Research Program

1. קובץ של עד 20 עמודים, עד 15 עמודים של טקסט ותרשימים ועד חמישה עמודי ביבליוגרפיה. יש להקפיד על היקף ההצעה, אחד הגופנים הבאים: Arial, Georgia, Palatino Linotype רווח של 1.5, בגודל של 11 לפחות, עם שוליים של 2 ס""מ מכל צד לכל הפחות. התכנית תכלול את הסעיפים שלהלן:
   1. רקע מדעי - Scientific background – כולל סקירה על מצב המחקר בנושא המוצע.
   2. מטרות המחקר וחשיבותו - Research objectives & expected significance.
2. c)תיאור מפורט של המחקר המוצע - Detailed description of the proposed research ובו:
   * 1. היפותזת העבודה - ;working hypothesis
3. ii.תכנית ושיטות עבודה (כאשר הבקשה מוגשת בתחום מדעי הרוח, יש לציין את רמת השליטה בשפות החיוניות למחקר) – Research design & methods בחלק זה יש להתייחס גם לאישורי הרשויות הנדרשים לביצוע המחקר.
4. iii. תוצאות מוקדמות – Preliminary resultsהתנאים העומדים לרשות החוקר לביצוע המחקר (פירוט כח אדם ותשתיות – כולל נגישות וזמינות).
5. iv.הקרן ממליצה להתייחס בתכנית המחקר לתוצאות (expected results) ומכשלות (pitfalls) צפויות. וכן להצעת אלטרנטיבות לגישות ולשיטות למקרה שהשיטה /הניסוי המוצעים לא יעבדו כצפוי. מהדורות ולקסיקונים: כאשר תוצר מקווה של המחקר הוא מילון, לקסיקון, הוצאה מדעית, תרגום או פרשנות של טקסט, יש להוסיף לבקשה, בסעיף זה, מספר דוגמאות.

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# Research Program (7.1)

## Scientific background (7.1.1)

### Sudden Cardiac Arrest (SCD), Arrhythmia and Ventricular Fibrillation (VF)

Sudden cardiac death (SCD) is a sudden, unexpected death caused by loss of heart function (i.e., sudden cardiac arrest; SCA). The World Health Organization (WHO) defines sudden cardiac death (SCD) as a sudden unexpected death that occurs within 1 hour of symptom onset or within 24 hours of having been last seen well. SCD is a major global public health issue, accounting for up to 20% of deaths in Western societies.1 In the United States alone, SCD appeared among the multiple causes of death on 13.5% of death certificates in 2017 (379,133 of 2,813,503), which suggests that one in every 7.4 people in the United States died of SCD. SCD is responsible for half of all heart disease deaths, it occurs most frequently among adults in their mid-30's to mid-40's, and it affects men twice as often as it does women. Interestingly, for patients aged 35 and under, no cause is identified in up to 30% of SCD cases after forensic analysis.2 SCA is not a heart attack (i.e., myocardial infarction). Heart attacks occur when there is a blockage in one or more of the coronary arteries, which prevents the heart from receiving enough oxygen-rich blood. If the oxygen in the blood cannot reach the heart muscle, the heart becomes damaged. In contrast, SCA occurs when the electrical system to the heart malfunctions and one’s heartbeat suddenly becomes very irregular; these conditions, which are characterized by irregular heartbeats, are called arrhythmias.

Arrhythmia is a major cause of SCD. It refers to any change from the normal sequence of electrical impulses that synchronize heartbeats. The electrical impulses may occur too quickly (i.e., tachycardia), too slowly (i.e., bradycardia), or erratically (i.e., conduction disorders). These irregularities in heartbeat may affect the upper or lower heart chambers, leading to conditions called Atrial Fibrillation (AF) or Ventricular Fibrillation (VF), respectively. When the heart does not beat properly, it cannot pump blood effectively and, consequently, the lungs, brain and all other vital organs cannot function properly, creating a potential for the organs to shut down or become damaged, thereby leading to SCD.

Abnormalities in cardiac rhythms are associated with substantial morbidity rates and economic costs. Atrial fibrillation, for example, affects at least 2.3 million people in the United States alone and is associated with an increased risk of stroke and mortality. **Ventricular arrhythmia (VA) is even more severe. VA is a life-threatening cardiac condition which is considered to be the most significant cause of cardiac electrical instability, a condition that leads to SCD**. **This condition encompasses a number of different types of arrythmias, including VF.** VF is the leading cause of SCD, secondary only to myocardial infarction, or "heart attack."3 During VF, cardiac output drops to zero and, unless remedied promptly, death typically ensues within minutes. Ventricular arrhythmias are thus thought to cause 75% to 80% of SCD cases, and are estimated to result in 184,000 to 450,000 lives lost in the United States alone per year.3,4

The cause of ventricular fibrillation is not always known; however, the most common known cause is a problem in the electrical impulses traveling through the heart after a first heart attack occurs, or problems that result from a scar in the muscle tissue of the heart after a prior heart attack.5 Some cases of VF begin with a rapid heartbeat, otherwise known as ventricular tachycardia (VT). This rapid, but regular, beating of the heart is caused by abnormal electrical impulses that begin in the ventricles. Most cases of VF are linked to some form of heart disease. Traditional risk factors that are associated with VF include: previous episode of VF and heart attack; congenital heart disease; heart muscle disease (cardiomyopathy); injuries that had caused damage to the heart muscle, such as electrocution; use of illegal drugs, such as cocaine or methamphetamine; and significant electrolyte abnormalities, for example low levels of potassium or magnesium.

Accurate early detection and prediction of life-threatening VA episodes, such as VF, is challenging given that the majority of SCD are unwitnessed and sudden by nature (and definition). This lack of detection and prediction is problematic given that VF is the final underlying SCD mechanism.6–8 Beyond the physiological components of VF, there are behavioral and psychological factors that are additional causal factors of VF, as well as factors that influence biological risk factors. However, behavioral and psychological factors are much harder to monitor and study. Our proposed research aims to address this issue and significantly contribute to the current gap in knowledge regarding the behavioral and psychological factors underlying VF.

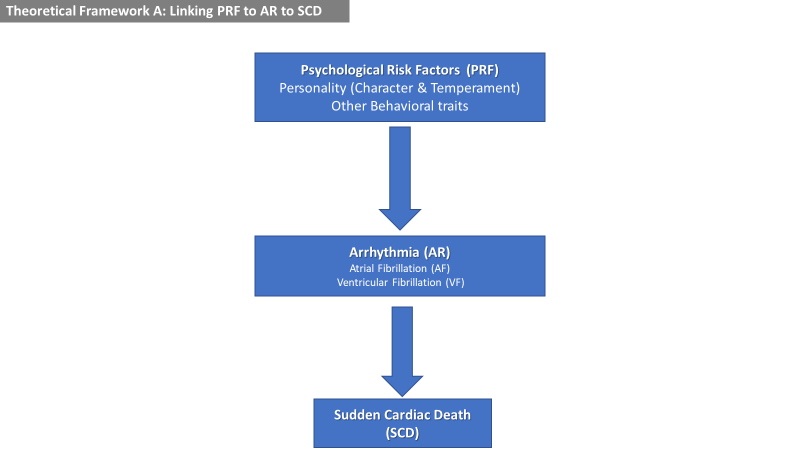


Figure . Theoretical Framework A: Linking PRF to AR to SCD

### Socio-Cultural, behavioral, and psychological risk factors for AF and VF SCD

Economic, behavioral, social, and psychological factors are increasingly being shown to be useful predictors of mortality rates in general, and of SCD in particular.9 In particular, during the past several decades, a considerable body of research has accumulated on the role of psychosocial factors in the development of both AF and VA.10–13 Biological as well as behavioral mechanisms that may explain the association between psychosocial risk factors and VA have been extensively studied.14 Among the psychosocial risk factors, psychopathological symptomatology such as depression, anxiety, and posttraumatic stress symptoms have been shown to be associated with an increased risk for cardiovascular events, including death.15 Other psychosocial risk factors of VA include individual personality characteristics. For example, Type D personality – characterized by negative affect and social inhibition – has been shown to be associated with an increased risk of VA.16 Furthermore, recent studies have suggested that negative emotions, such as hostility and anger, can trigger potentially lethal VA.17 Exposure to stress and perceived stress have been also suggested as risk and prognostic factors for cardiovascular disease.18 It has been suggested that the association between the proposed psychosocial risk factors and the risk for VA may be explained by biological as well as behavioral pathways.19

#### Biological mechanisms linking psychosocial factors to VAs

Psychosocial risk factors are associated with biological as well as behavioral mechanisms, which are linked to a poor prognosis of VA. The biological mechanisms involved in this association include the autonomic nervous system (ANS) and the HPA (hypothalamus-pituitary-adrenal) axis. The ANS is of importance in the etiology and treatment of various pathophysiological conditions including VA. Psychosocial factors are associated with ANS dysfunction (including increased outputs of the sympathetic nervous system (SNS), such as increases in catecholamine levels) and with the parasympathetic nervous system (PNS)/vagal withdrawal.14 These autonomic changes impact ventricular repolarization, an important factor in arrhythmogenesis.20 Psychosocial risk factors are also associated with alterations in HPA axis function, 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 that result in myocardial dysfunction-induced arrhythmias.21

There are well-documented findings showing sex differences in the ANS.22 The underlying mechanism for these differences may be due to differences in sex hormone levels. Sex hormones, including androgens, estrogens, and progestins are chemical messengers secreted by the gonads (ovaries in women and testes in men) and by the adrenal glands through the HPG (hypothalamus-pituitary-gonads) axis.23 Among women, variations in estrogen and progesterone secretions create differences between women across different phases of the menstrual cycle, and among pre-, peri-, and postmenopausal women.22 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.22 Recently, Barel and colleagues demonstrated that sex hormones modulated the HPA axis and the SNS reactivity to psychosocial stress, emphasizing the need to include sex hormone fluctuations when examining stress effects in typical, as well as clinical samples.24 The effects of sex differences in cardiac electrophysiology have been well-studied.25 However, only a few studies to date have examined the effects of sex hormones on VA.

Although there are controversial findings regarding the effects of estrogen and progesterone on repolarization parameters,25 testosterone appears to play a major role in one’s susceptibility to repolarization-related tachyarrythmias.26 Furthermore, a few studies have explored QT interval as a non-invasive method for measuring inhomogeneities in ventricular recovery, with high levels of interrelated dispersion associated with an increased risk of VA.27,28 Whereas some studies have shown that estrogen replacement therapy increases QT interval in postmenopausal women,29 other studies have shown that estrogen replacement therapy does not affect QT dispersion.30,31 Given the interconnectivity between the HPG axis and the ANS, cardiac responsivity to stress has been examined by measuring sex hormones and ANS biomarkers. Studies have emphasized the important role of estrogen in reducing the risk for cardiac and vascular morbidity.32–34 Del-Rio and colleagues examined estrogen administration in menopausal women exposed to stress. They found that the administration of estrogen modified the cardiovascular and catecholamine responses to stress.35 In comparison, Pico-Alfonso and colleagues examined the role of estrogen on cardiac and HPA axis activity, as well was on stress responsivity across different phases of the menstrual cycle in healthy women. Their findings did not show a clear buffering effect of estrogen in cardiovascular responses to acute stressors.36 In sum, a clear picture of the role of sex hormones in the association between the ANS and VA has yet to be revealed; a systematic investigation which carefully controls for hormonal profiles and includes various age groups and hormonal statuses (e.g., oral contraceptive users and non-users) is needed.37

#### Behavioral mechanisms linking psychosocial factors to VAs

The behavioral mechanisms that explain the association between psychosocial risk factors and VA include adverse lifestyle behaviors such as smoking, poor diet, alcohol consumption, and physical inactivity.14 Besides these adverse behaviors, the role of individual differences in behavioral responses to stress have been studied in relation to cardiovascular diseases.38,39 For example, Sgoifo and colleagues found that there was a close relationship between the degree of autonomic/neuroendocrine arousal and patterns of behavioral adaptation to psychosocial stressors.40

Consistent with health behavior models linking personality traits to health,41,42 certain personality traits may manifest in health practices that indirectly influence cardiometabolic risk.43–47 For instance, components of the personality “meta-trait” of stability48–53 have been found to be associated with health behaviors such as substance use, imprudent diet, and physical inactivity. In particular, neuroticism is positively associated with the aforementioned behaviors, whereas agreeableness and conscientiousness are negatively associated.54,55 Moreover, physical inactivity or sedentariness, is a well-established correlate and predictor of the metabolic syndrome; this suggests that physical inactivity may contribute to the associations found between the stability meta-trait and cardiometabolic risk.56

Following these lines of inquiry, Dermody et al. (2016) examined dispositional correlates of cardiometabolic risk within a hierarchical model of personality, which proposes higher‐order traits of stability (composed of agreeableness, conscientiousness, and the inverse of neuroticism) and plasticity (comprised of extraversion and openness). Using this model, Dermody and colleagues (2016) tested the hypothesized mediation pathway (via biological and behavioral factors) in an observational study of 856 participants.56 Latent variable FFM traits (using multiple‐informant reports) and aggregated cardiometabolic risk (indicators: insulin resistance, dyslipidemia, blood pressure, adiposity) were estimated using confirmatory factor analysis (CFA). The cardiometabolic factor was regressed on each personality factor or higher‐order trait. Cross‐sectional indirect effects via systemic inflammation, cardiac autonomic control, and physical activity were tested. CFA models confirmed the stability meta‐trait, but not the plasticity trait. Lower levels of stability were associated with heightened cardiometabolic risk; this association was mediated by inflammation, autonomic function, and physical activity. Among the FFM traits, only openness was associated with cardiometabolic risk over and above stability, and, unlike stability, the relationship between openness and cardiometabolic risk was not explained by any mediating variables. The stability meta‐trait covaried with midlife cardiometabolic risk, and this association was accounted for by three candidate biological and behavioral factors.

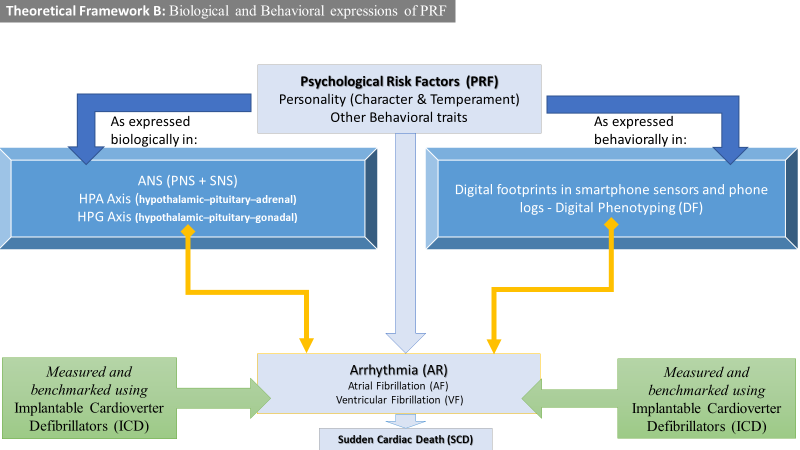


Figure . Theoretical framework 2: Biological and behavioral expressions of psychological risk factors (PRF). The figure presents a theoretical model of the association between psychosocial risk factors and ventricular arrhythmia through biological mechanisms (modulated by the HPG axis) and behavioral mechanisms (objectively measured via digital footprints). PTSS = posttraumatic stress symptoms; HPG = hypothalamus-pituitary-gonads; ANS: autonomic nervous system; HPA = hypothalamus-pituitary-adrenal.

### Digital Phenotyping: The new 24X7 behavioral monitoring platforms

Smartphone technology now allows researchers to passively collect data about human behavior using the native mobile sensors and system logs that are already embedded in the devices (e.g., GPS, accelerometer, microphone, camera, log of outgoing and incoming calls and text messages). The current number of smartphone users in the world is estimated to be 3.8 billion. Accordingly, 45.04% of the world’s population uses a smartphone.57,58 The exponential growth of data generated through the use of these devices offers researchers unprecedented opportunities for tracking, analyzing, and predicting human behavior. For the first time in the history of personality and behavioral research, we can now continuously monitor a plethora of behavioral expressions and thus, improve our empirical understanding of various personality traits. Further, we can apply this knowledge to related medical domains. For example, the field of eHealth, or digital health, uses emerging communication and information technologies to improve health across a variety of aspects (research, diagnoses, disease monitoring etc.). Additionally, mHealth, a subsegment of eHealth, refers to the use of mobile computing and communication technologies (e.g., mobile phones, wearable sensors) for health services and research purposes, and incorporates techniques and advanced concepts from an array of disciplines.59

Over the past few years, smartphones and other digital platforms have become promising sources through which to learn 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.60  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. In other words, digital phenotyping is defined as the moment-by-moment quantification of human behavior using data collected from personal digital devices (e.g., smartphones, smartwatches, wearables) in order to monitor and model human behavior and personality in various domains.61 Examples of theoretical and applied digital phenotyping efforts include clinical monitoring,60 behavioral prediction62 and the development of predictive models of human personality.63 Studies examining the adverse health effects of smartphone use found that problematic smartphone use was associated with negative health symptoms64 and weakened immunity.65 Several digital phenotyping apps are currently being used in various commercial contexts, as well as for monitoring both physical and mental illnesses. For example, in a range of clinical studies, the Mindstrong app has used powerful machine learning methods to demonstrate that specific digital features correlate with cognitive functions, clinical symptoms, and measures of brain activity.66

These methodologies have been applied to the fields of psychology and psychiatry; for example, researchers have recently investigated issues related to mental health in a smartphone-based digital phenotyping study.67 In another example, Onnela and Rauch62 demonstrated that smartphone-based digital phenotyping has the potential to offer the field of psychiatry a wealth of data on phenotypic expressions of disease. Torous and colleagues68 affirmed that the application of digital phenotyping research methodologies early in life could yield important insights for understanding and detecting early risk factors related to mental illness. Additionally, it has been shown that phone call data extracted from smartphones were associated with extraversion.69,70 Another study demonstrated a link between longer use of a social media application and lower levels of conscientiousness.71 Further, studies examining the relationship between smartphone use and psychopathological symptomatology found a link between smartphone use and depression,72,73 as well as anxiety severity.73 There have also been a few studies that have focused on the relationship between smartphone use and health outcomes.

### Digital Phenotyping of Implantable Cardioverter Defibrillators (ICD) & Smartphones data to detect and model physical and psychological risk factors associated with Ventricular Fibrillation (VF) leading to Sudden Cardiac Death (SCD)

Smartphone technology, and in particular advances in smartphone sensors, can also offer a new approach to the study of cardiovascular health.74–79 According to the American Heart Association, mobile devices and wearable technology present a potentially novel avenue for aiding in the recognition of unwitnessed cardiac arrests and the implementation of earlier intervention. Research is needed to determine the feasibility of using mainstream mobile devices or wearable technology to detect unwitnessed cardiac arrests, facilitate early intervention, and improve survival. There might also be an opportunity to use these devices to study the early warning signs of sudden cardiac arrest. For example, emerging wearable technologies and sensors are capable of communicating various bio-metrics signals, including heart rate, respiration rate, fall detection, stress, skin temperature, activity, caloric burn, and body posture, to a mobile device.80

Bort-Roig and colleagues systematically reviewed the evidence on the viability of using smartphone technology for measuring and influencing individuals’ physical activity in general, and cardiovascular-related activity in particular. They found that smartphone technology had average-to-excellent levels of accuracy for various behaviors.79 In another large-scale recent review and meta-analysis of 69 studies, which investigated the use of mobile technologies (including the use of smartphones)81 to reduce CVD risk behaviors, the authors concluded that monitoring activity with mHealth tools provides clinical data that far exceeds what can be measured in a brief clinical encounter. A further advantage of these technologies is that they measure individuals’ physiological and behavioral activity in their natural settings.

In another large-scale study, McConnell and colleagues assessed the feasibility of obtaining lifestyle data from smartphones to learn about activity patterns associated with cardiovascular health.82 Participants provided 4-7 days of motion data, assessed by a motion coprocessor chip in their smartphone, as well as completed self-report questionnaires regarding their well-being, diet, risk perception, physical activity, sleep, and cardiovascular health. Findings showed that different patterns of activity were associated with participants’ self-reported presence of disease. Furthermore, there was a poor association between perceived and recorded physical activity (monitored by smartphone sensors, such as accelerometers, as described below), as well as perceived and formally estimated risk. Apart from the authors' conclusion regarding the feasibility of conducting a smartphone-based study of cardiovascular health, they highlighted the potential usefulness of smartphones as personalized informational tools.

Implantable cardioverter defibrillators (ICD) are devices designed for the prevention of sudden cardiac death (SCD) in selected patients. SCD often occurs as a consequence of malignant ventricular arrhythmias, such as ventricular tachycardia (VT) or VT that degenerated to ventricular fibrillation (VF). Current ICDs are capable of delivering multiple therapies, including antitachycardia pacing (ATP), cardioversion, and defibrillation, as well as providing support during episodes of bradycardia or heart block with a rate-response pacing and automatic switching mode function. Modern devices can also provide resynchronization therapy, an important progress in selected patients requiring advanced heart failure therapies.

Given their wide array of sensors and real-time wireless transmission capabilities, modern ICD devices can also be used as platforms for data collection.83 Sensors that can be used for data collection and monitoring include accelerometers, body temperature sensors, sensors that measure electrophysiological signals and other heart rate data, sensors that monitor real-time ECG signals and more. Smartwatch technology is now beginning to offer these types of external arrhythmia-detection capabilities, but with much less accuracy.84 Several early attempts to use ICD data for research purposes have proven successful83,85–87 but, to our knowledge, none have attempted to integrate data gathered from smartphone sensors and ICDs with the wealth of biological and psychological data that we propose to collect. Our aim is to use these varied sources of data to detect possible associations between psychological risk factors and VT/VF, which subsequently lead to SCD.

In conclusion, despite consistent evidence for the possible associations between certain psychological traits and arrythmia-related SCD88–94 (using biological and behavioral expressions and measurements), we do not know of any large-scale digital phenotyping studies that integrate ICD data, smartphone data, and biological and personality assessments to study the psychological risk factors of VF and SCD. To that end, the proposed objectives of the current research are outlined below.

## Research objectives & expected significance (7.1.2)

### Research Objectives

Our research will examine biological and behavioral mechanisms that link psychosocial risk factors to a poor prognosis and adverse clinical outcomes in patients who are at high risk for developing VA. Based on previous findings,88,89,94 the main hypothesis of this proposal is that careful examination of clustering and associations between smartphone sensors data (expressing manifestations of personality and behavior) and ICD sensors data (expressing arrythmia and other cardiac data) both compounded with biological data, will enable accurate modeling of the relationship between certain psychosocial risk factors and VA. Furthermore, we predict that the HPG axis will moderate the associations between psychosocial variables, stress, and VA. An accurate modeling of the relationship between psychosocial risk factors and VT (that leads to SCD) may enable early detection and prediction of VT-related SCD events. Further, accurate modeling would improve treatment for arrythmias by enabling a personalized personality and behaviorally-based treatment. The specific aims of the current study are as follows:

1. To examine the associations between psychosocial variables (i.e., anxiety; depression; and personality traits related to temperament and character such as insecure attachment styles, neuroticism, distress tolerance and tolerance for ambiguity) and ventricular arrhythmia (VA). The goal is to explore the predictors of VA and to identify patients who are at high risk of developing VA due to their psychosocial profile.
2. To examine the mediating role of the interconnectivity among the HPG axis, the ANS and the HPA axis in the relationship between psychosocial profiles and stress among individuals with VA. Previous studies have demonstrated the associations among the HPG axis, the ANS and the HPA axis. Furthermore, the role of each system in predicting clinical outcomes in patients with VA was explored independently. However, to the best of our knowledge, the interconnectivity among these systems, and specifically their joint role as a mediator, both in general and specifically in the cardiovascular context, has not yet been investigated.
3. To examine the behavioral mechanisms that link psychosocial risk factors with clinical outcomes in patients with VA, and patients with arrhythmias in general, using digital footprints from smartphones and ICDs (i.e., digital phenotyping).
4. To examine the relationship between the biological and behavioral mechanisms involved in the association between a given psychosocial/personality profile and VA, as well as in arrhythmias in general.

### Expected significance

Using the unprecedented 24X7 data collection and monitoring abilities of contemporary digital sensors on implantable cardioverter defibrillators (ICD) and modern smartphone devices, our findings will shed light on the interrelated biological and behavioral mechanisms mediating the linkage between psychosocial and behavioral profiles and ventricular arrhythmia (VA). Uncovering such associations and relationships among the variables may serve to validate the use of digital footprints (collected from smartphones and other wearable devices) to predict VAs which may, in turn, promote the use of this technology to create preventive programs. Importantly, we do not know of any digital phenotyping studies that integrate ICD sensor data and smartphone sensor data with biological data to understand the psychological risk factors of SCD in general, and of arrhythmia and VAs in particular.

Furthermore, studying behavioral mechanisms through digital footprints would help to identify specific psychosocial profiles that are indicative of being at higher risk for VA; in particular, the use of digital footprints allows for examining objective behavioral manifestations, as opposed to relying on self-report measures. Findings of the proposed research are also expected to contribute to a better understanding of the cardiac ANS modulation, specifically in VAs, and its direction of modulation through its relationship with the HPG axis. Our findings will thus have implications for personalized medicine, as it could allow for customized interventions for VA patients, that are gender-specific and specific to patients’ sex hormone profiles.

## Detailed description of the proposed research (7.1.3)

### Working Hypothesis (7.1.3.1)

Individualized patient profiles that consider behavioral expressions of temperament and personality traits (measured by smartphone sensors, e-diaries, self- and peer-report questionnaires), as well as biological expressions (measured through blood/saliva sample levels of cortisol, epinephrine, norepinephrine, testosterone, estrogen, progesterone) will constitute predictable psychological risk factors for ventricular fibrillation and other arrhythmia-related phenomena (measured using implantable cardioverter defibrillators; ICDs) that may lead to sudden cardiac death (SCD).89,95

1. ICD Patients with VA will exhibit higher levels of anxiety and depression than patients without VA.
2. ICD Patients with VA will exhibit higher levels of stress and perceived stress than patients without VA.
3. ICD Patients with VA will exhibit lower levels of distress tolerance and tolerance for ambiguity than patients without VA.
4. ICD Patients with VA will exhibit insecure attachment styles at higher rates relative to patients without VA.
5. ICD Patients with VA will exhibit higher levels of stress biomarkers (i.e., cortisol, epinephrine, norepinephrine) and lower levels of estrogen than patients without VA.
6. The interaction of the HPG axis, the ANS, and the HPA axis will mediate the association between VA patients’ psychosocial profiles and stress levels.
7. Biomarkers of the ANS and HPG axis will be associated with patients’ behavioral measures (measured through digital phenotyping), and will be involved in the association between a given psychosocial/personality profile and VA (arrhythmias in general).
8. ICD patients with VA will have longer periods of “active screen state” on their smartphones per 24 hours (see research tools section below) than patients without VA, which may reflect higher degrees of restlessness.
9. ICD patients with VA will exhibit higher rates of “compulsive” frequent phone checkouts (calculated as the ratio of “short screen time on” to “total active screen state”) than patients without VA, which may reflect lower levels of distress tolerance and tolerance for ambiguity.
10. ICD patients with VA will receive higher numbers of incoming calls and will place higher numbers of outgoing calls within a 24-hour period than patients without VA, which may reflect an increased amount of, and more intense, social interactions.
11. ICD patients with VA will exhibit higher intensity of motion/activity (as measured by accelerometers on smartphones and ICD devices) than patients without VA.

### Research design & Methods (7.1.3.2)

#### Participants

Participants in the study would include patients at the time of ICT (by Medtronics) implant at the Cardiology & ICCU Department at the Hillel Yaffe Medical Center (HYMC). Exclusion criteria would include significant psychiatric illness, an inability to read Hebrew or participate in an interview, an inability to operate a digital diary smartphone app in Hebrew, and having underwent total abdominal hysterectomy with bilateral ovariectomies (women). Enrollment would be set to begin in November 2021.

#### Research procedure

אפרת אנחנו צריכים לאזור סופית את החלק הזה – יש את כל המרכיבים. צריך לדייק את האיורים בהתאמה כמובן

Study Timetable:

September 2021 – January 2022: Digital phenotyping programming and digital data extraction from the ICD.

January 2022 – April 2025: Data collection will begin. Patients will be enrolled at the time of their ICD implantation and will complete baseline psychological and biological assessments, along with e-diary assessments. Follow-up assessments will be completed every three months for the 24 months after the implantation.

April 2025– April 2026: Data collection will continue – psychological, biological, and electrophysiological follow-up assessments will be conducted.

April 2026 – July 2026: Data analyses will be conducted, and a research summary will be prepared.

Additional notes:

The first four months of the research study will be devoted to the development of relevant research tools. Digital phenotyping programming of the psychosocial variables predicting VA. Computation of digital data extraction from the ICD in order to quantify the dependent variables with regard to VA clinical outcomes.

The first three years of the study will focus on data collection. Patients will include those undergoing ICD implantation at the department of Cardiology at the Hillel Yaffe Medical Center. Patients will complete psychological assessments (including e-diary assessments and measures of allostatic overload), as well as biological assessments prior to the intervention and up to 24 months after the implantation. Data that is stored in the ICD, including electrograms and event details, will be extracted from the device.

The fourth year will be devoted to conducting follow-up assessments of psychological, biological, and electrophysiological measures.

Three months will be dedicated to data analyses, including psychological, biological, and electrophysiological analyses and statistical testing of the research hypotheses. The analyses will be followed by a summary stage towards publication of the study’s results.

לארוז את הלמעלה עם הלמטה....

The current study will combine between-subject (patients with VAs vs. patients without VAs) and within-subject (each patient acting as his or her own control) research designs. The study will begin following the approval from the HYMC 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).96,97

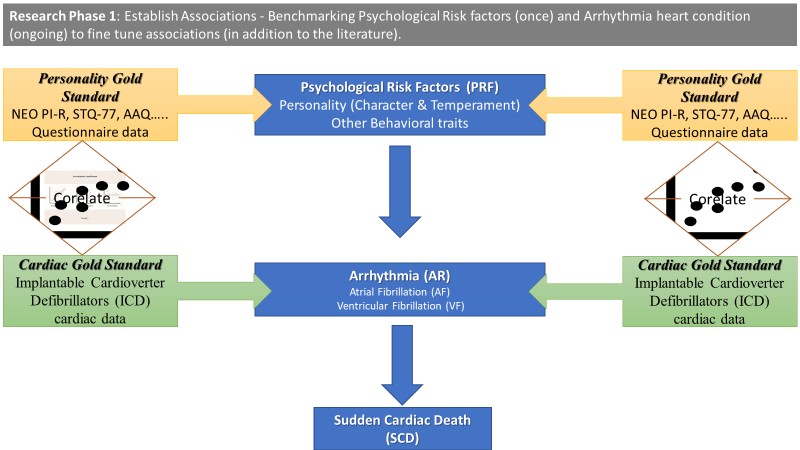
At entry into the study, assessments of baseline personality characteristics and biological markers will be collected. QT interval and heart rate variability (HRV) will be calculated from patients' electrocardiogram(ECG) data. To obtain other biomarker data (cortisol, epinephrine, norepinephrine, testosterone, estrogen, progesterone), patients will be asked to provide blood samples at several assessment points – at baseline and at multiple follow-up timepoints, up to 24 months after implantation.

Self and peer personality and behavioral assessments will be collected within the three months following the implant. Patients will also be provided with an e-diary and will receive a detailed explanation about how to use the e-diary. Patients will be asked to call the study team on days in which they receive shocks, and will be contacted by the study coordinator within 24 hours to review the diary questions. Patients will then be re-contacted one week later, at the same time of day and the same day of the week, and will be asked to answer the same questions; their responses to the questions the second time around will serve as a control. Furthermore, during each follow-up assessment, participants will complete a report twice per hour (which will be prompted by the e-diary). The e-diary smartphone app will also include a digital phenotyping sensor that will monitor accelerometer data, smartphone power states, number of incoming/outgoing calls, etc.).

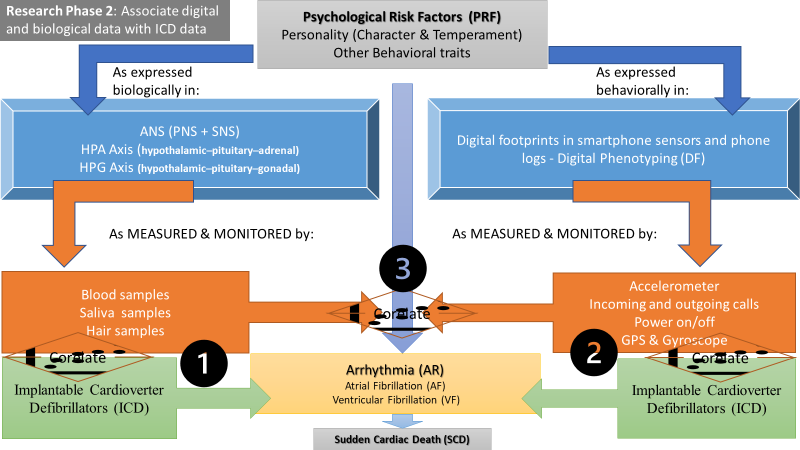
VAs will be assessed through the information downloaded from the ICD; this data will be downloaded every three months for up to 24 months after implantation, and after ICD shocks are delivered (Andersen et al., 2020).87

Overall, the research plan can be divided into the following broad stages:

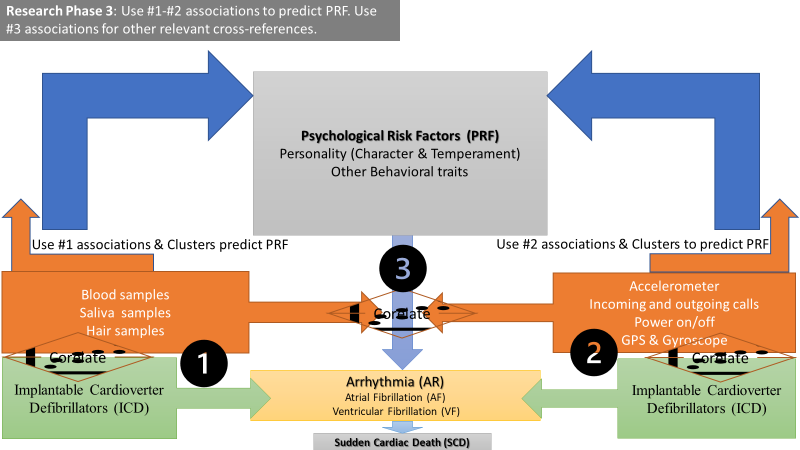
**Research Phase 1**: Establish associations - benchmarking psychological risk factors (once) and arrhythmia heart condition (ongoing) to fine tune associations (in addition to the literature).



**Research Phase 2**: Establish associations among digital data, biological data, and ICD data.



**Research Phase 3**: Use #1-#2 associations to predict PRF. Use #3 associations for other relevant cross-references.



Research design and research plan:

**Phase I:** Utilize data collected from smartphones and from personality questionnaires to explore the associations between users’ digital footprints and their personality traits. This phase includes several steps:

1. Data Collection
   1. [Questionnaires](https://docs.google.com/forms/d/1znd4Tc0T2K5jyxl-elzKx-q2OqVzHp3acMYd3534DQw/viewform?chromeless=1&edit_requested=true): Participants will be asked to complete an online questionnaire that contains approximately 250 questions, which will be used to assess approximately 43 individual traits. The questions included in the questionnaires were compiled from measures utilized in past research; all measures are reliable and valid. Questionnaire responses will be considered to be the “ground truth” reference point for each person's personality (Kim, Domenico & Connelly, 2019).
   2. Smartphone sensors and logs: Participants will be asked to download the “[Beiwe](https://www.hsph.harvard.edu/onnela-lab/beiwe-research-platform/)” app (which we will run on our AWS servers) on their smartphones for a few weeks.
2. Application of advanced statistical tools to explore participant data. For example, we will conduct various analyses including dimensionality reduction, clustering, classification, logistic and multinomial regressions, factor analysis multivariate analyses, and structural equation modeling (SEM).
3. Identification of associations and patterns between personality traits and digital data collected form smartphone devices.

**Phase II:** Build one or more predictive models based on smartphone sensor data and personality trait assessments, and improve the predictive accuracy of existing models. To achieve this goal, we will conduct a number of key steps:

1. Identify key features of one or several models.
2. Identify key features that improve or impair the algorithm's performance in predicting personality traits (Stachl et al., 2020).
3. Develop visualization techniques to illustrate the contribution and relationship of features of the model.
4. Evaluate the machine learning (ML) algorithm's prediction performance by utilizing feature selection (Stachl et al., 2020).
5. Propose key actions required to maintain and improve prediction.

##### Data analyses and statistical plans

We will explore digital expressions of personality and behavioral data, as well as the associations between them by using biological data sources and digital footprints (collected through smartphones and ICDs).

Digital manifestations and associations between personality and behavioral traits on the one hand (see below for a list of the Self-Report Questionnaires) and digital footprints (as collected by Smartphones and ICD sensors as explained below)

SPSS software version 25 and … will be used to conduct data analyses. The statistical significance level will be set to an alpha of 0.05, such that the null hypothesis would be rejected if p < .05. Pearson's correlation analyses will be performed between endocrine parameters and heart rate parameters. Patients who receive 1 relevant ICD interventions for VA during the 24-month follow-up period after ICD implantation will be part of the experimental group (VA patients), whereas patients who do not receive any ICD interventions will be part of the control group (patients without VAs). Hypotheses regarding differences in psychosocial variables, biomarkers, allostatic overload (AO), and digital footprints between VA patients and patients without VAs will be tested using t-tests for independent samples. Hierarchical logistic regressions will be used to test the moderation hypotheses with regard to the role of the interaction between the HPG axis and the ANS in the associations among psychosocial variables, AO, and VA. 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 psychosocial variables and VA.

Data pipeline software

Data analysis software for machine learning

Data collection software (Beiwe and e-diary software)

#### Research tools

We intend to utilize a number of research tools, which fall under four broad categories, to measure indicators that we deem to be potentially relevant to important psychological risk factors of VF and SCD: (1) tools that measure cardiac electrophysiological and stress-related biological indicators; (2) tools that measure behavioral and personality traits; (3) digital phenotyping using smartphones to obtain digital expressions of behavior and personality; (4) digital phenotyping using data from implantable cardioverter defibrillators (ICD) that are related to arrhythmia and other cardiac conditions. 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.

##### 1. Measuring electrophysiological & biological indicators that are potentially related to psychological risk factors of VF and SCD

1. **ANS function –** ANS function will be assessed through two complementary parameters: **QT interval and HRV.** The QT interval is defined as the interval between the earlier indication of ventricular depolarization (i.e., the onset of the QRS complex) and the latest indication of ventricular repolarization (i.e., the end of the T wave) and will be obtained through patients' ECGs. All ECGs will be recorded, and the measurements will be performed by board-certified cardiologists using computerized workstations with high resolution.98,99
2. **HRV –** HRV is measured with the use of an ECG. It is calculated by using the standard deviation of normal-to-normal RRR intervals at baseline and during multiple follow-ups. All ECGs will be recorded, and the measurements will be performed by board-certified cardiologists using computerized workstations with high resolution.100
3. **Biological markers for stress and HPG** – Peripheral blood samples will be drawn to test for cortisol, epinephrine, norepinephrine, testosterone, estrogen, and progesterone. Blood samples will be analyzed in the endocrine laboratory of the Hillel Yaffe Medical Center.

##### 2. Measuring behavioral and personality expressions that are potentially related to psychological risk factors of VF and SCD

Relatively *stable* personality traits (i.e., temperament-related and character-related), as well as more *dynamic* behavioral characteristics, will be measured through self- and peer-report questionnaires. Three broad personality dimensions will be measured: (1) Character (FFM/Big 5 - BFAS); (2) Temperament (FET-STQ77) and (3) Cultural Values (PVQ-RR). Further, a number of additional supplementary traits will be measured (see specific measures below). The more dynamic behavioral states will be measured with self- and peer-report questionnaires and through the use of an e-diary smartphone application that can monitor stress, depression, and anxiety.

Dynamic states of stress, depression, and anxiety + e-Diary for qualitative event-specific reporting

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.101,102 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.103 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 determined if the participant’s self-report satisfies both criteria.104
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. 105
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).106
4. **Emotional surveillance** - Emotional surveillance will be accomplished with an electronic diary (e-diary) that will be programmed and installed as an app on participants’ smartphones. Participants’ levels of emotional intensity will be assessed using a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). Participants will note the degree to which they experience 6 different emotions -- happiness, sadness, anger, anxiety, stress, and impatience (Lampert et al., 2019).

“Stable” personality traits

1. Type D personality will be assessedwiththe type-D scale (DS14). The DS14 contains two scales, each consisting of seven items. The two scales include negative affectivity and social inhibition. Items are answered on a 5-point Likert scale ranging from 0 to 28 for both subscales.107–109
2. The five-factor model (FFM/Big 5) of personality will be measured with the Big Five Aspects Scales (BFAS) (100 items). Hierarchical model of the FFM covering meta-traits (Dopamine + Serotonin), traits, aspects, and facets.110
3. Adult attachment style (AAS) will be measured using the relationship style questionnaire (RSQ) (30 items). Research on adult attachment is guided by the assumption that the same motivational system that gives rise to the close emotional bond between children and their parents is responsible for the bond that develops between adults in emotionally intimate relationships.117
4. The distress tolerance (DT) (15 items) scale will be used to measure individuals’ ability to effectively cope with extreme anxiety, sorrow, or pain.119
5. The tolerance for ambiguity scale (MSTAT-II) (13 items) will be used to measure individuals’ tolerance for situations that are unfamiliar, insoluble, or complex.120
6. Emotional and social intelligence (ESI) will be measured by a 16-item scale. This measure assesses one’s social skills by examining one’s display of desirable emotions to others, as well as the extent to which a person attends to processes, and acts upon information, of an emotional nature.121
7. The dark triad (DT) of personality will be measured with the short dark triad questionnaire (SD3) (12 items), which includes items examining Machiavellianism (manipulation and exploitation of others), narcissism (grandiosity, pride, egotism, and a lack of empathy), and psychopathy (continuing antisocial behavior, impulsivity, selfishness, callousness and remorselessness).122
8. The 15-item risk-taking behavior (RTB) scale assesses an individual’s tendency to engage in activities that have the potential to be harmful or dangerous.123
9. Social desirability (SD) will be measured with the X#-item social desirability scale. Social desirability bias is a type of response bias that refers to the tendency for survey respondents to answer questions in a manner that will be viewed favorably by others. It is included in this study to assess the reliability of the participants’ response.124
10. Functional ensemble of temperament (FET) will be measured with the structure of temperament questionnaire (STQ-77) (77 items). A neurochemical model suggesting specific functional roles of main neurotransmitter systems in the regulation of behavior measured measuring 12 biologically and neurochemically based individual differences.111–114
11. The refined theory of basic values is operationalized by the PVQ-RR measure (57 items). The PVQ-RR measures 19 universal values, which are recognized throughout all major cultures. The values are concentrically organized in four higher-order groups, such that each of the 19 universal values represents an individual’s central personal goal, as well as the corresponding value that is the underlying motivator.115,116
12. The locus of control (LOC) (7 items) measures the degree to which individuals believe that they, as opposed to external forces (beyond their influence), have control over the outcome of events in their lives.118

##### 3. Digital phenotyping measurements of smartphone data: Behavioral and personality data

Maintaining a reliable data collection platform that uses smartphone sensors (which is limited to Android smartphones) is a major challenge. We plan to use the open source Beiwe platform, a platform with which we have already gained experience in the past year. The Beiwe research platform was developed by the Onnela Lab at the Harvard T.H. Chan School of Public Health with funding from the National Institutes of Health (NIH). The app collects phone sensor data (e.g., by the use of a GPS, accelerometer) and phone usage data (e.g., communication logs and screen activity). Below are the parameters we plan to use:57,125

Note: Daytime = 06:00-18:00; Evening = 18:00-24:00); Nighttime = 24:00-07:00.

**Power states as expressions of tolerance for ambiguity**

* Mean/Median/Mode/SD of total duration of “active screen state” per hour, per daytime period, per evening period, and per nighttime period; calculated as the sum of active screen time in seconds between two screen-off events
* Mean/Median/Mode/SD of “power on” events per daytime, per evening, and per nighttime; calculated as the sum of each press of the power on button on the smartphone
* Mean/Median/Mode/SD of “short screen on” durations; short screen on refers being on a screen on state for five seconds or less; calculated per daytime, per evening, and per nighttime
* “Compulsive” phone checkout #1: calculated as the ratio of “short screen on” to the total “active screen state” (ratios will then be converted to percentages)
* “Compulsive” phone checkout #2: calculated as the ratio of “short screen on” to total “screen state off” (ratios will then be converted to percentages)

**Phone calls as expressions of social interactions**

* Mean/Median/Mode/SD of incoming calls and of outgoing calls; this measure may indicate levels and direction of social interaction
* Ratio of outgoing to incoming calls per daytime, per evening and per nighttime, as well as per week; this measure may indicate passive vs. active modes of social interaction
* Variability of incoming and outgoing callers and call destinations per week; calculated as the amount of unique phone numbers (known as “hashed phone numbers” in Beiwe); this measure may reflect one’s variability of social interaction
* Median call duration of incoming and outgoing phone calls per week
* Mean/Median/Mode/SD of the number of missed/unanswered calls per 24-hour calendar day, and per week
* Mean/Median/Mode/SD of the number of unanswered calls; calculated as the number of outgoing calls with a duration of zero seconds, as recorded on the Beiwe system
* Additionally, composite variables will be created based on the above parameters

**Text messages**

* Mean/Median/Mode/SD of the number of text messages per 24-hour calendar day, and per week
* Mean/Median/Mode/SD of the number of sent/received text messages per 24-hour calendar day, and per week

**Accelerometer & GPS**

* Accelerometer activity: motion/activity index per hour, per daytime, per evening, per nighttime, per 24-hour calendar day, and per week; calculated as XYZ axis composite index, standardized on a 1-5 scale; this data may provide an indication of participants’ levels of physical activity and movement
* GPS location: Mean/Median/Mode/SD of the number of location changes greater than 5 km; calculated per 24-hour calendar day, and per week

##### 4. Digital phenotyping measurements of implantable cardioverter defibrillators (ICD): Arrhythmia and other cardiac data obtained from ICD sensors

The following data will be extracted from the Medtronic implantable cardioverter defibrillators (ICDs). Similar data from the Biotronic and the Boston Scientific ICDs may also be added during the course of the research project.

1. Number of Ventricular Fibrillation (VF) events since implant
2. Number of Ventricular Tachycardia (VT) events since implant
3. Number of Sustained Ventricular Tachycardia (SVT) events since implant
4. Number of Non-Sustained Ventricular Tachycardia (NSVT) events since implant
5. Number of Atrial Fibrillation (AF) events since implant
6. Average time in AT/AF (in hours and by % of days) since implant
7. Percentage of time in AF since implant
8. Percentage of time under ICD treatment since implant
9. Average patient activity (hours per day) since implant
10. Heart rate variability
11. Therapy Summary VT/VF
12. Pace-Terminated Episodes, % of time since implant
13. Shock-Terminated Episodes, % of time since implant
14. Total Shocks, % of time since implant
15. Aborted Charges, % of time since implant
16. Number of treated VT/VF episodes since implant (one or more shocks a day)
17. Percent of pacing a day of VF/VA event
18. Mean V. rate (BPM) per day and per night
19. Mean, Median and Mode of patient activity (calculated as hours/day) since implant
20. Mean heart rate variability (ms) since implant

### Preliminary results (7.1.3.3)

Links between smartphone data and meta-traits?

Digital phenotyping preliminary????? אישיות וסמטרטפון וככה....

### Available resources (אנושי ותשתיתי וזמינות משאבים באופן כללי) (7.1.3.4)

#### Human resources and gained experience

The proposed research represents an interdisciplinary collaboration of experts in the fields of cardiology (electrophysiology…), psychology and behavioral science (personality and stress), and computer and data science. Prof. Ariel Roguin received his MD from the Technion and is the Director of the Cardiology and ICCU department at the Hillel Yaffe Medical Center. Prof. Roguin is one of the leading cardiologists in Israel, he has published numerous papers, and he is involved in many clinical and basic science cardiology-related studies. Dr. Ofer Kobo received his MD from the Technion MD and MHA from the Hebrew University. He is a senior cardiology trainee at the Hillel Yaffe Medical Center, and has a wide range of experience in clinical and multidisciplinary studies. Prof. Yonathan Mizrachi received his PhD in Anthropology from Harvard University and…

Dr. Efrat Barel received her PhD in Psychology from Haifa University, 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 and its relation to physiological stress and reproductive systems. Further, she is well-experienced in the performance and interpretation of biochemical tests. An additional collaborator, Dr. Mark Kazatsker, MD (Head of Electrophysiology, Pacemaker & Arrhythmias Service; Hillel Yaffe Medical Center) is a well-established electrophysiologist, who has vast experience with implanting and managing pacemakers and ICDs. Dr. Kazatsker will be advising on all ICD-related aspects of this proposal.

The laboratory staff of the Hillel Yaffe Medical Center will carry out the measurement of biomarkers levels in the blood samples. Catecholamine samples will be analyzed in separate laboratory (Rambam or Ichilov Medical Centers).

Dr. Noa….. (נועה תשלח לי היום מחר)

#### Technological resources

* Elaborate: our Beiwe platform over AWS system for Android phones data collection.
* Data pipeline (Android sensor data pipeline) (ICT sensor data pipeline) Machine learning data platforms…. (to be expanded to IOS systems).
* Hillel Yaffe Medical Center’s relevant technological systems (for biology and other data and for electrophysiological data…).
* The Hillel Yaffe Medical Center operates a high-volume pacemaker service and has full access to labs, new generation devices and state-of-the-art technology.

### Expected results, potential pitfalls, and alternative research plans (7.1.3.5)

The proposed research aims to bridge this gap by exploring a border range of personality traits that have not yet been examined within a research framework which utilizes smartphone-based digital phenotyping. Personality traits that we wish to explore include risk-taking behavior, adult attachment, temperament (which is biologically-based), and more. Additionally, we plan to develop a practical and applicable predictive framework to test the aforementioned associations.

The proposed research is divided into two phases. In Phase I, we plan to use advanced statistical methodologies to conduct multidimensional analyses of information supported by visualization techniques. We will explore possible associations between various psychological and behavioral traits, as well as digital footprints from smartphones. Phase II will be focused on building an applied predictive model, using AI technology (e.g., ML), that is based upon insights gained from Phase I.

The main engineering challenges that will need to be resolved are as follows:

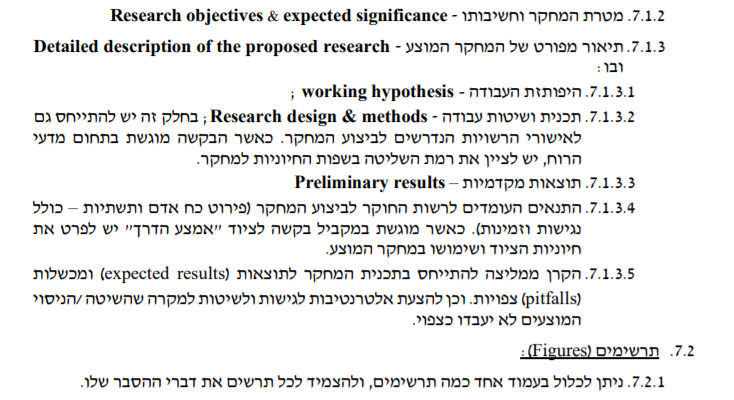
1. Maintaining a reliable smartphone data collection platform (which is currently limited to Android smartphones). We plan to use the open source Beiwe platform.[[1]](#footnote-2)

2. Developing a reliable data cleaning and preparation process that links between the data collected through mobile sensors and participants’ smartphones. We may be able to utilize R and Python 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 the expected study dropout rates. However, the initial recruitment may still be insufficient and the potential high dropout rates may require the recruitment of additional participants, which may extend the time needed for completing data collection.

Despite the challenges, the current study has several strengths, including: the prospective study design, which includes a two-year follow-up; the use of validated psychosocial measures; the inclusion of biomarkers; and the innovative application of digital phenotyping to behavioral mechanisms that play a role in cardiac diseases. Additionally, our study will have high external validity as the population will include those who are eligible for ICD implementation (i.e., history of heart failure and under consideration for primary prophylactic ICD).



# Figures (7.2)

As in the text above…

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1. The Beiwe research platform was developed by the Onnela Lab at the Harvard T.H. Chan School of Public Health with funding from the National Institutes of Health (NIH). The app collects passive phone sensor data (e.g., from the GPS and accelerometer) and phone usage data (e.g., communication logs and screen activity). [↑](#footnote-ref-2)