Biological sensor detection of volatile organic compounds associated with post-traumatic stress disorder in the blood plasma of major depressive disorder patients

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Abbreviations: post-traumatic stress disorder (PTSD), major depressive disorder (MDD), gas chromatography (GC), volatile organic compound (VOC), Patient Health Questionnaire (PHQ-9), Penn Vet Working Dog Center (PVWDC), three-alternative forced choice (3AFC), Primary Care PTSD Screen (PC-PTSD-5),

Abstract

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric illness that frequently co-occurs with major depressive disorder (MDD), which can complicate accurate diagnostic attempts. No laboratory-based test exists for PTSD, and overlapping symptoms can lead to misdiagnoses. An emerging avenue for diagnostics of various medical conditions involves the use of volatile organic compounds (VOCs). This study used two trained detection dogs as biological sensors to assess the extent to which VOCs differentiate blood samples from patients with comorbid PTSD+MDD from those with MDD alone. After training on 84 demographically-matched sample pairs, two dogs completed five double-blind tests containing 10 test lineups. Each test lineup included one novel PTSD+MDD sample, one novel MDD sample, and one previously-trained MDD sample. On first trial encounter, Dog 1 correctly alerted to 8/10 PTSD+MDD samples and correctly passed 8/10 novel MDD samples and 4/5 previously-seen MDD samples, performing significantly above chance. Dog 2 performed above chance, but with a lower accuracy (alerted on 4/10 PTSD+MDD samples, correctly passed 4/10 MDD-only samples and 5/5 previously-seen MDD samples). However, on exclusively novel samples, only Dog 1 was above chance; however, just Dog 1's performance alone demonstrates that differentiation at 80% sensitivity and specificity via VOCs is possible. These findings provide preliminary evidence that PTSD+MDD may be associated with a detectable VOC signature in blood plasma, which supports and endorses further development of VOC-based diagnostics.

Post-traumatic stress disorder (PTSD) is a severe psychiatric illness marked by recurrent intrusive thoughts, dissociative episodes, and heightened vigilance following trauma. Diagnosis currently relies on clinical interviews and self-report questionnaires, with no laboratory-based test available. Because PTSD symptoms often overlap with other psychiatric disorders, particularly major depressive disorder (MDD), accurate diagnoses can be challenging (Brady et al., 2000). In one study, nearly half of PTSD patients were initially misdiagnosed with MDD (Gates et al., 2012). This is not surprising given the high comorbidity rate; approximately 36% of individuals with MDD also meet criteria for PTSD (Campbell et al., 2007). People with comorbid PTSD and MDD may only receive the MDD diagnosis due to the comparatively lower frequency of PTSD (Campbell et al., 2007). Given the risk of missed diagnosis or misdiagnosis, examination of novel methods for PTSD diagnosis is crucial for accurate treatment.

One emerging topic in diagnostics is the detection of disease-associated volatile organic compounds (VOCs). VOC detection could aid in the development of fast, noninvasive, inexpensive early screening tools for a variety of different diseases. Studies have shown that VOC signatures can identify diseases including COVID-19 (Grandjean et al., 2020, Angeletti et al., 2021, Eskandari et al., 2021, Essler et al., 2021, Grandjean et al., 2021, Gokool et al., 2022), different cancers (Pickel et al., 2004, Willis et al., 2004, Moser and McCulloch, 2010, Cornu et al., 2011, Sonoda et al., 2011, Edwards et al., 2017, Murarka et al., 2019, Essler et al., 2020, Kane et al., 2022), metabolic states like hyper- and hypoglycemia (Hardin et al., 2015, Wilson et al., 2019), and arousal states like psychological stress (Wilson et al., 2022, Wang et al., 2025).

Current VOC detection studies tend to focus on diseases with biologic diagnostic criteria (e.g., cancers, COVID-19) as opposed to symptom-based diagnostic criteria (e.g., psychiatric conditions). However, recent work has shown that people with major depressive disorder (MDD)

emit different VOCs in their breath compared to healthy controls, and that those differences are classifiable with high accuracy using gas chromatography and other analytic approaches alongside machine learning (Lueno et al., 2022). These VOCs may reflect shifts in inflammation, metabolism, or microbiome-related processes, all of which have been shown to be linked to depression. Furthermore, other studies have reported altered VOCs in other mental illnesses like schizophrenia, which could suggest that mental health conditions more broadly may have unique VOC signatures. Thus far, no studies have explored PTSD, and very few studies have explored anxiety disorders specifically as opposed to transient stress states.

Trained detection dogs serving as high-performing biosensors can detect VOCs from blood samples and other biological material, distinguishing between samples from those impacted by the target disease versus healthy samples and samples from patients with other illnesses. Dogs' detection accuracy often outperforms chemical analytic techniques (Kybert et al., 2020, Gokool et al., 2022). While there are many methods of examining VOC-based diagnostics, current technology rarely outperforms trained detection dogs in identification of VOC differences between disease states. Dogs excel at generalizing learned category information to novel types of samples; for example, gas chromatography (GC) VOC analyses of blood plasma and nasal secretions from patients with sinonasal inverted papilloma (SNIP) indicate that there are two completely different VOC disease profiles for these sample types. However, dogs trained only on plasma samples spontaneously alerted to nasal secretion samples from SNIP patients, suggesting that their ability to identify and generalize VOC profiles is superior to current analytical techniques (Mallikarjun et al., 2023).

Exploratory efforts with detection dogs can inform future advances in VOC detection technology, leading to improved diagnostic tools. Each detection dog serves as an individual

learning algorithm; each dog will often use different aspects of samples in the category learning process, allowing us to identify the robustness of the VOC differences. In an ovarian cancer detection study, headspaces from blood plasma samples were fractioned using micro-preparative gas chromatography into three groups of VOCs that eluted at different times, roughly corresponding to lighter, medium, and heavier compounds. Dogs were shown these different VOC groups alongside negative samples and distractors to potentially narrow down the VOCs signature to ovarian cancer. Different dogs showed different patterns of detection; one dog performed the best on the heaviest fraction, two on the middle fraction, one on the earliest fraction, and one dog struggled to discriminate any of the samples from the negative samples (Kane et al., 2022). Much like how different diagnostic tests for disease can have different accuracy and rely on different biomarkers, dogs can serve as individual tests for disease, allowing us to understand the potential sensitivity and specificity of a diagnostic test. Further, much like how poor performance by one proposed diagnostic test does not preclude high performance by another test, the dog that failed to discriminate the odor does not suggest that the diagnostic differentiation is impossible, given the other dogs' high accuracy. This dog may have had difficulty with differentiation for a multitude of potential reasons, from difficulty learning the odor to unrelated health issues impacting the dogs' attention or odor detection capabilities.

Proper diagnosis of PTSD can be difficult due to its overlap with other mental disorders. A noninvasive, biological diagnostic method would be helpful to assist in accurate diagnosis. The exploration of VOCs as a biological signature of different cancers and diseases has been increasing and is very promising for noninvasive diagnostics. This study aimed to assess 1) the extent to which trained detection dogs can identify the signature odor of PTSD+MDD patients

and differentiate them from patients with just MDD; and 2) the impact of demographic factors on PTSD+MDD prediction rates.

Methods

Participants

Two privately-owned detection dogs participated in this study (see Table 1). The dog owners provided informed consent prior to the dogs' participation. Prior to participation, dogs were trained to search a set of three olfactometers (described further in *Equipment*), find a target odor, and perform an at least 2-second stand-and-stare alert at the target odor. Continued inclusion in the study required that dogs remain in good health; if dogs displayed physical discomfort or signs of illness, the session was terminated, and dogs did not continue with study training or testing sessions until cleared.

In the middle of the study, one dog experienced a knee injury and subsequently underwent surgery. Training was paused until the dog's behavior and clinical signs suggested that she was healthy enough to continue training and testing.

Samples

This study used 198 banked blood plasma samples from veterans who participated in the PRIME Care study, a randomized clinical trial examining pharmacogenetic testing (Oslin et al., 2022). PTSD+MDD status was defined by endorsement of significant trauma and PTSD diagnostic symptoms; MDD was determined by clinician diagnosis supported by elevated Patient Health Questionnaire depression scale (PHQ-9) (Kroenke et al., 2001). Of the 198 total samples, 99 represented a joint PTSD+MDD diagnosis, and 99 represented an MDD diagnosis. Pairs of

PTSD+MDD and MDD-only samples were assembled based on sex, smoking history (current, former, never), and psychiatric medication status (taking medicine / no medicine). A total of 89 paired sample sets were used for training. An additional 10 sample sets were reserved for testing and were selected to reflect the full demographic range of collected samples.

For training and testing, each sample was aliquoted into three 20 mL clear borosilicate vials. Each vial contained 100 microliters each (a total of 300 microliters of each sample per session).

Equipment

Canine olfactometers are specialized devices designed to present controlled odor stimuli to dogs for the purpose of assessing their olfactory capabilities (Aviles-Rosa et al., 2023) Each olfactometer consists of an enclosed apparatus that delivers air containing odorants to a set of ports accessible to the dog. The system includes airflow regulation, precise odorant dilution mechanisms, and automated controls to ensure consistent delivery of odor samples. These features allow for highly controlled experiments to evaluate a dog's ability to detect specific odorants at varying concentrations. In this study, a three-alternative forced choice (3AFC) procedure was used. The 3AFC paradigm is a well-established methodology to assess odor recognition and categorization, and has been used extensively in studies of canine olfaction (Aviles-Rosa et al., 2021, Aviles-Rosa et al., 2023).

In each trial using the 3AFC method, dogs were presented with a three-olfactometer lineup, where two olfactometers contained distractor odors and one contained the target odor. The lineup was in a room out of sight from the handler to reduce any potential outside influence (see Figure 1). The dogs sniffed each olfactometer and indicated on the olfactometer containing

the target odor by performing a trained final response behavior (a stand-stare for at least 2 seconds). Correct responses were reinforced with a reward (e.g., food or a toy), while incorrect responses were ignored. After a trial finished, the system was flushed with air in preparation for the next trial.

Procedure

Training sessions

Training occurred in two phases: first, odor acclimatization, followed by odor category training. In the odor acclimatization phase, nine sessions with one target sample and one non-target sample were used to introduce the dogs to the PTSD+MDD odor profile. Dogs were reinforced for alerting on targets (PTSD+MDD samples) and ignoring non-targets (empty containers or MDD-only samples). Once dogs successfully differentiated the PTSD+MDD sample from the empty containers at least twice in the olfactometers, they were shown the PTSD+MDD sample alongside the MDD-only sample in the olfactometers to encourage category formation and odor differentiation. Dogs were progressed to the next stage of training after achieving a 90% accuracy across all trials completed in one session.

Subsequently, dogs participated in the odor category training phase. Each training session contained 8-15 lineups. Each training lineup (3 olfactometers) involved one target sample (PTSD+MDD) and two non-target samples (MDD-only). This stage of training aimed to introduce diverse novel samples to the dog to aid in their understanding of the PTSD+MDD sample odor signature. Training sessions were customized to facilitate dogs' learning; for example, if the dogs demonstrated performance decline across training trials in previous sessions, they received fewer training trials in subsequent sessions.

If dogs reached an 80% sensitivity and 80% specificity on novel samples across 5 odor category training sessions, they were tested in a double-blind setting on novel samples to demonstrate their understanding of the PTSD+MDD odor category.

Test Sessions

Over five test sessions, ten novel-sample test lineups were presented, embedded amongst training lineups containing previously-seen samples. Each test lineup contained one novel PTSD+MDD sample, one novel MDD sample, and one previously-seen MDD sample that had only been seen by each dog in one training session a month or more prior. Dogs had never encountered the novel samples prior to test. The inclusion of the previously-seen MDD sample ensures that there are no lineups in which dogs can use the process of elimination to determine the positive sample; if presented with a positive and two of the same negative, they can logically eliminate the two near-identical-smelling samples rather than using their learned categories. All testing was performed double-blind, such that neither the handler nor the experimenter in the room knew the location of the PTSD+MDD sample in each lineup.

Results

Training session accuracy

Prior to test, Dog 1 achieved the test benchmark (80% sensitivity and 80% sensitivity across 5 sessions) after 49 training sessions. Dog 2 met this benchmark after 44 training sessions.

Test accuracy

At test, Dog 1 alerted to 8 of 10 novel PTSD+MDD samples, passed 8 of 10 novel MDD-only samples, and passed 4 of 5 previously-seen MDD-only samples. Dog 2 alerted to 4 of 10 novel PTSD+MDD samples, passed 4 of 10 novel MDD-only samples, and passed 5 of 5 previously-seen MDD-only samples. A one-sample proportion test against chance level (33.33%) confirmed combined performance was significantly above chance, $\chi^2 = 22.563$, $p < .0001$. If the previously-seen MDD-only samples are excluded and the one-sample proportion test against chance level (33%) is done only on novel samples, combined performance was significantly above chance, $\chi^2 = 8.4$, $p = 0.0038$.

Dog comparisons

A generalized linear model was used to assess whether one of the dogs was significantly more accurate as a PTSD+MDD biosensor. Dog 1 was significantly more accurate than Dog 2, $z=2.039$, $p=0.041$. Dogs' accuracy was then examined individually using one-sample proportion tests against chance level (33.33%). Both Dog 1 and Dog 2 were significantly above chance at detection of PTSD+MDD samples compared to all MDD-only samples (Dog 1: $\chi^2 = 17.913$, $p < .0001$; Dog 2: $\chi^2 = 3.125$, $p = 0.039$).

When excluding previously-seen MDD-only samples, a one-sample proportion test confirmed Dog 1's performance was still significantly above chance (33.33%), $\chi^2 = 14.4$, $p < .001$. However, Dog 2's performance on only novel samples was not significantly above chance, $\chi^2 = 2.4$, $p = 0.061$.

Demographic analysis

A generalized linear mixed-effects model was used to examine the effect of Sample Status, Sex, Smoking Status, Medication Status, and Age on dogs' alert accuracy on each presented sample. Dog was included as a random intercept. The interaction between Sample Status and each of the demographic factors was included to assess whether certain demographic factors influenced dogs' alert behavior.

Samples presented to the dogs in training session 30 and beyond, as well as all test session samples, were included in the analysis; this was the timepoint, approximately halfway through the study, where dogs began showing correct sample categorization on their initial encounter with the sample. There was a significant main effect of Sample Status, $z=2.327$, $p=0.020$, such that dogs alerted more on PTSD+MDD samples than MDD-only samples. There were no other main effects of any demographic feature and no interactions, suggesting that sex, smoking status, medication status, and age did not have significant effects on dogs' sample categorization.

Discussion

This study assessed the extent to which blood plasma samples from patients with PTSD+MDD could be differentiated from blood plasma samples from patients with MDD alone using detection dogs as biological VOC sensors. Dogs' overall and individual accuracies were both above chance, but one dog outperformed the other. Individual demographic features of the samples did not significantly influence dogs' detection performance. This promising result suggests that there is a detectable VOC signature for PTSD+MDD samples that differentiates

248 them from MDD-only samples; further research and collaboration with engineers and chemists
249 can aid in the development of minimally invasive VOC-based diagnostic tools.

250 Given that psychiatric diagnoses are currently defined by symptom-based criteria as
251 opposed to biological criteria, the development of a biosensor that could detect a reliable
252 difference between samples from two overlapping groups with psychiatric diagnoses would be
253 extremely valuable. Dog 1's performance alone suggests that there is a robust VOC difference
254 between these diagnostic categories that can be detected at approximately 80% sensitivity and
255 specificity. This finding holds even though Dog 2 did not perform at the same level of accuracy,
256 as dogs can use different VOC profiles to differentiate samples, and the poor performance of one
257 dog does not invalidate the existence of the VOC signature detected by the other dog (Kane et
258 al., 2022). Dog 1's superior performance suggests that the specific VOC profile he used can
259 differentiate PTSD+MDD and MDD-only samples at 80% sensitivity and specificity.

260 Dog 1's test performances in this study approached that of established screening tools.
261 The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) achieved 89.7% sensitivity and 79.9%
262 specificity in veterans at a cut score of 3 (Bovin et al., 2021), and 100% sensitivity and 85%
263 specificity in civilians at a cut score of 4 (Williamson et al., 2022). Survey accuracy shifts
264 depending on the cut score point, highlighting limitations of self-report tools. While the
265 sensitivity and specificity in this study are not measured in the same way as the survey tools, the
266 values are comparable, which is a promising initial outcome. A VOC-based screening method
267 can offer an objective complement to surveys, which may reduce misdiagnosis, particularly in
268 comorbid cases.

269 Despite both dogs reaching the benchmark of 80% sensitivity and 80% specificity across
270 5 sessions in the training phase, Dog 2's performance dropped at test, while Dog 1's did not.

Many different external factors, including ambient temperature, diet, and medication, have been shown to potentially impact detection canine performance (Jenkins et al., 2018, Troisi et al., 2019). Importantly, Dog 2 was recovering from a knee injury during this study. Pain is known to significantly impact attention, learning, and memory in rats (Low, 2013) and humans (Moriarty et al., 2011). Since complex category learning and category perception tasks heavily recruit working memory and sustained attention, pain likely disrupts both learning and task performance. Further, pain can impact decision making; one study showed that pain can shift rats' normal task strategy to a more high-risk strategy (Pais-Vieira et al., 2009). Pain could similarly have changed Dog 2's standard search strategy to a more guess-prone strategy. Even mild discomfort or illness may impact dogs' detection; for example, in one previously-conducted study, a knee injury in a detection dog caused a significant drop in detection of a complex biological odor this biological odor category is highly complex, so performance may be disproportionately impacted by discomfort.

Importantly, this study does not propose that dogs should be used clinically; many different factors can impact both performance between different dogs and individual dogs' day-to-day performance. Rather, the dogs served as a proof-of-concept sensor for evaluating whether detectable VOC patterns exist. Identification of such patterns opens the door to scalable diagnostic tools. While dogs remain among the most sensitive biosensors available, their use is not feasible in most clinical settings.

This study provides preliminary evidence that PTSD+MDD may produce a distinct VOC signature in blood plasma. Future work should identify patterns of volatile compounds specific to diseases of interest and develop electronic or chemical sensors (e.g., e-noses, gas chromatography) that can identify these pattern signatures. Further, studies should replicate these

findings in larger, more diverse populations and use analytical chemistry to isolate relevant VOCs. If validated, VOC-based diagnostics could offer scalable, biologically grounded tools to improve psychiatric assessment.

Conflict of Interest Statement:

CMO is a founding member of VOCHealth. No funding was received from VOCHealth, and they did not have any role in study design, data review or manuscript preparation.

CRediT Statement

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Conceptualization-Lead, Data curation-Lead, Formal analysis-Lead, Methodology-Lead, Investigation-Lead, Visualization-Lead, Software-Lead, Writing - original draft-Lead, Writing - review & editing- Lead

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Ethics Statement

317 The animal study protocol was approved by the University of Pennsylvania Institutional Animal
318 Care and Use Committee (IACUC POAP number 807129).
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322 Tables

323

324 Table 1: Demographics and information about the detection dogs that participated in the Post

325 Traumatic Stress Disorder + Major Depressive Disorder detection study

Dog	Breed	Sex and Status	Age	Prior Known Odors
Dog 1	Belgian Malinois	M/I	2	Explosives, UDC
Dog 2	Dutch Shepherd	F/S	3	HR, UDC

326 NB: UDC = Universal detector calibrant, HR = Human remains, M = Male, F = Female, I =

327 Intact, S = Spayed

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329 Figures

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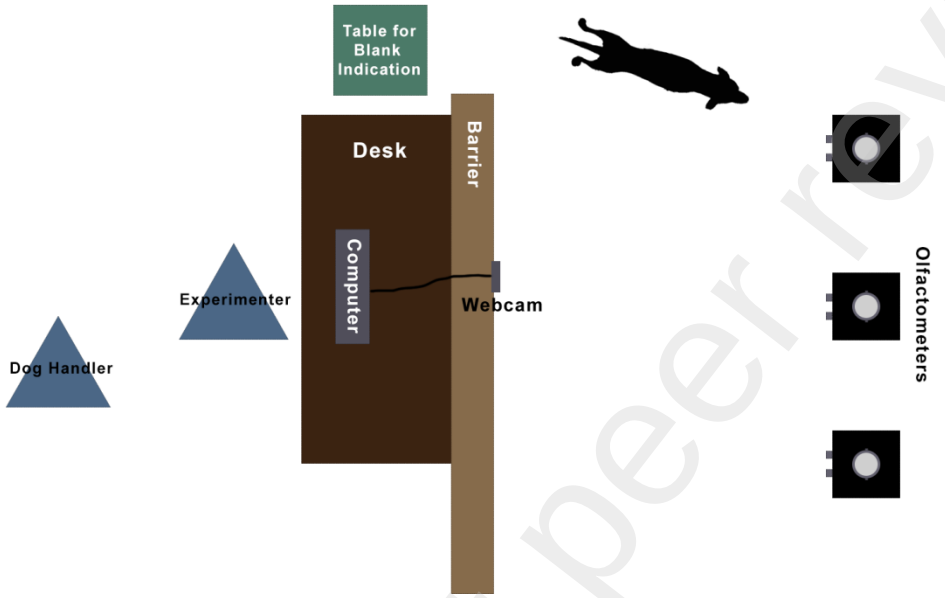
331 Figure 1: A diagram of the orientation of the olfactometers, dog, handler, and experimenter

332 within the testing room



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During the preparation of this work the authors used Perplexity to identify academic research articles that were relevant to this topic to read and potentially include (depending on relevance) in the introduction and/or discussion. Additionally, ChatGPT was used sparingly to provide title suggestions and for wording suggestions of certain sentences. After using these tools, the authors extensively reviewed and edited all content and take full responsibility for the content of the published article.

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