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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.

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 antihypertensive 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).