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Vagally mediated heart rate variability and heart rate entropy as predictors of treatment outcome in flight phobia

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Abstract

In the present study a computer-assisted exposure-based treatment was applied to 54 flight phobics and the predictive role of vagally mediated heart rate (HR) variability (high frequency, 0.15–0.4 Hz band power) and heart rate entropy (HR time series sample entropy) on treatment outcome was investigated. Both physiological measures were taken under controlled breathing at 0.2 Hz and during exposure to a fearful sequence of audiovisual stimuli. Hierarchical regression analyses were conducted to assess the predictive power of these variables in these conditions on treatment self-report measures at the end of treatment and at 6 months follow-up, as well as on the behavioral treatment outcome (i.e. flying at the end of treatment). Regression models predicting significant amounts of outcome variance could be built only when HR entropy was added to the HR variability measure in a second step of the regression analyses. HR variability alone was not found to be a good predictor of neither self-reported nor behavioral treatment outcomes.

Keywords: Heart rate variability; Sample entropy; Complexity; Specific phobia; Fear of flying

Specific phobia is one of the most prevalent mental disorders and the most common anxiety disorder (Kessler et al., 2005). The most successful treatment for specific phobias is exposure *in vivo* (Marks, 1987). Effective virtual reality or computer-assisted exposure procedures are also currently available for several phobias (Bornas et al., 2006a; Botella et al., 2005; Maltby et al., 2002; Mühlberger et al., 2003). However, a number of patients with specific phobia do not respond to exposure-based treatments. This raises the question of whether some pre-treatment variables are associated with a different prognosis. As Steketee and Chambless (1992) point out, ‘‘If we can identify characteristics of clients that are associated with poor response to treatment, we may (...) be able to match clients to treatments that work best for those with their particular characteristics.’’ (p. 387). Research on treatment outcome predictors is an appropriate way to identify such characteristics but this kind of research in anxiety disorders, including specific phobia, has been disappointing so far. The use of demographic or clinical variables as outcome predictors has yielded very inconsistent results (see Hellstrom and Öst, 1996; Fullana, 2000, for a review). Psychophysiological variables have been less studied, but with more promising results. According to Foa and Kozak's model of emotional processing of fear (Foa and Kozak, 1986) heightened initial arousal, as indexed by increased heart rate (HR), is predictive of superior outcome (Foa and McNally, 1996; Lang et al., 1970; Watson and Marks, 1971). In a study with spider, injection or blood phobics who received exposure-based treatments, significant outcome predictors were found only for blood phobia, where diastolic blood pressure during a behavioral test predicted 16% of the outcome variance (Hellstrom and Öst, 1996). In the study by Beckham et al. (1990) on flight phobia, participants who attended the 2-month follow-up session were divided into two groups: those who had flown and those who

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had not after the last treatment session, which consisted of an exposure flight. Then the authors compared the mean HR of both groups during that flight (HR was measured just before taking-off) and found that the mean HR of the group of participants who had flown was significantly higher than the mean of the group that had not flown. That is, increased physiological activation when confronted to the feared stimuli was related to positive treatment outcome.

In recent years, a new psychophysiological measure has gained interest from researchers: heart rate variability (HRV). One of the most studied sources of HRV is the variability due to the inhibitory action of the parasympathetic or vagal system, i.e. the so-called vagally mediated HRV. This variability can be successfully measured in the frequency domain since it is widely accepted that the spectral power in the 0.15–0.4 Hz band (usually called the high frequency band) reflects exclusively or overwhelmingly the vagal influence on HR (Camm et al., 1996). Research on HRV has suggested a link between low vagally mediated HRV and anxiety disorders (see Friedman, 2007, for a review). Friedman and Thayer (1998) compared panic disorder patients, blood phobics, and normal controls using several measures of HRV, and found lower high frequency (0.18–0.35 Hz) power and shorter mean successive differences (MSD) in panic disorder patients than in blood phobics, and lower high frequency power and shorter MSD in blood phobics than in controls. Johnsen et al. (2003) found decreased root mean square successive differences (RMSSD) in a sample of dental phobics during exposure to feared stimuli (videoclips) as well as during a Stroop task performed after exposure and during a 5 min recovery period following the task.

Regarding fear of flying, Wilhelm and Roth (1998) found decreased respiratory sinus arrhythmia – high frequency power measured during the first 128 s after taking off – in flight phobics. Bornas et al. (2005) found that low vagally mediated HRV fearful fliers reported higher levels of anxiety than high HRV fearful fliers when confronted with flight-related stimuli.

These data suggest that having low vagally mediated HRV is less advantageous for health than having high HRV. Thayer and Lane (2000) have presented an interesting theoretical justification of this statement within a dynamic systems framework. Briefly stated, highly variable systems are more flexible and more able to adapt themselves (and their own behavior) to the demands of an ever-changing environment. Therefore, a relationship between vagally mediated HRV and therapy outcome could be expected. Patients with more variable heart rate would show greater adaptability to therapy and would have better treatment outcomes. However, to date, the relationship between vagally mediated HRV and treatment response has not been explored.

Other features of heart rate deserve attention. From a dynamic systems perspective, the cardiovascular system can be characterized by a number of properties (e.g. complexity, nonlinearity, predictability, regularity, and so on) which can be measured on the HR time series derived from the ECG. Yeragani and co-workers have conducted most of the studies in this field since the early 1990s (Rao and Yeragani, 2001; Yeragani et al., 2000, 2002a,b), and several interesting links between nonlinear properties of HR and anxiety disorders have begun to emerge. For example, it was found that panic disorder patients have increased complexity (assessed by the minimum embedding dimension, MED) and predictability (assessed by the largest Lyapunov exponent, LLE) than controls (Rao and Yeragani, 2001). Lower LLE has also been reported in patients with major depression (Yeragani et al., 2002a,b).

However, several nonlinear methodologists recommend caution when using measures derived from the study of low dimensional chaos to investigate physiological signals (Heath, 2000; Kantz and Schreiber, 1997; Sprott, 2003) because biological systems are probably much more complex (i.e. they have higher dimensionality) than the mathematical ones. Partly as a solution to this problem, approximate entropy (ApEn) was introduced as a measure of regularity and complexity (Pincus, 1991, 1995) in relatively short and noisy time series typical from living systems. While variability refers to the degree of dispersion that successive values in a HR time series show around a central value (e.g. the mean), the concept of regularity refers to the time order of the values. Regularity can be as important as variability since the output from healthy systems is characterized by a greater irregularity (Goldberger et al., 2002; Guastello, 2004).

Richman and Moorman (2000) introduced the sample entropy (SampEn) as a new and related complexity measure which ‘‘is largely independent of record length and displays relative consistency under circumstances where ApEn does not’’ (p. H2039). The SampEn index, like the ApEn index, is a nonnegative number assigned to a time series, with larger values corresponding to greater irregularity in the process, and smaller values corresponding to more recognizable patterns in the data. Hence, periodic data (e.g. a sine wave) should have an index closed to zero.

Following the idea that complexity (like variability) is a sign of health in biological systems, and adding to a growing literature confirming the association between low entropy (complexity) and disease (Pincus, 2000; Vigo et al., 2004; Wagner and Persson, 1998; Wessel et al., 2000), Bornas et al. (2006b) found lower SampEn values in ECG (mV) time series of fearful fliers than in non-fearful controls in several threatening conditions but also during baseline and relaxing situations, thus revealing reduced complexity in the ECG output from fearful fliers. Further, a multiscale entropy analysis (MSE; Costa et al., 2002) – which uses the SampEn measure – of the ECG mV time series of a large group of flight phobics revealed a significant fear induced complexity loss (Bornas et al., 2006c).

To sum up, a growing body of research provided support for the idea that enhanced complexity and predictability in the cardiac system could be associated to panic disorder and depression, though some of those studies measured properties that characterize low dimensional systems more than the high dimensional ones of living organisms. Entropy measures (e.g. ApEn and SampEn) should better estimate the complexity of such systems. Unfortunately, HR entropy has been much less investigated than HRV, but studies using entropy measures show that the output from healthy systems is more complex than the output from impaired or impoverished systems.