Nanobiosensing-Enabled Biorhythm Tracking for Psychiatric Disorders

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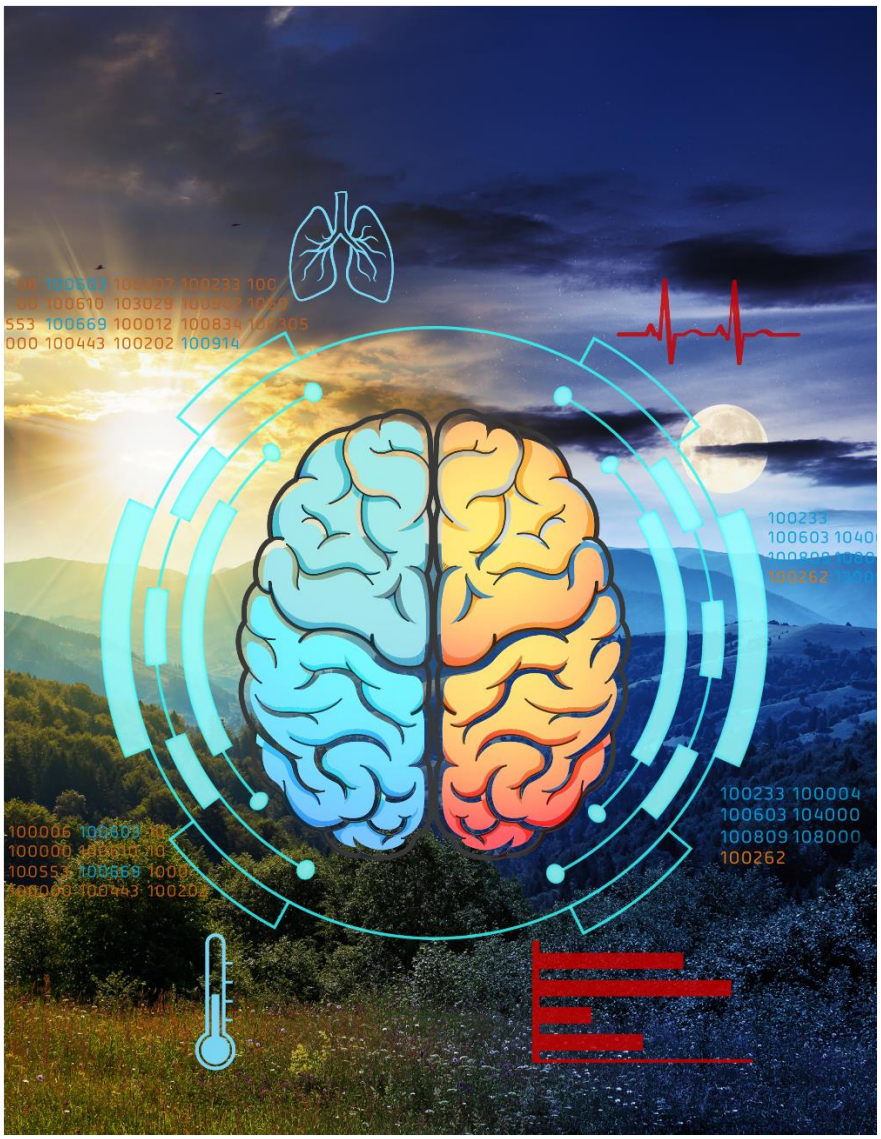
Abstract

This review paper explores the transformative potential of nanobiosensing in biorhythm tracking for psychiatric disorders. Psychiatric diseases, characterized by a complex, heterogeneous and multifactorial pathophysiology, pose challenges in both diagnosis and treatment. Common denominators in the pathophysiology of psychiatric diseases include disruptions in the stress response, sleep-wake cycle, energy metabolism and the immune response: all of these are characterized by a strong biorhythmic regulation (e.g., circadian), leading to dynamic changes in the levels of biomarkers involved. Technological and practical limitations have hindered the analysis of such dynamic processes to date. The integration of nanobiosensors marks a paradigm shift in psychiatric research. These advanced technologies enable multiplex, non-invasive and continuous analysis of biorhythmic biomarkers in real time, overcoming the constraints of conventional approaches. Focusing on the regulation of the stress response, sleep/wake cycle, energy metabolism, and immune response, nanobiosensing allows for a deeper understanding of the heterogeneous and multifactorial pathophysiology of psychiatric diseases. Continuous monitoring of biomarkers can provide a foundation for personalized medicine in Psychiatry, and allow for the transition from syndromal diagnostic entities to pathophysiology-based psychiatric diagnoses. This evolution promises enhanced disease tracking, early relapse prediction, and tailored disease management and treatment strategies. As nanobiosensing continues to advance, its integration into biorhythm tracking holds promise not only to unravel the intricate etiology of psychiatric disorders but also for ushering in a new era of precision medicine, ultimately improving the outcomes and quality of life for individuals grappling with these challenging conditions.



Graphical Abstract- Unlocking the Mind with Nanobiosensing-Enabled Biorhythm Tracking for Precision Psychiatry

1. INTRODUCTION

Psychiatric disorders account for 43% of years lived with disability (YLD) and 20-24% of disability-adjusted life years (DALY) lost in the United States and European countries ("Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019," 2022). The social and economic burden of psychiatric diseases is therefore immense. Biomarkers are physiological indicators of disease presence (diagnostic), susceptibility and prognosis (prognostic biomarkers), monitoring (disease management and treatment), (prediction of) treatment response or toxicity (Califf, 2018). Biomarkers therefore hold great promise in healthcare. The field of oncology has arguably benefited the most from the discovery of biomarkers, which are utilized daily by clinicians to aid in the clinical workflow, from prevention to treatment response determination

(Lightbody et al., 2019). However, in the field of Psychiatry, the discovery of clinically meaningful biomarkers is lagging behind, with hardly any biomarkers currently being clinically adopted. Rare exceptions include for instance the determination of genetic variations in liver enzymes metabolizing psychiatric drugs to predict treatment failure.

To date, the great promise of biomarkers has failed Psychiatry. The reasons behind this failed promise are manifold but include the complex, multifactorial nature of psychiatric diseases themselves: Psychiatric disorders are currently exclusively diagnosed through the recognition of symptom patterns; additional testing like blood work or imaging is only used to rule out non-psychiatric causes of complaints. Furthermore, symptoms generally vary within a diagnostic category, and overlap between different diagnostic categories, thereby blurring diagnostic lines. Combined with their complicated nature, this means psychiatric diagnoses at present do not reflect comprehensive underlying disease mechanisms and as such cannot in and of themselves correlate well with disease-specific biomarkers. A personalized, patient-centric approach towards biomarker discovery and validation could therefore prove more successful (Kraus et al., 2023). Another important reason explaining the ongoing lack of clinically relevant biomarkers in Psychiatry is how biomarkers are measured: at discrete time points. Biological processes are typically highly dynamic in nature, governed by acute adaptations to environmental stimuli, superimposed on predictable periodicities (biorhythms) in reaction to e.g., the light/dark cycle. Shared pathophysiological mechanisms in Psychiatry all have a strong biorhythmic regulation in common: disruptions in the stress response, sleep/wake cycle, energy metabolism and the immune response are involved in many psychiatric disease entities.

So far, pathophysiological research in Psychiatry has been hampered by a lack of technological options to continuously measure biorhythmically controlled biomarkers. As such, the biorhythmic dynamics of many systems are at best known to a limited extent. Biorhythmic processes are characterized by dynamic changes in the levels of biomarkers involved. Intrinsically, highly dynamic biomarker fluctuations can only be captured with (near) continuous measurements, not with discrete measurements. As such, it makes sense that complicated, multi-factorial disease mechanisms represented by various interacting and fluctuating biomarkers cannot be unraveled using single time-point tests. Recently, the real time, continuous detection of biomarkers using nanobiosensors has become a technological possibility (Bhalla, Jolly, Formisano, & Estrela, 2016). A biosensor is an analytical tool that detects and quantifies a biological signal. Biosensors at the nano scale (nanobiosensors) offer various advantages such as high sensitivity, low detection limits, miniaturization and multiplex measurements of target molecules. Multiplexed wearable nanobiosensors have been developed to accurately detect multiple biomarkers simultaneously and non-invasively in passive sweat (Bhide, Muthukumar, & Prasad, 2018; Bhide, Muthukumar, Saini, & Prasad, 2018). Nanobiosensors continuously monitoring biomarkers could revolutionize the field of Psychiatry by providing insight into dynamic biomarker patterns over time. Table 1 depicts examples of a few applications of nanobiosensing to understand the pathophysiological pathways and the biomarkers associated with it.

Table 1- Application of nanobiosensing to understand the pathophysiological pathways and the biomarkers associated with it.

Pathway	Nanobiosensor	Analyte	Biofluid	Reference

Metabolism	Graphene based Electrochemical sensor	Vitamins, amino acids	Sweat	(Wang et al., 2022)
Metabolism	Gold nanostar CoFe2 sensor	NADH	In Vivo Cells	(Zhao et al., 2022)
Metabolism	Genetically encoded fluorescent biosensors	Lactate, Glucose	In Vivo astrocytes, neurons	(Díaz-García et al., 2019)
Metabolism	Fluorescence resonance Energy transfer sensor	Lactate	In Vivo astrocytes, neurons	(Mächler et al., 2016)
Sleep	Gold nanourchin and graphene based electrochemical nanobiosensor	Alprazolam	Blood	(Sadrabadi et al., 2022)
Stress, Metabolism	Silver nanoflakes based surface enhanced raman scattering sensor	Cortisol, Creatine	Sweat	(H. S. Kim et al., 2021)
Stress	Label free aptamer based nanobiosensor	Cortisol	Saliva	(Mortazavi Moghadam, Bigdeli, Tamayol, & Shin, 2021)
Inflammation	Antibody conjugated Gold nanoparticles based electrochemical sensor	CRP	Sweat	(Tu et al., 2023)

In this review, we will first provide an overview of the recent technological developments in nanobiosensing. Next, we will describe how the stress response, the sleep-wake cycle, energy metabolism and the immune response are dynamically organized, interrelated and involved in the pathophysiology of various psychiatric disorders. Finally, we will discuss how continuous biomarker monitoring using passive sweat nanobiosensor-wearables could help fulfill the promise of biomarkers in Psychiatry, by providing a better transdiagnostic pathophysiological understanding of psychiatric diseases, and aiding in their prevention, diagnosis, treatment and management.

2. Biorhythms in Psychiatric Diseases

Biology is governed by predictable changes in daylight (circadian rhythm), lunar (circalunar: e.g. the menstrual cycle), seasonal and yearly (circannual) cycles (Rietveld, 1990). Life has adapted to and harmonized with these cycles by generating endogenous biological rhythms (biorhythms) corresponding to these predictable cycles, which are synchronized based on external cues (such as daylight) (Švorc, 2019).

The best-known biorhythm in humans arguably is the circadian rhythm, orchestrating a wide array of biological functions over a (near) 24-hour cycle (Meyer, Harvey, Lockley, & Dijk, 2022). The circadian rhythm determines not only the sleep-wake cycle, but also predicts when the body 'rests and recovers' versus is 'active and alert'. This translates to predictable changes in for instance metabolic, stress and immune responses, core body temperature, cognitive functioning (reduced at night), appetite (increased during daytime) and mood (Foster, 2020). Disruptions in the circadian rhythm (e.g., due to shift work) can lead to adverse health effects, including sleep disturbances, mood changes, and increased susceptibility to metabolic disorders (Mohd Azmi et al., 2020). Many of these core biorhythmic responses are affected across psychiatric diseases: sleep disturbances are found in a majority of psychiatric disorders ranging from anxiety and mood disorders to psychotic disorders and ADHD (Abad & Guilleminault, 2003). Changes in appetite exhibit a similar 'across diseases' pattern in Psychiatry (e.g., reduced in major depressive disorder -MDD-, anxiety disorders (Cosgrove et al., 2020)). Overall, disturbances in the stress response, the sleep/wake cycle, energy metabolism and/or immune function are found in a majority of psychiatric diagnoses. These four systems are highly interrelated and exhibit a strong biorhythmic regulation.

Cortisol and the Hypothalamic-Pituitary Adrenal (HPA)-axis

The hypothalamic-pituitary-adrenal (HPA-) axis is a neuroendocrine system regulating homeostasis and the stress response in the body (Figure 1). Stress occurs when the body's homeostasis is (perceived to be) threatened, and serves to restore homeostasis (Chrousos, 2009). Stress is the major trigger for HPA-axis activation. The hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH induces cortisol release by the adrenals. Cortisol exerts widespread effects on multiple systems throughout the body. It acts on target cells by binding to glucocorticoid receptors (GR), present in virtually all organs and tissues. GR acts as a hormone-dependent transcription factor, regulating gene expression after binding to cortisol. The HPA-axis is tightly regulated through positive feedforward (CRH, ACTH) and negative feedback (cortisol) mechanisms. The negative feedback of cortisol on both the hypothalamus and pituitary gland ensures that cortisol levels remain within an optimal range and prevents excessive cortisol responses.

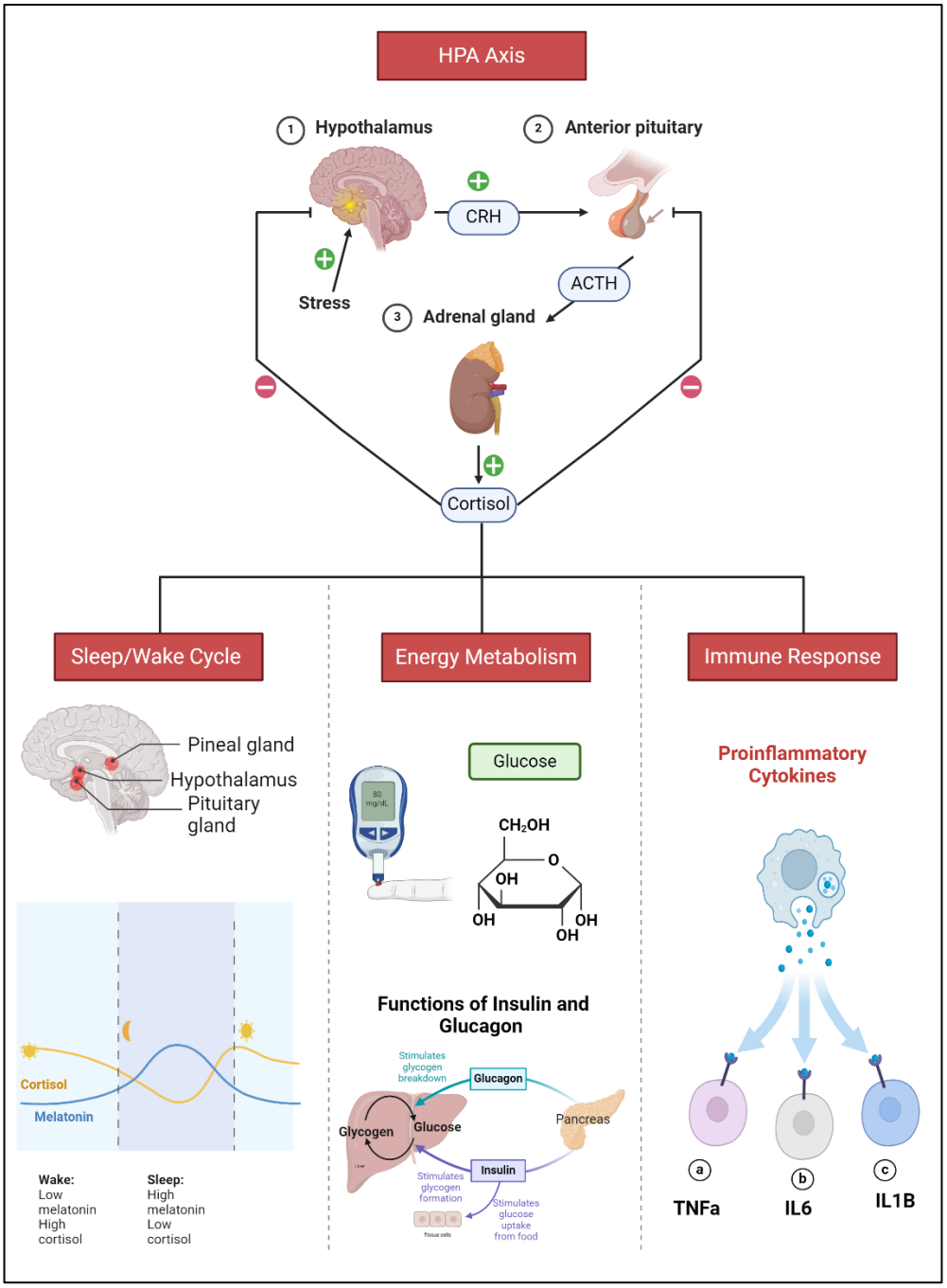


Figure 1-Role of HPA-Axis in inflammation, sleep and metabolism.

Maintenance of homeostasis requires continuous adaptations, both to predictable periodicities like the light-dark cycle and seasons, and to acute physical requirements. As such, the HPA-axis exhibits circadian (low levels of cortisol at night, high levels during the day, peaking around waking time), and ultradian rhythmicity in cortisol secretion, on top of which acute responses to triggers occur. This ensures a highly dynamic system which can be quickly steered into any direction required to restore homeostasis. Because of its central role in guarding homeostasis, the HPA-axis regulates many processes in the body, varying from e.g., digestion and metabolism to the sleep-wake cycle, immune function, and brain functions

including mood, the reward and fear system, behavior and cognition. Therefore, when the stress system becomes maladapted, various physical and mental symptoms ensue.

Many of the processes under the influence of the HPA-axis are commonly dysregulated across various psychiatric diseases. Indeed, dysregulation of the HPA-axis is found in various psychiatric disorders. Conditions like MDD (Carroll et al., 2007)(Gold, 2015)(Gold & Chrousos, 2002), childhood trauma (Murphy et al., 2022), post-traumatic stress disorder (PTSD) (Yehuda, 2002), bipolar disorder (BD) (Belvederi Murri et al., 2016) and schizophrenia (Borges, Gayer-Anderson, & Mondelli, 2013)(Bradley & Dinan, 2010)(Mikulska, Juszczyk, Gawrońska-Grzywacz, & Herbet, 2021)(Yeap & Thakore, 2005) have been associated with abnormalities in HPA-axis function (Charmandari, Tsigos, & Chrousos, 2005). In MDD, the direction of HPA-axis dysregulation varies between patients: hyperactive in severe melancholic depression (characterized by reduced appetite, insomnia, and worst depressed mood in the morning when cortisol levels peak) but inhibited in atypical depression (worst symptoms at night, increased appetite and hypersomnia) (Carroll et al., 2007). While the role of the HPA-axis in Psychiatry is interesting because of its transdiagnostic involvement and manifold effects, research has so far yielded conflicting results (Plag, Schumacher, Schmid, & Ströhle, 2013). Studying the HPA-axis is complicated by its highly dynamic nature, which cannot be appreciated by discrete measurements (Spencer & Deak, 2017). As such, single time-point measurements of cortisol have yielded inconsistent results in various psychiatric diseases (Murphy et al., 2022). Some studies have used invasive and intensive sequential discrete cortisol measurements to investigate dynamic levels over time, sometimes using dexamethasone (a potent synthetic glucocorticoid hormone) to quantify HPA-axis suppression (Spencer & Deak, 2017). However, this approach restricts studies to short periods of time, and to clinical settings with a high patient burden. The value of nanobiosensors continuously and non-invasively monitoring cortisol over extended periods of time in psychiatric patients could help unravel the role of the HPA-axis in the pathophysiology of psychiatric diseases, and lead to the discovery of meaningful subsets of patients requiring different treatment and management (e.g., hyperactive vs hypoactive HPA-axis, delayed or absent cortisol morning peak)(Trusso Sfrazzetto & Santonocito, 2022). In addition, disease states could be monitored or even predicted, allowing for early intervention and secondary prevention.

Cortisol and the Sleep/Wake Cycle

Sleep is essential to our survival: complete sleep deprivation is lethal within days to weeks (Besedovsky et al., 2019). Sleep is required for proper functioning of the central nervous system, including neurodevelopment, synaptic plasticity (Blumberg, Dooley, & Tiriac, 2022), cognitive function (Brown, Basheer, McKenna, Strecker, & McCarley, 2012), emotion regulation (Palmer & Alfano, 2017) and mood (Brown et al., 2012). Furthermore, sleep is a prerequisite for adequate immune function (Besedovsky et al., 2019) and energy metabolism (Brown et al., 2012). Unsurprisingly therefore, sleep disorders negatively impact major physical and mental functions. The sleep-wake cycle is regulated by the internal master biological clock in the suprachiasmatic nucleus (SCN), which is synchronized to the light-dark cycle by daylight hitting the retina (Meyer et al., 2022). The SCN regulates both the HPA-axis and the pineal gland. HPA-axis derived cortisol stimulates wakefulness and arousal, while pineal-derived melatonin induces sleepiness. Cortisol levels peak around awakening, remain high during the day, and drop at night to allow sleep to set in. Sleep itself further downregulates cortisol secretion, while disrupted sleep increases cortisol levels (Nicolaides, Vgontzas, Kritikou, & Chrousos, 2000). Contrarily, failing daylight at night induces the release of melatonin by the pineal gland, reducing alertness, lowering body temperature and stimulating sleepiness (Cajochen, Kräuchi, & Wirz-Justice, 2003). Daylight suppresses melatonin secretion (O'Byrne, Yuen, Butt, & Liu, 2021). A well-synchronized sleep-wake cycle is characterized by high melatonin

and low cortisol levels at night during sleep, and low melatonin and high cortisol levels during the day, when active (Meyer et al., 2022).
Sleep disturbances are a common symptom of various psychiatric diseases (Abad & Guilleminault, 2005). While psychiatric disorders can lead to sleep disorders, sleep disorders themselves can exacerbate or induce psychiatric symptoms (Baglioni et al., 2011)(Harvey, Kaplan, & Soehner, 2015). Disruptions in the circadian rhythm can underlie sleep disturbances in psychiatric patients, even during periods of remission of psychiatric symptoms (Mansur, Lee, McIntyre, & Brietzke, 2020)(Wulff, Dijk, Middleton, Foster, & Joyce, 2012). Hence, the management of sleep disorders in psychiatric patients is an essential part of their treatment. However, since sleep homeostasis is a multifactorial and dynamic process, disrupted sleep can have multiple causes. Recognizing the causes of sleep disturbances in individual psychiatric patients is the first step towards offering targeted, personalized treatment. For instance, a disrupted circadian rhythm underlying sleep disturbances can be treated with chronotherapy (e.g., light therapy, scheduled activity, melatonin suppletion) (Meyer et al., 2022). Continuous, non-invasive monitoring of cortisol and melatonin (combined with e.g., actigraphy, body temperature measurement, standardization of light/dark cycle) could offer an easy, patient-friendly way of unravelling the variety of sleep disorders in Psychiatry, including in an outpatient setting. This can aid in both diagnosis and treatment of sleep disorders in Psychiatry, and overall disease management.

Cortisol & Energy Metabolism

Energy metabolism is adapted to the circadian needs of the organism (Bailey, Udoh, & Young, 2014)(Langmesser & Albrecht, 2006). In humans and other diurnal species, energy is conserved and stored (anabolic state) at night during sleep, and released and spent (catabolic state) during the active daytime (Brown et al., 2012). The sleep-wake cycle and energy metabolism are therefore highly interconnected. The HPA-axis, in particular cortisol, is again an important regulator of the circadian metabolic rhythm (Nieuwenhuizen & Rutters, 2008): During the night, low levels of cortisol shift the body towards energy conservation and recovery. Upon awakening in the morning, the rise in cortisol levels mobilizes energy sources allowing for activity and alertness during the day (Geer, Islam, & Buettner, 2014). Glucose, for example, is released by the liver by inducing glycogenolysis and gluconeogenesis, leading to elevated blood glucose levels which can be used by peripheral tissues as an energy source. Cortisol also acutely increases insulin resistance, leading to a further elevation of blood glucose levels (RIZZA, MANDARINO, & GERICH, 1982). Once cortisol levels drop after the cortisol awakening response, the mobilized energy sources can readily be used to generate activity during the day (Tsigos, Kyrou, Kassi, & Chrousos, 2000). Additionally, cortisol increases appetite, thus stimulating food seeking behavior and food intake during the active daytime. Mitochondria, the energy power houses within our cells, also exhibit circadian regulation of their biogenesis and morphology, and of mitochondrial respiration itself (de Goede, Wefers, Brombacher, Schrauwen, & Kalsbeek, 2018). Disruptions of the circadian rhythm, for instance due to shift work, therefore have major effects on appetite and metabolism (Scheer, Hilton, Mantzoros, & Shea, 2009), and can lead to a (pre)diabetic state (Eckel-Mahan & Sassone-Corsi, 2013) which can be restored to normal by a recovery of a healthy sleep pattern (Brown et al., 2012). Energy metabolism disturbances, especially in glucose metabolism and mitochondrial function, are increasingly believed to underlie major psychiatric disorders (Y. Kim et al., 2019) like MDD (Milaneschi, Simmons, van Rossum, & Penninx, 2019), BD (Mansur et al., 2020) and schizophrenia (Henkel et al., 2022).

In bipolar depression, resting energy expenditure is reduced, particularly in the morning (Mansur et al., 2020). Patients with BD and first-episode psychosis (Çakici et al., 2020)(Pillinger et al., 2017), exhibit

glucose metabolism disorders (elevated fasted glucose levels, insulin resistance, increased risk of developing diabetes mellitus type 2) independent of side effects of psychiatric medication. Furthermore, psychiatric diseases themselves (due to e.g., poor lifestyle) and their pharmacological treatment can worsen metabolic health further (Çakici, Sutterland, Penninx, de Haan, & van Beveren, 2021)(Mazereel, Detraux, Vancampfort, van Winkel, & De Hert, 2020), leading to increased morbidity and mortality in psychiatric patients. The relationship between metabolic disturbances and psychiatric diseases is therefore bidirectional, multifactorial and intricate, with different contributors in each individual patient. This prevents patients from receiving proper care to limit metabolic complications, partially responsible for the high morbidity and mortality of major psychiatric diseases (Mazereel et al., 2020).
Multiplexed continuous nanobiosensing of a comprehensive panel of metabolic analytes (e.g., cortisol glucose, insulin) could help unravel the etiological role of metabolic aberrations in psychiatric diseases, pinpoint patients at risk for adverse metabolic health outcomes, and optimize and personalize treatment and management.

Cortisol & The Immune Response

The immune system protects us against harmful pathogens and neoplastic disease, and aids in tissue recovery, but when the immune response gets out of control, inflammatory and auto-immune conditions can arise. As such, the immune system is under tight homeostatic control. Unbeknownst to most, the immune system exhibits biorhythmicity (Haus & Smolensky, 1999)(Logan & Sarkar, 2012). Cellular clocks within leukocytes, the SCN 'master clock' in the brain, as well as systemic signals regulate biorhythmic immune function (Logan & Sarkar, 2012). Vice versa, the immune system can modulate internal biological clock phasing through cytokines (Logan & Sarkar, 2012). Indeed, circadian rhythm disruptions (e.g., due to shift work or jet lag) can impair immune function (Haus & Smolensky, 1999). Because of its central role in guarding homeostasis, the HPA-axis is a major regulator of immune function (Webster, Tonelli, & Sternberg, 2002). Cortisol suppresses the immune system by inhibiting the differentiation, maturation and proliferation of immune cells and their homing to areas of inflammation and by reducing the levels of pro-inflammatory cytokines like IL-6 and TNF-α (Webster et al., 2002). Hence, the levels of these pro-inflammatory cytokines show an inverse relationship with cortisol blood levels (Haus & Smolensky, 1999). Inflammation itself induces the HPA-axis and cortisol release, in a negative feedback loop preventing the immune reaction from getting out of control (Rhen & Cidlowski, 2005). A dysregulation of the HPA-axis can therefore lead to either immune suppression and increased sensitivity to infections, or to inflammatory conditions (Rhen & Cidlowski, 2005)(Webster et al., 2002).

While cortisol acts as a general immunosuppressant, melatonin antagonizes cortisol's immunosuppressant effects. Melatonin and cortisol, apart from their role in sleep homeostasis, are therefore two major endocrine factors influencing immune function (Logan & Sarkar, 2012)(Drazen, Bilu, Bilbo, & Nelson, 2001). Indeed, sleep and immune function are tightly interlinked: inflammation commonly induces fatigue and increases sleep duration and intensity (immune-to-brain signaling), for instance because various pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1) have somnogenic effects (Brown et al., 2012)(Alexandros N Vgontzas et al., 2003). Vice versa, healthy sleep improves immune function (brain-to-immune signaling), while prolonged sleep disturbances can lead to a phase shift in IL-6 and TNF-α levels (A.N. Vgontzas et al., 2002) and systemic low-grade inflammation (Besedovsky et al., 2019). Immune activation can cause (mild) neuro-inflammation through pro-inflammatory neuropeptides, cytokines and neurotransmitters secreted by leukocytes, affecting the brain via efferent nerve fibers or by passing the blood-brain barrier; leukocytes

themselves can also migrate into the brain parenchyma and lead to neuro-inflammation. Neuro-inflammation induces sickness behavior like fatigue, increased sleep and pain perception, reduced appetite, social withdrawal, depressed mood, reduced motivation and inactivity (Besedovsky et al., 2019). Similar symptoms are present in various psychiatric diseases too; indeed, many psychiatric disorders are associated with a pro-inflammatory state. This includes findings of increased levels of pro-inflammatory cytokines, neuronal auto-antibodies and neuro-inflammation in various psychiatric diseases (Frick, Williams, & Pittenger, 2013)(Khandaker et al., 2015)(Najjar & Pearlman, 2015)(Pape, Tamouza, Leboyer, & Zipp, 2019). Inflammation is one of the hypothesized pathophysiological mechanisms of psychiatric diseases, including MDD (Dantzer, O'Connor, Lawson, & Kelley, 2011)(Rosenblat, Cha, Mansur, & McIntyre, 2014), schizophrenia (Norbert Müller, 2018)(N Müller, Weidinger, Leitner, & Schwarz, 2016) and BD (Rosenblat et al., 2014)(Henkel et al., 2022)(Solmi et al., 2021). Chronic stress and subsequent HPA-axis dysregulation are considered important contributors to immune activation in psychiatric diseases (Iob, Kirschbaum, & Steptoe, 2020). Various meta-analyses across psychiatric disorders highlight elevated levels of pro-inflammatory cytokines in treatment-naïve patients, in particular IL-6 and TNF-α: MDD (Çakici et al., 2020)(Köhler et al., 2017); schizophrenia (Çakici et al., 2020); BD (Henkel et al., 2022). After treatment with psychiatric medication, levels of pro-inflammatory cytokines decrease (IL-6 in schizophrenia, TNF-α in MDD) (Çakici et al., 2021). Likewise, anti-inflammatory agents can improve disease symptoms in schizophrenia (Çakici et al., 2020). To date, however, cytokines have only been measured at discrete time points as biomarkers for psychiatric diseases, leaving a lack of knowledge regarding the dynamic changes in immune function in these disorders. Similarly, the role of the HPA-axis in driving inflammation in psychiatric diseases remains obscure.

To conclude, the HPA-axis, with cortisol as its central hormone, is a major regulator of the stress response in humans. The HPA-axis regulates all major bodily functions including the sleep-wake cycle, energy metabolism and the immune system. Vice versa, these systems influence the HPA-axis and each other in a complicated interplay to maintain homeostasis. Disruptions in the stress response, sleep/wake cycle, energy metabolism and the immune response are believed to play a part in the pathogenesis of various psychiatric disorders. Due to technical limitations to date, little is known about the dynamics of and interrelationship between the HPA-axis, the sleep/wake cycle, energy metabolism and immune function in psychiatric disorders. HPA-axis dysregulation and/or circadian misalignment may, at least in a subset of patients, lie at the pathophysiological core of psychiatric disorders (Androulakis, 2021). Continuous, non-invasive, multiplex nanobiosensing of a panel of informative biomarkers (e.g., cortisol, melatonin, glucose and other metabolic biomarkers, cytokines) over an extended period of time, in a naturalistic setting, could therefore help unravel the complicated and multifactorial etiology of psychiatric disorders. This could in turn translate into much needed personalized treatment and management options, as will be discussed in the next section.

3. Integrating Intelligent Systems and Nanobiosensing in Psychiatric Clinical Workflow

Psychiatric diseases pose complex challenges due to their multifaceted nature, and advancements in technology, particularly at the nanoscale, are opening new frontiers in monitoring and treating these conditions (Figure 2). In the new digital health era, modern medicine has adapted machine learning (ML) in many levels of the clinical workflow (Table 2). In the field of Psychiatry, however, technological advancements have been integrated to a limited extent. Nevertheless, a meta-analysis showed that 66.6% of psychiatrists see value in advancing patient care through digital technology (Wu et al., 2021). Medical technologies empowered by ML are called intelligent systems. These intelligent systems have

revolutionized healthcare in the past decade by integrating vast amounts of patient electronic health records, delineating both subtle and major patterns in the data. Data-driven decision making in healthcare could lead to quicker disease detection and outcome prediction at high precision and accuracy (Chen et al., 2022). The trifecta of nanotechnology, biosensing and intelligent systems has immense potential to create a patient-centric healthcare system in Psychiatry. Integrating nanobiosensors with ML would create an intelligent system enhancing the functionality of nanobiosensors. If these intelligent systems are implemented in the field of Psychiatry, they hold immense potential to analyze complex patterns and predict onset or recurrence of psychiatric events.

Table 2- Applications of Machine Learning in Psychiatry for Clinical Purposes

Clinical Purpose	**Machine Learning Application**	**Methods employed**	**Specific tasks**	**References**
Diagnosis	Supervised Classification	Identifying discriminative biomarkers for specific disorders	Distinguishing a disorder from a healthy condition or other mental illnesses	(Nielsen, Barch, Petersen, Schlaggar, & Greene, 2020)
	Unsupervised Clustering	Identifying disease subtypes for clinical and biological heterogeneity	Offering new perspectives in defining psychiatric conditions	(Zhang et al., 2020) (Pelin et al., 2021)
Prognosis	Classification Models	Distinguishing different course trajectories (e.g., progressor vs. non-progressor)	Predicting the development of symptoms during the disease	(Janssen, Mourão-Miranda, & Schnack, 2018)
	Regression Models	Predicting symptom development during the disease course	Understanding and forecasting individual responses to treatment	(Gao, Calhoun, & Sui, 2018)
Treatment	Classification Methods	Predicting individual responses to treatment	Distinguishing responders from non-responders	(Gao et al., 2018)
Integration	Feature Reduction/Mapping Approaches and Knowledge-Driven Feature Engineering	Enhancing model interpretability and biomarker pattern identification	Incorporating strategies for more informative and interpretable results	(Nielsen et al., 2020)

Non-invasive nanobiosenors built on supervised ML algorithms such as ensemble learning have been shown to allow real time tracking of inflammatory cytokines (Jagannath et al., 2022), and metabolism (Sardesai et al., 2023). Future studies can examine interaction effects that are evident in these pathways of psychiatric disorders by unlocking the capabilities of multiplexed detection. Multiplexed detection leads to better prediction models (Meehan et al., 2022). Machine learning models can be personalized and utilized in conjunction with wearables and biosensors (Shahub, Upasham, Ganguly, & Prasad, 2022), allowing for personalized medicine. Several studies have showcased the power of such algorithms in the context of disease driven diagnosis (Xia et al., 2018). In a study done by Zhang et al., the researchers used a data-driven framework aimed at performing feature selection and subtyping based on the resting-state EEG source-reconstructed signals. This innovative approach effectively delineated two transdiagnostic subtypes exhibiting unique functional connectivity patterns in PTSD and MDD within a cohort of 648 participants. These transdiagnostic subtypes predicted treatment response (Zhang et al., 2020). Additionally, systematic reviews have illustrated the importance of machine learning models defining subtypes that have well-defined phenotypes in the manifestation of psychiatric disorders (Walter et al., 2019).

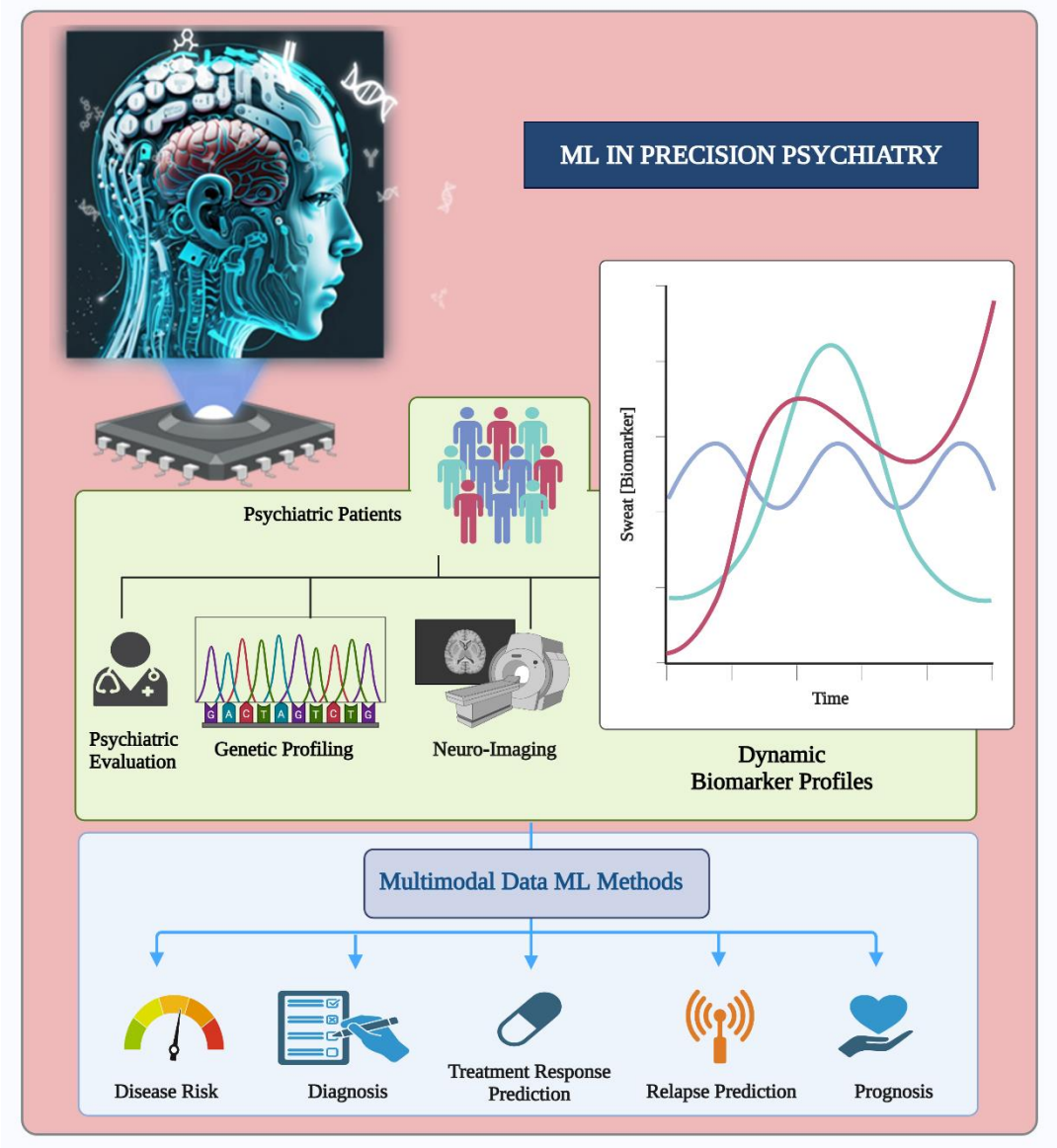


Figure 2- Various Applications of Machine Learning in Precision Psychiatry

Nanoscale sensors offer the capability for real-time monitoring of biochemical changes in response to psychiatric treatments. As such, continuous nanobiosensing could eventually allow healthcare professionals to dynamically adjust treatment plans based on individual patient responses. The ability to track treatment efficacy in real-time enhances the adaptability of interventions, offering a more patient-centric approach to psychiatric care. The latest developments in non-invasive, continuous multiplex nanobiosensing in passive sweat could revolutionize medicine by offering the ability to discover the dynamics of biomarker patterns over extended periods of time. This ability can be especially meaningful in diseases characterized by a relapsing/remitting course (disease tracking, relapse prediction) and with a complex, multifactorial etiology (personalized pathophysiology), for which existing biomarkers offer insufficient actionable data. Biomarkers known to exhibit biorhythmic regulation would be ideal candidates for continuous nanobiosensing, as discrete measurements are unable to decipher complex dynamic changes in these biomarkers. Psychiatric diseases, characterized by all the above (complex,

multifactorial etiology, insufficient actionable data from existing biomarker analyses, biorhythmic biomarkers) could benefit to a great extent from implementing continuous nanobiosensing (Habtewold et al., 2020). As nanobiosensing integrates with digital parameters in psychiatric healthcare, ethical considerations and privacy safeguards become paramount (Bickman, 2020). Striking a balance between harnessing the benefits of advanced technologies and protecting patient privacy requires a thoughtful approach. Ethical frameworks must be established to guide the responsible development and implementation of these technologies, fostering trust among patients and healthcare professionals.

4. Continuous Non-Invasive Nano Biosensing in Psychiatry: Future Avenues

Disruptions in the HPA-axis, sleep/wake cycle, energy metabolism and immune function are trans-diagnostically involved in the pathophysiology of Psychiatric disorders. As the main HPA-axis effector molecule, cortisol plays a central role in regulating these four systems, all of which are characterized by a marked biorhythmic regulation. Biorhythmically regulated biomarkers relay information not only through their concentration (as measured by e.g., single time-point analysis), but more so by changes in their concentration over time (Carroll et al., 2007): this vital time dimension is lacking with traditional biomarker analysis on discrete moments only, rendering them unfit to capture the mechanisms of dynamically organized systems. Historically, gaining some insight into the fluctuations of circulating biomarkers such as cortisol was only possible by frequent sequential blood analyses in a lab setting (Dziurkowska & Wesolowski, 2021). This greatly limits the timeframe of analysis (several hours), is invasive and burdensome for patients, and can only take place in the artificial setting of a clinical lab, thus yielding limited information.

The recent technological development of continuous, non-invasive, multiplex nanobiosensing in passive sweat could radically change the field of Psychiatry by shedding light on the patterns of biomarker dynamics in psychiatric diseases over long periods of time (weeks/months), in a naturalistic setting, and in relation to psychiatric symptoms: Firstly, continuous nanobiosensing could help unravel the complicated and multifactorial pathophysiology of psychiatric diseases, especially when combined with other data modalities such as genomics and neuro-imaging; continuous nanobiosensing could provide the dynamic missing link coupling these data modalities into a comprehensive whole. Once the pathophysiology of a disease becomes clearer, new diagnostic categories can be formulated representing the underlying disease mechanism; this is happening in oncology, where cancer molecular pathological signatures can subdivide histological diagnoses into meaningful subcategories with a different prognosis and treatment response (Funkhouser, 2020). As such, continuous nanobiosensing could change the way we diagnose psychiatric diseases from a syndromal (i.e., recognition of symptom clusters) to a disease mechanism-oriented approach, allowing for the optimization of treatment selection and the development of novel treatment approaches. One promising line of future treatments could for instance be HPA-axis modulation, made to fit the need of the individual patient based on the specific HPA-axis involvement in their illness (e.g., suppressed/hyperactive) (Menke, 2019). Indeed, continuous nanobiosensing could prove an indispensable ingredient for personalized or precision Psychiatry (Chen et al., 2022; Meehan et al., 2022). We know from the literature that a subset of patients with schizophrenia-spectrum disorders exhibits a marked pro-inflammatory phenotype both in peripheral blood (N Müller et al., 2016) and in the brain (Cai et al., 2020), as opposed to other patients with no or less marked inflammation (Trépanier, Hopperton, Mizrahi, Mechawar, & Bazinet, 2016). Determining both the presence of inflammation, and the dynamics of pro-inflammatory cytokines in multiplex with metabolic, sleep/wake cycle, and HPA-axis biomarkers could pinpoint the underlying causes of hyperinflammation in the individual patients (e.g., primary immune

process, circadian misalignment, as part of a metabolic syndrome etc.). This could help design targeted, personalized treatment approaches in Psychiatry with for instance immunomodulatory agents (e.g., N-acetylcysteine), metabolic interventions (e.g., ketogenic diet, metformin), and chronotherapy (e.g., timed melatonin suppletion, light therapy). Other applications of continuous nanobiosensing in Psychiatry could include personalized biomarker profile tracking for disease monitoring (e.g., early relapse prediction) (Kanbes-Dindar, Demirtaş, & Uslu, 2024). Once significant changes in biomarker patterns between a disease episode (e.g., psychosis relapse) and steady state (remission) are recognized in an individual patient, a patient-specific biomarker panel can be established for long-term monitoring to allow for early relapse detection and timely interventions as secondary prevention.

Similarly, individualized dynamic biomarker profiles could prove useful to predict early treatment response or non-response: for many psychiatric medications, like antidepressants, the clinical effect will only be noticeable after 6-8 weeks of treatment at a therapeutic dose (Bruno et al., 2023). Many patients will need to switch to other antidepressants afterwards due to lack of efficacy, putting a large burden of both side effects and delayed episode remission on patients. As yet, it is not possible to predict efficacy in earlier treatment stages. However, a normalization of biomarker profiles might precede and predict clinical effect, thus improving treatment selection and time to remission. Finally, with an improved understanding of both the pathophysiology of psychiatric diseases, and (personalized) biomarker profile dynamics, we may be better able to determine disease susceptibility, for instance in family members of patients with a major psychiatric disorder: in spite of multiple efforts to recognize patients at risk of developing psychiatric diseases, no valid risk prediction tools exist so far. Altogether, we believe the recent technological breakthroughs in continuous, non-invasive, multiplex nanobiosensing in passive sweat will revolutionize the field of Psychiatry. The integration of nanobiosensing in monitoring biochemical and digital parameters marks a transformative moment in psychiatric healthcare (Figure 3). From early detection to real-time treatment monitoring, nanoscale innovations hold the promise of revolutionizing how we understand, diagnose, and treat psychiatric disorders. As these technologies advance, it is crucial to address ethical concerns, establish robust privacy measures, and collaborate across disciplines to ensure that the benefits of nanobiosensing are harnessed responsibly for the betterment of mental health care (Wilkinson et al., 2020).

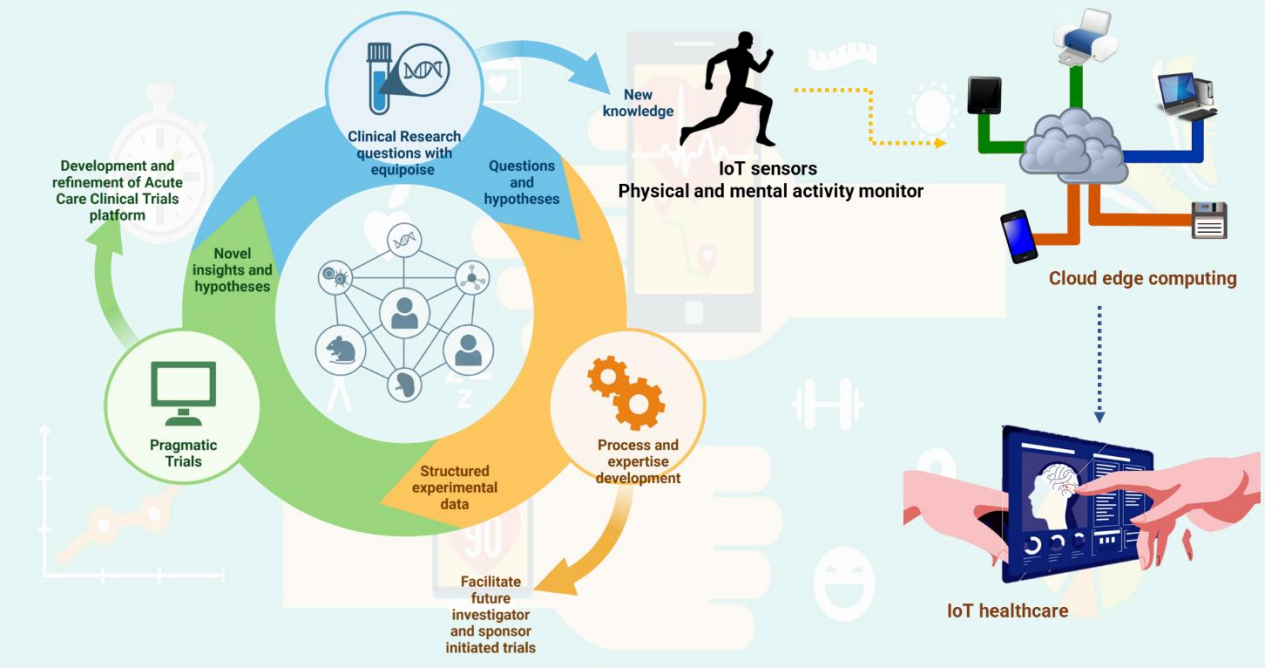


Figure 3-Schematic representation of the workflow in the clinical avenue towards advancements in clinical Psychiatry

Conclusion:

In conclusion, the heterogeneous, multifactorial and intricate nature of psychiatric diseases has posed significant challenges in understanding and treating these prevalent and often debilitating disorders. The intertwined involvement of the stress response, sleep-wake cycle, energy metabolism, and the immune response in various psychiatric conditions adds layers of complexity to their pathophysiology. Despite efforts to investigate these dynamic processes, both technical and practical constraints have limited our insights. The emergence of nanobiosensors presents a transformative opportunity to revolutionize psychiatric research, diagnosis and treatment. These innovative technologies offer the potential for continuous, non-invasive, and multiplex analysis of biorhythmic biomarkers over extended periods, all within a non-clinical setting. Overcoming the limitations of traditional methods, nanobiosensors provide a promising avenue for gaining deeper insights into the intricate dynamics of the stress response, sleep/wake cycle, energy metabolism, and the immune response in Psychiatry. By continuously monitoring relevant biomarkers, a more nuanced understanding of pathophysiological mechanisms in Psychiatry becomes possible, unveiling aspects that were previously obscured. This advancement has the potential to shift the current diagnostic paradigm from syndromal entities to pathophysiology-based psychiatric diagnoses, aligning more closely with the actual disease processes at an individual level. The continuous patterns of biomarkers in individual patients open new avenues for disease tracking, including early prediction of relapses, as well as improved disease management and treatment strategies. This signifies a pivotal step towards realizing true personalized medicine in Psychiatry, where interventions can be tailored to the unique needs and responses of each patient. As nanobiosensors continue to evolve, they hold the promise of not only transforming our understanding of psychiatric disorders but also ushering in a new era of precision and individualized care in mental health.

Conflict of Interest: Shalini Prasad and Sriram Muthukumar has a significant interest in EnLiSense LLC, a company that may have a commercial interest in the results of this research and technology. The potential individual conflict of interest has been reviewed and managed by The University of Texas at Dallas and played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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