Research report on

Infrared Pupillometry and Eye-tracking as Next-generation Non-Intrusive Means to Identify Subjects Under Influence of Psychoactive Drug and Vision-related Harms

Submitted to

Beat Drugs Fund Association

Submitted by
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Contents

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SKH Holy Trinity Church Secondary School

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2. Background:

Pupillary light reaction (PLR) is known to subject to the effects of psychoactive substances (PAS) through the autonomic nervous system. Stimulants such as crystal methamphetamine (Ice), ketamine, and cocaine cause pupil dilatation (mydriasis) while narcotics including heroin cause pupil constriction (miosis). Although definition of a "normal" pupil size is currently lacking due to inter-individual variation of pupil size secondary to the effect of age, emotion, fatigue, medical and ocular condition as well as systemic and ocular medications, the above PAS were shown to impair PLR which in turn can be quantified by infrared pupillometry (iP) as the temporal sequence of changes in the size of the pupil upon light stimulus. The basic components include response time, 2/3 constriction time, 1/3 redilatation time and slow-phase dilatation velocity using light of low, medium, and highest intensities (PLR 64, 128, 255) or that based on initial pupil diameter (PLR+).

The applicability and validity of iP as a standardised and objective method to indicate the Influence of Psychoactive Drug (iPAD) have been demonstrated by Monticelli et al. to evaluate driving abilities of each participant. In particular, the shorter response time (at PLR 20, PLR 60, PLR 254), the shorter 2/3 constriction time (at PLR 60, PLR 254, PLR+), the lower slow phase dilatation velocity (at PLR 60 and PLR 254) from all recruited psychoactive substance abusers (PSA) (n=105) showed no overlap when compared to an age-matched control group (n=41). Drug status was classified by venous blood toxicology screening as gold standard.

Advances in technologies allow high-speed iP to be measured within a virtual-reality (VR) headset. It provides a portable, enclosed and standardized testing environment without ambient light disturbance which is crucial for iP. It can also track eye movements during display of pictures or videos designed for further evaluation or education. Eye-tracking (ET)

detects cognitive components of PAS use, such as attentional biases, which are related to drug-seeking behaviour and relapse during rehabilitation. Attentional bias for PSA means their subconscious tendency to focus on or pay attention to PAS-related cues such as crystals, pills, powder, and paraphernalia. Attentional bias may explain why PSA seem to be surrounded by relatively many temptations, which makes abstinence even more challenging. Recent research supports the idea that attentional bias towards drug cues is related to the intensity and persistence of the addictive behaviours. Dependent subjects were found to exhibit greater anti-saccade errors, longer reaction time latencies, and greater pupil diameters (during fixation) on drug-related stimuli. Saccade (eye movement)-based measurement of attentional bias was found useful to assess reactivity to drug cues and to screen for potential relapse prevention interventions.

Objectives:

1. Building normative and drug-specific local database of Infrared Pupillometry and Eye-Tracking (iP&ET) data with **300 cases** and vision-related harm by partnering with tertiary institutions/vacation training centres, counselling centres for psychotropic substance abusers, rehabilitation centres and accident & emergency department and specialty clinics attended by PSA.

2. Evaluating test performance (sensitivity, specificity, positive and negative predictive values) of iP&ET compared to the existing urine & hair tests for different drugs and target groups. Develop specific testing algorithm and modelling to further pinpoint the effect of the four most commonly abused psychoactive substances in Hong Kong including Ice, ketamine, cannabis, and cocaine.

3. Conduct pre-test and post-test surveys on the acceptance and uptake of headsets-based iP&ET, urine, and hair tests at organizational and individual levels.

4. Distribute information on drug-related harm when subjects watch the VR video.

5. Collect local prevalence on eye-related symptoms and visual harm among PSA.

Output indicator:

1. Organize health talks with topics on the damage of drug abuse on visual systems for 3,000 secondary school students
2. Provide 200 participants with VR experience (games or videos) using the VR headsets with iP&ET function
3. To organize 5 workshops for 50 anti-drug workers/teachers for using iP&ET in screening test
4. To use iP&ET as monitoring tools for prevention of drug abuse among 100 rehabilitees

Outcome indicator:

1. 80% of health talk participants understand the damage of psychoactive substance abuse on visual system
2. 80% of anti-drug workshops participants learn how to use iP&ET screening test
3. Successful quitting psychoactive substance rate of rehabilitee used iP&ET for monitoring is higher than that of rehabilitee without used iP&ET for monitoring

3. Methods:

3.1 Design

Number and nature of subject involved in iP&ET

A total of 625 subjects participated in iP&ET while 606 completed all study procedures, they were divided into 4 groups.

1. **Group 1: 300** secondary school students participating in the Healthy School Programme with a Drug Testing Component
2. **Group 2: 100** students from tertiary institutes
3. **Group 3: 100** high-risk youth and young adults outside school network who are clients of the collaborating non-governmental organizations
4. **PSA group: 106** rehabilitees recruited from Counselling Centres for Psychotropic Substance Abusers (CCPSA), drug treatment and rehabilitation centres (DTRC) and clinics attended by PSA with 2 sets (initial and follow-up) VR iP&ET done
5. **PSA group: 19** rehabilitees only 1 set of VR iP&ET test

Table 1. Descriptive statistics of groups of participants involved in VR iP&ET (N=625)

Group	Healthy Group	PSA Group
Group 1 (Secondary School students) Group 2 (Tertiary school students) Group 3 (High-risk youth)	500	Not Applicable
PSA group (Rehabilitee) (Completed two VR iP&ET test)		106
PSA group (Rehabilitee) (Completed one VR iP&ET test)	Not Applicable	19

3.2 Research activities conducted

3.2.1 Health Seminars

Because of the COVID-19 pandemic, apart from face-to-face format, we also arrange virtual health seminars. We organized 10 health seminars on substance abuse and related eye health in general given by faculty members of the Department of Ophthalmology & Visual Sciences, the Chinese University of Hong Kong for participating secondary schools.

A total of **3099** secondary students participated in the health talks, with 83.4% of participants found to have improved their understanding of the impacts of drug abuse on health after the seminar.

3.2.2 Exhibition in Tertiary institutes

We collaborated with the Chinese University of Hong Kong to set up booths inside the campus to provide free VR experience using the VR headsets and VR-based eye examination. Apart from booths, we also recruited tertiary students via university mass email and snowballing. We recruited **100** tertiary students to participate in the iP&ET screening test. Demographic and visual-related data were recorded after obtaining consent from the participant. A $50 supermarket coupon as incentive were provided to the subjects who completed all study procedures (iP&ET, VR educational video, pre-test and post-test questionnaire, urine test and eye examination).

3.2.3 Exhibitions in community centres for high-risk youth

A total of **100** high-risk youth had participated in our study and each subject was given a $50 supermarket coupon after completion of all study procedures (iP&ET, VR educational video, pre-test and post-test questionnaire, urine test and eye examination).

We partnered H.K.S.K.H. Shatin Children and Youth Integrated Service Centre to hold an exhibition, which introduced a VR-based eye examinations. We also promoted the recruitment through social media, snowballing and exhibitions in CUHK Eye Centre.

3.2.4 Workshops for frontline anti-drug workers

We have organized **5** workshops with a total of 51 frontline anti-drug social workers. Workshops included a sharing session by the research team on the background, basic iP&ET knowledge and significance, tutorial on how to use VR iP&ET and hands-on experience session. All participate filled in post-workshop online questionnaire to evaluate their understanding on VR iP and ET.

Below are the centres that had participated in the frontline workshop (arranged in alphabetical order):

1. Tung Wah Group of Hospitals Integrated Centre on Addiction Prevention and Treatment (ICAPT)
2. The Society of Rehabilitation and Crime Prevention, Hong Kong (SRACP) - Kin Sang Revival Hub (Tuen Mun)
3. The Society of Rehabilitation and Crime Prevention, Hong Kong (SRACP) - Kin Sang Revival Hub (Chuk Yuen Revival Hub)
4. The Society for the Aid and Rehabilitation of Drug Abusers (SARDA) - Kowloon Hostel
5. The Society for the Aid and Rehabilitation of Drug Abusers (SARDA) - Luen Ching Centre

Figure 1: Sharing and tutorial material to frontline anti-drug participants

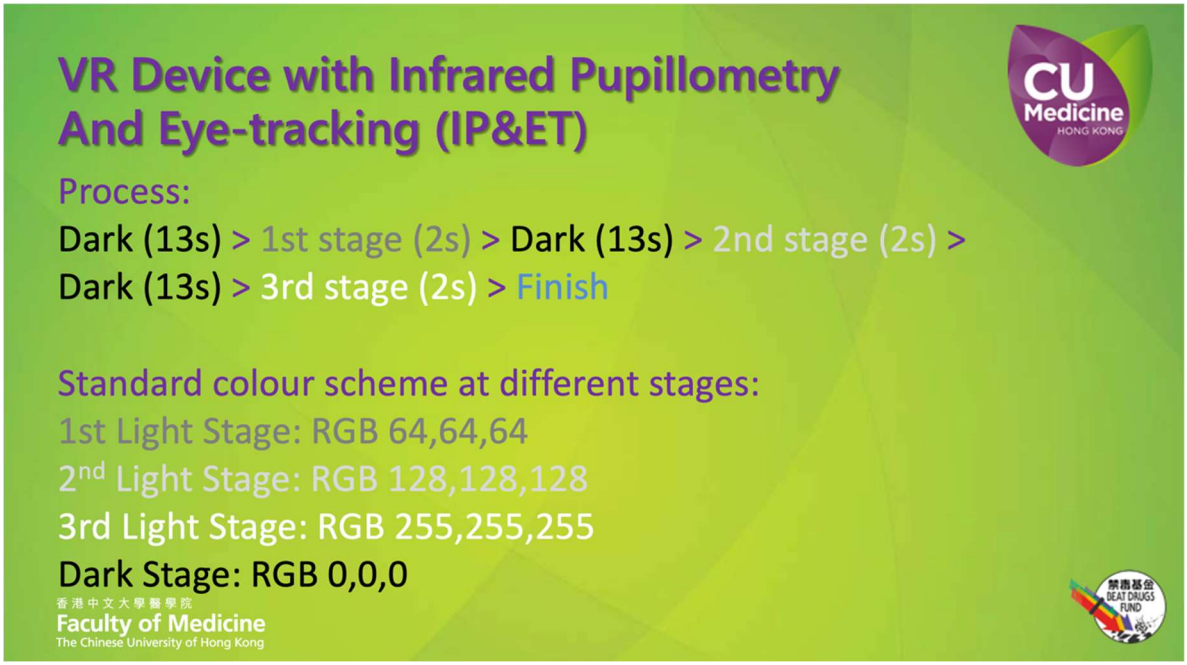

Figure 2: Post-workshop online questionnaire

BDF iP&ET Workshop Pre-Test (東華三院心瑜軒)

登入 Google即可儲存您的進度。瞭解詳情

*必填

名字 *

您的答案

Q1: 你有否使用過虛擬實境裝置? *

有

沒有

Q2: 你認為自己在多大程度上明白虛擬實境系統測試的背後原理? *

	1	2	3	4	5	6	7	8	9	10	
最不明白	○	○	○	○	○	○	○	○	○	○	最明白

Q3: 你認為自己在多大程度上能夠獨立操作虛擬實境系統? *

	1	2	3	4	5	6	7	8	9	10	
最不能夠	○	○	○	○	○	○	○	○	○	○	最能夠

Q4: 你認為自己在多大程度上能夠跟隨虛擬實境系統的指示? *

	1	2	3	4	5	6	7	8	9	10	
最不能夠	○	○	○	○	○	○	○	○	○	○	最能夠

Q5: 你認為自己在多大程度上能從旁指導虛擬實境系統使用者時提供清晰的指示? *

	1	2	3	4	5	6	7	8	9	10	
最不能夠	○	○	○	○	○	○	○	○	○	○	最能夠

3.2.5 Using pupillometry as drug abuse monitor in rehabilitation centres

We cooperated with the rehabilitation centres to use our VR-based iP&ET as a repeatable, low-cost, and non-intrusive monitoring tool to monitor rehabilitees' progress and prediction of relapse.

Below are the rehabilitation centres that collaborated with us on the VR-based iP&ET (arranged in alphabetical order):

1. Kowloon Hostel, The Society for Aid and Rehabilitation of Drug Abusers
2. The Society of Rehabilitation and Crime Prevention, Hong Kong (SRACP) - Kin Sang Revival Hub (Tuen Mun)
3. The Society of Rehabilitation and Crime Prevention, Hong Kong (SRACP) - Kin Sang Revival Hub (Chuk Yuen Revival Hub)
4. Tung Wah Group of Hospitals Integrated Centre on Addiction Prevention and Treatment (ICAPT)
5. The Society for the Aid and Rehabilitation of Drug Abusers (SARDA) - Luen Ching Centre

All subjects were invited to use our VR-based iP&ET after three months of first visit. Upon the completion of 2 visits, a total of $300 supermarket coupon as incentive were provided for the subjects who completed all study procedures (iP&ET, VR educational video, pre-test and post-test questionnaire, urine test and eye examination).

3.2.6 Conducting psychoactive substance screening test using iP&ET

300 teenagers were recruited after health seminars and from the siblings of Hong Kong Children Eye programme participants.

300 pupillometric and urine test result for screening test were collected to evaluate of accuracy of iP&ET. And they watched VR-based anti-drug educational video after VR test.

300 participants were completed pre-test and post-test questionnaire on acceptance of iP&ET compare to urine test.

Below are the secondary schools that collaborated with us on the VR-based iP&ET (arranged in alphabetical order):

1. Caritas Yuen Long Chan Chun Ha Secondary School
2. SKH Holy Trinity Church Secondary School
3. S.K.H. Bishop Mok Sau Tseng Secondary School
4. The Assn. of Directors & Former Directors of Poi Oi Hospital Ltd. Leung Sing Tak College

3.3 Participants

Referral sources

1. Students from the secondary schools participating in the Healthy School Programme and tertiary institutes
2. At-risk students (those with poor academic results, or have skipped schools, demonstrated delinquent or violent behaviour, or had conflicts with school authority) and high-risk youths (those who dropped out from schools, or identified by outreaching team) and young adults outside school network who are as casework clients of the collaborating non-governmental organizations
3. Clients recruited from Counselling Centres for Psychotropic Substance Abusers (CCPSA), drug treatment and rehabilitation centres (DTRC) and clinics attended by PSA (psychiatry, urology, medical and accident & emergency)

3.4. Inclusion and exclusion criteria

Inclusion criteria

1. Informed consent to participate the study
2. Completion of the study procedures (iP&ET, VR educational video, pre-test and post-test questionnaire and urine test).

Exclusion criteria

1. Known systemic (such as diabetes), neurological (such as stroke) or ophthalmic (such as uveitis, nystagmus) disorders affecting the autonomic nervous systems
2. History of brain or eye related trauma (including surgeries)
3. Failure to provide informed consent or to complete any part of the study procedures (iP&ET, questionnaires, urine sample)

Figure 3: Questions/exclusion criteria to participants

	問題/排除標準 Questions/ Exclusion Criteria	有 Yes	沒有 No
1.	你有沒有患有吸食毒品相關的眼部症狀(例如:紅眼症,乾眼症)? Do you have common substance-abuse related ocular symptoms (e.g. Red eye, dry eye)? If yes, please specify.	☐	☐
2.	你有沒有患有系統性疾病 (例如:糖尿病)? 如有，請說明之。 Do you have systemic disorders (e.g. diabetes)? If yes, please specify	☐	☐
3.	你有沒有患有神經疾病 (例如:腦腫瘤)? 如有，請說明之。 Do you have neurological disorders (e.g. brain tumors)? If yes, please specify	☐	☐
4.	你有沒有患有眼科疾病(例如:白內障)?如有，請說明之。 Do you have ophthalmic disorders, Eye diseases (e.g. cataracts)? If yes, please specify	☐	☐
4.1	你有沒有患有紅眼，乾眼，眼線模糊，重影等疾病? Do you have red eye, dry eye, blurry vision, double vision?	☐	☐
5.	你有沒有患有影響自主神經系統的疾病?如有，請說明之。 Do you have any kind of disorders that affect autonomic nervous system? If yes, please specify	☐	☐
6.	你有否曾經患有腦部創傷 (包括手術)? 如有，請說明之。 Do you have history of brain related trauma (including surgeries)? If yes, please specify	☐	☐
7.	你有否曾經患有眼部創傷(包括手術)? 如有，請說明之。 Do you have history of eye related trauma (including surgeries)? If yes, please specify	☐	☐

3.5 Informed consent and ethics approval

Our study is approved by Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Ref.No.:2019.007).

All participants signed the informed consent during first visit. Basic information, drug use status, iP and ET data, urine sample for toxicology screening, and ophthalmic investigation results will be collected. Subject identity and test results are kept confidential. Informed consent also includes the risks and possible adverse side effects from virtual environment including motion sickness, disorientation, eye discomfort and dizziness, where a very small portion of the population may experience epileptic seizures in susceptible individuals (such as pre-existing seizures) when viewing certain kinds of flashing lights or patterns that are commonly present in daily activities.

3.5. Apparatus

Earlier experiments were done using HTC Vive Pro Eye with Pupil Lab eye-tracking add-on. But due to technical compatibility and hardware consistency, the results reported were captured by HTC cosmos head mounted display with Droolon F1® eye-tracking add-on.

HTC Cosmos head mounted display (HMD) is integrated with eye-tracking Droolon F1® add-on. HMD with dual 3.4” diagonal screen ad 1440x1700 pixels per eye (2880x1700 pixels combined) and 90hz refresh rate and 110 degrees field of view. VR experiments described below followed the HTC VIVE VR safety and regulatory guidelines.

3.6 Infrared pupillometry (iP) and Eye-Tracking (ET)

3.6.1 Infrared pupillometry

Infrared pupillometry is first performed using the VR headset with the Droolon F1® eye-tracking add-on cameras, which provides latency less than 5ms and 120hz sampling rate. Measurements will be taken on each eye and results of both eyes will be selected for use. Initial pupil size, response time, 2/3 constriction time, 1/3 re-dilatation time and slow-phase dilatation velocity using light of low (PLR 64) (RGB 64, 64, 64), medium (PLR 128) (RGB 128, 128, 128) and highest intensities (PLR 64) (RGB 255, 255,255) that based on initial pupil diameter (PLR+) will be recorded.

Repeatability and reproducibility were evaluated based on the definitions adopted by the British Standards Institution. Under repeatability conditions, independent test results are obtained with the same method, on the same subject, by the same operator, and on the same set of equipment with the shortest time lapse possible between successive sets of readings. We investigate repeatability by completing 10 sets of iP&ET tests. All scanning will be performed by the same operator. The time elapsed between successive test will correspond to the time taken to save the previous data and the headset will be adjusted if necessary for not more than a few seconds. Repeatability will be evaluated with 5 urine-negative healthy volunteers. Inter-session reproducibility will be examined with another 5 urine-negative healthy volunteer 2 weeks apart for three sets of iP&ET tests.

3.6.2 Eye-tracking

Eye-tracking technology is adopted to measure performance on counterbalanced blocks of pro-saccade and anti-saccade trials featuring drug-related and neutral stimuli (pictures). Dependent measurements including anti-saccade errors, saccadic response times and latencies, and pupil diameter during fixation on stimuli will be recorded.

3.6.3 Procedure

For Group 1 (secondary school student), Group 2 (tertiary student), and Group 3 (high-risk youth), participants were required to provide basic demographic information, sign the consent (for Group 1 participants, the consent form will be signed by parents or guardians), and finish Pre-VR and Post-VR questionnaire and eye examination datasheet. For PSA group, rehabilitees had to fill in additional information, including drug use status, Chinese Drug Involvement Scale (C-DIS) form.

After finishing all documents, participants wore the VR headset and were asked to follow instructions to complete calibration. Participants needed to follow the light blue circle with their eyes (Figure 4), allowing the eye-tracking sensor to calibrate with the eyeball spatial position and ensure the accuracy of data collected via eye-tracking sensor.

After calibration, the VR display shows 3 cycles of light stage, where the protocol of cycles of light stage is shown in Table 2. Subjects' pupil size will be captured with 120Hz sampling rate via Infrared pupillometry in VR headset.

Table 2: Protocol of 3 cycles of light stage

Stage	Stage:	PLR/RGB	Duration (second)
1st	Dark Stage	(PLR 0) (RGB 0, 0, 0)	13s
1st	Low light intensity	(PLR 64) (RGB 64, 64,64)	2s
2nd	Dark Stage	(PLR 0) (RGB 0, 0, 0)	13s
2nd	Medium light intensity	(PLR 128) (RGB 128, 128,128)	2s
3rd	Dark Stage	(PLR 0) (RGB 0, 0, 0)	13s
3rd	High light intensity	(PLR 255) (RGB 255,255,255)	2s
4th	Dark Stage	(PLR 0) (RGB 0, 0, 0)	13s

After 3 stages of light stimuli, 13 sets of pictures will be shown (figure 7), including 3 sets of control picture and 10 sets picture with either normal or drug related content. Under the eye-tracking part, we keep the environment quiet and comfortable to let subjects to undergo the test in a relaxed manner. And each subject is instructed to look freely around to minimize any bias caused by unintentional gaze on either type of picture.

Figure 4: Introduction video during VR iP&ET test

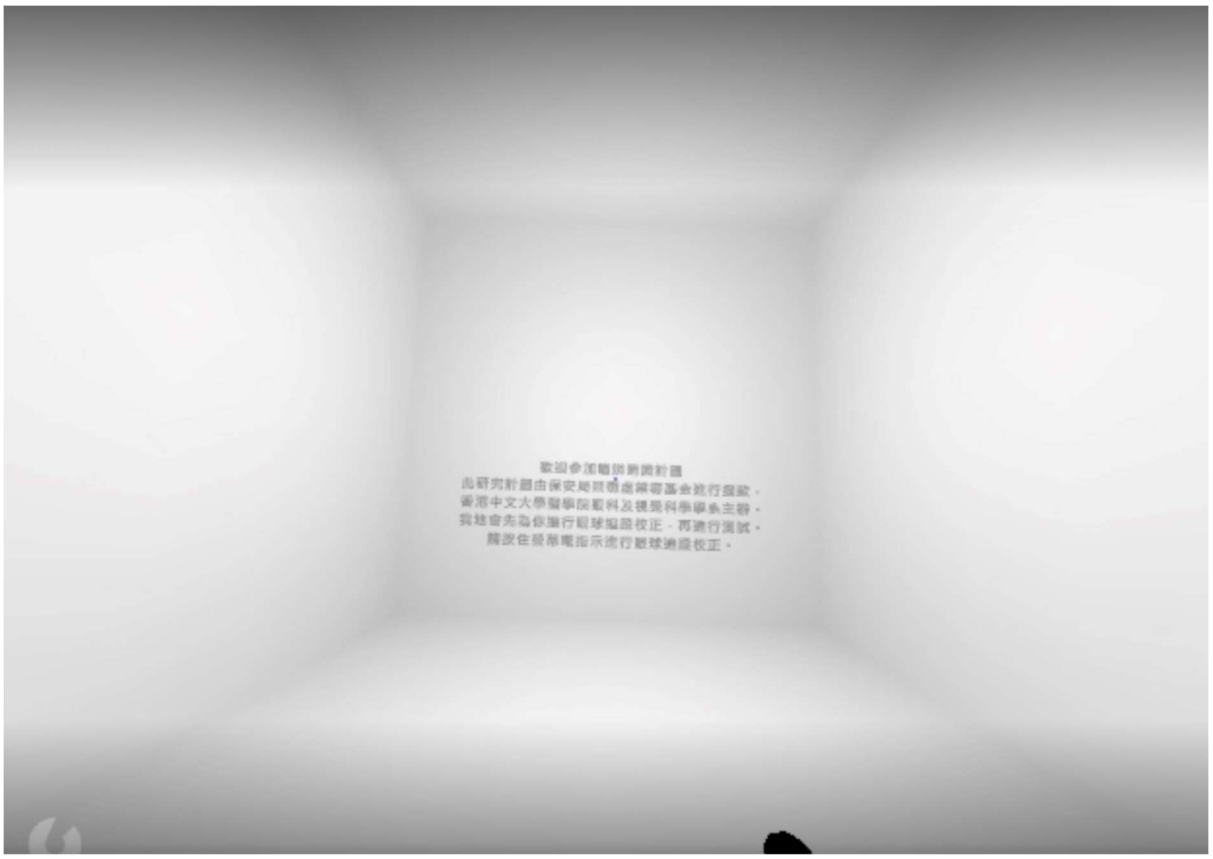

Figure 5: Calibration during VR iP&ET test

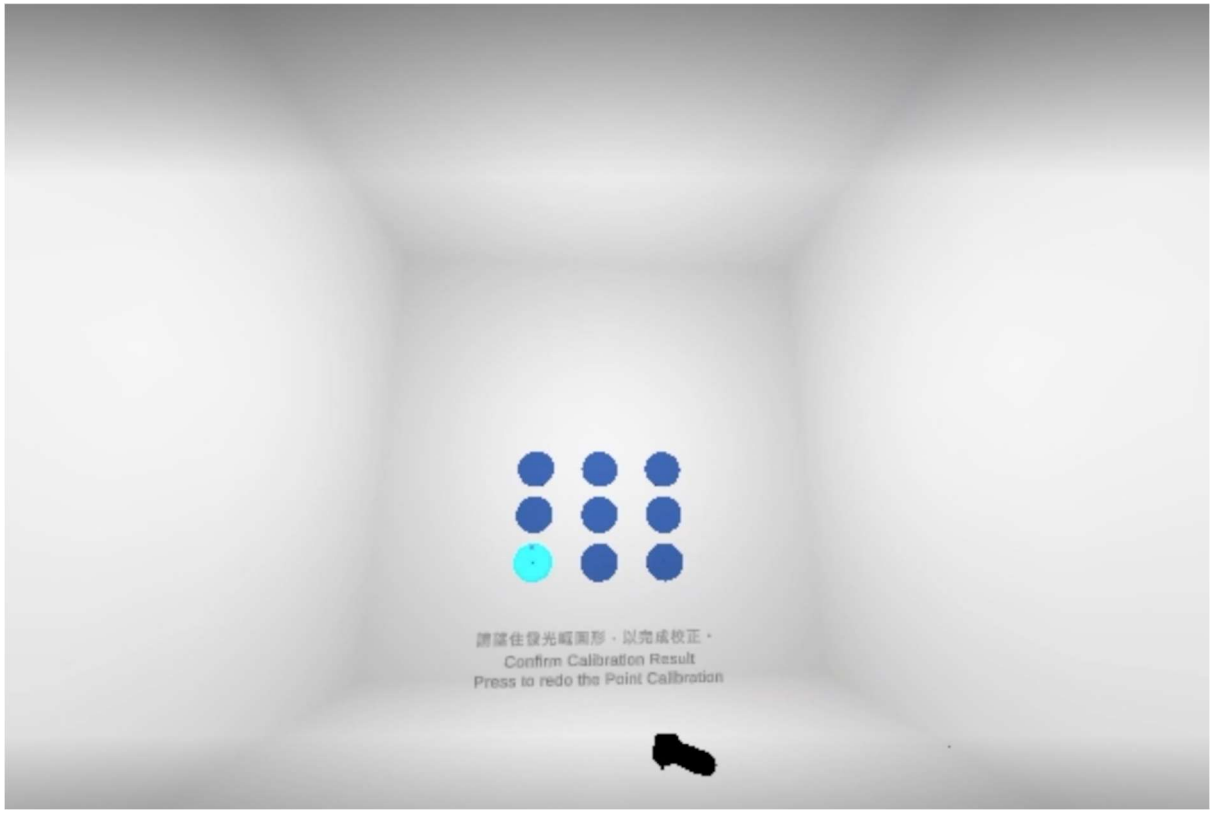

Figure 6: Light stage (moderate intensity) (PLR 128)

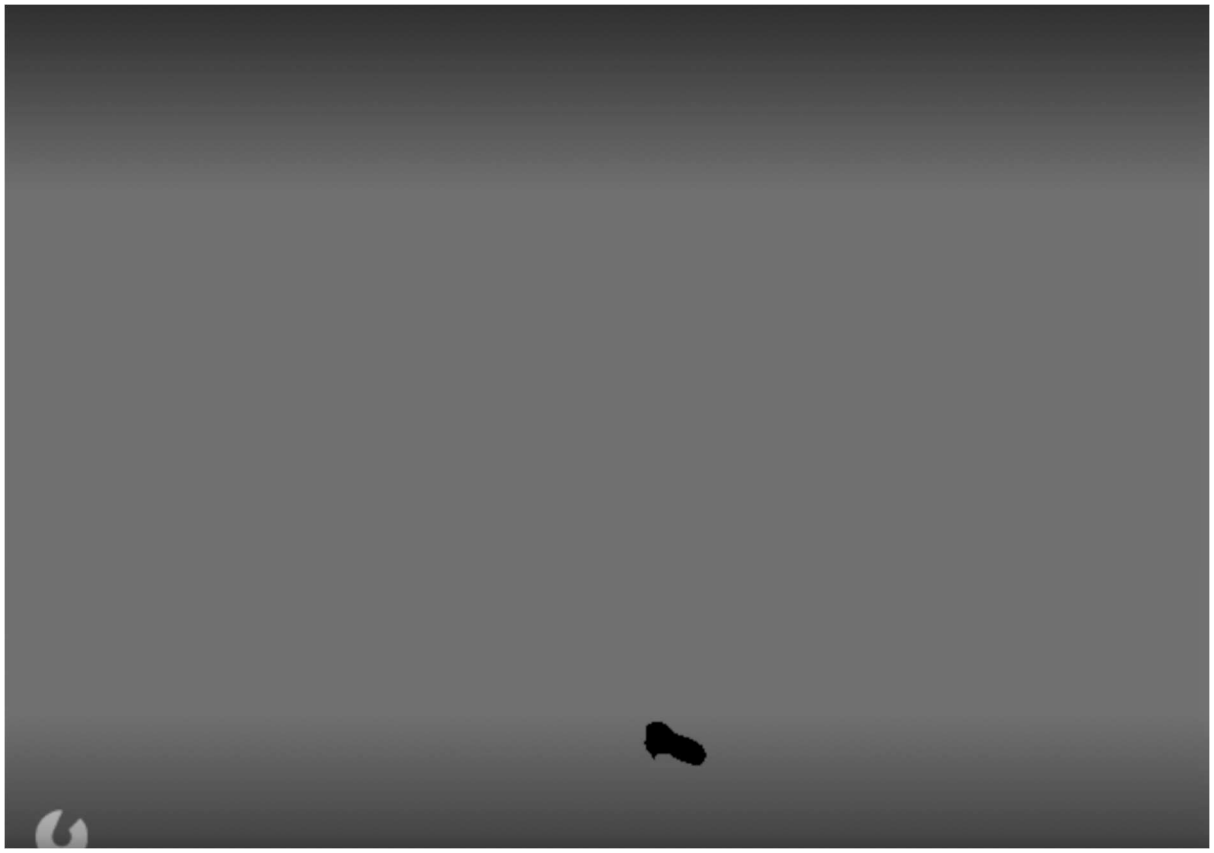

Figure 7: Eye-tracking part in VR iP&ET test

3.6.4 VR video for education

A 5-minute VR educational video based on real-case referral from Department of Psychiatry, the Chinese University of Hong Kong, was provided after iP and ET test. The video content includes a real-case story, directed by an ex-drug addict to convey the message of mental and physical harm caused by drug abuse.

Figure 8: VR video clip for education

3.7 Ophthalmic investigation and examination

A complete ophthalmic examination performed by ophthalmologists will be provided in Chinese University of Hong Kong Eye Centre for Group 2, Group 3, and PSA Group subjects. Systemic and ophthalmic history including all known eye diseases, systemic diseases, smoking status, Ocular Surface Disease Index (OSDI) will be taken. And the ophthalmic examinations include visual acuity (VA), extraocular movement (EOM), Ishihara and D-15 colour test, Schirmer's test (ST), slit lamp examination and a series of dry eye investigations.

Figure 9: Eye examination sheet (1)

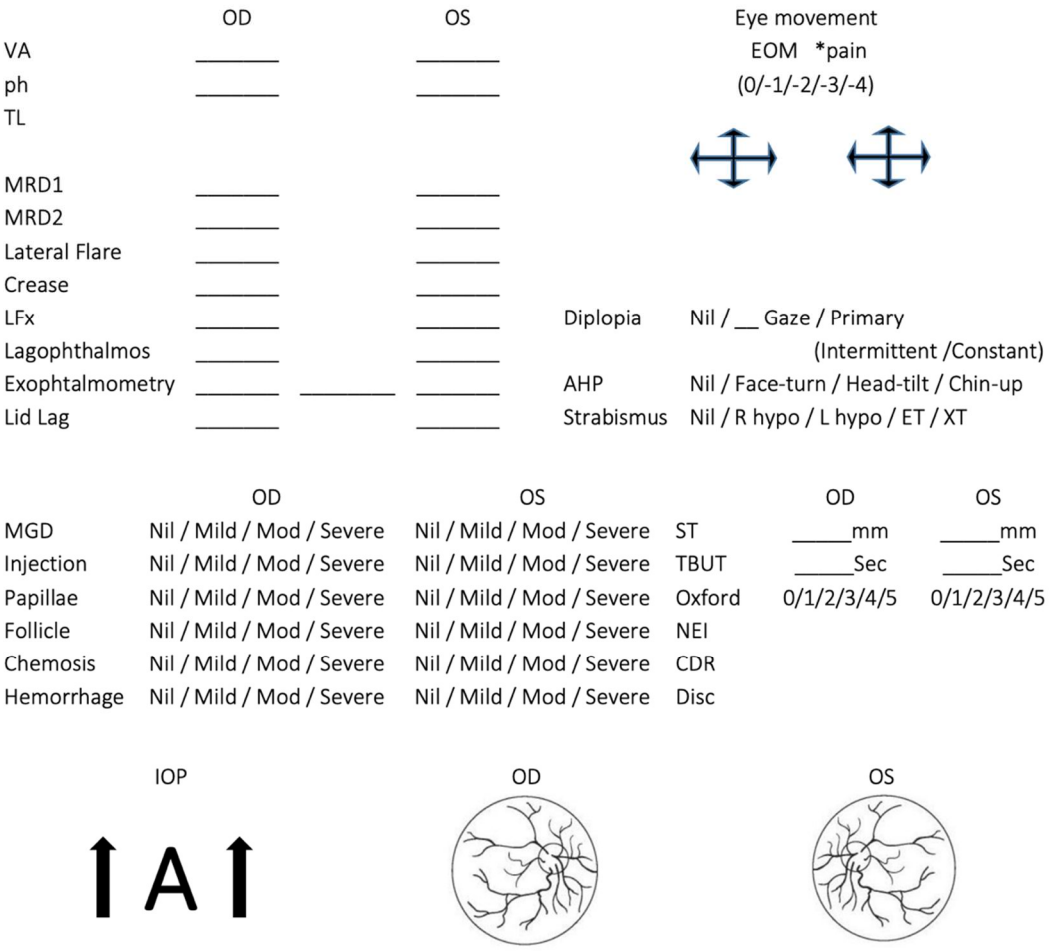

Figure 10: Eye examination sheet (2)

Drug Related Eye Symptoms

Eye Movements

	OD	OS
Nystagmus	✓ / ✗	✓ / ✗
Others	_____	

Sclera

	OD	OS
Episcleritis	✓ / ✗	✓ / ✗
Scleritis	✓ / ✗	✓ / ✗
Others	_____	

Iris

	OD	OS
Miosis	✓ / ✗	✓ / ✗
Mydriasis	✓ / ✗	✓ / ✗
Bloodshot eyes	✓ / ✗	✓ / ✗
Others	_____	

Eyelid

	OD	OS
Blepharospasm	✓ / ✗	✓ / ✗
Ptosis	✓ / ✗	✓ / ✗
Lid retraction	✓ / ✗	✓ / ✗
Others	_____	

Conjunctival

	OD	OS
Blanching	✓ / ✗	✓ / ✗
Erythema	✓ / ✗	✓ / ✗
Hyperemia	✓ / ✗	✓ / ✗
Others	_____	

Cornea

	OD	OS
Crack Cornea	✓ / ✗	✓ / ✗
Anesthesia	✓ / ✗	✓ / ✗
Keratitis	✓ / ✗	✓ / ✗
Ulceration	✓ / ✗	✓ / ✗
Opacification	✓ / ✗	✓ / ✗
Others	_____	

Retina

	OD	OS
Talc retinopathy	✓ / ✗	✓ / ✗
Retinal ischemia	✓ / ✗	✓ / ✗
Retinal emboli	✓ / ✗	✓ / ✗
Retinal venous occlusion	✓ / ✗	✓ / ✗
Intraretinal hemorrhage	✓ / ✗	✓ / ✗
Toxoplasmic chorioretinitis	✓ / ✗	✓ / ✗

Visual Performance

	OD	OS
Color		
D-15		
Others	_____	

3.8. Urine toxicology investigation

3.8.1 Point-of-care test

For Group 1, spot urine stored in a plastic cup will be tested using point-of-care test kits, BOSON BIOTech Rapid DOA – 5 panel Test card and read as positive, negative, or inconclusive.

3.8.2 Definitive test

For Group 2, Group 3, and PSA group, 10ml of urine will be collected and stored in a plain urine specimen bottle at 2-8C up to 3 days. The samples were sent to the chemical pathology laboratory at the Prince of Wales Hospital using mass spectrometry to screen any drug metabolites based on the existing urine drug libraries with over 100 types of drugs, including Ketamine, Cannabis, Crystal methamphetamine, Cocaine.

3.9 Statistical method

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences Inc., Chicago, Illinois, USA) version 25.0.

4. Results

4.1. Demographics and basic information

A total of 625 subjects had participated in iP&ET, which were classified into 300 secondary school students (Group 1), 100 tertiary students (Group 2), 100 high-risk youth (Group 3) and 125 rehabilitees (PSA Group). Only 106 out of 125 rehabilitees (PSA Group) completed the 2 visits and regarded as finishing the whole study.

Group 1, Group 2, and Group 3 are included into healthy group. 106 rehabilitees who completed 2 visits and all data collection procedures are included into the PSA group.

4.1.1. Healthy Group

Table 3. Descriptive statistics of demographic characteristics of the healthy group (N=500)

Demographic characteristics	Healthy group
Age, mean ± SD (Range)	19.46±8.74 (11 to 66)
Gender (male), n (%)	237 (47.4%)
Smoking history	
Current/Ex, n (%)	10 out of 500 (0.02%)

4.1.2. Rehabilitee

Table 4. Descriptive statistics of demographic characteristics of the PSA group (N=106)

Demographic characteristics	
Age, mean ± SD (Range)	47.95±18.50 (14 to 79)
Gender (male), n (%)	88 (70.4%)
Drug Abuse Duration (Years)	19.47
Smoking history	
Current/Ex, n (%)	47 out of 106 (44.34%)
Mean smoking duration (years)	25.38
Mean number of cigarettes per week	89.36

4.2 Drug Use Pattern

Drug use pattern was documented during the first visit for PSA group subjects and there were 60 mono-drug users and 46 poly-drug users. The most common drug abused in the PSA group was heroin (62.26%), followed by cannabis (33.96%) and Ice (24.53%).

Table 5. Descriptive statistics of self-report of drug use from PSA group in last six months

Types of drugs abused	**Number of cases (Poly-drug user data included)**	
	N	**(%)**
Heroin	66	62.26%
Cannabis	36	33.96%
Crystal Methamphetamine (Ice)	26	24.53%
Ketamine	20	18.87%
Cocaine	13	12.26%
3,4-Methylenedioxymethamphetamine (MDMA)	3	2.83%
Zopiclone	3	2.83%
Midazolam	16	15.09%
Codeine	6	5.66%
Lysergic acid diethylamide (LSD)	2	1.89%
Happy Water (Mixture of methamphetamine, amphetamine, and ketamine)	1	0.94%
Methaqualone	3	2.83%

4.3 Ophthalmic examination

Table 6. Descriptive statistics of the ophthalmic examination result in healthy and PSA group

	Healthy Group (N=200)	PSA Group (N=106)
Visual Acuity		
Good (20/20 or above)	79%	30%
Poor (20/25 or below)	21%	70%
Ocular Surface Disease Index		
0-12 (Normal)	58%	50%
13 or above (Mild to severe)	42%	50%
Schirmer's Test (Average in second)		
>15 (normal tear function)	49%	14%
<15 (mild to severe dry eye)	51%	86%
Color deficits	NA	11.11%
Iris		
Miosis	NA	19%
Mydriasis	NA	2.72%
Bloodshot eyes	NA	3.66%
Conjunctival		
Erythema	NA	3.63%
Hyperemia	NA	3.63%

4.4 Education Seminars

A total of 10 education seminars in secondary school in both virtual and face-to-face format were conducted, which covers the topics of current local drug use trends, the adverse effect of drug abuse, anti-drug messages. 3099 secondary school students participated in the education seminars and completed pre- and post-seminar tests (Figure11) to evaluate the extent of improvement or gain in knowledge about drug. And 2584 (83.4%) participants show improvements compared to pre-seminar test.

Figure 11: Post-seminar test

瞳辨睛識計劃 iP&ET Scheme

Faculty of Medicine
The Chinese University of Hong Kong

活動後評估問卷

班別（學號）：_____

請細心閱讀各題，然後選出你認為最適合的答案。這份問卷只作評估用途，所有資料絕對保密。

1. 吸食氯胺酮 (Ketamine) 會導致以下哪種問題?
   A. 尿頻及小便失禁　B. 煩躁　C. 血壓低　D. 呼吸困難

2. 吸食氯胺酮 (Ketamine) 會對眼睛有什麼影響?
   A. 減弱瞳孔擴張反應　B. 近視　C. 視網膜缺血　D. 沒有影響

3. 吸食大麻 (Cannabis) 會導致以下哪種眼睛疾病?
   A. 近視　B. 青光眼　C. 結膜白化　D. 白內障

4. 以下哪一種不是吸食大麻 (Cannabis) 所引致的問題?
   A. 影響分別顏色的能力　B. 導致閱讀困難　C. 角膜混濁　D. 眼皮退縮

5. 吸食可卡因 (Cocaine) 會導致以下哪種眼睛疾病?
   A. 角膜感覺減退　B. 眼眶炎症　C. 瞳孔放大　D. 以上皆是

6. 以下哪一種不是吸食可卡因 (Cocaine) 所引致的問題?
   A. 影響記憶力　B. 精神錯亂　C. 幻覺　D. 昏睡

7. 吸食海洛因 (Heroin) 會導致以下哪種眼睛疾病?
   A. 白內障　B. 青光眼　C. 視網膜缺血　D. 飛蚊症

8. 以下哪種毒品不會令瞳孔放大?
   A. 甲基安非他命，冰　B. 氯胺酮　C. 海洛因　D. 可卡因

9. 吸食甲基安非他命，冰 (Crystal Methamphetamines,Ice) 會導致以下哪種眼睛疾病?
   A. 角膜感覺神經受損　B. 飛蚊症　C. 視網膜缺血　D. 青光眼

10. 我會提高警覺，遠離毒品。
    A. 同意　B. 不同意

大學醫學院
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University of Hong Kong *Transforming our* Passion *into* Perfection

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香港中文大學 The Chinese University of Hong Kong
保安局禁毒處 Narcotics Division, Security Bureau
禁毒基金 BEAT DRUGS FUND

4.5 Frontline Workshop

5 frontline workshops were held for 51 frontline social workers. The workshops included sharing session with iP&ET and small group hands-on session of learning the use of iP&ET. All 51 participants (100%) were able to perform and demonstrate the iP&ET test.

4.6 VR Perception (Pre and Post VR Questionnaire)

Subjects participated in VR iP&ET test were required to complete pre-VR and post-VR questionnaire, which evaluated their perception towards the use of VR device as drug testing means before and after the experience of iP&ET test. And the comparison between healthy and rehabilitee group is table 9.

4.6.1 Healthy Group

A total of 500 subjects completed the pre-VR and post-VR questionnaire. There were four parts in the questionnaire, 1. acceptance of VR device to replace traditional urine test (Range: 0-10), 2. preference to VR device versus urine test in drug testing (Range: 0%-100%), 3. VR advantages and 4. Urine test advantages (Table 7).

4.6.2 Rehabilitee group

A total of 106 subjects completed the pre-VR and post-VR questionnaire. There were four parts in the questionnaire, 1. acceptance of VR device to replace traditional urine test (Range: 0-10), 2. preference to VR device versus urine test in drug testing (Range: 0%-100%), 3. VR advantages and 4. urine test advantages (Table 8).

Table 7. Descriptive statistics of impression of VR test before and after participation in healthy group (N=500)

Impression of subject on VR	Pre-VR	Post-VR	Changes (%)
Acceptance of VR device to replace traditional urine test (Range: 0-10)	6.75	7.63	**+13.04%**
Preference to VR device versus urine test in drug testing (Range: 0%-100%)	68.28%	81.28%	**+19.04%**
VR test advantages (higher score is better)			
High convenience	1.15	1.27	**+10.43%**
Short waiting time	1.03	1.10	**+6.80%**
High accuracy	0.48	0.57	**+18.75%**
Low geographical limitations	0.89	0.97	**+8.99%**
High entertainment values	1.11	1.30	**+17.12%**
High privacy protection	0.04	-0.03	**-175.00%**
Provision of eye checkup	1.08	1.22	**+12.96%**
High acceptance	1.02	1.15	**+12.75%**
Low labelling effect	0.29	0.19	**-34.48%**
High accessibility in daily life	0.90	1.10	**+22.22%**
Total Score (Range 20 to -20)	7.51	8.24	**+9.72%**
Urine test advantages (higher score is better)			
High convenience	-0.23	-0.37	**-60.87%**
Short waiting time	-0.17	-0.33	**-94.12%**
High accuracy	0.67	0.57	**-14.93%**
Low geographical limitations	-0.28	-0.32	**-14.29%**
High entertainment values	-0.86	-0.97	**-12.79%**
High privacy protection	0.02	-0.03	**-250.00%**
Provision of eye checkup	-0.67	-0.77	**-14.93%**
High acceptance	-0.12	-0.22	**-83.33%**
Low labelling effect	0.08	-0.01	**-112.50%**
High accessibility in daily life	-0.14	-0.30	**-114.29%**
Total Score (Range 20 to -20)	-1.58	-2.52	**-59.49%**

Table 8. Descriptive statistics of impression of VR test after 1st and 2nd experience VR test in rehabilitee group (N=106)

Impression of subject on VR	**1st VR test**			**2nd VR test**		
	Pre-VR	**Post-VR**	**Changes (%)**	**Pre-VR**	**Post-VR**	**Changes (%)**
Acceptance of VR device to replace traditional urine test (Range: 0-10)	6.20	6.71	**+8.23%**	6.17	6.62	**+7.29%**
Preference to VR device versus urine test in drug testing (Range: 0%-100%)	45.6%	56%	**+22.81%**	46.22%	55.66%	**+20.42%**
VR test advantages (higher score is better)						
High convenience	0.70	0.78	**+11.43%**	0.45	0.54	**+20.00%**
Short waiting time	0.47	0.60	**+27.66%**	0.40	0.33	**-17.50%**
High accuracy	0.43	0.40	**-6.98%**	0.24	0.25	**+4.17%**
Low geographical limitations	0.47	0.52	**+10.64%**	0.38	0.25	**-34.21%**
High entertainment values	0.82	0.93	**+13.41%**	0.50	0.48	**-4.00%**
High privacy protection	0.21	0.72	**+242.86%**	0.08	0.15	**+87.5%**
Provision of eye checkup	0.56	0.63	**+12.50%**	0.37	0.29	**-21.62%**
High acceptance	0.59	0.68	**+15.25%**	0.35	0.31	**-11.43%**
Low labelling effect	0.19	0.20	**+5.26%**	0.17	0.16	**-5.88%**
High accessibility in daily life	0.61	0.82	**+34.43%**	0.43	0.38	**-11.63%**
Total Score (Range 20 to -20)	5.05	6.28	**+24.36%**	3.37	3.14	**-6.82%**
Urine test advantages (higher score is better)						
High convenience	0.28	0.16	**-42.86%**	0.05	0.16	**+220.00%**
Short waiting time	0.24	0.32	**+33.33%**	-0.03	0.04	**+233.33%**

High accuracy	0.54	0.52	**-3.70%**	0.24	0.17	**-29.17%**
Low geographical limitations	0.16	0	**-100%**	-0.14	-0.10	**+28.57%**
High entertainment values	-0.29	-0.51	**-75.86%**	-0.30	-0.19	**+36.66%**
High privacy protection	0.19	0.88	**+363.16%**	0.04	-0.02	**-150.00%**
Provision of eye checkup	-0.12	-0.28	**-133.33%**	-0.16	-0.16	**+0.00%**
High acceptance	0.11	0.72	**+554.55%**	-0.07	-0.07	**+0.00%**
Low labelling effect	0.17	0.16	**-5.88%**	-0.02	-0.03	**-50.00%**
High accessibility in daily life	0.40	0.16	**-60.00%**	-0.08	-0.10	**-25.00%**
Total Score (Range 20 to -20)	1.68	2.13	**+26.79%**	-0.47	-0.3	**+36.17%**

Table 9. Descriptive statistics of comparison of VR test impression between healthy and PSA group

Impression of subject on VR and urine test	Average score of pre-VR and post-VR		
	Healthy group	**PSA group**	**Difference**
Acceptance of VR device to replace traditional urine test (Range: 0-10)	7.19	6.43	0.76 (10.57%)
Preference to VR device versus urine test in drug testing (Range: 0%-100%)	74.78%	50.87%	23.91%
VR test advantages (higher score is better)			
High convenience	1.20	0.62	0.58 (48.33%)
Short waiting time	1.06	0.45	0.61 (57.54%)
High accuracy	0.52	0.33	0.19 (36.53%)
Low geographical limitations	0.93	0.41	0.52 (55.91%)
High entertainment values	1.20	0.68	0.52 (43.33%)
High privacy protection	0.00	0.29	0.29 (100.00%)
Provision of eye checkup	1.15	0.46	0.69 (60.00%)
High acceptance	1.09	0.48	0.61 (55.96%)
Low labelling effect	0.24	0.18	0.06 (25.00%)
High accessibility in daily life	1.00	0.56	0.44 (44.00%)
Total Score (Range: -20 to 20)	7.87	4.46	3.41 (43.32%)
Urine test advantages (higher score is better)			
High convenience	-0.30	0.16	0.46 (153.33%)
Short waiting time	-0.25	0.14	0.39 (156.00%)
High accuracy	0.62	0.37	0.25 (40.32%)
Low geographical limitations	-0.30	-0.02	0.28 (93.33%)
High entertainment values	-0.92	-0.32	0.60 (65.21%)
High privacy protection	0.00	0.27	0.27 (100.00%)
Provision of eye checkup	-0.72	-0.18	0.54 (75.00%)
High acceptance	-0.17	0.17	0.34 (200%)
Low labelling effect	0.05	0.07	0.02 (40%)
High accessibility in daily life	-0.23	0.10	0.33 (143.47%)
Total Score (Range 20 to -20)	-2.05	0.76	2.81 (137.07%)

4.7. Chinese Drug Involvement Scale (C-DIS)

All PSA group subjects (N=106) completed C-DIS at their 1st and 2nd visits. A higher score denotes more problematic beliefs and values relating to drug abuse. We use C-DIS as a tool to evaluate the change of PSA group subject's perception and belief on drug abuse before and after VR iP&ET. The average total score of 1st visit is 64.12, while 2nd visit is 60.94, and an improvement shown as 4.95%.

Table 10. Descriptive statistics of scores of Chinese Drug Involvement Scale in PSA group subjects (N=106)

PSA group	Average total score (Lower score is better)
1st visit	64.12
2nd visit	60.94
Improvement rate	4.95%

4.8. Infrared Pupillometry (iP)

4.8.1 Assessment of pupillometry data

All pupillometry data evaluated by 3 masked observers is categorized into either normal pupillary response (NPR) or pupillary unrest (PU). The observers were instructed to grade the pupillometry graphs with the standard example of NPR and PU (standard example 1, 2, 3, 4 with figure 12-15) and reference to following criteria.

4.8.2 Normal pupillary response (NPR)

An NPR graph shows the following characteristics and criteria:

1. Steady pupil constriction and re-dilatation at the end of the light stage
2. Smooth pupil dilation during dark stage
3. Shorter time to recover to baseline of pupil size after each light stage

Figure 12: Standard example 1 on normal pupillary response

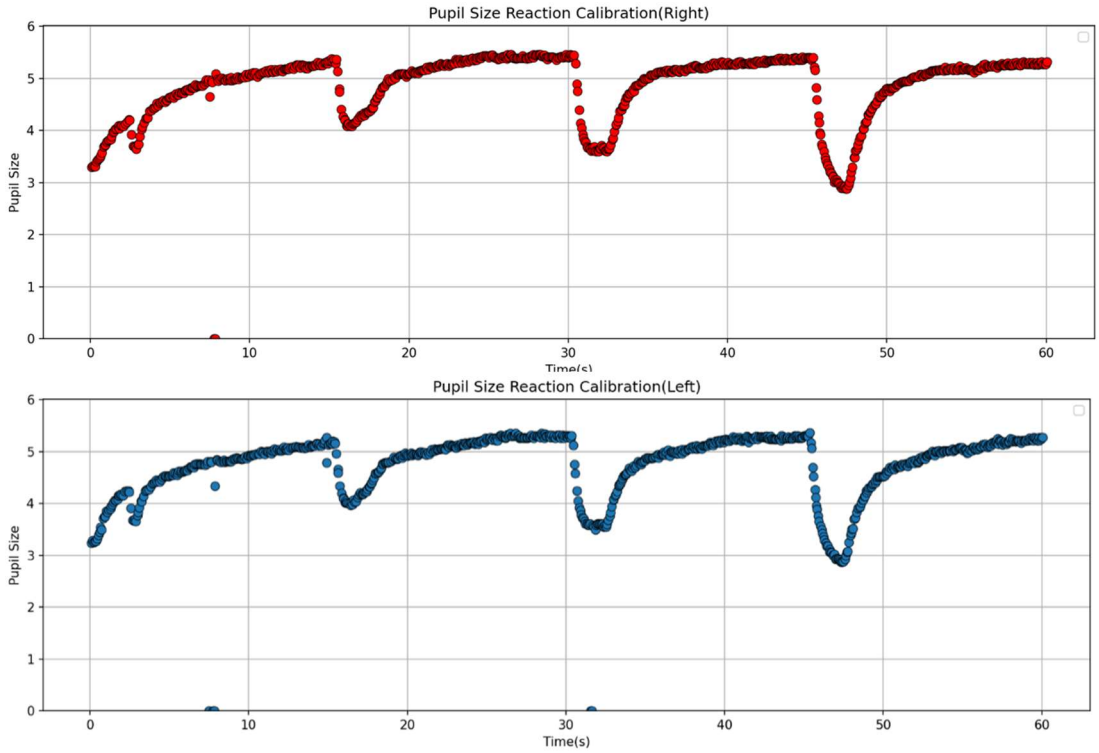
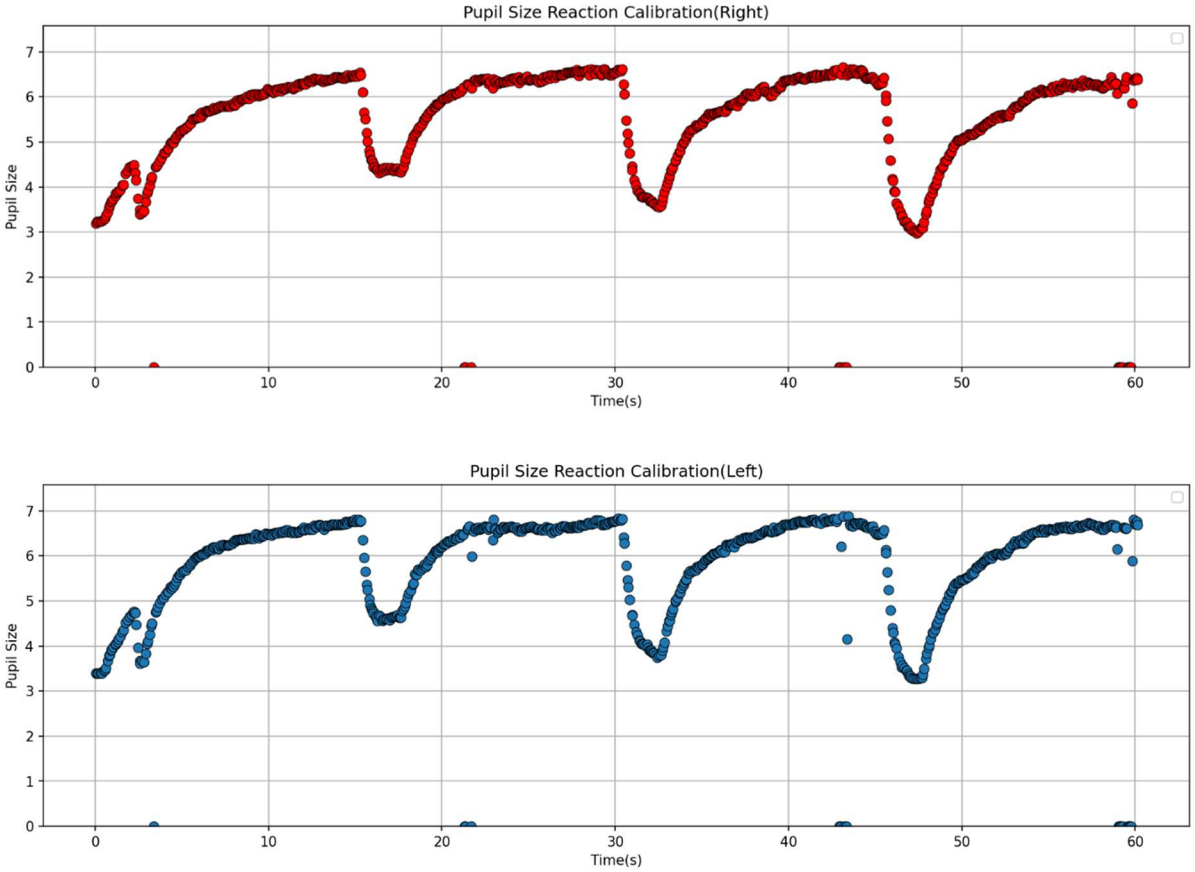


Figure 13: Standard example 2 with normal pupillary response in both eyes, showing steady pupil constriction and smooth pupil dilation



4.8.3 Pupillary unrest (PU)

PU shows the following characteristics and criteria:

1. Fluctuating pupil constriction and dilatation

2. Unrest pupil dilatation during dark stage

3. Longer time to recover to baseline pupil size after light stage

4. Latency

Figure 14: Example 2 on typical pupillary unrest in pupillometry tracing of both eyes from a poly-drug subject with 15 years history of PSA

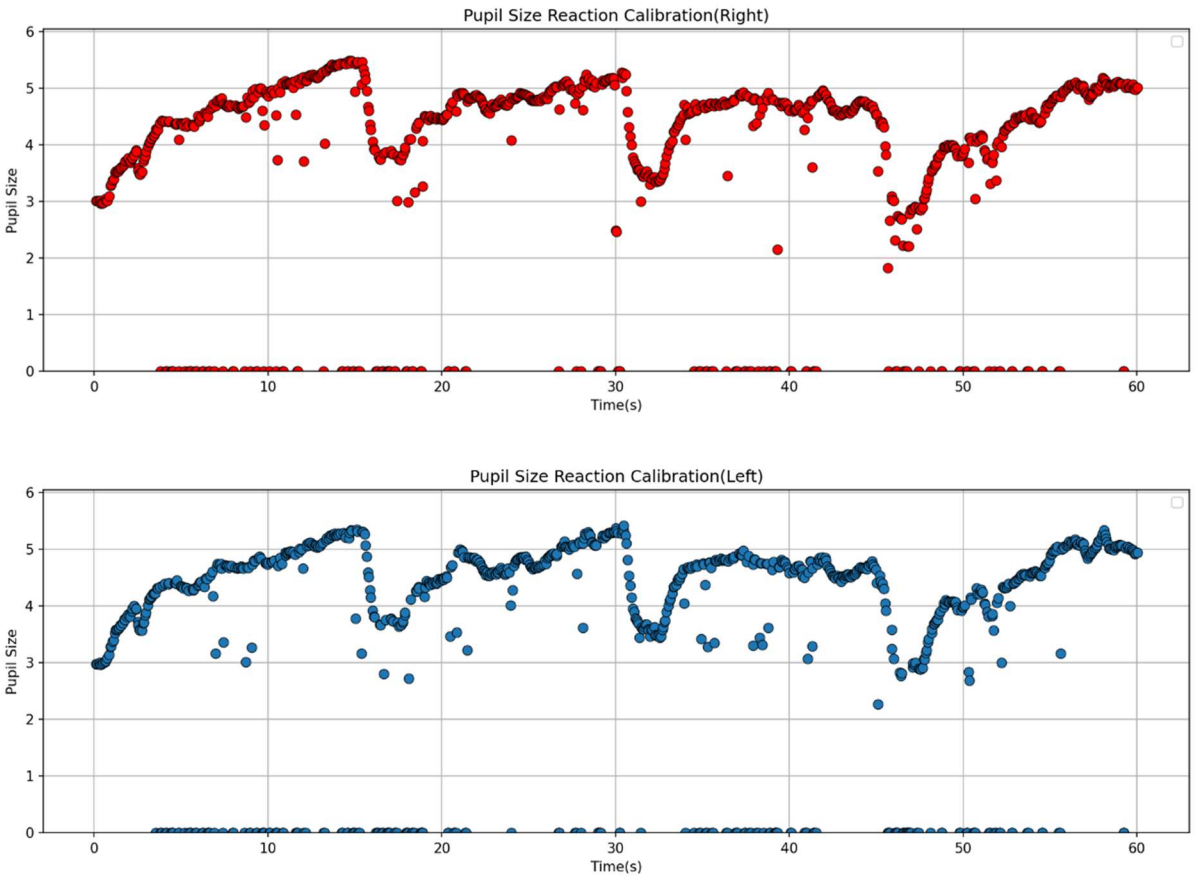


Figure 15: Standard example 4 on typical pupillary unrest in both eyes with 15 years history of a poly-drug subject

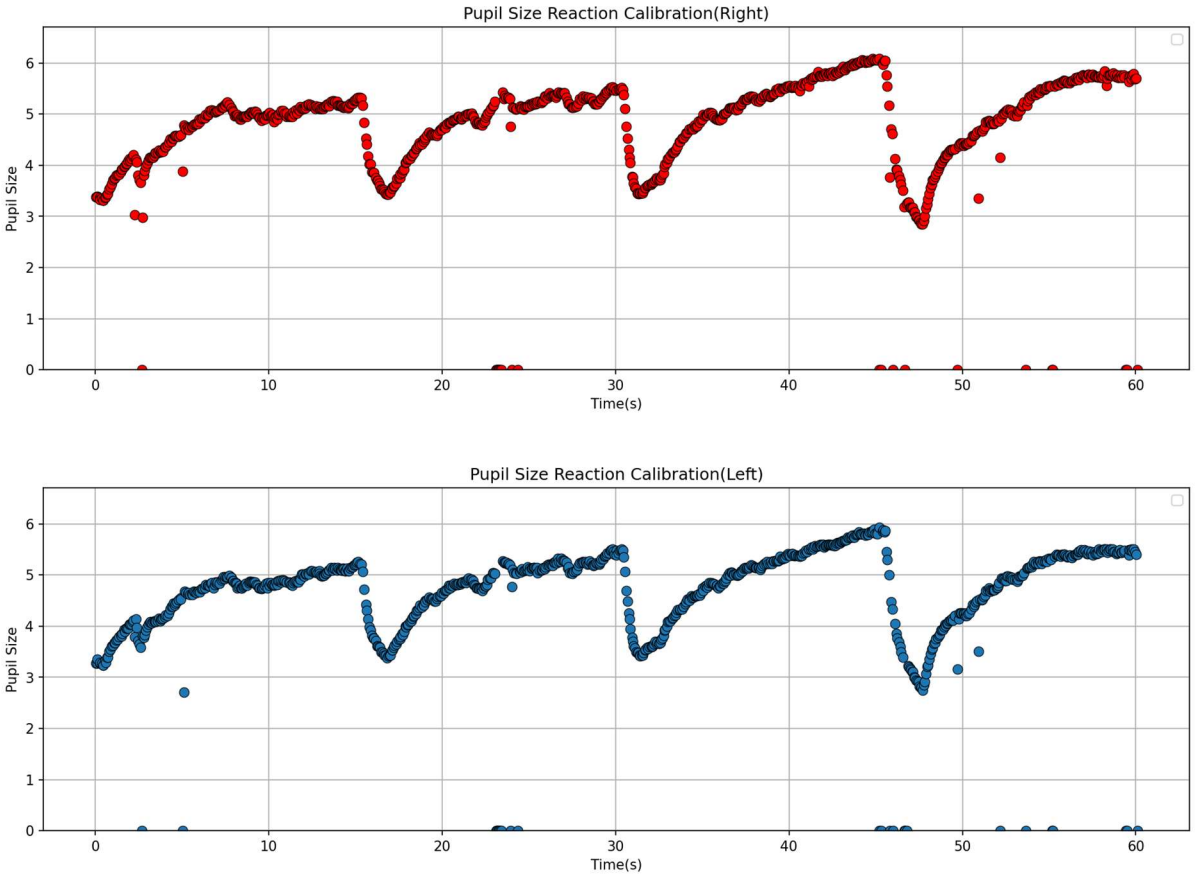


Table 11a. Descriptive statistics of normal pupillary response and pupillary unrest in different groups

Group	Normal pupillary response (N, %)	Pupillary unrest (N, %)
Healthy		
Group 1 (N=300)	291 (97%)	9 (2.6%)
Group 2 (N=100)	99 (99%)	1 (1%)
Group 3 (N=100)	92 (92%)	8 (8%)
Total (N=500)	482 (96.4%)	18 (3.6%)
Rehabilitee		
1st visit (N=125)	6 (4.8%)	119 (95.2%)
2nd visit (N=106)	7 (6.6%)	99 (93.3%)

Table 11b. Descriptive statistics of normal pupillary response and pupillary unrest in different groups

Group	Healthy Group	Rehabilitee	Chi-Square (P value)
Normal pupillary response	482	13	595.51 (P<0.05)
Pupillary unrest (PU)	18	218	
Total	500	231	

4.8.4 Pupil size

All subject pupil size captured during VR iP&ET test with 120Hz sampling rate. And there were three light stages of different intensity of light stimuli (PLR 64, 128, 255).

$$constriction\ power = \frac{-(minimum\ pupil\ size - maximum\ pupil\ size)}{maximum\ pupil\ size} \times 100\%$$

In Table 12b, the mean of Initial pupil size of healthy group in 1st stage (PLR 64) is 6.08mm, σ=0.7, where PSA group is 4.40mm, σ=0.86, P(T<=t) two-tail=0.017 ($p<0.05$). Similar result shown in mean of maximum and minimum pupil size of heathy group in 1st Stage (PLR 64) is 6.22mm and 4.25mm, σ=0.6 and σ=0.62, while in PSA group is 6.0mm and 3.56mm, σ=0.77 and σ=0.65, P(T<=t) two-tail=0.015 ($p<0.05$) and 0.4.

And in table 12a, we can see a notable difference (38.49%) of 1st stage initial pupil size between healthy and PSA group, and the difference of initial pupil size in 2nd and 3rd stage initial pupil size is widening (42.14% and 69.06%).

And we can see overall constriction power of healthy group is greater than PSA group by 3-5%, meaning overall healthy group subjects have bigger size of pupil size and better ability in pupil constriction. This can be explained by the type of drugs taken by the PSA , which will be further illustrated in the discussion section.

Table 12a: Descriptive statistics of pupil size between healthy and PSA groups

Parameter	Healthy Group (N=500)	PSA Group (N=106)	Difference
1st Stage (PLR 64)			
Initial pupil size (mm)	6.08	4.40	1.69 (38.49%)
Maximum pupil size (mm)	6.22	6.00	0.21 (3.5%)
Minimum pupil size (mm)	4.25	3.56	0.69 (19.43%)
Constriction power	31.70%	32.40%	0.07%
2nd Stage (PLR 128)			
Initial pupil size (mm)	6.24	4.40	1.85 (42.14%)
Maximum pupil size (mm)	6.38	6.13	0.24 (3.9%)
Minimum pupil size (mm)	3.62	3.37	0.25 (7.41%)
Constriction power	43.14%	39.48%	3.66%
3rd Stage (PLR 255)			
Initial pupil size (mm)	6.12	3.63	2.5 (69.06%)
Maximum pupil size (mm)	6.32	6.02	0.31 (5.14%)
Minimum pupil size (mm)	3.11	2.94	0.16 (5.44%)
Constriction power	50.85%	45.88%	4.97%

Table 12b: Descriptive statistics of subjects characteristics with pupil size between healthy and PSA groups

	Heathy Group	PSA Group	p-value (Two Tailed Test)
Subjects (n)	500	106	
Gender			
Male	237 (47.4%)	88 (83.0%)	0.12
Female	263 (52.6%)	18 (17.0%)	
Mean Age, years ±SD	19.46± 8.74	47.95± 18.50	
Positive Urine test result (%)	0 (0%)	29 (27.36%)	
Initial pupil size (mm) Mean ±SD (95%CI)			
1st Stage (PLR 64)	6.08±0.70 (5.94, 6.23)	4.40±0.86 (4.25,4.55)	
2nd Stage (PLR 128)	6.24±0.68 (6.10,6.39)	4.40±0.89 (4.24,4.56)	0.017
3rd Stage (PLR 255)	6.12±0.79 (5.95,6.29)	3.63±1.12 (3.43,3.82)	
Maximum pupil size (mm) Mean ±SD (95%CI)			
1st Stage (PLR 64)	6.22±0.60 (6.09, 6.35)	6.00±0.77 (5.87, 6.14)	
2nd Stage (PLR 128)	6.38±0.63 (6.24,6.51)	6.13±0.8 (5.99, 6.27)	0.014
3rd Stage (PLR 255)	6.32±0.62 (6.20,6.46)	6.02±0.97 (5.85, 6.19)	
Minimum pupil size (mm) Mean ±SD (95%CI)			
1st Stage (PLR 64)	4.25±0.62 (4.11,4.38)	3.56±0.65 (3.45,3.67)	
2nd Stage (PLR 128)	3.62±0.54 (3.51,3.74)	3.38±0.60 (3.27, 4.48)	0.40
3rd Stage (PLR 255)	3.11±0.47 (3.00,3.21)	2.94±0.62 (2.83,3.05)	

4.8.3 Eye-tracking (ET)

ET of the subject is performed on 13 sets of pictures including 3 sets of control and 10 sets of pictures with either normal or drug-related content. We recorded the subject's first sight, duration and total number of attentions towards two types of pictures.

At first, the subject will look at a book which displays 3 sets of non-drug related pictures on both the left- and right-hand side. Then there are 10 sets of pictures, with one being drug-related picture and one being similar picture but without drug-related content. The drug-related picture will be shown on either the left or right side of the book. The system will record the subject's first attention on either drug-related picture or normal control picture, and we calculated the average number of first sight on 10 sets of drug-related picture or normal picture as following (First sight). Also, VR iP&ET system will record the total duration of time (second) and total number of attentions on normal picture or drug-related picture. The higher score at first sight, durations and total number of attentions suggests the implication of higher tendency or higher risks on substance abuse (Saladin et al., 2006).

In table 14, it is similar result of first sight with normal or drug -related picture in healthy and PSA group (3.9%, 4%). But it is obvious to note the significant difference of gaze duration on normal or drug-related pictures in healthy and PSA group, suggesting PSA group have longer duration of gaze on drug-related picture compared to healthy group.

Table 13: First sight, duration, and total number of attentions in different groups of subjects

	First Sight			Duration (s)			Total number of attentions		
	Normal	**Drug**	**Change**	**Normal**	**Drug**	**Change**	**Normal**	**Drug**	**Change**
Healthy Group									
Group 1	0.52	0.45	0.07 (15%)	2.21	1.92	0.29 (15%)	50.46	44.09	6.37 (14.4%)
Group 2	0.48	0.51	0.03 (5.8%)	2.32	2.02	0.3 (14.8%)	51.80	45.28	6.52 (14.4%)
Group 3	0.52	0.50	0.02 (4%)	3.51	1.98	1.53 (77%)	52.85	48.82	4.03 (8.3%)
Average	0.51	0.48	0.03 (6.3%)	2.68	1.97	0.71 (36%)	51.70	46.06	5.64 (12.2%)
PSA Group									
1st Visit	0.49	0.50	0.01 (2%)	2.13	2.16	0.03 (1.3%)	48.92	49.98	1.06 (2.1%)
2nd Visit	0.49	0.50	0.01 (2%)	2.00	2.21	0.21 (9.5%)	47.86	52.37	4.51 (8.6%)
Average	0.49	0.50	0.01 (2%)	2.06	2.18	0.12 (5.5%)	48.39	51.17	2.78 (5.4%)

Table 14: Comparison of first sight, duration, and total number of attentions between the healthy group and the PSA group

	Healthy	PSA	Difference
First sight			
Normal	0.51	0.49	0.02 (3.9%)
Drug	0.48	0.50	0.02 (4%)
Duration (s)			
Normal	2.68	2.06	0.62 (23%)
Drug	1.97	2.18	0.21 (11%)
Total number of attentions			
Normal	51.70	48.39	3.31 (6.4%)
Drug	46.06	51.17	0.21 (10.6%)

4.9. Urine toxicology investigation

All subject participated in VR iP&ET test provided urine sample to screen 100 drug metabolites with the use of liquid chromatography time-of-flight mass spectrometry (LC-TOFMS) based on the existing urine drug libraries in chemical pathology laboratory at the Prince of Wales Hospital or point-of-care test (POCT) by BOSON BIOTech Rapid DOA – 5panel Test Card.

4.9.1 Healthy Group

For Group 1, we provide point-of-care (POC) by BOSON BIOTech Rapid DOA 5 panel Test card, which includes the detection of cocaine, ketamine, methamphetamine (Ice), opiates and marijuana (cannabis).

For Group 2 and Group 3, we collected 10-15ml urine and sent the sample to Prince of Wales hospital chemical pathology laboratory for mass spectrometry within 3 days.

Figure 16: BOSON BIOTech Rapid DOQ 5 panel Test Card

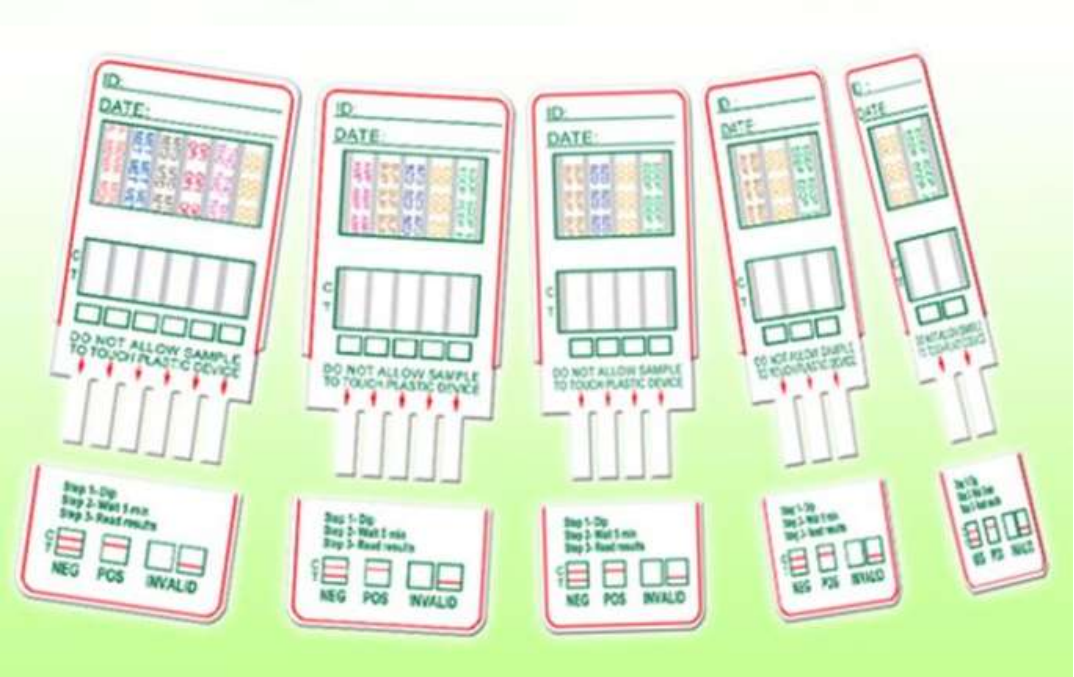


Table 15. Descriptive statistics of urine results in healthy group (Group 1, 2, 3) (N=500)

Group 1 Secondary school student	
Negative N (%)	300 (100%)
Positive N (%)	0 (0%)
Group 2 Tertiary school student	
Negative N (%)	100 (100%)
Positive N (%)	0 (0%)

Group 3 High-risk youth	
Negative N (%)	100 (100%)
Positive N (%)	0 (0%)

4.9.2 PSA group

PSA group's urine samples were collected during the 1st and 2nd visit and sent to Prince of Wales hospital chemical pathology laboratory for screening 100 drug metabolites.

Table 16. Descriptive statistics of urine results in Rehabilitee group 1st visit (N=125) and 2nd visit (N=106)

	1st visit (N=125)	2nd visit (N=106)
PSA group Rehabilitee		
Negative	85 (68%)	77 (72.64%)
Positive	40 (32%)	29 (27.36%)
Type of drug detected		
Heroin	13	10
Cannabis	5	3
Ketamine	1	1
Crystal Methamphetamine (Ice)	8	4
Cocaine	5	3
3,4-Methylenedioxy methamphetamine (MDMA)	1	0
Zopiclone	4	1
Midazolam	7	9
Codeine	15	13
Lysergic acid diethylamide (LSD)	0	0
Methaqualone	0	0

4.10 iP&ET as monitoring tool

We partnered with Kowloon Hostel, The Society for Aid and Rehabilitation of Drug Abusers, and set up several VR iP&ET devices in their centres to act as a monitoring tool of drug usage. We documented participant's drug use status and found the rate of rehabilitees successfully quitting PAS using iP&ET for monitoring is higher than that of rehabilitee without using iP&ET. There were 60 (56.6%) rehabilitees who used iP&ET for monitoring quitting psychoactive substance while 7 (43.8%) rehabilitees who without using iP&ET for monitoring quitting psychoactive substance.

5. Discussion

5.1. VR Perception

Pre-VR and post-VR questionnaire were distributed to all groups of subjects. Pre-VR and post-VR questionnaire were used to evaluate the general impression and preference on using the VR device as a drug testing tool.

5.1.1) Healthy Group (difference between pre- and post-VR test)

Table 7 shows the changes of impression between VR and urine test before and after VR test in the healthy group. In general, healthy group showed positive (average 7.19/10) impression in replacing traditional urine test with VR device and 13.04 % increase after the use of VR test. Similar result was shown in another question on the preference of using the VR device in drug testing. There was 68.28% (pre-VR test) and 81.28% (post-VR test) of the participants that support in using the VR device for drug testing.

VR advantages (higher score is better)

1. Higher convenience (1.15)
2. Higher entertainment values (1.11)
3. Provision of eye checkup during VR test (1.08)
4. Shorter waiting time (1.03)
5. Higher acceptance (1.02)

Also, we found the total score of urine test as drug testing tool is -2.52 (Range 20 to -20), compared to 8.61 in VR device, which showed huge differences in the impression towards the two methods (urine test and VR device) as drug testing tool. The health group showed explicitly negative on urine test but highly positive to VR device. The results were

good examples to show the immense potential of using the VR device as the next generation or standard of first-line drug use screening tool at the community level.

5.1.2) PSA Group (difference between pre- and post-VR Test)

In Table 8, for the 1st visit of PSA group, it showed positive (6.20 and 6.71 score in pre- and post-VR) impression in replacing traditional urine test with VR device, and there was 8.23% increase in acceptance after their first attempt of VR iP&ET test. Similar results were shown in 2nd VR test, and there was a 7.29% increase in acceptance of the VR device.

And there was 56% of the subjects that supported choosing VR device as drug testing tool after their VR iP&ET attempt. The following VR advantages were the key reasons for choosing VR device as a testing tool.

VR advantages (higher score is better)

1. Higher entertainment values (0.68)
2. Higher convenience (0.62)
3. Higher accessibility in daily life (0.56)
4. Higher acceptance (0.48)
5. Shorter waiting time (0.45)

It is vital to know rehabilitees favor the VR device as drug screening tool because of entertainment values, convenience, accessibility, and acceptance. In the future development, we should highlight these advantages and characteristics of the VR device as a drug testing tool.

5.1.3) Healthy group and PSA group

In Table 9, when we are comparing the impression of the VR device between healthy group and PSA group subjects, we found the VR device is more appealing as drug testing tool to healthy group (7.19 in healthy group, 6.43 in PSA group)

There are 74.78% support of choosing the VR device as drug testing tool in healthy group compared to only 50.87% in PSA group. Our data showed significant difference in two groups of subjects reflect the fundamental difference in two group of mindsets, where healthy group subject might see VR device as a means which is convenient, more accessible, less labelling and entertaining compared to traditional urine test. Traditional urine test in drug testing tool for healthy group is an unpleasant choice for them, given that it was the first time for most of the healthy subjects to do a urine test during study. Also, stereotypes of urine test are still quite common in our society, where it may imply potential substance abuse.

In contrast, PSA group subjects had more experience of doing the urine test, and it is less resistant for them to leave a urine sample for drug testing, so VR iP&ET may be less appealing to them. With that being said, the total score of VR device in PSA group is still higher than that of urine test (VR test: 4.46, Urine test: 0.76), where it showed PSA group believed VR device could still act as a better alternative to urine test as drug screening tool.

In future development, VR iP&ET test has immense potential in primary screening tool at the community level, such as deployment in schools and community centres to act as first line screening tool for potentially high-risk people. Furthermore, we should improve the whole testing process, including shorter testing time, optimizing both the VR software and hardware, adding more interesting and appealing elements (such as gaming element in eye-tracking part).

5.2. Infrared Pupillometry

5.2.1 Assessment of pupillometry

We had collected 606 sets of pupillometry data. In preliminary analysis, we analyzed the pupil size along the time with several light stimuli. Three independent assessors were instructed to classify the graphs into normal pupillary response and pupillary unrest with reference to the standard example (Figure 12-15). And we found 96.4% (N=482) of subjects fall into the NPR category and 3.6% (N=18) of their graphs have PU in healthy group (Table 11).

While in PSA group, there were 95.2% (N=119) and 93.5% (N=99) subjects having PU in 1st visit and 2nd visit, respectively.

We found that the significant differences and apparent characteristics between NPR and PU can be easily recognized by a nonprofessional who was trained in a short period of time. The abnormal characteristics of PU, such as unorganized pupil constriction and dilatation activity, fluctuating pupil size and irregular rhythm of pupil dilatation during dark stage in pupillometry are easily perceived compared to the smooth wave of pupil constriction and dilatation in NPR.

Nevertheless, it is notable that the use of psychoactive drug is not the only dependent variable in pupillometry (Verster et al., 2006). Optical interference by spectacles, cognition including visual awareness, covert visual attention, eye-movement preparation, and subjective brightness can also be the factors affecting pupillometry results.

During VR iP and ET test, we found that more failure was experienced in the calibration part when the subject was wearing glasses, and even more attempts of calibration were needed for the subjects who wear astigmatism lens or higher diopter lens, suggesting the effect of optical interference in VR iP&ET test is common manifestation in lens with greater thickness and refractive index. To prevent the effect of optical interference during VR iP&ET

test, our instructor recommended the subject to take off the glasses prior to conducting the test. More details on optical interference will be discussed in the coming limitation section.

5.2.2 Pupil size

Normal pupil size in adults varies from 2 to 4 mm in bright light and 4 to 8 mm in dark environment. We recorded the initial pupil size (mm), maximum pupil size (mm), minimum pupil size (mm) during the VR iP&ET test under the three light stages. The interpretation of pupil size and its implication is in Table 17.

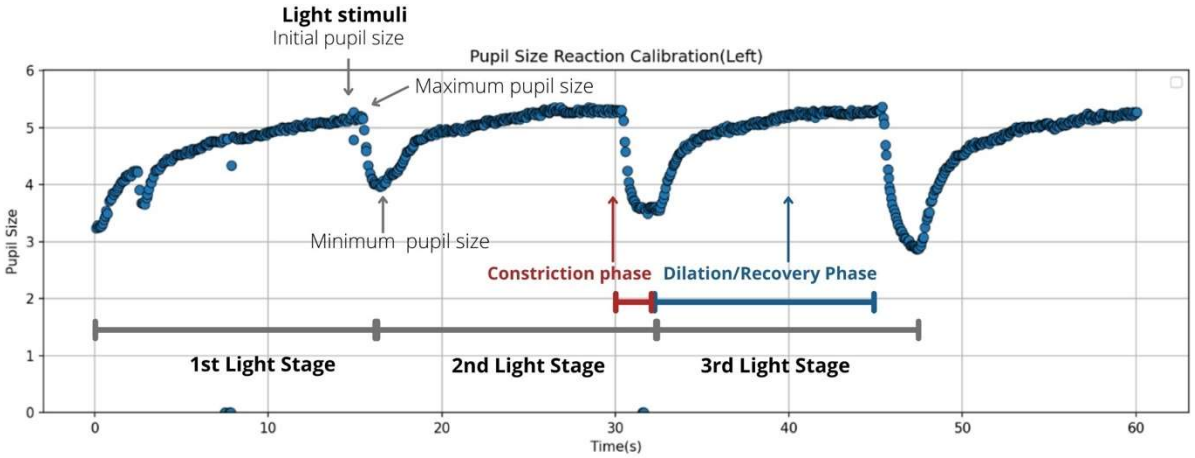
With the formula and calculation, we have the constriction power of healthy group and PSA group in different light stages, where constriction power implicated the maximum degree of pupil constriction in a fixed duration.

$$constriction\ power = \frac{-(minimum\ pupil\ size - maximum\ pupil\ size)}{maximum\ pupil\ size} \times 100\%$$

Table 17. Pupil size and its implication

Pupil Size	Phase	Environment setting	Implication	Normal Range
Initial pupil size	Dilatation/ Recovery Phase	First second of light stimuli in each stage	The extent of recovery after light stimuli	4-8mm
Maximum pupil size	Dilatation/ Recovery Phase	13 second of darkness (PLR 0)	The greatest extent of pupil dilatation under dark environment	4-8mm
Minimum pupil size	Constriction phase	During 2 seconds of light stage (PLR 64, 128, 255)	The greatest extent of pupil constriction under light stimuli	2-4mm

Figure 17. Pupillometry results in different phases and parameter highlights



In Table 12, as we noticed an overall greater initial pupil size in healthy group than PSA group (pupil size difference with 38%, 42% and 69% in three light stages). It can be explained that more than 62% and 33% subjects in the PSA group had previous history of abusing drugs with pupillary constriction effects, like heroin and cannabis in the last six months. The long-term intake of drugs with pupillary constriction effects induces the small pupil size phenomenon in PSA group, and the pupillary constriction effects caused by drugs like heroin and cannabis are long-lasting (Ortiz-Peregrina et al., 2021), which will be further discussed in the 4th case study (AC4001) in the case study section.

5.3 Eye-tracking

Business and marketing sector is utilizing eye-tracking technology to study customer's patterns and elements of human behavior for years (Wedel & Pieters, 2006). Studying eye movement can reveal a person's desire, intention, and cognition. By integrating the eye-tracking technology into a VR device, we can reveal the extent of exposure risk to the

subject by analyzing eye-tracking parameters like first sight, duration, and total number of attentions.

Eye-tracking is a double-blind setting, which neither participants nor the experimenters know the display sequence of the drug-related pictures. VR software will reorder the sequence of displaying normal and drug picture set in each test. Participants were told to look freely during eye-tracking part (Holmqvist & Andersson, 2017). These measures can prevent the bias caused by placebo effect and demand characteristics (Carter & Luke, 2020).

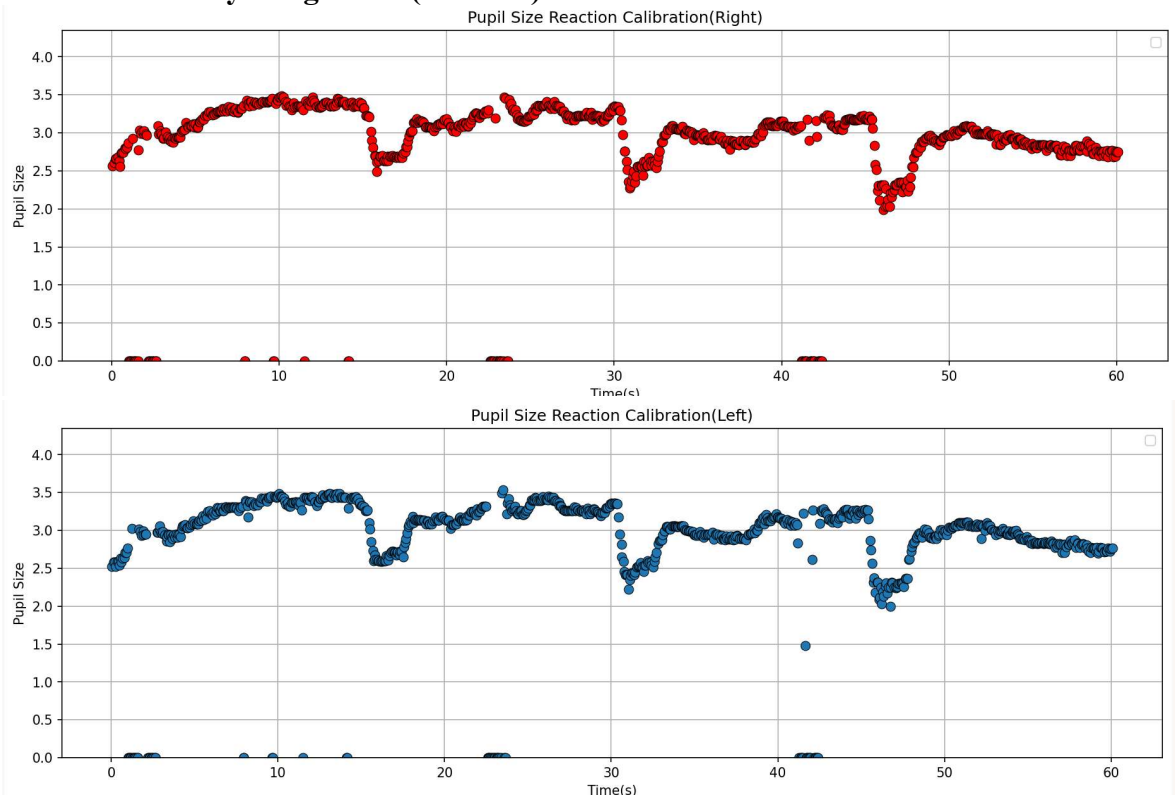
In Table 13, we can see PSA group has a higher rate of first sight and a longer duration of focusing on drug set pictures than healthy group. The result is reflecting the fact that PSA group subject will unintentionally focus on the scenes or pictures related to drug abuse and using eye-tracking data can be a method to analyze the risks of exposure to drug abuse of a subject (Mertens & Allen, 2008).

The data and difference of duration on focusing drug or normal picture set in healthy and PSA group can be used to set a baseline to define the threshold of low or not at risk of exposure to drug abuse.

5.4 Case Studies

It is known that some psychoactive drugs (such as heroin and cannabis) have pupillary constriction effects, while some (such as Ice, ketamine, and cocaine) can cause pupillary dilatation response. For poly-drug abusers who take both stimulants and narcotics, the complexity of analyzing the drug effects on pupillometry results and pupil size data will increase. In the following case studies, we will study on 4 individual cases covering the difference of poly-drug, mono-drug effect on VR iP&ET test, and the long-lasting effect of cannabis to subject's ocular health.

5.4.1 Case 1: Poly-drug effect (AC4057)



Subject AC4057 is a 49-year-old gentleman with 20 years of poly-drug abuse history including cannabis, Ice, ketamine, and heroin. Previously the subject took the drugs 3 times a day and last date of use is March 2021. We conducted the VR iP&ET test in July 2021. Subject was in the absence of drug for four months, and no drug metabolites were found in

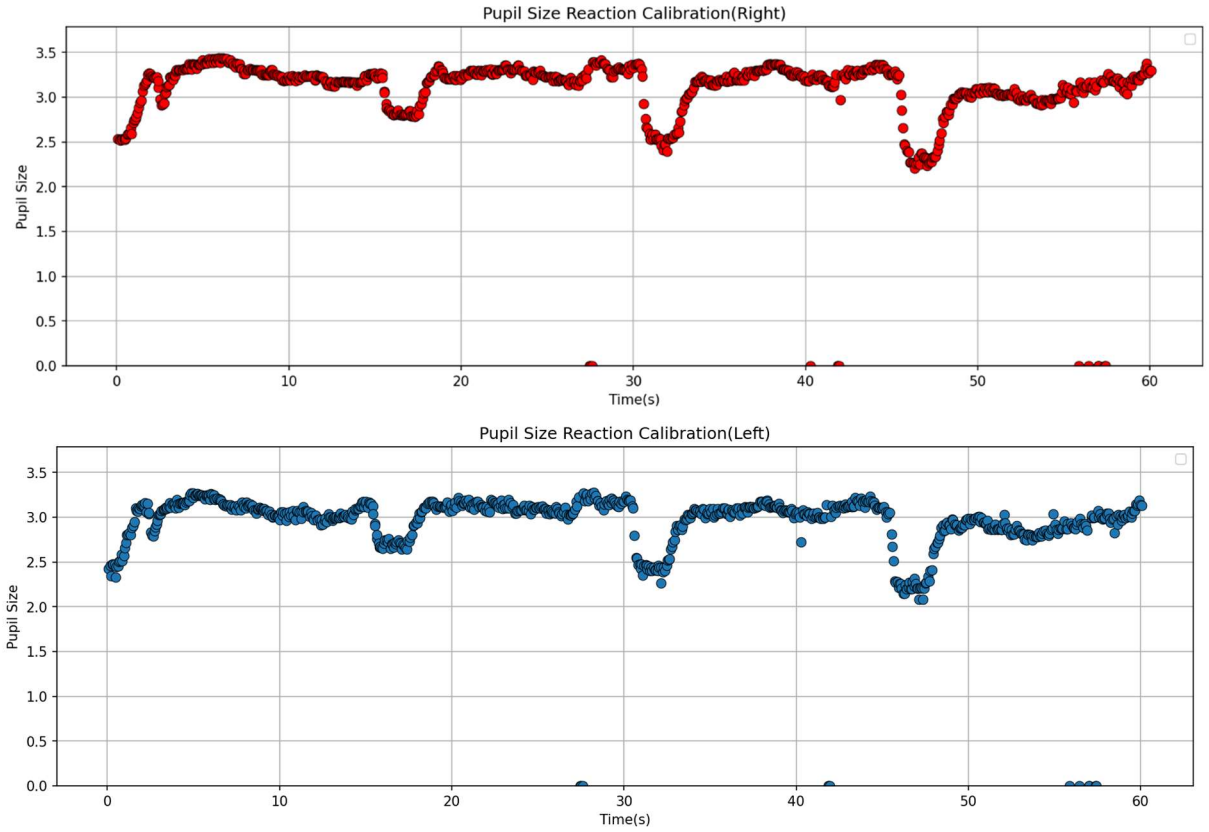
urine test, suggesting that the VR iP&ET test and the pupillometry data were obtained under the drug-free condition for the previous 24-48 hours when the subject conducted the tests (Moeller et al., 2008).

In ophthalmic examination, the subject had a good best corrected visual acuity (20/20 BE), OSDI was 35 implicating subjective severe dry eye, but none of severe drug-related eye symptoms was found under slit-lamp examination. During consultation, subject had complained of blurred and poor vision in the last week.

For his pupillometry results, pupillary unrest was seen from the fluctuating but non-rhythmic pupil dilatation and constriction during dark stage. The initial and maximum pupil size of the subject was 5.55 mm while minimum pupil size was 2.62mm which was within normal range. The constriction power was 31.71%, 43.40% and 50.00% in 1st, 2nd, and 3rd light stage, which was below the average in both healthy and PSA groups. With that being said, the subject's pupil size was not as small as the following case, AC4048, even though both subjects had history of heroin and cannabis, which were narcotics and can cause pupillary constriction. The relatively "normal" pupil size in this subject may be due to the antagonistic effect caused by poly-drug intake. Both pupillary dilatation and constriction effects caused by different drugs might cancel out and oppose one another, but still the subject's pupil constriction power was weaker than that of healthy group.

The long history of drug abuse played a key role in the unstable and irregular rhythm and wave of pupillary activity, suggesting severe damage to automatic nervous system. The severity of the effect is dependent to the duration and dosage of drug intake.

5.4.2 Case 2: Mono-drug effect (AC4048)



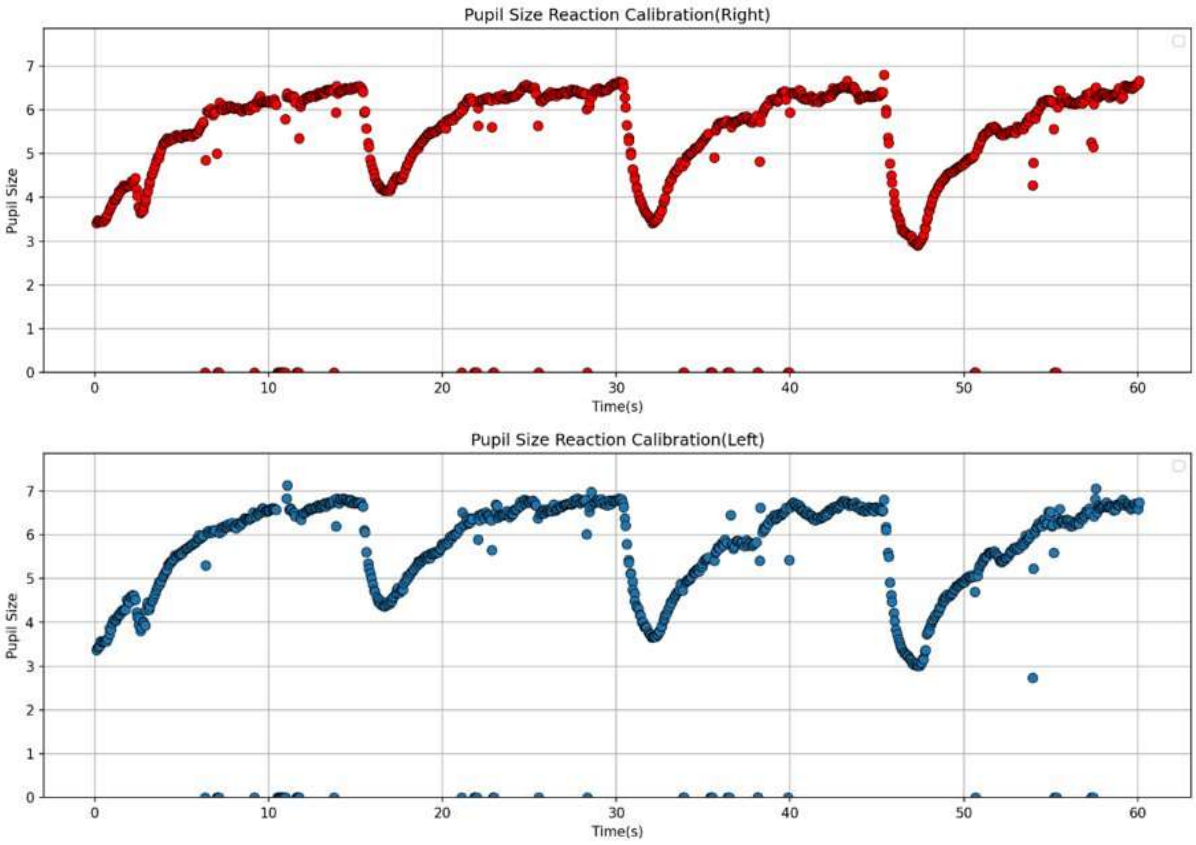
Subject AC4048 is a 42-year-old gentleman and a 10-year smoker with 15-year heroin abuse history. Previously the subject took heroin once a day, and the last date of use is April 2021. We conducted the VR iP&ET test in July 2021. Subject was in the absence of drug for three months, and no drug metabolites were found in urine test, suggesting that the VR iP&ET test and the pupillometry data were obtained under the drug-free condition for the previous 24-48 hours when the subject conducted the tests (Moeller et al., 2008).

In ophthalmic examination, the subject had a good best corrected visual acuity (20/20 BE), OSDI was 0 implicating no dry eye disease, but none of severe drug-related eye symptoms was found under slit-lamp examination. During consultation, subject had no complaint of vision problems.

For his pupillometry results, similarly, pupillary unrest was seen from the signature fluctuating and unstable pupil dilatation and constriction during dark stage. The initial and maximum pupil size of the subject was 3.28 mm while minimum pupil size was 2.08mm,

which is abnormally small in darkness (normal is 4-8mm in darkness). The constriction power was 16.45%, 26.33% and 31.80% in 1st, 2nd, and 3rd light stage, which was below average when compared to both healthy and rehabilitee groups. It is a good example to show the significantly small pupils and weak pupillary constriction response possibly caused by long-term heroin intake.

5.4.3 Case study 3: 4 years of history of cannabis (AC4003)



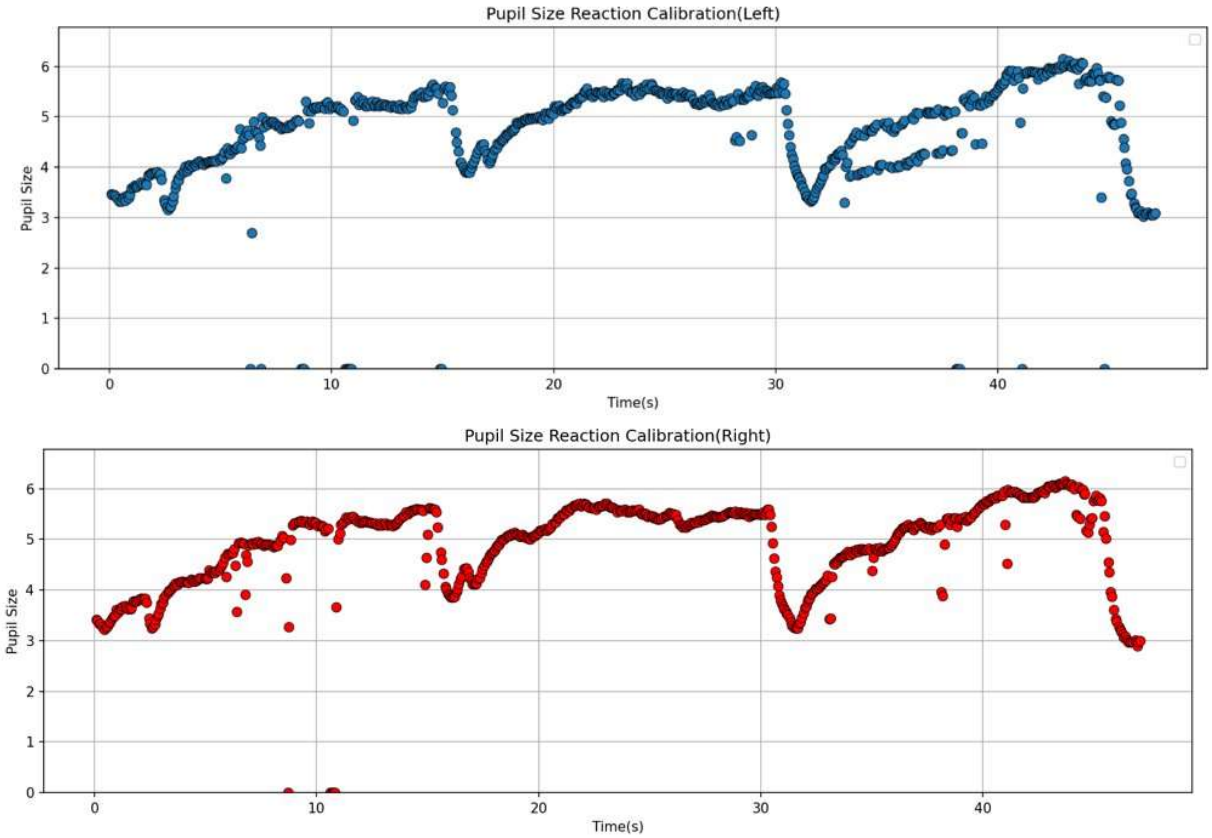
Subject AC4003 is a 26-year-old gentleman, and a 10-year smoker with 4-year cannabis abuse history. Previously the subject took cannabis 4 times per week, and the last date of use is early April 2021. We conducted the VR iP&ET test in late April 2021. Subject was not using drug for a month, and no drug metabolites were found in urine test, suggesting that the VR iP&ET test and the pupillometry data were obtained under the drug-free condition for the previous 24-48 hours when the subject conducted the tests (Moeller et al., 2008).

In ophthalmic examination, the subject had an excellent best corrected visual acuity (RE 20/16, LE 20/13). Under slit-lamp examination, BE miosis, bloodshot eyes, mild papillae and MGD was found. During consultation, subject had no vision complaint.

For his pupillometry result, pupillary unrest was identified with fluctuating pupil dilatation and constriction during the recovery stage (darkness). The unstable dilatation and constriction can be seen especially at 10s, 25s, 40s and 55s of the graphs.

The initial pupil size of the subject was 4.32 mm, maximum pupil size was 6.8mm while minimum pupil size was 3.00mm. The constriction power was 44.00%, 48.64% and 55.98% in 1st, 2nd, and 3rd light stage, which was greater than healthy group. Cannabis had pupillary constriction effect which contributes to the strong pupil constriction power in subject AC4003. To compare the pupillary effect on shorter intake history of cannabis, we shall discuss it in the coming case.

5.4.4 Case 4: Cannabis and detection windows (AC4001)



Subject AC4001 is a 22-year-old gentleman with good past health. He had tried cannabis 3 times in social gatherings, and the last date of use was December 2020. He participated the VR iP&ET test in March 2021. Subject was in the absence of drug for 3 months, and no drug metabolites were found in urine test, suggesting that the VR iP&ET test and the pupillometry data were obtained under the drug-free condition for the previous 24-48 hours when the subject conducted the tests (Moeller et al., 2008).

In ophthalmic examination, the subject had a good visual acuity (20/20 BE), OSDI is 0 implicating no dry eye disease, and no severe drug related eye symptoms was found under slit-lamp examination. During consultation, subject had no complaint of vision problems.

For his pupillometry results, pupillary unrest was clearly identified with evidence of fluctuating pupil dilatation and constriction during dark stage.

The initial pupil size and maximum pupil size of the subject was 3.9mm and 6.14mm respectively while minimum pupil size was 2.89mm, which was abnormally small in darkness (normal is 4-8mm in darkness). The constriction power was 42.25%, 43.15% and 52.93% in 1st, 2nd, and 3rd light stage.

Compared the constriction power to case 3 (AC4003) who had 4 years of cannabis history, this case had slightly lowered constriction power. It was worthwhile to note that only few times of attempt of cannabis can cause profound and long-term effect on pupillary response and irregular pupillary activity.

The adverse effect of cannabis has long been disregarded in general public, and it is a case in point that few times of attempt can already cause noteworthy damage to ophthalmic and nervous system.

Also, we can see that iP&ET test has longer detection windows, as most of the cases we discussed above had quitted drugs for several months, but the abnormal pupillometry results can still be detected.

6. Limitations

There are limitations on both infrared pupillometry and eye-tracking which can affect the accuracy of result we collected in VR iP&ET test.

6.1 Infrared pupillometry

6.1.1 Optical interference

It is known that the infrared pupillometry will be affected by optical lens. During our VR iP&ET test, our research staff advised the subject to take off the eyeglasses if they only have mild refractive errors (myopia, hyperopia, astigmatism) to prevent optical interference. Subject with mild refractive errors can pass the calibration and complete the whole test, but for the subjects with moderate to severe refractive errors, they had to keep wearing the corrective spectacles to correct refractive errors to pass the calibration, but the pupillometry results will be affected by optical interference. For the results of subjects that are heavily influenced by glasses, we advised the subject to repeat the VR iP&ET test. Also, if the subject has refractive errors, that they may not see the pictures in the second part very clearly and will have to squeeze the eye to look at the pictures, and this may affect the pupil size.

In the market, there are VR prescription lens inserts that can magnetically attach to the VR display lens. User can take off their glasses and prevent optical interference during VR iP&ET test. But these VR lens inserts are not customizable and adjustable, tailor-made lenses with specific SPH, CYL, AXIS and PD are required to fit each specific subject. Therefore, it will not be an economical option.

Figure 18: Showing optical interference during VR iP&ET test with infrared dot on the glasses

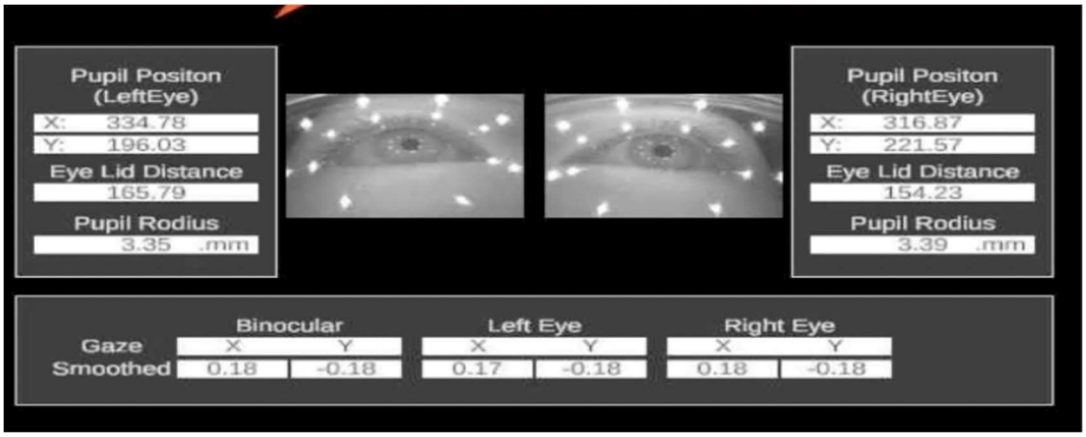
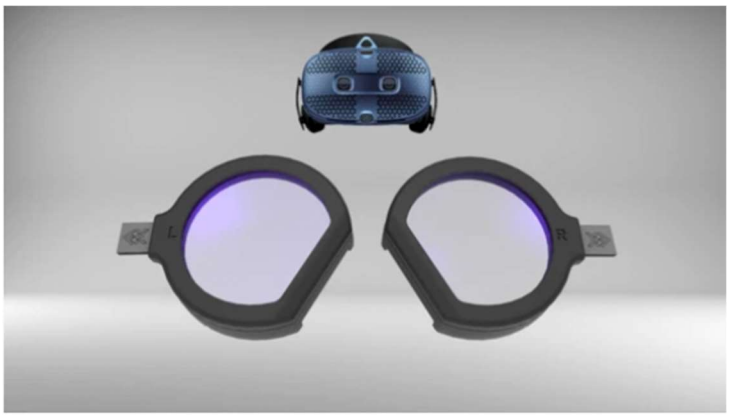


Figure 19: VR prescription lens to prevent optical interference



Multi-drug compensation

Stimulants such as crystal methamphetamine (Ice), ketamine, and cocaine cause pupil dilatation (mydriasis) while narcotics including heroin cause pupil constriction (miosis). As mentioned before, stimulants will cause the side effect of pupil dilatation while narcotics will

cause the opposite effect. If the subject is a poly-drug user and taking both classes of drugs, then we may not know if the combined effects on pupil size, or which one will outweigh the other with different amount, dosage, and frequency.

6.1.2 Aging effect

Senile miosis means a reduction in size of a person's pupil in old age (Govenlock et al., 2010). The reduction in pupil size with the effect of aging is natural degeneration in human body. In our study, quite a number of PSA are over 40 years old, so the miosis seen in those subjects could partly be due to their old ages.

Subjects with abnormal facial anatomy with too large or too small inter-pupillary distance also affects the accuracy of iP. As the VR headset is not tailor-made for every subject, the device may not fit perfectly on some of the subjects that the infrared sensor might not stay perfectly aligned with the subject's pupils, so the measurement of the subject's pupil may have certain deviation due to the angle caused by the un-fit wearing of the VR headset. Ptosis or dermatochalasis are also seen in some of our older age subjects. In these cases, during the whole test, we advise the subject to try to open wide their eyes as much as possible, and not to blink to reduce the effect of affecting the pupillometry results. Yet, some of the subjects will feel uncomfortable that they cannot maintain for the whole test, or a part of their pupil may still be blocked by the eye lid even when they try to open wide their eyes. Dry eye causing constant blinking is another limitation. If the subject is blinking at a high rate while it is in the pupillometry part especially during the transition of the light or dark stage, the result will also be affected.

6.1.3 Repeatability and reproducibility

Under the current protocol, the VR display shows 3 cycles of light stage with different light intensities when the subject's pupil size was captured with 120hz sampling rate via infrared pupillometry in VR headset. Intra-tester reliability can be improved and thus the accuracy of the result by repeating 3 successive sets of the whole iP test, that is, a total of 9 light stages, to obtain more accurate and repeatable results under the repeatability conditions with the same method, on the same subject, by the same operator, and on the same set of equipment with the shortest time lapse possible between successive sets of readings.

6.2 Eye-tracking

The eye-tracking test is very subjective, that the subject can just look at one side of the picture or avoid looking at the pictures that are drug-related. If the subject has the habit of looking from left to right, and the randomly ordered pictures on left-hand side mostly are drug-related pictures, then the average number of first sight on 10 sets of drug-related pictures might be overestimated. Also, if the subject has refractive errors and cannot see the pictures very clearly, he might have to look at the pictures at a longer time so that he knew what he was staring at. In similar cases, the total duration of time and total number of attentions on drug-related picture will also be overestimated. As mentioned before, higher score at first sight, durations and total number of attentions suggests the implication of higher tendency or risks on substance abuse. Therefore, the subject may have overestimated tendency or risks of drug abuse. With the VR prescription lens, this problem can be minimized, and a more realistic video mimicking the drug taking scenarios can be applied for the ET test to obtain an even more accurate result.

7. Conclusion

This study, Infrared Pupillometry and Eye-tracking as Next-generation Non-Intrusive Means to Identify Subjects Under Influence of Psychoactive Drug and Vision-related Harms, is a successful proof of concept (POC) on VR iP&ET test. Throughout the research, we attempted different phototypes and versions of VR iP&ET device, and eventually we successfully obtained a model with stable software and hardware. Our VR iP&ET setup has a lot of advantages, including low-cost and portability which can unleash immense potential and can be deployed in various locations. Also, across the study, we received lots of positive feedbacks from the public, rehabilitees, community centres. Some of the rehabilitee centres also show interests in future cooperation towards our non-intrusive VR device.

During the project period, our study recruitment was significantly affected by a series of social events in 2019, and the COVID-19 pandemic outbreak. With that being said, under these difficult backgrounds, we built a strong and resilient partnership and connection with members of local community, volunteering service organization, anti-drug service parties, and rehabilitee centres.

The preliminary results we collected has clearly shown some significant differences in both infrared pupillometry (iP) and eye-tracking (ET) data between healthy and PSA group, especially for the subjects with cannabis history. We are excited to work and improve our VR iP&ET setups in the coming future and focus on new trendy drug, cannabis.

In future development, VR iP&ET test has enormous potential in primary screening tool in community level, such as deployment in schools, community centres to act as first line screening tool of potentially high-risk clients. Further improvement of the whole testing

process, including shorter testing time, optimizing both VR software and hardware can be done to obtain even more accurate results.

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9. Abbreviations

Both eye (BE)

Eye-tracking (ET)

Crystal methamphetamine (Ice)

Cylinder correction (CYL)

Extraocular movement (EOM)

Head mounted display (HMD)

Influence of psychoactive drug (iPAD)

Infrared pupillometry (iP)

Infrared pupillometry and eye-tracking (iP&ET)

Liquid chromatography time-of-flight mass spectrometry (LC-TOFMS)

Meibomian gland dysfunction (MGD)

Normal pupillary response (NPR)

Ocular surface disease index (OSDI)

Point-of-care test (POCT)

Proof of concept (POC)

Psychoactive substance abuser (PSA)

Psychoactive substance (PAS)

Pupillary distance (PD)

Pupillary light reaction (PLR)

Pupillary unrest (PU)

Red, green, blue (RGB)

Schirmer's test (ST)

Spherical power (SPH)

Virtual reality (VR)

Visual acuity (VA)