



Review article

Olfactory dysfunction in Multiple Sclerosis: A scoping review of the literature



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ABSTRACT

Objective: Olfactory dysfunction in Multiple Sclerosis (MS) has been reported, but results have been inconsistent. In this review we describe, synthesize, and interpret the existing literature on olfactory dysfunction in Multiple Sclerosis and identify gaps in the current level of knowledge.

Methods: The study design was a scoping review of the literature covering several study designs. Systematic Searches of the PubMed, CINAHL, Cochrane Library, Web of Science, PsycARTICLES, PsycINFO and Google Scholar databases were conducted that included key words related to Multiple Sclerosis and Olfaction Disorders. Literature that met the criteria of pertaining to both Multiple Sclerosis and olfactory dysfunction was identified, with the aim of providing an overview of the extent and types of research available in this area.

Results: Sixty-one reports were identified in the initial search, with 40 meeting the study criteria. Twenty-five clinical studies were included. Among them, 23 studies measured for olfactory dysfunction in MS patients, ten evaluated MRI correlates of olfactory dysfunction, and five evaluated neurophysiology correlates of olfactory dysfunction. Six of the included studies were abstracts. In addition, thirteen reviews/commentaries and two case studies were included. The majority of the studies identified some degree of olfactory dysfunction in MS patients, and various aspects and correlations with olfactory impairment were observed.

Conclusions: The overall weight of the literature suggests that olfactory dysfunction may occur in MS. Although there is variability in reported frequency, the more robust studies suggest the prevalence is significant, ranging from 20% to 45% in the MS population. Despite this, the mechanisms are unknown and the clinical relevance of this association has not been well explored. Interesting findings relating mood disorders, cognition, and olfactory dysfunction in MS are also suggested but remain poorly developed and require further investigation. Future studies are also warranted to understand the dynamic changes in olfactory function during the course of MS, and to correlate olfactory function with relapses/disease activity.

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Contents

1. Introduction	2
2. Methods	3
2.1. Data sources and searches	3
2.2. Review of identified studies	3

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3.	Results	3
3.1.	Diagnosis of MS	4
3.2.	Measurements of olfactory dysfunction	4
3.2.1.	Clinical studies of olfactory dysfunction	4
3.2.2.	TDI and related testing	4
3.2.3.	UPSIT and related testing	4
3.2.4.	Other Olfactory Testing	4
3.3.	Other Clinical Measurements	4
3.3.1.	Studies using MRI imaging	6
3.3.2.	Studies using electrophysiological testing	6
3.4.	Reviews and commentaries	6
3.5.	Case studies	6
3.6.	Gap analysis and future directions	7
4.	Discussion	7
5.	Conclusions	8
	Author Roles	8
	Financial disclosures	8
	Disclosure	8
	Acknowledgments	8
	Appendix	8
	References	8

1. Introduction

Multiple Sclerosis (MS) is a chronic neurologic disorder typically characterized by clinical relapses and remissions, which can result in disability ranging from minor deficits to severe invalidity (Erb et al., 2012). Several pathophysiological mechanisms are thought to be involved that include axonal/neuronal damage, demyelination, inflammation, gliosis, remyelination and repair, oxidative injury and excitotoxicity, and/or alteration of the immune system (Barresi et al., 2012).

Olfactory disturbances are one of the most common early manifestations of certain CNS neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Lewy body disease (Silva et al., 2012). Although not a commonly reported symptom of MS, olfactory dysfunction can be a rare first symptom of MS (Bartosik-Psujek et al., 2004) and some investigators report that up to two-thirds of MS patients exhibit demonstrable smell loss (Pinching, 1977). There has been considerable controversy, however, regarding the presence of olfactory dysfunction in MS, and the findings from several studies have been variable and mixed, with some authors denying any olfactory alterations in MS (Ansari, 1976).

Initial pathologic reports suggested that the olfactory tracts and bulbs were spared in MS, and that this might relate to the anatomical properties of myelin basic protein (Lumsden, 1983). Early researchers were unable to find any plaques in the olfactory tract of MS patients (Zimmerman and Netsky, 1950), but subsequently others have shown convincing evidence of demyelination in the olfactory tract (McDonald, 1986; Peters, 1958; Hawkes and Doty, 2009). A recent comprehensive study on this topic explored olfactory pathology in three demyelinating diseases including MS, neuromyelitis optica, and acute disseminated encephalomyelitis and compared these to herpes simplex virus encephalitis, Alzheimer's disease, and non-neurologic controls (DeLuca et al., 2014). Olfactory bulb/tract demyelination was seen frequently in all three demyelinating diseases and was absent in the other groups. The highest prevalence of olfactory bulb/tract axonal loss was found in the MS group (12/17 patients; 71%) and its presence correlated with the extent of demyelination in the brain, particularly the inferior frontal cortex.

Olfactory function is not localized only to the olfactory bulb and tract. Functional MRI (fMRI) studies have implicated function of

the orbitofrontal region and the cerebellum, visual and cingulate cortex, and the insula in the perception and processing of various odorants (Yousem et al., 1997; Fulbright et al., 1998). As MS involves multifocal damage to the central nervous system, and olfactory functions may involve distributed neural regions and networks with multiple areas and pathways (Doty, 1997), it would be reasonable to postulate that an olfactory deficit may be a marker of widespread dysfunction in the brain.

It has been suggested that olfactory dysfunction may correlate with relapses and disease activity (Lutterotti et al., 2011) and can be an early indicator of disease progression in MS (Barresi et al., 2012). Currently, other than MRI measures, which can be costly and time-consuming, there is a lack of clinically useful biomarkers to assess these phases of disease in MS (Comabella and Montalban, 2014). The use of clinical disability scales may inadequately reflect the patient's true or complete disease state (Amato and Portaccio, 2007; Cohen, 1998). Therefore, the discovery of a reliable clinical marker or surrogate for disease activity or progression is an important goal. Whether or not measurements of olfactory function could play such a role has yet to be determined, but is worthy of investigation as this is a relatively quick and inexpensive bedside tool. Therefore, a broad literature review examining olfactory dysfunction in MS could provide important insights into this topic as well as identify areas for future research.

The objectives of this study were to evaluate the literature on olfactory dysfunction in MS and identify gaps in the existing literature by performing a scoping review, which is a technique aimed at mapping relevant literature in a broad field of interest where several study designs may be represented (Arksey and O'Malley, 2005; Landa, 2011). Such reviews can be used to develop an overview of the existing evidence and to help identify gaps in the literature for potential future studies. These reviews are appealing since they produce a broad map of the evidence (Armstrong et al., 2011). Though the methodologies of a scoping review, systematic review, and meta-analysis are similar, the scoping review embodies the larger literature landscape and can often be the first step in performing a larger systematic review (Arksey and O'Malley, 2005).

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