Available online at www.sciencedirect.com
ScienceDirect
Schizophrenia Research 99 (2008) 294–303
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Heart rate variability response to mental arithmetic stress in patients with schizophrenia
Autonomic response to stress in schizophrenia

Mariana N. Castro [a,b,c], Daniel E. Vigo [c,d], Hylke Weidema [a,e], Rodolfo D. Fahrer [b], Elvina M. Chu [f], Delfina de Achával [a], Martín Nogués [a], Ramón C. Leiguarda [a], Daniel P. Cardinali [c,d], Salvador M. Guinjoan [a,b,c,d,*]

[a] *Department of Neurology, Fundación Lucha contra Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, Argentina*
[b] *Department of Psychiatry, Fundación Lucha contra Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, Argentina*
[c] *Department of Physiology, University of Buenos Aires School of Medicine, Buenos Aires, Argentina*
[d] *CONICET, Argentina*
[e] *Rijksuniversiteit Groningen, The Netherlands*
[f] *Institute of Neurology, University College London, London, United Kingdom*

Received 3 July 2007; received in revised form 23 August 2007; accepted 24 August 2007
Available online 30 October 2007

Abstract

Background: The vulnerability-stress hypothesis is an established model of schizophrenia symptom formation. We sought to characterise the pattern of the cardiac autonomic response to mental arithmetic stress in patients with stable schizophrenia.
Methods: We performed heart rate variability (HRV) analysis on recordings obtained before, during, and after a standard test of autonomic function involving mental stress in 25 patients with DSM-IV schizophrenia (S) and 25 healthy individuals (C).
Results: Patients with schizophrenia had a normal response to the mental arithmetic stress test. Relative contributions of low-frequency (LF) HRV and high-frequency (HF) HRV influences on heart rate in patients were similar to controls both at rest (LF 64±19% (S) vs. 56±16% (C); HF 36±19% (S) vs. 44±16% (C), $t=1.52$, $p=0.136$) and during mental stress, with increased LF (S: 76±12%, C: 74±11%) and decreased HF (S: 24±12%, C: 26±11%) in the latter study condition. Whilst healthy persons recovered the resting pattern of HRV immediately after stress termination (LF 60±15%, HF 40±15%, $F=18.5$, $p<0.001$), in patients HRV remained unchanged throughout the observed recovery period, with larger LF (71±17%) and lower HF (29±17%) compared with baseline ($F=7.3$, $p=0.013$).
Conclusions: Patients with schizophrenia exhibit a normal response to the mental arithmetic stress test as a standard test of autonomic function but in contrast with healthy individuals, they maintain stress-related changes of cardiac autonomic function beyond stimulus cessation.

Keywords: Schizophrenia; Stress; Autonomic nervous system; Heart rate variability

* Corresponding author. Cognitive Neurology & Neuropsychiatry Section, FLENI — Montañeses 2325 8th floor, C1428AQK Buenos Aires, Argentina. Tel.: +54 11 57773200x2824; fax: +54 11 57773209.
E-mail address: sguinjoan@fleni.org.ar (S.M. Guinjoan).

0920-9964/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2007.08.025

1. Introduction

Schizophrenia is characterised by macroscopic and histopathological abnormalities of cortical structures concerned with autonomic control, including the hippocampi, and temporal, cingulate, and prefrontal areas. (McDonald et al., 2004). Although it is well established that schizophrenia is highly heritable (Kendler et al., 1994; Cardno et al., 1999), the syndrome probably requires the concerted effect of several susceptibility genes, in addition to exposure to environmental noxious stimuli (e.g. perinatal damage and psychosocial stressors) in order to be expressed (McDonald and Murray, 2000). Environmental stress influences the time of emergence of symptoms of psychosis (Doering et al., 1998), and according to this "vulnerability-stress model" (Nuechterlein and Dawson, 1984), psychotic symptoms appear whenever stressors exceed the afflicted person's vulnerability level, which is considered a stable, or "trait," characteristic (Nuechterlein and Dawson, 1984).

The autonomic nervous system is a major bodily mediator of stressful emotions, hence theories of symptom development in schizophrenia have long incorporated the notion of autonomic dysfunction as central to the manifestation of psychosis. Kraepelin (1899) identified extensive autonomic alterations in schizophrenic patients, including pupillary, vasomotor, sweating, heart rate, salivation, and temperature changes, most of them suggesting increased sympathetic output, decreased parasympathetic activity, or both. Later studies on the subject have confirmed and extended those early observations (Lindstrom, 1996). Most available data about autonomic responses to environmental stress in schizophrenia refer to alterations of electrodermal responses (Venables, 1992; Grossberg, 2000). Although skin conductance orienting "hyporesponsiveness" in schizophrenia was suggested to be related to attentional and arousal deficits characteristic of the disorder (Dawson et al., 1994), skin lacks significant parasympathetic innervation.

In the last two decades heart rate variability (HRV) analysis has been developed as a tool to probe the peripheral autonomic output in the cardiovascular territory (Boettger et al., 2006). Most available data obtained with this tool in schizophrenia refer to acute states and show vagal withdrawal or decreased baroreflex sensitivity (Boettger et al., 2006), which support a status of baseline autonomic "hyperarousal" (Williams et al., 2004) in acute schizophrenia. We sought to probe the autonomic reaction to stress in patients with schizophrenia using this tool.

In light of previous observations, we hypothesised that in the patient sample the cardiovascular autonomic status at rest would be characterised by an increased sympathetic/vagal balance and response to stress would be less intense than in controls, paralleling the "hyporesponsiveness" observed in electrodermal studies. Patients with schizophrenia have increased cardiovascular morbidity and cardiac autonomic alterations have been implicated in the increased cardiovascular mortality (Ewing, 1992; Hennekens et al., 2005). Alterations of the cardiac autonomic response to stress may therefore have a cardiovascular prognostic value as well.

2. Methods

2.1. Participants

2.1.1. Patients

Psychiatry outpatients reaching DSM-IV diagnostic criteria were invited to participate in the study if (a) diagnosis was confirmed with a Composite International Diagnostic Interview (Robins et al., 1988) administered by a psychiatrist participating in the study, (b) aged 18 to 75 years, and (c) on stable medication for at least two weeks. Exclusion criteria were (a) use of illegal substances in the previous 6 months or a history of substance abuse/dependence (b) active symptoms having recently (<2 weeks) warranted antipsychotic dose adjustment or admission to the hospital, (c) history of mental retardation, (d) cardiac arrhythmias, (e) presence of diseases associated with neuropathy or autonomic nervous system involvement (e. g. diabetes), (f) use of medication with anticholinergic activity in the preceding week. Patients were identified by a staff-grade psychiatrist and referred only after both patient and accompanying first-degree relative signed an informed consent, as approved by the local ethics committee. Severity of schizophrenia symptoms was measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) administered the day of the heart rate testing session by a psychiatrist who was blind to the results of heart rate variability analysis.

2.1.2. Controls

Healthy comparison individuals were recruited from staff at FLENI, and from local community attendees to free lectures related to health promotion as advertised in posters and the media. Individuals were selected to match patients' gender and age. All participants signed an informed consent form as approved by the ethics committee. Exclusion criteria included (a) the lifetime presence of any DSM-IV Axis I anxiety, mood, or psychotic disorder diagnosis as detected by a psychiatric interview with a consultant psychiatrist and a medication