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# A Wearable Sweat Band for Noninvasive Levodopa Monitoring

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## KEYWORDS.

wearable sweat sensor, Parkinson's disease, levodopa detection, noninvasive drug monitoring, dosage optimization

## ABSTRACT.

Levodopa is the standard medication clinically prescribed to patients afflicted with Parkinson's disease. In particular, the monitoring and optimization of levodopa dosage is critical to mitigate the onset of undesired fluctuations in the patients' physical and emotional conditions, such as speech function, motor behavior and mood stability. The traditional approach to optimize levodopa dosage involves evaluating the subjects' motor function, which has many shortcomings due to its subjective and limited quantifiable nature. Here, we present a wearable sweat band on a nano-dendritic platform that quantitatively monitors levodopa dynamics in the body. Both stationary iontophoretic induction and physical exercise are utilized as our methods of sweat extraction. The sweat band measures real-time pharmacokinetic profiles of levodopa to track the dynamic response of the drug metabolism. We demonstrated the sweat band's functionalities on multiple subjects with implications towards the systematic administering of levodopa and routine management of Parkinson's disease.

Levodopa is the medication administered to treat patients with Parkinson's disease.<sup>1-7</sup> Despite its success, an individual's responses to levodopa can vary due to factors such as dietary intake, age, gender and drug administration history.<sup>8-12</sup> These variations can lead to unfavorable fluctuations of the subject's motor and cognitive functions if the levodopa dosage is not tailored towards the individuals.<sup>12-14</sup> Therefore, levodopa monitoring is an essential part of the treatment for Parkinson's disease. The gold standard for optimizing levodopa dosage involves an assessment of the motor function of a Parkinson's disease patient.<sup>9</sup> This method requires clinicians to evaluate the subject's motor functions, leading to difficulty of point-of-care testing and ambiguity in drug dosage. To address this challenge, monitoring blood levodopa concentration stands out as a viable solution.<sup>15-18</sup> However, blood-based detection is hampered by its need for invasive sampling and separate analytical tools, making it inappropriate for the long-term and frequent measurements that are necessary due to the dynamic nature of drug metabolism.

Taking this into consideration, human sweat is an alternative to blood due to its accessibility through noninvasive procedures and its abundance of biomolecules. Like other drug molecules that undergo xenobiotic metabolism pathway, levodopa excretes through sweat with its concentration in sweat exhibiting a potential correlation with that in human plasma.<sup>19-22</sup> Additionally, under standard levodopa dosage, sweat levodopa level shows up in the micro-molar ranges,<sup>17-19</sup> making it amenable for reliable detection with

current technologies.<sup>23,24</sup> For these reasons, sweat presents an ideal means for non-obstructive monitoring of levodopa for dosage optimization. Sweat sensing patches have been employed for drug tests in athletic doping control, drug abuse investigation and forensic inspection.<sup>25,26</sup> Recently, sweat sensors for drugs and their related biomolecules have also been demonstrated via optical and electrochemical techniques.<sup>27-32</sup> In particular, the electrochemical approach represents an attractive method owing to its advantages for electronic integration, economical cost, sensitivity and selectivity.<sup>29-36</sup>

In this work, we expand the strength of the electrochemical sensor through integrated surface innovations at the physical and chemical levels. The incorporation of gold dendritic nanostructures onto the electrodes remarkably enhanced the detection limit of the levodopa sensor down to about 1  $\mu\text{M}$  in sweat solution, a couple times of improvement compared to previous work tested in human fluid.<sup>37</sup> Moreover, the crosslinking mechanisms with glutaraldehyde provides us chemically robust enzymatic structures to achieve sensor stability for long-term and continuous usage.<sup>37-40</sup> This approach effectively connects existing sensor enhancement technologies into a consolidated platform for prolonged sensor operation. Our solutions effectively address the challenges for drug detection, which are attributed to the generally low concentration of drugs in human sweat and the long time scale of drug metabolism.

The design of the wearable sensor packaged into a sweat band (s-band) is illustrated in Figure 1a. The sensor is fabricated on a polyethylene terephthalate (PET) substrate and it employs a standard three-electrode configuration with a functionalized levodopa sensing electrode as working electrode, a Ag/AgCl top layer as reference electrode and a Au top layer as counter electrode. As shown in Figure 1b, during amperometric measurement, levodopa excreted in sweat can be oxidized via tyrosinase enzyme to dopaquinone.<sup>37</sup> This process generates a Faradaic current that can be further calibrated into its corresponding sweat levodopa concentration. The cross-section schematic of the electrodes is shown in Figure 1c, and Figure 1d shows a scanning electron microscope image of the gold dendrite to validate the successful growth and density of the nanostructures. To achieve the enhancement on sensitivity, gold nano-dendrites with largely increased surface area are synthesized via over-potential deposition approach on the evaporated Au/Cr conductive layer.<sup>38,39</sup> Further, thionin acetate salts are deposited via cyclic voltammetry (CV) method conformally on the as-synthesized dendritic gold structure and glutaraldehyde/tyrosinase are drop-casted onto the working electrode. Glutaraldehyde serves as the cross-linker to immobilize the tyrosinase enzyme that facilitates the electrochemical oxidation of levodopa.<sup>37,40</sup> It is also worth mentioning that the dendritic gold plays a pivotal role to provide adequate interface for enzyme loading and molecular contact to achieve an improved sensing performance. The final modification step for the working

electrode involves the drop-casting of Nafion, which enhances the long-term stability and anti-fouling features of the electrochemical sensor.<sup>41</sup> The prospective application of the sensor is illustrated in Figure 1e, which shows the application of iontophoresis for noninvasive and stationary stimulation of sweat to monitor levodopa levels after a subject consumes the drug. The s-band enables continuous monitoring of levodopa, which allows for personalized optimization of levodopa dosage.

The functionalized levodopa sensing electrode was characterized with CV scanning, which indicates the oxidation peak of levodopa. Figure 2a shows the CV curves using the functionalized electrode in phosphate-buffered saline (PBS) with different concentrations of levodopa. The oxidation and reduction peaks for levodopa are around 0.34 V and 0.30 V (method of peak identification is illustrated in Supporting Information Figure S1), respectively, which are consistent with the literature.<sup>23</sup> Figure 2b shows a CV in the proximity of levodopa's oxidation peak in the physiologically relevant concentration range.<sup>19</sup> The functionalized electrode responds to levodopa with high sensitivity in the micro-molar range. This is a remarkable enhancement of more than two orders of magnitude compared to the response of a bare Au electrode (Supporting Information Figure S2). Figure 2c shows the amperometric response of levodopa at the oxidation potential (0.34 V). The inset displays the calibration curve with a sensitivity of 15 nA/ $\mu$ M, which is on par with the best levodopa sensors reported.<sup>23</sup> This is

notable considering the simplicity of electrode functionalization and the electrode's excellent stability for long-term usage.

The sensors were further characterized in sweat solution to demonstrate its practical applications for noninvasive monitoring. Figure 3a shows a CV in the proximity of levodopa's oxidation peak, which is identified to be 0.25 V. The amperometric response of levodopa was similarly tested at the oxidation potential, shown in Figure 3b. The corresponding calibration curve in sweat is displayed in Figure 3c, and the sensitivity is found to be 1.7 nA/ $\mu$ M. This value is different from that in PBS and it is expected due to bio-fouling activity.<sup>29</sup> For the purpose of the study, we define drift as the maximum change in the signal of the amperometric response of a fixed concentration (e.g., 10  $\mu$ M) over a period of operation (e.g., 30 minutes). The sensor drift is approximately 18 nA as shown in Supporting Information Figure S3. The error of concentration measurement due to drift is estimated to be 1.2  $\mu$ M. The limit of detection is 1.25  $\mu$ M as shown in Figure 3b. The signal-to-noise ratio (SNR) is the ratio of the square of the amplitude of the signal to the background noise. Based on Supporting Information Figure S3b, the amperometric response signal is found to be 225 nA. During the measurement, the noise level is observed to be approximately 50 nA, which results in a SNR of 20. The selectivity of the sensor is essential in the presence of other common sweat biomolecules. Therefore, the amperometric response of the addition of levodopa and its potential interferents such as uric acid (20  $\mu$ M), glucose (166  $\mu$ M) and ascorbic acid (16  $\mu$ M) is recorded in



Figure 3d. The concentrations are chosen to be in their physiologically relevant ranges.<sup>29-32</sup> The result shows that the interference on the levodopa sensor performance is within an error range of 0.35  $\mu\text{M}$ .

To explore the viability of using the *s*-band to track the metabolism of levodopa in human subjects, sweat was extracted from a healthy volunteer through iontophoresis and after *vicia faba* (fava bean) consumption. Fava beans are levodopa-containing legumes consumed for culinary and medicinal purposes.<sup>18</sup> The use of fava beans allows for extensive testing of the *s*-band's functionalities on non-vulnerable, healthy subjects.

Figure 4a shows the time progression panel of fava beans consumption and iontophoresis application, as well as continuous sensor readings of the sweat levodopa concentration. The result demonstrates that the *s*-band can continuously capture the sweat levodopa trend that resembles the blood levodopa profile observed.<sup>15-18</sup> During iontophoretic stimulation, sweating begins after iontophoresis and lasts for about 20 to 45 minutes. Therefore, two consecutive applications of iontophoresis are performed at -20 minutes and 25 minutes, with respect to the time of fava beans intake, to cover a broad time range that captures levodopa's metabolic trend. The subject consumes 450 grams of fava beans after 12 hours of fasting, and its sweat levodopa concentration is monitored after each iontophoresis. The observed sweat levodopa level versus time shows an increasing trend up to 6.6  $\mu\text{M}$  at about 47 minutes, after which the concentration begins to decrease. The

levodopa concentration decreases to 3.3  $\mu\text{M}$  at about 74 minutes, so the half-life of the decay is found to be 27 minutes. The time scales of levodopa's half-life and its time of peak concentration are expected based on previous observations.<sup>15-18</sup> In Figure 4b, the subject first consumes a 426-gram sandwich (see Methods), followed by 450 grams of fava beans. Three consecutive applications of iontophoresis are performed at -20, 25 and 80 minutes, with reference to the time of fava beans consumption. The result shows a slight delay of 13 minutes in the pharmacokinetic peak time compared to that in Figure 4a. This finding is expected as dietary intake can affect the pharmacokinetic profile of levodopa in human secretory systems.<sup>11</sup> The data in Figures 4a and 4b verifies the *s*-band's capability of continuous levodopa measurement.

While sweating caused by iontophoresis can be limited in its duration, sweating generated through exercise can typically last longer and allow us to capture a more complete picture of the drug's pharmacokinetics. Figure 5 explores the possibility of exercise as a means to extend the sweating period. Figure 5a shows the time progression panel of fava beans intake and an image of a subject engaging in ergometer cycling. The representative pharmacokinetic profiles of sweat levodopa for three different subjects are included. In each trial, the subject consumes 450 grams of fava beans and exercises on a stationary ergometer. Each subject exercises for multiple trials and the cumulative result is shown in Figure 5b, with the averaged time of peak concentration for subject 1, 2 and 3 being  $44 \pm 20$  minutes,  $42 \pm 26$

minutes and  $67 \pm 14$  minutes. It is worth noting that Figure 4a and Subject 1 of Figure 5a correspond to the same subject. The results from iontophoresis and exercise sweat show similar time of peak concentration (47 minutes versus 50 minutes). The set of on-body studies are compared to the case where no fava beans are consumed, which demonstrates almost zero concentration of levodopa (Supporting Information Figure S4). The on-body experiments demonstrate the novelties and feasibilities of the wearable s-band for noninvasive and continuous monitoring of levodopa's dynamic metabolic rate. We envision that this sensor platform can enable clinical understanding of xenobiotic metabolisms and dosage optimizations.

In summary, we demonstrated the performance of a wearable sweat band for monitoring the metabolic behavior of levodopa, the standard medication prescribed to Parkinson's disease patients. The levodopa s-band integrates various material innovations and enables us to gain fundamental insights into the pharmacokinetic behavior of levodopa noninvasively. Dendritic growth, enzyme immobilization and stabilizing film are seamlessly incorporated to improve the robustness and stability of the electrochemical sensor. We have also demonstrated the application of the s-band for prolonged, continuous and noninvasive drug monitoring in human subjects after fava beans intake. Through analyzing sweat generated via iontophoresis and physical activities, the metabolism of the drug can be tracked in real-time to allow for dosage optimization. Future directions include investigating pharmacodynamics between drugs, lengthening

iontophoresis sweating duration and improving electrode lifetime upon repeated use. We envision that the wearable s-band can be leveraged to study the intrinsically complex drug profiles, optimize drug dosages to regulate Parkinsonian behaviors in patients and integrate with drug delivery systems. This platform serves as a pathway towards drug management for increasingly personalized, point-of-care medicine for the future.

**Methods.** Sensor fabrication. The flexible electrodes were fabricated on PET substrates via photolithography and evaporation. The electrodes were patterned through photolithography with positive photoresist (Shipley Microposit S1818) and electron-beam evaporation of Cr (30 nm) and Au (50 nm). Afterwards, lift-off in acetone solution was performed. Au nano-dendrites were grown on top of the electrodes with a Gamry Electrochemical Potentiostat (signal type: square wave; signal frequency: 50 Hz; amplitude: 1V; DC offset -1 V; cycles: 6000) and chloroauric acid solution (mixture of 50 mM AuCl<sub>3</sub> and 50 mM HCl). The precursor concentration will affect the morphology and length of the nanostructures; while increasing the deposition time will normally increase the length of the nanostructures.<sup>42</sup> The 6000 cycles (120 seconds) of Au deposition were chosen because the resulting functionalized electrode shows the largest current change upon the addition of 10 μM of levodopa, as shown in Supporting Information Figure S3. The electrodes were immediately cleaned with deionized water and left in room temperature for 2 hours for drying. On top of the Au nano-dendrites, 0.25 mM of thionin acetate salt (Sigma-Aldrich) was deposited

electrochemically with CV (initial potential: -0.6 V; final potential: 0.1 V; scan rate: 0.1 V/s; segment: 40). The electrodes were then left in room temperature for 2 hours. Subsequently, a mixture of enzyme and crosslinker solution was drop-casted on top of the electrodes (2.5  $\mu$ L). The solution was prepared by mixing tyrosinase (Sigma-Aldrich. 1 mg) with 2% glutaraldehyde (Sigma-Aldrich. 0.866  $\mu$ L) in PBS (66.6  $\mu$ L). The electrodes were left in room temperature for 12 hours. Finally, Nafion 117 (Sigma Aldrich. 1  $\mu$ L) was drop-casted on top of the electrodes, and the electrodes were left in room temperature for 2 hours. For the reference electrodes, Ag/AgCl paste was painted on top of the Au electrodes and left in room temperature for 12 hours.

Sensor characterization and calibration. The functionalized electrodes were characterized electrochemically using CHI 1230C potentiostat (CH Instrument) in CV and amperometric measurements. The CV and amperometric responses corresponding to different concentrations of levodopa were subsequently evaluated. The interference test involved the addition of various biomolecules at the physiologically relevant concentrations. In Figure 2, the functionalized working electrodes were characterized with commercial Ag/AgCl reference electrode in PBS. In Figure 3, on-body functionalized electrode arrays, including functionalized working electrodes, Ag/AgCl pasted reference electrodes and Au counter electrodes (all on PET substrate), were characterized in sweat solutions collected from the exercise trials.

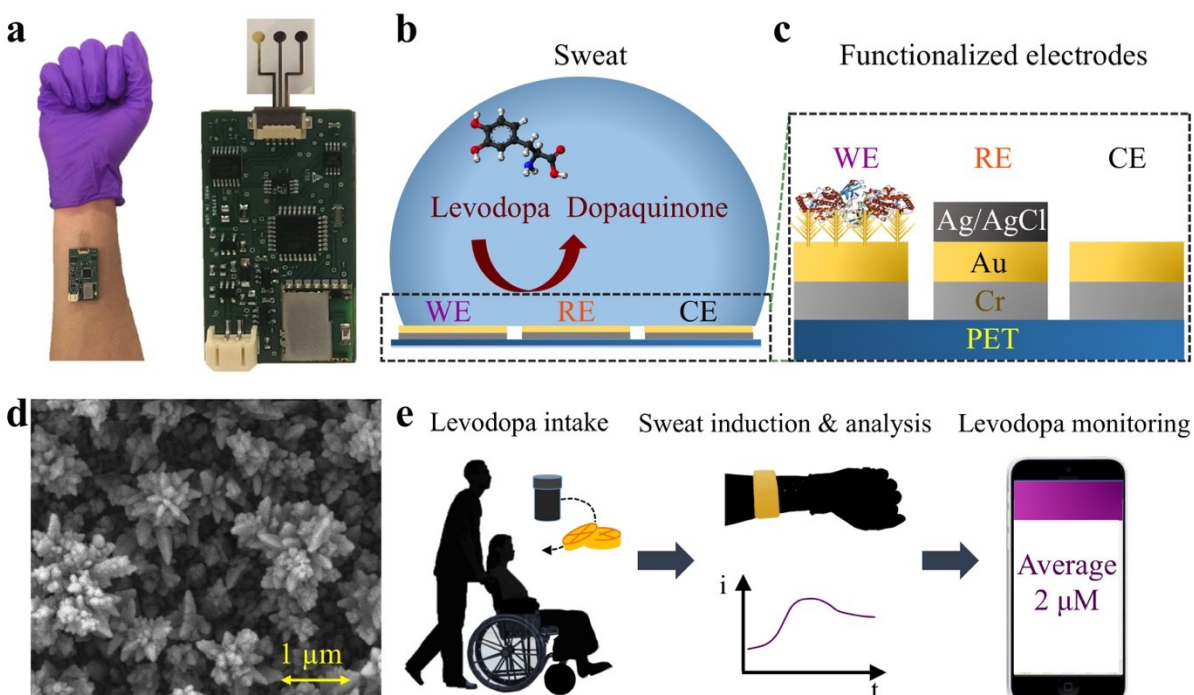
Iontophoresis sweat analysis. Iontophoresis was conducted by gently mounting pilocarpine hydrogel (ELITechGroup SS-023 Pilogel) on a subject's wrist for 5 minutes at 1 mA DC current (ELITechGroup Model 3700 Webster Sweat Inducer). During in situ evaluation, electrode arrays were placed conformal to the skin and connected to the CHI 1230C potentiostat. The on-body sweat analysis of human subjects was approved by the institutional review board (CPHS 2016-06-8853) at the University of California, Berkeley. The on-body sweat analyses were processed with MATLAB's Hampel and Smooth functions for noise reduction.

Exercise sweat analysis. The subjects engaged in stationary cycling on an ergometer (Gold's Gym 290C Upright Cycle Trainer) at a biking power of 100 W. The electrode arrays were calibrated and tested with the same method as that in the iontophoresis sweat analysis section. The continuous data is plotted when the sensor starts to respond in sweat solutions. This corresponds to the time when we observe obvious sweating on the subject and sufficient accumulation of sweat around the sensor. The uncertainty for the time of peak concentration in Figure 5b was defined as the standard deviation of all the exercise trials for the same subject. One trial was performed for subject 3, and the uncertainty was estimated from the slope (concentration/time) around the proximity of the pharmacokinetic peak and the sensor drift (uncertainty in concentration).

Food intake. Fava beans were purchased from a local community market (Berkeley Bowl). 250 g of fava beans consumption is equivalent to

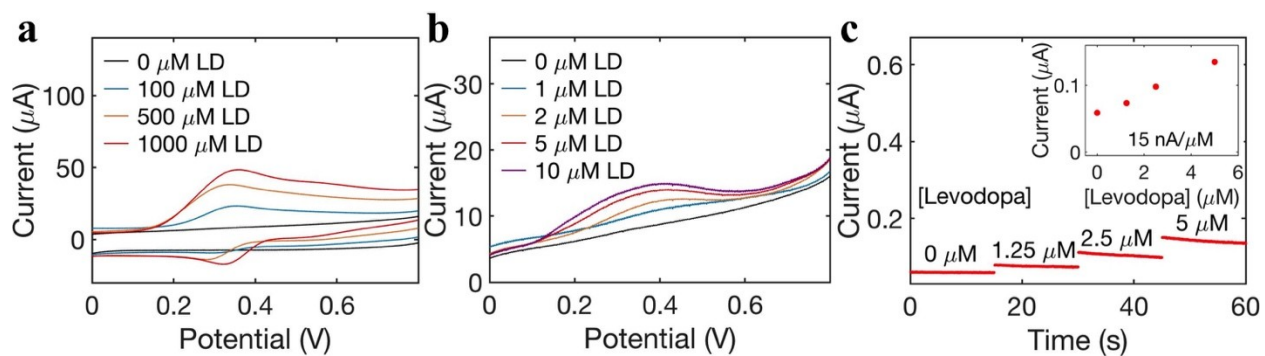
about 125 mg of levodopa intake.<sup>18</sup> The sandwich was a 12-inch Italian B. M. T. sandwich (Subway®). The fava beans' seeds were taken out from the bean pods and cooked in boiling water for 20 minutes prior to consumption.

FIGURES.

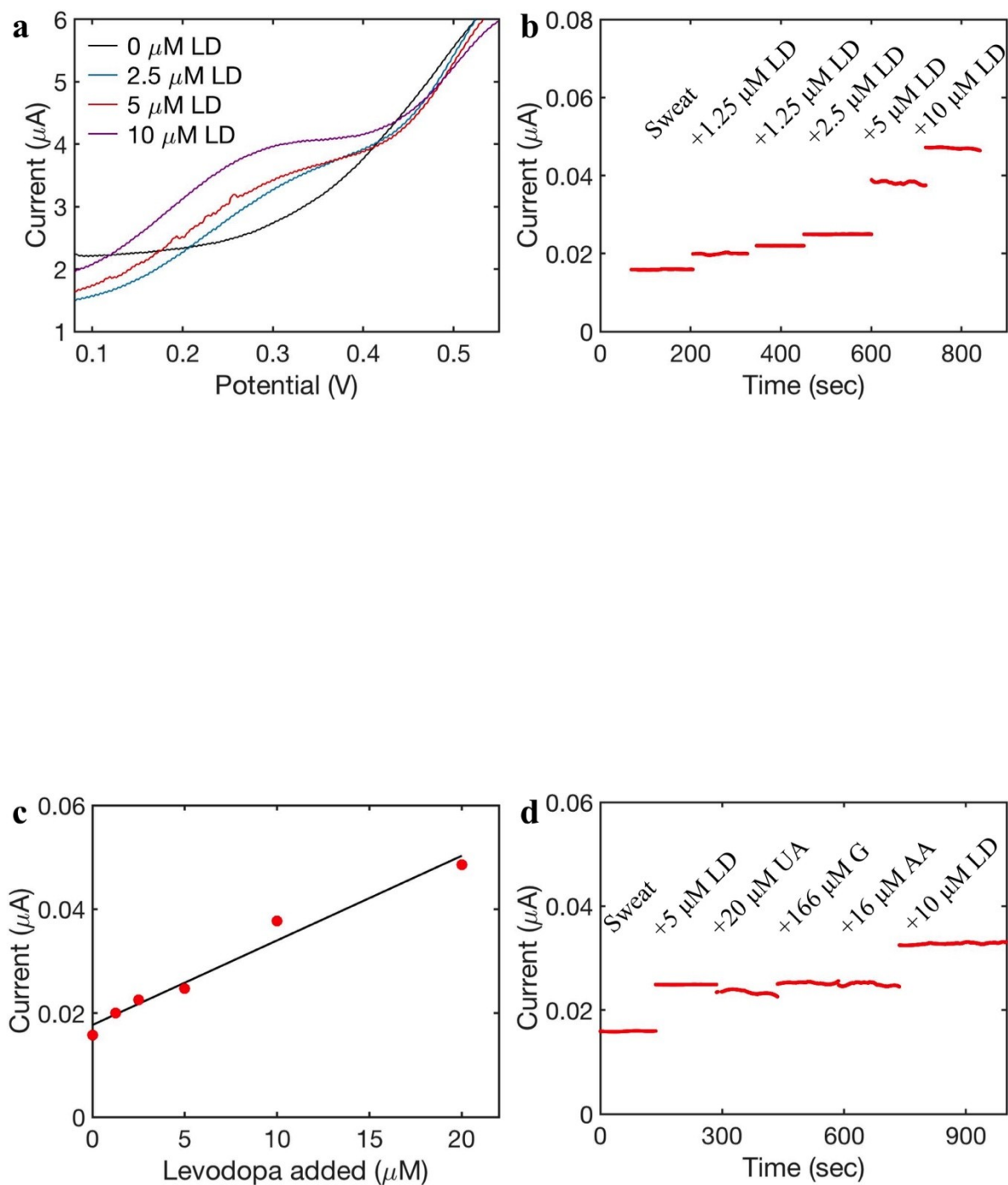


**Figure 1.** Schematic of the s-band and drug sensing mechanism. (a) Optical image of the s-band worn on a subject's wrist. (b) Sensing mechanism of the levodopa sensor. WE, RE and CE are working electrode, reference electrode and counter electrode. (c) The cross-section view of the gold electrode on a flexible sensor patch. (d) Scanning electron microscope image of the gold dendritic structure. (e) Real-time sweat levodopa monitoring using the s-band after levodopa intake.



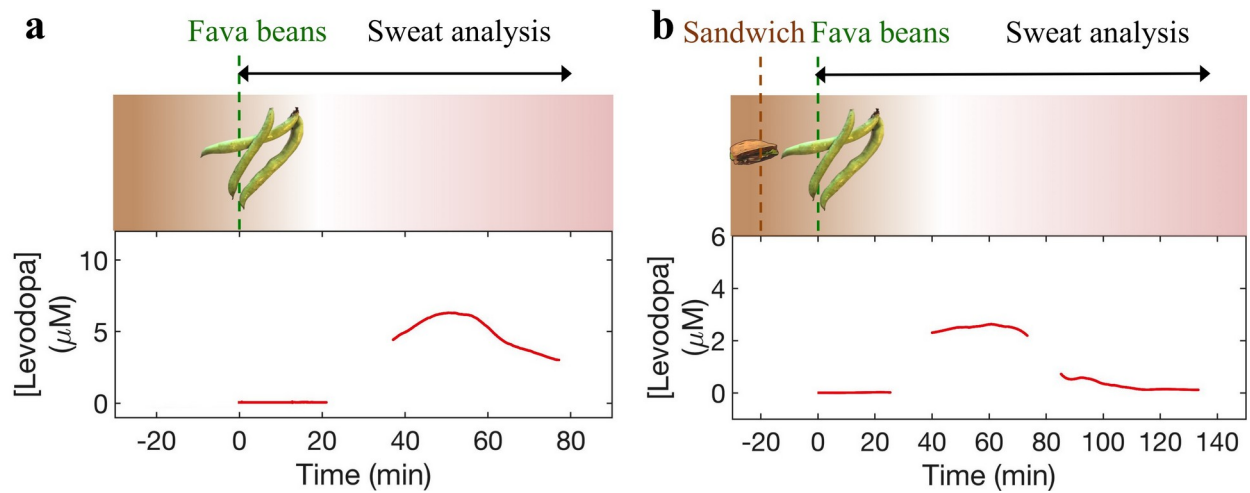


**Figure 2.** Characterization of the functionalized working electrode in PBS. (a) CV of levodopa (LD) dissolved in PBS and (b) zoom-in view for smaller concentration range. (c) Amperometric response of levodopa dissolved in PBS. Inset shows the calibration curve.

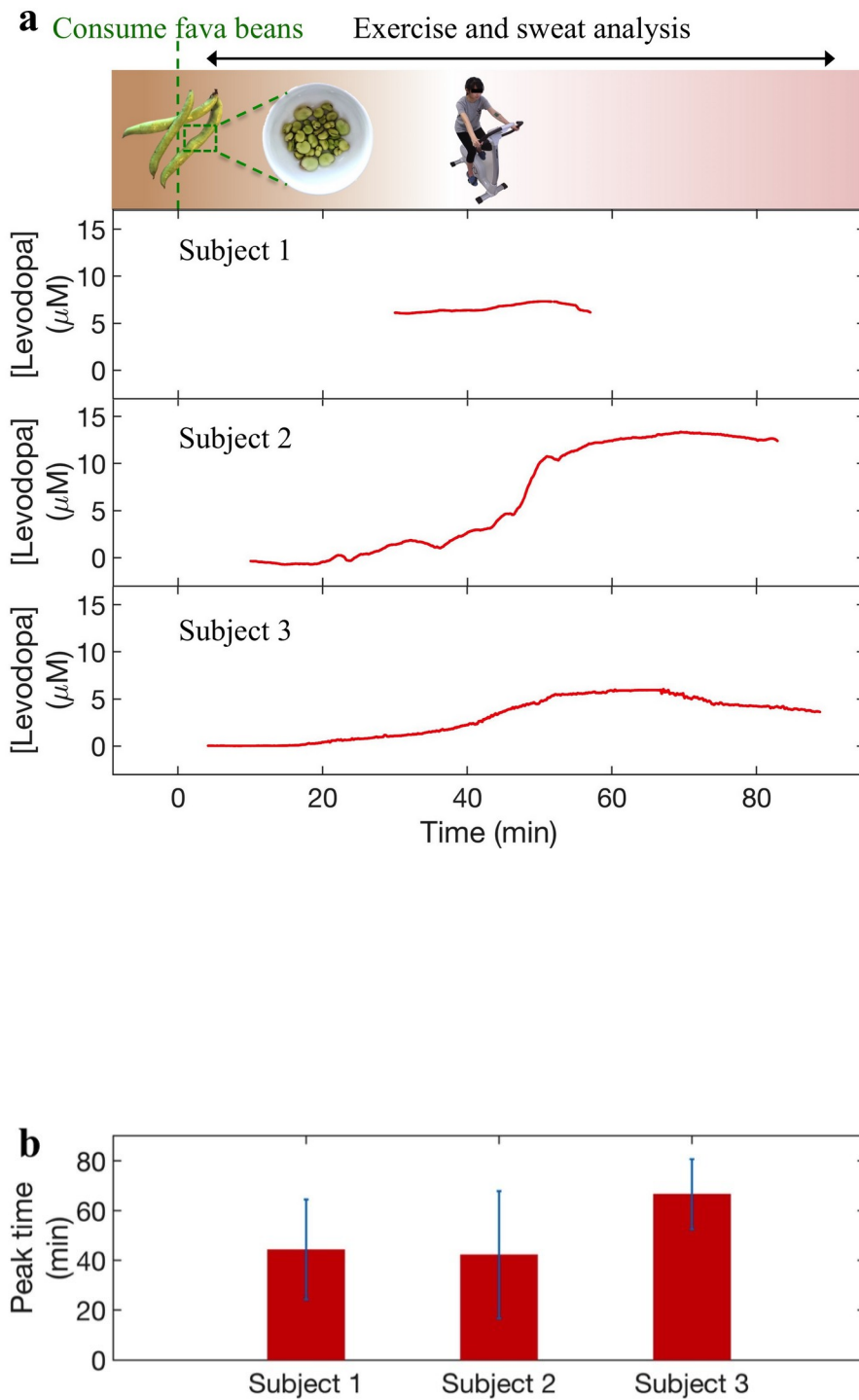


**Figure 3.** Characterization of the levodopa sensor in sweat solution. (a) CV of levodopa dissolved in sweat. (b) Amperometric response of levodopa

dissolved in sweat, and (c) the corresponding calibration curve. (d) Interference study of the levodopa sensor after the addition of levodopa (LD), uric acid (UA), glucose (G) and ascorbic acid (AA).



**Figure 4.** Levodopa monitoring via iontophoresis-induced sweat. Sweat levodopa concentration is monitored continuously after fava beans consumption and subsequent applications of iontophoresis (a) without and (b) with prior dietary consumption. The horizontal axis indicates the time elapsed after the subject consumes 450 mg of fava beans.



**Figure 5.** Levodopa monitoring via exercise induced sweat. (a) Cycling and sweat analysis. Examples of sweat levodopa concentrations for three different subjects after they consume 450 mg of fava beans. (b) Averaged

time of peak levodopa concentration for three different subjects across multiple exercise trials.

## ASSOCIATED CONTENT

### **Supporting Information.**

Figure S1. Method of determining the peak potential.

Figure S2. CV of levodopa dissolved in PBS tested with bare Au working electrode.

Figure S3. Long-term drift test for the functionalized working electrode.

Figure S4. Levodopa sensor response with iontophoresis-induced sweat without fava beans consumption.

(Word Document)

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### **Author Contributions**

L.-C.T. and A.J. designed the experiments. L.-C.T., T.S.L., Y.L., and A.J. contributed to data collection, analysis and interpretation. L.-C.T., T.S.L., Y.L., H.Y.Y.N., M.B., W.J., M.H., and C.Z. contributed to sensor fabrication and preparation. L.-C.T. and A. J. wrote the paper and all authors provided feedback.

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# TABLE OF CONTENTS. A Wearable Sweat Band for Noninvasive Levodopa Monitoring.

