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Heart rate variability and treatment outcome in major depression: A pilot study



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ABSTRACT

Variations in heart rate variability (HRV) have been associated with major depressive disorder (MDD), but the relationship of baseline HRV to treatment outcome in MDD is unclear. We conducted a pilot study to examine associations between resting baseline HRV and MDD treatment outcome. We retrospectively tested several parameters of HRV in an MDD treatment study with escitalopram (ESC, $N = 26$) to generate a model of how baseline HRV related to treatment outcome, and cross-validated the model in a separate trial of MDD treatment with Iyengar yoga (IY, $N = 16$). Lower relative power of very low frequency (rVLF) HRV at baseline predicted improvement in depressive symptoms when adjusted for age and gender ($R^2 > .43$ and $p < 0.05$ for both trials). Although vagal parasympathetic measures were correlated with antidepressant treatment outcome, their predictive power was not significant after adjusting for age and gender. In conclusion, baseline resting rVLF was associated with depression treatment outcome in two independent MDD treatment studies. These results should be interpreted with caution due to limited sample size, but a strength of this study is its validation of the rVLF predictor in an independent sample. rVLF merits prospective confirmation as a candidate biomarker.

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1. Introduction

Major depressive disorder (MDD) is characterized by affective symptoms such as negative mood, anhedonia, and reduced interest, as well as by disturbances in biological rhythms that impact sleep, energy, and appetite (American Psychiatric Association, 2000). Perturbations in biological rhythms in MDD may reflect alterations in autonomic nervous system function. For example, increases in catecholamine levels found in depressed subjects (Veith et al., 1994) may (1) cause shunting

of blood away from the gastrointestinal tract, which might reduce appetite, and (2) may cause papillary dilatation resulting in increased light entry into the retina, which may contribute to insomnia. There are often reductions in both non-verbal and verbal emotional expression in depression, and these may also be related to changes in autonomic function. For example, facial blushing during states of anxiety or excitement is mediated by the sympathetic nervous system, and pharyngeal function which subserves verbal expression is impaired with reduction in vagal output (Porges, 1995; Rottenberg, 2007). One validated measure of autonomic function is heart rate variability (HRV), which refers to the variation in the intervals between heartbeats (Task Force Report, 1996).

1.1. HRV and depression

Reductions in the time domain of 24-hour and resting HRV have been associated with both the presence (Brunoni et al., 2013; Carney et al., 1995; Imaoka et al., 1985; Kemp et al., 2010) and severity of MDD (Agelink et al., 2002; Kemp et al., 2010), although studies in some populations have not demonstrated these effects (Gehi et al.,

Abbreviations: a (prefix), absolute; ACE-I, angiotensin converting enzyme inhibitor; ECG, electrocardiogram; ESC, escitalopram; HAM-D, Hamilton Depression Rating Scale; HF, high frequency; HRV, heart rate variability; IY, Iyengar yoga; LF, low frequency; r (prefix), relative; MDD, major depressive disorder; QIDS-C, Quick Inventory of Depressive Symptoms – Clinician Rated; VLF, very low frequency.

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2005; Licht et al., 2010). These reductions are consistent with stereotyped autonomic nervous system output in depression, and might signal a reduction in other facets of adaptive functioning in depression. In the frequency domain, HRV has been subdivided into high frequency (HF, 0.15 to 0.4 Hz), low frequency (LF, 0.04 to 0.15 Hz), and very low frequency (VLF, 0.0033 to 0.04 Hz) components (Task Force Report, 1996).

HF-HRV is a measure of vagal parasympathetic activity (Akselrod et al., 1981; Task Force Report, 1996). Lower HF-HRV have been associated with MDD in several studies (Davydov et al., 2007; Rechlin et al., 1994) and two meta-analyses (Kemp et al., 2010; Rottenberg, 2007). In contrast, LF-HRV is thought to reflect a mixture of both sympathetic and parasympathetic activity (Billman, 2013; Task Force Report, 1996). Although absolute LF-HRV has not been consistently associated with depression symptoms (Kemp et al., 2010), its relative power was found to be higher in MDD patients compared to healthy controls (Davydov et al., 2007).

The physiological underpinning of VLF is unclear, but biological rhythms operating within the same frequency range that have been correlated with VLF include thermoregulatory mechanisms (Lindqvist et al., 1990), peripheral vascular tone fluctuations (Hyndman, 1974), renin activity (Taylor et al., 1998), and leptin secretion (Takabatake et al., 2001). A mechanistic relationship to depression has not been conclusively demonstrated for VLF; however, disturbances in regulation of biological rhythms in the VLF frequency range including energy metabolism might contribute to the fatigue observed in depression. Alterations in regulation of blood flow indicated by changes in VLF could adversely affect functions of the peripheral or central nervous system that contribute to emotional well-being.

Reductions in VLF have been found shortly after a myocardial infarction in those patients suffering from depression in comparison with those without depression (Carney et al., 2001), but not in depressed patients with stable coronary heart disease (Gehi et al., 2005). VLF may predict mortality in patients with MDD and comorbid cardiovascular conditions (Carney et al., 2005), as well as all cause mortality in subjects with cardiovascular risk factors who are not depressed (Bigger et al., 1992). VLF alterations have also been observed in non-hypertensive depressed patients relative to control subjects without depression (Yeragani et al., 2002). Moreover, in contrast to other bands of HRV, higher relative power of VLF significantly corresponded to lower baroreflex sensitivity coupled with lower gain of its efferent component regulating cardiac rhythm, and this cardiovascular pattern was associated with higher depression severity in depressed patients (Davydov et al., 2007).

1.2. Depression treatment and HRV

Treatment of depression with medication, exercise, or neurostimulation methods has been associated with treatment specific changes in HRV. Whereas there is consensus that tricyclic antidepressant medication reduces HRV (Kemp et al., 2010; Licht et al., 2010), whether SSRI medication alters HRV is controversial. While a large longitudinal cohort study found that SSRI medication decreased HRV (Licht et al., 2010), a meta-analysis of MDD treatment trials found no such change (Kemp et al., 2010). Exercise has been shown to increase time-domain HRV in depressed patients with cardiovascular disease (Blumenthal et al., 2012). Correlations have been found between response to antidepressant medication treatment and HRV time domain increases (Balogh et al., 1993) or stability relative to non-responders (Khaykin et al., 1998). Correlations have also been found between antidepressant response and LF-HRV stability (Glassman et al., 2007). While transcranial magnetic stimulation may increase time domain measures of HRV and HF-HRV (Udupa et al., 2007), electroconvulsive therapy has been shown to decrease HF-HRV (Schultz et al., 1997), and transcranial direct current stimulation has not been found to result in any change in either time-domain or HF-HRV (Brunoni et al., 2013).

Baseline HRV parameters have previously been associated with change in depressive symptoms during subsequent treatment. Fraguas et al. (2007) found that baseline changes in HRV (within the LF frequency band and LF/HF ratio) in response to the presentation of emotional stimuli were associated with reduction in MDD symptoms with subsequent fluoxetine treatment. Previously, we found that subjects with MDD who achieved remission during yoga treatment evidenced differences in HRV parameters at baseline as compared to non-remitters, notably higher HF-HRV and lower LF-HRV (Shapiro et al., 2007). However, the VLF frequency band was not assessed. The purpose of the present study was to determine whether resting baseline HRV measures, which have been associated with the severity and prognoses of MDD, were associated with improvement from an acute episode of MDD in two independent samples undergoing different methods of treatment.

2. Materials and methods

2.1. Trials

Data were drawn initially from a treatment trial of escitalopram for MDD that was conducted in the UCLA Laboratory of Brain, Behavior, and Pharmacology (principal investigator IAC), and used to generate a model of how resting heart rate variability related to depression treatment outcome. Subsequent validation of the model was performed with data obtained from a trial of Iyengar Yoga for MDD that was conducted in the UCLA Psychophysiology Laboratory (principal investigator DS). Subjects in both trials underwent diagnostic evaluation with the MINI (Sheehan et al., 1998) and met DSM-IV criteria for MDD (ICD-9 codes 296.2 or 296.3). Severity of depressive symptoms was assessed with either the Quick Inventory of Depressive Symptoms – Clinician Rated (QIDS-C; Rush et al., 2003) or the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Diagnosis of depressive and other psychiatric disorders were made by research staff with at least 15 years of experience working with research level diagnostic assessments and who have been trained to high inter-rater reliability using the MINI. Electrocardiograms (ECGs) were recorded at baseline.

The first study, which was used to generate the model of how resting heart rate variability related to depression treatment outcome, was a 12-week open-label trial of escitalopram (ESC) for patients (N = 30) meeting DSM-IV diagnostic criteria for MDD; no subjects had taken any antidepressant medications for at least ten days prior to entry into the study. Exclusion criteria for the ESC study included history of psychosis or other primary psychiatric disorder, bipolar disorder, active substance abuse, pregnancy or breast-feeding, or unstable general medical condition precluding active participation in a research trial.

The second trial, which was used to cross validate the model, utilized Iyengar yoga (IY) as augmentation therapy for patients (N = 17) with MDD in partial remission (HAM-D score of 7–18) who were taking antidepressant medications at the time of entry into the trial (Shapiro et al., 2007). Subjects participated in three yoga sessions per week for 8 weeks. Exclusion criteria for the IY study included Axis I diagnoses of bipolar disorders, delirium or dementia, schizophrenia or other psychotic disorders, or current substance-related or eating disorders, general medical illness precluding safe participation in yoga, and suicidality.

2.2. Sample

To avoid confounding effects, subjects who were taking anti-hypertensive medications (3 in ESC sample and 1 in IY sample), or had coronary heart disease (1 in ESC sample) were excluded from our HRV analyses. Thus, 26 subjects were utilized for the analysis in the ESC sample, and 16 in the IY sample (Table 1).

Table 1
Demographic and clinical variables by study.

	ESC (N = 26)	IY (N = 16)
Age	41.9 ± 14.0	46.1 ± 12.5
Ethnicity		
Caucasian	65%	81%
Asian	4%	13%
Black	4%	0%
Hispanic	4%	6%
Unknown	23%	0%
Gender (F)	58%	62%
N prior episodes	2.4 ± 1.2	3.0 ± 1.4
Smoking	28%	13%
HAM-D base	n/a	12.9 ± 3.3
HAM-D end	n/a	5.9 ± 4.5
QIDS-C base	13.6 ± 3.0	n/a
QIDS-C end	5.4 ± 4.0	n/a

end = end of study, ESC = escitalopram group, IY = Iyengar yoga, N = number, base = baseline, HAM-D = 17-Item Hamilton Depression Rating Scale, QIDS-C = Quick Inventory of Depressive Symptoms Clinician Rated.

2.3. Assessment instruments

Demographic and clinical measures included age, gender, ethnicity, smoking, and number of prior depressive episodes. The primary outcome measure in the ESC study was the QIDS-C. The primary outcome measure in the IY study was the HAM-D. The QIDS-C and HAM-D depression rating scales are commonly used and known to be very highly correlated, with 92.5% agreement for identifying treatment response (Rush et al., 2006).

2.4. Physiological recordings

Electrocardiogram (ECG) was recorded at 1000 Hz with participants resting quietly, without any other activity, and instructions only to remain awake. ECG recordings from the ESC study were obtained with a 16-bit resolution Neurodata QND system (Neurodata, Inc.; Pasadena, CA) during simultaneous electroencephalography recordings, with a dedicated electrode applied to the middle of the left subclavicular region at the second intercostal space; while ECG recordings from the IY study were obtained with AcqKnowledge MP100 (Biopac Systems, Inc., Santa Barbara, CA). During recordings, participants were supine in the ESC study, and seated in the IY study. Recording length was 5 min in the ESC study and 20 min in the IY study.

Recordings were visually inspected, and only the maximum artifact-free, premature ventricular contraction-free data segments were utilized for further analysis, yielding a mean of 268 ± 68 s (4.5 ± 1.0 min) usable data per subject in the ESC sample, and 1191 ± 22 s (19.9 ± 0.3 min) in the IY sample. A post hoc analysis was performed with the IY data on the first 268 s of recording per subject, to determine the correlation of this shorter epoch with the longer (19.9 min) epoch.

2.5. Heart rate variability calculations

R-wave detection, and HRV parameter calculations, were performed utilizing Kubios HRV Version 2.0 (Niskanen et al., 2004). An exploratory analysis utilizing nine baseline parameters of heart rate variability was performed in the ESC trial. These included the square root of the mean successive differences between R-R intervals (RMSSD); standard deviation of normal to normal intervals (SDNN), absolute and relative power in low frequency (aLF and rLF, 0.04 to 0.15 Hz) and high frequency (aHF and rHF, 0.15 to 0.4 Hz) bands; LF/HF ratio; and absolute and relative power in the very low frequency band (aVLF and rVLF, 0.0033 to 0.04 Hz) according to the Task Force Guidelines (Task Force Report, 1996). Absolute power was calculated (in ms²) utilizing the autoregression spectrum, with model order 16, as previously recommended (Niskanen et al., 2004). Relative power was calculated as follows: rVLF [%] = VLF [ms²] / total power [ms²] × 100%, rLF [%] = LF

[ms²] / total power [ms²] × 100%, rHF [%] = HF [ms²] / total power [ms²] × 100%. The LF/HF ratio was computed as the ratio between aLF and aHF band power.

2.6. Data analysis

The data were analyzed utilizing SPSS 21. Descriptive statistics were performed on demographic variables utilizing independent samples t-tests (two tailed) for continuous variables, and Chi-square tests for categorical variables.

Analysis of the association of HRV with depression severity and treatment outcome was conducted in a two-step process to minimize the risk of false positives associated with retrospective exploratory analyses (Ioannidis, 2005; Simmons et al., 2011).

In the first step, data from the ESC trial were analyzed to generate a model of how resting baseline HRV related to depression symptoms and treatment outcome. Linear regression was utilized to examine baseline depression severity and absolute symptomatic change as predictors of HRV within *a priori* models that included age and gender as covariates because both age and gender have been associated with variations in HRV (Antelmi et al., 2004; Liao et al., 1995; Umetani et al., 1998). Separate models were examined for each of the nine HRV parameters. Bonferroni testing was performed in this step, and only results in which the model reached $p < 0.006$ (.05/9) were considered statistically significant.

In order to confirm the results and reduce the risk of false positives, cross-validation was subsequently performed in a second step utilizing an independent, non-overlapping, sample of subjects with MDD from the IY study. Significant HRV measures only were tested in this second step in order to limit the number of comparisons. Linear regression was performed as described above.

As a final step, unadjusted Pearson correlations among study variables were performed to help explicate our results.

3. Results

3.1. Descriptive statistics

In both studies, our sample consisted predominantly of non-smoking Caucasian females in their 40s with recurrent depression (Table 1). Depression symptoms were of mild to moderate severity at baseline, and improved to no to low depressive symptoms by study end.¹

3.2. HRV associations with depression severity

We found no evidence for age- or gender-controlled associations of RMSSD, SDNN, aHF, rHF, aLF, rLF, aVLF, rVLF, and LF/HF ratio with baseline depression severity measures in the ESC or IY trials ($p > 0.15$ for all comparisons).

3.3. HRV predictors of change in depressive symptoms: exploratory analysis

Of the nine HRV parameters assessed in the ESC study, we found evidence only for one statistically significant predictor of change in depressive symptoms after adjusting for age and gender: rVLF. The overall model utilizing rVLF significantly predicted change in depressive symptoms on the QIDS-C ($R^2 = 0.44$, $p < 0.005$, Fig. 1A). Predictors within the model included rVLF ($\beta = 0.130$, $p < 0.036$) and age ($\beta = 0.159$, $p < 0.009$), but not gender ($\beta = -3.126$, $p < 0.074$). Lower baseline rVLF predicted reduction in depressive symptom severity. rVLF was significantly higher in males ($t = 2.6$, $p = 0.01$), but we did not find

¹ Dichotomous response to treatment ($\geq 50\%$ change in depressive symptoms from baseline) was 81% in the ESC study and 63% in the IY study.

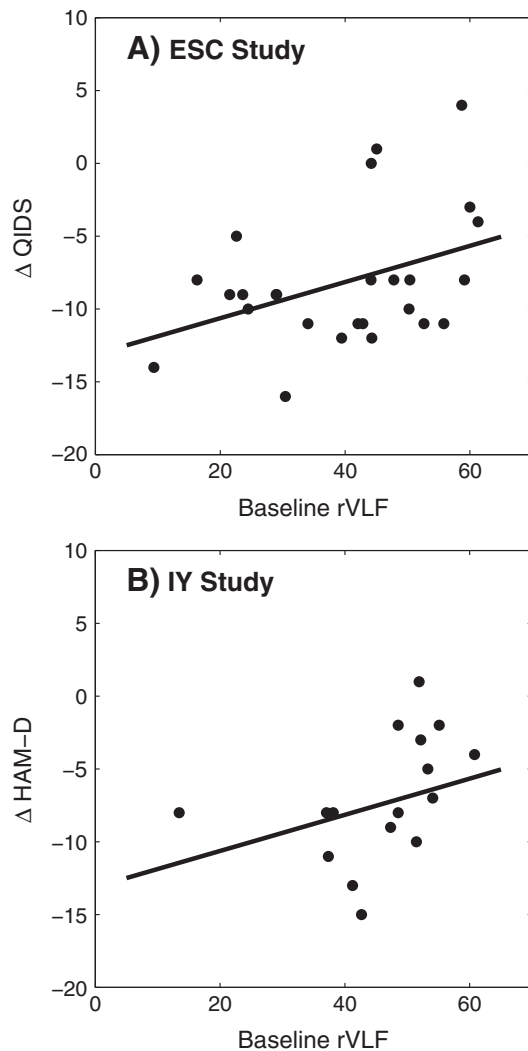


Fig. 1. Correlation of rVLF with change in depression symptoms. a) ESC Study, b) IY Study, rVLF = relative very low frequency power, ESC = escitalopram, IY = Iyengar Yoga, QIDS = Quick Inventory of Depressive Symptoms Clinician Rated, HAM-D = 17-Item Hamilton Depression Rating Scale.

evidence for a correlation with age, baseline QIDS-C score, number of prior episodes, or smoking ($p > 0.10$ for remaining bivariate correlations).

3.4. Cross-validation of rVLF in the IY sample

In the IY sample, rVLF was similarly associated with change in depressive symptoms. The overall model with rVLF adjusting for age and gender significantly predicted change in depressive symptoms on the HAM-D ($R^2 = 0.49$, $p < 0.037$, Fig. 1B). Within the model, statistically significant predictors included rVLF ($\beta = .18$, $p < .047$) and gender ($\beta = -4.7$, $p < 0.020$), but not age ($\beta = .05$, $p < 0.492$). We found no evidence for a correlation of rVLF with age, gender, baseline HAM-D score, number of prior episodes, or smoking ($p > 0.35$ for all bivariate correlations).

3.5. Post-hoc analysis of correlation between recording lengths

In order to examine the comparability of different recording lengths across the two studies, we additionally calculated rVLF from the first 268 s of recordings in the IY sample (the same recording length as the mean of the ESC sample). rVLF derived from these shorter recordings correlated with rVLF derived from the longer (19.9 min) IY recordings

(Pearson $r = 0.79$, $p = 0.0003$). Similar to the longer recordings, rVLF derived from the shorter recordings in the IY sample correlated with absolute change in depressive symptoms when adjusted for age and gender ($\beta = .599$, $p = 0.01$).

3.6. Unadjusted correlations among study variables

As a final step, we examined the unadjusted correlations among study variables in order to assist with the interpretation of our results (Table 2). Correlation among HRV variables was higher with the longer recording time in the IY study; however, only rVLF was consistently strongly associated with a change in depression symptoms. Vagal parasympathetic measures, including aHF and SDNN, were also highly correlated with depression symptom change in the ESC study, as was age. Also in the ESC study, gender was strongly correlated both with rVLF and rHF. In the IY study, change in symptoms was inversely associated with number of prior episodes and gender, but these variables were not strongly associated with HRV variables.

4. Discussion

These pilot analyses suggest that resting baseline cardiovascular biorhythms may be stably associated with response to antidepressant treatments. Relative power within the VLF band predicted change in depression symptoms. While rVLF was found to have a strong and consistent relationship to treatment outcome in this investigation, it is unclear whether lower rVLF may represent a stable trait marker of good prognosis, or a state marker that indicates a phase of depressive illness in which a patient is more likely to respond to treatment. Because of a lack of control groups in both studies, whether rVLF predicted response to specific or non-specific (placebo) elements of MDD treatment was uncertain.

In contrast to previous studies, HF and LF absolute power, as well as their ratio, were not significantly associated with depression severity or treatment outcome in these samples, which might be a Type II error due to our modest sample sizes and limited power. Although unadjusted correlations in the ESC suggested that measures of vagal parasympathetic outflow including aHF and SDNN were associated with treatment outcome, these were also highly correlated with age, and adjusting for the effects of age lowered their predictive power. Our results are consistent with those of Glassman et al. (2007), who also did not find a significant correlation between absolute measures of VLF power and antidepressant response; however, that study did not report on relative measures of VLF. Because we measured HRV at rest, our findings are not directly comparable to those of Fraguas et al. (2007), who demonstrated an association between HF and LF/HF ratio and depression symptom reduction in the context of an emotional challenge paradigm. Nevertheless, our present results expand the evidence base suggesting that baseline cardiovascular biorhythms may be associated with depression symptom change.

A strength of our study design was its two-step approach: model generation from exploratory analyses in the ESC study, followed by cross-validation in the IY study. An important problem in retrospective, exploratory analyses concerns the generation of false positive results (Ioannidis, 2005; Simmons et al., 2011). Because analyses often involve multiple “researcher degrees of freedom”, the rate of false positive findings at the 5% level is “necessarily greater than 5%” (Simmons et al., 2011). For these reasons, we designed our study not only to meet conventional standards of significance at the 5% level, but also to cross-validate our findings in an independent sample. Despite the small sample size in each study, our two-step approach yielded greater external validity of our results than a retrospective analysis alone, and also identified a predictor that explained a large proportion of the variance.

Table 2
Pearson correlation (r) of heart rate variability parameters with study variables in A) escitalopram study and B) Iyengar yoga study.

A. ESC Study	Age	Gender	N episodes	Ethnicity	Smoking	QIDS pre	Change	RMSSD	SDNN	aVLF	rVLF	aLF	rLF	aHF	rHF	LF/HF
Age	1.00															
Gender	0.22	1.00														
N episodes	-0.02	-0.43	1.00													
Ethnicity	0.35	0.33	-0.12	1.00												
Smoking	-0.07	0.04	0.20	-0.02	1.00											
QIDS pre	-0.25	-0.11	-0.06	-0.26	-0.12	1.00										
Change	0.53**	-0.04	0.16	0.14	0.10	-0.53	1.00									
RMSSD	-0.39*	-0.29	-0.40	-0.33	-0.28	0.17	-0.37	1.00								
SDNN	-0.41*	-0.13	-0.38	-0.27	-0.22	0.25	-0.40*	0.92**	1.00							
aVLF	-0.28	0.13	-0.41	-0.25	-0.02	0.08	-0.26	0.62**	0.78**	1.00						
rVLF	0.30	0.47*	-0.03	0.21	0.04	-0.18	0.40*	-0.53**	-0.39	0.12	1.00					
aLF	-0.20	-0.19	-0.15	-0.03	-0.17	0.22	-0.32	0.68**	0.76**	0.37	-0.59**	1.00				
rLF	0.15	-0.03	0.21	0.22	0.16	0.18	-0.22	-0.09	-0.02	-0.35	-0.56**	0.49*	1.00			
aHF	-0.44*	-0.28	-0.28	-0.35	-0.22	0.26	-0.42*	0.95**	0.87**	0.57**	-0.56**	0.70**	-0.06	1.00		
rHF	-0.46*	-0.53**	-0.14	-0.45*	-0.19	0.11	-0.29	0.68**	0.45*	0.13	-0.72**	0.27	-0.17	0.72**	1.00	
LF/HF	0.49*	0.30	0.19	0.32	0.21	0.10	0.07	-0.50**	-0.32	-0.21	0.30	-0.08	0.51**	-0.52**	-0.76**	1.00
B. IY Study	Age	Gender	N episodes	Ethnicity	Smoking	HAM-D pre	Change	RMSSD	SDNN	aVLF	rVLF	aLF	rLF	aHF	rHF	LF/HF
Age	1.00															
Gender	0.10	1.00														
N episodes	-0.16	0.28	1.00													
Ethnicity	0.21	-0.21	0.00	1.00												
Smoking	-0.59*	0.10	0.28	0.30	1.00											
HAM D pre	0.28	0.31	0.20	0.46	-0.27	1.00										
Change	0.03	-0.53*	-0.58*	0.02	-0.13	-0.33	1.00									
RMSSD	0.19	-0.13	0.18	0.13	-0.09	-0.08	-0.17	1.00								
SDNN	0.00	-0.05	0.28	0.04	0.07	-0.10	-0.18	0.97**	1.00							
aVLF	-0.04	-0.04	0.33	0.04	0.15	-0.09	-0.16	0.94**	0.99**	1.00						
rVLF	-0.14	0.02	-0.22	-0.12	0.24	0.00	0.43	-0.85**	-0.79**	-0.73**	1.00					
aLF	0.16	-0.16	0.23	0.11	-0.08	-0.05	-0.11	0.99**	0.97**	0.95**	-0.79**	1.00				
rLF	0.06	0.14	0.34	0.10	-0.20	0.32	-0.26	0.16	0.17	0.17	-0.33	0.24	1.00			
aHF	0.18	-0.19	0.19	0.12	-0.09	-0.07	-0.08	0.99**	0.96**	0.94**	-0.79**	0.99**	0.20	1.00		
rHF	0.29	-0.12	0.04	0.27	-0.25	-0.12	-0.37	0.75**	0.64**	0.55*	-0.85**	0.64**	-0.08	0.66**	1.00	
LF/HF	0.17	0.31	-0.03	0.01	-0.03	0.22	0.31	-0.31	-0.30	-0.26	0.38	-0.22	0.50	-0.23	-0.61*	1.00

aHF = absolute high frequency; aLF = absolute low frequency; aVLF = absolute very low frequency; Change = difference of QIDS between baseline and post-treatment; ESC = escitalopram; HAM-D = Hamilton depression rating scale; IY = Iyengar yoga; rHF = relative high frequency; rLF = relative low frequency; rVLF = relative very low frequency; LF/HF = low frequency to high frequency ratio; N = number; QIDS = Quick Inventory of Depressive Symptoms; RMSSD = root mean square of the successive differences; SDNN = standard deviation of normal to normal intervals.

* $p < 0.05$.

** $p < 0.01$.

4.1. Physiology of rVLF and depression treatment outcome

The physiological basis of rVLF, and its relationship to depression treatment outcome, is unclear. Prior research has focused on correlations of physiological measures with absolute levels of VLF, and although rVLF is a related measure, it also varies based on total power. However, speculations on how rVLF might mechanistically relate to depression treatment outcome rely on our understanding of absolute VLF. No correlation has been identified between VLF and physical activity measured either over a 24-hour daily routine (Aoyagi et al., 2003) or in a controlled laboratory setting (Hautala et al., 2010), suggesting that VLF does not correlate with or predict changes in physical activity levels that might signal improvements in depression. Taylor et al. (1998) reported that atropine but not atenolol reduced overall power in VLF, suggesting that it relied on cholinergic (parasympathetic) neurotransmission. This corresponds with our finding of a correlation between HF and VLF (both absolute and relative measures) in both ESC and IY studies, and the finding of a significant relationship between relative power of VLF and baroreflex sensitivity in general, and its efferent component regulating cardiac rhythm in particular (Davydov et al., 2007). If intact parasympathetic function is necessary for rVLF, and rVLF is prospectively confirmed to predict depression treatment response, this would support the literature that autonomic function is dysregulated in depression (Veith et al., 1994).

VLF levels may be related to alterations in blood flow, and this might provide an additional mechanism via which rVLF provides prognostic value for recovery from MDD. Regulation of overall vascular tone has been associated with VLF, both via the renin–angiotensin–aldosterone system and peripheral vascular tone. Blockade of angiotensin converting enzyme inhibition (ACE-I) modestly increases VLF power in healthy adults (Taylor et al., 1998) and in patients with heart disease post myocardial infarction (Bonaduce et al., 1994). The apparent suppressive effect of ACE-I on VLF may be explained by the association of VLF with slow oscillations of peripheral vascular tone (Hyndman, 1974). VLF oscillations of systolic blood pressure have been found to be largely mediated by L-type calcium channels (Langager et al., 2007), which are known to be expressed in both heart and brain tissue. It may be that VLF biorhythms as captured by heart rate variability reflects either alterations in blood flow in peripheral or central circuits, or, alternatively that perturbations in VLF reflect dysregulation of a molecular mechanism (such as L-type calcium channels) common to both brain and heart that influences depression treatment outcome.

Control of energy metabolism and thermoregulation also takes place on the VLF timescale. The diurnal rhythm in variations of VLF power has been correlated with pulsatile secretion of leptin over a 24 hour cycle (Takabatake et al., 2001), and pulsatile insulin secretion has been found to occur within the VLF frequency range (Porksen et al., 1997). Lindqvist et al. (1990) found an association of changes in VLF with thermoregulation. It may be that rVLF marks a phenotype in which energy metabolism or thermoregulation is altered in ways that predispose to poor depression outcome.

4.2. Limitations

There are several limitations to this pilot study. First, the oscillatory period of the VLF frequency range is from 30 s to 5 min, and the ESC study recorded HRV over an average of 268 s (~4.5 min) per patient. Our recording length thus represented on average slightly less than one period of the lowest frequency of VLF. Although this recording length is comparable to another recent study of VLF in depression, which utilized 256 s of data (Yeragani et al., 2002), the Task Force guidelines recommend using recordings of more than 5 min (Task Force Report, 1996). Concern about the brevity of the recording period in the ESC sample is somewhat mitigated by confirmation of the finding in the IY sample, in which 20-minute recordings captured at least 4 periods of VLF, as well as by unadjusted correlations between rVLF and

other HRV measures that demonstrated high stability across studies. Our post hoc analysis also showed a .79 correlation between rVLF derived from 268 second epochs with rVLF derived from longer 20-minute epochs. The stability of rVLF in our study may be due, in part, to the controlled laboratory environment in which recordings were obtained, with participants stationary, alert, and at rest.

The second major limitation concerns clinical heterogeneity of the studies we utilized. These studies utilized two different interventions for treating depression (escitalopram monotherapy vs adjunctive yoga), different outcome measures (QIDS and HAM-D), and assessed patients in different phases of their depressive illness (acute MDD vs. MDD in partial remission), and this complicates interpretation of the results. However, this heterogeneity also may be seen as a strength, as it suggests that rVLF may be a robust biomarker for readiness to respond to a depression treatment that is independent of treatment type and stage of illness, at least in otherwise healthy subjects. There is some precedent for the robustness of VLF as a biomarker for cardiovascular mortality, as it has previously been found to predict all cause mortality in patients with cardiovascular illness, both with (Carney et al., 2005) and without depression (Bigger et al., 1992).

Although a previous analysis of heart rate variability in the yoga sample yielded differences in HF and LF in patients who achieved remission with yoga treatment (Shapiro et al., 2007), that study utilized different frequency bands for HF and LF and another (optimal band-pass filtering by moving averaging) method for the HRV calculation that are not comparable to those of the current study, which utilized those frequency ranges recommended by the Task Force Guidelines and autoregressive spectral models of HRV (Task Force Report, 1996). It is possible that other measures of heart rate variability might additionally predict treatment response in the yoga sample; however, the approach of our study was to identify HRV associations with treatment outcome in the ESC trial and cross-validate the associations in an independent trial of MDD using a different treatment modality. Therefore, our methods focused only on analyzing parameters in the IY study that were significant in the ESC trial.

Finally, subjects were not excluded from either study on the basis of comorbidities such as anxiety disorders, which are known to affect HRV, and this precludes us from making conclusions regarding the role of rVLF in predicting response to anxious versus non-anxious depression.

5. Conclusion

Because an initial antidepressant treatment for MDD leads to response only about 50% of the time (Trivedi et al., 2006), understanding which biological factors are associated with this heterogeneity could assist in the design of clinical trials, as well as interpretation of their results. Our data suggest that baseline rVLF may be a replicable predictor of response to treatment for MDD. Due to its low cost, non-invasiveness, and ease of measurement, rVLF offers promise as a practical biomarker for treatment response prognosis in MDD. However, because of heterogeneity of the subject populations and limitations of recording length, the findings of this study require confirmation in larger samples of patients suffering from MDD before firm conclusions can be drawn. Future studies should assess the possible role of rVLF as a biomarker for depression treatment outcome in patients with MDD who are otherwise healthy, as well as those with comorbid cardiovascular disease.

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