Olfactory Neurotechnology: A Perspective on Awareness Biomarker Discovery for Mild Cognitive Impairment and Dementia

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Abstract

Early detection of dementia is crucial. We propose a novel approach using neurotechnology to assess olfactory awareness, hypothesizing that deficits in this domain precede traditional cognitive decline markers. Employing EEG and EBG to monitor olfactory bulb activity during scent presentation, we aim to capture real-time neural responses. This shift from scent recognition to awareness provides deeper insight into cognitive processing in mild cognitive impairment and dementia, potentially enabling earlier and more sensitive detection.

Keywords: EEG; olfactory neurotechnology; MCI and dementia biomarker

Introduction

Dementia is one of the most significant global health challenges, with the number of people living with dementia worldwide continuing to increase while the age of those at risk is decreasing (Livingston et al., 2024). Cognitive decline is closely associated with dementia and is characterized by deficits in cognitive functions, including working memory and awareness (Saunders & Summers, 2010). Impaired awareness has been identified as a potential diagnostic marker for dementia, underscoring its importance in healthcare (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005). Researchers describe awareness as a flexible process that starts with essential alertness and sensing of the environment and extends to more complex abilities, like monitoring one's behavior and understanding oneself in social situations (Clare, Marková, Verhey, & Kenny, 2005). Moreover, impaired olfactory function has been identified as a possible early indicator in the diagnosis of Alzheimer's disease (Murphy, 2019). Researchers investigated the relationship between olfactory function and working memory in relation to assessment correlates in healthy young individuals (Ninenko, Kleeva, Bukreev, Gritsenko, & Lebedev, 2022; Kasprzak, Niewińska, Komendziński, Otake-Matsuura, & Rutkowski, 2024; Morozova, Bikbavova, Bulanov, & Lebedev, 2023). Building upon the established link between attention and working memory (Sklar, Kardosh, & Hassin, 2021), we posit that a certain level of conscious awareness is required for working memory to operate effectively. For the purpose of the current study we define olfactory awareness as neural capacity to detect and process olfactory stimuli, regardless of conscious perception. This process is characterized by subjective sensory experience or measurable neural responses in brain activity patterns. Under controlled experimental paradigms, olfactory awareness is measured objectively using neurotechnological methods such as electroencephalography (EEG) and electrobulbography (EBG). Specifically, EBG technique enables the measurement of signals from the olfactory bulb (Iravani, Arshamian, Schaefer, Svenningsson, & Lundström, 2021). This study proposes the integration of olfactory stimulation within a neurotechnology experimental protocol designed to evaluate awareness and assess dementia-related cognitive decline through the combined analysis of EEG and EBG modalities. This paper outlines the development of a fully automated neurotechnology application for predicting dementia onset or progression, derived from the established Sniffin' Sticks Test (SST) by Kobal et al. (1996). The following section details the methodology used in this extension, and the final section summarizes the proposed research perspective and its implications.

Methods

We propose to advance olfactory neurotechnology by developing a scent-based paradigm that investigates olfactory awareness, which serves as an early indicator of dementia onset (Saunders & Summers, 2010). Findings from previous studies have shown that olfaction and the classical oddball paradigm form a practical approach for investigating executive function, explicitly working memory (Kasprzak et al., 2024). Leveraging olfaction in various experiments investigating cognitive function, an intriguing next step is integrating smell with odor awareness. This experimental method is based on two olfactory tasks. The Sniffin' Sticks Test (SST) is a comprehensive assessment that enables the evaluation of various aspects of olfactory sensitivity and is one of the most widely used tools for olfactory testing worldwide (T. Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). Experiments involving olfactory stimulation focus on olfactory awareness, with brain responses monitored using neurotechnology techniques such as EEG and EBG. These recordings enable precise measurement of both cortical and olfactory bulb activity in response to odor stimuli, allowing for the identification of early neural alterations preceding cognitive decline. Shifting the focus from working memory investigation to olfactory awareness offers a novel approach to identifying early indicators of dementia. The study received approval from the Institute of Psychology Ethical Committee for Experiments with Human Subjects at the Nicolaus Copernicus University in Toruń, Poland, and adhered to The Declaration of Helsinki's ethical principles.

The proposed new paradigm uses SST to assess olfactory abilities in participants, which evaluate odor identification, discrimination and threshold (Kobal et al., 1996). The olfactory detection threshold is assessed using the SST, following a standardized staircase procedure with n-butanol (a widely used reference substance for measuring olfactory sensitivity) (Oh et al., 2019) or 2-phenylethyl alcohol (rose-like odour) (Sipos, Galambosi, Bozóki, & Szádoczki, 2025) as the target odorant. In this study sixteen concentrations of 2-phenylethanol in rose-scented stick are prepared, ranging from 4% to 0.00012% (T. Hummel et al., 1997). During the task, each concentration is presented in triplets of pens, consisting of one odorant pen and two odorless solvent pens. The participant is asked to identify which pen contains the odor. Each pen is presented for approximately three seconds, positioned about 2 cm from each nostril in sequence. Triplets of pens are presented at intervals of $20 \sim 30$ seconds. The participant keeps their eyes closed throughout the task to eliminate visual cues. The procedure begins at the lowest concentration. The concentration increases step by step until the participant correctly identifies the odorant pen for the first time. After this first correct response, the direction of concentration changes — decreasing after correct identifications and increasing after errors — following the staircase protocol. This continues until seven turning points are reached. The olfactory threshold is then calculated as the average of the last four turning points (C. Hummel et al., 2012). SST provides information about each participant's olfactory function at the perceptual level, as responses are given only when the participant detects a specific odor. Notably, the test highlights that while olfactory receptors may not always register the odor or the participant may not consciously respond, the brain can still process olfactory information. The results of the SST for each participant are then used to first classify the quality of their sense of smell at the perceptual level and serve as a strong basis for comparison with the experiment monitoring brain responses. In connection with the above, we propose a new olfactory paradigm inspired by the SST that investigates the olfactory threshold while monitoring brain responses, offering more accurate insights into odor perception.

We propose to investigate olfactory awareness as a paradigm with fewer scents but different intensities compared to previous studies (Kasprzak et al., 2024). In this experiment, olfactory stimulation is delivered using the ETT Olfactometer 2^s. The device includes seven channels: six for odor delivery and one flush channel with an odorless solution. An internal air pump generates airflow, directing odorants from bottles through an application tube positioned in front of the participant's nose. The olfactometer is connected to a laptop via USB and controlled using ETT Direct Control software with a custom Python 3.11 script developed in our project to interface with the software during the experiment. This study utilized four odorant channels: three containing a rose scent at different concentrations (targets) to modulate intensity and one without an odor solution (distractor). A flush (odorless)

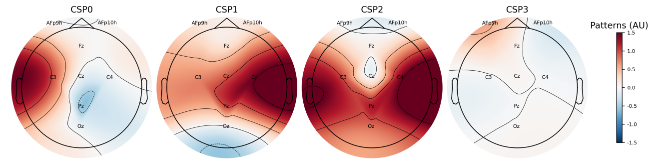

Figure 1: CSP weights on EEG channels representing three odorant levels and no aroma stimuli.

solution was used to mix airflow with the scent from the active channel during stimulation. A single odorant was used in three different intensities. The default stimulus airflow rate was 5.5 L/min, with a second intensity adjustment lowered to 0.055 L/min made via the ETT Direct Control software and our Python script. Higher airflow rates correspond to higher odor intensities, and lower to weaker, respectively. In this study additionally, rose scent was used at three different concentrations: 0.185% (lowest intensity), 0.465% (medium level), and 0.835% (highest intensity). Each experimental trial consisted of a ten-second activation of one channel. After a short break, the second channel was activated. One of the channels delivered a scent at a specified intensity (target), while the other was an odorless channel serving as a distractor. All trials were presented in a random sequence. Each experimental trial consisted of a 4-second activation of the odorless channel and then one of the odor channels at a specified intensity. Participants were instructed to press a button as soon as they perceived the odor. This allowed both detection performance and reaction times to be recorded. Simultaneously, brainwave data is recorded using the Unicorn EEG headset (g.tec medical engineering, Austria). Eight channels were used: six EEG electrodes placed at Fz, C3, Cz, C4, Pz, and Oz, and two EBG electrodes placed over each eyebrow to record activity from the olfactory bulb. Following data acquisition, the recorded EEG and EBG time series were utilized to train machine learning algorithms. The primary goal of these algorithms was to establish a regression model for the ACE-III cognitive scores, with the aim of predicting the cognitive status of participants across the diagnostic categories of normal, mild cognitive impairment (MCI), and dementia.

Results and Discussion

Olfactory neurotechnology, integrating EEG and EBG, offers a novel and objective approach to early cognitive decline detection by focusing on olfactory awareness over traditional recognition. This framework precisely measures olfactory processing at cortical and olfactory bulb levels, capturing early neurophysiological changes linked to MCI and dementia. Our study, combining behavioral (Sniffin' Sticks) and neurophysiological assessments of olfactory awareness, showed strong alignment, validating this integrated approach for early diagnosis. Future work will involve further validation, advanced machine learning for predictive models, and longitudinal studies to refine risk assessment and guide targeted interventions in neurodegenerative disorders.

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