Application No.:

PI1 Name:

**Research Program**

**Scientific background**

Schizophrenia is a neuropsychiatric disorder characterized by positive symptoms (delusions, hallucinations, abnormal flow of thoughts), negative symptoms (withdrawal, apathy, anhedonia), and cognitive deficits.1 It affects approximately 1% of the worldwide population and presents a substantial domestic and global burden due to the presence of comorbidities, risk of relapse, and excess early mortality.2-3 Schizophrenia is likely a product of interacting genetic and environmental influences, and despite the considerable research advances in the underlying molecular genetics, the pathogenesis of schizophrenia, as well as the presentation and course of the illness, remain poorly understood. Clinical management of schizophrenia often requires antipsychotic medication, which can provide symptomatic remission. Nevertheless, even with appropriate medication, up to 40% of patients still relapse within 1 year.4 Relapse can have devastating consequences and it is associated with poorer prognosis, higher risk of injury, decreased quality of life, and decreased cognitive ability.5 Predicting relapse is challenging given the complexity of schizophrenia. A reliable prediction of risk for relapse would enable early intervention and reduce its devastating repercussions. The present study aims to address this issue by proposing an integrative model that includes biological and psychological risk factors that predict relapse, and which suggests digital phenotyping as the behavioral measurement that can mediate this prediction. In an era that aspires for personalized medicine, providing a multifactorial predictive model would aid in identifying people at varying risk of relapse, and could allow for customized risk management of relapse.

*Stress-vulnerability model for onset and relapse in schizophrenia.* According to the stress-vulnerability framework, a combination of neurobiological and psychosocial factors is responsible for the onset and course of schizophrenia. Relapse in schizophrenia is recognized as the reemergence or worsening of psychotic symptoms. Noteworthy is that about half of patients are non-adherent to treatment.6 The non-adherence may be due to various factors, which are depicted in the stress-vulnerability model. Stress is thought to emerge from exposure to a single life event or multiple, ongoing life events. In the last two decades, researchers have focused on both objective and subjective levels of stress exposure, naming the perceived stress in response to events.7 Vulnerability is assumed to arise from a combination of biological and psychological factors. Among the psychological factors that have been identified as increasing the likelihood of relapse are depression, anxiety, and lack of motivation.6 Vulnerability to relapse also involves biological antecedents, including various bodily systems involved in the neuroimmunology of relapse.

*Neuroimmune factors for relapse in schizophrenia.* Biological factors that predict relapse in schizophrenia have been studied extensively over the past decade and they include aspects of the immune, neural, metabolic, and endocrine systems.8 There is evidence for immune system abnormalities, including inflammatory responses, among schizophrenia patients.9 The autonomic nervous system (ANS) regulates the immune system through the sympathetic (SNS) and parasympathetic (PNS) networks. Dysfunction of the ANS may contribute to the inflammatory profile reported in schizophrenia.10 Schizophrenia patients tend to exhibit autonomic imbalance with low heart rate variability (HRV), suggesting a reduced parasympathetic and increased sympathetic tone.11 Stress has been associated with ANS dysfunction (including increased outputs of the SNS, such as increases in catecholamine levels) and with PNS/vagal withdrawal.12 Stress has been also associated with alterations in HPA (hypothalamus-pituitary-adrenal) axis functioning, including higher levels of circulating cortisol (a glucocorticoid; the main end product of the HPA axis in humans), which in turn cause focal or general inflammation.13 Accumulative evidence of HPA axis abnormalities in the risk for psychosis suggest a tonic (chronic) HPA hyperactivation and phasic (acute) HPA blunting.7

Research conducted in the last two decades has expanded upon our understanding about the links among stressors, the HPA axis and the ANS, and the risk for developing schizophrenia; this body of research has demonstrated the role of the microbiota-gut-brain (MGB) axis signaling on brain function and neurochemistry.14 The MGB axis communicates with the brain through the vagus nerve, immune system, enteric nervous system, and enteroendocrine signaling15. The microbiome is comprised of dynamic ecological communities of commensal microorganisms that consist of bacteria, viruses, fungi, and protozoa which are diverse and personalized, and are influenced by lifestyle factors including stress.14,16 Studies have shown that schizophrenia is related to the dysfunction of the MGB17, and that improving the gut microbiota may produce beneficial effects.18 These effects are explained through the MGB axis signaling on various systems involved in the pathogenesis of schizophrenia. Gut microbiota perform a central function in the development of the neuroimmune system. Immune system alterations are key factors in the etiology of schizophrenia, with studies showing that infections increase the risk of schizophrenia.19 Recent studies with schizophrenia participants who were receiving probiotic supplements (e.g., Lactobacilli, Bifidobaterium breve) provided preliminary evidence that probiotic supplementation has anti-inflammatory effects20,21 through transforming growth factor-*β* signaling.13 Additionally, the MGB axis affects the development and regulation of the HPA axis. Animal studies have shown that significant changes in the HPA axis are associated with elevated ACTH and cortisol levels in germ-free stressed mice.22 However, there is a scarcity of human studies addressing the crosstalk between the HPA and MGB axes in schizophrenia. In a recent review, Seeman examined the role of gut microbiota in treatment resistance among schizophrenia patients.23 He postulated that there is a drug refractory form of psychosis for which the composition of gut bacteria is responsible.

There are well-documented findings indicating sex differences in regard to the disease risk, course of illness, and outcomes of schizophrenia. There are sex differences in the age-at-onset of schizophrenia, such that males reach peak onset between the ages of 18 and 24 whereas, for females, it occurs up to 4 years later.24 Furthermore, in females, there is a second peak age-at-onset that occurs at 45-50 years old.25 Females tend to present a less severe course of illness, a more favorable antipsychotic treatment response, and improved outcomes and quality of life compared to males.26-28 In light of these sex differences, it has been hypothesized that sex hormones may play a role in explaining individual differences in the development of schizophrenia. Sex hormones – including androgens, estrogens, and progestins – are chemical messengers secreted by the gonads (ovaries in females and testes in males) and by the adrenal glands by way of the HPG (hypothalamus-pituitary-gonads) axis.29 Among females, variations in estrogen and progesterone secretions create differences between them across different phases of the menstrual cycle, and among pre-, peri-, and postmenopausal women.30 Further, it has been proposed that differences in the ANS may be due to differences in several potential functions of the nervous system, such as differences in afferent stimulation, central reflex transmission, and post-synaptic signaling.30 Recently, Barel and colleagues demonstrated that sex hormones modulated the HPA axis and SNS reactivity to psychosocial stress, emphasizing the need to include sex hormone fluctuations when examining stress effects in typical, as well as clinical, samples.31

The underlying mechanism for these sex differences in schizophrenia involves a complex interplay of various factors. Among the biological factors identified, sex hormones have been suggested as an important factor. The leading explanation is the estrogen hypothesis, which postulates that estrogen plays a protective role against schizophrenia.32 Studies have demonstrated increased symptom severity, greater relapse rates, and higher symptoms scores during times of low circulating estrogen.33 Apart from the role of estrogen in schizophrenia, the role of androgens has been studied as well. For example, a few studies have shown that lower total and free testosterone levels were associated with severe negative symptoms in men with schizophrenia.34 A recent meta-analysis concluded that a blunted testosterone response to acute stress is associated with relapse of schizophrenia.35 The authors suggested to further investigate alterations in testosterone in patients with schizophrenia, along with indices of the HPA axis and other biological mechanisms involved in psychotic disorders. Indeed, previous studies have investigated the involvement of the MGB in the association between sex hormones and the development of diseases. They found a bidirectional relationship between estrogen and gut microbiota in the influence on brain function, cardiovascular disease, and cancer.36 Furthermore, testosterone has been shown to enrich gut microbiota with specific bacteria, which in turn reduced inflammation.37 In their recent review regarding the etiology of depression, Markis and colleagues showed that the interconnection between the gut microbiota and the brain is affected by several factors such as inflammation, sex hormones, and stress. This communication is facilitated by the activation of the HPA-axis following stress, which stimulates the immune system and, in turn, causes gut dysbiosis which, subsequently, leads to hypoestrogenic conditions including depression.38

*Digital phenotyping: 24/7 behavioral monitoring platforms*. Smartphone technology, particularly advances in smartphone sensors, can offer a new approach to the study of mental health in general, and to schizophrenia in particular.39 In addition to patients’ real-time self-reporting of specific factors of interest, smartphone technology allows researchers to passively collect data about human behavior using mobile sensors and system logs that are already embedded in the devices (e.g., GPS, accelerometer, gyroscope, application use statistics, battery states and charges, network activity, rotation, magnetometer, logs of outgoing and incoming calls, text messages logs, and more).40,41 Over the past few years, smartphones and other digital platforms have become promising sources through which to learn about and investigate various psychological factors. The fields of psychological, as well as medical, science could benefit from analyzing digital footprints left on various digital sources.42 Digital phenotyping refers to the act of collecting and using data from smartphones and other personal digital devices, and subsequently connecting that data to behavioral and personality data. Studies examining the adverse health effects of smartphone use have found that problematic smartphone use was associated with negative health symptoms43 and weakened immunity.44 These methodologies have been applied to the fields of psychology and psychiatry; for example, phone call data extracted from smartphones were associated with extraversion, agreeableness, and conscientiousness.45,46 Another study demonstrated a link between longer use of a social media applications and lower levels of conscientiousness.47 Further, studies examining the relationship between smartphone use and psychopathological symptomatology have found links between smartphone use and depression severity (lower depression severity predicted increased smartphone use),48,49 as well as anxiety severity (anxiety severity was negatively associated with frequency of phone screen unlocking).49

*Digital phenotyping of schizophrenia.* Digital phenotyping research that uses the intensive data collection capabilities of modern smartphones are just beginning to be applied to the study of schizophrenia. Smartphone-based early digital phenotyping studies have shown that schizophrenic patients exhibited reduced motor activity, which was correlated with high interview-based apathy levels.50,51 Studies aimed at using technology to augment relapse prediction have demonstrated that detecting early relapse signs, via simple SMS weekly communication and patient reporting of relapse symptoms (along with increasing medication during the warning state), is an effective intervention during the early stages of relapse.52,53 Another study tested for changes in mobility patterns and social behavior over time (measured through smartphone use) to identify anomalies in patient behavior in the days prior to relapse.54 The study found that the rate of behavioral anomalies detected in the 2 weeks prior to relapse was 71% higher than the rate of anomalies during other time periods. Autonomic dysfunctions in people with schizophrenia were also measured with Mobile Health (mHealth) methods; for example, wearable technology.55 Compared to controls, people with schizophrenia exhibited lower levels of HRV, movement and functioning. In people with schizophrenia, illness severity, particularly positive symptoms, was associated with parasympathetic deregulation proving that autonomic abnormalities can be detected in people's everyday lives with the use of wearable technology. Thus, this method may be utilized to monitor well-being and relapse prevention.

In conclusion, there is ample evidence to suggest that relapse is associated with biological factors involved in immune, neural, metabolic, and endocrine systems, as well as psychosocial risk factors such as depression, anxiety, exposure to stress and perceived stress. Furthermore, the capability of many smartphones and wearable sensors to collect psychological and physiological data from subjects can enable the use of digital phenotyping for relapse prediction, and allow for a comprehensive predictive model for relapse prediction to be generated. To that end, the proposed objectives of the current research are outlined below.

**Research objectives and expected significance**

Our research will apply the stress-vulnerability model to the prediction of relapse in schizophrenia and will examine biological markers, psychological factors, stress and perceived stress through behavioral mechanisms (measured by digital footprints). Based on previous findings, the specific aims of the current study are as follows:

1. To examine the associations between biological markers (i.e., gut microbiota, ANS, HPA axis, HPG axis), as well as biomarker interrelations, and relapse in schizophrenia.
2. To examine the associations between psychological variables (i.e., depression, anxiety) and relapse in schizophrenia.
3. To examine the role of interconnectivity among the HPG axis, the ANS and the HPA axis in relapse prediction. Previous studies have demonstrated associations among the HPG axis, the ANS and the HPA axis. Furthermore, the role of each system in predicting relapse was explored independently. However, to the best of our knowledge, the interconnectivity among these systems, both in general and specifically in a psychopathological context, has not yet been investigated.
4. To examine the associations between smartphone-based digital phenotyping sensors data and novel biosensors/biomarkers, as well as to generate predictive clusters combining bio + digital data for predicting SD relapse.
5. To examine the behavioral mechanisms associated with relapse using digital footprints from smartphones (i.e., digital phenotyping) that predict relapse.

With the use of unprecedented monitoring and data collection abilities that modern smartphone devices allow, we expect our findings to shed light on the mediating role of behavioral mechanisms in the association between individuals’ psychological/biological states and relapse. Uncovering such associations and relationships among the variables may serve to validate the use of digital footprints (collected from smartphones) to predict relapse which may, in turn, promote the use of this technology to create preventive programs. Importantly, studies measuring behavioral mechanisms through digital footprints in the context of schizophrenia have only recently emerged and are limited by very small sample sizes. Nevertheless, they provide promising preliminary results that indicate the feasibility of predicting relapse via digital phenotyping. Findings of the current research are also expected to contribute to a better understanding of the predictive role of the joint modulation of the ANS and the HPG axis. Our findings will thus have implications for personalized medicine, as it could allow for customized interventions for relapse prevention that consider gender-specific factors and patients’ sex hormone profiles.

**Detailed description of the proposed research**

**Our working hypotheses**

Individualized patient profiles that consider behavioral expressions of psychological factors (measured by smartphone sensors, digital diaries, and self-report questionnaires), as well as biological expressions (measured through saliva sample levels of cortisol, alpha-amylase, testosterone, estrogen, progesterone; epithelial samples for gut microbiota; and ANS activity through wearable devices) will constitute predictable risk factors for relapse (measured using XXXX). The following are our specific hypotheses (see section on digital phenotyping measurements of smartphone data below for a precise definition of a smartphone-related sensor, as well as measurement terms):

1. Patients experiencing relapse will exhibit higher levels of anxiety and depression than patients without relapse within 1-7 days prior to the relapse.
2. Patients experiencing relapse will exhibit higher levels of stress and perceived stress than patients without relapse within 1-7 days prior to the relapse.
3. Patients experiencing relapse will exhibit higher levels of stress biomarkers (i.e., cortisol, alpha-amylase), autonomic abnormalities, gut-microbiota anomalies, and lower levels of estrogen than patients without relapse within 1-7 days prior to the relapse.
4. The interaction of the HPG axis, the ANS, and the HPA axis will mediate the association between psychological factors and stress levels among patients experiencing relapse.
5. Biomarkers of the ANS and HPG axis will be associated with patients’ behavioral measures (measured through digital phenotyping) and will act as the mediator in the association between psychological/biological factors and relapse.
6. Patients experiencing relapse will have longer periods of “active screen state,” will exhibit higher rates of “compulsive” smartphone use and non-use, will receive higher numbers of incoming calls and will place higher numbers of outgoing calls, and will receive higher numbers of incoming calls and will place higher numbers of outgoing calls within a 24-hour period (see research tools section below) than patients without relapse.
7. Patients’ behavioral measures (measured through digital phenotyping) will act as mediators in the association between psychological/biological factors and relapse.

**Methodology**

**Participants**. Two-hundred participants with schizophrenia will be recruited to take part in the study (age range: 18-45; both men and women). Participants must have been diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V)x. All participants will be interviewed using the Structured Clinical Interview for DSM-5 (SCID-5). Patients will be recruited from Maale HaCarmel Mental Health Center (and other centers) from November 2021 to XXX. All patients must receive a stable dose of antipsychotic medication for at least 30 days prior to the start of the study. Additionally, they must be judged as clinically stable by the principal investigator in the XXX. Exclusion criteria will include another DSM-V Axis I diagnosis, Axis II diagnosis of borderline personality or antisocial personality disorder, substance dependence or abuse, medical illness…. XXXXX, an inability to participate in an interview or to complete an online questionnaire, an inability to operate a digital diary smartphone app, and having undergone total abdominal hysterectomy with bilateral ovariectomies (women). Enrollment would be set to begin in XXX.

**Research procedure**

The current study design is between-subject (patients experiencing relapse vs. patients without relapse). The study will begin following approval from the XXX Helsinki Committee. All patients will be asked to provide their informed consent prior to starting the study. Standard data privacy and security practices will be followed, in accordance with the General Data Protection Regulation (GDPR).62,63

Upon entry into the study, assessments of baseline psychological characteristics and biological markers will be collected. To obtain other biomarker data (cortisol, alpha-amylase, testosterone, estrogen, progesterone), patients will be asked to provide saliva samples at several assessment points – at baseline and at multiple follow-up timepoints, up to X months. Epithelia….Patients will also be provided with a digital diary and will receive a detailed explanation about how to use it. The digital diary smartphone app will also include a digital phenotyping sensor that will monitor accelerometer data, smartphone power states, number of incoming/outgoing calls, etc.). Relapse will be assessed with the Brief Psychiatric Rating Scale (BPRS).xx

**Data analysis and statistical plan**

Digital footprints from smartphone data (digital phenotyping), biological markers, and self-report questionnaires assessing psychological states will be associated with XXXX in order to detect potential behavioral predictors of relapse.

Data collection: Smartphone sensor and logs data collection software (open-source Aware digital phenotyping framework) will be customized for our research goals (Android and iOS environment). Data preparation: Various R and Python packages for data preparation will be utilized. Data will be analyzed using software for machine learning and other AI modeling, for example, machine learning packages for Python and RapidMiner server installation on AWS. Statistical analysis will be completed using Jamovi open-source R statistical package for R, R software, and SPSS software version 25. The statistical significance level will be set to an alpha of 0.05, such that the null hypothesis will be rejected if p < .05. Pearson's correlation analyses will be performed between endocrine parameters and ANS parameters. Patients who experienced relapse during the XX-month follow-up period will be designated as the experimental group (relapse patients), whereas patients without relapse will be designated as the control group. Hypotheses regarding differences in psychological variables, biomarkers, allostatic overload (AO), and digital footprints between relapse patients and control patients will be tested using XXXXX. Hierarchical logistic regressions will be used to test the moderation hypotheses regarding the role of the HPG axis and the ANS interaction, as well as the MGB, in the associations among psychological variables, AO, and relapse. Logistic regression and linear regression analyses will be used to test the mediation hypotheses regarding the role of digital phenotyping in explaining the association between psychological and biological variables and relapse.

**Research tools**

We intend to utilize several research tools, which fall under four broad categories, to measure indicators that we deem to be potentially relevant to important psychological and biological risk factors for relapse. In addition, a general demographic questionnaire will be administered, which will include questions about participants’ age and gender, as well as contact information for follow-up questionnaires and email addresses to obtain participants’ consent to take part in the study.

**Measuring behavioral indicators that are potentially related to psychological and biological risk factors for relapse**

**Biological factors:**

**1) ANS function –** ANS function will be assessed through a wrist-worn wearable device that will record electrodermal activity (i.e., sympathetic nervous system arousal); blood volume pulse [from which it is possible to extract inter-beat intervals (IBIs), and in turn, from IBIs it is possible to extract HRV]. 2) **Biological markers for stress and HPG** – Saliva samples will be collected to test for levels of cortisol, alpha-amylase, testosterone, estrogen, and progesterone. Saliva samples will be analyzed in the endocrine laboratory of the Rambam health care campus. 3) Gut microbiota

**Psychological factors:**

**1) Stress and perceived stress** – Measures of stress and perceived stress will be based on the concept of allostatic overload (AO). AO occurs when one’s cumulative life events and chronic stressors exceed one’s resources.67,68 To experience AO, two criteria must be met. First, it requires the presence of an identifiable stressor that is perceived as exceeding or taxing the individual's coping skills. The presence of a stressor, and one’s perceived inability to effectively cope with the situation, will be measured using the self-report psychosocial index, specifically the stress subscales.69 The second criteria is that the stressor must be associated with at least one of the following: psychiatric symptoms, psychosomatic symptoms, impaired functioning, or compromised well-being. The presence of AO will be established if the participant’s self-report satisfies both criteria.70 **2) Depressive symptoms –** The Beck Depression Inventory (BDI) will be used to assess depressive symptomatology. This measure contains 21 self-report items, each of which are rated on 0 to 3 scale. 71 **3) Anxiety** – Anxiety will be assessed using the state anxiety subscale of the State Trait Anxiety Inventory (STAI). The subscale consists of 20 items, each of which are rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much so).72 **4) Sleep quality XXX 5) Psychosis XXXX 6) Warning symptom scale XX 7)** Treatment adherence XXX

**Digital phenotyping measurements of smartphone data: Behavioral data:**

Maintaining a reliable data collection platform that uses smartphone sensors is a major challenge. We will use the open-source Aware-light platform, a platform with which we have already gained considerable experience in the past year in two different studies. The Aware research platform is part of the broader Aware framework and was developed by the Academy of Finland and by the University of Melbourne, Australia.13 AWARE captures hardware, software, and human-based data from smartphones. Aware is fully compliant with GDPR standards. By design, AWARE does not collect any personal identifiers in its data and stores data locally on the users’ phones. Integrating the mobile client with an AWARE server allows replication of the data to a secure remote database. AWARE offers data encryption and obfuscation by default, which is crucial to safeguard the transition between local-only data and shared data. During a study deployment, users can withdraw and remove the collected data from the server and the mobile phone at any time, directly from their phones. As the data is primarily stored on users’ devices, it will be backed up to a secure AWS RDS MySQL database using an SQLite client.79 The app collects phone sensor data (e.g., using GPS, accelerometer, magnetometer smartphone sensors) and phone usage data (e.g., communication logs and screen activity). The Aware app also allows for administrating an e-diary (experience sampling module), which is a method used to measure participants’ behaviors, thoughts, and feelings as they go about their daily lives. Data will be collected through study participants’ self-reports. We plan to additionally use the experience sampling module for short, daily and weekly questionnaires. Below are the parameters that we plan to use.23,67,80–83 The data will be collected across three time periods: Daytime = 06:00-18:00; Evening = 18:00-24:00; Nighttime = 24:00-06:00. We will collect many types of sensor and log data. The following are examples of the main four categories of data that will be collected:

**Examples of experience sampling online pop-up daily questionnaire (e-Diary) categories:** Depression, sleep quality, psychosis, warning symptoms scale, medication use, anxiety.

**Examples of smartphone mobility indicators**: Percent of time spent at home in a 24-hour period, distance traveled from home, radius of gyration, maximum travel diameter, maximum distance from home, number of signiﬁcant locations visited, fraction of the day spent stationary, signiﬁcant location entropy, minutes of missing GPS data, physical circadian rhythm, physical circadian rhythm stratiﬁed.

**Examples of** **smartphone indictors of sociability**: Hours spent on social media applications, number of outgoing texts, total outgoing text length, texting out-degree, number of incoming texts, total incoming text length, texting in-degree, texting reciprocity, texting responsiveness, number of outgoing calls, total outgoing call duration, call out-degree, number of incoming calls, total incoming call durations.

**Examples of smartphone indictors of agitated, irritable, and compulsive behavior:** Total duration of “active screen state” per hour/day, sum of number of power button presses per hour/day, total event of short "screen on” per hour/day, total “compulsive” phone checks per hour/day, battery charging events per day, frequency of checking/refreshing social media applications.

**Available resources**

**Intellectual capital and experience**

The proposed research represents an interdisciplinary collaboration of experts in the fields of psychiatry, psychology, psychobiology, and computer and data science.

Prof. Michael Poyurovsky, a psychiatric specialist, is the head of the Department of First Admissions and the Research Unit at a state psychiatric hospital. He is an Associate Professor of Psychiatry at the Rappaport Faculty of Medicine, at the Technion, Israel Institute of Technology, and is a visiting professor at Stanford University. Prof. Poyurovsky is an eminent psychiatric specialist, well-known in Israel and abroad for his expertise as a diagnostician and in administrating psychopharmacological therapy, in particular for obsessive-compulsive disorder, schizophrenia and complex conditions in which there is a co-occurrence of the two disorders. His book on schizo-obsessive disorder was published by the Cambridge University Press (2013). Prof. Yonathan Mizrachi (PhD in Anthropology, Harvard) is the former head of the Department of Information Systems and the Department of Anthropology and Sociology at YVC Academic College. He is an ICT4D and BPR information systems specialist, as well as the former CTO of several startups. He is also an affiliated Research Scientist (focusing on digital phenotyping research) at the Lambda School and in Tel Aviv University’s Laboratory for AI, Machine Learning, Business + Data Analytics. Dr. Efrat Barel received her PhD in Psychology from Haifa University and is currently a faculty member in the Department of Behavioral Sciences at Emek Yezreel Academic College, and a member of the Psychobiology Laboratory at Emek Yezreel Academic College. Dr. Barel has an extensive background in stress research, including its relation to physiological stress and reproductive systems. Further, she is well-experienced in the performance and interpretation of biochemical tests. Dr. Noa Cohen completed her PhD in computer science and computational biology from the Hebrew University. Dr. Cohen is currently a researcher and senior lecturer (Israeli equivalent to assistant professor) in the Department of Software Engineering at the Azrieli College of Engineering Jerusalem and is experienced in machine learning, deep learning, and data science research. Dr. Fruchter is a Project Advisor, who has served in many leading positions in the field of mental health in the Israeli Defense Force (IDF). In his last position, as Colonel, he headed the mental health department in the IDF Medical Corps. During his military service, Dr. Fruchter also earned an M.H.A. from Ben Gurion University of the Negev. Dr. Fruchter recently returned from a year at USC in Los Angeles, where he was studying treatment and prevention of PTSD (Post Traumatic Stress Disorder). He joined the staff at Rambam Hospital’s in-patient psychiatric ward and subsequently became the director of the division. Dr. Fruchter is a leading clinician and researcher in the fields of suicide prevention and PTSD. He participates in conferences and collaborative research with many professionals in the US and Europe. Dr. Fruchter has published over 40 English-language articles in leading professional journals, with many more in Hebrew, as well as two chapters in professional books, all on the topic of suicide prevention and aviation psychology.

**Physical facilities and other resources**

The Maale Carmel Mental Health Center (MCMHC), which is a branch of the Faculty of Medicine at the Technion, provides treatment for a variety of mental disorders among teenagers, adults and the elderly. The center aims to improve the mental health and functioning of its patients, while considering and employing the help of their families. The treatment is provided with a sense of purpose and a desire for constant improvement. The center serves a population of half a million people living in Haifa, its suburbs, and nearby towns (the Krayot, Kiryat Tivon, Nesher, Carmel City, Tirat Carmel, Atlit, and the Carmel beach towns). Biomarker testing of saliva samples will be conducted by the laboratory staff of the \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Medical Center. Stable digital phenotyping and data science platform. An accumulated 3 years of experience with the open-source digital phenotyping platforms using the AWS-based system for Android smartphone devices for the purposes of data collection. The system includes an initial smartphone sensors data pipeline (Android-based) for machine learning data cleansing (which will be later expanded to work with IOS systems).

**Expected results, potential pitfalls, and alternative research plans**

Given the precision of our expected measurements for both the dependent and the independent variables, we believe that the current study offers a unique opportunity to examine the multifaceted associations between psychological/biological factors and the risks of relapse in schizophrenia. We do not foresee major pitfalls, but we have secured alternative data collection methods if necessary. For the predictor variables, given that we have several complementary measures, we do not foresee any problems in collecting or recollecting data, if needed. The main engineering challenges that will need to be resolved are as follows:

1) Maintaining a reliable smartphone data collection platform (which is currently performing better on Android smartphones than other types of smartphones). We plan to use the open-source Aware digital phenotyping platform and run its back-end on the reliable Amazon AWS infrastructure.

2) Developing a reliable data cleaning and preparation process that links between the data collected through mobile sensors and participants’ smartphones. We plan to utilize the relevant R and Python packages to overcome this challenge.

3) Modeling a prediction framework that utilizes the above features. We may utilize R, Python and/or non-open-sourced commercial tools, such as RapidMiner and SparkBeyond, to overcome this challenge.

Additionally, we anticipate a sample size challenge. We plan to recruit a large number of participants to offset expected participant dropout rates. However, the initial recruitment may still be insufficient and the potential for high dropout rates may require the recruitment of additional participants, which may extend the time needed for completing data collection. A relatively high compensation will be offered to participants, together with some “softer” incentives (personal connection with medical staff and research assistants) to encourage participants to take part in the study.

Despite the challenges, the current study has several strengths, including: a prospective study design, which includes a XX follow-up; the use of validated psychological measures; the inclusion of various biomarkers; and the innovative application of digital phenotyping to behavioral mechanisms that play a role in schizophrenia. Additionally, our study will have high external validity, as the population will include patients who have experienced a psychotic episode.

**Figure**

**Figure 1:**

**Bibliography**

1. Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *The Lancet, 363,* 2063-2072.
2. James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Briggs, A. M. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789-1858.
3. Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess early mortality in schizophrenia. *Annual review of clinical psychology*, *10*, 425-448.
4. Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. (2013). The nature of relapse in schizophrenia. *BMC psychiatry*, *13*(1), 1-8.
5. Taylor, M., Chaudhry, I., Cross, M., McDonald, E., Miller, P., Pilowsky, L., & Strickland, P. (2005). Towards consensus in the long‐term management of relapse prevention in schizophrenia. *Human Psychopharmacology: Clinical and Experimental*, *20*(3), 175-181.‏
6. Kazadi, N. J. B., Moosa, M. Y. H., & Jeenah, F. Y. (2008). Factors associated with relapse in schizophrenia. *South African Journal of Psychiatry*, *14*(2), 52-62.‏
7. Shah, J. L., & Malla, A. K. (2015). Much ado about much: stress, dynamic biomarkers and HPA axis dysregulation along the trajectory to psychosis. *Schizophrenia research*, *162*(1-3), 253-260.‏
8. Tomasik, J., Rahmoune, H., Guest, P. C., & Bahn, S. (2016). Neuroimmune biomarkers in schizophrenia. *Schizophrenia Research*, *176*(1), 3-13.‏
9. Miller, B. J., & Goldsmith, D. R. (2019). Inflammatory biomarkers in schizophrenia: implications for heterogeneity and neurobiology. *Biomarkers in Neuropsychiatry*, *1*, 100006.‏
10. Corsi-Zuelli, F. M. D. G., Brognara, F., Quirino, G. F. D. S., Hiroki, C. H., Fais, R. S., Del-Ben, C. M., ... & Loureiro, C. M. (2017). Neuroimmune interactions in schizophrenia: focus on vagus nerve stimulation and activation of the alpha-7 nicotinic acetylcholine receptor. *Frontiers in immunology*, *8*, 618.‏
11. Bär, K. J., Letzsch, A., Jochum, T., Wagner, G., Greiner, W., & Sauer, H. (2005). Loss of efferent vagal activity in acute schizophrenia. *Journal of psychiatric research*, *39*(5), 519-527.‏
12. Pedersen, S. S., von Känel, R., Tully, P. J. & Denollet, J. Psychosocial perspectives in cardiovascular disease. *European Journal of Preventive Cardiology* **24**, 108–115 (2017).
13. Raison, C. L., Lowry, C. A., & Rook, G. A. (2010). Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Archives of general psychiatry*, *67*(12), 1211-1224.‏
14. Hoffman, K. W., Lee, J. J., Corcoran, C. M., Kimhy, D., Kranz, T. M., & Malaspina, D. (2020). Considering the Microbiome in Stress-Related and Neurodevelopmental Trajectories to Schizophrenia. *Frontiers in Psychiatry*, *11*.‏
15. Kelly, J. R., Minuto, C., Cryan, J. F., Clarke, G., & Dinan, T. G. (2020). The role of the gut microbiome in the development of schizophrenia. *Schizophrenia research*.‏
16. Szeligowski, T., Yun, A. L., Lennox, B. R., & Burnet, P. W. (2020). The Gut Microbiome and Schizophrenia: the current state of the field and clinical applications. *Frontiers in psychiatry*, *11*, 156.‏
17. Shen, Y., Xu, J., Li, Z., Huang, Y., Yuan, Y., Wang, J., ... & Liang, Y. (2018). Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: a cross-sectional study. *Schizophrenia Research*, *197*, 470-477.‏
18. Dickerson, F., Severance, E., & Yolken, R. (2017). The microbiome, immunity, and schizophrenia and bipolar disorder. *Brain, behavior, and immunity*, *62*, 46-52.‏
19. Brown, A. S. (2012). Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Developmental neurobiology*, *72*(10), 1272-1276.
20. Ghaderi, A., Banafshe, H. R., Mirhosseini, N., Moradi, M., Karimi, M. A., Mehrzad, F., ... & Asemi, Z. (2019). Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. *BMC psychiatry*, *19*(1), 1-10.‏
21. Okubo, R., Koga, M., Katsumata, N., Odamaki, T., Matsuyama, S., Oka, M., ... & Matsuoka, Y. J. (2019). Effect of bifidobacterium breve A-1 on anxiety and depressive symptoms in schizophrenia: a proof-of-concept study. *Journal of affective disorders*, *245*, 377-385.‏
22. Huo, R., Zeng, B., Zeng, L., Cheng, K., Li, B., Luo, Y., ... & Xie, P. (2017). Microbiota modulate anxiety-like behavior and endocrine abnormalities in hypothalamic-pituitary-adrenal axis. *Frontiers in cellular and infection microbiology*, *7*, 489.‏ ‏
23. Seeman, M. V. (2020). The gut microbiome and treatment-resistance in schizophrenia. *Psychiatric Quarterly*, *91*(1), 127-136.‏
24. Eranti, S. V., MacCabe, J. H., Bundy, H., & Murray, R. M. (2013). Gender difference in age at onset of schizophrenia: a meta-analysis. *Psychol Med*, *43*(1), 155-167.‏
25. Häfner, H., Riecher-Rössler, A., Der Heiden, W. A., Maurer, K., Fätkenheuer, B., & Löffler, W. (1993). Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. *Psychological medicine*, *23*(4), 925-940.‏
26. Canuso, C. M., & Pandina, G. (2007). Gender and schizophrenia. *Psychopharmacol Bull*, *40*(4), 178-190.‏
27. Goldstein, J. M., & Link, B. G. (1988). Gender and the expression of schizophrenia. *Journal of psychiatric research*, *22*(2), 141-155.‏
28. Seeman, M. V. (1983). Interaction of sex, age, and neuroleptic dose. *Comprehensive Psychiatry*, *24*(2), 125-128.‏
29. Halpern, D. F. Sex Differences in Cognitive Abilities. (2013) doi:10.4324/9780203816530.
30. Dart, A. Gender, sex hormones and autonomic nervous control of the cardiovascular system. *Cardiovascular Research* **53**, 678–687 (2002).
31. Barel, E. *et al.* Gonadal hormones modulate the HPA-axis and the SNS in response to psychosocial stress. *Journal of Neuroscience Research* **96**, 1388–1397 (2018).
32. Seeman, M. V. (1996). The role of estrogen in schizophrenia. *Journal of Psychiatry and Neuroscience*, *21*(2), 123.‏
33. Gogos, A., Sbisa, A. M., Sun, J., Gibbons, A., Udawela, M., & Dean, B. (2015). A role for estrogen in schizophrenia: clinical and preclinical findings. *International journal of endocrinology*, *2015*.
34. Ko, Y. H., Jung, S. W., Joe, S. H., Lee, C. H., Jung, H. G., Jung, I. K., ... & Lee, M. S. (2007). Association between serum testosterone levels and the severity of negative symptoms in male patients with chronic schizophrenia. *Psychoneuroendocrinology*, *32*(4), 385-391.‏‏
35. Misiak, B., Frydecka, D., Loska, O., Moustafa, A. A., Samochowiec, J., Kasznia, J., & Stańczykiewicz, B. (2018). Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *89*, 92-102.‏
36. Baker, J. M., Al-Nakkash, L., & Herbst-Kralovetz, M. M. (2017). Estrogen–gut microbiome axis: physiological and clinical implications. *Maturitas*, *103*, 45-53.‏
37. Markle, J. G., Frank, D. N., Mortin-Toth, S., Robertson, C. E., Feazel, L. M., Rolle-Kampczyk, U., ... & Danska, J. S. (2013). Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science*, *339*(6123), 1084-1088.‏
38. Makris, A. P., Karianaki, M., Tsamis, K. I., & Paschou, S. A. (2020). The role of the gut-brain axis in depression: Endocrine, neural, and immune pathways. *Hormones*, 1-12.‏
39. Torous, J. & Keshavan, M. A new window into psychosis: The rise digital phenotyping, smartphone assessment, and mobile monitoring. *Schizophrenia Research* **197**, 67–68 (2018).
40. Renn, B. N., Pratap, A., Atkins, D. C., Mooney, S. D. & Areán, P. A. Smartphone-based passive assessment of mobility in depression: Challenges and opportunities. *Mental Health and Physical Activity* **14**, 136–139 (2018).
41. 14.    Potier, R. The Digital Phenotyping Project: A Psychoanalytical and Network Theory Perspective. *Frontiers in Psychology* **11**, (2020).
42. Dermody, S. S. *et al.* Personality Correlates of Midlife Cardiometabolic Risk: The Explanatory Role of Higher-Order Factors of the Five-Factor Model. *Journal of personality* **84**, 765–776 (2016).
43. Xie, X., Dong, Y. & Wang, J. Sleep quality as a mediator of problematic smartphone use and clinical health symptoms. *Journal of behavioral addictions* **7**, 466–472 (2018).
44. Cao, H., Sun, Y., Wan, Y., Hao, J. & Tao, F. Problematic Internet use in Chinese adolescents and its relation to psychosomatic symptoms and life satisfaction. *BMC public health* **11**, 802 (2011).
45. Montag, C. *et al.* Correlating Personality and Actual Phone Usage. *Journal of Individual Differences* **35**, 158–165 (2014).
46. Stachl, C. *et al.* Personality Traits Predict Smartphone Usage. *European Journal of Personality* **31**, 701–722 (2017).
47. Montag, C. *et al.* Smartphone usage in the 21st century: who is active on WhatsApp? *BMC Research Notes* **8**, (2015).
48. Elhai, J. D. *et al.* Depression and emotion regulation predict objective smartphone use measured over one week. *Personality and Individual Differences* **133**, 21–28 (2018).
49. Rozgonjuk, D., Levine, J. C., Hall, B. J. & Elhai, J. D. The association between problematic smartphone use, depression and anxiety symptom severity, and objectively measured smartphone use over one week. *Computers in Human Behavior* **87**, 10–17 (2018).
50. Berle, J. O., Hauge, E. R., Oedegaard, K. J., Holsten, F. & Fasmer, O. B. Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Research Notes* **3**, (2010).
51. Kluge, A. *et al.* Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. *Schizophrenia Research* **195**, 176–182 (2018).
52. Komatsu, H. *et al.* Effectiveness of Information Technology Aided Relapse Prevention Programme in Schizophrenia excluding the effect of user adherence: A randomized controlled trial. (2013) doi:10.1016/j.schres.2013.08.007.
53. Spaniel, F., Hrdlicka, J., Novak, T., Motlova, L. & Hoschl, C. ITAREPS: Information technology aided relapse prevention programme in schizophrenia. A two-year mirror design follow up evaluation. *European Psychiatry* **23**, S148 (2008).
54. Barnett, I. *et al.* Relapse prediction in schizophrenia through digital phenotyping: A pilot study. *Neuropsychopharmacology* **43**, 1660–1666 (2018).
55. Cella, M. *et al.* Using wearable technology to detect the autonomic signature of illness severity in schizophrenia. *Schizophrenia Research* **195**, 537–542 (2018).
56. Lecomte, T., Potvin, S., Samson, C., Francoeur, A., Hache-Labelle, C., Gagné, S., ... & Mueser, K. T. (2019). Predicting and preventing symptom onset and relapse in schizophrenia—A metareview of current empirical evidence. *Journal of abnormal psychology*, *128*(8), 840.‏