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Reduced heart rate variability in a treatment-seeking early psychosis sample

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ABSTRACT

Reduced cardiac autonomic function is associated with increased risk of cardiovascular disease (CVD), with heart rate variability (HRV) providing an accessible index of cardiac autonomic function. HRV may provide a candidate physiological mechanism linking reduced cardiac autonomic function to increased risk for CVD in schizophrenia illness. This study examines whether HRV is also reduced in a community sample of treatment-seeking participants experiencing early psychosis (n = 48) compared to healthy volunteers (n = 48) and social anxiety control groups (n = 48) matched by gender and age. HRV was assessed during a five-minute interbeat interval recording at rest. Participants also completed self-report psychiatric symptom measures. Early psychosis participants showed significant reductions in HRV compared to social anxiety and healthy control groups. Reductions in HRV were also observed in early psychosis participants taking anticholinergic medications compared to both control groups taking cardio-benign medications or who were non-medicated. Lastly, whether or not early psychosis participants were taking anticholinergic medications was not associated with reductions in HRV. Findings provide preliminary evidence that early psychosis is associated with reduced HRV. This study supports further research with larger sample sizes to precisely determine the influence of anticholinergic drugs on HRV in early psychosis populations.

1. Introduction

The single most common cause of death in patients with schizophrenia is cardiovascular disease (CVD) (Capasso et al., 2008; Tiihonen et al., 2009). The relationship between schizophrenia and cardiovascular-related mortality may be mediated by reduced autonomic cardiac control (Bär et al., 2008b), which can be indexed non-invasively via the measurement of heart rate variability (HRV). HRV is defined as the fluctuation of heart period over time, commonly measured by electrocardiogram via the identification of variations between interbeat intervals. The heart-brain axis is purported to reflect the complex interaction that exists between the nervous and cardiovascular systems. A large network of cortical and subcortical brain regions direct cardiovascular function via sympathetic and parasympathetic outflow (Porges, 1995, 2003). Reduced HRV has been recognised as an early marker of cardiovascular disease (Thayer et al., 2010) and has been associated with CVD risk factors such as hypertension (Singh et al., 1998) and high cholesterol (Christensen et al., 1999). Evidence suggests that shared genetic susceptibility for schizophrenia and abnormal metabolism, as well as lifestyle issues such as smoking and poor diet, may also account for the increased risk of cardiovascular disease in patients (McCreadie, 2003). Long-term use of antipsychotic medication such as clozapine has also been speculated to increase risk for CVD (Stahl et al., 2009).

Although there is a well-established body of evidence demonstrating reductions in HRV in chronic schizophrenia (Alvares et al., 2016; Castro et al., 2008; Kim et al., 2011; Quintana et al., 2016), research is needed to determine whether a reduction in HRV has potential to provide an early biomarker that could be linked with development of psychotic illnesses (Jindal et al., 2009). “The early psychosis” period typically refers to the first three years of illness onset characterised by sustained psychotic disturbances as well as marked social, cognitive, and functional decline (Cacciotti-Saija et al., 2015a,b). This critical period coincides with several developmental challenges for young people, such as completing their education, first entering the workforce, and establishing new social networks (Birchwood, 2000; McGorry, 2000; Penn et al., 2011).

A number of theories have suggested that HRV may play a causal

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physiological role in accelerating social approach behaviour, whilst others have argued that a reduction in HRV is a consequence of adverse lifestyle factors including social withdrawal. For example, polyvagal theory proposes that the autonomic nervous system (ANS) evolved in mammals to modulate an individual's affective experience and social behaviour (Porges, 1995). This theory highlights the role of the vagus nerve (the primary nerve of the parasympathetic nervous system) in facilitating social engagement or disengagement. It suggests that optimal social interaction involving social cognitive abilities such as emotion recognition is facilitated by a calm physiological state (Porges, 2003). Thus, efficient control of the vagal 'brake' and the ANS allows for rapid engagement and disengagement with conspecifics.

Only a few studies to date have examined HRV during the early or acute stages of psychosis (Bär et al., 2008a, 2007, 2008b). For example, Jindal et al. (2009) found reduced HRV in a group of 24 first episode neuroleptic-naive psychosis patients compared to 26 healthy controls. Similarly, Valkonen-Korhonen et al. (2003) demonstrated a reduced level of integrity and reactivity in autonomic nervous function for 17 first-episode drug-naïve patients compared to 21 healthy controls. These studies however were limited by the use of inpatients, small and male-biased samples, as well as non-medicated patients, thereby limiting the generalizability of findings. Indeed, pharmacological treatments are typically used in early psychosis as a first-line of treatment (Early Psychosis Guidelines Writing Group, 2010).

Research examining neuroleptic effects on HRV in clinical populations has provided mixed findings to date. The cardiovascular impact of neuroleptics is of large clinical importance given reported associations with ventricular arrhythmias and sudden cardiac death (Agelink et al., 2001; Ray et al., 2009). While some studies have shown that tricyclic antidepressants (TCA) (for example, amitriptyline, doxepine, imipramine) and neuroleptics such as clozapine strongly reduce HRV (Agelink et al., 2001; Bär et al., 2008b; Huang et al., 2013; Rechlin et al., 1994a; Zahn and Pickar, 1993) due to their anticholinergic properties (Jakobsen et al., 1984; Rechlin et al., 1994b), other studies report no significant negative effects of neuroleptics on HRV (Bär et al., 2005; Chang et al., 2010; Malaspina et al., 2002). There appears to be more agreement however regarding the lack of a parasympathetic effect associated with selective serotonin reuptake inhibitors (SSRIs) (Kemp et al., 2010; Rechlin et al., 1994b). A recent meta-analysis involving 140 case-control (mood, anxiety, psychosis, dependent disorders) and 30 treatment studies (antidepressants, antipsychotics) by Alvares et al. (2016) investigated the effect of psychiatric illness and medication use on HRV. Results revealed reduced HRV in all patient groups compared to controls with a large effect for psychotic disorders ($g = -0.948$). Psychotropic medications were shown to have only a small impact on further reducing HRV, specifically related to mood disorders as well as TCA and Clozapine use. Interestingly, effect sizes for reduced HRV remained highly significant for medication-free patients compared to controls across all disorders suggesting that reduced HVR may have capacity to signal an underlying elevated risk for CVD in psychotic disorders. In this research, however, it is very difficult to control for the many other factors that could also mediate this association such as substance use, body mass index and physical activity due to inconsistent reporting patterns in the literature.

It is clear that more studies are needed investigating HRV in psychotic patients receiving pharmacological intervention to further understand the association between psychotic illness and cardiovascular mortality risk. In addition, research is needed about the relationship between HRV and key features of psychotic illness. It remains unclear whether HRV may provide an important marker for social functioning or other symptom severity measures (Quintana et al., 2013). For example, while Bär et al. (2008b) reported a significant negative association between HRV and symptom severity in a sample of participants with paranoid schizophrenia, other research has failed to find such an association (Jindal et al., 2009).

The primary objective of the present study was to investigate resting-state HRV in a representative sample of young people with early psychosis compared to healthy control and psychiatric control groups. For this study, our psychiatric control group were patients diagnosed with social anxiety disorder, which is also characterised by poor social functioning and reductions in autonomic cardiac control (Alvares et al., 2013). We hypothesized that individuals with early psychosis would exhibit reduced HRV relative to a healthy control group and more pronounced reductions compared to participants diagnosed with social anxiety. Moreover, we hypothesized that reduced HRV would be associated with clinical measures of symptom severity for both individuals with early psychosis and social anxiety. Lastly, we hypothesised that use of medications with potential anticholinergic or anti-muscarinic properties would result in significantly reduced levels of HRV compared to more cardio-benign medications (for example, SSRIs), as well as no medication use across groups.

2. Methods

2.1. Participants

A power analysis was conducted to assess the participants required to detect a medium effect size ($f = 0.25$; Cohen, 1988) for the main effect of group on HRV with 80% statistical power and an alpha of 0.05. This analysis revealed that 52 participants would be required per diagnostic group (early psychosis, social anxiety disorder, healthy controls), which was the recruitment target for this study. Early psychosis outpatients were recruited as part of a larger clinical trial (see Cacciotti-Saija et al., 2015a) from specialised tertiary referral services for the assessment and early intervention of mental health problems in young people (Youth Mental Health Clinic, YMHC, at the Brain and Mind Centre, BMC; and *headspace*, Campbelltown, Sydney, Australia; Inner West Area Health Service First Episode Psychosis Intervention Services) (Hickie et al., 2013). Forty-eight early psychosis outpatients were recruited (70.8% male) that met the following inclusion criteria: (a) aged between 16 and 35 years; (b) current or past diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder according to The Structured Clinical Interview for DSM-IV Axis I Diagnosis – Patient version (SCID-P), and; (c) within the first three years of treatment for psychosis. Exclusion criteria included: (a) current substance dependence on alcohol or drugs, (b) insufficient English language skills, (c) intellectual disability (IQ < 70) and; (d) history of a significant neurological disorder. Of the early psychosis group (EP group), 93.8% ($n = 45$) were taking at least one or more psychotropic medications including combinations of antipsychotics, antidepressants, mood stabilizers, anticonvulsants, anticholinergics, benzodiazepines and other medications (e.g., pain killers).

Data from social anxiety disorder and control participants were collected as part of a larger database examining autonomic cardiac control in disorders associated with social dysfunction. HRV data from 68.75% of social anxiety participants and 14.58% from controls have previously been reported in (Alvares et al., 2013), with the remainder of controls being reported in (Quintana et al., 2012). Social anxiety and control participants were individually matched to the early psychosis participants on age and gender. The social anxiety disorder group (SAD group) were recruited from the same tertiary referral services (YMHC and headspace), with general participants characteristics described elsewhere (Alvares et al., 2013). Healthy controls (Control group) were recruited from either the University of Sydney student population or the general community through advertisements and received university course credit or compensation for their participation. Exclusion criteria included a self-reported history of psychiatric illness or any other medical condition (for example, diabetes). Healthy controls were excluded if they reported current use of psychotropic medications. Social anxiety participants reported 58.3% ($n = 28$) psychotropic medication use including combinations of antipsychotics, antidepressants, mood stabilizers, anticonvulsants, stimulants, benzodiazepine and other

medications (e.g., pain killers). Out of the fifty-two social anxiety participants originally recruited for the study, four were excluded from analyses due to taking medication with known appreciable anticholinergic effects. Three subjects used quetiapine and one subject used olanzapine.

In order to prevent any confounding influences of other substances on psychophysiological functioning, all participants were asked to abstain from caffeine, cigarettes, alcohol and illicit substances on the day of testing. All participants gave written informed consent in accordance with Australian National Health and Medical Research Council guidelines. The University of Sydney Human Research Ethics Committee provided ethical approval for this research.

2.2. Measures

2.2.1. Clinical assessments

The Structured Clinical Interview for DSM-IV Axis I Diagnosis – Patient version (SCID-P; First et al., 1995) was administered to confirm diagnosis of individuals in the early psychosis group. The Anxiety Disorder Interview Schedule for DSM-IV (Brown et al., 1994) was administered to confirm diagnosis in the social anxiety group.

2.2.2. Heart rate variability

HRV data was reported in accordance with Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH) (Quintana et al., 2016). Interbeat intervals (IBIs) were collected for 5 minutes using the Polar RS800CX (Polar Electro Oy, Kempele, Finland) heart rate monitoring system at 1000 Hz. Participants were fitted with a two-lead chest strap that transmits IBIs wirelessly to the heart rate monitor. After a 2–3 minute rest period, resting IBIs were collected for 5 minutes, whilst in the seated position. Excellent agreement has been reported between Polar monitors and traditional electrocardiograms (Weippert et al., 2010).

2.2.3. Symptom severity measures

The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and The Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) are widely used tools to measure positive and negative symptoms that characterise schizophrenia. SAPS and SANS total scores are generated by summing the four and five global ratings respectively. The Depression, Anxiety and Stress Scales (DASS 21; Lovibond and Lovibond, 1995) measure the tripartite negative emotional states of depression, anxiety and stress experienced over the last week.

The Social Interaction Anxiety Scale (SIAS; Mattick and Clarke, 1998) measures anxiety and distress related to social interactions.

The Kessler Psychological Distress Scale (K-10; Kessler et al., 2002) measures levels of distress experienced over the past four weeks based on questions about anxiety and depressive symptoms.

2.3. Procedure

Clinical interviews to confirm diagnosis were administered by experienced clinical psychologists or research psychologists. A second assessment session occurred within a two-week period and involved the administration of self-report symptom severity measures, with the EP group additionally completing the SAPS and SANS with trained research psychologists. Early psychosis participants were enrolled to commence a six-week social cognition training program as part of a broader clinical research trial (Cacciotti-Saija et al., 2015a). Accordingly, IBI data were collected on the first day of group treatment, which occurred two weeks following the initial clinical assessment point. Social anxiety participants were assessed prior to commencement of a group cognitive-behavioural therapy program. The control group completed all assessments in a single session.

2.4. Data analysis

IBI data was exported from the Polar heart rate monitors to Polar ProTrainer software (PPT; version 5, Polar Electro Oy, Kempele, Finland). A text file for each IBI recording was then exported from PPT for analysis in Kubios (version 2.0, 2008, Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland, MATLAB). Five-minute IBI samples were visually inspected for movement artifacts, ectopic beats, undetected beats, or false beats. Depending on the degree visually identified artifacts, either a medium or strong (RR intervals deviating from the local mean RR interval by at least 0.25 or 0.15 seconds, respectively) correction level were selected in Kubios for corrections, using a piecewise cubic spline interpolation method. Kubios was then used to calculate absolute High Frequency (HF) HRV values (0.15–0.4 Hz), as an approximation of parasympathetic modulation of the heart (Berntson, 1997). This HRV measure was selected as it has the largest theoretical knowledgebase underlying its representation of parasympathetic modulation of the heart rate (Camm et al., 1996). The correlation between HF HRV and the root mean square of successive differences (RMSSD), which is a popular time domain HRV measure, was also calculated. A Fast Fourier transform was applied to calculate HF HRV using Welch's Periodogram (window width 256 s, 50% overlap, resampled at 4 Hz). Absolute HF HRV values were then log transformed to conform to parametric assumptions.

Analyses were conducted using the R statistical environment (version 3.3.2) using the “jmv” R package (Version 0.7.3.1; Selker et al., 2017) and “cocor” (Diedenhofen and Musch, 2015) packages, with statistical significance set at $p < 0.05$. The analysis script is available at https://osf.io/8c5sj/. Chi-squared distributions were also performed to explore differences in smoking habit distributions between groups. Univariate ANOVAs compared differences between the three groups (i.e., EP, SAD and Control groups) for demographic characteristics scores (i.e., age, DASS scores, social anxiety, and psychological distress) and HF HRV, with pairwise comparisons conducted to follow-up any significant differences and Holm corrections applied for multiple comparisons. Given a medium effect size ($d = 0.5$; Quintana, 2017) and sample of 48 participants per group, these pairwise comparisons had 68% statistical power to observe a statistically significant effect. An ANCOVA was also conducted to examine the role of age in the main effect of diagnostic group on HF HRV. To examine whether medication had any potential impact on HRV, diagnostic groups were further divided into four groups reflecting medication usage; early psychosis participants taking medications with anti-cholinergic effects (EP with AC group), early psychosis participants who were non-medicated or taking medications without appreciable anticholinergic effects (EP without AC group), social anxiety participants who were either non-medicated or taking medications without appreciable anticholinergic effects (SAD group) and healthy controls (Control group). Medications classed as ‘anticholinergic’ included antipsychotics associated with a high muscarinic affinity (e.g., chlorpromazine, olanzapine, quetiapine and clozapine), which are often multi-acting, receptor targeted antipsychotics. Additional medications classed as ‘anticholinergic’ included tricyclic antidepressants (e.g., imipramine) and anticholinergics (e.g., biperidin, benztropine) known to reduce parasympathetic modulation and subsequently impact HRV (Alvares et al., 2016; Huang et al., 2013). Psychotropic medication use for EP with AC, EP without AC and SAD groups is outlined in Table 1. In the EP without AC and SAD groups, three and nineteen participants respectively were non-medicated. Univariate ANOVAs with Holm-corrected pairwise comparisons were conducted to explore any differences in HF HRV between groups. Given a medium effect size ($d = 0.5$; Quintana, 2017) and sample of 17–48 participants per group, these pairwise comparisons had 37–68% statistical power to observe statistically significant effects. To estimate a measure of effect size for univariate ANOVAs, η^2 was calculated with effects sizes of $\eta^2 = 0.02$ interpreted as small, $\eta^2 = 0.13$ medium, and $\eta^2 = 0.26$ large (Cohen, 1988). Cohen's d was used as an effect size

Table 1
Number of early psychosis and social anxiety participants taking medications with and without anticholinergic effects.

	EP with AC (n = 31)	EP without AC (n = 17)	SAD (n = 48)
HMA Antipsychotic	19 (61.3%)	–	–
Antipsychotic	2 (6.5%)	23 (135.3%)	–
Antidepressant			
SSRI	4 (12.9%)	7 (41.2%)	6 (12.5%)
SNRI	1 (3.2%)	1 (5.9%)	5 (10.4%)
MAOI	–	–	2 (4.2%)
TCA	1 (3.2%)	–	–
Mood Stabiliser/ Anticonvulsant	–	5 (29.4%)	8 (16.7%)
Anticholinergics	1 (3.2%)	–	–
Benzodiazapine	–	1 (5.9%)	–
Stimulant	–	–	3 (6.3%)
Other	–	5 (29.4%)	10 (20.8%)

Note. Subjects took combinations of one or more medications listed.
Abbreviations: HMA/High Muscarinic Affinity. SSRI/Selective Serotonin Reuptake Inhibitor. SNRI/Serotonin-Norepinephrine Reuptake Inhibitor. MAOI/Monoamine Oxidase Inhibitor. TCA/Tricyclic Antidepressant.
Other = combination of pain killers, antibiotics, contraceptive pill, reflux medications, circadian and asthma relievers.

estimate between groups, with effects sizes of $d = 0.25$ interpreted as small, $d = 0.5$ medium, and $d = 0.9$ large (Quintana, 2017). Lastly, bivariate correlational analyses were conducted to determine associations between HF HRV with symptom severity measures using Pearson correlation coefficients, two-tailed. Fisher's z test was used for the comparison of correlations between the SAD and EP groups. A statistically significant test suggests that the magnitude of two correlations are different.

3. Results

Participant characteristics are presented in Table 2. As expected, the EP group significantly differed from controls on all self-report measures. The SAD group also reported significantly higher levels of psychiatric symptom severity than both the EP and control groups, with pairwise comparisons indicating higher levels of psychological distress in participants with social anxiety compared to the early psychosis group, which were on the border of statistical significance. Chi-squared tests revealed no differences in smoking habits ($p = 0.51$) between the three groups (i.e., EP, SAD and Control groups) and four groups (i.e., EP with AC, EP without AC, SAD and Control groups; $p = 0.61$). There was also no difference in the severity of positive $F(1, 46) = 0.97$, $p = 0.33$; $\eta^2 = 0.02$) or negative $F(1, 46) = 0.43$, $p = 0.52$; $\eta^2 = 0.01$) schizophrenia symptoms between the EP with AC and EP without AC groups. HF HRV was highly correlated with RMSSD ($r = 0.94$; $p < 0.001$; 95% CI: 0.91–0.95).

Table 2
Participant characteristics.

	Early Psychosis (n = 48)	Social Anxiety (n = 48)	Controls (n = 48)	Pairwise comparisons[a]
Age	21.94 (4.34)	22.60 (4.45)	21.96 (4.68)	–
Male/Female	34/14	34/14	34/14	–
Regular smokers (%)	9 (18.8%)	7 (14.6%)	5 (10.4%)	N.S.
DASS-D[b]	16.64 (12.52)	21.85 (9.67)	2.35 (2.86)	B < A < C
DASS-A[c]	11.66 (9.85)	17.83 (7.84)	1.67 (2.39)	B < A < C
DASS-S[c]	13.85 (10.56)	22.77 (7.89)	4.35 (4.14)	B < A < C
K10[d]	25.02 (8.67)	28.30 (7.36)	14.69 (3.00)	A = B < C
SIAS[e]	36.13 (18.79)	53.00 (13.51)	17.15 (9.48)	B < A < C

Note. A = Early Psychosis, B = Social Anxiety, C = Controls. DASS = Depression, Anxiety and Stress Scale; Depression (D), Anxiety (A), and Stress (S) subscales. K10 = Kessler Psychological Distress Scale. SIAS = Social Interaction Anxiety Scale.
[a] Pairwise comparisons derived from univariate analyses of variance.
[b] Early Psychosis n = 47, Social Anxiety n = 47, Controls n = 46.
[c] Early Psychosis n = 47, Social Anxiety n = 47.
[d] Early Psychosis n = 47, Social Anxiety n = 44, Controls n = 39.
[e] Social Anxiety n = 43, Controls n = 40.

3.1. Group differences in HRV

As shown in Fig. 1A, the overall ANOVA revealed a significant difference in HF HRV between the three groups, $F(2, 141) = 6.86$, $p = 0.001$; $\eta^2 = 0.1$). Pairwise comparisons with Holm corrected p-values indicated that HF HRV was significantly reduced in the EP group compared to the healthy control ($p = 0.001$; $d = 0.61$) and SAD ($p = 0.029$; $d = 0.42$) groups. There were no significant differences between the SAD and healthy control groups ($p = 0.25$; $d = 0.19$). An ANCOVA with these diagnostic groups as a fixed factor and age as a covariate revealed that when explaining away the error variance attributed to age, there is still a main effect of diagnostic group on HF HRV $F(2, 140) = 6.96$, $p = 0.001$; $\eta^2 = 0.09$). Posthoc pairwise comparisons of means adjusted for age with Holm corrected p-values revealed that HF HRV was significantly reduced in the EP group compared to the healthy control ($p = 0.001$; $d = 0.61$) and SAD ($p = 0.02$; $d = 0.43$) groups. There were no significant differences between the SAD and healthy control groups ($p = 0.28$; $d = 0.18$). When examining the impact of medication use on HRV, univariate ANOVA analysis indicated a significant difference in HF HRV between the four groups, $F(3, 140) = 5.50$, $p = 0.001$; $\eta^2 = 0.11$). Pairwise comparisons with Bonferroni corrections indicated that HF HRV was significantly reduced in the EP with AC group (M = 2.24, SD = 0.92) compared to healthy control (M = 2.81, SD = 0.42; $p = 0.002$; $d = 0.80$) and SAD groups (M = 2.68, SD = 0.49; $p = 0.021$; $d = 0.60$); Fig. 1B. There were no significant differences between the SAD and healthy control groups ($p = 0.32$; $d = 0.29$) or the EP without AC group (M = 2.50, SD = 0.47; $p = 0.32$; $d = 0.37$). Lastly, there were no significant differences in HF HRV between the EP with AC group and the EP without AC group ($p = 0.32$; $d = 0.18$). The EP without AC group did not significantly differ in HF HRV compared to controls ($p = 0.058$; $d = 0.70$).

3.2. Associations between HRV and symptom severity

As depicted in Table 3, bivariate correlations revealed no significant associations between absolute HF HRV scores and symptom severity scores in either the control or EP groups (Fig. S1A,B,C,D,E), all p-values > 0.05. There were, however, significant negative correlations between HF HRV and measures of anxiety, stress, and social interaction anxiety in the SAD group (Fig. S1B,C,D) There were no significant correlations between HF HRV and psychotic symptoms in the EP without AC or EP with AC groups (Fig. S2A,B), all p-values > 0.05. Fisher's z tests revealed a significant difference in correlation magnitudes between the SAD and EP groups for SIAS and HF HRV (z = 2.67, $p = 0.008$) and DASS-S and HF HRV correlations (z = 2.12, $p = 0.034$). There was no statistical difference between SAD and EP group correlations for DASS-D (z = 1.44, $p = 0.15$), DASS-A (z = 1.65, $p = 0.098$), or K10 scores (z = 0.20, $p = 0.84$) This indicated that individual variations in reported psychiatric symptoms varied with HRV in the SAD group for stress and social interaction anxiety, but not in the EP group.

4. Discussion

The primary aim of this study was to investigate resting-state HRV

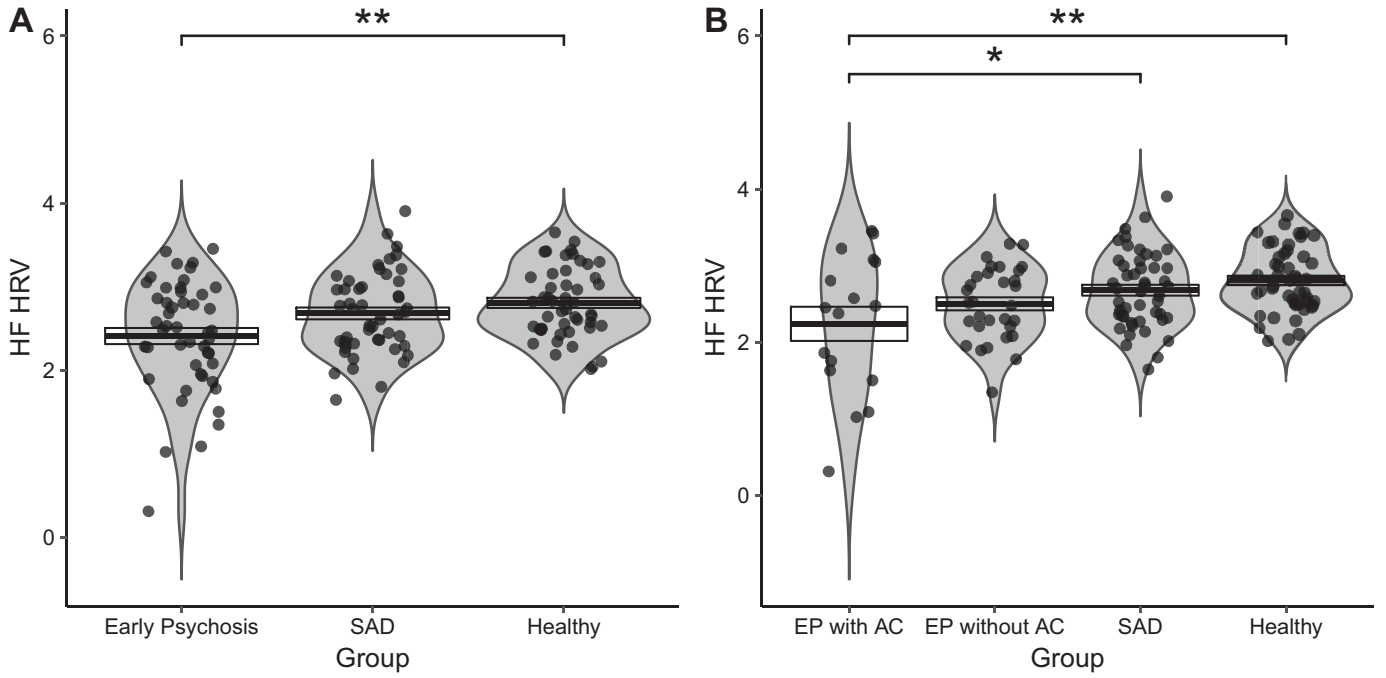

Fig.1. Violin plots with group means (thick horizontal line) and standard deviations (thin horizontal lines) for log transformed high frequency HRV (A: Clinical groups, and B: Medication use groups). *Note:* Violin plots illustrate the distribution of data by showing the probability density of the data at different values. EP with AC = early psychosis participants taking medications with anticholinergic effects, EP without AC = early psychosis participants who were non medicated or taking medications without appreciable anti-cholinergic effects, SAD = social anxiety disorder. *$p < 0.05$, **$p < 0.01$.

Table 3
Bivariate correlation coefficients between log-transformed high frequency heart rate variability (HF HRV) and self-reported symptom measures in early psychosis, social anxiety, and control groups.

	Early Psychosis (n = 48)	Early Psychosis with AC (n = 31)	Early Psychosis without AC (n = 17)	Social Anxiety (n = 48)	Controls (n = 48)
SAPS	−0.08	−0.24	0.11	–	–
SANS	−0.21	−0.20	−0.21	–	–
DASS-D	0.09	0.22	0.00	−0.21	0.07
DASS-A	0.05	0.17	−0.04	−0.29*	−0.05
DASS-S	0.07	0.21	0.03	−0.36*	0.02
K10	−0.22	−0.12	−0.25	−0.26	0.12
SIAS	0.00	−0.04	0.09	−0.51**	0.10

Note. HF HRV is log-transformed.
* $p < 0.05$.
** $p < 0.01$ (two tailed).

in a representative sample of young people with early psychosis compared to healthy control and psychiatric control groups. We found that HRV was reduced in young people with early psychosis in comparison to healthy control and social anxiety participants with effect sizes suggestive of large and medium effects, respectively. Findings support evidence for decreased HRV in earlier studies of acute psychosis (Jindal et al., 2009; Valkonen-Korhonen et al., 2003) but in a larger, more representative community-based sample of patients.

A secondary and exploratory focus of our study showed that patients with early psychosis taking anticholinergic medications exhibited significantly reduced HRV compared to healthy control and social anxiety participants but not in comparison to non-medicated early psychosis participants or those taking medications without appreciable anti-cholinergic effects. These reductions were associated with large-to-medium effect sizes. Given the lack of statistical power in the present study for the comparison of medication groups, it is more accurate to conclude that whilst early psychosis individuals demonstrate reductions in HRV compared to control groups, we cannot determine in this study whether the effects of anticholinergic medications contribute to these differences. Significant negative correlations were also observed between HRV and symptom severity for social anxiety participants. Importantly, we did not find any significant difference in positive or negative schizophrenia symptom severity between participants with early psychosis taking medications without appreciable anti-cholinergic effects and those that did not were not did not. This suggests that differences in HF HRV between these groups are not likely to be due to symptom severity.

Considering reduced HRV is strongly associated with risk factors for CVD (Christensen et al., 1999; Singh et al., 1998), the current findings suggest the importance of minimizing modifiable risk factors associated with cardiovascular disease during the early phase of a psychotic illness. This may include increasing exercise, changing diet and reducing or eliminating smoking behavior. Findings from the present study are partly consistent with polyvagal theory, which proposes that disorders of social dysfunction are associated with reductions in autonomic cardiac control (Porges, 1995). We did not however find evidence for an association between HRV abnormalities and measures of symptom severity in the EP group as the theory would predict. Findings may be explained by a floor effect on HRV in early psychosis, which could be influenced by psychotropic medication. This effect may limit observed variation in HRV and subsequently hinder the identification of a meaningful association between variables. Findings may also suggest that altered HRV is not likely to be related to state measures of symptomology characterising the early stages of psychosis (Bär et al., 2008a).

Neuroimaging studies implicate frontolimbic structures in the pathogenesis of schizophrenia (Phillips et al., 2003; Shenton et al., 2001), and the relationship between these structures and the role in a network regulating autonomic function (Thayer et al., 2012) has been described elsewhere (Barbas et al., 2003; Öngür and Price, 2000). Intriguingly, these same brain regions have also been associated with autonomic cardiac control. Therefore, the relationship between HRV abnormalities and neurobiological alterations caused by psychosis warrants further investigation within psychotic disorders. Lastly, there is extensive

evidence that unhealthy lifestyle factors (e.g., smoking, poor diet, sedentary lifestyle and increased alcohol consumption), psychosocial stressors (e.g., work stress and stressful life events), poor medical health (e.g., diabetes, hypertension, cholesterol, metabolic syndrome and obesity) and medication use are strongly associated with cardiovascular autonomic dysfunction in psychotic samples (Glassman and Bigger, 2001; Ruschena et al., 1998; Thayer et al., 2010). It may be that such lifestyle and biological risk factors mediate the relationship between reduced HRV and cardiovascular related morbidity and mortality (Kemp and Quintana, 2013). Indeed, there is some evidence that reduced HRV is amenable to behavioural intervention that may improve future health outcomes (Rennie et al., 2003; Stein et al., 1999). In sum, mechanistic studies coupled with novel biomarkers across diagnostic categories and phases of illness are required to more accurately describe the role of HRV in psychiatric illness.

Findings provide evidence that HRV is reduced in early psychosis individuals taking neuroleptics with higher anti-cholinergic and anti-muscarinic properties in comparison to healthy controls and social anxiety participants taking cardio-benign medications or who were non-medicated. Previous studies have suggested an association between reductions in HRV and chronic antipsychotic administration (Agelink et al., 2001; Alvares et al., 2016) as well as plasma clozapine concentration (Rechlin et al., 1994a). In fact, Rechlin et al. (1994a) reported that as plasma clozapine concentration increases, HRV decreases. Findings that showed no difference in HRV for psychotic individuals taking vs not taking cardio-benign medications partially supports the meta-analytic results by Alvares et al. (2016) and suggest that reduced HRV may represent a significant mechanism contributing to elevated cardiovascular risk in this population.. More studies with larger sample sizes are required before firm conclusions can be made about HRV independent of the possible mediating effects of anticholinergic drug use in early psychosis.

These findings highlight the importance of closely monitoring cardiovascular health early in the phases of psychosis. Greater reduction in HRV in these patients may be reflective of reduced general physical health and subsequently an increased likelihood to engage in unhealthy lifestyle behaviours. Future research is needed to investigate whether HRV alterations in early psychosis vary or remain stable over time and the extent to which they are associated with illness severity, lifestyle factors, pharmacological treatment and/or increased cardiovascular related mortality observed in psychotic illness.

In this study, we did not measure all of the possible lifestyle, psychosocial, and biological risk factors associated with CVD. This includes body mass index, water consumption, time of day and respiration (Karson et al., 1999; Quintana and Heathers, 2014; Routledge et al., 2002). Despite our efforts to control some important confounds (e.g., age and gender), it is also possible that the presence of unknown confounds on HRV may have influenced our results via residual confounding. Future research should incorporate broad-based assessments to improve understanding about the potential mediating role of lifestyle and biological factors in the relationship between HRV and CVD health-related outcomes. We also relied on self-report questionnaires to assess symptom severity which can be subject to reporting bias (DeVylder and Hilimire, 2014). It cannot be ruled out the lack of an association between HRV and symptom severity occurred due to measurement error in self-reported symptomatic functioning. However, the questionnaires employed are frequently used and have been validated in the target population (e.g.,Williams et al., 2008). Lastly, the effect size between non-medicated and medicated patients was small and was not significant in this sample size. Larger sample sizes in early psychosis will be needed to determine the effect of anticholinergic medications. We do note that the three-group clinical diagnosis and four-group medication group pairwise comparisons had 68% and 37–68% statistical power, respectively, to detect statistically significant effects (given a medium effect size of $d = 0.5$), this is higher than the median statistical power of 21% in neuroscience (Button et al., 2013). Future studies incorporating larger samples sizes are warranted to further replicate findings.

In summary, this study presented evidence for reduced HRV in young people with early psychosis compared to a healthy control group and participants with social anxiety disorder. No significant associations were observed between HRV and measures of symptom severity in individuals with early psychosis. We also provided evidence that HRV is reduced in early psychosis individuals taking anticholinergic medications in comparison to social anxiety and healthy control participants. Treatment implications include the importance of early screening and targeting modifiable risk factors associated with cardiovascular disease (for example, changing diet, physical activity and smoking behavior) to attenuate risk during the early phase of psychosis. Future research should focus on early detection in patients with schizophrenia who may be at greater risk of cardiovascular related mortality and develop targeted treatment interventions. Lastly, future research should examine whether gold-standard psychosocial treatments for early psychosis (e.g., social cognition training and cognitive behavior therapy) and novel biological interventions for social dysfunction disorders (Cacciotti-Saija et al., 2015a; Guastella et al., 2013) known to increase HRV impact upon HRV and everyday functional outcome.

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Contributors

Conceived and designed the experiments: CCS DSQ GAA AJG. Performed the experiments: CCS DSQ GAA. Analyzed the data: CCS DSQ GAA. Wrote the paper: CCS DSQ. Approved the final version of the paper: CCS DSQ GAA IBH RL AJG.

Conflict of interest

CCS, DSQ, GAA, RL and AJG have no conflicts of interest to declare. IBH is a Senior Principal Research Fellow of the Australian National Health and Medical Research Council (AppID 1046899). He is the executive director of the Brain and Mind Centre (BMC), at the University of Sydney, which operates two early-intervention youth services under contract to headspace. He is a commissioner of the Australian National Mental Health commission and was previously the CEO of beyondblue: the national depression initiative and a director of headspace: the national youth mental health foundation until January 2012. Previously, he has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs. He has led depression and other mental health research service evaluation or investigator-initiated research projects that have been supported by a variety of pharmaceutical partners. Current investigator-initiated studies are supported by Servier (manufacturers of agomelatine) and Pfizer. He has received honoraria for his contributions to professional educational seminars related to depression, youth mental health and circadian-rhythms research. He has received travel support from Servier to attend scientific meetings related specifically to circadian-rhythm disorders.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.08.068.

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