High psychosis liability is associated with altered autonomic balance during exposure to Virtual Reality social stressors

Jacqueline Counotte a,⁎, Roos Pot-Kolder a,b, Arie M. van Roon c, Olivier Hoskam d, Mark van der Gaag a,b, Wim Veling a,e,f

a Parnassia Psychiatric Institute, Kiwistraat 43, 2552 DH The Hague, The Netherlands
b VU University, Department of Clinical Psychology, De Boelelaan 1105, 1081 HV Amsterdam, The Netherlands
c University of Groningen, University Medical Center Groningen, Department of Vascular Medicine, PO Box 30.001, 9700 RB Groningen, The Netherlands
d GGZ Delfland, Sint Jorisweg 2, 2612 GA Delft, The Netherlands
e Maastricht University, Department of Psychiatry and Neuropsychology, PO Box 616, 6200 MD Maastricht, The Netherlands
f University of Groningen, University Medical Center Groningen, Department of Psychiatry, PO Box 30.001, 9700 RB Groningen, The Netherlands

1. Introduction

Experiences of social stress are likely to be involved in the aetiology of psychotic disorders (van Os et al., 2010, 2008). Developmental trauma, densely populated urban environments and ethnic minority status are consistently associated with increased risk for psychotic disorders (van Os et al., 2010). Repeated exposure to social stress may lead to stress sensitisation, an increased response to social stressors in daily life, with cumulative effects resulting in lasting liability to emotional and psychotic reactivity (Collip et al., 2008). Stress sensitisation may involve neuroendocrine and physiological responses, including the autonomic stress response. The autonomic nervous system regulates unconscious bodily functions including heart rate, respiratory rate, sweat production and digestion. It is divided into the parasympathetic and the sympathetic branch, classically associated with “rest-and-digest” vs. “fight-and-flight” responses, respectively. Both parasympathetic and sympathetic activity is generally present and increase of activity in one branch is not necessarily accompanied by decreased activity in the other branch. Spectral analysis of heart rate variability can be used as a tool to study autonomic balance and relative contributions of each branch. The heart rate naturally fluctuates and variability in heart rate is considered a sign of cardiac adaptability. Rhythms of fluctuations occur at different frequencies. Parasympathetic input by the vagal nerve is related to respiration and mostly increases variance in the high frequency (HF) spectrum (Akselrod et al., 1981; European Society of Cardiology, 1996). On the other hand, oscillations at the low frequency (LF) band are determined by both sympathetic and parasympathetic activity and are correlated with baroreflex activity (European Society of Cardiology, 1996; Pagani et al., 1986; Pomeranz et al., 1985). Previous research of cardiac autonomic control suggests the overall balance of the autonomic nerve system is disrupted in psychosis.

Keywords: Schizophrenia; Virtual Reality; Psychological stress; Parasympathetic nervous system; Sympathetic nervous system; Heart rate variability; Heart rate; Cardiac autonomic control; High psychosis liability; Virtual Reality social stressors.

Article history:
Received 13 April 2016
Received in revised form 16 November 2016
Accepted 16 November 2016
Available online 22 November 2016

Abstract

Background: Social stressors are associated with an increased risk of psychosis. Stress sensitisation is thought to be an underlying mechanism and may be reflected in an altered autonomic stress response. Using an experimental Virtual Reality design, the autonomic stress response to social stressors was examined in participants with different liability to psychosis.

Method: Fifty-five patients with recent onset psychotic disorder, 20 patients at ultra-high risk for psychosis, 42 siblings of patients with psychosis and 53 controls were exposed to social stressors (crowdedness, ethnic minority status and hostility) in a Virtual Reality environment. Heart rate variability parameters and skin conductance levels were measured at baseline and during Virtual Reality experiments.

Results: High psychosis liability groups had significantly increased heart rate and decreased heart rate variability compared to low liability groups both at baseline and during Virtual Reality experiments. Both low frequency (LF) and high frequency (HF) power were reduced, while the LF/HF ratio was similar between groups. The number of virtual social stressors significantly affected heart rate, HF, LF/HF and skin conductance level. There was no interaction between psychosis liability and amount of virtual social stress.

Conclusion: High liability to psychosis is associated with decreased parasympathetic activity in virtual social environments, which reflects generally high levels of arousal, rather than increased autonomic reactivity to social stressors.

© 2016 Elsevier B.V. All rights reserved.
Compared to healthy controls, patients with psychotic disorders had increased heart rate and decreased heart rate variability (Bär et al., 2005; Boettger et al., 2006; Chang et al., 2013; Clamor et al., 2014; Moon et al., 2013). Spectral analysis of heart rate variability consistently showed reduced power in the high frequency (HF) spectrum, thus pointing to decreased parasympathetic activity (Montaquila et al., 2015). Decreased parasympathetic input was correlated with more severe psychopathology (Chung et al., 2013; Toichi et al., 1999) and may result in an impaired capacity to recover from sympathetic activation in response to tasks or stressors (Akar et al., 2015; Castro et al., 2008; Montaquila et al., 2015).

It is yet unknown whether this aberrant autonomic response to stressors in psychosis patients generalizes to social stressors. One study investigated autonomic response to social stress using a video-recorded speech anticipation task, but this experiment did not trigger an autonomic response in psychosis patients or controls (Lincoln et al., 2015). To facilitate further understanding of autonomic stress response and the mechanism of stress sensitisation, there is a need for new experimental designs that allow control of intensity and type of ecological valid social stressors. Using Virtual Reality (VR), we designed an interactive 3-dimensional virtual world containing the social stress paradigms of high population density, ethnic minority status and hostile social environments, allowing the random allocation of individuals with different liability for psychosis to controlled experimental social stress environments (Yung et al., 2005). Exposure to social virtual stressors elicited paranoid thoughts and subjective distress in a dose-response manner (Yung et al., 2014). Participants with a high liability for psychosis reported more self-reported paranoia and subjective distress to virtual social environments.

The aim of this study was to examine the autonomic stress response in participants with different liability to psychosis before and during exposure to virtual social environments with varying levels of social stressors. We hypothesized, first, parasympathetic input is decreased in people with higher psychosis liability. Second, we expected increased sympathetic activation when the number of virtual social stressors is increased. Third, we expected an increased reactivity to increased social stressors in the high liability group related to a lack of parasympathetic compensation.

2. Methods

2.1. Participants

Individuals aged 18–35 with different phenotypic liability to psychosis were included: (1.) 55 patients with a first diagnosis of any psychotic disorder - except for substance-induced psychotic disorder and psychotic disorder due to a medical condition - established within the last five years, (2.) 20 patients at ultra-high risk (UHR) for psychosis, according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria (Yung et al., 2005), (3.) 42 unaffected siblings of patients diagnosed with a psychotic disorder and (4.) 53 controls with a negative (first-degree family) history of any psychotic disorders. UHR and psychosis patients were classified as having high psychosis liability and siblings and controls as low psychosis liability, based on (a) phenotype of (subsyndromal) psychotic symptoms, which is present in UHR and psychosis patients and uncommon in siblings and controls (b) life time risk for psychosis, which is 100% in psychosis patients, 36% in UHR patients (Fusar-Poli et al., 2013), 10% in siblings and 3% in controls from the general population (van Os et al., 2009). Patients and siblings were recruited from four psychiatric institutions in the Netherlands. Controls were recruited from the same communities through flyers in public facilities, including schools for vocational education and dentistry practices. Exclusion criteria were poor command of the Dutch language, an IQ lower than 75 and a history of epilepsy. The study was approved by the medical ethical committee of Leiden University Medical Centre. Written informed consent was obtained from all participants.

2.2. Virtual Reality experiments

The experiments are described in detail elsewhere (Veling et al., 2016). The virtual environment was a bar with an indoor and outdoor area, built by CleVR using Vizard software. Participants wore a Sony HMZ-T1 Head Mounted Display with a HD resolution of 1280 × 720 per eye, a 51.6 diagonal field of view, a built-in 3DOF tracker for head rotation and built-in headphones. Participants navigated the VR environment using a joystick on a Logitech F310 gamepad. Virtual humans (avatars) were sitting or standing at a table, chatted and had drinks. Bar background noises were played. The number of avatars, their ethnic appearance (white European vs. mainly North-African) and their reactions towards the participant (friendly vs. hostile staring) were manipulated to created five conditions. In the (1.) no stress condition, the café was quiet, with friendly avatars of mostly the same ethnicity as the participant. In the (2.) condition with one stressor, the café was crowded. There were two conditions with two stressors; (3.) a crowded café with friendly avatars mostly of an ethnicity other than that of the participant and (4.) a crowded café with hostile avatars of mostly the same ethnicity. In the (5.) condition with three stressors, the café was crowded with hostile avatars of mostly another ethnicity. All subjects were exposed to all five conditions for 4 min each in one session in the morning. The design was cross-over with a random order of experiments, except that the last experiment always had at least two stressors. Participants were asked to refrain from use of alcohol and illicit drugs 48 h before the experiment.

2.3. Measures

In all subjects, electronic self-report questionnaires were administered to obtain information about medical history, length, weight, use of psychotropic and other (including over-the-counter) medication, substance use (smoking, alcohol, cannabis/THC and illicit drugs) and sociodemographic characteristics including sex, age, ethnicity and education level. Subjects were classified Dutch if both parents and subject were born in the Netherlands. The self-report Simulator Sickness Questionnaire (SSQ) (Kennedy et al., 1993) was administered before and after Virtual Reality experiments. The SSQ score before was subtracted from the SSQ score after Virtual Reality to quantify the occurrence of cyber sickness symptoms, which can occur due to the slight delay between vestibular input and visually-induced perception of self-motion during Virtual Reality exposure.

Heart rate (HR) and skin conductance level (SCL) were recorded on the non-dominant hand in standing position for 3 min at baseline and for 4 min while participants engaged in the Virtual Reality environment. SCL was measured using a sensor with two finger electrodes on the middle and ring finger of the same hand with a sampling rate of 10 Hz. HR was assessed by non-invasive pulse wave measurement using a Mindmedia Nexus 4 with a photo-electric plethysmograph on the index finger. After initial visual inspection of interbeat intervals (IBIs) and exclusion of unusable signals, artefacts were corrected by linear interpolation using the CARSPAN software program. Only recordings with at least 90 s of adequate signal and no >10% correction of the signal were included. The standard deviation of the normal-to-normal IBIs (SDNN) was calculated. Spectral analysis (Fast Fourier transformation) of corrected IBIs was performed with CARSPAN with the low frequency (LF) domain defined as 0.04–0.14 Hz and the high frequency (HF) domain as 0.15–0.40 Hz. LF was considered to reflect parasympathetic activity only and LF both parasympathetic and sympathetic input. The LF/HF ratio was calculated as a measure of sympathetic activity. The average SCL was calculated over the same time intervals. SCL was considered a pure measure of sympathetic activity, as sweat glands are only innervated by sympathetic nerves.
2.4. Statistics

All analyses were conducted with IBM SPSS version 23. Continuous variables were inspected for normal distribution and log transformed (ln) to achieve a normal distribution if necessary. Sociodemographic characteristics were compared between groups using a one-way analysis of variance (ANOVA) with Dunnett’s post-hoc comparisons for continuous variables and χ² tests for categorical variables. Group differences on baseline measures of HR, ln(SDNN), ln(LF) and ln(HF) were examined by multivariate analysis of variance (MANOVA), as these variables theoretically represent a similar underlying concept and were intercorrelated. If the multivariate test statistic was significant, one-way ANOVAs with three predetermined contrasts (high vs. low liability, psychosis vs. UHR and siblings vs. controls) were used to examine group differences in detail. For ln(LF/HF ratio) and ln(SCL), only one-way ANOVAs were performed. If covariates (age, sex, ln(BMI), smoking, cannabis/THC use, ethnicity, education and use of psychotropic, contraceptive or other relevant medication) were associated with outcome measures at significant or trend level (p < 0.1) in separate MANCOVAs, they were included in an adjusted MANCOVA model and post-hoc ANCOVAs to examine if differences between groups persisted.

For the analyses of the effects of virtual social stressors on heart rate variability parameters, multilevel random intercept regression models were used, taking into account the repeated measure structure of the data and allowing for missing data. The unadjusted model was built in five steps, each adding one parameter. First, a regression model with HR, ln(SDNN), ln(LF), ln(HF), ln(LF/HF ratio) or ln(SCL) as dependent variable and number of virtual stressors as independent variable was fitted. The model was adjusted by entering variability parameters, multilevel random intercept regression models are shown in Table 3. The adjusted MANCOVA remained significant at trend level (V = 0.225, F(12, 300) = 0.029, p = 0.022) with a moderate effect size (η² = 0.075). The direction or significance of effects in post-hoc ANCOVA’s was not affected.

3. Results

3.1. Sociodemographics

Heart rate variability data was available for 45 controls, 37 siblings, 17 individuals at ultra-high risk (UHR) for psychosis and 44 patients with a recent onset psychotic disorder. Sociodemographic characteristics of the study sample are displayed in Table 1. Patients with a psychotic disorder were more likely to be male and have lower education levels than controls. UHR patients were relatively younger and more likely to have smoked in the last 24 h than controls. Both UHR and psychosis patients were more likely to use psychotropic medication than controls. For none of the participants of the UHR group this included an antipsychotic.

3.2. Baseline measures

Baseline results are depicted in Fig. 1. Using Pillai’s trace, the MANOVA performed on heart rate (HR), SDNN, low frequency (LF) and high frequency (HF) indicated a significant effect of group on heart rate variability parameters (V = 0.207, F(12, 312) = 1.927, p = 0.031) with a moderate effect size (η² = 0.069).

Post-hoc ANOVA’s (Table 2) indicated group differences in HR, SDNN and LF. High liability groups (UHR and psychosis patients) had significantly increased HR and significant decreased SDNN, LF and HF compared to low liability groups (unaffected siblings and controls). Psychosis patients did not differ significantly from UHR patients on heart rate variability parameters, nor did siblings differ from controls. However, there was a trend for increased HR and decreased SDNN and HF in siblings compared to controls. The LF/HF ratio did not significantly differ between groups. The skin conductance level (SCL) did not differ significantly between groups at baseline.

When covariates were added to the MANOVA one at a time, sex, age, ethnicity and contraceptive use were associated with outcome measures at significant or trend level (p < 0.1). However, contraceptive use was not associated with outcome measures when sex was also considered. Thus, only sex, age and ethnicity were included in the adjusted models. The adjusted MANCOVA remained significant (V = 0.225, F(12, 300) = 0.029, p = 0.022) with a moderate effect size (η² = 0.075). The direction or significance of effects in post-hoc ANCOVA’s was not affected.

3.3. Virtual Reality experiments

Means of heart rate variability parameters and SCL for each group during Virtual Reality experiments are displayed in Fig. 2. Adjusted B coefficients of parameters that contributed significantly to the fit of the multilevel random intercept regression models are shown in Table 3. Similar to findings at baseline, groups with a high likelihood of psychosis had increased HR, decreased SDNN, decreased LF and decreased HF compared to groups with low psychosis likelihood. SCL and LF/HF ratios did not differ between psychosis liability groups.

The number of stressors significantly affected HR, HF, LF/HF and SCL. Both mean HR and SCL first increased from the no stress condition to the condition with one virtual stressor (crowdedness) and subsequently decreased with the addition of more virtual stressors, HF and SDNN first decreased and then increased as virtual social stressors were added. This effect was significant for HR, SCL and HF, but not for SDNN. LF/HF ratio slightly increased when the virtual environment contained more social stressors. There was no significant effect of virtual stressors on LF. Adjustment for age, sex, ethnicity and symptoms of cyber sickness did not affect direction or significance of effects of social stressors and psychosis liability on outcome measurements.

For none of the measures an interaction effect between psychosis liability group and number of virtual stressors was found, indicating that the effect of increasing social stress on heart rate variability and skin conductance level did not differ between psychosis liability groups.

Table 1

<table>
<thead>
<tr>
<th>Sociodemographic characteristics of the study sample.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups of participants</td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Native Dutch</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Note. Values displayed are median (interquartile range) or N (%). p-Values of ANOVA (for continuous variables) or χ² tests (for categorical variables) are given. UHR = patients at ultra-high risk for psychosis, BMI = body mass index.

* Percentage of all females within group.
4. Discussion

4.1. Main findings

High psychosis liability was associated with increased heart rate and decreased heart rate variability at rest and during exposure to virtual social environments. Both HF and LF power were decreased, whereas LF/HF ratio and skin conductance levels were unaltered compared to low liability groups. The differences indicate decreased parasympathetic activity and mostly unaltered sympathetic input in individuals with high psychosis liability. Increase of social stress in virtual social environments resulted in increased heart rate, skin conductance level and decreased heart rate variability at rest and during exposure to virtual social riskors.

HF power in all liability groups – an increase in sympathetic activity and decrease in parasympathetic activity. There was no interaction effect of psychosis liability with increasing social stress on autonomic activity. Thus, the high level of arousal of patients with (ultra-high risk for) psychosis during exposure to social stressors reflects generally high levels of arousal, rather than increased autonomic reactivity to increase in social stressors.

4.2. Meaning of findings

These findings complement our previous work showing increased subjective stress in high psychosis liability groups in virtual social risk environments, but no interaction between psychosis liability and number of stressors (Veling et al., 2016) and show high psychosis liability is associated with chronically increased subjective and autonomic stress levels, rather than increased stress reactivity. If autonomic and subjective stress is chronically high and increases in reaction to daily social stress as our results show, this may result in excessive dopamine release in the striatum, which in turn could lead to aberrant assignment of salience to stimuli, the cognitive interpretation of which may produce negative affective and psychotic symptoms (Garety et al., 2007; Howes and Murray, 2014).

Our findings are in line with previous studies showing psychosis patients had similar autonomic responses as control subjects to an arithmetic task (Castro et al., 2009) and white noise (Akar et al., 2015), but were characterized by prolonged activation during recovery or when listening to calming music (Akar et al., 2015; Castro et al., 2008). In contrast to our findings, studies using the experience sampling method (ESM) found evidence for increased stress reactivity of affective and psychotic symptoms in UHR and psychosis patients (Myin-Germeys et al., 2001; Palmier-Claus et al., 2012; Reininghaus et al., 2016). The social stressors in our Virtual Reality study were relatively minor stressors, experimentally controlled and therefore the same for each participant in the study, whereas ESM studies rely on the subjectively self-report of naturally occurring stressors, whose exact nature is unknown to the researcher, different on each occasion for each participant and potentially more personally relevant and intense. Impaired recovery from stress could be more easily misinterpreted as increased reactivity.

Table 2

One-way ANOVA of group difference in heart rate (variability) and skin conductance level at baseline.

<table>
<thead>
<tr>
<th>ANOVA</th>
<th>Post hoc contrasts</th>
<th>$F$</th>
<th>$df$</th>
<th>$p$</th>
<th>$\eta^2$</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>High vs. low liability</td>
<td>3.000</td>
<td>3, 105</td>
<td>0.034</td>
<td>0.799</td>
<td>2.599</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.730</td>
<td>0.467</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.349</td>
<td>0.180</td>
</tr>
<tr>
<td>ln(SDNN)</td>
<td>High vs. low liability</td>
<td>5.263</td>
<td>3, 105</td>
<td>0.002</td>
<td>0.131</td>
<td>-3.248</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.342</td>
<td>0.733</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.472</td>
<td>0.144</td>
</tr>
<tr>
<td>ln(LF)</td>
<td>High vs. low liability</td>
<td>4.863</td>
<td>3, 105</td>
<td>0.003</td>
<td>0.122</td>
<td>-3.329</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.470</td>
<td>0.639</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.658</td>
<td>0.512</td>
</tr>
<tr>
<td>ln(HF)</td>
<td>High vs. low liability</td>
<td>3.716</td>
<td>3, 105</td>
<td>0.014</td>
<td>0.096</td>
<td>-2.242</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.934</td>
<td>0.352</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.535</td>
<td>0.128</td>
</tr>
<tr>
<td>ln(LF/HF)</td>
<td>High vs. low liability</td>
<td>1.713</td>
<td>3, 105</td>
<td>0.169</td>
<td>0.407</td>
<td>-2.087</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.529</td>
<td>0.598</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.043</td>
<td>0.299</td>
</tr>
<tr>
<td>ln(SCL)</td>
<td>High vs. low liability</td>
<td>0.928</td>
<td>3, 102</td>
<td>0.430</td>
<td>0.027</td>
<td>0.958</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>UHR vs. psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.550</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>Siblings vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.343</td>
<td>0.732</td>
</tr>
</tbody>
</table>

Note. HR = heart rate, SDNN = standard deviation of the normal-to-normal interbeat intervals, LF = low frequency, HF = high frequency, SCL = skin conductance level, UHR = patients at ultra-high risk for psychosis, $\eta^2$ = partial eta squared effect size (0.01 = small effect, 0.06–0.14: moderate effect, >0.14 large effect).
in ESM studies, whereas our VR model was possibly not sensitive enough to detect impaired stress recovery, as we did not include post-exposure resting phase measures. Furthermore, the psychosis patients in our study were treated naturalistically at outpatient facilities and their stress reactivity may have been somewhat dulled by treatment effects. Indeed, they reported lower levels of paranoid symptoms than the UHR group, suggesting partial recovery (Veling et al., 2016).

We classified UHR and psychosis patients as having high liability for psychosis and siblings and controls as having low liability for psychosis, based on phenotype and lifetime risk for psychosis. This dichotomous classification was used to optimize statistical power and limit multiple testing issues. However, it clearly represents a simplification of what is in reality considered a continuum of psychosis liability. The somewhat artificial cut-offs used by us and others might explain seemingly contradictory results. For example, within the high liability group, we did not find any significant difference between psychosis and UHR patients, whereas an earlier study found that individuals with attenuated psychosis symptoms had autonomic responses similar to healthy controls (Clamor et al., 2014). Our UHR population consisted of help-seeking individuals with attenuated psychotic symptoms and affected social functioning, with a yearly conversion risk to psychosis of over 20% (Rietdijk et al., 2012). This risk is vastly lower in populations of non-help seeking individuals with attenuated psychosis symptoms (<1%) (Kaymaz et al., 2012). Within the low liability group, we found a trend for unaffected siblings to have increased heart rate, decreased SDNN and HF power at baseline. Attenuated abnormalities in parasympathetic input were previously found in unaffected first-degree relatives of schizophrenia patients (Bør et al., 2010; Berger et al., 2010), but not replicated in others (Castro et al., 2009). Other studies also included parents and offspring, who have higher genetic risk and more pronounced autonomic dysfunction (Bør et al., 2010) than siblings. Overall, our results indicate that psychosis symptoms in siblings and ultra-high risk patients increase stress reactivity beyond what is observed in unaffected siblings and ultra-high risk patients, adding to previous work and suggesting that autonomic dysregulation occurs more along the continuum of the extended psychosis phenotype.

Table 3

<table>
<thead>
<tr>
<th>Parameter estimates</th>
<th>HR</th>
<th>Ln(SDNN)</th>
<th>Ln(LF)</th>
<th>Ln(HF)</th>
<th>Ln(LF/HF)</th>
<th>Ln(SCL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>80.30</td>
<td>4.25</td>
<td>7.67</td>
<td>7.15</td>
<td>0.50</td>
<td>7.93</td>
</tr>
<tr>
<td>Stressors</td>
<td>1.06 [0.21; 1.90]</td>
<td>0.014</td>
<td>0.731</td>
<td>0.663</td>
<td>&lt;0.001</td>
<td>0.013 [0.014-0.012]</td>
</tr>
<tr>
<td>Stressors²</td>
<td>−0.40 [−0.67; 0.06]</td>
<td>0.005</td>
<td>0.640</td>
<td>0.620</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Liability</td>
<td>7.11 [3.13; 11.08]</td>
<td>0.001</td>
<td>−0.19 [−0.30; 0.00]</td>
<td>0.001</td>
<td>−0.33 [−0.62; 0.04]</td>
<td>0.025</td>
</tr>
<tr>
<td>Variance components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>107.99</td>
<td>0.07</td>
<td>0.46</td>
<td>0.55</td>
<td>0.30</td>
<td>0.44</td>
</tr>
<tr>
<td>Residual</td>
<td>8.50</td>
<td>0.02</td>
<td>0.13</td>
<td>0.09</td>
<td>0.11</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Note: Values displayed are adjusted B coefficients [95% confidence intervals] and p-values for fixed effects and variance components of multilevel random intercept regression models, adjusted for age, sex, ethnicity and cyber sickness symptoms. Models include only parameters that significantly improved the fit of the model for specified outcome measure. HR = heart rate, SDNN = standard deviation of the normal-to-normal interbeat intervals, LF = low frequency, HF = high frequency, UHR = patients at ultra-high risk for psychosis.

* High liability (ultra-high risk and psychosis patients) vs. low liability (unaffected siblings and controls).
The relation between amount of social stress and heart rate, skin conductance level and HF was not linear. Instead, there was a reverse U-shaped effect of social stressors and measures of autonomic activation. We do not have a ready explanation for this finding. A sensitivity analysis showed experiment order could have confounded the increased sympathetic activity, but not the decreased parasympathetic activity (results available on request).

4.3. Limitations

There was a relatively high level of missing data during Virtual Reality experiments. Some participants were unable to complete all Virtual Reality experiments due to cyber sickness, resulting in missing data. Cyber sickness is comparable to motion sickness, which is associated with altered parasympathetic input (Farmer et al., 2014). Increase of symptoms during virtual experiments was included in the statistical models and was not associated with outcome measures of included experiments. Other measures were excluded because of a high level of artefacts. We used photoplethysmography to detect interbeat intervals. While this is considered a reliable alternative to ECG data, artefacts may have been induced by movement of participants, who were navigating the Virtual Reality environment using a joystick and by turning their body.

Known or unknown confounders could have affected the results. Use of antipsychotic medication has been shown to aggravate HRV abnormalities (Huang et al., 2013; Iwamoto et al., 2012). In our study use of psychotropic medication was not correlated significantly nor at trend level with outcome measures. Moreover, our sample included psychosis patients that did not use antipsychotics and none of the UHR patients used antipsychotic medication. Thus, it is unlikely that antipsychotic use can account for the results of this study, which is consistent with previous studies (Bär et al., 2005; Malaspina et al., 2002).

4.4. Implications

Decreased parasympathetic input and reduced heart rate variability is an independent risk factor for cardiovascular mortality and often co-occurs with other, modifiable cardiovascular risk factors (Thayer et al., 2010). Life expectancy in schizophrenia is reduced by 10–25 years, mostly due to excess mortality from cardiovascular disease (Laursen, 2011). This highlights the importance of prevention, screening and treatment of modifiable cardiovascular risk factors, such as smoking, inactivity, glucose intolerance and obesity in psychosis patients. Our findings also highlight the importance of stress management programs.

Conflict of interest

The authors have no conflict of interest.

Contributors

Authors M.G. and W.V. designed the study. Authors J.C., R.-P., and O.H. conducted the study. Authors J.C. and A.R. conducted the data analysis. Author J.C. undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Acknowledgements

This work was supported by a Veni laureate to Dr. Veling from the Netherlands Organisation for Health Research and Development (916.12.013). The authors wish to thank Mathijs Deen, who assisted with the statistical analysis.

References

Anderson, C., So, S.H., Hubbard, K., Beards, S., Dazzan, P., Paramante, C., Mondelli, V.,
Fisher, H.L., Mills, J.G., Viechtbauer, W., McGuire, P., van Os, J., Murray, R.M., Wykes,
T., Myin-Germeys, I., Morgan, C., 2016. Stress sensitivity, aberrant salience, and threat
anticipation in early psychosis: an experience sampling study. Schizophr. Bull. 42,
712–722.

Rietdijk, J., Klaassen, R., Ising, H., Dragt, S., Nieman, D.H., van de Kamp, J., Cuipers, P.,
Linszen, D., van der Gaag, M., 2012. Detection of people at risk of developing a first
21–30.

141, 122–131.

Toichi, M., Kubota, Y., Murai, T., Kamio, Y., Sakihama, M., Toriuchi, T., Inakuma, T.,
Sengoku, A., Miyoshi, K., 1999. The influence of psychotic states on the autonomic
nervous system in schizophrenia. Int. J. Psychophysiol. 31, 147–154.

van Os, J., Rutten, B.P., Poulton, R., 2008. Gene-environment interactions in schizophrenia: a
review of epidemiological findings and future directions. Schizophr. Bull. 34,
1066–1082.

van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systemat-
ic review and meta-analysis of the psychosis continuum: evidence for a psychosis
proneness-persistence-impairment model of psychotic disorder. Psychol. Med. 39,
179–195.

van Os, J., Kenis, G., Rutten, B.P.F., 2010. The environment and schizophrenia. Nature 468,
205–212.

Veling, W., Brinkman, W.-P., Dorrestijn, E., van der Gaag, M., 2014. Virtual reality experi-

Veling, W., Pot-Kolder, R., Counotte, J., Van Os, J., van der Gaag, M., 2016. Environmental

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell’Olio, M., Franey, S.M.,
Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckley, J., 2005. Mapping the
onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust.