International Journal of Psychophysiology 86 (2012) 269–275

Contents lists available at SciVerse ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder

Anders Hovland [a,b,*], Ståle Pallesen [c], Åsa Hammar [d], Anita Lill Hansen [c], Julian F. Thayer [e], Mika P. Tarvainen [f], Inger Hilde Nordhus [a]

[a] Department of Clinical Psychology, University of Bergen, Norway
[b] Solli District Psychiatric Centre (DPS), Osveien 15, 5227 Nesttun, Norway
[c] Department of Psychosocial Science, University of Bergen, Norway
[d] Department of Biological and Medical Psychology, University of Bergen, Norway
[e] Department of Psychology, The Ohio State University, Columbus, USA
[f] Department of Applied Physics, University of Eastern Finland, Finland

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form 4 October 2012
Accepted 7 October 2012
Available online 13 October 2012

Keywords:
Panic disorder
Anxiety
Heart rate variability
Executive functions
Attention
Inhibition

ABSTRACT

Heart rate variability (HRV) is reduced in patients who suffer from panic disorder (PD). Reduced HRV is related to hypoactivity in the prefrontal cortex (PFC), which negatively affects executive functioning. The present study assessed the relationships between vagally mediated HRV at baseline and measures of executive functioning in 36 patients with PD. Associations between these physiological and cognitive measures and panic-related variables were also investigated. HRV was measured using HF-power (ms^2), and executive functions were assessed with the Wisconsin Card Sorting Test (WCST) and the Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS). Panic-related variables comprised panic frequency, panic-related distress, and duration of PD. Performance on the neuropsychological measures correlated significantly with HRV. Both panic-related distress and duration of PD were inversely related with measures of HRV and cognitive inhibition. The current findings support the purported relationship between HRV and executive functions involving the PFC.

1. Introduction

Due to its pronounced autonomic activation (e.g. tachycardia and palpitations) panic disorder (PD) has long been investigated with regard to possible cardiac dysregulation (Friedman, 2007). It has been established that patients who suffer from PD have an altered pattern of cardiac control, characterised by reduced heart rate variability (HRV; Cohen et al., 2000; Klein et al., 1995; Middleton et al., 1994; Yeragani et al., 1990, 1993). The HRV of patients with PD is reduced in both panicogenic as well as in resting conditions, which indicates that PD is associated with abnormal cardiac control in both tonic and phasic states (Friedman, 2007).

HRV is believed to reflect the integration of heart rate (HR), emotions, and the higher-level cognitions required for flexible and goal-directed behaviour (Appelhans and Luecken, 2006; Kashdan and Rottenberg, 2010). Although a variety of factors influence HR and HRV, the autonomic nervous system (ANS) is considered the most important of these, through which the parasympathetic branch exerts a tonic, inhibitory control over the heart via the vagus nerve (Thayer et al., 2009). A number of studies have linked vagal regulation of cardiac control to activation in areas in the prefrontal cortex (PFC; Ahern et al., 2001; Barbas et al., 2003; Lane et al., 2009; Ter Horst, 1999), and in a recent meta-analysis, Thayer et al. (2012) found significant associations between HRV and neuronal activity in areas in the ventromedial PFC. The PFC is the part of the brain most closely associated with executive functions (Alvarez and Emory, 2006; Goldman-Rakic, 1998; Ridderinkhof et al., 2004) such as sustained and shifted attention, working memory, inhibition and general mental flexibility. Consequently, reduced activity in the PFC would be expected to affect cognitive abilities linked to this brain region (Barbas et al., 2003; Thayer et al., 2009). As HRV seems to reflect activity in the PFC, associations between vagally mediated HRV and measures of executive functioning would be expected (Thayer et al., 2009). So far, it is well documented that there are performance-related alterations in HRV during the assessment of executive abilities (Duschek et al., 2009; Mathewson et al., 2010), and that HRV decreases during such assessments. Perhaps more importantly, studies with infants (Richards and Casey, 1991), children (Suess et al., 1994), and adults (Hansen et al., 2004, 2003; Mathewson et al., 2010) have shown that also resting or baseline HRV levels are associated with performance on measures of attention, although not without exception (Duschek et al., 2009). Still, the direction of these relationships has been consistent; HRV is positively associated with performance.

* Corresponding author at: Solli District Psychiatric Centre (DPS), Osveien 15, 5227 Nesttun, Norway. Tel.: +47 93287565; fax: +47 55618201.
E-mail address: Anders.Hovland@psykp.uib.no (A. Hovland).

0167-8760/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpsycho.2012.10.004

Furthermore, in the study by Hansen et al. (2004) HRV levels were manipulated through detraining, where approximately half of the participants discontinued an ongoing training program. This led to a reduction in vagally mediated HRV that was accompanied by reduction of performance on measures of executive functioning.

However, while it has been shown that baseline levels of HRV are related to executive functioning in healthy subjects, we have less knowledge as to whether this relationship also exists in anxious subjects. Investigating a sample of dental phobics, Johnsen et al. (2003) found that subjects with low vagally mediated HRV did indeed have longer reaction times on the Stroop. In that study, HRV was measured across four conditions that included baseline, in vitro exposure to dental treatment, the Stroop assessment, and recovery. The high and low HRV groups were based on the average of HRV levels measured across these four conditions. As such, it is unclear to what degree the relationship between HRV and Stroop performance reflected a tonic state in these patients, and how much the results were influenced by performance-related alterations elicited by the Stroop assessment. This means that it is presently not known if the association between baseline HRV levels and executive functioning that has been documented for healthy subjects, extends to patients suffering from an anxiety disorder such as PD.

Regarding PD and cognitive impairments, previous findings have been mixed. Gladsjo et al. (1998) found no differences between groups of patients with PD and controls on measures of attention and other executive functions. However, in that study IQ was used as a covariate between groups, although there is reason to believe that using IQ as a covariate between non-randomised groups can partial out important variance (Dennis et al., 2009; Miller and Chapman, 2001). Another study showed that young adults suffering from PD were not impaired on measures of executive functioning (Castaneda et al., 2011). However, as noted by the authors themselves, at least 50% of the PD patients were in remission, questioning the validity of these findings. Still, van den Heuvel et al. (2005) reported similar findings, showing patients with PD to perform normally on the Stroop test relative to controls. On the contrary, Asmundson et al. (1994) found patients with PD to exhibit impaired overall neurocognitive performance compared to healthy controls, but concluded that these impairments were of modest practical relevance. Those authors also found that general anxiety levels were not predictive of these impairments. Airaksinen et al. (2005) also found patients with PD to be significantly impaired on executive measures, but this effect was not significant when subjects with comorbid alcohol dependence were excluded from the analysis. Dupont et al. (2000) found that patients with PD committed more commission errors relative to controls on an attentional task, and that the number of errors was positively related to measures of anxiety and tension. Those authors suggested that these cognitive impairments were due to deficient response inhibition processes. Lautenbacher et al. (2002) found that patients with PD were as impaired as those with depression on measures of divided attention, and those authors emphasised the importance of using complex tests with high attentional load in order to detect impairments among patients with PD.

Although several studies have documented reduced HRV in patients with PD, assessments of the associations between panic-related clinical variables and HRV have yielded few consistent findings. Yeragani et al. (1993) found either no, or small (Yeragani et al., 1990) associations between state anxiety and different HRV measures, whereas a more recent study found no relationship between scores on the Anxiety Sensitivity Index (ASI) and HRV (Alvarenga et al., 2006).

To the best of our knowledge, no previous study has investigated the relationship between executive functioning and baseline HRV in patients with PD. The study on dental phobics by Johnsen et al. (2003) suggested that such a relationship not only exists in healthy groups, but possibly also in anxious subjects. The current study aims to replicate and extend the study by Johnsen et al. (2003), by specifically assessing the relationship between baseline HRV and a broader range of measures of executive functioning in a larger and well-diagnosed group of patients with PD. The use of baseline HRV levels in the current study is significant, as this could provide insights into the tonic state of these patients. Furthermore, the current knowledgebase concerning the relationship between panic-related variables and measures of vagally mediated HRV is scarce. Likewise, little is known on the relationship between panic-related variables and neuropsychological measures of executive functioning. More research on these topics could help us to improve our understanding of the development and consequences of PD.

Based on the studies cited above (Hansen et al., 2004, 2003; Johnsen et al., 2003; Mathewson et al., 2010; Richards and Casey, 1991; Suess et al., 1994), we expected to find a positive relationship between the levels of vagally mediated HRV and performance on measures of executive functioning, with reduced HRV being associated with impaired performance and vice versa. Due to scarce and previous inconsistent findings, we wanted to explore possible relationships between HRV and panic-related variables as well as possible relationships between measures of executive functioning and panic-related variables.

2. Material and methods

2.1. Participants

Thirty-six patients between the age 18 and 50 years old were recruited for participation in a randomised controlled trial for PD treatment. Participants provided written informed consent prior to enrolment, and the Regional Committee for Medical and Health Research Ethics in Western Norway as well as the Norwegian Social Science Data Services approved this study. A trained clinical psychologist (the first author) confirmed that all participants met the diagnostic criteria for PD with or without agoraphobia using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1995). Participants were excluded if they met any of the following criteria at the time of the study: 1) organic brain disorder, 2) psychotic disorders, 3) substance-abuse, including the habitual use of benzodiazepines, 4) medical conditions that preclude participation in physical exercise, or 5) severe major depressive episode. Study exclusions based on 2, 3, or 5 were established via the SCID-I, whereas exclusions based on 1 and 4 were determined by an interview with the participant, and if necessary, by consultation with the participant's general practitioner (GP). Following the SCID-I exclusions, participants waited a mean of 68 days (range: 7–138 days) before the HRV and the neuropsychological and clinical measures reported in the current study were employed. This waiting period took place prior to treatment, and was related to recruitment and randomisation not relevant to the current study. Ratings of *panic frequency* or *panic distress and disability* (these measures are described below) were however assessed both before and after this wait (one subject did not complete this assessment together with the SCID): Wilcoxon signed-rank tests indicated that no spontaneous recovery occurred during the waiting period on either panic frequency or panic distress and disability, $z = -0.71$, $p = .48$ and $z = -1.39$, $p = .16$, respectively. Note that the ratings of panic frequency and panic distress and disability included in the main analyses are those assessed after this waiting period. Psychotropic medications were stabilized prior to the assessments. Medication stabilization was confirmed via patient self-report. Assessments of HRV and neuropsychological functioning were conducted on separate occasions in different clinics. With reference to distance of travel, some participants preferred to complete both assessments on the same day, whereas others conducted the assessments within the timeframe of a few days.

The sample had a mean age of 37.9 years ($SD = 8.6$) and 13.6 years of education ($SD = 2.5$). 80.6% of participants were female and 27.8% lived alone. Approximately half of the sample (47.2%) was

employed full-time six months prior to inclusion, whereas 19.4% of participants were in rehabilitation programs, on sick leave or without regular work. The mean duration of PD was 10.1 years ($SD = 9.5$), and 80.6% of the sample suffered from agoraphobia. In addition to agoraphobia, the mean number of comorbid Axis 1 disorders (agoraphobia not included) was 2.1 ($SD = 1.2$). Further, 38.9% of the sample was diagnosed with mild or moderate depressive episode, and 36.1% used a selective serotonin reuptake inhibitor (SSRI). Risk-factors for cardiovascular disease (CVD) were routinely assessed, and none of the participants had previously suffered from myocardial infarction or other forms of CVD. For two participants, scores on the WCST were not available due to technical problems that occurred during the assessments.

2.2. Measures

2.2.1. HRV

HRV measures were obtained using a three-lead electrocardiogram (ECG) acquired with an ambulatory monitoring system (VU-AMS; de Geus et al., 1995) in a recording session that lasted a total of approximately 20 min. The ECG sampling rate was 1000 Hz, and the data were obtained using Ag/AgCl electrodes (1700 Cleartrace™, Conmed, Utica, NY) placed in the following locations: One below the right clavicle, 4 cm to the right of the sternum; one on the right side between the two lower ribs; and one under the left breast, 4 cm below the nipple. Recordings were conducted individually in a quiet location with an investigator available. In accordance with Yeragani et al.'s (1993) recommendations, ECG recordings were performed while participants were standing. QRS-detection was inspected visually for each recording using the ECG QRS scoring utility (version 1.0.5.8; Vrije Universiteit van Amsterdam). Further processing and HRV measure analyses were conducted using the Kubios HRV (version 2.0; University of Eastern Finland). To get a stable and artefact-free recording as recommended by Malik et al. (1996), the first and last 30 s of the 5 minute recordings were excluded, providing a stable 4-minute recording for each subject. The need for artefact correction was investigated for each recording. Corrections were conducted manually and kept at a minimum by consulting with the corresponding ECG signal. High frequency (HF) HRV, was used as our primary measure of vagally mediated HRV (Malik et al., 1996), and was based on HF-power (ms^2). The HF-power (ms^2) estimates were derived using an autoregressive (AR) algorithm with a standard model order of 16 and a frequency-band of 0.15–0.40 Hz. Trend components were removed using the smoothness priors method (Tarvainen et al., 2002), a method that has been found to provide a robust measure of vagal functioning (Lewis et al., 2012). The root mean squared successive differences (rMSSD) time domain measure and HR were used as secondary cardiac indices. Both HRV measures were transformed to their natural logarithms. HF HRV and rMSSD were significantly correlated ($r = .90$, $p < .01$); thus only HF HRV was used to assess the relationships with neuropsychological measures.

2.2.2. Neuropsychological measures

A professional test-technician administered both neuropsychological tests at a university-based neuropsychological polyclinic as part of a larger neuropsychological battery with the total assessment lasting approximately 1 h.

The Wisconsin Card Sorting Test (WCST) is considered a measure of executive functioning (Alvarez and Emory, 2006; Barceló and Knight, 2002; Welsh and Pennington, 1988) and dysfunction in the frontal lobes (Alvarez and Emory, 2006; Butler et al., 1991). The current study used a computerised version of the WCST; Wisconsin Card Sorting Test: Computer Version 4 research edition (WCST: CV4; Heaton et al., 2003) because of its standardised and automated administration. The scoring procedures of this instrument are in accordance with the principles of the original WCST. Based on recommendations, a professional technician familiar with the original version administered WCST: CV4. The current study reports T-scores adjusted for age and education level for *Total Errors*, *Perseverative Responses* and *Perseverative Errors*. According to Miyake et al. (2000), Perseverative Errors is the measure most closely linked to attentional shifting.

The Color-Word Interference Test (CWIT) is also a measure of executive functioning, and consists of four conditions. 1) In *Color Naming*, participants name the colours of coloured patches. 2) In *Word Reading*, participants read the names of colours printed in black ink. 3) In *Inhibition*, participants name the colour of the ink that the different colour names are printed in when the ink and words are incongruous. 4) In *Switching* (e.g., Inhibition/Switching), participants either read the words when the words are presented in a box or the name of the colour the words are written in when the box is not present. The first three conditions are equivalent to the original Stroop (Stroop, 1935); a prototypical test of the ability to inhibit prepotent responses (Miyake et al., 2000). However, the fourth condition is intended to measure cognitive flexibility and complex attentional shifting as it requires participants to alternate between the demands of the Inhibition condition (e.g., Stroop) and regular Word-reading. Conditions 1 and 2 are control-conditions. The test yields age-adjusted scaled scores for all four conditions with regard to the *time* needed to complete the tasks and for the total number of *errors* for Condition 3 and 4. Scaled scores have mean of 10 and a standard deviation of 3. Higher scores indicate better performance.

A latent-variable analysis of executive tasks identified the inhibition of prepotent responses and the shifting of attentional control as two out of three[1] basic executive functions (Miyake et al., 2000). As such, the WCST and the CWIT provide suitable assessments of EFs for the current purposes.

2.2.3. Clinical measures

The Agoraphobia Cognitions Questionnaire (ACQ; Chambless et al., 1984) is a 14-item inventory that assesses the frequency of thoughts common in people with agoraphobia. Chambless et al. (1984) reported that normal controls have a mean of 1.4 ($SD = 0.3$) on the ACQ. The ACQ Cronbach's alpha was .72 in this study. The Mobility Inventory (MI; Chambless et al., 1985) is a 27-item questionnaire that assesses the frequency of avoidance across a range of situations relevant to daily life. The MI consists of two subscales that measures avoidance of these situations both when the participant is alone and when accompanied (hereafter MI-Alone and MI-Accompanied, respectively). Normal controls have means of 1.3 ($SD = 0.2$) and 1.1 ($SD = 0.1$) on the MI-Alone and the MI-Accompanied, respectively (Chambless et al., 1985). The Cronbach's alpha for both scales was .91. The Body Sensations Questionnaire (BSQ; Chambless et al., 1984) is a 17-item inventory that measures the fear of bodily sensations. Chambless et al. (1984) reported that normal controls have a mean of 1.5 ($SD = 0.6$) on this measure. The BSQ Cronbach's alpha was .85 in this study. General anxiety was measured using the Beck Anxiety Inventory (BAI; Beck and Steer, 1993) and the State-Trait Anxiety Inventory-Trait version (STAI-T; Spielberger et al., 1983). Normal controls score 7.8 ($SD = 5.7$) on the BAI (Beck and Steer, 1993), and working adults have a mean of 34.8 ($SD = 9.2$) on the STAI-T (Spielberger et al., 1983). The Cronbach's alphas for the BAI and STAI-T in the current study were .91 and .93, respectively.

A clinical psychologist (the first author) rated both *panic frequency* and *panic-related distress and disability* (hereafter *panic-related distress*) using a two-item scale with one item for each domain. Panic frequency experienced during the last two weeks was rated on a 5-point scale that ranged from 0 (*no panic attacks*) to 4 (*one or more panic attacks per day*). Subjects rated their present experience of panic-related distress on a 9-point scale that ranged from 0 (*not at all disturbing*) to 8 (*very disturbing*).

[1] Updating and monitoring of working memory was the third function.

The estimates for *panic duration* were obtained during the SCID-I assessment.

2.3. Statistical procedures

All analyses were conducted using PASW (SPSS) version 17.0. The relationships between the investigated variables were assessed using Pearson's *r* correlations for continuous variables. Non-parametric measures were used in analyses that contained the panic frequency and panic-related distress variables because these covariates were assessed using short scales, which yielded many tied ranks. Wilcoxon signed-rank test (Field, 2009) was used to investigate clinical stability following the SCID-I assessment (please refer to Section 2.1 Participants), whereas Kendall's tau (τ; Howell, 2012) was used to assess relationships between these scales and other variables. Due to the hypothesised directional relationship between HF HRV and the neuropsychological measures of executive functioning, the significance of these questions was assessed using one-tailed tests (Ferguson and Takane, 1989). All other tests were two-tailed. Partial correlations were assessed using Pearson's correlations.

3. Results

Table 1 describes the sample means on cardiac and clinical measures. Fig. 1 displays the sample means on the WCST and CWIT together with the corresponding correlations with HF HRV. This figure reveals significant correlations between HF HRV and all WCST subscores. With regard to the CWIT, HF HRV was significantly correlated with Inhibition for both time and errors. The figure also shows that the sample's mean T-scores on the WCST and scaled scores on the CWIT were within the normal range, as T-scores have mean norm values of 50 ($SD = 10$) and the scaled scores on the CWIT have mean norm values of 10 ($SD = 3$). The associations between these neuropsychological measures and frequency of panic attacks, panic-related distress, and PD duration are displayed in Table 2. This table shows that there were no significant associations between the WCST and these clinical variables. With regard to the CWIT, time on Inhibition was significantly correlated with PD duration, whereas errors performed on Inhibition was significantly associated with panic-related distress. Table 2 also lists the correlations between the cardiac and clinical measures. HF HRV showed significant associations with PD duration and panic-related distress. As found in previous studies (Schwartz et al., 1991), HF HRV correlated negatively with age, $r = -.41$, $p < .013$. Therefore a partial correlation that controlled for age was calculated. HF HRV was significantly correlated with PD duration also when the participant age was controlled for, $r = -.34$, $p < .047$. The frequency of panic attacks was not significantly related with neuropsychological or cardiac measures.

Assessments of the associations among the three clinical variables of panic-related distress, panic frequency, and panic duration investigated the independence of these variables. No significant relationships were found between panic-related distress and panic duration ($\tau = .11$, $p < .38$), panic-related distress and panic frequency ($\tau = .17$, $p < .21$), or panic duration and panic frequency ($\tau = -.17$, $p < .18$).

Table 1
Baseline values for cardiac and clinical measures.

Measure	Mean	*SD*
Cardiac measures		
Heart rate per minute	81.7	11.4
HF-power[a]	2.0	0.6
rMSSD[a]	1.3	0.3
Clinical measures		
Panic frequency	1. 8	1.4
Panic-related distress	6.2	1.7
ACQ	2.2	0.5
MI — Alone	2.4	0.7
MI — Accompanied	1.9	0.6
BSQ	2.5	0.6
BAI	22.2	10.5
STAI-T	50.8	10.8

Note. HF = High frequency; rMSSD = root mean squared successive differences; ACQ = Agoraphobic Cognitions Questionnaire; MI = Mobility Inventory; BSQ = Body Sensations Questionnaire; BAI = Beck Anxiety Inventory; STAI-T = State-Trait Anxiety Inventory-Trait version.
[a] Log-transformed values.

4. Discussion

Our primary hypothesis was confirmed. The results demonstrated that there was a positive relationship between performance on neuropsychological measures of executive functioning and baseline vagally mediated HRV in the current sample. Greater HF HRV was associated with higher standardised scores on the neuropsychological tests, and vice versa. This result was found consistently in the WCST scores. With regard to the CWIT, the current findings indicated a selective association between HF HRV and the Inhibition subscore. This was consistent for both time and errors; the strongest association was found for errors. No relationship was found between HF HRV and the control conditions. The apparent lack of associations between HF HRV and scores on Switching was somewhat surprising. Both CWIT Switching and Inhibition have correlated positively with WCST Perseverative errors (Delis et al., 2001). However, Lippa and Davis (2010) recently found that the youngest part of their outpatient sample performed better on the Switching task than on the Inhibition task. These authors concluded that, contrary to the intentions of the CWIT, Switching was an easier task than Inhibition for these patients. Considering the age range of the patients in that study, these results are likely relevant for a large part of the sample in the present study. Thus, this task may not have been sufficiently demanding to require executive functioning related to vagal cardiac control. Nevertheless, Miyake et al. (2000) have identified WCST as a key test for assessing attentional shifting; thus, our results appear to relate HF HRV to both cognitive inhibition and attentional shifting.

These results provide support for the hypothesised associations between executive functioning related to the PFC and cardiac control via the vagus nerve. This association has previously been found in healthy infants, children, adults, and dental phobics (Hansen et al., 2004, 2003; Johnsen et al., 2003; Mathewson et al., 2010; Richards and Casey, 1991; Suess et al., 1994); however, it has not previously been demonstrated in patients with PD. The present study thus provides an important replication and extension of the study by Johnsen et al. (2003). As the present study specifically recorded HF HRV at baseline, these associations are independent of the cardiac responses elicited by the neuropsychological testing (Boutcher and Boutcher, 2006; Delaney and Brodie, 2000; Waldstein et al., 1997). Furthermore, we found this association to be true for two key executive functions, and we also found that on the CWIT there was a selective association between HRV and both Inhibition subscores. As patients with PD are known to have deficient vagal cardiac control, the current findings suggest that the relationships between vagally mediated HRV and executive functions are present across the whole range of HRV from healthy subjects to patients.

The two CWIT Inhibition measures as well as HF HRV were related to panic duration and panic-related distress. This could indicate that both cognitive and physiological functioning are related to clinical status and clinical development. Although previous research in this area has been scarce and seemingly inconsistent, the current results appear to be in line with some of these previous findings. Dupont et al. (2000) suggested that the elevated number of perseverative errors committed during the assessment of attention in patients with PD could be related to impaired inhibitory ability. Although that study compared patients with PD to controls, the present study, like Dupont

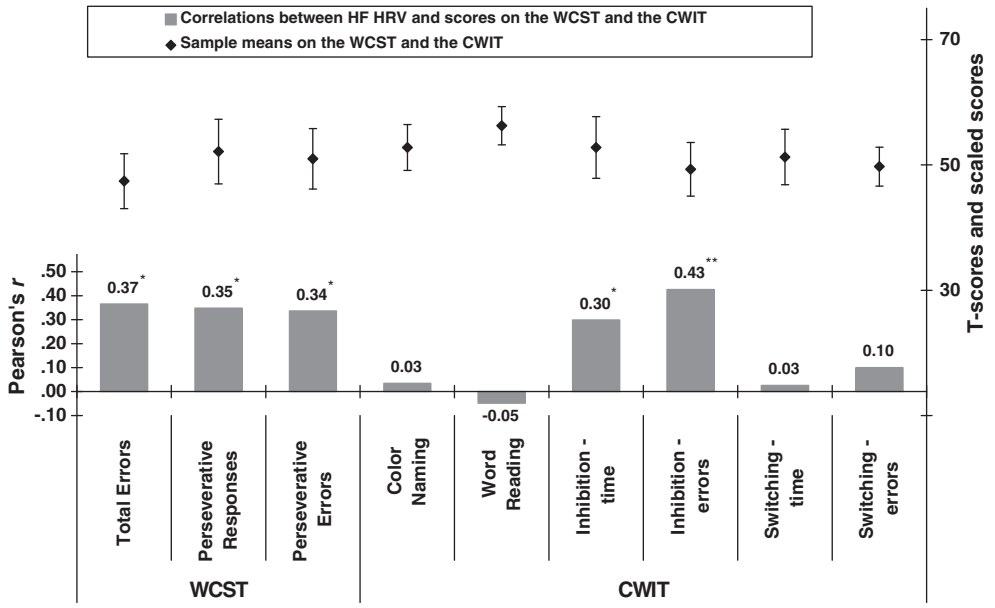

Fig. 1. Bar chart of the correlations between high frequency (HF) HRV and subscores on the WCST (Wisconsin Card Sorting Test) and the CWIT (Color-Word Interference Test). The line-graph shows the sample means for the corresponding tests, and error-bars provide 95% confidence interval. Note that CWIT scaled scores and corresponding confidence widths have been multiplied by five, and that non-significant correlations have been greyed out for illustration. *=$p<.05$; **=$p<.01$ (one-tailed).

et al.'s, suggests that cognitive inhibition is related to the clinical state of PD. However, the association between clinical variables and executive functioning found in the current study are at odds with the findings by Asmundson et al. (1994). Regarding HRV and panic-related variables, previous assessments of the relationship between these have mainly yielded negative findings (Alvarenga et al., 2006; Yeragani et al., 1990, 1993). Yeragani et al. (1990, 1993) assessed the relationship between HRV and state anxiety, and concluded that fluctuations in state anxiety levels did not seem to affect the relationship between HRV and the clinical state of PD. Alvarenga et al. (2006) on the other hand, investigated the association between the ASI and HRV. Anxiety sensitivity has been shown to play an important part in PD (Schmidt et al., 1999) predicting spontaneous panic attacks. Although anxiety sensitivity is related to PD, it is unclear how the current findings can be reconciled with the previous findings cited above. It is noteworthy that panic frequency was not correlated with either cognitive or physiological measures, although previous studies have shown that frequency of panic attacks are not necessarily related to measures of severity and duration (Chambless, 1985; Craske and Barlow, 1988). The current results suggest that the abovementioned cognitive and physiological variables are more closely related to clinical variables reflecting the development of PD (i.e. panic duration), and the impact the disorder is having on the patient (i.e. panic-related distress). However, as the associations between clinical variables and cognitive and physiological variables were investigated exploratory, these findings should be interpreted with caution.

As the present study is based on a cross-sectional design, we are precluded from concluding that HRV and executive functions, such as cognitive inhibition, change in concert, although both the current results and those of previous studies have shown that these variables are positively related. However, the previously mentioned study by Hansen et al. (2004) indicated that a decrease in HRV was indeed accompanied by equivalent changes on measures of executive functioning. Furthermore, results from a study by Brosschot et al. (2006) indicated that it is the perseverative cognitive processing that augments and reinforces the impact of events on the individual. Research on the relationship between infant temperament and cardiac vagal tone has found low baseline cardiac vagal tone to be related to more negativity and greater need for calming (Huffman et al., 1998). An attempt to synthesise these previous and current findings with regard to clinical development in PD might thus be as follows: Stressful life events cause temporary changes in PFC-functioning, resulting in impaired ability for cognitive inhibition, with concomitant changes in cardiac regulation and ANS balance (Thayer et al., 2009). With reference to the study by Huffman et al. (1998), pre-existing low HRV could represent a vulnerability factor that render people more susceptible to react with stress to challenging life events. Such stressful life events are linked to the onset or exacerbation of PD (American Psychiatric Association, 2000). Such cognitive and physiological changes are believed to reduce the individuals' overall flexibility and adaptability, and render him or her vulnerable to developing hypervigilance and perseverative functioning (Eysenck et al., 2007; Thayer et al., 2009). Stressors, such as worry and spontaneous panic attacks, are then interpreted within this

Table 2
Panic-related variables and associations with neuropsychological measures and HRV.

	Panic		
	Frequency[a]	Distress[a]	Duration[b]
WCST ($N=34$)			
Total errors	.25	.05	−.26
Perseverative responses	.23	.01	−.31
Perseverative errors	.24	.03	−.31
CWIT ($N=36$)			
Color naming	−.03	−.06	−.09
Word reading	−.05	−.05	.09
Inhibition — time	.13	−.15	**−.37***
Inhibition — errors	.09	**−.27***	−.09
Switching — time	.09	−.16	−.23
Switching — errors	.22	.04	−.11
Cardiac measures ($N=36$)			
HF HRV	.05	**−.29***	**−.45****
Heart rate (HR)	.04	.23	.27

Note. WCST=Wisconsin Card Sorting Test; CWIT=Color-Word Interference Test; HF=High frequency. *=$p<.05$; **=$p<.01$ (two-tailed). Significant associations are highlighted with bold characters.
[a] Kendall's τ was used.
[b] Pearson's r was used.

vulnerable cognitive and physiological state. For some individuals, this condition is augmented and perpetuated, leading to the development of PD. With regard to the current findings, this line of reasoning could suggest that impaired cognitive inhibition lead to greater distress and an increased likelihood for patients to develop a prolonged state of anxiety and panic. The physiological changes in HRV mirror these changes. In a recent study, increased startle potentiation during anticipatory anxiety was found for patients with PD as well as those with low resting HRV (Melzig et al., 2009). Those authors concluded that both patients with PD and people with low resting HRV are in a perpetual state of apprehension, thus supporting the aforementioned developmental pattern.

The current findings highlight the importance of providing rapid help and treatment to patients with PD. HRV has been linked to all-cause mortality (Jouven et al., 2001; Thayer et al., 2010), and the predictive properties of vagally mediated HRV for participants who suffer from CVD have been widely demonstrated (Malik et al., 1996). In fact, reduced HRV in patients with PD has been linked to increased mortality (Alvarenga et al., 2006; Garakani et al., 2009; Habib, 1999; Weissman et al., 1990). Taking the high prevalence of PD in patients with CVD (American Psychiatric Association, 2000) into consideration, the link found here between PD duration and vagally mediated HRV points to the importance of early intervention. Clinical improvements following cognitive therapy for PD result in increased HRV (Garakani et al., 2009; Middleton and Ashby, 1995), which suggests that therapy for these patients might have cardioprotective properties (Friedman, 2007). Furthermore, if impaired cognitive functioning and HRV are related to clinical factors, then this finding might be relevant for understanding the increased risk of comorbidity and adverse clinical developments associated with PD and panic attacks (Goodwin and Hamilton, 2002; Kessler et al., 2006; Roy-Byrne et al., 2000).

The major limitation of the current study is the correlational nature of its results; thus inferences regarding cause and effect can only be suggested. Furthermore, the investigation of relationships between clinical variables and neuropsychological and physiological variables entailed many correlations increasing the risk of Type 1 errors. In the current study subjects' HRV were assessed while standing, as this has been recommended as a sensitive and reliable measure of HRV in patients with PD (Yeragani et al., 1990, 1993). However, most of the research in this area has been conducted with subjects seated, thus questioning the generalisability of the current findings. In this regard it should be noted that we also obtained HRV-measurements with subjects seated. Seated and standing HRV correlated highly ($r = .89$, $p < .001$).

Although our aim with the current study was to investigate whether the association between HRV and executive functioning previously documented for healthy subjects also could be documented in a clinical sample of patients with PD, the inclusion of a control group would have strengthened the current findings. Another limitation of the present study concerns the time gap between the SCID-I assessment and the other measures. However, spontaneous recovery is rare in PD (Wittchen and Essau, 1993), and the repeated ratings of panic severity in the current study indicated stability of the diagnosis also in the present study. Still, as the exclusion criteria were not reassessed following this time gap, the possibility, although probably small, that some of the subjects could have changed clinical status during this time can not be completely excluded.

Among the strengths of the current study is the use of sound and recommended measures in a clinically relevant sample. Furthermore, the use of diverse (clinical, physiological and cognitive) measures reduces the risk of common method bias. Future studies should attempt to investigate these associations using longitudinal designs in at-risk samples, such as patients who suffer from CVD, a condition in which PD is prevalent (American Psychiatric Association, 2000). This design would enable researchers to investigate the temporal relationship among the factors examined in the current study.

Disclosure statement

The authors report no biomedical financial interests or other potential conflicts of interest.

Acknowledgements

Trond V. Sjøbø, Anne Øfsthus and the staff at the Solli day care unit are specifically acknowledged for their contribution to the study. We would also like to thank all other staff and participants for their help and cooperation.

This study was supported by "The National Program for Integrated Clinical Specialist and PhD-training for Psychologists" in Norway. This program is a joint cooperation between the Universities of Bergen, Oslo, Tromsø, The Norwegian University of Science and Technology (Trondheim), the Regional Health Authorities, and the Norwegian Psychological Association. The program is funded jointly by The Ministry of Education and Research and The Ministry of Health and Care Services. The study was also supported by Academy of Finland (project number 126873).

References

Ahern, G.L., Sollers, J.J., Lane, R.D., Labiner, D.M., Herring, A.M., Weinand, M.E., Hutzler, R., Thayer, J.F., 2001. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia 42, 912–921.

Airaksinen, E., Larsson, M., Forsell, Y., 2005. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. Journal of Psychiatric Research 39, 207–214.

Alvarenga, M.E., Richards, J.C., Lambert, G., Esler, M.D., 2006. Psychophysiological mechanisms in panic disorder: a correlative analysis of noradrenaline spillover, neuronal noradrenaline reuptake, power spectral analysis of heart rate variability, and psychological variables. Psychosomatic Medicine 68, 8–16.

Alvarez, J., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychology Review 16, 17–42.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. American Psychiatric Association, Washington, DC.

Appelhans, B.M., Luecken, L.J., 2006. Heart rate variability as an index of regulated emotional responding. Review of General Psychology 10, 229–240.

Asmundson, G., Stein, M., Larsen, D., Walker, J., 1994. Neurocognitive function in panic disorder and social phobia patients. Anxiety 1, 201–207.

Barbas, H., Saha, S., Rempel-Clower, N., Ghashghaei, T., 2003. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neuroscience 4, 25.

Barceló, F., Knight, R.T., 2002. Both random and perseverative errors underlie WCST deficits in prefrontal patients. Neuropsychologia 40, 349–356.

Beck, A.T., Steer, R.A., 1993. Beck Anxiety Inventory manual. The Psychological Corporation, San Antonio, TX.

Boutcher, Y.N., Boutcher, S.H., 2006. Cardiovascular response to Stroop: effect of verbal response and task difficulty. Biological Psychology 73, 235–241.

Brosschot, J.F., Gerin, W., Thayer, J.F., 2006. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. Journal of Psychosomatic Research 60, 113–124.

Butler, M., Retzlaff, P.D., Vanderploeg, R., 1991. Neuropsychological test usage. Professional Psychology: Research and Practice 22, 510–512.

Castaneda, A.E., Suvisaari, J., Marttunen, M., Perälä, J., Saarni, S.I., Aalto-Setälä, T., Lönnqvist, J., Tuulio-Henriksson, A., 2011. Cognitive functioning in a population-based sample of young adults with anxiety disorders. European Psychiatry 26, 346–353.

Chambless, D.L., 1985. The relationship of severity of agoraphobia to associated psychopathology. Behaviour Research and Therapy 23, 305–310.

Chambless, D.L., Caputo, G.C., Bright, P., Gallagher, R., 1984. Assessment of fear of fear in agoraphobics: the body sensations questionnaire and the agoraphobic cognitions questionnaire. Journal of Consulting and Clinical Psychology 52, 1090–1097.

Chambless, D.L., Caputo, G.C., Jasin, S.E., Gracely, E.J., Williams, C., 1985. The Mobility Inventory for Agoraphobia. Behaviour Research and Therapy 23, 35–44.

Cohen, H., Benjamin, J., Geva, A.B., Matar, M.A., Kaplan, Z., Kotler, M., 2000. Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. Psychiatry Research 96, 1–13.

Craske, M.G., Barlow, D.H., 1988. A review of the relationship between panic and avoidance. Clinical Psychology Review 8, 667–685.

de Geus, E.J.C., Willemsen, G.H.M., Klaver, C.H.A.M., van Doornen, L.J.P., 1995. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biological Psychology 41, 205–227.

Delaney, J.P.A., Brodie, D.A., 2000. Effects of short-term psychological stress on the time and frequency domains of heart-rate variability. Perceptual and Motor Skills 91, 515–524.

Delis, D.C., Kaplan, E., Kramer, J.H., 2001. Delis-Kaplan Executive Function System (D-KEFS). Norwegian version Pearson Assessment, Stockholm.

Dennis, M., Francis, D.J., Cirino, P.T., Schachar, R., Barnes, M.A., Fletcher, J.M., 2009. Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. Journal of the International Neuropsychological Society 15, 331–343.
Dupont, H., Mollard, E., Cottraux, J., 2000. Visuo-spatial attention processes in panic disorder with agoraphobia: a pilot study using a visual target discrimination task. European Psychiatry 15, 254–260.
Duschek, S., Muckenthaler, M., Werner, N., Reyes del Paso, G.A., 2009. Relationships between features of autonomic cardiovascular control and cognitive performance. Biological Psychology 81, 110–117.
Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion 7, 336–353.
Ferguson, G.A., Takane, Y., 1989. Statistical analysis in psychology and education. McGraw-Hill, New York, 587 pp.
Field, A.P., 2009. Discovering statistics using SPSS. SAGE publications Ltd., London.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). Biometric Research Departement, New York State Psychiatric Institute, New York.
Friedman, B.H., 2007. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biological Psychology 74, 185–199.
Garakani, A., Martinez, J.M., Aaronson, C.J., Voustianiouk, A., Kaufmann, H., Gorman, J.M., 2009. Effect of medication and psychotherapy on heart rate variability in panic disorder. Depression and Anxiety 26, 251–258.
Gladsjo, J.A., Rapaport, M.H., McKinney, R., Lucas, J.A., Rabin, A., Oliver, T., Davis, J., Auerbach, M., Judd, L.L., 1998. A neuropsychological study of panic disorder: negative findings. Journal of Affective Disorders 49, 123–131.
Goldman-Rakic, P., 1998. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. In: Roberts, A.C., Robbins, T.W., Weiskrantz, L. (Eds.), The Prefrontal Cortex: Executive and Cogntive Functions. Oxford University Press, Oxford, pp. 87–102.
Goodwin, R.D., Hamilton, S.P., 2002. Early-onset fearful panic attack: a possible prodrome of early-onset severe psychopathology. Comprehensive Psychiatry 43, 22–27.
Habib, G., 1999. Reappraisal of heart rate as a risk factor in the general population. European Heart Journal Supplements 1, 2–10.
Hansen, A.L., Johnsen, B.H., Thayer, J.F., 2003. Vagal influence on working memory and attention. International Journal of Psychophysiology 48, 263–274.
Hansen, A.L., Johnsen, B.H., Sollers, J.J., Stenvik, K., Thayer, J.F., 2004. Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. European Journal of Applied Physiology 93, 263–272.
Heaton, R., Staff, P.A.R., Goldin, J., 2003. WCST: CV4 Wisconsin Card Sorting Test: Computer Version 4 research edition user's manual. Psychological Assessment Resources. Inc., Lutz, FL.
Howell, D.C., 2012. Statistical methods for psychology. Wadsworth Pub Co, Belmont.
Huffman, L.C., Bryan, Y.E., Carmen, R.d., Pedersen, F.A., Doussard-Roosevelt, J.A., Porges, S.W., 1998. Infant temperament and cardiac vagal tone: assessments at twelve weeks of age. Child Development 69, 624–635.
Johnsen, B.H., Thayer, J.F., Laberg, J.C., Wormnes, B., Raadal, M., Skaret, E., Kvale, G., Berg, E., 2003. Attentional and physiological characteristics of patients with dental anxiety. Journal of Anxiety Disorders 17, 75–87.
Jouven, X., Zureik, M., Desnos, M., Guérot, C., Ducimetière, P., 2001. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. Cardiovascular Research 50, 373–378.
Kashdan, T.B., Rottenberg, J., 2010. Psychological flexibility as a fundamental aspect of health. Clinical Psychology Review 30, 865–878.
Kessler, R.C., Chiu, W.T., Jin, R., Ruscio, A.M., Shear, K., Walters, E.E., 2006. The Epidemiology of Panic Attacks, Panic Disorder, and Agoraphobia in the National Comorbidity Survey Replication. Archives of General Psychiatry 63, 415–424.
Klein, E., Cnaani, E., Harel, T., Braun, S., Ben-Haim, S.A., 1995. Altered heart rate variability in panic disorder patients. Biological Psychiatry 37, 18–24.
Lane, R.D., McRae, K., Reiman, E.M., Chen, K., Ahern, G.L., Thayer, J.F., 2009. Neural correlates of heart rate variability during emotion. NeuroImage 44, 213–222.
Lautenbacher, S., Spernal, J., Krieg, J.-C., 2002. Divided and selective attention in panic disorder. European Archives of Psychiatry and Clinical Neuroscience 252, 210–213.
Lewis, G.F., Furman, S.A., McCool, M.F., Porges, S.W., 2012. Statistical strategies to quantify respiratory sinus arrhythmia: are commonly used metrics equivalent? Biological Psychology 89, 349–364.
Lippa, S.M., Davis, R.N., 2010. Inhibition/switching is not necessarily harder than inhibition: an analysis of the D-KEFS color-word interference test. Archives of Clinical Neuropsychology 25, 146–152.
Malik, M., Bigger, J., Camm, A., Kleiger, R., Malliani, A., Moss, A., 1996. Guidelines: Heart Rate Variability, Standards of measurement, physiological interpretation, and clinical use. European Heart Journal 17, 354–381.
Mathewson, K.J., Jetha, M.K., Drmic, I.E., Bryson, S.E., Goldberg, J.O., Hall, G.B., Santesso, D.L., Segalowitz, S.J., Schmidt, L.A., 2010. Autonomic predictors of Stroop performance in young and middle-aged adults. International Journal of Psychophysiology 76, 123–129.
Melzig, C.A., Weike, A.I., Hamm, A.O., Thayer, J.F., 2009. Individual differences in fear-potentiated startle as a function of resting heart rate variability: implications for panic disorder. International Journal of Psychophysiology 71, 109–117.
Middleton, H.C., Ashby, M., 1995. Clinical recovery from panic disorder is associated with evidence of changes in cardiovascular regulation. Acta Psychiatrica Scandinavica 91, 108–113.
Middleton, H.C., Ashby, M., Robbins, T.W., 1994. Reduced plasma noradrenaline and abnormal heart rate variability in resting panic disorder patients. Biological Psychiatry 36, 847–849.
Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. Journal of Abnormal Psychology 110, 40–48.
Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cognitive Psychology 41, 49–100.
Richards, J.E., Casey, B.J., 1991. Heart rate variability during attention phases in young infants. Psychophysiology 28, 43–53.
Ridderinkhof, K.R., van den Wildenberg, W.P.M., Segalowitz, S.J., Carter, C.S., 2004. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain and Cognition 56, 129–140.
Roy-Byrne, P.P., Stang, P., Wittchen, H.-U., Ustun, B., Walters, E., Kessler, R.C., 2000. Lifetime panic-depression comorbidity in the National Comorbidity Survey. The British Journal of Psychiatry 176, 229–235.
Schmidt, N.B., Lerew, D.R., Jackson, R.J., 1999. Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: replication and extension. Journal of Abnormal Psychology 108, 532–537.
Schwartz, J.B., Gibb, W.J., Tran, T., 1991. Aging effects on heart rate variation. Journal of Gerontology 46, M99–M106.
Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1983. Manual for the State-Trait Anxiety Inventory (Form Y). Consulting Psychologists Press, Palo Alto, CA.
Stroop, J.R., 1935. Studies of interference in serial verbal reactions. Journal of Experimental Psychology 18, 643–662.
Suess, P.E., Porges, S.W., Plude, D.J., 1994. Cardiac vagal tone and sustained attention in school-age children. Psychophysiology 31, 17–22.
Tarvainen, M.P., Ranta-Aho, P.O., Karjalainen, P.A., 2002. An advanced detrending method with application to HRV analysis. IEEE Transactions on Biomedical Engineering 49, 172–175.
Ter Horst, G.J., 1999. Central autonomic control of the heart, angina, and pathogenic mechanisms of post-myocardial infarction depression. European Journal of Morphology 37 (4), 257–266.
Thayer, J.F., Hansen, A.L., Saus-Rose, E., Johnsen, B.H., 2009. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Annals of Behavioral Medicine 37, 141–153.
Thayer, J.F., Yamamoto, S.S., Brosschot, J.F., 2010. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. International Journal of Cardiology 141, 122–131.
Thayer, J.F., Åhs, F., Fredrikson, M., Sollers, J.J., Wager, T.D., 2012. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neuroscience & Biobehavioral Reviews 36, 747–756.
van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Witter, M.P., Merkelbach, J., Cath, D.C., van Balkom, A.J.L.M., van Oppen, P., van Dyck, R., 2005. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Archives of General Psychiatry 62, 922–933.
Waldstein, S.R., Bachen, E.A., Manuck, S.B., 1997. Active coping and cardiovascular reactivity: a multiplicity of influences. Psychosomatic Medicine 59, 620–625.
Weissman, M.M., Markowitz, J.S., Ouellette, R., Greenwald, S., Kahn, J.P., 1990. Panic disorder and cardiovascular/cerebrovascular problems: results from a community survey. The American Journal of Psychiatry 147, 1504–1508.
Welsh, M.C., Pennington, B.F., 1988. Assessing frontal lobe functioning in children: views from developmental psychology. Developmental Neuropsychology 4, 199–230.
Wittchen, H.-U., Essau, C.A., 1993. Epidemiology of panic disorder: progress and unresolved issues. Journal of Psychiatric Research 27 (Supplement 1), 47–68.
Yeragani, V.K., Balon, R., Pohl, R., Ramesh, C., Glitz, D., Weinberg, P., Merlos, B., 1990. Decreased R R variance in panic disorder patients. Acta Psychiatrica Scandinavica 81, 554–559.
Yeragani, V.K., Pohl, R., Berger, R., Balon, R., Ramesh, C., Glitz, D., Srinivasan, K., Weinberg, P., 1993. Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. Psychiatry Research 46, 89–103.