Psychiatry Research 269 (2018) 293–300

Contents lists available at ScienceDirect

Psychiatry Research

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

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

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ARTICLE INFO

Keywords:
First episode psychosis
Schizophrenia
Heart rate variability
Cardiovascular disease
Social anxiety disorder
Neuroleptics

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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https://doi.org/10.1016/j.psychres.2018.08.068
Received 11 September 2017; Received in revised form 17 June 2018; Accepted 17 August 2018
Available online 23 August 2018
0165-1781/

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