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 demonstrated significant reductions in HRV compared to control groups but not compared to medication free healthy controls. 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 did not significantly impact reductions in HRV. Findings provide preliminary evidence that early psychosis is associated with reduced HRV. Treatment implications include the importance of early screening and targeting modifiable risk factors associated with CVD to attenuate risk.

Keywords: first episode psychosis, schizophrenia, heart rate variability, cardiovascular disease, social anxiety disorder, neuroleptics.

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. 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), others have emphasised the need for research to determine whether HRV may represent an early biomarker associated with the development of psychotic illness (Jindal et al., 2009). The early psychosis 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). Difficulties in these domains have been associated with poor social cognition, the perception and generation of responses to

the intentions and behaviour of others, as well as subsequent long-term social and occupational consequences (Green et al., 2008).

A number of theories have suggested that HRV may play a causal 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; Bär et al., 2007; Bär et al., 2008b). For example, Jindal and colleagues (2009) found reduced HRV in a group of 24 first episode neuroleptic-naïve psychosis patients compared to 26 healthy controls. Although findings support previous evidence for reduced HRV in early psychosis (Valkonen-Korhonen et al., 2003), these other studies were limited by the use of inpatients, small sample sizes, male-biased samples, and 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 the neuroleptic effects on HRV in clinical populations has revealed 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; 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 therefore suggesting that reduced HRV may be a putative mechanism underlying elevated risk for CVD particularly in psychotic disorders.

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

Early psychosis outpatients ($n=48$, 70.8% male) were recruited 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). Early psychosis participants 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 (combinations of antipsychotics, antidepressants, mood stabilizers and benzodiazepines; one participant additionally reported adjunctive use of an anticholinergic medication).

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

(combinations of antidepressants, mood stabilizers, antipsychotics, stimulants, and beta-blockers).

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)*. The SAPS and SANS are widely used tools for the measurement of positive and negative symptoms that characterise schizophrenia. The SANS is divided into 31 item ratings and four global factor ratings. Each item is scored on a six point scale (0-5). The SAPS global total is the sum of the four global ratings, while the SAPS composite total is the sum of the thirty one item ratings. The scale has been shown to have good interrater and test-retest reliability (Andreasen and Flaum, 1991; Norman et al., 1996). The SANS is divided into 19 items ratings, and 5 global factor ratings. Each item is scored on a six point scale (0-5). The SANS global total is the sum of the five global ratings, while the SANS composite total is the sum of the nineteen item ratings. The SANS has demonstrated sound psychometric properties, such as interrater reliability, internal consistency, and predictive validity (Andreasen, 1982, 1990). Total scores based on global ratings were used in the present study due to reports that they are a more sensitive index than composite scores for the both the SAPS and SANS (Andreasen, 1982).

Depression, Anxiety and Stress Scales (DASS 21; Lovibond and Lovibond, 1995). The DASS is a self-report instrument that measures negative emotions of depression, anxiety and stress over the last week, with high internal consistency and reliability (Bieling et al., 1998). Ratings are made on a series of 4-point scales (0 = did not apply to me at all, 3 = applied to me very much, or most of the time). The DASS is comprised of three scales, Depression, Anxiety, and Stress, each containing 7 items.

Social Interaction Anxiety Scale. The SIAS is a 20-item self-report questionnaire that assesses anxiety and distress related to social interactions (Mattick and Clarke, 1998). Items are scored on a 5-point scale (0 = not at all characteristic of

me, to 4 = extremely characteristic of me) and the total score is obtained by summing all 20 items.

Kessler Psychological Distress Scale. The K-10 is a 10-item self-report questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms experienced in the last 4 weeks (Kessler et al., 2002). Items are rated on a 5-point scale (1= “None of the time” to 5 = “All of the time”) and the total score is obtained by summing individual items.

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., 2015). 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). A Fast Fourier transform was applied to calculate HF HRV using Welch's Periodogram (window width 256s, 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 & Musch, 2015) packages, with statistical significance set at $p < .05$. 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 Bonferroni corrections applied for multiple comparisons. 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; for example, olanzapine), early psychosis participants who were non-medicated or taking medications without appreciable anti-cholinergic effects (EP without AC group; for example, aripiprazole) social anxiety participants (SAD group; either non-medicated or taking medications without appreciable anti-cholinergic

effects such as escitalopram) and controls (Control group). Univariate ANOVAs with Holm-corrected pairwise comparisons were conducted to explore any differences in HF HRV between groups. 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 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 1. 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 ($p = .51$) 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; $p = .61$). There was also no difference in the severity of positive $F(1, 46) = .97$, $p = .33$; $\eta^2 = 0.02$) or negative $F(1, 46) = .43$, $p = .52$; $\eta^2 = 0.01$) schizophrenia symptoms between the EP with AC and EP without AC groups.

3.1. Group differences in HRV

As shown in Figure 1A, the overall ANOVA revealed a significant difference in HF HRV between the three groups, $F(2, 141)=6.86$, $p=.001$; $\eta^2 = 0.1$). Pairwise comparisons indicated that HF HRV was significantly reduced in the EP group compared to the healthy control ($p=.001$; $d=0.71$) and SAD ($p=.029$; $d=0.46$) groups. There were no significant differences between the SAD and healthy control groups ($p=.25$; $d=0.28$). When examining the impact of medication use on HRV, univariate ANOVA analysis indicated a significant difference in HF HRV between the four groups, $F(3, 140)=5.50$, $p=.001$; $\eta^2 = 0.11$). 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 ($M=2.81$, $SD=0.42$; $p=.002$; $d=0.80$) and SAD groups ($M = 2.68$, $SD = 0.49$; $p=.021$; $d = 0.60$); Figure 1B. There were no significant differences between the SAD and healthy control groups ($p=.32$; $d=0.29$) or the EP without AC group ($M = 2.50$, $SD = 0.47$; $p = .32$; $d = 0.37$). Lastly, there were no significant differences in HF HRV between the EP with AC group and the EP without AC group ($p = .32$; $d = 0.18$). The EP without AC group did not significantly differ in HF HRV compared to controls ($p=.058$; $d= 0.70$).

3.2. Associations between HRV and symptom severity

As depicted in Table 2, 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 $> .05$. 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 $> .05$. Fisher's z tests revealed a

significant difference in correlation magnitudes between the SAD and EP groups for SIAS and HF HRV ($z = 2.67, p = .008$) and DASS-S and HF HRV correlations ($z = 2.12, p = .034$). There was no statistical difference between SAD and EP group correlations for DASS-D ($z = 1.44, p = .15$), DASS-A ($z = 1.65, p = .098$), or K10 scores ($z = .20, p = .84$) 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 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. Interestingly however, findings also revealed no difference in HRV between EP and healthy control groups who were non medicated. Whilst this may suggest that reductions in HRV are not necessarily biomarkers unique to psychiatric illness, the small sample size and lack of power associated with this study means that firm conclusions about the mechanistic role of HRV underlying increased cardiovascular risk in psychotic disorders cannot be made.

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. 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. 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).

Evidence for reduced HRV in the EP group compared to the control and SAD group may suggest that HRV is related to the core pathology of psychotic disorder. 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).

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 between reduced levels of HRV for medicated compared to non-medicated psychotic individuals or those taking medications without appreciable anti-cholinergic effects support some of the meta-analytic results by Alvares et al. (in press) and suggest that reduced HRV may represent a significant mechanism contributing to elevated cardiovascular risk in this population. The lack of power however in the current study means that larger samples are required to replicate these findings.

Findings that revealed an impact of anticholinergic medication on autonomic cardiac control for young people with early psychosis compared to the control groups highlights the importance of closely monitoring cardiovascular health early in the phases of psychosis. Moreover, 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.

One limitation of the study was the failure to measure a range of lifestyle, psychosocial, and biological risk factors associated with CVD. 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. A second limitation was the reliance 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). Our findings are also limited by the absence of respiration data to explore the potential impact of respiration on HRV differences. While the impact of respiration on HRV is an important consideration during social-emotional tasks (Quintana and Heathers, 2014), some have argued that controlling for respiration is not essential during resting state recordings (Denver et al., 2007). This does however remain an ongoing, contentious issue (Grossman and Taylor, 2007) and may need extra consideration for populations with psychosis (Quintana et al., 2016). Lastly, the preliminary nature and lack of statistical power associated with the medication analysis in this study limits any firm conclusions being made about the impact of psychotropic medication on HRV in early psychosis. 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. It would be beneficial for clinicians to minimize modifiable risk factors associated with cardiovascular disease (for example, changing diet, physical activity and smoking behavior) 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., 2015; 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.

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Figure Legends

Figure 1. Violin plots with group means (thick horizontal line) and standard deviations (thin horizontal lines) for 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. * $p < .05$, ** $p < .01$.

Supplementary Figure 1. Relationship between mean HRV and symptom severity scores by group.

Note. DASS = Depression, Anxiety and Stress Scale; Depression (D), Anxiety (A), and Stress (S) subscales. K10 = Kessler Psychological Distress Scale. SIAS = Social Interaction Anxiety Scale.

Supplementary Figure 2. Relationship between mean HRV and psychotic symptom scores by medication group.

Note. SAPS = The Scale for the Assessment of Positive Symptoms; SANS = The Scale for the Assessment of Negative Symptoms.

Table 1. 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;

Table 2. 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	-.08	-.24	.11	-	-
SANS	-.21	-.20	-.21	-	-
DASS-D	.09	.22	.00	-.21	.07
DASS-A	.05	.17	-.04	-.29 *	-.05
DASS-S	.07	.21	.03	-.36 *	.02
K10	-.22	-.12	-.25	-.26	.12
SIAS	.00	-.04	.09	-.51 **	.10

Note. HF HRV is log-transformed. * $p < .05$ ** $p < .01$ (two tailed)

A **B** **C** **D** **E**

A **B**