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Specificity of resting-state heart rate variability in psychosis: A comparison with clinical high risk, anxiety, and healthy controls

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ABSTRACT

Maladaptability, particularly of autonomic activity, is described as a central component of vulnerability-stress-models for the pathogenesis of psychotic symptoms. Investigating heart rate variability (HRV) as an index of autonomic adaptability is thus likely to improve our understanding of psychosis. In clinically vulnerable groups for psychosis, it is unclear whether maladaptability is already evident. Moreover, to investigate specificity, direct comparisons to other mental disorders are required. In the present study, we analyzed 3 min of resting-state heart rate, HRV, and negative affect in 130 participants; consisting of participants with psychotic disorders (PSY; $n = 44$), clinical high-risk for psychosis (CHR; $n = 22$), anxiety disorders (anxiety controls, AC; $n = 29$) and healthy controls (HC; $n = 35$). ANCOVAs controlling for age revealed significant group differences for both investigated vagal HRV parameters, which were reduced in PSY compared to HC. The high-frequency domain HRV in PSY was also lower than in CHR and – in a non-significant trend – than in AC. Also, ANOVAs for heart rate and negative affect revealed significant increases in PSY compared to HC. Exploratory analyses of medication effects showed moderate dosage associations with heart rate and high-frequency HRV. Thus, in the present study, the activity of the autonomic nervous system was altered in psychosis but not in an at-risk group. A potential specificity of the effect can be speculated in contrast to anxiety disorders. Future studies should investigate the predictive value of HRV for increased stress-sensitivity or transition to clinical symptoms as well as the implications for daily threat perception and symptom maintenance.

1. Introduction

The conventional idea that health resembles complete well-being has been challenged by a redefinition of the concept, wherein health is described as "the ability to adapt and to self-manage" (Huber et al., 2011). In line with this conception, the lack of adaptability (i.e., *maladaptability*) is a central component in different vulnerability-stress-models that explain the occurrence of mental disorders. In the pathogenesis of psychotic symptoms, maladaptability of the autonomic nervous system has been considered to be important, both as part of the enduring vulnerability and as characterizing the states prior to the transition to clinical symptoms (Nuechterlein and Dawson, 1984). In recent years, there has been a resurge of interest in autonomic processes due to a better understanding of the role of heart rate variability (HRV), an informative and readily assessable index of autonomic adaptability that stems from the regulatory fluctuations of the heart rate and reflects vagal activity in particular (see Laborde et al., 2017). Therefore, by investigating HRV, researchers seek to improve the understanding of the formation of psychotic symptoms in light of potential autonomic maladaptability. In fact, previous research has found significantly reduced resting-state HRV in patients with manifest psychotic disorders when compared to healthy controls, that appears to occur irrespective of age, duration of disorder or medication status (for a recent meta-analysis see Clamor et al., 2016). However, several questions remain unanswered. One is whether autonomic alterations are also evident in vulnerable groups without a manifest clinical disorder. Another is whether and to what extent autonomic maladaptability is specific to psychotic disorders. Finally, the potentially exacerbating influence of antipsychotics needs further exploration.

The vulnerability-stress-models (Nuechterlein and Dawson, 1984) would predict that autonomic alterations are also evident in vulnerable groups. Although there are several studies showing this in individuals at familial risk for psychosis (e.g., Bär et al., 2012; Castro et al., 2009) and at early/prodromal, acute first-episode stages (e.g., Cacciotti-Saija et al., 2018; Valkonen-Korhonen et al., 2003), studies with individuals screened for established clinical high-risk criteria are scarce. In one study on participants with increased symptomatic vulnerability, no alterations were found compared to healthy controls (Clamor et al., 2014). However, in a recent study applying the full ultra-high-risk criteria for psychosis, these individuals were found to exhibit greater autonomic alterations than non-risk

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controls (Counotte et al., 2016). Thus, further research in samples meeting the high-risk criteria is needed.

In addition, it is not clear to what extent autonomic maladaptability is specific to psychotic disorders, as reduced vagal activity has also been found in other disorders such as depression (e.g., Kemp et al., 2010), borderline personality disorder (Koenig et al., 2016) or anxiety disorders (Chalmers et al., 2014). Putatively though, the extent of reduction varies among disorders. In a meta-analysis across different disorders, the findings alluded to a large effect size, indicating lower HRV in psychosis, as opposed to small effect sizes for other disorders, when contrasted with healthy controls (Alvares et al., 2016). Potentially, anxiety may be an important factor that could contribute to the autonomic maladaptivity: In a subgroup with comorbid anxiety, a large effect of diminished HRV was found when individuals with major depressive disorders were compared to healthy controls, which was medium in size in the subgroup without anxiety (Kemp et al., 2012). However, research that *directly* compares people with psychosis to those with anxiety disorders or comparisons with other disorders are rare. In one such study, young participants with early psychosis showed significantly reduced HRV compared to the socially anxious controls (Cacciotti-Saija et al., 2018). In another study, we compared participants with psychosis to participants with depression and found significantly lower HRV in the psychosis group (Clamor et al., 2014). Taken together, HRV seems to be more reduced in psychosis than in other disorders when contrasted with healthy controls, but further studies with direct comparisons of different mental disorders are required to corroborate this assumption. Anxiety disorders are a meaningful comparison group for psychosis due to the relevance of anxiety for positive symptom formation (Garety et al., 2001) and several similar maintenance mechanisms, such as safety behaviours and avoidance.

Finally, autonomic alterations have been reported for medicated as well as unmedicated patients, suggesting that medication does not fully explain the effect (see Clamor et al., 2016). However, an exacerbating influence of antipsychotics on cardiac risk and particularly detrimental effects of clozapine have been discussed (Alvares et al., 2016). It has been proposed that the muscarinic affinity of antipsychotic medication leads to autonomic alterations and that anticholinergic medication may further influence HRV (Huang et al., 2013). Previous studies have attempted to account for this by controlling for chlorpromazine equivalents (Kimhy et al., 2010) or categorizing medication by potential relevance (Clamor et al., 2014). Nevertheless, for an effective handling in research and practice, precise knowledge on the impact of classes, doses or interaction of different medication is needed.

Thus, in the present study, we investigated whether participants with psychotic disorders (PSY), participants at clinical high-risk for psychosis (CHR), participants with anxiety disorders (anxiety controls, AC) and healthy controls (HC) differ in their pattern of baseline autonomic activity and the corresponding self-reported affect (i.e., a subjective comparison dimension). In detail, we hypothesized that PSY would show more stress at rest (i.e., maladaptivity). This would be evident in increased heart rate, decreased HRV, and increased negative affect compared to HC and CHR. Furthermore, CHR were expected to show more alterations compared to HC, and PSY were expected to show more alterations compared to AC. Finally, we considered potential effects of medication type and dosage in exploratory analyses.

2. Methods

2.1. Participants

The study was conducted at the Universität Hamburg as part of a project on emotion regulation (DFG: LI-1298/7-1; see also Lincoln et al., 2017). The presented physiological data from the project has not been published before. We recruited the participants in in- and outpatient treatment settings and via databases of our laboratory, leaflets, advertisements in local newspapers, and the Internet. Inclusion criteria were age 18 to 65 years, sufficient German language abilities, the ability to provide informed consent, and an estimated IQ > 85. Exclusion criteria were the presence of acute suicidality, macroscopic neurological disorders, dementia, bipolar disorder, and substance dependence in the last 6 months.

Diagnostic criteria for all participants were verified with the structured Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). PSY were required a) to fulfill the criteria for a current psychotic disorder, or b) to either have met the criteria for a psychotic disorder within the past two years or c) to have met the criteria for a psychotic disorder at an earlier time point and to still be receiving antipsychotic medication and to be presenting with at least two symptoms rated ≥3 or one symptom ≥4 in the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). CHR had to fulfill the criteria of a prodromal syndrome, defined by the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003). The syndromes include attenuated positive symptoms, brief intermittent psychotic symptoms or genetic risk plus reduced functioning by 30% within at least one month during the past year. Exclusion criteria were present or past psychotic disorders. For AC, inclusion criteria were diagnoses of at least one of the following disorders: a) social phobia, b) panic disorder (with agoraphobia), or c) generalized anxiety disorder (GAD). Exclusion criteria were a psychotic disorder or prodromal syndrome. For HC, exclusion criteria were a) any clinically relevant current Axis-I disorder, b) any disorder that required treatment in the past, c) any first-degree relative with a psychotic disorder, and d) taking medication for any type of mental problem. AC and HC were matched to PSY for age, gender, and education.

The final sample consisted of 165 participants. For the psychophysiological analyses in this study, additional exclusion criteria needed to be applied, which were (a) nonsufficient quality or absence of three-minute baseline blood volume pulse data ($n = 1$, AC), (b) current intake of cardiac medication (e.g., beta-blocking, angiotensin converting enzyme inhibitors; $n = 17$ [$n = 6$ PSY, $n = 2$ CHR, $n = 7$ AC, $n = 2$ HC]), (c) cardiac illness or reported abnormalities ($n = 16$ [$n = 9$ PSY, $n = 1$ CHR, $n = 3$ AC, $n = 3$ HC]), and potentially relevant substance abuse (e.g., daily cannabis consumption, $n = 1$, PSY).

In total, 130 participants were analyzed. PSY comprised 44 participants (diagnoses: $n = 31$ schizophrenia, $n = 11$ schizoaffective disorder, $n = 1$ delusional disorder, $n = 1$ brief psychotic disorder), either acute ($n = 24$) or remitted ($n = 20$) with a mean total PANSS score of 56.5 ($SD = 13.4$). CHR comprised 22 participants, $n = 17$ fulfilled the prodromal syndrome with attenuated positive symptoms, $n = 1$ prodromal syndrome with genetic risk and functioning reduction, and $n = 4$ prodromal syndrome with attenuated positive symptoms and genetic risk with functioning reduction. All of the CHR participants fulfilled a diagnosis (present or past). The present diagnoses (comorbidities possible) were affective disorders ($n = 11$), PTSD ($n = 4$), anxiety disorders ($n = 10$), eating disorders ($n = 2$) or substance abuse ($n = 1$). Within the $n = 29$ AC participants, the diagnoses were social phobia ($n = 4$), panic disorder with ($n = 4$) or without agoraphobia/lifetime ($n = 8$), agoraphobia without panic disorder ($n = 1$), GAD ($n = 3$), or several of the aforementioned anxiety disorders in comorbidity ($n = 9$). All but one AC participant additionally fulfilled the criteria for another disorder (present or past), the majority being major depressive episodes. The mean duration of disorder (in months) from the participants reporting it was 150 ($SD = 126$) for $n = 44$ PSY, 167 ($SD = 170$) for $n = 2$ CHR, and 228 ($SD = 155$) for $n = 27$ AC. Finally, HC comprised 35 participants.

For more detailed sample characteristics, see Table 1. The groups did not differ significantly in regard to gender, age, or cigarette consumption but in years of education (PSY > CHR, AC), symptoms of depression (CHR > PSY, AC > HC) and paranoia (PSY, CHR > AC > HC).

2.2. Procedure

We prescreened individuals via telephone. Those who met inclusion criteria for one of the groups were invited to the lab and provided

written informed consent before participation. The procedure involved three assessment days, including two different experiment days in randomized order (see Lincoln et al., 2017). After the total procedure, the participants were debriefed and received monetary compensation for their time. The procedure was approved by the Ethics Committee of the German Psychological Society (DGPs).

The psychophysiological data reported here were recorded at the baseline assessment prior to a social exclusion paradigm (either experimental day one or two). All participants were instructed to refrain from caffeine and nicotine at least 2 h prior to the assessments. After connecting the participants to the psychophysiology system, they were instructed to sit still and relax for about 5 min. From this baseline, we extracted a three-minute period for the analyses (see Section 2.3.1).

2.3. Outcome parameters

2.3.1. HRV

Heart rate was recorded with Nexus 32A, MindMedia, using the software Biotrace+ via photoplethysmography to detect the blood volume pulse from index finger of the non-dominant hand with a sampling rate of 256/s. An interval length of 3 min was chosen to estimate baseline heart rate and HRV. R-peak detection was manually corrected and heart rate and time- and frequency-domain HRV analyses were conducted with Kubios HRV Premium 3.0.1 and 3.0.2 (© Kubios Oy). For HRV, two recommended parameters reflecting vagal activity were calculated (see Laborde et al., 2017): First, the root mean square of successive differences (RMSSD) and second, the high-frequency (HF, 0.15–0.4 Hz) HRV, applying the Fast Fourier Transformation for spectral analyses (e.g., Task Force, 1996). The values were logarithm transformed.

2.3.2. Negative affect

After the baseline, participants were asked to rate the extent of their current negative emotions within a well-validated 4-item, 11-point rating scale (1 = “not applicable”, 11 = “applicable”; Stemmler et al., 2001). Each of the four items consisted of four descriptive adjectives to describe one emotion (i.e., shame: embarrassed/ridiculed/ashamed/foolish, fear: frightened/timid/afraid/scared, sadness: sad/depressed/miserable/dejected, and anger: angry/annoyed/mad/sore). To capture the total extent of negative affect, items were combined to one mean scale with acceptable internal consistency (0.79).

2.4. Current medication

Medication (defined as daily oral intake/depot injection of prescriptive drugs) was categorized (see Clamor et al., 2014 for details on the procedure) as a) no medication of any type during past month (*No*); b) medication with muscarinic receptor activity (*ACh*); c) medication with influences via α-adrenergic or other relevant pathways (i.e., K+ inflow, Ca disposal, indirect sympathomimetic characteristic, agonist β2 activity, interaction with β1-receptors; *OthRel*); and d) medication with no or minor relevant activity (*Minor*). In cases of multiple drugs, we assigned the category with most potential influences on the autonomic nervous system (No < Minor < OthRel < ACh). Additionally, in PSY, we calculated chlorpromazine equivalents (Benkert and Hippius, 2006). Finally, we categorized whether PSY participants were receiving a) no antipsychotic, b) monotherapy with an antipsychotic, c) more than one antipsychotic, or d) one antipsychotic plus another type of medication (e.g., benzodiazepines).

2.5. Statistical analysis

One-way analyses of variance (ANOVAs) or χ^2-tests were used to compare demographic data across groups and univariate analyses of covariance (ANCOVAs) were used to analyze group differences in heart rate, HRV, and self-reported negative affect. Partial η^2 was reported as an indicator of effect size. In the first analyses, covariates to explore putative confounding effects included years of education (due to the between-group differences) as well as number of cigarettes smoked per day and age (due to the potential effects on autonomic activity). In this step, only age was a significant covariate of the analyses with HRV as the dependent variable. Thus, we retained age as the only covariate in the analyses of HRV and conducted ANOVAs in the remaining cases. For significant group effects, post-hoc pairwise comparisons (Sidak adjusted) were calculated.

To analyze potential medication effects, the AN(C)OVAs with physiological values as the dependent variables were additionally conducted with medication category as a second between subject factor next to group (excluding the interaction from the design). Within PSY only, Pearson's correlations were calculated for chlorpromazine equivalents and the dependent variables and nonparametric Kruskal-Wallis tests were calculated to analyze the effect of categorization regarding monotherapy.

Table 1
Sample characteristics and analyses of between-group differences.

	Total sample	Groups of participants				*F*	χ^2
	N = 130	PSY *n* = 44	CHR *n* = 22	AC *n* = 29	HC *n* = 35	*p*	*p*
Female *n*	85	27	16	19	23		.840
Age	37.8 (11.9)	37.6 (11.2)	33.0 (14.1)	40.4 (12.0)	38.9 (10.8)	.151	
Education in years	11.7 (1.6)	12.1_a (1.4)	11.2_b (1.5)	11.2_b (1.6)	$11.9_{a,b}$ (1.6)	.032	
k Cigarettes per day	3.4 (7.9)	4.8 (9.8)	2.8 (5.6)	4.3 (9.3)	1.0 (3.6)	.169	
BDI	15.3 (11.6)	16.9_a (9.9)	24.5_b (11.8)	18.9_a (10.0)	4.6_c (5.8)	<.001	
PCL	31.4 (15.5)	39.1_a (18.5)	40.4_a (13.2)	27.1_b (9.7)	19.5_c (2.3)	<.001	
Medication *n*							<.001
None	59	6	11	10	32		
ACh	31	24	1	6	0		
OthRel	24	7	6	8	3		
Minor	16	7	4	5	0		
With antipsychotic medication *n*	43 (33%)	36 (82%)	4 (18%)	3 (10%)	0 (0%)		

Note. Values indicate group means (standard deviations) unless otherwise specified. Education refers to school education, without academic degrees. PSY = psychosis; CHR = clinical high-risk for psychosis; AC = anxiety controls; HC = healthy controls; BDI = Beck Depression Inventory; PCL = Paranoia Checklist; None = no regular intake of oral/injective prescriptive drugs within last month; ACh = muscarinic receptor activity; OthRel = other relevant influences, α-adrenergic or other activity; Minor = no or minor autonomic influences.
Values in each row that share subscripts do not differ significantly (Least Significance Difference post-hoc, $p \geq .05$).

3. Results

3.1 Main analyses

The observed group means and standard deviations are presented in Table 2. The ANCOVAs with age as a significant covariate revealed significant group differences for RMSSD, $F(3,125) = 6.216$, $p = .001$, $\eta^2_p = 0.130$, and for HF, $F(3,125) = 7.205$, $p < .001$, $\eta^2_p = 0.147$. Post-hoc pairwise comparisons (see Fig. 1) revealed that RMSSD was significantly lower in PSY compared to CHR ($p = .006$) and to HC ($p = .002$). In HF, PSY differed significantly from CHR ($p = .004$), from HC ($p < .001$) and in a nonsignificant trend from AC ($p = .065$). The ANOVAs for heart rate, $F(3,126) = 3.681$, $p = .014$, $\eta^2_p = 0.081$, and for negative affect, $F(3,126) = 6.114$, $p = .001$, $\eta^2_p = 0.127$, were both significant. Post-hoc pairwise comparisons (see Fig. 1) revealed that HR was significantly increased in PSY compared to HC ($p = .024$) and in a non-significant trend compared to CHR ($p = .066$). In negative affect, HC had significantly lower ratings that PSY ($p = .001$) and CHR ($p = .005$). Additionally, dot-plot figures showing the individual, unstandardized predicted values of the ANCOVAs are presented in the online supplementary material (Appendix A).

3.1. Medication effects

In the AN(C)OVAs for autonomic arousal with medication category as a second between subject factor, all analyses continued to yield at least trend effects for group (heart rate: $p = .092$, RMSSD: $p = .004$, and HF: $p = .003$), while the between-subject factor of medication category was nonsignificant (heart rate: $p = .577$, RMSSD: $p = .498$, HF: $p = .746$).

Putative further effects of medication were analyzed in PSY only. We found significant correlations for the chlorpromazine equivalent dose ($M = 472.6$, $SD = 478.6$, $n = 41$) with heart rate, $r = 0.398$, $p = .010$, and HF, $r = -0.329$, $p = .036$, but not with RMSSD, $r = -0.172$, $p = .283$. In the non-parametric comparisons of autonomic arousal of PSY receiving no antipsychotics ($n = 8$), PSY receiving antipsychotic monotherapy ($n = 11$), PSY receiving more than one antipsychotic ($n = 15$) and PSY receiving an antipsychotic plus another type of medication ($n = 10$), no significant differences were evident. However, there was a non-significant trend towards differences in RMSSD ($p = .052$; see Fig. 2). In exploratory post-hoc tests, the RMSSD in the participants receiving antipsychotics plus another medication was higher than in the group receiving multiple antipsychotics ($p = .038$), but also than in the group receiving no antipsychotic ($p = .048$). Non-significant trends were evident for the group receiving a mono-therapeutic antipsychotic to show increased RMSSD compared to no antipsychotics ($p = .067$) and multiple antipsychotics ($p = .056$).

Table 2
Means (standard error) for outcome variables.

	PSY $n = 44$	CHR $n = 22$	AC $n = 29$	HC $n = 35$
Heart rate	82.44 (2.01)	74.12 (3.83)	77.58 (2.57)	73.29 (1.85)
HF	299.92 (57.83)	1379.26 (609.67)	619.10 (157.05)	870.92 (200.65)
RMSSD	28.22 (2.13)	49.39 (8.08)	34.84 (4.15)	44.00 (4.29)
Negative affect	13.20 (1.40)	13.73 (1.82)	10.66 (1.27)	6.60 (0.76)

Note. PSY = psychosis; CHR = clinical high-risk for psychosis; AC = anxiety controls; HC = healthy controls; HF = high frequency HRV; RMSSD = root mean square of successive differences HRV.

3.2. Supplementary analyses

To investigate whether the found effects were attributable to other disorder related factors, we additionally correlated the HRV measures with symptom scores and duration of disorder in PSY. The PANSS scores of the positive subscale were significantly associated with RMSSD ($r = -0.335$, $p = .026$) but not HF ($r = -0.286$, $p = .060$). The general symptoms subscale was significantly associated with both, RMSSD ($r = -0.323$, $p = .032$) and HF ($r = -0.305$, $p = .044$). For the negative symptoms subscale, a nonsignificant trend in the non-expected direction was shown with RMSSD ($r = 0.293$, $p = .053$) but not with HF ($r = 0.132$, $p = .393$). Neither RMSSD ($r = -0.104$, $p = .503$) nor HF ($r = -0.149$, $p = .334$) were significantly associated with the duration of disorder in months.

4. Discussion

The present study investigated autonomic arousal and subjective negative affect in a sample with acute and remitted psychotic disorders, comparing the participants to diverse control groups. To our knowledge, the study is the first to directly compare a psychosis sample to a control group with different anxiety disorders and concurrently to participants who meet the ultra-high-risk criteria of psychosis verified in a structured interview.

First of all, a large effect of reduced vagal HRV, increased heart rate, and increased negative affect at rest was replicated when comparing a sufficiently large sample of individuals with psychotic disorders to HC. The findings went beyond the effects of age, which was included as a covariate. Importantly, reduced HRV was associated with more positive and general symptomatology measured in the PANSS interview and not associated with duration of disorder. Thus, it might be tentatively speculated that disorder related processes (i.e., symptoms) rather than the associated progress in health deterioration (e.g., immobility, length or medication exposure) are associated with the effect. Thus, reduced vagal HRV is highly relevant for investigating psychopathology (see Kemp and Quintana, 2013), also given its close links to processes such as threat inhibition, emotion regulation and executive functioning (e.g., Clamor et al., 2015; Thayer et al., 2012; Williams et al., 2015). The findings concur with previous evidence on HRV in psychosis (Clamor et al., 2016), arguing for robustness of findings.

Contrary to the expected, we did not find significant differences in autonomic arousal between CHR and HC, despite of the more pronounced negative affective state in CHR. Moreover, the high-frequency-domain HRV and heart rate were significantly higher in CHR than in PSY. Thus, the expectation that the alterations of arousal would reflect the vulnerability state was not confirmed. In line with previous research (Clamor et al., 2014), this would argue for the idea that autonomic alterations are linked to diagnosable clinical psychosis rather than constituting a general vulnerability characteristic that is evident before the onset of a full disorder. It needs noting, though, that our findings contradict other research arguing for maladaptivity by showing increased autonomic arousal for at-risk individuals to be similar to psychosis (Counotte et al., 2016). However, both samples were rather small and further research is needed to draw more definite conclusions. On a different note, previous research comparing subjective and physiological indicators of stress showed a larger discrepancy in patients with psychosis and depression than in healthy controls (Söder et al., 2018). Thus, it could be an important aspect of maladaptivity that CHR diverged most in subjective and physiological adaptivity when each was compared to HC. Another explanation one could speculate upon is that in samples at-risk for psychosis, a relatively increased HRV could serve as a protective factor, thus reflecting the status of non-transition of that group at that time. Like in our sample, participants with experiences of psychotic symptoms characteristically represent the majority of the at-risk samples (Peralta et al., 2018), however, transition rates might be as low as 16% (Yung et al., 2008). As we did not follow-up

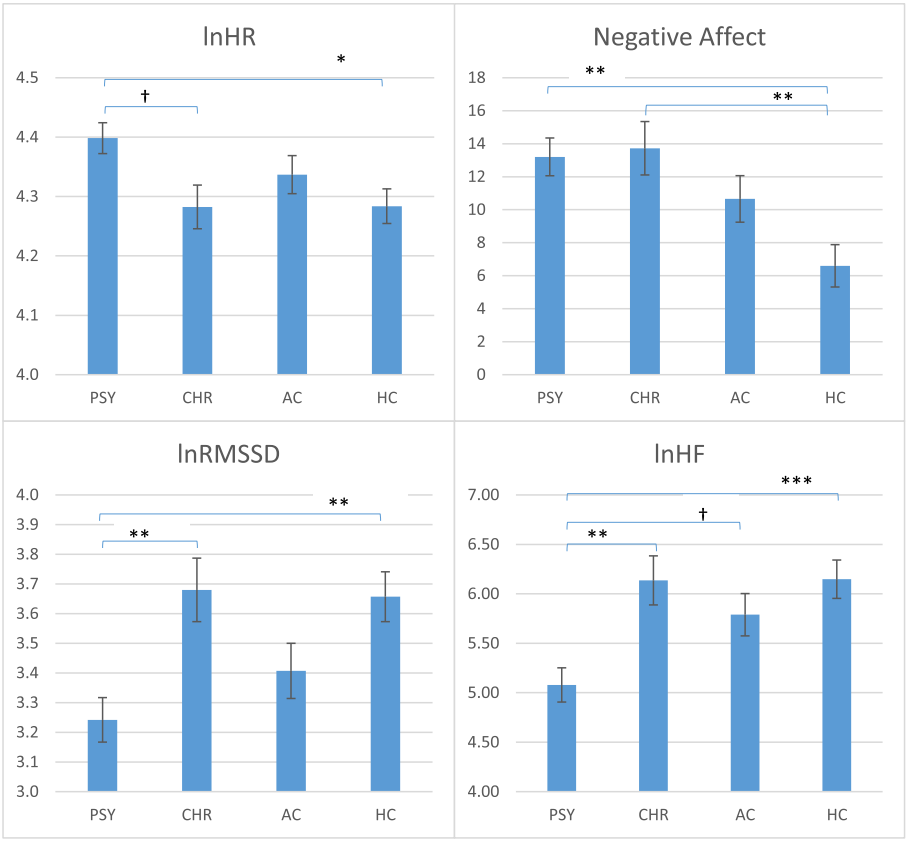

Fig. 1. Analyses of variance (lnHR, negative affect) and covariance (lnRMSSD, lnHF) and post-hoc group comparisons. PSY = participants with psychotic disorders; CHR = participants at clinical high-risk for psychosis; AC = clinical control participants with anxiety disorders, anxiety controls; HC = healthy controls; HR = heart rate; RMSSD = root mean square of successive differences; HF = high frequency HRV. Values display mean levels and standard error. Post-hoc Sidak adjusted pairwise comparisons; ***: $p < .001$, **: $p < .01$, *: $p < .05$, †: $p < .10$.

the group, comparing the "true" prodromal states to "non-transitioners" will be important for future prospective research on symptomatic vulnerability or resilience factors respectively.

In terms of specificity, we did not find significant differences in the post-hoc comparisons of PSY and AC although there was a non-significant trend indicating potentially lower high-frequency HRV for PSY. We also did not find differences in autonomic activity for AC compared to HC, which is in contrast to previous reports of reduced HRV in anxiety disorders (e.g., Chalmers et al., 2014). As this review found obsessive-compulsive disorders to be different from other anxiety disorders, we exploratorily excluded the five participants meeting the current diagnostic criteria. Still, no significant difference was evident between AC and HC in HRV. Nevertheless, it is important to note that comorbidities, particularly major depressive disorders, were prevalent in our sample, which could also be interesting in interpreting the results as indicating differences between psychosis and "common mental health conditions" rather than being specific to anxiety. Therefore, the present study contributes further evidence that at least the extent of autonomic alterations could be specific to psychosis.

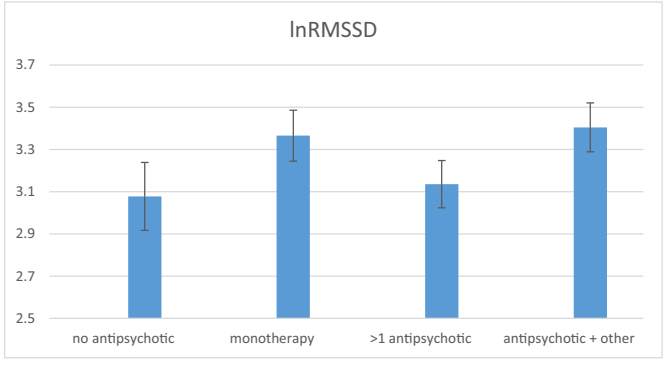

Fig. 2. Means and standard errors of the root mean square of successive differences (RMSSD) separate for categories of medication intake in the subsample with psychotic disorders.

Medication category as an additional between-group factor did not explain these group effects. This is in line with studies showing lower HRV in participants with psychotic disorders that was not solely attributable to medication effects (e.g., Clamor et al., 2014; Malaspina et al., 2002). At the same time, however, we found a higher dose of medication in PSY (i.e., chlorpromazine equivalent) to be moderately correlated with an increased heart rate and decreased high-frequency HRV. This could argue for potential medication add-on effects, which have also been found before. For example, particularly clozapine has been found to exert further detrimental effects on HRV (e.g., Alvares et al., 2016). Thus, although medication effects do not seem to explain the reduced HRV in psychosis per se, it cannot be ruled out that they account for the extent of the effects compared to other disorders (e.g., Clamor et al., 2014). Moreover, in an exploratory comparison within PSY, we showed that receiving monotherapy or receiving an antipsychotic plus another type of medication was associated with more autonomic adaptivity than receiving no or multiple antipsychotic agents. This would concur with some prospective studies indicating a reduction in autonomic arousal after antipsychotic treatment (e.g., Hempel et al., 2009). This could putatively have driven the effect of CHR showing more autonomic adaptivity than PSY, however, in that group only one participant received antipsychotic plus another type of medication and the majority ($n = 18$) received no antipsychotic. Including the four participants with

antipsychotics into the calculation of correlations with chlorpromazine dosage did not influence the reported results. In sum, despite not explaining low HRV in total, add-on effects of particular substances or dosage need to be considered. In the future, beneficial as well as harmful influences need to be investigated and the common practice of prescribing multiple antipsychotic agents should receive further attention if the presented results are confirmed.

Some limitations of the study need to be considered. First, photoplethysmography is more comfortable and easy in procedure, however, less accurate than electrocardiogram measures. Furthermore, despite meeting the recommendation of a minimum assessment of 1 min that enables an adequate measure of vagal tone and allows for frequency analysis, we were not able to report the 5 min of resting HRV that has been recommended for cross-study comparisons (Laborde et al., 2017). Also, body mass index, physical activity, and hormonal cycle were not assessed and may have impacted on the findings. Furthermore, the necessary additional exclusion criteria for the psychophysiological analyses led to a decrease in group sizes, resulting in less power for some of the comparisons. Also, as some participants had been exposed to stressors on the previous experimental day, we cannot exclude that expectation effects might have influenced the baseline on the second day. Generally, in a laboratory session, it is hard to obtain a baseline without any anticipation effects, which should be kept in mind for the interpretation of the results. Importantly though, participants were randomized for that sequence and no group differences were found for randomization plan. Finally, we did not randomize the participants to different medication groups, so no causal interpretation may be inferred and further, pre-planned analyses of these potential effects are needed.

Despite its limitations, the present study contributes to the field by once again confirming a large effect of reduced HRV in psychosis. In the presented sample, the effect of reduced HRV in psychosis was pronounced in a direct comparison to both other maladaptive threat-processing states (i.e., anxiety disorders) and clinical risk states. As we did not find the expected alterations in a high-risk sample, the extent of autonomic maladaptivity appears to be specific for clinical psychosis. While medication does not seem to explain this effect, the correlation with dosage could imply that the effect-size may not only be disorder but also treatment related – which should be investigated further. To explore the predictive value of autonomic functioning, longitudinal studies are needed to disentangle possible vulnerability from protective states. Also, it is important that future studies on autonomic functioning in psychotic disorders assess patients' cardiometabolic fitness in order to disentangle disorder from inactivity related effects. Moreover, promising new ways of assessing autonomic functioning in daily life (Cella et al., 2018) will be important to further unravel the processes associated with symptom formation and symptom maintenance.

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Conflict of interest

The authors state that no potential conflicts of interest are associated to this manuscript.

CRediT authorship contribution statement

Annika Clamor: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Johanna Sundag:** Investigation, Data curation, Formal analysis, Writing - review & editing. **Tania M. Lincoln:** Project administration, Conceptualization, Funding acquisition, Methodology, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.009.

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