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Biomarkers of Mental Illness—What Can We Learn from Circadian Heart Rate?

Hans G. Stampfer[1]* , Simon B. Dimmitt[2]

[1]Division of Psychiatry, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia
[2]Division of Internal Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia
Email: *hans.stampfer@uwa.edu.au, *stampferH@ramsayhealth.com.au, simondimmitt@gmail.com, sdimmitt@bigpond.com

Abstract

Background: Much research in psychiatry has been a search for diagnostic biomarkers of mental illness but practically useful markers have remained elusive. The problem may be unrealistic expectations and the aim in this paper is to show that the relationship between circadian heart rate and psychiatric status can contribute to useful understanding in this regard. **Aim:** To discuss the biomarker implications of changes in circadian heart rate (CHR) in psychiatric disorders. **Methods:** Comparisons of CHR were made between and within individuals receiving treatment for different psychiatric disorders diagnosed according to criteria defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). **Results:** Broadly different DSM-5 disorders are associated with distinctly different changes in CHR. Some disorders are more consistently associated with distinctive changes but CHR does not predict symptoms or specific clinical diagnoses reliably. Changes in CHR, particularly during sleep, are state-dependent. Clinical improvement is associated with normalisation of CHR. **Conclusion:** Changes in CHR are a part of the physiological changes in mental illness. Distinctly different changes in CHR suggest distinctly different physiological changes that may constitute diagnostic discrimination at a physiological level. An analysis of CHR can add objective adjunct information to clinical assessment and the evaluation of treatment but does not predict symptoms or clinical diagnoses reliably. Much the same is likely to apply to all candidate biomarkers of mental illness.

Keywords

Circadian Heart Rate, Anxiety, Depression, Mania, Schizoaffective Disorder, Schizophrenia, Personality Disorder

'*There are no laboratory tests to date that can be used by clinicians to diagnose patients with psychiatric disorders.*' [1]

'… *there is little evidence that the majority of recognized mental disorders are separated by natural boundaries. Diagnostic categories defined by their clinical syndromes should be regarded as 'valid' only if they have been shown to be truly discrete entities. Most diagnostic concepts in psychiatry have not been demonstrated to be valid in this sense…*' [2]

1. Introduction

Mental illness is defined by symptoms and signs and it has long been suspected that clinically classified syndromes are not discrete biological entities. Biological heterogeneity is suggested clinically by the wide variation in symptoms and signs that is often evident between individuals given the same diagnosis. For example, two individuals given a diagnosis of 'major depression' may reveal different, even opposite symptoms such as hypersomnia or insomnia, weight gain or weight loss, psychomotor agitation or psychomotor retardation. Under such circumstances, no single biomarker is likely to demonstrate practically useful diagnostic specificity and it is not surprising that the search for biomarkers of clinically defined disorders has been disappointing despite numerous studies [3] [4] and not infrequent reports of positive findings [5] [6] [7] [8] [9]. Attempts to validate clinical syndromes at a biological level are likely to remain unrewarding [1] and there is a need to review assumptions and expectations in this regard. Neither state nor trait biomarkers are likely to prove usefully specific if, as suggested by Jablensky [2], there is little evidence that classified mental disorders are separated by natural boundaries. However biological variables that reveal a dependent relationship with mental or psychiatric status may provide clinically useful information, even if not diagnostically specific for clinically defined disorders, much like C-reactive protein provides a useful metric of inflammation without indicating a specific diagnosis.

2. Background

In psychiatry, heart rate is generally regarded as a diagnostically non-specific indication of 'arousal'. However, this is a simplistic appraisal, not least because 'arousal' is not a one dimensional variable or process. More relevant for present purposes is that circadian heart rate (CHR) is subject to visceral sleep-wake regulation and it has long been recognized that mental illness is associated with visceral dysregulation. This leaves the possibility that evidence of such illness-related visceral or autonomic dysregulation might be signalled by changes in CHR. If that is the case, then the important question is to what extent is the visceral dysregulation and associated changes in CHR relevant from a biomarker perspective.

Unlike C-reactive protein which varies only quantitatively, CHR is a multidimensional variable and it can readily be verified that that broadly different states of mental illness reveal distinctly different changes in CHR, particularly during sleep, when confounding influences on heart rate are minimal. All other things being equal, evidence of distinctly different changes in heart rate during sleep, is

evidence of different regulatory changes and differences in this regard may constitute biomarker information about mental illness at a physiological level. The state-dependent variation of CHR, as revealed in serial within-individual recordings, provides the most compelling evidence that CHR is involved in the biological changes of mental illness. Clinical improvement is associated with a 'shift' towards a normal pattern of CHR, much as recovery from infections is associated with a return to normal circadian variation in body temperature. The combination of distinctly different changes in CHR and their state-dependent variation in psychiatric disorders, suggests there is biomarker information in CHR at a physiological level. Variation in CHR between individuals given the same clinical diagnosis can provide potentially useful adjunct information and indicate the extent of physiological or biological heterogeneity in clinically defined disorders.

Presented data illustrate distinctly different changes in CHR, their relationship to clinical diagnoses and their state-dependent variation. Only illustrative examples are presented because discriminatory features of CHR are degraded or not at all evident in aggregated data. It is suggested that the evident relationship between psychiatric status and CHR provides a useful model for understanding the inevitable limitations of all candidate biomarkers in psychiatry, even if, like CHR, they can provide practically useful adjunct information for diagnostic assessment and clinical monitoring.

3. Heart Rate (HR) vs Heart Rate Variability (HRV)

Heart rate is a function of the time interval between successive heartbeats. Each inter-beat interval (IBI), measured in milliseconds, gives the instantaneous heart rate and a healthy heart beats with subtle variations in IBI. This time-dependent variation in IBI at different frequencies is referred to as 'heart rate variability' (HRV). Too regular, as well as too irregular, beat repetition is a sign of ill-health and numerous studies have reported changes in HRV (predominantly a reduction) across a wide range of physical illness [10] [11] [12] [13] [14] and mental illness [15] [16] [17]. The focus here is on heart rate measured in beats per minute (bpm). There is no direct or consistent relationship between rate and rate variability [18] [19] and questions remain about the reliability of HRV measures [20] [21]. Heart rate (HR) depends on the mean autonomic nervous system (ANS) input to the heart, whereas HRV depends on the balance of sympathetic (SNS) and parasympathetic (PNS) input [22]. HR varies about the mean of ANS input and mean ANS input can vary independently of HRV. Heart rate and HRV provide complementary information but investigations to date suggest that psychiatric status is more closely related to circadian HR, rather than HRV—in other words, more closely related to mean autonomic input. This is especially evident in serial data from individuals treated with psychotropic medications. Effective treatment is associated with normalization of the circadian 'rate architecture' even if HRV remains abnormally low due to medication effects [23] [24] [25].

4. Methods

4.1. Acquisition of Heart Rate Data

Heart rate data were obtained with a two-lead Bodyguard-2 cardiac monitor that also monitors activity as displacement in the x, y and z planes. Presented data were obtained from physically healthy adults, 18 - 65 years of age, who were admitted for inpatient treatment of a psychiatric disorder diagnosed according to DSM-5 criteria [26]. Exclusion criteria included a history or evidence of cardiac disease, obstructive sleep apnoea, alcohol dependence, medication with a recognized cardiac effect (e.g. beta-blocker, thyroxine, dexamphetamine). Patients prescribed first generation antipsychotics or antidepressants were excluded as were patients prescribed clozapine or ziprasidone. Sertindole, which has a recognized effect on HRV, is not prescribed in Australia.

4.2. Clinical Assessment

Clinical assessment did not go beyond diagnoses made by senior psychiatrists familiar with DSM-5 diagnostic criteria. The limitations of a clinical diagnosis are well recognized [27] and the focus here was on the variation in the physiological indicator of CHR, between individuals given the same and different clinical diagnoses, as well as the serial variation in CHR within individuals under treatment.

4.3. Quantitative vs Temporal or Circadian Variation in Heart Rate

Variations in CHR can be broadly classified as 'quantitative' and 'temporal' or 'circadian'. Quantitative variation means variation in the mean and standard deviation of rates measured in bpm over a specified time interval. 'Temporal' or 'circadian' variation means variation in the rate architecture or circadian rate pattern. Both temporal and quantitative aspects of CHR can vary on a continuum and independently in the sleep and awake state [28].

5. Results

5.1. Normal CHR

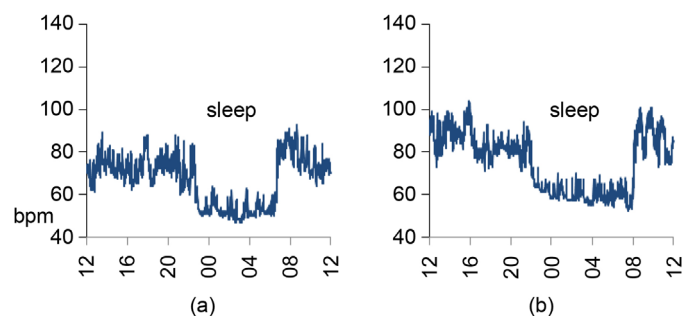Examples of normal CHR, obtained from two volunteers identified here as 'a' and 'b', are shown below in Figure 1.

Figure 1. Examples of normal CHR.

Table 1. Basic heart rate statistics for data plotted in Figure 1.

Figure	awake (bpm)		sleep (bpm)	
	$\overline{x}$	σ	$\overline{x}$	σ
1 (a)	74	6.9	52	3.0
1 (b)	84	8.0	60	3.2

Figure 1(a) data were obtained from a 35 years old male, Figure 1(b) data from a 33 years old female. Both 'a' and 'b' were physically healthy, well adjusted individuals without a personal or family history of mental illness. Both their recordings show a typically normal circadian rate architecture, with a rectangular pattern of down regulation in rates during sleep, save for REM-sleep-related increases in rates and rate variability. Basic statistics are given in Table 1 and reveal normal rates as reported in the literature [29] [30].

5.2. Normal Serial Variation in CHR

Serial variation in CHR, particularly in sleep-related activity, is an important metric in evaluating changes in psychiatric status and the effectiveness of treatment. Serial recordings from healthy individuals living a stable life, show closely similar CHR as illustrated below in Figure 2.
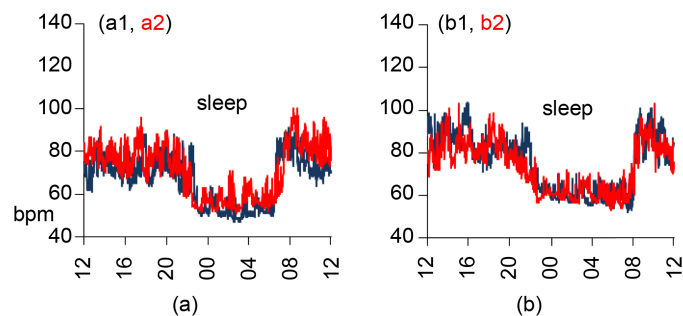

Figure 2. Examples of normal serial variation of CHR.

Table 2. Basic statistics for normal serial variation in CHR plotted in Figure 2.

Figure	awake (bpm)		sleep (bpm)	
	$\overline{x}$	σ	$\overline{x}$	σ
2(a1)	74	7.0	52	2.9
2(a2)	78	8.2	57	4.0
2(b1)	85	7.0	60	3.7
2(b2)	81	7.2	61	4.4

Figure 2 shows Figure 1 data (blue plot) with a superimposed second recording (red plot) obtained three weeks after the first. A comparison of basic statistics is given in Table 2. There is no statistically significant difference in rates and the circadian rate architecture is closely similar in each case.

5.3. Examples of CHR Changes in Mental Illness

Figure 3 data were obtained from three patients, identified here as 'a', 'b', and 'c', who were obviously manic at the time of recording. The circadian patterns show a closely similar deviation from the typically normal patterns in Figure 1, despite the gender differences and wide difference in age, as detailed in Table 3. The waking state is characterized by dense rate variability throughout, over a range of around 20 bpm. Sleep is reduced to around 4 hours in 3(a) and 3(c) and to around 5 hours in 3(b). Sleep rates are abnormally elevated in each case, as are awake rates in 3(a) and 3(c). Figure 3 plots are examples of where the same clinical diagnosis shows much the same changes in CHR. However this is not always the case, as illustrated below in Figure 4.
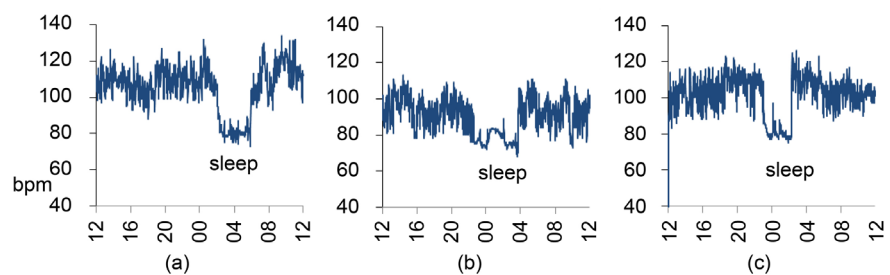

Figure 3. CHR changes in mental illness: same diagnosis, similar changes in CHR.

Table 3. Basic statistics for data plotted in Figure 3.

Figure	Clinical Diagnosis	Medication	age	gender	awake (bpm)		sleep (bpm)	
					$\bar{x}$	σ	$\bar{x}$	σ
3(a)	Mania	olanzapine lithium	23	M	109	7.8	81	3.4
3(b)	Mania	olanzapine valproate	43	F	94	7.4	78	3.9
3(c)	Mania	olanzapine valproate	55	M	104	7.3	80	3.4

Figure 4 data were obtained from four patients identified here as 'a', 'b', 'c' and 'd'. Relevant clinical details and basic statistics are given in Table 4. Patients 4(a) and 4(b) show a closely similar pattern of CHR despite the difference in gender, wide difference in age and different diagnosis. In each case, the waking state shows recurrent episodes of abrupt rate elevation to around 140 bpm. Both individuals were involuntary patients under close nursing observation throughout the day and there was no suggestion that these episodes of rate elevation were related to activity. 4(a) and 4(c), as well as 4(b) and 4(d), show distinctly different patterns of CHR despite the same gender, similar age and same diagnosis. By far the majority of patients with a diagnosis of schizophrenia and schizoaffective disorder show patterns respectively like 4(c) and 4(d), but as illustrated by 4(a) and 4(b), in some cases there may be significant variation in the pathophysiology
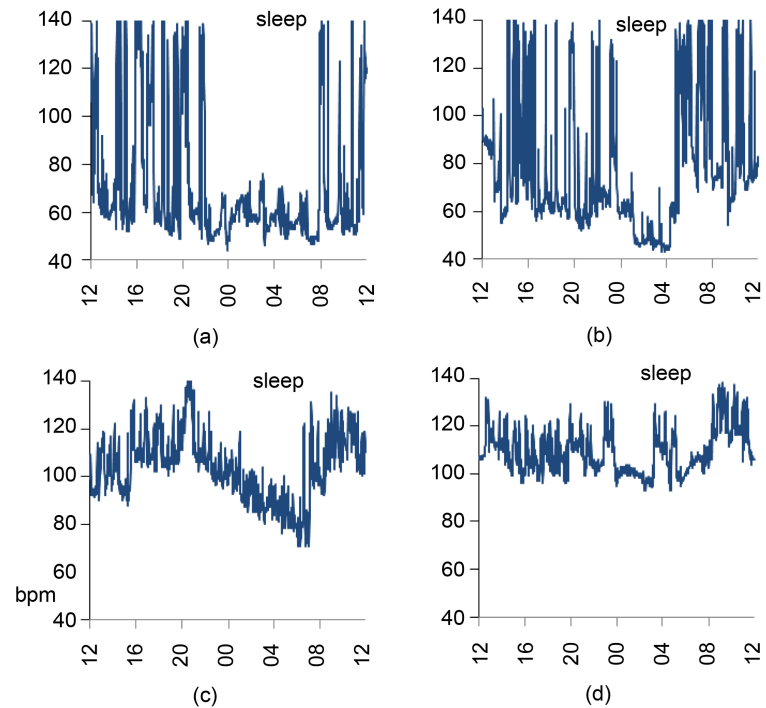
indicated by CHR.

Figure 4. Same diagnosis different changes in CHR: different diagnosis similar changes in CHR.

Table 4. Diagnoses, medication and basic statistics for data plotted in Figure 4.

Figure	Clinical Diagnosis	Medication (daily dose)	age	gender	Awake (bpm)		Sleep (bpm)	
					$\bar{x}$	σ	$\bar{x}$	σ
4(a)	Paranoid Schizophrenia	olanzapine 15 mg quetiapine 300 mg	23	M	81	31.4	57	9.3
4(b)	Schizoaffective Disorder	olanzapine 10 mg valproate 1500 mg	53	F	82	26.0	47	3.2
4(c)	Paranoid Schizophrenia	olanzapine 15 mg	27	M	110	11.2	91	10.4
4(d)	Schizoaffective Disorder	olanzapine 15 mg quetiapine 500 mg lorazepam 3 mg	49	F	102	8.5	94	6.8

5.4. State vs Trait Changes in Personality Disorder

DSM Axis II Personality Disorders, especially Borderline Personality Disorder (BPD) show persisting deviations in CHR along with superimposed state changes during acute crises. The superimposed state changes usually abate with treatment but the underlying trait deviation persists. Examples of this are shown below in Figure 5.
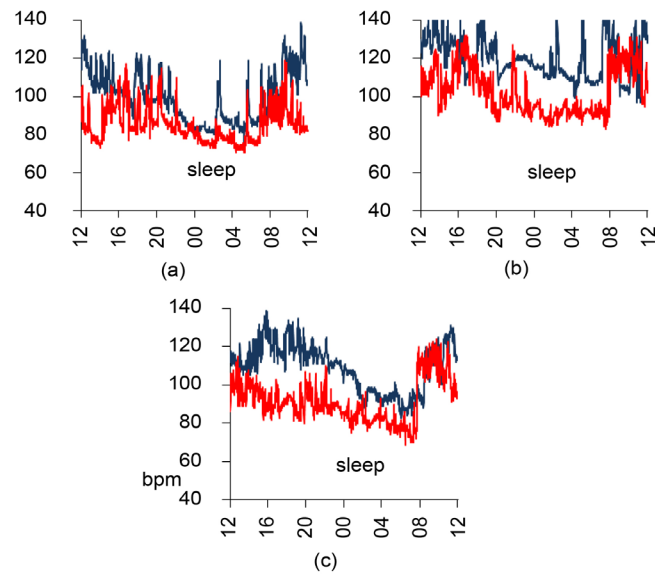
Figure 5. State vs trait changes in CHR.

Table 5. Comparison of basic statistics at time of admission and discharge for data plotted in Figure 5.

Figure	Time of HR Recording	Medication (daily dose)	age	Awake (bpm)		Sleep (bpm)	
				$\bar{x}$	σ	$\bar{x}$	σ
5(a)	Admission	quetiapine 500 mg	28	108	9.7	89	8.8
	Discharge	lorazepam 3 mg		88	6.6	78	4.1
5(b)	Admission	olanzapine 15 mg valproate 1500 mg sertraline 100 mg	32	124	11.6	108	11.1
	Discharge			108	7.2	92	3.2
5(c)	Admission	olanzapine 10 mg quetiapine 300 mg valproate 750 mg	34	117	7.6	96	6.5
	Discharge			95	8.4	81	4.6

Figure 5 data were obtained from three females identified here as 'a', 'b' and 'c'. Each had a well-established diagnosis of BPD, with a history of recurrent admissions for self-harm, overdose, and in the case of 5(b) and 5(c), transient psychotic symptoms of derogatory auditory hallucinations. Blue plots are of data obtained at the time of admission, red plots of data at the time of discharge. A comparison of basic statistics at admission and discharge is given in Table 5. It can be seen that awake and sleep rates lessened substantially in each case but remained abnormally elevated, severely so in the case of 5(b). The sleep rate-architecture at the time of admission is abnormal in each case, severely so in 5(b) and 5(c). It improved a little in 5(b) but remained much the same in 5(a) and 5(c).

5.5. Normalisation of CHR

Serial recordings of CHR from patients undergoing treatment may show no

change, worsening, improvement or normalisation and provide objective indications of the effectiveness of treatment because of the state-dependent relationship between CHR and psychiatric status. All three serial recordings in Figure 5 show relative improvement or worsening depending on whether the time reference is admission or discharge. The serial data from healthy individuals in Figure 2 show 'no change'. Clinical improvement is always associated with a shift towards a typically normal pattern even if only a partial shift in that direction as shown in each of the three examples in Figure 5. Improvement in the circadian pattern can be described as 'normalisation' the more it approximates to the normal patterns shown in Figure 2. Clinical improvement is never associated with greater deviation in the rate magnitude and/or circadian rate architecture. Examples of normalisation are shown below in Figure 6.
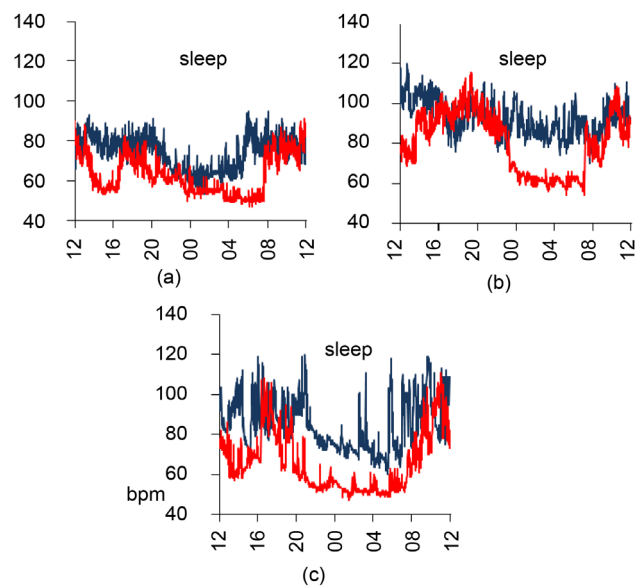

Figure 6. Examples of normalisation of CHR.

Table 6. Comparison of basic statistics at time of admission and discharge for data plotted in Figure 6.

Figure	Clinical Diagnosis	Medication (daily dose)	age	gender	Time of recording	Awake (bpm)		Sleep (bpm)	
						$\overline{x}$	σ	$\overline{x}$	σ
6(a)	Major Depression	sertraline 100 mg temazepam 20 mg	42	F	admission	79	5.1	64	4.4
					discharge	68	8.6	53	3.0
6(b)	Drug-induced Psychosis	olanzapine 15 mg	24	M	admission	95	8.4	87	6.4
					discharge	89	10.0	62	3.1
6(c)	Acute Stress Reaction	quetiapine 300 mg	27	M	admission	91	10.1	75	8.1
					discharge	75	13.0	53	2.5

Figure 6 data were obtained from three patients identified here as 'a', 'b' and 'c', Blue plots are of data at the time of admission, red plots of data at the time of

discharge. Table 6 is a summary of clinically relevant information. The serial improvement in each case can be described as 'normalisation' even though there is some variation in the extent to which the serial improvement approximates to the signature normal patterns in Figure 1. The improvement in sleep rates and sleep rate architecture is particularly relevant. Evidence of this degree of normalisation is reliable evidence of clinical improvement.

5.6. Clinical Correlates of Variation in Rate Magnitude and Rate Architecture

Rate magnitude and rate architecture can vary independently [28]. The same 24-hour mean may reveal a distinctly different rate architecture, particularly during sleep, and the same circadian rate architecture can persist over a wide scalar offset, as illustrated below in Figure 7.
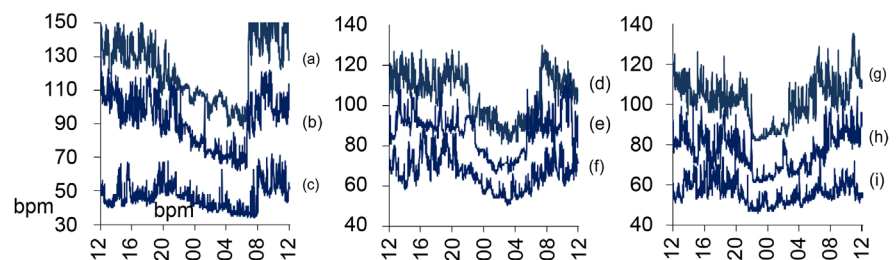

Figure 7. Examples of variation in rate magnitude and rate architecture.

Table 7. Diagnoses corresponding to data plotted in Figure 7.

	Clinical Diagnosis		Clinical Diagnosis		Clinical Diagnosis
7(a)	Schizophreniform Disorder	7(d)	Schizoaffective Disorder	7(g)	Psychotic Depression
7(b)	Generalized Anxiety Disorder	7(e)	Mixed Anxiety/Depression	7(h)	Melancholic Depression
7(c)	Adjustment Disorder	7(f)	Major Depression	7(i)	Dysthymia

Figure 7 data were obtained from 9 individuals identified here with lower case letters from 'a' to 'i'. Corresponding clinical diagnoses are given in Table 7. The three plots on the left [7(a), 7(b), 7(c)] show a similar down-ramp pattern during sleep, the three plots on the right [7(g), 7(h), 7(i)] a similar up-ramp pattern and the three plots in the middle [7(d), 7(e), 7(f)] a mix of down- and up-ramp pattern. Figure 7 shows that a closely similar rate architecture, particularly during sleep, can persist over a wide range of scalar offset and that clinical diagnoses vary with both the circadian rate architecture and scalar offset, as indicated by the diagnoses listed in Table 7. The scalar threshold for transition from non-psychotic to psychotic disorders can vary between individuals and whilst the down-ramp pattern remains associated with broadly defined 'anxiety' (generalized, not phobic or panic disorder) and the up-ramp pattern with broadly defined 'depression' (with melancholic features), clinical diagnoses can overlap

on both down-ramp, up-ramp and mixed patterns. For example, Figure 7(b) may be associated with clinical diagnoses of 'Generalized Anxiety Disorder', 'Obsessive Compulsive Disorder', 'Post-traumatic Stress Disorder' or 'Acute Stress Reaction': Figure 7(f) with 'major depressive disorder', 'dysthymia' or 'adjustment disorder with depressed mood'.

6. Discussion

The clinical heterogeneity and etiological complexity of psychiatric disorders makes the search for diagnostic biomarkers a daunting task. This applies particularly to hypothesized genetic markers. Genetic studies may demonstrate trait vulnerability for mental illness but are unlikely to provide clinically useful diagnostic information because of the number of genes involved [31] and the unpredictable epigenetic effects on their expression [32]. State markers, especially a battery of state markers, are more likely to provide clinically useful information that may also amount to diagnostic information, as suggested by changes in CHR. Dimensions of independent variation in CHR [28] effectively constitute a battery of state markers. Variation in these different dimensions of activity can give rise to distinctly different changes in CHR that suggest discriminatory differences at a physiological level.

The ANS plays a key role in the regulation of heart rate and evidence of abnormalities in CHR, especially during sleep, is evidence of abnormalities in ANS regulation, all other things being equal. The state-dependent nature of the relationship between CHR and psychiatric status suggests that changes in ANS regulation, as revealed in CHR, are an integral part of, or perhaps constitute, the biological changes of mental illness. Clinically relevant changes in CHR are deviations from a typically normal pattern and in broad terms, the greater the deviation in rate magnitude and/or rate-architecture, the greater the clinical significance. Deviations in CHR are not confined to diagnosed mental illness and this situation is analogous to what is found in hypertension. Many people in the community are living with undiagnosed hypertension [33]. Similarly, many individuals in the community will show deviations in CHR without having been diagnosed as mentally ill. The clinical consequences will depend in large part on the severity and duration of the deviation and this is generally the case with all dimensional bodily variation, be it weight, temperature, blood pressure or CHR.

Circadian heart rate qualifies as a biomarker primarily because of its state-dependent variation. Normalisation of CHR with clinical improvement is like normalisation of circadian temperature with recovery from an infection. It is diagnostically non-specific but provides clinically useful information. The biomarker information in CHR is suggested by findings that broadly different disorders are associated with distinctly different changes in CHR, as shown in Figure 3, Figure 4 and Figure 7. Unfortunately, CHR does not reliably predict specific symptoms or specific classified diagnoses. Similar changes in CHR may be associated with different clinical diagnoses and similar clinical manifestations

may be associated with different changes in CHR, as shown in Figure 4. Such imperfect correlation is not surprising given that symptoms may vary widely between individuals given the same clinical diagnosis and that the presentation of psychiatric disorders can vary considerably. For example, 'depression' can present as somatisation [34], 'depression without sadness' [35], conversion disorder [36], and in other culturally diverse ways [37] [38]. It may be that biomarkers can group such diverse presentations under the same diagnostic rubric if they involve similar biological changes, but if found, one would not expect markers of the biological changes to reliably predict the variations in clinical presentation.

Changes in CHR involve at least two broadly different dimensions of independent variation, namely, rate magnitude and rate architecture. The distinctive and unmistakably different down- and up-ramp variations in sleep rate architecture that are respectively associated with 'anxiety' and 'depression', suggest categorically different biological states. However, given the key role played by the ANS in the regulation of heart rate, these mirror-opposite patterns may merely reflect variation in relative SNS and PNS dominance or dysregulation, with dominance of SNS activity in the down-ramp pattern and initial dominance of the PNS in the up-ramp pattern. This conclusion is supported by evidence of 'mixed' patterns, shown in Figure 7, that are often associated with a clinical diagnosis of 'mixed' affective disturbance. However, variations in CHR are not confined to down-ramp and up-ramp. Entirely different changes, such as plots (a) and (b) in Figure 4, whilst also a manifestation of SNS/PNS dynamics, do suggest categorically different pathophysiology. Unlike biomarkers such as C-reactive protein, which vary only quantitatively, the changes in CHR reveal multidimensional and unmistakably different deviations from normal and since these deviations are state-dependent, they are an indication of diagnostic discrimination at a physiological level even if the clinical manifestations or clinical diagnoses are not fully predictable. Discrimination at a physiological level may be more relevant clinically because of its relative objectivity, potential relevance to pharmacotherapy, evaluation of a patient's response to treatment and understanding the different pathophysiological pathways involved.

The persistence of distinctive rate architecture patterns over a wide scalar range as shown in Figure 7, is interesting from a biomarker and theoretical perspective, in that it suggests the patterns are a manifestation of stable physiological or dys-regulatory states. This idea is supported by the fact that scalar shifts of much the same circadian pattern are evident not only between individuals, but also serially within individuals [28]. What is of interest from a biomarker perspective, is that a scalar increase may initially merely signal an increase in severity, but then progressively involve a change in clinical manifestations. For example, a scalar increase of a down-ramp pattern may initially signal more severe anxiety, but with further increases, signal psychotic symptoms. Evidence of such major variation in clinical manifestations with what seems like purely quantita-

tive variation in rate magnitude, leaves a question mark over any hoped-for biomarker specificity, since the threshold for the emergence of psychotic symptoms can vary between individuals.

Deviations in CHR are also found in Personality Disorders. Severe deviations can be found in DSM-5 'cluster B' disorders, particularly BPD, as shown in Figure 5. Such 'trait' changes persist and remain when superimposed 'state' changes have abated just as symptoms of a Personality Disorder remain after superimposed state disorders have abated. From this perspective, CHR reveals a cross-sectional and serial or longitudinal perspective. Cross-sectional changes may reflect purely state changes or a combination of state and underlying trait or personality-related changes. Purely state changes are suggested when there is a reversion to a typically normal pattern with clinical recovery, as illustrated in Figure 6. Persisting deviations may reflect chronic state changes, personality disorder trait changes, or a combination of trait and chronic state changes.

Circadian heart rate data suggest that the biological underpinnings of mental illness are dynamic and on a continuum from fully reversible, to persisting, seemingly irreversible changes, as evident for example, in chronic schizophrenia. From this perspective, changes in CHR are not unlike changes in blood pressure that can also vary from transient, reversible elevations to persisting elevations in hypertensive disease.

7. Conclusion

Circadian heart rate qualifies as a biomarker of mental illness because of its demonstrable state-dependent relationship with psychiatric status and persisting changes in personality disorders. However, CHR does not specify classified disorders reliably because whilst there are distinctly different 'deviations' in CHR between broadly different disorders, each of these different deviations may be associated with more than one classified disorder. This situation is likely to apply to all candidate biomarkers since many clinically classified disorders are probably not separated by natural boundaries. Serial recordings of CHR suggest that the biology of mental illness is not a static 'lesion', but a dynamic disturbance with variable outcomes ranging from fully reversible to varying degrees of persisting abnormality. Although not a reliable indication of clinical diagnoses, CHR provides objective physiological adjunct information which can be used in clinical assessment and in the evaluation of treatment. Also, distinctly different changes in CHR amount to discrimination at a physiological level and this information is potentially relevant from a clinical and theoretical perspective.

Limitations

Questions about normal variation in heart rate and rate architecture, particularly with respect to sleep-related changes, have not been addressed in detail. Our reference for 'deviation' in the magnitude of heart rate, is published normative data [29] [30], despite continuing debate about normal limits [39] and concern about

study shortcomings. Specifically, normative studies do not appear to have controlled for undiagnosed psychiatric disorders and this would challenge the assumption of normally distributed heart rate in the general population and add support to the idea of mixed distributions as suggested by Palatini [39]. We have given examples of signature normal circadian patterns and normalisation of rate architecture but have not addressed questions about normal variation in this regard. Very little research has addressed circadian rate architecture, particularly sleep-related changes. There are reports of nocturnal 'dipping' and 'non-dipping' heart rate [40] [41] but no detailed consideration has been given to the wide variation in sleep rate architecture, such as the mirror-opposite and 'mixed' patterns shown in Figure 7, or variation in the sleep-wake rate difference, where in some instances, sleep rates may be higher than awake rates. Accepting that more robust definitions of normal variation in rate and rate architecture are needed, existing shortcomings in this regard do not detract from the biomarker status of CHR, which is based on its demonstrable state-dependent relationship with psychiatric status. A similar argument applies to uncertainty as to whether ANS dysregulation, as signalled by CHR, is a primary or secondary, 'downstream' manifestation. The biomarker status of CHR would remain either way.

The only psychotropic drugs relevant to presented data were sertraline, olanzapine, quetiapine, valproate and lorazepam. These drugs do not affect HR or HRV to any significant extent [17] [24] [42] and could not in any event account for the demonstrated variations in CHR because the same medications were taken by individuals showing distinctly different patterns (see Figure 4).

Conflicts of Interest

SB Dimmitt has no conflict of interest.

HG Stampfer is currently conducting an ethics approved study on the usefulness of CHR for monitoring the response to antidepressant medication in the treatment of depression and/or anxiety. Funding for this study was provided by Medibio, a biotech company interested in developing the CHR technology.

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