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Validation of a small cough detector

Manuel Kuhn [a,b] , Elif Nalbant [c], Dario Kohlbrenner[b], Mitja Alge [c], Alexandra Arvaji [b], Noriane A. Sievi MSc [b], Erich W. Russi [a] and Christian F. Clarenbach[a,b]

[a]*Faculty of Medicine, University of Zurich, Zurich Switzerland*

[b]*Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland*

[c]*SIVA Health AG, Zurich, Switzerland*

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Correspondence

Manuel Kuhn

Department of Pulmonology

University Hospital Zurich

Raemistrasse 100

8091 Zurich

Switzerland

E-mail: manuel.kuhn@usz.ch

Phone: +41 44 255 17 12

Abstract

Research question: The assessment of cough frequency in clinical practice relies predominantly on the patient's history. Currently, objective evaluation of cough is feasible with bulky equipment during a brief time (i.e., hours up to one day). Thus, monitoring of cough has been rarely performed outside clinical studies. We developed a small wearable cough detector (SIVA-P3) that uses deep neural networks for the automatic counting of coughs. This study examined the performance of the SIVA-P3 in an outpatient setting.

Methods: We recorded cough epochs with SIVA-P3 over eight consecutive days in patients suffering from chronic cough. During the first 24 hours, the detector was validated against cough events counted by trained human listeners. The wearing comfort and the device usage were assessed by a questionnaire.

Results: In total, 27 participants (50±14 y) with either chronic unexplained cough (n=12), COPD (n=4), asthma (n=5) or interstitial lung disease (n=6) were studied. During the daytime, the sensitivity of SIVA-P3 cough detection was 88.5 ± 2.49%, and the specificity was 99.97 ± 0.01%. During the night-time, the sensitivity was 84.15 ± 5.04% and the specificity was 99.97 ± 0.02%. The wearing comfort and usage of the device was rated as very high by most participants.

Conclusion: SIVA-P3 enables automatic continuous cough monitoring in an outpatient setting for objective assessment of cough over days and weeks. It shows comparable or higher sensitivity than other devices with fully automatic cough counting. Thanks to its wearing comfort and the high performance for cough detection, it has the potential for being used in routine clinical practice.

Introduction

Chronic cough in adults is defined as cough lasting eight weeks or longer (1) and is estimated to affect approximately one in ten people worldwide (2). It can be caused due to different etiologies, such as, bronchial asthma, upper respiratory tract pathology, gastroesophageal reflux, as well as rarer causes such as a lung tumor, chronic inflammation, or interstitial lung disease. Additionally, patients can be also diagnosed to suffer from unexplained chronic cough called refactory chronic cough (3). Currently, there is a lack of effective treatments for patients suffering from chonic cough especially if underlying cause has not been identified. Due to its high prevalence and severe impact on quality of life, there is a high interest in developing treatments for choring cough (4).

In clinical practice, the assessment of cough relies on the patient's history and is evaluated by questionnaires and scored using a visual analogue scale for cough intensity (VAS) (5). Cough has been also monitored by electronic sound registration. Early versions of automated cough monitors, such as the Hull Automated Cough Monitor (HACC), the LifeShirt or the Pulmotrack, suffered from insufficient accuracy, therefore their use for automatic cough detection has been limited (6-9). Later versions, such as the Leicester cough monitor (LCM) (10) and the VitaloJak (11) have demonstrated good validity and have been used more widely in as part of clinical trials. The VitaloJak is a device worn around a patient's hip and uses a microfone to record sounds. The final assessment of cough counts require the listener to count coughs during a condensed cough recordings (11). The LCM combines continuous recording with automatic cough detection and counting (6, 10, 12). However, it needs a manual calibration in every patient for optimal cough detection (6, 13). Due to the relatively time-consuming evaluation or initialization, both systems have not been widely used in clinical practice.

Better understanding of chronic cough is also hindered by the lack of objective long-term continuous data that does not rely on patient recall (14). Due to the size of the devices and time-consuming analysis, both LCM and VitaloJak have been mainly used up to 24 hours

(6). The registration of cough in a nonobtrusive way for longer than 24 hours and the evaluation of cough frequency (and – potentially – other qualities of cough) in a fully automatic way, could be used in clinical research for developing novel therapies and in clinical practice for symptom and treatment monitoring.

We have developed a small wearable cough detector (SIVA-P3) for continuous cough monitoring that uses deep neural networks for the automatic detection and counting of coughs. We evaluated the performance of the SIVA-P3 cough detector in an outpatient setting among 27 patients diagnosed with chronic cough.

Material and methods

STUDY SUBJECTS

Patients were recruited from the pulmonary outpatient clinic at the University Hospital Zurich between April 2021 and September 2021. Patients had to be 18 years or older and have a pulmomologist`s diagnosis of a chronic cough of unknown origin, COPD, asthma or interstitial lung disease. Patients were required to use a smartphone with the minimum version of iOS 13/Android 10 to install the mandatory smartphone application.

Pregnant patients or patients with a mental or physical disability diagnosis that precludes informed consent or compliance with the study protocol were excluded. The study was conducted in accordance with the declaration of Helsinki and all subjects provided written informed consent. The Ethics Committee of the Canton of Zurich approved the study (EK-ZH-NR: 2021-00330)

STUDY DESIGN

The main study objective was to validate the SIVA-P3 system in a real-world setting of patients diagnosed with chronic cough. This explorative study had a monocentric, non-controlled, open-label framework. It was conducted at the outpatient division of the pulmonary department of the University Hospital Zurich, Switzerland. Due to observational nature of this study no formal sample size calculation was done and a sample size of 27 was considered to be sufficient to test the SIVA-P3 system adequately. Patients who consented to participate in the study were first asked to rate their baseline cough severity on a visual analogue scale (VAS) (5) and to install the SIVA-P3 app on their smartphones. Second, the patients received the cough detector including accessories and an envelope with a second VAS. Patients had to place the cough detector between two layers of clothing on chest (using a commercially available sports strap to secure it around the neck, Figure 1) and wear it for eight consecutive days. At night, they had to charge the cough detector on their

bedside table, where it continued to record. Study participants were instructed to remove their cough detector only during showering or swimming. Every day, the smartphone application prompted patients once in the evening to indicate the timing of their main meals. After eight days, a research associate called the study participants for an interview. The phone interview included instructing the patient to fill in the follow-up VAS, asking the Participant User Feedback Questionnaire questions, and instructing the patient to send the device back to the trial site using the return envelope.

As primary outcome, the number of detected time-stamped cough epochs in the first 24 hours was compared between the SIVA-P3 algorithm and the human listener. The algorithms performance was evaluated by specificity and sensitivity and related metrics (positive and negative predictive values, rates of false positive and false negative detections per hour).

As a secondary outcome, we assessed the user-friendliness and wearing comfort over the 8-day study period with a questionnaire via a structured interview at the end of each participant's study period.

METHODS

SIVA-P3 System

The SIVA-P3 system consists of several components that interact and share data (Figure 1). The cough detector records audio and movement data and pre-processes it so that only relevant data is stored (i.e., sound segments that exceed a specific loudness). The cough detection algorithm processes this data, resulting in a stream of time-stamped cough events, which does not allow for the reconstruction of conversations or other audio information. For the first 24 hours of the study, segments of original audio data have been stored to enable to

evaluate the performance of the cough detection algorithm. In this explorative study movement data were not analysed.

Automatic cough counting (SIVA-P3 algorithm)

The SIVA-P3 cough detection algorithm analyses the audio data, and labels single cough events at the resolution of individual cough explosion sounds using a deep neural network. The deep neural network has been trained using a large dataset of cough and non-cough sounds. The training dataset consists of data that has been collected in preliminary experiments with previous prototypes of the SIVA device and of data that is publicly available. The COUGHVID (15) dataset is used as an additional source for cough training data and the AudioSet (16) dataset is used as an additional training data for background noise. The training dataset consists of a total of ~82'000 coughs and of ~ 1100h background noise. The final algorithm's performance was analysed for detection of cough epochs, which is defined as continuous coughing sounds without a 2-s pause between the coughs (14).

Confidence intervals

A bootstrapping method was used for determining confidence intervals for the performance metrics (17). The data was split into 1h segments, resulting in 24h * 27 patients = 648 segments (449 day segments, 199 night segments). We chose to analyze 1h segments because that data is displayed to health care professionals with same resolution. For day and night distributions,10'000 new datasets were iteratively sampled with replacement from the respective segments, and for each iteration the performance metric was calculated enabling to determine the 95% confidence intervals.

Consistency analysis between ground truth and the device measurements

To evaluate how consistently the cough detection algorithm performs between different patients, the average rate of cough epochs per hour during the first 24 hours was determined (separately for day and night) for each participant based on the algorithm's results and human listener. Spearman’s rank correlation coefficients were calculated and a Bland-Altman analysis was performed to determine the agreement between the SIVA-P3 algorithm and human listener.

Participant User Feedback Questionnaire

The Participant User Feedback Questionnaire included five questions asking participant to rate wearing comfort, acceptance, likeliness to wear for a longer period of time, and data privacy on 4-degree Likert scale (see Appendix I).

Analysis tools

The descriptive statistics was calculated using R version 4.1.2 (R Core Team 2019, R Foundation for Statistical Computing, Vienna, Austria). The cough detection algorithm was developed and inferred using the machine learning framework TensorFlow version 2.4.2 (Google Brain Team, Mountainview California, USA) running in Python version 3.8.0 (Python Software Foundation, Delaware, USA).

ANALYSIS

The performance of the algorithm was determined using the first 24h of the audio recordings. First, a pre-screening algorithm identified all sound events starting with a sudden increase in loudness (preliminary testing has shown that this procedure detects cough events with 100%

sensitivity and is thus suited as a privacy-enhancing pre-screening). Second, a research assistant trained in recognizing cough sounds inspected one second of audio data for each identified sound event and rated it as “cough” or “non cough” for producing the ground truth data. The labeled cough samples were doublechecked by a second listener and in case of disagreement, a third listener. During the cough epochs, every explosive cough phase triggers the pre-screening algorithm, allowing for the inspection of the individual cough explosions within one cough epoch. During the inspection the research assistant was unaware of the predictions of the algorithm and therefore unbiased. Third, the ground truth was compared to the automatic cough detection of the SIVA-P3 algorithm to determine the performance metrics. The algorithm predictions were compared to the ground truth on a local (time-wise) level, meaning the algorithm had to detect the cough at the correct point in time to count as a true positive. Because of this local comparison, false positives and false negatives cannot cancel out as would be the case if the predictions were calculated on a time segment level, e.g. during one day.

The 24h data was split into day and night data points, i.e., data points where the device had been worn or was placed on the charger, as the sound profiles for day and night differ due to the bigger distance from device to the patient during the night. The algorithm uses a different cough acceptance threshold for day- and night-time predictions. This parametrization was optimized on the validation set, which was distinct from the test set. The different parametrization of the algorithm leads to different performance profiles during day and night. The 24h device data from the patients were evaluated with a 4-fold cross-validation approach with separated validation and test set. During the evaluation and testing, the data was used as recorded to ensure that the evaluated performance represents the real-world use case without the algorithm overfitting on data augmentation patterns.

RESULTS

Patient population

A total of 46 patients were screened between April 2021 and September 2021. Of these, 15 patients did not meet the inclusion criteria. After including 31 patients in the study, 4 patients had to be excluded (due to technical problems (n=2), wrong way of wearing the device (n=1) or withdrawal of consent (n=1)). This resulted in a sample size of 27 patients which were analyzed in this study (online supplement). Among 27 participants, there were 15 men and 12 women with a mean (SD) age of 50.6 (13.7, min 25 years, max 79 years). 12 (44%) participants had a diagnosis of chronic cough of unknown origin, 4 (15%) were diagnosed with COPD, 5 (18%) with asthma, and 6 (22%) with interstitial lung disease (Table 1).

Table 1. Study participant demogrpahics. All data are presented as mean (SD) (standard deviation) unless stated otherwise.

Baseline Characteristics	**Values (s.d)**
No of patients	27
Age (years)	
Mean (SD)	50.3 (13.9)
Median (min-max)	53 (25-79)
Sex	
Male:female (n:n)	15:12
BMI, kg/m^2	24.4 (0.8)
Cough Severity VAS in mm	41.6 (23.4)
Average cough epochs first 24h	88.5 (79)
Underlying condition	N (%)
Chronic cough of unknown origin	12 (45%)
COPD	4 (15%)
Asthma	5 (18%)

Interstitial lung disease n (%)	6 (22%)

Out of the 27 included participants, 24 were wearing the device over the full 7 days (one participant stopped early due to holidays, and two lost motivation to keep wearing the device). 21 of these 24 participants provided data over 7 days. Data gaps in the participants with less than 7 days of coverage were caused due to usability-related issues with charging the device and connectivity issues with older smartphone models.

We evaluated the performance of the algorithm using cough epochs which is defined as continuous coughing sounds without a 2-s pause between the coughs (14). Each cough epoch is made up of one or several cough explosions. Next, we compared the number of cough epochs and cough explosions (labeled first-day data) (Figure 2). We observed a strong correlation between cough explosions and cough epochs, with a Spearman's rank correlation of 0.88 for the day and 0.89 for the night. On average, there were 2.39 cough explosions (std = 0.95) per cough epoch during the day and 2.36 cough explosions (std = 1.06) per cough epoch during the night.

The number of cough explosions and cough epochs varied a lot between patients and individual days. On average, the number of cough epochs per patient across days had a variation of 65% (69% for cough explosions) (Figure 3). The overall maximum recorded number of cough explosions per hour was 38.9 epochs/h (78.55 explosions/h for cough explosions) and the minimum 0.17 epochs/h (0.26 explosions/h for cough explosions).

Cough detection performance

We first evaluated the algorithm's performance by calculating specificity, sensitivity and other related metrics (positive and negative predictive values, rates of false positive and false

negative detections per hour). The algorithm reached 88.55% (C.I. 85.86 to 90.85) sensitivity and negative predictive value of 99.97 (C.I. 99.96 to 99.97) (Table 2). The specificity and false positive rate per hour of the device during daytime was 99.97% and 0.4 coughs/h, respectively. During nighttime, the specificity and false positive rate per hour of the device were 99.97% and 0.3 coughs/h, respectively. The algorithms performance for day and night time was not significantly different for most measures except for specificity (two-sample Kolmogorov-Smirnov test, p = 0.028) and negative predicitve value (two-sample Kolmogorov-Smirnov test, p = 0.043). A Receiver Operating Characteristic (ROC) curve (Figure 4a) and plotting of the positive predictive value against sensitivity (Figure 4b) confirmed a high performance of the cough detection algorithm across different operating points.

*Table 2: depicts the mean value with the 95 percent confidence interval for day and night usage. * indicates significant difference (p < 0.05) between day and night.*

Metric	Day	Night
Sensitivity (Recall) [%]	88.55 [85.86 to 90.85]	84.24 [79.11to 89.06]
Specificity [%] *	99.97 [99.96 to 99.98]	99.97 [99.95 to 99.99]
Positive Predictive Value [%]	89.68 [87.64 to 91.57]	87.06 [82.91to 90.64]
Negative Predictive Value [%] *	99.97 [99.96 to 99.97]	99.97 [99.94 to 99.98]
False Positives/hour [1/h]	0.39 [0.49 to 0.31]	0.24 [0.33 to 0.15]
False Negatives/hour [1/h]	0.44 [0.57 to 0.33]	0.3 [0.42 to 0.19]

As part of quality assurance, we examined the agreement between the algorithm and the ground truth for average cough per hour during the first 24 hours using Spearman's rank correlation and the Bland-Altman plots. We observed a high correlation for the average cough epochs per hour for both daytime (rs = 0.95 [C.I. 0.90 to 0.98]) and night-time (rs = 0.94 [C.I. 0.88 to 0.97]) measurements (Figure 5). For the Bland-Altman analysis (Figure 6) we plotted the difference in cough epochs per hour between the algorithm and a human listener over the average cough epochs per hour for each patient. We observe high

agreement between the Siva P3 Algorithm and the human listener, with a slight overestimation of cough number from the algorithm for daytime.

Secondary outcomes

As part of secondary outcomes, we assessed wearing comfort using Participant User Feedback Questionnaire (n= 25). 44% (n=11) of the participants agreed, 20% (n=5) rather agreed, 12% (n=3) neither agreed nor disagreed, 24% (n=6) rather disagreed, and 0% (n=0) disagreed with SIVA-P3 being comfortable (Figure 7). The main reason why the six participants did not find the cough detector so comfortable was that the cough detector interfered with taking on and off clothes or because the collar was too wide, which made one sweat more. Assuming that wearing the SIVA-P3 continuously for longer time will facilitate better diagnosis of cough-related pathologies, we asked the participants if they were willing to use SIVA-P3 daily for a period of eight weeks if it was recommended by the doctor. 36% (n=9) of participants agreed, 24% (n=6) rather agreed, 20% (n=5) neither agreed nor disagreed, 8% (n=2) rather disagreed, and 12% (n=3) disagreed with the statement. The questionnaire results also showed that the users were not bothered by the cough monitor during night-time, and they were not concerned about data privacy.

Discussion

The SIVA-P3 automatic cough monitoring decive showed high performance for cough detection (sensitivity 88.5% for day, and 84.2% for nigh-time), and was rated highly for wearing comfort over the eight-day wearing period. This is the first study that has monitored coughing patterns continuously over an eight-day period among patients with common chronic cough etiologies such as , asthma, COPD, and Interstitial lung disease.

Compared to other electronic cough monitoring approaches, the SIVA-P3 algorithm’s performance is better than fully automatic cough monitoring systems such as the LifeShirt® (sensitivity: 78.1%, specificity: 99.6%) (8), Pulmotrack (sensitivity: 96%, specificity: 94%) (9), and the Hull automatic cough monitor (sensitivity: 80%, specificity: 98%) (7). SIVA-P3 is

comparable to approaches limited to nighttime use in a quiet environment, such as the LEOSound® Monitor (sensitivity: 89.7% specificity: 98.7%,) (18), and to approaches requiring additional manual calibration such as the Leicester Cough Monitor (sensitivity: 91%, specificity: 99%, FP: 2.5 patient-1 h-1) (13). Only cough detection by human listeners as used by VitaloJAK has both higher sensitivity and specificity than SIVA-P3 (11). However, VitaloJAK's processing requires a trained professional to perform the cough count by listening to an abbreviated version of the 24-hour recording (median 62.4 min) (12). Cough counting with fully automated system such as SIVA-P3 allows continuous cough monitoring over extended time periods without manual calibration facilitating its use across large number of patients and in routine clinical use.

In addition to the approaches with dedicated body-worn devices, solutions are emerging that rely solely on the patient's smartphone for data recording such as the Hyfe App (Hyfe Inc., Delaware, USA, no published performance metric available) and Asthma Guardian smartphone application (Resmonics AG, Zürich, Switzerland, sensitivity 99.9% and specificity of 91.5% for night time use) (19). The main limitation of such approaches is that recording with consistent quality can only be guaranteed under well-defined circumstances (mobile phone openly placed on table or nightstand next to the user) and during certain times of day (at home or in other silent environments). For conditions where, e.g., the nightly cough burden can be used as a surrogate marker for the general patient state, these approaches may be a cost-effective alternative to monitor disease progression (20-22). However, obtaining a complete (24/7), unbiased picture of the patient's coughing patterns during all activities of daily life requires a dedicated device with robust cough detection performance and high patient acceptance SIVA-P3 facilitates such usage, and further studies are necessary to investigate the value of these cough patterns with respect to differential diagnostics.

This study has some limitations. We performed a convenience sampling approach that was balanced in terms of diseases with respect to the sample and the sample size was proposed

to serve as a pretest for a larger experimental study. For a more generalizable statement about the validity of the device, follow-up studies with a larger sample size need to be conducted

Conclusion

In summary, SIVA-P3 as a fully automated ambulatory cough monitoring system, was successfully tested in a clinical outpatient setting and shows similar or better performance metrics than other automated cough detection solutions while requiring significantly less evaluation and installation effort for personnel than not fully automated alternatives. Further, the SIVA-P3 cough detector is small and lightweight which the patients tolerate very well even over a longer period (24h/7 days).

Conflict of Interest statement

The study was sponsored by Evoleen AG, a company that owns shares in SIVA Health AG. SIVA Health AG intends to commercialize the SIVA-P3 system.

C.F. Clarenbach reports consulting fees from GSK, Novartis, Vifor, Boehringer Ingelheim, Astra Zeneca, Sanofi, Vifor and Daiichi Sanko outside the submitted work. He reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from GSK, Novartis, Vifor, Boehringer Ingelheim, Astra Zeneca, Sanofi and Vifor.

M. Alge is employed by and owns shares in SIVA Health AG.

E. Nalbant has received consulting fees from Siva Health AG

L. Kuett is employed by SIVA Health AG

E. W. Russi has received consulting fees from Siva Health AG-. He participates in the ESTxENDS Trial (study supported by SNF, University of Bern) and is a participant in the Data and Safety Monitoring Board

N. A. Sievi, A. Arvaij, D. Kohlbrenner and M. Kuhn have no conflicts of interests

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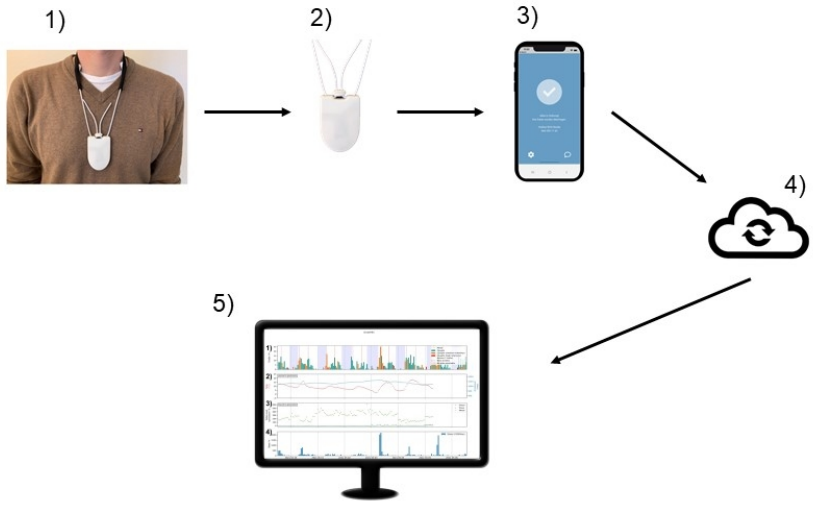


Figure 1: The SIVA-P3 cough detector worn on the patient's chest. Note that in this pilot study, it is intended to be worn between one or two layers of clothing. For the illustration of the coguh detector it is worn over the clothes in this figure.; 2. Cough detector; 3. Application on the phone; 4. Cloud where the data are saved and processed; 5. Data is presented on a dashboard in a user-friendly way.

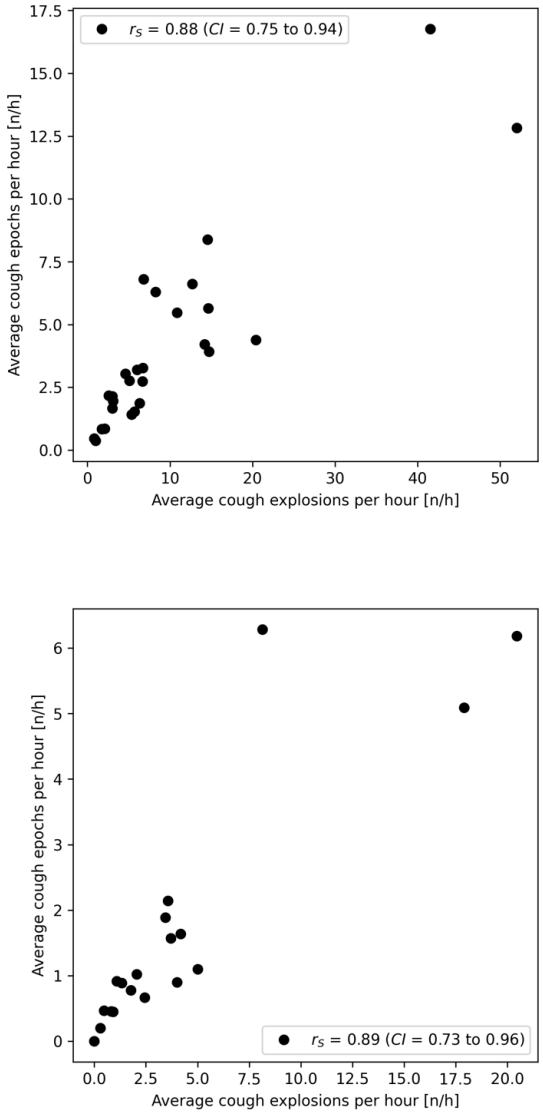


Figure 2. Relation between cough epochs and cough explosions for daytime (top) and nighttime (bottom). Each point depicts the data of one patient during the first day (n = 27).

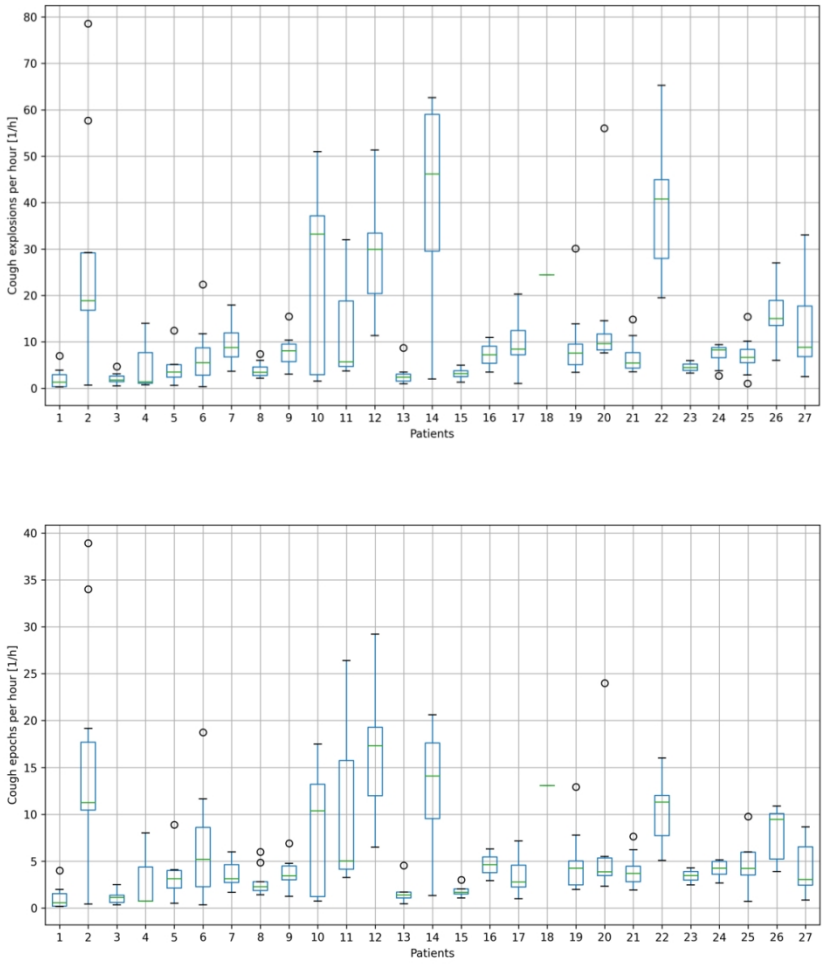
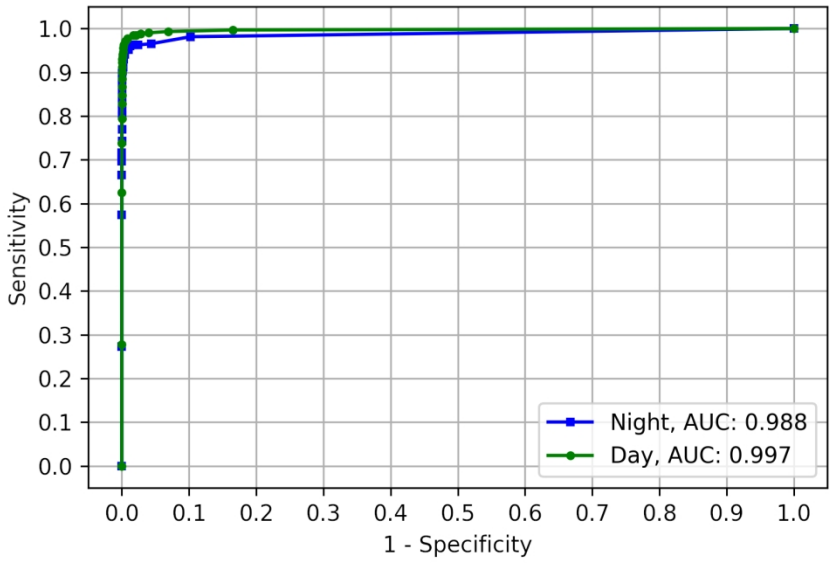


Figure 3. Box plots depicting the average cough explosions per hour for the full week (top) and average cough epochs per hour for the full week (bottom).



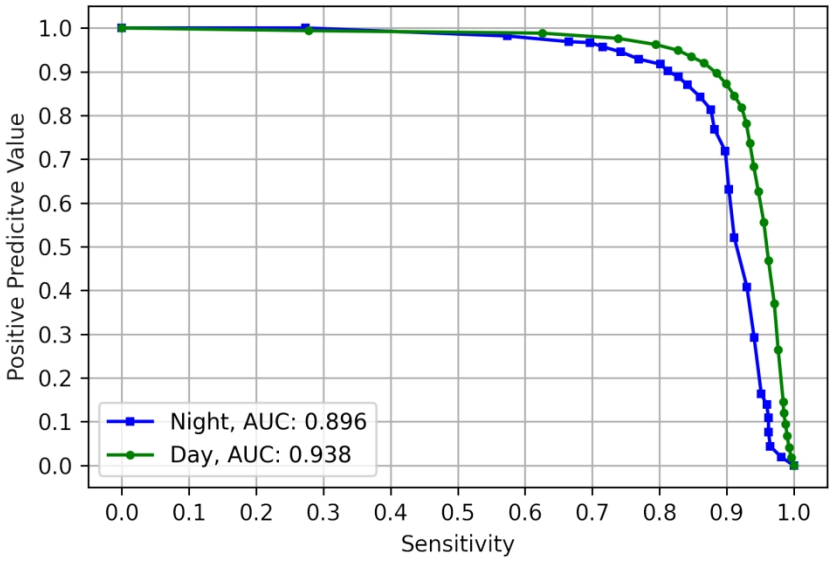


Figure 4a: Receiver operating characteristics curve for day and night, including the area under the curve (top). Figure 4b: Curve plotting positive predictive value against sensitivity for day and night, including the area under the curve (bottom).

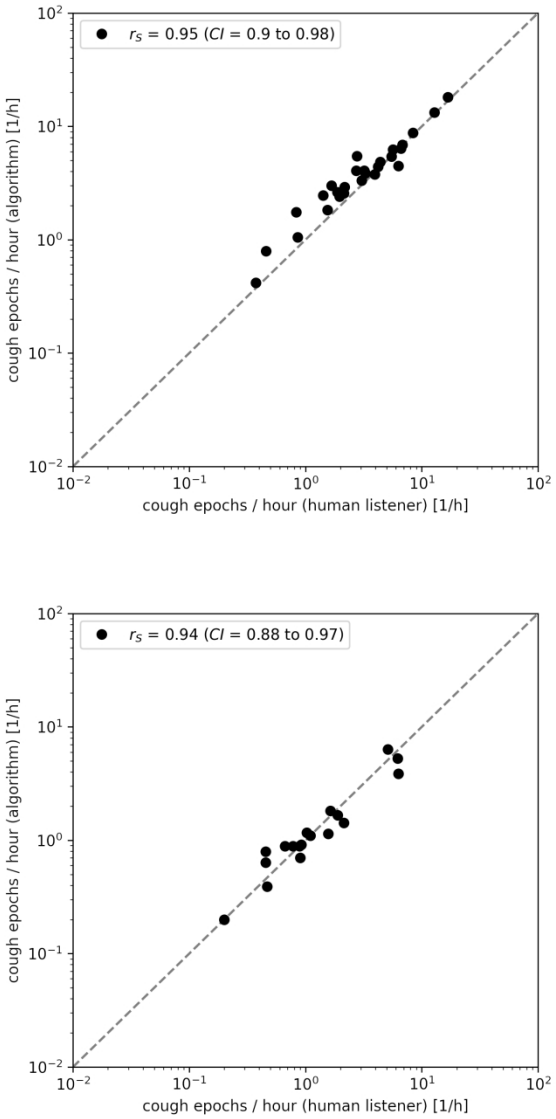


Figure 5: Correlation plot of daily average cough epochs per hour between the SIVA- P3 Algorithm and a human listener for daytime use (top) and nighttime use (bottom). Each point depicts the data of a single patient the first 24 hours. The Spearman's correlation coefficient for daytime use is 0.95 with a 95% confidence interval from 0.9 to 0.98. The Spearman's correlation coefficient for nighttime use is 0.94 with a 95% confidence interval from 0.88 to 0.97.

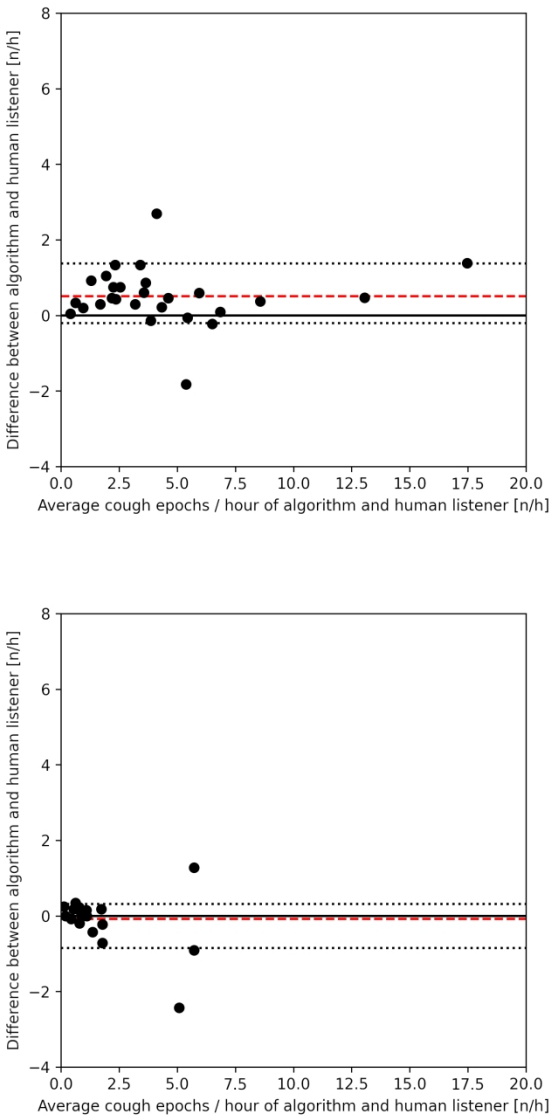


Figure 6: Bland-Altmann Plot of the daily average cough epochs per hour showing the difference between a human listener and the SIVA P3 Algorithm for daytime use (top) and nighttime use (bottom). Each point depicts the data of a single patient the first 24 hours. The dashed red line depicts the mean and the dotted lines show the 95% percentiles.

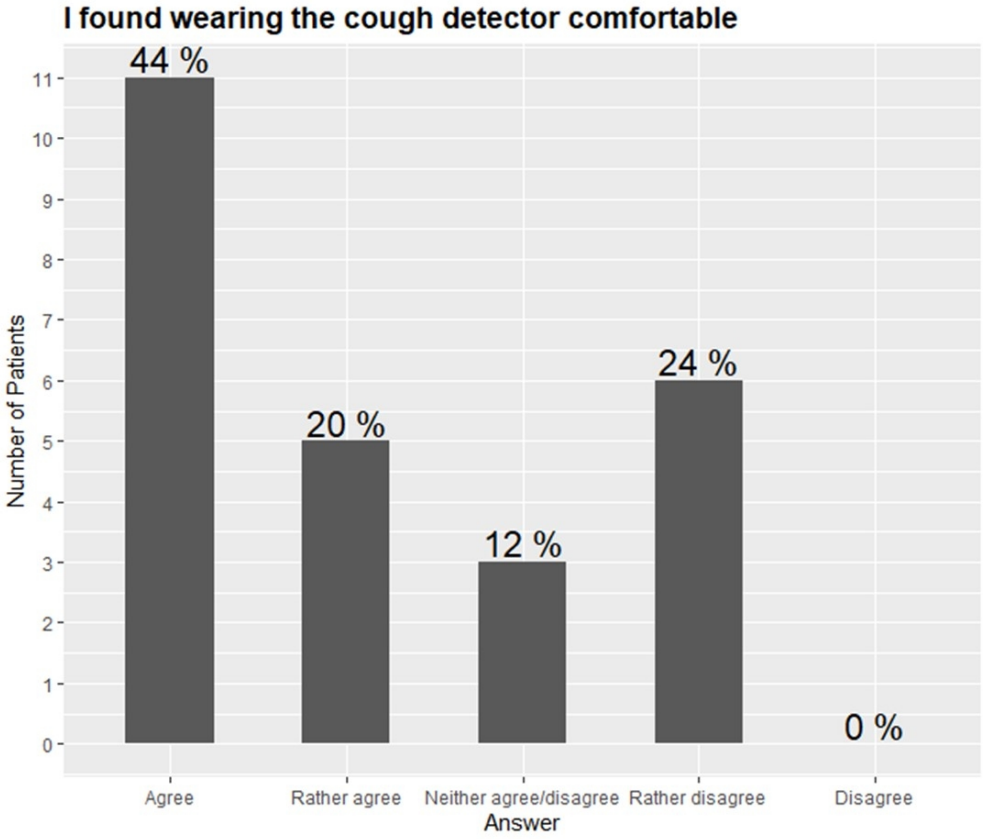
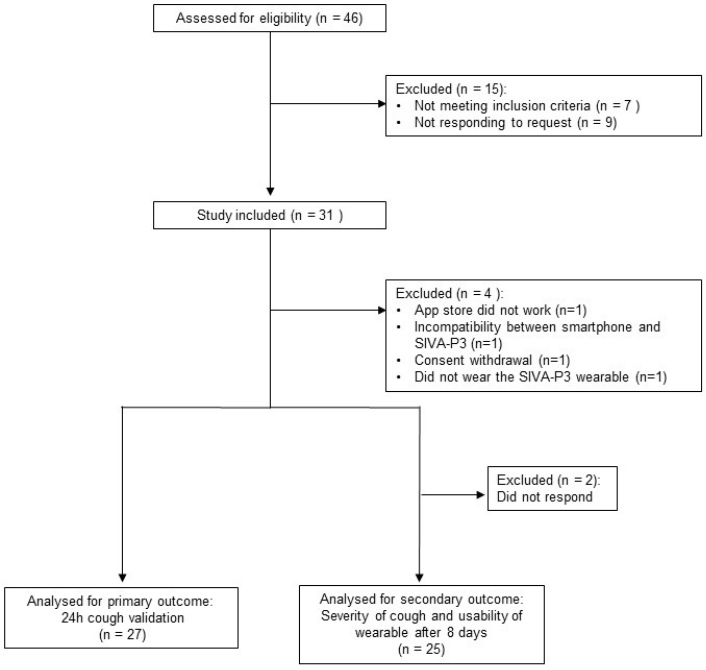


Figure 7: Wearing comfort (n:25)


Assessed for eligibility (n = 46)
Excluded (n = 15):
• Not meeting inclusion criteria (n = 7)
• Not responding to request (n = 9)
Study included (n = 31)
Excluded (n = 4):
• App store did not work (n=1)
• Incompatibility between smartphone and SIVA-P3 (n=1)
• Consent withdrawal (n=1)
• Did not wear the SIVA-P3 wearable (n=1)
Excluded (n = 2):
Did not respond
Analysed for primary outcome:
24h cough validation
(n = 27)
Analysed for secondary outcome:
Severity of cough and usability of wearable after 8 days
(n = 25)