Reduced heart rate variability and vagal tone in anxiety: Trait versus state, and the effects of autogenic training

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ABSTRACT

This study investigated heart rate variability (HRV) in healthy volunteers that were selected for extreme scores of trait anxiety (TA), during two opposite psychophysiological conditions of mental stress, and relaxation induced by autogenic training. R–R intervals, HF and LF powers, and LF/HF ratios were derived from short-term electrocardiographic recordings made during mental stress and relaxation by autogenic training, with respiratory rate and skin conductance being controlled for in all the analyses. The main finding was that high TA was associated with reduced R–R intervals and HF power across conditions. In comparison to mental stress, autogenic training increased HRV and facilitated the vagal control of the heart. There were no significant effects of TA or the psychophysiological conditions on LF power, or LF/HF ratio. These results support the view that TA, which is an important risk factor for anxiety disorders and predictor of cardiovascular morbidity and mortality, is associated with autonomic dysfunction that seems likely to play a pathogenetic role in the long term.

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1. Introduction

Patients with anxiety and affective disorders are at increased risk for cardiovascular disorders including ventricular arrhythmias, myocardial infarction, heart failure and sudden death (Gorman and Sloan, 2000). For instance, an epidemiological study that included over 18,000 adults from 5 cities in the United States showed that the risk for high blood pressure, myocardial infarction and stroke was higher in patients with panic disorder compared to healthy controls (Weissman et al., 1990). A more recent study indicated that indeed the association of anxiety disorders (e.g., generalized anxiety disorder, panic disorder, specific phobia) and cardiovascular disease (e.g., myocardial infarction) remains highly significant after adjusting for affective disorders, in contrast to specific affective disorders (e.g., major depression, bipolar disorder, dysthymia) whose association with cardiovascular disease does not remain significant after adjusting for anxiety disorders (Goodwin et al., in press). In addition, anxiety and affective disorders have been associated with increased mortality in cardiac patients (Sheps and Sheffield, 2001). However, the physiological mechanisms accounting for these associations between anxiety and affective disorders on the one hand, and cardiovascular morbidity and mortality on the other are not completely understood. Candidate mechanisms have included: lymbic and hypothalamic–pituitary–adrenal dysregulations, dysfunctions of the autonomic control of the heart (e.g., defective neuronal reuptake of neradrenalin), altered blood platelet function, and non-compliance to

medical treatments (Grippo and Johnson, 2002; Mujica-Parodi et al., in press; Alvarenga et al., 2006).

Heart rate variability (HRV) is an non-invasive electrocardio-graphic (ECG) index of the autonomic control of the heart, which has been extensively studied in anxiety and affective disorders (Cohen et al., 1999; Friedman and Thayer, 1998; Friedman et al., 1993; Gorman and Sloan, 2000). HRV reflects oscillations in the interval between consecutive heart beats. The analysis in the time domain of ECGs involves the identification of each cardiac cycle and the determination of mean intervals between successive R (R–R) or QT waves (Dinca-Panaitescu et al., 1999; "Heart rate variability. Standards of measure-ment, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996; Negoescu et al., 1997). Heart rate variability results from the dynamic or homeostatic interaction of sympathetic and parasympathetic (vagal) inputs to the sinoatrial node (Braun et al., 1998; Robinson et al., 1966). To date, the nature of the relationships between sympathetic and vagal influences on the heart has not been completely understood (Eckberg, 1997). However, reductions in the parasympathetic innervation is considered to leave the heart exposed to unopposed stimulation by the sympathetic nervous system, and consequently vulnerable to ventricular arrhyth-mia and sudden death (Gorman and Sloan, 2000). Indeed, reductions of R–R variability significantly predict ventricular arrhythmias and sudden death (Bigger et al., 1992). The analysis in the frequency domain involves the distribution of oscillations in at least two frequency bands and the determination of power in each of these bands. Power in the high frequency (HF) band (~0.15–0.4 Hz in adults) has been associated with respiratory sinus arrhythmia and it is

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considered to reflect vagal modulation of the heart, whereas power in the low frequency (LF) band (~0.05–0.15 Hz) probably reflects a complex interplay between sympathetic and vagal influences (Eckberg, 1997; "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996; Kingwell et al., 1994).

Reduced HRV has been empirically supported in anxiety and affective disorders. For instance, several studies reported that HRV is reduced in patients with panic disorder (Sullivan et al., 2004; Yeragani et al., 1991) and even children of patients with panic disorder (Srinivasan et al., 2002). Patients who reported frequent severe panic attacks showed reduced HRV during a variety of laboratory conditions (e.g., quiet rest, shock avoidance, face immersion, isoproterenol infusions), and a dominant sympathetic control of heart rate associated with reduced vagal tone (Friedman et al., 1993; Yeragani et al., 1995). The finding of reduced HRV has been replicated in affective disorders, at least in some laboratory conditions (e.g., deep breathing; (Agelink et al., 2001)). However, in a study in which the predictive power of lifetime symptoms of anxiety and depression were investigated in relation to HRV change after myocardial infarction, it has been found that only the former predict pathological HF reduction, after controlling for several important confounds (Martens et al., 2008). Moreover, there is increasing evidence that some of the risk factors for anxiety disorders (e.g., affective traits) are themselves important predictors of cardiovascular mortality, and this relationship might also be mediated by differences in HRV. For instance, emotional sensitivity and HF power predicted 8-year cardiac mortality after acute myocardial infarction (Carpeggiani et al., 2005). There has been a marked interest in investigating the relationship between risk factors for anxiety disorders, cardiovascular disease, and HRV (Friedman, 2007; Martens et al., 2008), for these studies might contribute to a mechanistic approach to the prevention and early diagnosis of these comorbid conditions, by targeting one of their key physiological mediators.

Trait anxiety (TA) reflects individual differences in the sensitivity to threat (Endler and Kocovski, 2001; Eysenck, 1997; Spielberger, 1983), and it has been established as a risk marker for anxiety disorders (Brandes and Bienvenu, 2006; Eysenck, 1997). Several studies investigated the association between TA and HRV differences. By recording ECGs at various intervals before and after an exam, Fuller (Fuller, 1992) found reduced heart rate, and increased LF and HF power in low TA compared to high TA participants and repressors (i.e., participants with low TA, but high social desirability self-reported scores; see (Eysenck, 1997)). A subsequent study in which HF power and the baroreflex cardiac control (i.e., the correlation between systolic blood pressure and R–R intervals) were measured, confirmed that TA was negatively correlated with HF power (Watkins et al., 1998). Specifically, participants with TA scores in the last quartile displayed HF power and baroreflex control that were 8 and 36% lower, respectively, than those of participants with TA scores in the first quartile. However, subsequent studies using more complex designs, either by controlling for possible confounds (e.g., perceived emotional stress during the past week, cardiorespiratory fitness, serotonin transporter genotype), or including various psychophysiological conditions (e.g., exercise (treadmill) test, fear induction, waking, sleep, CO_2 challenge) reported variable results (Brosschot et al., 2007; Dishman et al., 2000; Narita et al., 2007; Pauls and Stemmler, 2003; Schmidt et al., 2000; Virtanen et al., 2003). The heterogeneity of these results is probably related to differences in instruments, methods and procedures, including but not limited to the duration of ECG recordings, choice of HRV indices and psychometric instruments. However, it seems appropriate to investigate the relationship between TA and HRV in several contrasting psychophysiological conditions (i.e., not just rest) in order to allow the dissociation of HRV differences that are trait vs. state-dependent.

This study used established psychophysiological measures to investigate the relationship between TA and HRV. Participants were selected for extreme scores of TA, and their R–R intervals, LF, HF power, and the LF/HF ratio were derived from short-term ECGs made during two conditions, mental stress and relaxation induced by autogenic training. Our predictions were that TA would be related to a reduced HRV and vagal control of the heart irrespective of the experimental condition, and autogenic training would increase HRV and vagal control of the heart indepently of TA.

2. Materials and methods

2.1. Participants

Sixty three students from Babes-Bolyai University, with ages between 19 and 24 years (mean=20.3 years), were recruited for this study. The participants were selected based on TA scores (mean±SD: 32.19±6.95 for men, and 35.37±8.28 for women) that were below or over average, according to the norms of the Romanian version of Spielberger's State-Trait Anxiety Inventory (Pitariu and Peleasa, 2007; Spielberger, 1983). The sample included 36 high TA participants and 27 low TA participants. Sex was balanced between the groups. The trait part of STAI was administered one week before the experiment, and the state part was administered immediately after the mental stress condition of the experiment (see below). None of the participants reported cardiovascular or neurological problems, or any kind of treatment that would interfere with cardiovascular and autonomic functions. Participants were asked to refrain from alcohol, caffeine and smoking at least four hours before the experiment. All the participants signed an informed consent to participate to the experiment and the procedures complied to the recommendations of the Declaration of Helsinki for human studies.

2.2. Procedure

The experiment included two conditions, controlled relaxation and mental stress, each lasting for 7–10 min. The conditions were separated by breaks during which the experimenter debriefed the participant until he or she returned to a state of vigilant calm, and his/her psychophysiological indices (i.e., heart rate, skin conductance) returned to baseline. The relaxation phase involved the administration of the heaviness, warmth, and breathing suggestions from the autogenic training procedure, done by a trained experimenter, in comparable manner between participants and in the succession recommended by the standard clinical protocol (Schultz and Luthe, 1959). All the participants were naive to autogenic training. The mental stress condition involved the administration of a time-limited arithmetic task that included 50 items, which participants were supposed to solve mentally and then write the correct answer down as quick as possible.

2.3. Physiological measurements

ECG was recorded using a Biopac MP150 system (Biopac Systems, CA, USA), with electrodes placed in a bipolar precordial lead and a sample rate of 500 samples/s. The analyses were done on 5 min segments from the ECG recordings made during the two experimental conditions. After visual inspection of the recordings and editing to exclude artifacts in AcqKnowledge 3.7.1, all the recordings were analysed using Nevrokard 7.0.1 (Intellectual Services, Ljubljana, Slovenia). We estimated mean R–R intervals, HF and LF powers from the recordings made during both conditions, by analyzing the ECG segments in the time and frequency domains. We also calculated the ratio of LF/HF powers. Respiratory frequency and skin conductance were also recorded using the appropriate Biopac modules (RSP100C, GSR100C) and transducers (TSD201, TSD203). Respiratory rate and

Table 1
Means and standard deviations of autonomic measures by trait anxiety and experimental condition

		R–R (ms)	LF (ms^2)	HF (ms^2)
Trait anxiety	Low	738.69 ± 145.16**	52.64 ± 11.26^{NS}	38.31 ± 10.76*
	High	638.22 ± 122.42	57.4 ± 16.21	33.15 ± 9.45
Condition	Relaxation	709.79 ± 139.87**	55.44 ± 14.01 ^{NS}	37.93 ± 15.21**
	Stress	630.95 ± 124.78	56.18 ± 15.83	31.81 ± 12.6

Note: *$p<0.05$; ** $p<0.01$; ^{NS} non-significant.

skin conductance amplitude were included in all the analyses as covariates.

2.4. Statistical analyses

The data were analyzed by analysis of variance (ANCOVA) followed by post hoc Scheffé tests, and correlation tests run in Statview 5.0. Sex had no effect on HRV indices, regardless of experimental condition, so we dropped this variable from further analyses.

3. Results

A 2 (TA: high vs. low)×2 (condition: autogenic training vs. mental stress) ANCOVA indicated significant main effects of TA ($F[1, 61]=7.72$, $P<0.01$) and condition ($F[1, 61]=93.17$, $P<0.01$) on R–R intervals. Post hoc tests showed that high TA participants displayed significantly shorter R–R intervals than low TA participants across both experimental conditions (Table 1). Autogenic training was associated with increased R–R intervals compared to mental stress (Table 1). The ANCOVA analysis also indicated that the interaction of TA×condition was significant ($P<0.01$), with the high TA participants displaying the shortest R–R intervals during mental stress. Moreover, we found a significant negative correlation between state anxiety scores and R–R intervals in the mental stress condition ($r=-0.087$; $P<0.05$).

A similar ANCOVA indicated that TA ($F[1, 61]=6.01$, $P<0.05$) and condition ($F[1, 61]=5.25$, $P<0.05$) also had significant effects on HF power. High TA participants had significantly lower HF power than low TA participants across conditions (Table 1). Autogenic training was associated with higher HF power compared to mental stress (Table 1). The interaction of TA×condition was also significant ($P<0.01$), with the high TA participants displaying the lowest HF power during mental stress. There was a significant negative correlation between SA scores reported after the mental stress condition and HF power during mental stress ($r=-0.19$; $P<0.01$).

We identified no significant difference in LF power between low and high TA participants (Table 1). The experimental condition did not induce significant differences in LF power (Table 1), and the correlation between SA scores reported after the mental stress condition and LF power was also not statistically significant. The same pattern of non-significant differences and lack of correlation was found for the effects of TA and condition on LF/HF ratio (data not shown).

4. Discussion

This study investigated the trait and state-dependent effects of anxiety on time and frequency domain indices of HRV. The main findings were that high TA is associated with reduced HRV and vagal control of the heart. By comparing between mental stress and relaxation, this study was also able to indicate that autogenic training increased HRV and facilitated the vagal control of the heart.

High TA was associated in this study with shorter R–R intervals and decreased HF power. These findings are in line with previous studies in which HRV was measured for instance before and after a stressful event (Fuller, 1992), or it was correlated with baroreflex cardiac

control (Watkins et al., 1998). In contrast, several other studies have reported small or negative effects of TA on HRV (Brosschot et al., 2007; Dishman et al., 2000; Narita et al., 2007; Pauls and Stemmler, 2003; Schmidt et al., 2000). Considering that some of these studies attributed the initial finding of a significant effect of TA on HRV to the lack of control for possible confounds (e.g., stress in the preceding period), the present study used established autonomic measures to compare HRV in two opposite psychophysiological states. Our assumption was that this bifactorial design would allow us to disentangle the trait and state-dependent effects of anxiety. The results reported here strongly supported our prediction that TA significantly influences HRV irrespective of whether the participant is in a state of mental stress or relaxation induced by autogenic training. This difference in autonomic activity can therefore be added to the genetic (Lau et al., 2006; Lesch et al., 1996), neuroanatomical (Yamasue et al., 2008), neurochemical (Grachev and Apkarian, 2000), and functional neuroimaging differences (Morinaga et al., 2007; Sugiura et al., 2000) associated to date with TA (for reviews see (Miu, in press; Miu et al., 2008)). The differences accumulated around TA have recently started to be integrated in biobehavioral studies. For instance, a functional neuroimaging study indicated that TA is associated with decreased HRV and diminished temporal coupling between activity in several lymbic brain regions during the processing of emotional and neutral faces (Mujica-Parodi et al., in press). Such studies support the view that low HRV and cardiac vagal tone associated with dispositional anxiety are reliable indicators of both autonomic, and central nervous dysregulations (e.g., reduced inhibition resulting in inflexibility in multiple physiological response systems), which impact emotion and attention regulation (Friedman, 2007; Porges, 1995).

The present study thus shows that TA, which is a risk factor for some anxiety disorders (Brandes and Bienvenu, 2006; Eysenck, 1997; Schmidt et al., 2006), as well as a good predictor of cardiovascular morbidity and mortality (e.g., (Szekely et al., 2007)), is associated with reduced HRV and vagal control of the heart. Autonomic differences such as low vagal tone are present very early in the postnatal life (e.g., as early as 12 weeks of age; (Huffman et al., 1998)), and they are associated for instance with differences in temperament and emotion regulation (Bazhenova et al., 2001; Santucci et al., 2008). Despite similar results, the developmental and adult studies of HRV and affective traits have not been thoroughly integrated together. However, this continuity between individual differences in autonomic activity and affective traits from infancy to adulthood would suggest that low HRV/vagal tone and dispositional anxiety are the key aspects of a phenotype that might be associated with an increased long-term risk for anxiety and cardiovascular disorders. This phenotype would be marked by chronic cardiovascular vulnerability to sympathetic discharges due to increased trait-like vagal withdrawal (see (Sloan et al., 1995)), and biased information processing toward threat. Longitudinal studies that would investigate neonatal autonomic activity and affective traits as lifelong predictors of anxiety and cardiovascular disorders are long overdue. Such studies have the potential to disentangle to relationship between HRV, affective traits, and the risk for anxiety and cardiovascular disorders.

This study also indicated that, in comparison to mental stress, autogenic training increased R–R intervals and HF power. Autogenic training is a relaxation procedure that has been extensively used in the psychotherapy of anxiety disorders and other somatic or psychosomatic diseases (Ernst and Kanji, 2000; Manzoni et al., 2008). A meta-analysis indicated that autogenic training has a medium-size positive effect on clinical outcomes in patients with anxiety disorders, as well as coronary heart disease (Stetter and Kupper, 2002). Moreover, it highlighted that in addition to the modulations of mood, cognitive processing, and quality of life, autogenic training has significant physiological effects ((Stetter and Kupper, 2002); but see also (Banner and Meadows, 1983)). Our study compared two opposite controlled

conditions of mental stress and relaxation, and it found that autogenic training facilitates HRV and the vagal control of the heart. A previous study similarly reported that healthy volunteers that had been trained to use autogenic training for three months displayed increased R–R intervals and decreased baseline deflection of the plethysmogram (Mishima et al., 1999). Another study also found that autogenic training was associated with increased finger temperature during the final session of relaxation, as well as a facilitation of electroencephalographic activity in the delta and theta bands (Tebecis et al., 1976). The present research extended these results by showing that autogenic training facilitated HRV even in participants that had been naive to this relaxation procedure. Future studies might investigate the effects of autogenic training on HRV and other psychophysiological variables in clinical anxiety.

Neither TA, nor the psychophysiological conditions included in this study had an impact on LF and LF/HF ratio. More specifically, high TA and mental stress, which one might have expected to modulate sympathetic activity, were associated with equivalent LF powers and LF/HF ratios in comparison to low TA and relaxation by autogenic training, respectively. This is in line with other studies (Sloan et al., 1996) and suggests that either our independent variables did not modulate sympathetic activity, or LF power is not an specific index of sympathetic activity (Eckberg, 1997). The latter interpretation seem to be supported by studies in which parasympathetic blockade reduced HF, but also LF power (e.g., (Kim et al., 1997)). Moreover, LF power and LF/HF ratio do not correlate with neurohumoral indices of cardiac adrenergic activity, such as levels of plasma adrenalin and noradrenalin. In addition to sympathetic nerve firing rates, LF power also depends on multiple neural reflexes, cardiac adrenergic receptor sensitivity, postsynaptic signal transduction, and electrochemical coupling (Kingwell et al., 1994; Sloan et al., 1996).

One of the limits of the present study is that it did not complete the picture of sympathovagal balance in anxiety by using more reliable biochemical or electrophysiological indices of sympathetic activity. Direct recordings of sympathetic nerve traffic via microneurography and noradrenaline radiotracer methods are the most reliable ways to measure sympathetic activity (Grassi and Esler, 1999). Another limitation of the present study might be related to the lack of a baseline state anxiety measure. However, one should note that the scores obtained after the mental stress condition reliably indicated state anxiety according to the population norms for the Romanian version of STAI. In addition, it should be kept in mind that the state part of STAI is sensitive to repeated application. Nonetheless, we acknowledge that controlling for the baseline affective state by using a different instrument (e.g., PANAS) would have been possible and useful, although it is unlikely that this would have changed our results on the effect of TA on HRV.

In conclusion, this study indicates that high TA is associated with reduced HRV and vagal tone. In comparison to mental stress, autogenic training increases HRV and facilitates the vagal control of the heart. These results support the view that TA, which is an important risk factor for anxiety disorders and predictor of cardiovascular morbidity and mortality, is associated with autonomic dysfunction that seems likely to play a pathogenetic role in the long term.

5. Note added in proof

Since the submission of this manuscript, a report confirming the effects of trait anxiety on heart rate variability has been published. Please see (Bleil et al., 2008).

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