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Development of a VOC (Volatile Organic Compound) Measurement System to Identify Placebo Phenomenon in Emission Areas

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Abstract

VOCs (volatile organic compounds) can be used as a biomarker of placebo phenomenon, such as stress, panic disorder, health conditions, and many others. VOCs from the exhaled breath have different concentration levels that are also related to many health diseases. However, the use of VOCs as biomarkers in exhaled breath are very limited. Hence, this study aims to develop a novel e-nose (electric nose) system based on a VOC measurement system to identify placebo phenomenon in emission areas. For this purpose, a digital semiconductor VOC sensor and a microcontroller were used to detect VOC level. The developed system was tested inside a chamber for the initial calibration and comparation steps using fresh air and a comparator device. After calibration, the system was used to measure the VOC concentrations of 20 exhaled breath samples in the emission sampling areas (control and emission sources). In other sides, the VOC levels surrounding the emission areas were also measured using the comparator device. The placebo levels (PLS) of the exhaled breath samples were divided into PLS(-) or placebo negative and PLS(+) or placebo positive related to the placebo conditions. The sampling areas were divided into indoor and outdoor areas to identify the different placebo percentages and the dependence related to the emission levels. The results show that the emission levels of the emission sources are about 504-528 ppb, meanwhile, the control area (clean area) has <10 ppb of VOC levels. A higher VOC concentration, a higher PLS(+) percentage. The exhaled breath of PLS(+) samples contain >78 ppb of VOC levels, while PLS(-) samples has < 78 ppb of VOC levels ($p < 0.05$). It can be concluded that VOC concentrations in the emission sources has a potential to influence the placebo quantification in human psycological health. The developed e-nose system can be used to identify VOC levels as a biomarker of a placebo phenomenon.

INTRODUCTION

Air is a fundamental component or element of human life. Air also becomes a medium for human breathing or the respiratory system. Fresh air or clean air plays an important role in generating a life balance, such as photosynthesis (carbon dioxide - oxygen), combustion (oxygen - carbon monoxide - other gasses), and many others [1]. Several studies have shown that air consists of many gasses, such as nitrogen, oxygen, carbon dioxide, argon, and many others [2]. Due to its important role, air should be found in a fresh condition with zero emission.

Emission in the air is also known as an air pollutant. Air pollutants are generally classified as gaseous [3] and particulate emissions [4]. These pollutions are also related to the volatile organic

compound or VOC element that decreases the fresh air quality index [5]. In contrast, polluted air can be related to several health diseases and environmental issues. This emission is specific to VOC as a group of organic compounds that easily float and are volatile in the Earth's atmosphere [6]. There are more than 2000 VOCs that have been identified. However, more than 1000 VOC types are considered as exhaled breath components [7]. Several VOCs are known as carcinogenic agents in human health [8], including benzene and formaldehyde [9]. VOCs are generated from many activities, including combustion, mechanical, cooking, painting, etc. A study shows that long-term exposure to VOCs is related to coughs and sore throats [10].

In human breath, VOCs are found to correlate with various respiratory diseases. VOC levels between healthy people and people who suffer from chronic obstructive pulmonary disease, asthma, and interstitial pneumonia are significantly different [11]. These differences may be related to the different metabolic systems in the body that contribute to abnormalities or several symptoms. For example, the VOC levels in the exhaled breath of ulcer samples are higher than in healthy samples [12]. Interestingly, this condition is not instantly detected or diagnosed. In the psychological aspect, this condition is also found as a placebo phenomenon.

A placebo is a medical or psychological intervention designed to provide no therapeutic effect. The placebo effect has a focus on the mind-body connection. A person who is unable to overcome emotional symptoms due to psychological stress will experience psychosomatic symptoms such as stomach ulcers, headaches, shortness of breath, and so on. Suggestions and beliefs will stimulate positive thoughts and the belief that the body will feel better or healthier, and the disappearance of psychosomatic symptoms, thereby influencing the production of endorphins in the brain, which helps to heal [13]. Although the placebo response has not yet been fully explained in terms of the underlying mechanisms, there is strong evidence showing that placebos improve brain structure. It is not just a subjective symptom report but occurs through actual functional changes [14].

The placebo effect is not a single phenomenon but rather consists of various processes that may vary depending on the situation and person. Belief expectations and the therapeutic environment can cause real physiological changes in the body, such as the release of neurotransmitters and changes in brain activity, suggesting that placebos can have measurable effects in relieving pain [15]. This background becomes a fact that there is an urgent requirement to develop a novel placebo identification method, such as by using a specific VOC biomarker. In line with this, this study aims to develop a novel e-nose system based on a VOC measurement system to identify placebo phenomena in emission areas.

METHODS

Samples. This study used ten exhaled breath samples for each emission area (n = 10, population = 20). There was one control (clean room, C_0) and two different emission areas: a laboratory (C_1) and a cafe (C_2). These areas were chosen due to the high VOC levels measured in these areas. All the participants regularly stay and work in these areas every day (>4 hours per day). Besides, 30 exhaled breaths from different and classified participants were collected as the gold references for PLS(-) and PLS(+).

Calibration and Comparison. This study used a digital semiconductor VOC sensor, a suction pump (flowrate v = 180 cm/s), a sensor box, and an Arduino Uno microcontroller board as the e-nose system. This system was used to measure VOC levels (C) in the exhaled breath of the samples (Figure 1). The e-nose system was connected to a clean chamber (volume V = 4,410 cm^3) for the calibration and comparison processes. The calibration process was conducted using fresh air inside a chamber (the air was filtered using a HEPA filter) [5], while the measured concentration (C) was collected for t = 100 s (sampling interval = 5 s). For the comparison process, the e-nose system and a comparator gas were placed inside a chamber that was filled with HCHO (formaldehyde) gas (40-100 ppm). The detected concentrations were collected for 100 s per 5 s of the interval time.

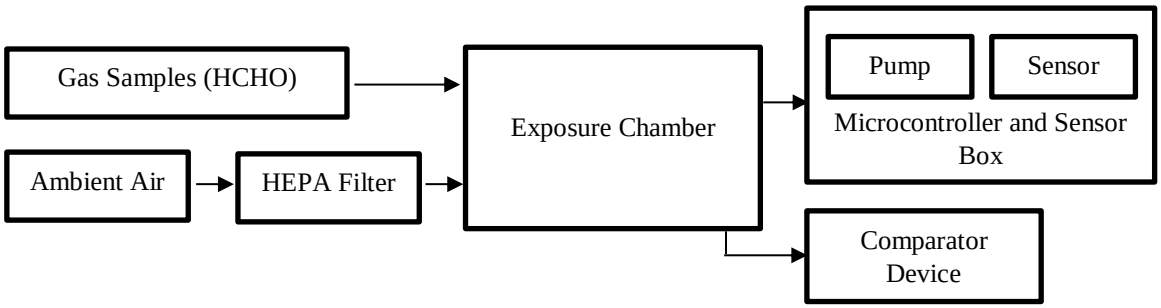

Figure 1. The schematics of the system calibration and comparison [16]

Exhaled Breath Sampling and Emission Measurement. Breath sampling was conducted by injecting the breath samples into the developed system for 5 seconds. Then, the VOC level inside the breath was analyzed using the system. The VOC concentration data was interpreted as C_s (in the unit of ppb). The concentrations were interpreted as a breath profile of the VOC components and were classified into PLS(+) and PLS(-). PLS(+) or placebo positive is defined as a person who has no psychological problem on the sampling day but has an illness history. PLS(+) criteria were divided into PLS(+)N (having psychological problems and health problems on the sampling day) and PLS(+)P (having no psychological problems but having health problems). PLS(-) has no psychological problems and no illness history [14].

In the last step, the number of PLS(+) or PLS(-) samples were quantitatively analyzed and interpreted as a percentage (%) using Eq. (1).

$$\%\text{PLS} = \frac{Total\ of\ PLS(+)\ or\ PLS(-)}{Population} \text{ x } 100\% \quad (1)$$

Besides, the emission concentration on the surrounding sampling areas (C_1-C_5) was measured using the comparator device. After the sample concentration data collection, an ANOVA test was carried out to verify the differences in VOC levels between each group (p-value).

RESULTS AND DISCUSSION

Calibration. Figure 2 depicts the indoor calibration results using filtered ambient air inside a chamber. It can be seen that the orange dots (comparator device) have an average value of 52±19 ppb, representing clean, fresh air. The maximum value is <100 ppb. This maximum value is not significantly different from the average concentration obtained from the e-nose system that has been developed (blue dots, 29±14). These conditions show that clean air quality was well obtained using the HEPA filter, and the developed system has good and calibrated measurement data related to a low level of VOC concentration.

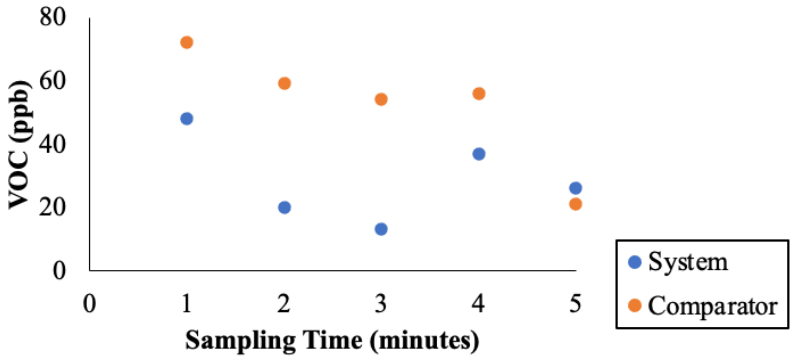

Figure 2. VOC concentration measurements using filtered ambient air

Comparison. Figure 3 shows the results of the HCHO measurement using the e-nose system. The comparison was conducted using four different HCHO concentrations: 40-100 ppm. It can be

seen that the system has good linear performance. The data show that the highest HCHO concentrations (as one of the VOC types) refer to 525 ppb (the maximum sensor's range is 1156 ppb), while the lowest one is 0 ppb. The linearity of the developed system is >0.89. These results show that the developed e-nose performs well in measuring HCHO concentration in the span of 525 ppb with an HCHO gas.

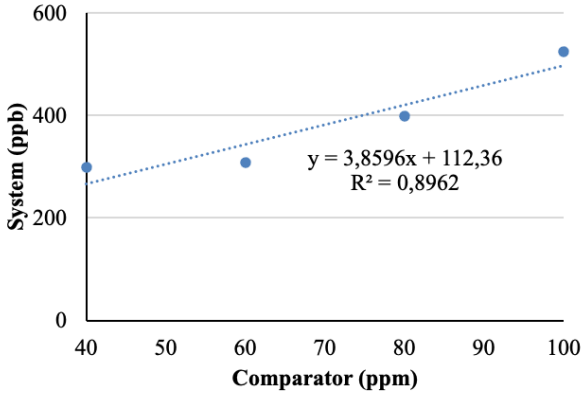

Figure 3. Comparison between the developed system and comparator

On-site VOC Measurements and Placebo Percentage. Figure 4 depicts the measurement results of each sampling site (C_0-C_5). It can be seen that each sampling area has different VOC levels. The lowest value is obtained at the laboratory as the indoor room. This area has a closed system with a full air conditioner system. However, this area is regularly used for work and research. That is why this room still has a high VOC level. The levels of VOCs are about 482-515 ppb. The average VOC concentration is 504±12 ppb. The outdoor area, the cafe, has a larger VOC level. The cafe area's emissions are about 518-538 ppb, with an average concentration of 528±7 ppb ($p < 0.05$). The different emission levels may influence the placebo conditions. It can be seen that there is a significant difference between PLS(+) and PLS(-) percentage levels in indoor and outdoor areas.

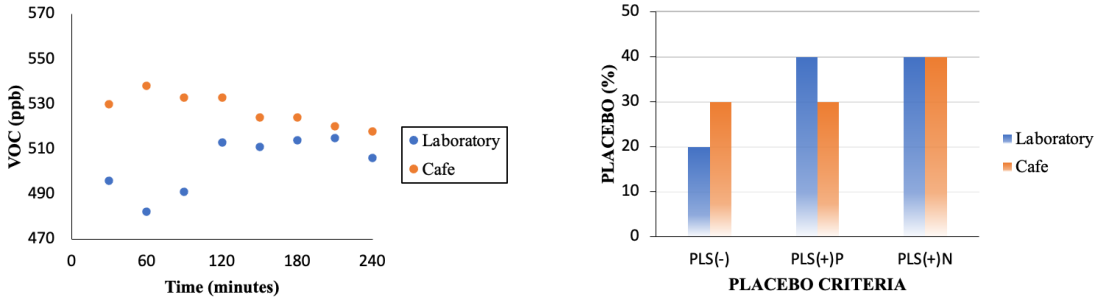

Figure 4. Placebo percentage in different areas and VOC concentrations

The resulting data indicate that there is little difference between the non-placebo (PLS(-)) and placebo-positive or PLS(+)P samples. As seen in Figure 4, the indoor area has a lesser PLS(-) percentage than the outdoor area. However, the PLS(+)P percentage is highly found in the laboratory area. These data indicate that indoor room with cleaner air has a positive vibe that triggers a placebo phenomenon. Since both areas have high VOC levels, it might influence the psychological conditions.

In the non-placebo samples, a higher percentage is found at the cafe. In contrast, similar values are obtained in the PLS(+)N category, indicating that long-term exposure to VOC correlates with health or psychological conditions. Long-term exposure to air pollution, such as nitrogen dioxide (NO_2), particulate matter (PM), and VOCs from vehicles and industrial activities is associated with an increased risk of mental disorders such as anxiety, depression, and cognitive decline. Continuous increases in exposure to pollution worsen mental health, especially among people living in areas exposed to heavy pollution. Additionally, air pollution triggers physiological and psychological stress

responses, further exacerbating its impact on overall health [17]. The results of this study also indicate that VOCs can be used as a unique and distinctive biomarker. A study successfully validated five types of VOCs as biomarkers in the diagnosis of acute respiratory distress syndrome through exhaled breath analysis. The five types of VOC are, 1-methylpyrrole, 1,3,5-trifuorobenzene, methoxyacetin acid, 2-methylfuran, and 2-methyl-1-propanol. This study also identified that the composition of VOCs in patients with acute respiratory distress syndrome was different from that of healthy individuals, although the concentration of these VOCs was lower in acute respiratory distress syndrome patients [18]. Other research also shows the potential of VOCs in respiratory air as biomarkers of cancer [19]. Breath analysis with e-nose technology used in research can differentiate VOC profiles in CRC (Colorectal Cancer) patients. There were differences in exhaled VOC profiles between patients analyzed with e-nose.

Other research proves the potential of VOCs as biomarkers via e-nose applications. This research shows that the e-nose can differentiate the VOC profile in exhaled breath from IPF (Idiopathic Pulmonary Fibrosis) patients from healthy samples and COPD (Chronic Obstructive Pulmonary Disease) patients. VOC levels in exhaled breath differ from person to person, indicating its potential as a biological response [20]. The results of this research that have been obtained and are supported by several previous studies prove that VOCs can be used as biomarkers for certain diseases, including their potential to identify placebos. On the other hand, further studies are still needed in the future for further diagnostic validation of e-nose in placebo cases.

CONCLUSION

There is a significant difference in VOC concentrations between indoor and outdoor areas. The outdoor area has a VOC concentration of 528±7 ppb. The indoor area has a VOC concentration of 504±12 ppb, indicating cleaner air than the outdoor area. Human exhaled breath can consist of 0 ppb to 1085 ppb, depending on many factors, including psychological conditions. The indoor area has a lesser PLS (-) percentage than the outdoor area. PLS(+)P percentage is highly found in the indoor area. These data indicate that indoor room with cleaner air has a positive vibe that triggers a placebo phenomenon. It can be concluded that VOC concentrations in human exhaled breath can be used as a biomarker of a psychological condition, such as a placebo effect. However, further study and analysis should be conducted.

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