Does The Occurrence of Sleep Disorder or Deficits in Olfaction Provide an Early Indication of Neurodegeneration and Subsequent Dementia?

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It is now well recognized that impairments in olfaction often provide the first sign of neurodegenerative disorders such as Alzheimer’s (AD) and Parkinson’s disease (PD) [1-5]. Recent studies have also revealed that olfactory deficits are observed in individuals living with psychiatric disorders including depression [6], and schizophrenia [7]. Accordingly, it is hypothesized that abnormalities in brain function may account for difficulties in the detection odor or identification of specific classes of odor. The first indications of an impairment in olfaction are often manifested as a difficulty in the recognition of specific odors whereas the detection threshold for odor does not differ from age-matched controls [5]. A subsequent progression to anosmia involves further impairment of the classification of odors, and finally an inability to detect the presence of an odor [5]. The ability to identify a specific odor is quite complex, involving as it does the capacity to encode and store in memory past perceptions of a unique volatile chemical signature, which can then be and recalled and categorized by a single name. Olfactory memory encoding and storage involves neural activity within the hippocampus and parahippocampus, and recall and recognition of the memory of a specific odor engages a neural network linking between amygdala-hippocampus and orbitofrontal cortex [8,9]. As with other forms of prospective memory function, the process by which specific odors are identified may be referred to as ‘traveling back to the future.”

The anatomical pathways involved in processing of odor are amongst the best characterized neural systems in the forebrain involving receptors on the terminal regions of olfactory within the nasal mucosa, which in turn project via the olfactory tubercle and piriform cortex, to structures within the limbic region including entorhinal cortex, amygdala and hippocampus [10]. It is now known that these olfactory limbic structures are damaged in the early stages of PD and AD, as well as psychiatric disorders also linked to neurodegenerative disorders [1-5, 6]. Accordingly, deficits in olfactory perception may reflect this underlying process of neurodegeneration. Related changes may include difficulty with the recall of emotional memory, a lack of appropriate emotional responses, as well as subsequent problems in cognition and social interactions.

In light of recent evidence, it is important to recognize that deficits in olfaction are often co-morbid with disturbances in sleep behavior including changes in the sleep cycle and insomnia [11]. Abnormalities in rapid eye movement (REM) sleep stage are observed in early stage of Parkinson’s disease [12,13]. REM sleep is characterized by rapid eye movements, cortical activation, vivid dreaming, skeletal muscle paralysis and muscle twitches, and is mediated by a distributed network within the brainstem, hypothalamus and limbic regions, including a key role for the amygdala in the regulation of REM sleep [14]. Disturbance in the neural control of REM sleep is linked directly to REM sleep behavior disorder (RBD), characterized by dream-enacted behavior associated with skeletal muscle atonia during REM sleep [15]. Schenck et al. [13] report that 11 out of 29 patients with RBD developed a parkinsonian disorder at a mean interval of 3.7 years after RBD onsets. Other findings indicate that RBD may proceed dementia or PD in 66.7% of patients [12]. When these observations are considered in conjunction with the finding that olfactory impairment has been observed within a similar time frame (7 years) prior to diagnosis of PD [16], it is tempting to speculate that both these impairments in olfaction and RBD may reflect common mechanisms of neurodegeneration.

In our previous case study, we examined decision-making skills, facial expression recognition which served as an index for social cognition, olfaction, and dopamine positron emission tomography imaging in RBD patients [17]. These detailed measures revealed a patient with impaired social cognition and decision-making skills, as well as impaired olfactory identification, and reduced dopamine positron emission tomography imaging indicating striatal terminal loss. Braak et al. [18] suggested that impairment of the amygdala and striatum occurs at the same stage as α-synucleinopathy, and we hypothesized that symptoms of RBD may follow the same progression as is the case for PD patients.

Given the role of amygdala in both REM sleep regulation [14,17] and deficits in olfaction [8,9,10] noted above, perhaps pathophysiological changes within the amygdala may contribute to abnormality in both RBD and olfaction. Indeed, Maquet et al. [19] postulate that activation of the amygdala complex during REM sleep contributes to memory processing that involves a functional link between the amygdala, the hippocampus formation and cortical areas. Accordingly, disturbance of REM sleep observed in RBD may be causally related to impairment of cognitive, social and memory tasks [17].

At this juncture it is difficult to specify whether the observed deficits in olfaction, as distinct from sleep disorder may provide the earliest signal of impending cognitive dysfunction. While 80% of PD, AD and other neuro generative disorders including patients with Type 1 Myotonic dystrophy have olfactory deficits, the majority are unaware of their condition [5]. In contrast, with respect to a sleep disorder, individuals who become self-aware of their condition or are informed by a family member often seek medical assistance. The extent of the co-occurrence of olfactory deficits and sleep disorders such as RBD remains to be determined, and it must also be noted that the occurrence of olfactory deficits of unknown origin with or without RBD may precede PD. Nevertheless, proof of their co-occurrence may provide a more accurate and reliable indication of early stages of neurodegeneration and the possible co-occurrence of mild cognitive impairment.

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