas, 2007). Not considering a biological explanation for MCS may bias physicians' ratings as to the origin of the symptoms, which is crucial for diagnostic accuracy. Sadly, it is not uncommon for physical illnesses to be misattributed to an ongoing mental health condition, which has resulted in abbreviated lifespans. This is made still more egregious since the mental health disturbances may be secondary to biological processes stemming from physical illnesses or share common underlying processes.

It has been observed that MCS patients are more likely to have a family history of alcohol dependency and abuse (Black et al., 1999), but paradoxically, they personally have lower levels of alcohol use and higher levels of alcohol intolerance (Miller and Prihoda, 1999; Bell et al.,

1996, 1996, 1997, 2001, 1995a, 1993).

A statistical association between MCS and psychiatric illness has been noted. Being associated means that the variables are more likely to occur together than just by chance, and it implies that they must be related in some way, sharing risk factors or pathophysiological mechanisms (Ko et al., 2016). Of significance is that multiple studies demonstrate that air pollution is associated with poor mental health (Buoli et al., 2018; Bakolis et al., 2020; Attademo et al., 2017; Kioumourtzoglou et al., 2017; Pelgrims et al., 2021; Power et al., 2015; Oudin et al., 2016; Khan et al., 2019; Mehta et al., 2015; Davoudi et al., 2021; de Prado Bert et al., 2018). A systematic review and meta-analysis found an association between long-term exposures to PM2.5 and depression and anxiety (Braithwaite et al., 2019). Furthermore, suicide and visits to the emergency department because of suicide attempts and ideations as the result of depression are linked to short-term increased air pollution exposure (Braithwaite et al., 2019; Szyszkowicz et al., 2010; Ng et al., 2016).

A shared mechanism linking air pollution and mental conditions may be inflammation and oxidative stress, which can also be promoted by psychosocial stressors (Piccinni et al., 2012; Bortolato et al., 2017; Michel et al., 2012). Metabolomic studies of anxiety disorders revealed metabolites related to oxidative stress and inflammatory processes (Humer et al., 2020). Oxidative modifications of proteins have actually been proposed as a potential factor in the onset and progression of several psychiatric disorders, including anxiety and depressive disorders (Fedoce et al., 2018). A systematic review and meta-analysis not only found an association of oxidative stress with depression, it also found that oxidative stress can be reduced with the use of antidepressant medication (Liu et al., 2015). Biomarkers of inflammation are reliably elevated in a significant proportion of patients with major depression, anxiety and posttraumatic stress disorders, and may be a causal factor driving behavioral symptoms (Felger, 2018).

Anxiety and depression disorders share the mechanisms of oxidative stress and systemic inflammation with MCS. Thus, upregulated TRPA1 and TRPV1 receptors can also be involved in the pathogenesis or pathophysiology of psychiatric disorders, including anxiety, altered mood, and contextual fear conditioning (de Moura et al., 2014; Aguiar et al., 2009; Campos and Guimarães, 2009; Santos, Jul et al., 2008; Terzian et al., 2009; Marsch et al., 2007; Edwards, 2014; Kasckow et al., 2004; Nakao et al., 2021; Uliana et al., 2020, 2016; Micale et al., 2009; Ho et al., 2012; Wang et al., 2017). Preclinical studies demonstrate that inhibiting these receptors has antidepressant and anxiolytic effects (Aguiar et al., 2009; Campos and Guimarães, 2009; Santos, Jul et al., 2008; Terzian et al., 2009; Marsch et al., 2007).

Given that studies suggesting an association with psychiatric illness are cross-sectional, i.e., performed well after the onset of MCS, causality cannot be construed (Fiedler and Kipen, 1997). Of course, association does not mean causation (Begg and March, 2018). Stress and anxiety are associated with many other medical conditions. Anxiety is comorbid with chronic cough (respiratory sensitivity), asthma, migraine, functional gastrointestinal disorders, inflammatory immune disorders, and neurodegenerative disorders, all of which are more likely to be comorbid with each other, and all are comorbid with MCS (Côté et al., 2020; McGarvey and Nishino, 2004; Hennel et al., 2015; Hulme et al., 2017; Rosenkranz et al., 2021; Weatherburn et al., 2017; Tay and Hew, 2018; Yilmaz et al., 2011; Di Stefano et al., 2019; Altamura et al., 2021; Liu et al., 2021; Chen et al., 2016; Kuring et al., 2018).

Table 5 illustrates that stress and anxiety share multiple risk factors and overlapping mechanisms with chronic migraine, asthma and MCS. They share multiple associated risk factors and mechanisms, i.e., overlapping chronic pain and sensitized UTC mechanisms, but cause-and-effect relationships among health conditions is not implied; rather, they share underlying factors.

Table 5
Shared associations of chronic migraine, asthma and MCS with stress/anxiety disorders.

	Chronic migraine	Asthma	MCS	Stress/anxiety
Air pollution exposure	✓	✓	✓	✓
Genotype for detoxification	No	✓	✓	?[a]
Triggered by chemical exposures	> 40%	70%	100%	✓
Oxidative stress	✓	✓	✓	✓
Systemic inflammation	✓	✓	✓	✓
Chronic pain	✓	✓	✓	✓
Central sensitization	✓	✓	✓	✓
Impaired cognition	✓	✓	✓	✓
TRPV1 upregulation	✓	✓	✓	✓
TRPA1 upregulation	✓	✓	✓	✓
Low vitamin D	✓	✓	Unknown	✓ (Silva et al., 2021)
Protein kinase activity	✓	✓	Unknown	✓ (Keil et al., 2016)
Mast cell activation	✓	✓	✓	✓ (Theoharides et al., 1995; Kempuraj et al., 2017)
Associated psychiatric disorders	✓	✓	✓	✓
Associated with neurodegenerative disorders	✓	✓	✓	✓

[a] There is some evidence for an association of genotypes for polymorphic antioxidant enzyme paraoxonase 1 (PON1) activity with anxiety and other psychiatric disorders (Moreira et al., 2019).

9. Discussion

Since the 1990 s, when multiple medical bodies declared that there was no evidence for the existence of MCS as a biological entity, the medical literature has advanced toxicology paradigms, including understanding of nonmonotonic responses, and vastly improved understanding of impacts of pollution on human health. Oxidative stress, systemic inflammation, upregulation of TRPV1 and TRPA1 receptors and central sensitization are some of the pathophysiological mechanisms in MCS that overlap in comorbid conditions, such as migraine, fibromyalgia, chronic cough, asthma, dyspepsia, IBS, ME/CFS and neuropsychiatric disorders. MCS, cough hypersensitivity, fibromyalgia and chronic migraine share significant pathophysiological mechanisms, such as sensory processing dysfunction, including increased sensory detection and reduced inhibition, causing an imbalance between facilitation and inhibition, with increased sensitization and decreased habituation to stimuli.

The evidence is robust that chemical pollution exposures can induce chemosensitive receptor sensitization in susceptible individuals and provides a strong foundation for the premise that receptor sensitization to chemicals is the primary etiological mechanism in MCS. There are some genotypes for TRPV1 and TRPA1 receptor function (Xu et al., 2007; Liviero et al., 2020; Okamoto et al., 2018; Boukalova et al., 2014; Vanden Abeele et al., 2019; Deering-Rice et al., 2016; Naert et al., 2020; Schütz et al., 2014) and xenobiotic detoxification (McKeown-Eyssen et al., 2004; Schnakenberg et al., 2007; La Du et al., 2001; Furlong et al., 2005; Caccamo et al., 2013; Cui et al., 2013; D'Attis et al., 2019) that may put some people more at risk to develop MCS.

There is no doubt that MCS is a unique and complex medical condition, with multiple potential contributory factors that need to be addressed in research and management, including variable but continuing exposures to pollutant mixtures, genetic predisposition, detoxification, oxidative stress, systemic inflammation, chemosensitive

receptors and their potential for sensitization, previous and resulting psychosocial issues, and the impact of comorbid conditions. The failure of studies and reviews purporting a psychiatric etiology to consider these mechanisms has skewed perspectives towards biased interpretations and conclusions. Indeed, to a significant extent, the failure to appreciate the biological underpinning of psychiatric disorders may have provided a counterproductive way of considering MCS and its treatment.

The impact of having MCS ranges from mild inconvenience to significant disability (Vuokko et al., 2018), but the medical and social needs of those afflicted are too often not being met (Government of Ontario M of H and LTC, 2018a). This adds a further negative impact on function, quality of life, and disability, including the emergence of psychiatric conditions. Although some jurisdictions provide the legal right to accommodation (Canadian Human Rights Commission, 2019), there continues to be an ongoing struggle for MCS patients to live and function in a society with ubiquitous chemical exposures. Having MCS can severely impact different aspects of everyday life, including lifestyle, social relations, and occupational situations, potentially leading to loss of family and social supports, reduced social interactions, access to health and public transportation, reduced income, increased disability and third party litigation (Government of Ontario M of H and LTC, 2018a; Ternesten-Hasséus et al., 2007; Driesen et al., 2020; Gibson and Vogel, 2009).

Multiple international prevalence studies suggest that millions of people experience doctor-diagnosed MCS, and that many more millions describe themselves as chemically sensitive. The numbers appear to be increasing (Steinemann, 2018b), with women at higher risk, possibly due to the fact that estrogen hormones can stimulate, upregulate and sensitize TRPV1 and possibly TRPA1 receptors (Payrits et al., 2017; Méndez-Reséndiz et al., 2020; Pohóczky et al., 2016). Various hormones, including those elicited by stressors, can also modulate the expression and function of neuronal functioning in the hippocampus, hypothalamus, cortex and brainstem (Ramírez-Barrantes et al., 2020; Kumar et al., 2018). Moreover, even in healthy participants, capsaicin inhalation challenges demonstrate that women have a lower threshold for TRPV1 activation than men (Mazzone et al., 2011). Women are also more frequent users of cleaning and personal care products, including cosmetics and hair, menstrual/intimate, and skincare products, all of which can be sources for VOCs that are inhaled and absorbed through the skin (Kovacs et al., 1997; Dodson et al., 2021).

MCS shares numerous mechanisms with neurodegenerative disorders, chronic cough, asthma, and chronic pain disorders like chronic migraine, all of which also have associations with psychiatric conditions (Santabárbara et al., 2020; Becker et al., 2018; Song et al., 2020; Karimi et al., 2020). Nevertheless, none of these are treated primarily as a psychiatric illness. The simplistic argument as to whether MCS is physical or mental needs to be put to rest.

What adds to the burden of MCS is patients' frequent experience of being met with mistrust and doubt by society in general and in particular by health care professionals and the social service systems together with measures to enhance a healthy environment (Dantoft et al., 2015). As described in the 2018 Final Report of the Ontario Task Force on Environmental Health, there is a discouraging lack of health care providers with knowledge of the underlying causes or a clear understanding of the impact and severity of living with MCS (Government of Ontario M of H and LTC, 2018a). These patients are offered insufficient healthcare solutions. They frequently experience being met with doubt and limited understanding of their condition by medical practitioners, and must deal with significant discrimination and stigma, resulting in barriers to accessing health care (Micarelli et al., 2019; Dantoft et al., 2015; Government of Ontario M of H and LTC, 2018a; Lipson, 2004; Hu and Baines, 2018).

MCS is clearly a complex condition. It is associated with genetics, gene-environment interactions, chronic exposures to complex chemical mixtures, oxidative stress, systemic inflammation, receptor sensitization, changes in cell function, multiple system involvement, psychosocial issues and multimorbidity. While understanding of MCS still needs a reductionist approach to identify and study individual factors, a systems biology perspective (Kasckow et al., 2004) is essential to understand what all the data means for patient health, functioning, and quality of life. Systems biology directs us to understand the interactions among genes, the systems of cells, tissues, and organs, the external environment, determinants of health and behaviour. In addition, systems medicine incorporates these complex interactions in order to understand the process of a chronic disease, rather than perceiving the disease as a single abnormal mechanism occurring in isolation, and then treating it accordingly (Nakao et al., 2021).

9.1. Treatment

There are currently no evidence-based treatment guidelines for MCS. Evidence of benefit thus far comes from the collective voice of the patients, i.e., qualitative reviews, which rate the creation of a safe living space and chemical avoidance as the most effective treatments for MCS (Gibson et al., 2003; Harter et al., 2020). A recently published pilot study measured the symptom severity of participants (n = 37) with chemical intolerance, conducted a structured home assessment including identification of products that were sources of VOCs, measured indoor air VOC levels, and made recommendations for alternative cleaning supplies and safer, fragrance-free cleaning practices (Perales et al., 2022). When compared to a reference group of participants with chemical intolerance and no treatment, there was a significant reduction in symptom severity associated with reduced levels of VOC exposures (Perales et al., 2022).

MCS patients need to self-manage their condition. Self-management consists of the following components: engaging in activities that promote physical and psychological health; interacting with healthcare providers and adhering to treatment recommendations; monitoring health status and making associated care decisions; and managing the impact of the illness on physical, psychological, and social functioning (Bayliss et al., 2007).

Patients diagnosed with MCS need to be guided and supported in their self-management by their medical providers. This includes educating the patient to be able to make properly informed decisions and to educate family members and others to understand their own responsibilities in providing support. Comorbid conditions also need to be addressed with their health care provider. In Canada and other jurisdictions, MCS is recognized as a disabling medical condition with the legal right to accommodation (Canadian Human Rights Commission, 2019). Therefore, physicians should be knowledgeable enough to advocate for their patients to obtain appropriate accommodation, when necessary. They should also be capable of providing support for third-party disability benefit applications if their MCS patients are unable to work.

9.2. Environmental health education

Environmental medicine, which is the clinical practice of environmental health, is largely omitted in medical education (Gehle et al., 2011; Kligler et al., 2021). Despite the call from numerous organizations to improve and expand training on environmental health for clinicians, environmental chemical exposure assessment is generally overlooked in clinical practice (Bijlsma and Cohen, 2016). Surveys of practicing clinicians demonstrate low rates of environmental health knowledge (Hamilton et al., 2005; Massaquoi and Edwards, 2015).

The first priority of public health is to prevent disease. The next is early detection. Medical practitioners need to learn to take a proper environmental exposure history (Marshall et al., 2002). They should be able to advise their patients to reduce exposures to assist in the prevention and management of chronic diseases associated with pollution. Medical residents lack training in environmental health and rate their

supervisors knowledge in this area as low (Sanborn et al., 2019). The most common resource for environmental health accessed by residents is the Internet, and the most commonly used Web resource is the software subscription site UpToDate® (Sanborn et al., 2019), which is self-described as an evidence-based, physician-authored, peer-reviewed clinical decision support resource that assists clinicians with point-of-care decisions. It is accredited as a continuing education resource by multiple colleges and medical associations (CME/CE/CPD Accreditations Internet, 2022).

Regarding MCS, UpToDate® states that many experiments and observational studies consistently identify psychopathology in these patients and implicate psychiatric causes for this illness (Black and Temple, 2021). It further states that the concept that symptoms result from toxic chemical substances is not consistent with the level of exposure, which is far below the established level of toxicity. There is no discussion of the potential for low-dose responses, no acknowledgment or review of chemosensitive receptors or their potential for sensitization, and no mention of the multiple studies reviewed earlier demonstrating receptor sensitization in MCS (and other chronic comorbid conditions that are not considered to be psychogenic). Instead, the website authors opine that psychotherapy is the primary treatment and that pharmacotherapy may be used as adjunctive treatment for MCS. It is stated that one aim of treatment is to help the patient understand the cause of the symptoms as less rooted in the environment and centered more on psychiatric issues. This is not to say that there are not benefits to psychological treatments, especially as these may facilitate appraisals of their situation and ways to cope effectively.

The UpToDate® article actually muses that MCS may be iatrogenic in some patients because their physicians assess patients with the goal of explaining symptoms in terms of their connection to environmental chemicals.

The same authors also provided the information on MCS available in the Merck Manual (Black, 2020), a well-known medical textbook, which is now available online for free. Key points listed are that MCS cannot be explained by non-psychologic factors, and that psychologic therapies such as graded exposure and drug treatment of coexisting psychiatric disorders should be encouraged (Black, 2020). It is important to note that graded exposure in this textbook refers to the treatment for specific phobic disorders, but there is no published evidence for efficacy or safety in MCS. In particular, this advice is in conflict with what is now known about TRPV1 and TRPA1 receptors; that repeated exposure to chemical agonists is likely to increase receptor upregulation and sensitization (Giorgi et al., 2019; Chuang and Lin, 2009; Susankova et al., 2006; Miao et al., 2019; Gu et al., 2019; Yoshida et al., 2006; Miller and Zhang, 2011; Andersson et al., 2017), which suggests that graded exposure is more likely to cause an iatrogenic exacerbation of MCS.

Thus, it appears that residents and health care professionals are relying on unregulated, misinformed sources for their information on MCS.

9.3. *The responsibility of medical profession self-regulation*

As part of a self-regulating group, physicians must be held accountable, to maintain a high level of evidence-based education. Self-regulation confers responsibility and accountability to self-govern, self-regulate, and to ensure the highest degree of professionalism (Bauchner et al., 2015). Undergraduate and postgraduate medical education and training standards required to fulfill and maintain the related responsibilities to patients are established by self-regulation. Physicians have an obligation and responsibility for lifelong evidence-based learning (Bauchner et al., 2015), and it is the educators who are accountable to provide it.

Significant gaps have been identified in the pre- and postgraduate education of physicians regarding environmental health in general (Gehle et al., 2011), and more specifically in how to diagnose, manage and treat MCS (Government of Ontario TF on EH, 2017). Many doctors and other health care providers lack a fundamental understanding of this environmentally linked condition, and do not understand the pathophysiology of MCS; many assume it is psychological (Government of Ontario TF on EH, 2017). There is a profound shortage of specialized doctors skilled in this area and only a handful of primary care practitioners who are knowledgeable and confident to manage MCS appropriately (Government of Ontario M of H and LTC, 2018b). As a result, MCS patients who reveal their reactions to low-dose, common chemical exposures are not being believed. Instead, they experience negative interactions with their health care providers and are stigmatized (Government of Ontario M of H and LTC, 2018a; Government of Ontario TF on EH, 2017; Lipson, 2004). Although patients with MCS are often at risk of also experiencing anxiety, depression, and other psychiatric conditions, the evidence does not indicate that MCS is primarily a disorder that emerges owing to psychological disturbances; rather, the stigmatization resulting from not being believed likely contributes to anxiety and depression (Government of Ontario M of H and LTC, 2018a). Psychiatric approaches to care for MCS have had very limited success. There is almost no evidence published in the past 30 years demonstrating any efficacy of psychiatric treatments for MCS (Katerndahl et al., 2012; Das-Munshi et al., 2007), which is based on only a few isolated case reports of improvement (Andiné et al., 1997; Stenn and Binkley, 1998; Spyker, 1995; Kakisaka et al., 2017). Deconditioning with the use of biofeedback has been theorized as a potential therapy (Giardino and Lehrer, 2000; Staudenmayer, 1996) after a review of just three cases (Guglielmi et al., 1994). Evidence provided from several qualitative reviews revealed that patients with MCS identified chemical avoidance as the single most helpful intervention and rated psychotropic medications as the least helpful for their chemical sensitivity condition (Skovbjerg et al., 2009; Lipson, 2001),. 631].

An MCS patient's health experience is also affected by other factors outside the health system, such as access to safe housing and working environments, flexible employment, income supports, social support, and more (Government of Ontario TF on EH, 2017). To reduce the stigma and to gain the recognition required to improve care and supports requires leadership at the highest levels in public health, medical and nursing educational systems. This includes academic and clinical leadership; researchers and clinicians who will champion MCS and undertake the work required to develop evidence-based, high quality care (Government of Ontario TF on EH, 2017). Professional education programs are needed to ensure that physicians and other health professionals are better equipped to understand and support those affected by environmentally linked conditions such as MCS. In general, there is little at the undergraduate level and there are too few postgraduate enhanced-skills training programs which include MCS. Clearly, much more is needed.

It is understood that it is challenging to build new clinical knowledge in health professions at all levels of education and practice. Medical schools face many competing demands, so it is difficult to incorporate new material into the curriculum. It is also challenging to add content to continuing education programs for health care providers already in practice (Gehle et al., 2011). Moreover, not only is environmental health education of pre- and postgraduate physicians lacking, information being accessed by those who choose to search for understanding MCS beyond mentorship is often biased and misinforming. Most importantly, this appears to have negative impacts on patients. With climate change escalating, the increasing numbers and levels of environmental toxicants will become an accelerating problem, potentially affecting the incidence and prevalence of MCS. There are few substitutes for preparedness to meet oncoming challenges.

It is espoused that the self-regulation system in medicine has evolved to "proactive identification and remediation of deficiencies in clinical competence to prevent patient harm." (Bauchner et al., 2015) Questions are therefore raised because of the longstanding lack of proper medical care and resulting negative, iatrogenic impacts on the health and quality of life for those with MCS. Who has the pedagogical responsibility to

teach evidence-based medical care for millions of people with MCS? Leaving the responsibility to the editors of online apps is not adequate. Shouldn't those responsible for pre- and post-graduate medical education be held accountable to urgently address deficiencies?

MCS is but one example of exceeding human limits to cope with pollution. There are many more, ranging from other chronic non-communicable diseases (NCDs) to several cancers (World Health Organization, 2021; Turner et al., 2020). The major source of urban air pollution is the burning of fossil fuels, which is also the major contributor to climate change (Manisalidis et al., 2020). People remain exposed to outdoor air pollution even while spending 90% of their time indoors (Leech et al., 2002), but the major contributor to indoor air pollution is chemicals from indoor sources (Leung, 2015; US EPA, 2017; Molot et al., 2021b; Tran et al., 2020). The quality of indoor air is dependent upon both ventilation, contamination from indoor and outdoor sources, and air cleaning or filtration. Reduction of contamination can occur by educating the public to make better selections when choosing items such as personal care and cleaning products and building materials and furnishings.

One common denominator for all NCDs associated with pollution exposures, including MCS, is oxidative stress. Should toxicology endpoints include oxidative stress and different polymorphisms for detoxification? What endpoint is most relevant – cancer? Specific organ damage or malfunction? (Health Canada and Water and Air Quality Bureau, 2017) What about the toxicology of mixtures? (Nachman et al., 2011).

Beyond medical care, the narrative denying that adverse environmental exposures can have physiological effects, such as receptor sensitization and associated symptoms, enables continuing use of harmful chemicals in commerce. Moving upstream to sources of chemicals in air, water and food, and from commercial products ranging from personal care, cleaning and building materials, governmental bodies such as Health Canada, Environment and Climate Change Canada, the United States Environmental Protection Agency, and the European Commission (working on a Chemicals Strategy for Sustainability) aspire to assess and regulate chemicals based on limited understandings of adverse effects (Canada, 2020; Environment and Climate Change Canada, 2020; US EPA, 2016; European Commission. Chemicals Strategy, 2022). Low dose effects are contested by vested interests, so misunderstandings such as environmental etiology of MCS must be addressed rigorously and not be dissuaded by dispute (Goldberg and Vandenberg, 2021; Soskolne et al., 2021). Legislation to improve assessment and regulation of chemicals is essential to require least-toxic alternatives and to reduce exposures at their source. Assessments typically consider limited animal testing, although New Approaches Methodologies are being advanced for pre-emptive detection of potential toxicities (Aspis, Project cluster for Implementation of novel Strategies, 2022).

10. Conclusion

MCS is a complex biological condition, and a major cause is receptor sensitization due to multiple environmental factors. The evidence that MCS is a biological condition is robust and can no longer be referred to as "controversial." There is ample evidence that chemosensitive receptor sensitization occurs in the CNS and respiratory systems of those with MCS - the two most commonly affected systems. The facts that this receptor dysfunction is found in other frequently affected systems and is involved in the generation of common symptoms experienced by those with MCS provide further support that the etiology of the pathophysiological mechanism for MCS involves sensitization of chemosensitive receptors.

To develop and enhance the multidiscipline perspective required to understand and treat MCS, a communicative braiding of input from various individuals, and better-informed specialty silos, is required. The time has come for medical educators, toxicologists and environmental regulators to become better informed regarding MCS as a distinct biological medical condition. Importantly, these concepts must be introduced into the medical education system, including pre- and postgraduate training, and continuing professional development programs. Similarly, public health practitioners must be knowledgeable, to address patients' needs for supports necessary for daily living and healing. Chemicals that initiate and trigger MCS must also be recognized and restricted by regulators, both to accommodate and importantly, to prevent further adverse events in the population. Those responsible for medical education need to encourage and guide practicing physicians now, in order to improve the provision of evidence-informed and appropriate support necessary for their MCS patients and to be able to properly advocate on their behalf, when necessary.

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