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Virtual reality as a treatment for acute antiemetic-induced akathisia

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Abstract

Many patients receiving common antiemetic medications for a variety of complaints ranging from gastroenteritis to headache to surgery experience the distressing extra-pyramidal neuropsychiatric side effect of akathisia due to the dopamine-antagonist mechanism of these drugs. Akathisia involves a persistent restlessness and urge to move, common in those taking antiemetics. Currently, a literature gap exists surrounding how virtual reality (VR) often used for general mental health treatment can be leveraged in a biosensor capacity toward neurotransmitter analysis and balancing among patients experiencing antiemetic-induced akathisia. In consideration of future research directions, this article examined the potential benefits of wearable VR technology as a non-pharmacological treatment solution for patients displaying signs of akathisia in an acute setting such as the emergency department. The paper concluded with a Python code foundation for two machine learning algorithms for a wearable biosensor to correlate neurochemical fluctuations of dopamine and stress-induced cortisol with VR audiovisual inputs among patients with akathisia stemming from these drugs. Potential obstacles included the risk of invasiveness implicated by administration of neurotransmitter saliva tests among wearers experiencing these stressful symptoms as well as the technical challenge of integrating biosensing capabilities into a virtual reality wearable device.

Key words: cyberpsychology; neuropsychiatry; virtual reality; emergency medicine; non-pharmacological treatment.

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Introduction

Several antipsychotic medications used for emergency antiemetic treatment in individuals without pre-existing psychiatric conditions are known to cause akathisia as an extra-pyramidal side effect in some users. Akathisia is a distressing neuropsychiatric syndrome that causes inner restless and the perpetual urge to move, occasionally resulting in suicidal feelings.[1] These medications include metoclopramide and prochlorperazine which are commonly administered in the emergency department (ED) and can lead to akathisia and associated anxiety due to a dopamine imbalance.[2] Provided the ubiquity of abdominal pain, vomiting, and headache as complaints of ED patients treated with these antiemetics, a potential solution to this phenomenon warrants investigation.[3]

While various sedative medications such as intravenous diphenhydramine and lorazepam have traditionally been administered to counteract acute antiemetic-induced akathisia experienced by patients in the ED with ambiguous success, less invasive sensory-based treatment options such as virtual reality (VR) exposure have not been widely explored.[4] This article examined existing literature surrounding antiemetic-induced akathisia and the neurobiological therapeutic potential of wearable VR immersive technology to help reverse neurochemical imbalances caused by these medications, namely, a decrease in dopamine.

Specifically, this article aimed to address the literature gap by exploring how machine learning (ML)-equipped VR exposure could help simultaneously increase dopamine and reduce cortisol levels resulting from antipsychotics used as antiemetics. The assessed research categories were the neurochemical roots of akathisia toward determination of which chemicals to target via biosensing, which antiemetic medications can cause akathisia so as to promote readiness, and how treatments such as wearable VR can help noninvasively increase dopamine and decrease cortisol associated with the stress of akathisia.

Methods

These studies were selected from the following databases: National Institutes of Health and Elsevier, Frontiers Media SA, Multidisciplinary Digital Publishing Institute (MDPI), and RELX. These studies included the following articles published within the 2021-2026 timeframe (with two outliers from prior to this range due to the overall scant research): Journal of Pharmacological Sciences, The American Journal of Emergency Medicine, Journal of Family Medicine and Primary Care, Frontiers in Pharmacology, Heliyon, Frontiers in Digital Health, Brain, Behavior, & Immunity - Health, International Journal of Clinical and Health Psychology, Frontiers in Human Neuroscience, Computers in Human Behavior, International Journal of Human-Computer Studies, Biosensors and Bioelectronics, Microsystems & Nanoengineering, Biosensors, and Sensors and Actuators Reports.

The article involved clinical case studies, case reports, and systematic literature reviews including the following keywords: akathisia, antiemetic, emergency medicine, virtual reality, and non-pharmacological.

In terms of population, this article focused on individuals without psychotic disorders who experienced acute akathisia following use of D2 receptor antagonist antiemetic medications in an emergency department setting. The target demographic included no trends in age or race.

The proposed intervention entailed a wearable VR treatment to provide the affected individual with real-time audiovisual distraction for the purpose of dopamine level balancing. The suggested comparison would be between patients given standard sedative treatment versus patients interacting with the proposed VR technology.

As of this time, the rudimentary algorithm framework would be improved based on the outcomes of the proposed clinical study exposing patients to the initial prototype design of this technology.

The inclusion criteria focused on i) clinical case studies, reports, and existing literature reviews surrounding antiemetic-induced acute akathisia treatment in an emergency setting, and ii) VR technology use in a mental health setting. The article excluded studies on chronic antiemetic-induced akathisia due to the difference in long-term palliative *vs* acute contexts. Thus far, few studies exist investigating VR used in an acute psychiatric setting (Table 1).

Table 1. Characteristics of each study reviewed, including databases and relevance to the present article.

Database	Keywords	Title	Author	Theme impact	Discussion	Conclusion	Further research
ScienceDirect	Acetaminophen, Clinical big data, Dopamine D_2 receptor, Indirect-pathway medium spiny, Neurons, Tardive akathisia	Acetaminophen improves tardive akathisia induced by dopamine D_2 receptor antagonists	Nagaoka *et al.*[5]	Pharmacological effect on acute akathisia improvement	Contrast of pharmacological *vs* VR treatment	Acetaminophen *vs* VR comparison is needed	Assess VR's potential in acute akathisia treatment of antiemetic-induced akathisia
ScienceDirect	Cariprazine, Antipsychotic, Schizophrenia, Molecularly imprinted polymer, Electrochemical sensor	Detection of the antipsychotic drug cariprazine using a low-cost MIP-based electrochemical sensor and its electrooxidation behaviour	Hosseinzadeh *et al.*[6]	Neurochemical analysis of effects of antipsychotics	Helpful for effects of antipsychotic/antiemetic medication on akathisia	These medications affect D_2 receptors	Assess real-time analysis of dopamine level fluctuations of a user of these drugs
ScienceDirect	Migraine, Headache, Dopamine antagonist	Comparison of efficacy and frequency of akathisia and dystonia between olanzapine, metoclopramide and prochlorperazine in ED headache patients	Chinn *et al.*[7]	Effects of antiemetics on ED patients	Beneficial for ED-specific contexts of akathisia	ED-specific settings require assessment	Study the effects of VR on patients in these settings
ScienceDirect	Virtual reality, Psychological well-being, Hospitalised patients, Serious illness, Critical review, SALSA method	The impact of virtual reality on the psychological well-being of hospitalised patients: a critical review	Du Plessis and Jordaan[9]	VR efficacy on psychological health of hospitalized patients	Useful for VR mental health t reatment in a hospital context	VR treatment found to have efficacy on patient mental state	Apply to patients with akathisia due to antiemetic drugs in an ED setting
ScienceDirect	Bright light therapy, Subthreshold depression, Cognitive functions, Functional connectivity	Bright light therapy-induced improvements of mood, cognitive functions and cerebellar functional connectivity in subthreshold depression: a randomized controlled trial	Chen *et al.*[10]	Visual-specific VR effects on psychological health	Helpful for studying efficacy of bright light on adverse psychological states	Bright light treatment improves adverse mental states	Apply to patients experiencing acute akathisia

To be continued on next page

Table 1. Continued from previous page.

Database	Keywords	Title	Author	Theme impact	Discussion	Conclusion	Further research
MDPI	Biosensors, Human-computer interaction, Machine learning, Affective computing, VR, EDA, PPG, EEG	Real-time classification of anxiety in virtual reality therapy using biosensors and a convolutional neural network	Mevlevioğlu *et al.*[11]	Real-time analysis of VR therapy for anxiety using biosensors	Useful for studying methods of VR therapy using biosensors	Biosensors can be used to study this efficacy	Apply to patients with antiemetic-induced akathisia
ScienceDirect	Akathisia, Emergency Medicine, Prochlorperazine	Prochlorperazine induces akathisia in emergency patients	Drotts *et al.*[12]	Tendency of antiemetic (antipsychotic) akathisia to induce acute akathisia	Helpful as an applied case study	This drug can cause akathisia	Patients experiencing akathisia from this drug can be included in future studies pertaining to the present article
Frontiers Media SA	Mental illnesses, neurological illnesses, electrophysiology, noninvasive device, electrodermal activity sensor, virtual reality, human-computer interaction, real time adaptation	Personalized virtual reality human-computer interaction for psychiatric and neurological illnesses: a dynamically adaptive virtual reality environment that changes according to real-time feedback from electrophysiological signal responses	Kritikos *et al.*[13]	Adaptive VR efficacy for neuropsychiatric symptoms	Useful for assessing adaptive, real-time VR therapy for adverse neuropsychiatric symptoms	Real-time VR exposure is useful for this purpose	Apply to patients with antiemetic-induced acute akathisia
ScienceDirect	Salivary cortisol, Biobehavioral research, Community setting	Measuring salivary cortisol in biobehavioral research: a systematic review and methodological considerations	Dong *et al.*[14]	Efficacy of salivary cortisol analysis for assessing psychological stress levels	Useful for the benefit of measuring cortisol levels via saliva	Saliva is a lucrative method to assess cortisol levels	Consider this method for integration into wearable VR technology
ScienceDirect	Virtual reality, Biofeedback, Heart rate variability, Stress management, Paced breathing	Virtual reality-supported biofeedback for stress management: beneficial effects on heart rate variability and user experience	Weibel *et al.*[15]	VR for assessing stress-based biofeedback	Useful for using VR to assess stress-specific biofeedback	VR is useful for measuring stress levels	Assess this VR analysis method for measuring stress due to antiemetic-induced acute akathisia
ScienceDirect	Neuroergonomics, Attention, Virtual reality, Working memory, Physiological computing, Adaptive systems	Designing and evaluating an adaptive virtual reality system using EEG frequencies to balance internal and external attention states	Chiossi *et al.*[16]	VR effects on distraction levels	Useful for assessing how VR can impact patient distraction from acute akathisia-induced distress	VR can help maintain user cognitive capacity via intermittent distraction	Investigate VR efficacy for distracting patients experiencing acute akathisia

The neurochemistry of akathisia

In their study, Nagaoka *et al*. discussed how tardive akathisia is a common side effect of long-term treatment with dopamine D2 receptor antagonists.[5] Their study used the FDA Adverse Event Reporting System and IBM MarketScan Research Database to identify a medication that could be used concurrently with dopamine D2 receptor antagonists to reduce the risk of akathisia. The study found that acetaminophen helped reduce akathisia induced by the antipsychotic haloperidol. In this specific case, the acetaminophen appeared to work on the ventral striata of these rats, thus preventing a haloperidol-induced decrease in the number of c-Fos+ preproenkephalin+ neurons. However, while this experiment indicated benefits of acetaminophen for mitigating akathisia in a neurochemical capacity, the study did not examine how a non-pharmacological treatment method such as wearable VR could work to help avoid and analyze the neurochemical mechanism behind akathisia stemming from antipsychotics used as antiemetics. Moreover, Nagaoka *et al*.[5] also did not explore the specific setting of an ED patient treated for a non psychosis-related ailment.

In terms of sensing methods for neurotransmitters, Hosseinzadeh *et al*. reviewed how to use electrochemical sensors to detect the presence of the akathisia-inducing antipsychotic cariprazine (CAR).[6] This study originally analyzed the voltametric behavior of CAR using an unmodified glassy carbon electrode (GCE). The researchers then applied electrochemical oxidation to isolate the CAR which showed a detection limit of 6.4 × 10-7 M (0.64 μM) and a broad linear dynamic range (2.5 × 10-6-5.0 × 10-5 M; 2.5-50.0 μM). Next, Hossinzadeh *et al*.[6] used a molecularly imprinted recognition system using the simple one-step electrochemical polymerization process, with CAR as the template molecule and 3-aminophenylboronic acid as the functional monomer. Once exposed to optimal conditions, the MIP/GCE returned an impressive sensitivity (177.25 μA/μM) and a detection limit of 1.27 × 10-14 M (12.7 fM) in a linear range from 1.0 × 10-13 to 2.5 × 10-12 M (0.1-2.5 pM). Thus, the sensor managed to identify CAR in both capsule and commercial serum samples. While promising for the objective of electrochemical detection of drugs causing extra-pyramidal side effects such as akathisia, this sensing method would likely most benefit the present study in the area of pharmacological chemical analysis rather than the specific neurochemical effects of the drug that cause akathisia.

Akathisia-inducing antiemetics

In their study, Chinn *et al*.[7] compared the likelihood of three antiemetics to cause akathisia in ED patients. These medications were metoclopramide, olanzapine, and prochlorperazine. The criteria were trauma patients aged ≥18 who arrived at the emergency department with a primary complaint of headache and received either of these three aforementioned medications. The results showed a trending need for treatment for akathisia or dystonia induced by the antiemetics. Logistic regression was used to identify differences between the three cohorts up to 72 h from initial presentation. Olanzapine was the most frequently used drug (n=2994, 53%) followed by prochlorperazine (n=2100, 37%) and metoclopramide (n=549, 10%). While this study explored the tendency of these antiemetics to cause conditions such as akathisia and dystonia in an acute setting, no non-pharmacological alternative such as VR was suggested as an option to help counteract the neurochemical imbalance triggered by these drugs. Additionally, no biosensing detective methods for identifying these imbalances were discussed.

Regarding specific neurotransmitters affected by these antiemetics, the following primary neurotransmitters impacted are serotonin, dopamine, histamine, muscarinic and neurokinin systems, and corticosteroids.[8] Serotonin and neurokinin antagonists like ondansetron and aprepitant have proved very successful in treating chemotherapy-induced nausea and vomiting. Metoclopramide and antihistamines are first-line options for nausea and vomiting in pregnancy. In this way, metoclopramide is a dopamine antagonist often used as a primary treatment for nausea and vomiting. Notwithstanding, the authors did not explore any less invasive or non-pharmacological alternatives such as VR wearable technology which could be used in conjunction with these dopamine antagonists with patients whose symptoms only respond to an antiemetic which causes akathisia. Moreover, this study was not included as part of the official tabled review in the *Recommendations* section of the present article due to the general nature of its subject matter unrelated to akathisia treatment.

Wearable VR as a non-pharmacological analysis and treatment option for antiemetic-induced akathisia

Various studies have explored the potential of wearable VR immersion for helping to quell anxiety. In their review, du Plessis et al. prioritized patients hospitalized for serious illness.[9] This review used reflexive thematic analysis to assess the success rate of VR for these patients. This review found the following benefits from VR exposure for these patients: i) positive psychological effects, ii) positive perception of new technologies, iii) characteristics that impact the effectiveness of VR, and iv) practical and statistical applicability and diversity of VR. Notwithstanding, despite revealing many advantages of VR for the well-being of hospitalized patients, du Plessis did not examine such applications in an acute setting nor how the wearable VR could be used specifically for dopamine increase and cortisol reduction in individuals affected by akathisia.

In their study, Chen et al. assessed the efficacy of various visual stimuli on psychological state.[10] While not specific to wearable VR, these findings could prove useful in determining which stimuli to implement into therapeutic VR technologies. In this case, the dopamine-raising benefits of bright light therapy (BLT) for helping reduce depression and improve cognitive function as well as cerebellar functional connectivity (FC) were explored. For this study, participants were randomly assigned to the BLT group (n=47) or placebo (n=41) in this controlled trial between March 2020 and June 2022. Depression severity and cognitive function were assessed, and a resting-state functional MRI scan performed before and after eight weeks of treatment. Seed-based whole-brain static FC (sFC) and dynamic FC (dFC) analyses of the bilateral cerebellar subfields were also performed. The researchers used a multivariate regression model to investigate whether baseline brain FC was connected to fluctuations in depression severity and cognitive function during BLT treatment.

The study's results showed an improvement in depressive symptoms among the participants treated with BLT. BLT also increased sFC between the right cerebellar lobule IX and left temporal pole, and decreased sFC within the cerebellum, and dFC between the right cerebellar lobule IX and left medial prefrontal cortex. While these results provide a wealth of data into BLT's usefulness for depression therapy, BLT as a feature of VR is not specified, nor was an experimental group used which had received akathisia-inducing antiemetic medication.

Finally, Mevlevioğlu *et al*. successfully used biosensors to track real-time anxiety level fluctuations in 29 participants during VR immersion.[11] These biosensors analyzed anxiety levels using biomarkers, namely, electrodermal activity, frontal brain activity, and heart rate, the latter of which is a relatively simpler-to-measure biomarker to incorporate for a patient undergoing wearable immersion in an acute setting. While this study did not focus specifically on akathisia or its neurochemical roots, it could serve as important related research surrounding a wearable VR device capable of tracking physiologic indicators in real time, such as neurotransmitters for the present study.

Literature gap

In the area of using wearable VR as a treatment for akathisia induced by antiemetics, the literature shows a gap in how VR stimuli could benefit patients experiencing such akathisia in an acute setting. While studies have explored the usefulness of VR in treating movement disorders such as Parkinson's Disease and psychiatric conditions like anxiety/depression, little attention has been paid to how VR can impact specific neurotransmitters such as dopamine and particularly in an acute context due to antiemetic-induced akathisia.

Indeed, the percentage of individuals who tend to experience akathisia as a side effect of antiemetics has not been investigated since 1999, when one study found the number to be 44%.[12] The sort of wearable device proposed in this article could serve as a means to measure neurochemical responses to neurotransmitter-balancing stimuli in real time.

Scant research also exists surrounding how real-time adaptive wearable VR can be used to help quell akathisia. In their study, Kritikos *et al*. focused on how adaptive VR could mitigate fear response to a specific external stimulus (e.g., arachnophobia) rather than abstract emotions due to the individual's neurochemistry.[13] To investigate and present this dynamically adaptive VR system we employ an anxiety disorder condition as a case study, namely arachnophobia. This research used VR to mimic arachnid-themed stimulus for 36 participants self-reported to have arachnophobia in this one-session trial. The electrophysiological responses of each individual were then recorded in real-time by an external electrodermal activity biosensor to track physiological changes. Participants were divided into two groups, the experimental group which was exposed to the proposed real-time adaptive virtual simulation, and the control group which experienced a pre-recorded static virtual simulation. The results illustrated the proposed VR system's ability to perpetually adapt the virtual environment's intensity at twice the rate of the pre-recorded static virtual simulation. Thus, while this level of adaptive virtual technology could prove promising for emotional regulation and mitigating central nervous system dysfunction, the study focused on an external stimulus rather than emotional response to a neurochemical imbalance.

Therefore, the literature does not explore how VR could be personalized to an individual's biometric reactions to help reduce symptoms of antiemetic-induced akathisia, particularly in an acute setting.

These results demonstrate a significant gap in research examining the specific intersection of therapeutic VR wearable technology applied in an emergency setting for patients experiencing antiemetic-induced acute akathisia. Therefore, this article proposed the framework for such a technology to be considered for future research in non-pharmacological treatment for akathisia in these contexts.

Limitations and future studies

This article and ensuing recommendations for future research have several limitations, including the proposed Python code not yet having been validated. Additionally, the potential invasiveness of a saliva test taken during a period of high stress as acute akathisia should be taken into consideration.[14] Moreover, the integration of a saliva analysis collector with a virtual reality headset could present various technical compatibility challenges, especially as biosensing for saliva analysis toward human cognitive prediction is still in its relatively early stages.[15] A potential solution to this challenge could involve the emerging biosensing wearable technology equipped for non-invasive saliva analysis capable of detecting neurotransmitter and cortisol levels.[16] The results of these VR sessions could also be measured against those of trials conducted surrounding opioids historically used in a limited capacity to treat acute drug-induced akathisia.[17] Such a comparison could help assess the prolificity of pharmacological versus non-pharmacological dopamine agonists.

Provided the abundance of patients receiving antiemetics for a variety of complaints ranging from gastroenteritis to headache to surgery, mitigation options for the relatively common extrapyramidal side effect of akathisia warrants further investigation. This article examined the potential benefits of wearable VR technology as a non-pharmacological treatment solution for patients experiencing antiemetic-induced akathisia in an acute setting such as the emergency room. Ideally, algorithms capable of correlating neurochemical fluctuations with user ML learning -equipped VR audiovisual inputs among symptomatic patients would be explored in clinical trials to determine the efficacy of this non-invasive therapeutic technology.

Recommendations

Future studies could explore the potential of a wearable VR headset device capable of adapting to anxiety-based biofeedback from patients experiencing antiemetic-induced akathisia. Patients could use this proposed program as a real-time distraction from akathisia symptoms, namely through bright, moving visuals with fluctuations measured in watts (W) and calming music with fluctuations measured in decibels (dB). The program in this device would analyze biofeedback such as heart rate spikes to indicate increased anxiety and alter the intensity of light changes and music volume, as needed to help reduce cortisol levels.[18] Further studies could also involve saliva samples to measure how dopamine and cortisol levels fluctuate in response to a wearer's immersive experience. The hormone cortisol was recommended here over the neurotransmitter epinephrine (adrenaline) as a stress indicator due to the former's ease of measurement in saliva compared to the latter which typically requires a blood or urine sample.

Given its usefulness in biofeedback gathering, Python was adopted as the base algorithmic code for this proposed technology.[19] The below Python code proposes a foundation for this technology based on previous innovations in ML for adaptive VR.[20]

Algorithm 1: Adaptive virtual reality algorithm

Dependencies

```
pip install pygame numpy
```

High-Level Architecture

- **HeartRateSensor** → provides live or simulated heart rate
- **AdaptiveController** → maps heart rate → tempo & visual speed
- **VisualEngine** → flickering colors + nature images
- **AudioEngine** → calming music with variable playback speed

Python Prototype Code

```
import pygame
import random
import time
import numpy as np

# ——————————————————————-
# Configuration
# ——————————————————————-
SCREEN_WIDTH = 1280
SCREEN_HEIGHT = 720
FPS = 60

BASE_HEART_RATE = 70
MAX_HEART_RATE = 120

MIN_COLOR_SPEED = 0.2
MAX_COLOR_SPEED = 2.0

MIN_MUSIC_SPEED = 0.6
MAX_MUSIC_SPEED = 1.2

NATURE_IMAGES = [
    “nature_forest.jpg”,
    “nature_ocean.jpg”,
    “nature_mountains.jpg”
]

CALMING_MUSIC = “calm_music.wav”

# ——————————————————————-
# Heart Rate Sensor (Mock)
# Replace with real sensor API
# ——————————————————————-
class HeartRateSensor:
    def __init__(self):
        self.heart_rate = BASE_HEART_RATE

    def read(self):
        # Simulate heart rate fluctuation
        self.heart_rate += random.uniform(-1.5, 1.5)
        self.heart_rate = max(55, min(self.heart_rate,
        MAX_HEART_RATE))
        return self.heart_rate
```

```
# ——————————————————————-
# Adaptive Mapping Logic
# ——————————————————————-
class AdaptiveController:
    @staticmethod
    def normalize(value, min_v, max_v):
        return (value - min_v) / (max_v - min_v)

    def compute_color_speed(self, heart_rate):
        t = self.normalize(heart_rate, BASE_HEART_RATE,
        MAX_HEART_RATE)
        return MAX_COLOR_SPEED - t * (MAX_COLOR_SPEED
         - MIN_COLOR_SPEED)

    def compute_music_speed(self, heart_rate):
        t = self.normalize(heart_rate, BASE_HEART_RATE,
        MAX_HEART_RATE)
        return MAX_MUSIC_SPEED - t * (MAX_MUSIC_SPEED -
        MIN_MUSIC_SPEED)


# ——————————————————————-
# Visual Engine
# ——————————————————————-
class VisualEngine:
    def __init__(self, screen):
        self.screen = screen
        self.current_color = np.array([50, 100, 200], dtype=float)
        self.target_color = self.random_color()
        self.last_switch = time.time()
        self.nature_images = [
            pygame.transform.scale(
                pygame.image.load(img), (SCREEN_WIDTH,
                SCREEN_HEIGHT)
            )
            for img in NATURE_IMAGES
        ]
        self.current_image = random.choice(self.nature_images)

    def random_color(self):
        return np.array([
            random.randint(100, 255),
            random.randint(100, 255),
            random.randint(100, 255)
        ], dtype=float)

    def update(self, color_speed):
        self.current_color += (self.target_color - self.current_color)
        * color_speed * 0.01

        if np.linalg.norm(self.current_color - self.target_color) < 5:
            self.target_color = self.random_color()

        if time.time() - self.last_switch > 10:
            self.current_image = random.choice(self.nature_images)
            self.last_switch = time.time()
```

```
    def render(self):
        overlay = pygame.Surface((SCREEN_WIDTH,
        SCREEN_HEIGHT))
        overlay.set_alpha(120)
        overlay.fill(self.current_color.astype(int))
        self.screen.blit(self.current_image, (0, 0))
        self.screen.blit(overlay, (0, 0))


# ————————————————————————-
# Audio Engine
# ————————————————————————-
class AudioEngine:
    def __init__(self):
        pygame.mixer.init()
        self.sound = pygame.mixer.Sound(CALMING_MUSIC)
        self.channel = self.sound.play(loops=-1)

    def set_speed(self, speed):
        # Pygame doesn’t natively support time-stretching;
        # this is a placeholder hook for real DSP processing
        self.channel.set_volume(speed)


# ————————————————————————-
# Main Application
# ————————————————————————-
def main():
    pygame.init()
    screen = pygame.display.set_mode((SCREEN_WIDTH,
    SCREEN_HEIGHT))
    pygame.display.set_caption(“Adaptive Calming VR
    Environment”)

    clock = pygame.time.Clock()

    heart_sensor = HeartRateSensor()
    controller = AdaptiveController()
    visuals = VisualEngine(screen)
    audio = AudioEngine()

    running = True
    while running:
        for event in pygame.event.get():
            if event.type == pygame.QUIT:
                running = False

        heart_rate = heart_sensor.read()

        color_speed = controller.compute_color_speed(heart_rate)
        music_speed = controller.compute_music_speed(heart_rate)

        visuals.update(color_speed)
        audio.set_speed(music_speed)

        visuals.render()

        pygame.display.flip()
        clock.tick(FPS)

    pygame.quit()


if __name__ == “__main__”:
    main()
```

How this responds to heart rate

Heart rate	Music	Colors
Low	Faster, brighter	More dynamic
High	Slower, softer	Smoother transitions

This creates a **biofeedback calming loop**, gently guiding the user toward relaxation.

Extending this into real VR

To make this production-ready:

- Replace Pygame with **Unity + OpenXR**
- Integrate real heart-rate hardware (Polar, Fitbit, BLE)
- Use real-time DSP for music tempo (e.g., Librosa)
- Add stereoscopic rendering & head tracking

Algorithm 2: Adjunctive neurotransmitter measurement Algorithm

While a slightly more invasive process, future studies could also gather a control group of consenting individuals experiencing antiemetic-induced akathisia (inside or outside the hospital setting) to provide saliva samples throughout their trial with the proposed wearable VR program.[21] This algorithm would function in unison with the VR program's changing music and visual settings as well as the corresponding biofeedback responses (namely, heart rate) to compare fluctuations of neurotransmitters in the saliva with heart rate due to the alternating stimuli.

The below Python code illustrates this algorithm.

- Simulated saliva-based neurotransmitter readings
- VR inputs (light brightness & music tranquility)
- Time-series analysis
- Detection of:

    - **Dopamine increase in response to brighter lights**
    - **Cortisol decrease in response to tranquil music**

- Live visualization and reporting

High-Level Architecture

Wearable Sensors (simulated)
↓
Neurochemical Signal Processor
↓
VR Event Stream (brightness, music calmness)
↓
Correlation & Fluctuation Analysis
↓
Visualization + Event-Based Report

Python Script (Simulation + Analysis)

```
import time
import random
import numpy as np
import matplotlib.pyplot as plt
from dataclasses import dataclass
from typing import List

# ——————————————————-
# Data Models
# ——————————————————-

@dataclass
class NeurochemicalSample:
    timestamp: float
    dopamine: float       # arbitrary units
    cortisol: float     # arbitrary units

@dataclass
class VREvent:
    timestamp: float
    light_brightness: float   # 0.0 (dark) → 1.0 (very bright)
    music_tranquility: float # 0.0 (intense) → 1.0 (very calm)

# ——————————————————-
# Simulated Wearable Sensors
# ——————————————————-

class SalivaNeuroSensor:
    “”“
    Simulated saliva-based neurotransmitter sensor.
    “”“

    def __init__(self):
        self.base_dopamine = 50.0
        self.base_cortisol = 40.0

    def read(self, vr_event: VREvent) -> NeurochemicalSample:
        “”“
        Generate simulated neurotransmitter values influenced by VR
        stimuli.
        “”“
        dopamine = (
            self.base_dopamine
            + 15 * vr_event.light_brightness   # brighter lights →
            dopamine increase
            + random.uniform(-2, 2)
        )

        cortisol = (
            self.base_cortisol
            - 12 * vr_event.music_tranquility  # tranquil music →
            cortisol decrease
            + random.uniform(-2, 2)
        )
        return NeurochemicalSample(
            timestamp=vr_event.timestamp,
            dopamine=dopamine,
            cortisol=cortisol
        )

# ——————————————————-
# VR Program Interface
# ——————————————————-

class WearableVRProgram:
    “”“
    Simulates VR visuals and music state.
    “”“

    def generate_event(self) -> VREvent:
        return VREvent(
            timestamp=time.time(),
            light_brightness=random.uniform(0.2, 1.0),
            music_tranquility=random.uniform(0.2, 1.0)
        )

# ——————————————————-
# Analysis Engine
# ——————————————————-
```

```
class NeuroVRAnalyzer:
    def __init__(self):
        self.samples: List[NeurochemicalSample] = []
        self.vr_events: List[VREvent] = []

    def add_data(self, sample: NeurochemicalSample, event: VREvent):
        self.samples.append(sample)
        self.vr_events.append(event)

    def analyze_and_report(self):
        dopamine = np.array([s.dopamine for s in self.samples])
        cortisol = np.array([s.cortisol for s in self.samples])
        brightness = np.array([e.light_brightness for e in self.vr_events])
        tranquility = np.array([e.music_tranquility for e in self.vr_events])

        dopamine_brightness_corr = np.corrcoef(dopamine, brightness)[0, 1]
       cortisol_tranquility_corr = np.corrcoef(cortisol, tranquility)[0, 1]

        print(“\n—- Neurochemical Response Report —-”)
        print(f”Dopamine ↔ Brightness Correlation: {dopamine_brightness_corr:.2f}”)
        print(f”cortisol ↔ Music Tranquility Correlation: {cortisol_tranquility_corr:.2f}”)

        if dopamine_brightness_corr > 0.5:
            print(“□ Dopamine increase detected in response to brighter lights.”)
        if cortisol_tranquility_corr < -0.5:
            print(“□ cortisol decrease detected in response to tranquil music.”)

    def visualize(self):
        time_axis = range(len(self.samples))

        plt.figure(figsize=(12, 6))
        plt.plot(time_axis, [s.dopamine for s in self.samples], label=”Dopamine”)
        plt.plot(time_axis, [s.cortisol for s in self.samples], label=”cortisol”)
        plt.plot(time_axis, [e.light_brightness * 50 for e in self.vr_events],
                 linestyle=”—”, label=”Light Brightness (scaled)”)
        plt.plot(time_axis, [e.music_tranquility * 50 for e in self.vr_events],
                 linestyle=”—”, label=”Music Tranquility (scaled)”)

        plt.xlabel(“Time (samples)”)
        plt.ylabel(“Level (arbitrary units)”)
        plt.title(“Neurochemical Fluctuations vs VR Stimuli”)
        plt.legend()
        plt.tight_layout()
        plt.show()


# ——————————————————————-
# Main Runtime Loop
# ——————————————————————-

def main():
    vr = WearableVRProgram()
    sensor = SalivaNeuroSensor()
    analyzer = NeuroVRAnalyzer()

    print(“Starting wearable neurochemical-VR analysis...\n”)

    for _ in range(30):
        event = vr.generate_event()
        sample = sensor.read(event)
        analyzer.add_data(sample, event)
        time.sleep(0.1)

    analyzer.analyze_and_report()
    analyzer.visualize()


if __name__ == “__main__”:
    main()
```

Key outcomes this script demonstrates

- **Dopamine increases correlate with brighter VR lighting**
- **Cortisol decreases correlate with calmer VR music**
- Visual time-series overlay of:
    - Neurochemical levels
    - VR stimuli intensity

Extensions

- Replace simulated sensors with real biosensor APIs
- Stream VR data via Bluetooth / WebSocket
- Add rolling-window analysis for real-time feedback
- Integrate into a Unity or Unreal VR telemetry pipeline

Additionally

- Adapt this for **real-time streaming**
- Convert it into a **microcontroller-friendly version**
- Add **machine learning prediction**
- Align it with a **specific VR engine (Unity/Unreal)**

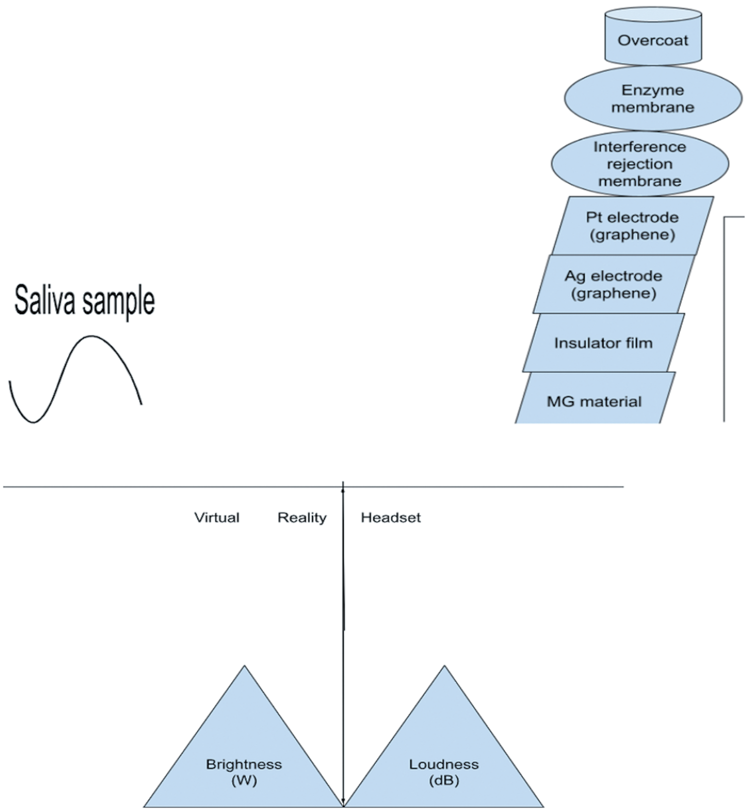

Figure 1. VR-neurotransmitter analysis biosensor design schematic.

Mechanism visual

Figure 1 shows the basic mechanics of how the saliva sensor would connect to the VR program, designed along similar lines to the wearable stomatology and ophthalmology device designed by Sheng *et al*. and the graphene COVID-19 detector by Silva *et al.,* only involving the saliva gathered *via* a collector within the headset rather than a blood sample.[22,23]

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