Schizophrenia Research 109 (2009) 134–140

Contents lists available at ScienceDirect

Schizophrenia Research

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

Heart rate variability response to mental arithmetic stress is abnormal in first-degree relatives of individuals with schizophrenia

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

[a] Departments of Neurology and Psychiatry, Fundación Lucha contra Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, Argentina
[b] Department of Physiology, University of Buenos Aires School of Medicine, Buenos Aires, Argentina
[c] Department of Psychobiology, University of Buenos Aires School of Psychology, Argentina
[d] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina
[e] Institute of Neurology, University College London, London, United Kingdom

ARTICLE INFO

Article history:
Received 8 July 2008
Received in revised form 15 December 2008
Accepted 22 December 2008

Keywords:
Schizophrenia
Stress
Autonomic nervous system
Heart rate variability
Endophenotypes

ABSTRACT

Background: Schizophrenia patients exhibit an abnormal autonomic response to mental stress. We sought to determine the cardiac autonomic response to mental arithmetic stress in their unaffected first-degree relatives.

Methods: Heart rate variability (HRV) analysis was performed on recordings obtained before, during, and after a standard mental arithmetic task to induce mental stress. 22 unaffected first-degree relatives of patients meeting DSM-IV criteria for schizophrenia (R) and 22 healthy individuals (C) were included in this study.

Results: Patients' relatives (R) had a normal response to the mental arithmetic stress test, showing an increased heart rate compared with controls. They also displayed the characteristic pattern of relative contributions of HRV components that consists of increased low-frequency (LF) HRV and decreased high-frequency (HF) HRV. Recovery of the resting pattern of HRV immediately after stress termination was observed in healthy subjects (LF 62 ± 16% vs. 74 ± 10%, HF 37 ± 16% vs. 25 ± 10%, $F = 9.616$, $p = 0.004$), but not in patients' relatives (LF 60 ± 19% vs. 70 ± 13%, HF 40 ± 19% vs. 29 ± 13%, $F = 8.4$, $p = 0.056$).

Conclusions: First-degree relatives of schizophrenia patients exhibit an abnormal pattern of protracted response to mental arithmetic stress, though less intense than that observed in patients in a previous study. This suggests that a pattern of autonomic response to stress may therefore be familial and heritable.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Schizophrenia has been demonstrated to be a highly heritable psychiatric disorder (Kendler et al., 1994; Sullivan et al., 2003) but its pathophysiology and genetic basis remain obscure (Venter et al., 2001; Lander et al., 2001; Cowan et al., 2002; Sklar, 2002; Gottesman and Moldin, 1997; Cloninger, 2002). Apart from the fact that the schizophrenia phenotype as currently defined probably encompasses heterogeneous entities (Crow, 1995a; Kendler, 2006; Andreasen et al., 1999; Andreasen, 2000; Chakravarti, 2002), the potential contribution of any single genetic mutation to the expression of the schizophrenia phenotype is probably quite modest (Kendler, 2006, Flint, 2003; Burian, 2004; Kendler and Greenspan, 2006). A good explanatory disease model of schizophrenia should probably incorporate the notion of noxious environmental stimuli such as perinatal damage and psychosocial

* Corresponding author. FLENI, Cognitive Neurology & Neuropsychiatry, Montañeses 2325 8th floor, C1428AQK Buenos Aires, Argentina. Tel.: +54 11 5777 3200x2824; fax: +54 11 5777 3209.
E-mail address: sguinjoan@fleni.org.ar (S.M. Guinjoan).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.12.026

stressors, which precipitate symptoms (McDonald and Murray, 2000), apart from genetic predisposition. According to this widely accepted "vulnerability-stress model" (Nuechterlein and Dawson, 1984; Kraepelin, 1899), psychotic symptoms appear whenever stressors exceed the affected person's vulnerability level, which is considered a stable, or "trait", characteristic (Nuechterlein and Dawson, 1984). We have recently reported that patients with chronic, stable schizophrenia have a normal cardiac autonomic response to stress, but whereas healthy individuals are able to "shut-off" the stress response immediately, patients with schizophrenia display responses protracted beyond stimulus termination (Castro et al., 2008).

Different authors have proposed that autonomic response to stress has a role in psychotic symptom formation, as schizophrenia might be characterized by a disjunction of autonomic arousal and processing of stressful signals by amygdala-prefrontal circuits (Castro et al., 2008; Williams et al., 2004b). In this model, excessive arousal combined with decreased amygdala activation might reflect a dysregulation of the normal positive feedback between amygdala function and autonomic activity, due to failure of regulation by prefrontal structures. In turn, this would lead to an exacerbation of arousal responses and then an internally generated cycle of hypervigilance and misattribution feeding into paranoid cognition (Castro et al., 2008; Williams et al., 2004b). Here we hypothesized that autonomic response to stress is a heritable vulnerability trait. This study characterizes the autonomic response to stress in first-degree relatives of schizophrenia probands, employing heart rate variability analysis during a standard test of autonomic function involving psychological stress (Castro et al., 2008; Ewing, 1992; Vigo et al., 2004).

2. Methods and materials

2.1. Participants

All participants gave written, informed consent for the study as approved by the local ethics committee. Exclusion criteria were (a) use of illegal substances in the previous 6 months or a history of substance abuse/dependence, (b) use of medications with anticholinergic activity in the preceding week, (c) history of mental retardation, (d) any cardiac arrhythmia or more than 10 ectopic beats per minute, (f) concurrent presence of disease (s) potentially associated with neuropathy or autonomic nervous system involvement (e. g. diabetes).

2.1.1. Relatives

Clinically unaffected, first-degree biological relatives were recruited from 22 families and consisted of the parents or the siblings (aged 18 to 75 years) of affected individuals meeting DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994). Between August 1, 2007, and April 30, 2008, recruited relatives included eight mothers, three fathers, four brothers, and seven sisters of probands who participated in our previous study (Castro et al., 2008). The participants psychiatric history was assessed with a semi-structured interview that follows DSM-IV diagnostic guidelines, and was based upon the report of the recruited participant. Two relatives included in the study had a history of Major Depressive Disorder and were taking sertraline 50 mg po qd and extended-release venlafaxine 37.5 mg po qd. The latter relative was additionally taking alprazolam 0.5 mg po bid. Two other relatives included in the analyses acknowledged regular use of clonazepam at night (0.5 mg and 1.5 mg) due to insomnia. No psychotic symptom scales were used in the present study as it focused in nonpsychotic relatives of schizophrenia probands.

2.1.2. Controls

Healthy comparison individuals were recruited from staff at FLENI, and from attendees to free lectures related to health promotion as advertised in posters and the media in the local area. Individuals were selected to match gender and age of the relatives. In addition to exclusion criteria mentioned above, it was required that healthy subjects also had no lifetime history of a DSM-IV Axis I anxiety, mood, or psychotic disorder diagnosis nor history of use of antidepressants, antipsychotics, anticonvulsants or lithium, as assessed by a consultant psychiatrist (SMG, EYC).

2.2. Testing session

Participants were tested between 0900 h and 1300 h, 2–4 h postprandial, having abstained from smoking for 2 h, consuming caffeinated beverages for 6 h, and performing vigorous exercise for 24 h. Testing was carried out while seated in a quiet, dimly lit room. After 10 min at rest, a baseline heart rate variability (HRV) recording with at least 550 beats was obtained prior to the test. We then carried out a standard test of autonomic function, the mental arithmetic task, to induce mental stress (Ewing, 1992), which consisted of subtracting serial 7's starting from 700. Patients were requested to keep their eyes closed and pronounce aloud each response. This test was chosen because it consistently induces sustained psychological stress resulting in an autonomic profile of sympathetic activation and parasympathetic inhibition, manifested by a sustained increase in heart rate and blood pressure (Ewing, 1992) during the time necessary to collect at least 550 beats. This was estimated to be 7 min from our previous study (Castro et al., 2008). Heart rate signal data were collected for an additional 7 min after participants were instructed to stop the task to assess the autonomic recovery from mental stress. The respiratory rate was visually monitored simultaneously during the recovery phase.

2.3. Heart rate data acquisition and analysis

We analysed HRV on recordings of successive RR intervals of sinus node origin as described previously (Task Force, 1996; Guinjoan et al., 2004). Patients were connected to an interphase which detected R-waves in a surface electrocardiographic signal (as obtained from a V4 or a V5 lead) and fed into a computer which stored RR intervals sampled at 1250 Hz (VariaDat® HRV package, University of Entre Ríos School of Bioengineering, Argentina). Premature and lost beats were individually identified and manually tagged in the file of RR intervals. These abnormal beats were replaced with RR intervals resulting from linear interpolation (Task Force, 1996). Time- (non-spectral) and frequency- (spectral) domain measures of HRV were obtained (Task Force, 1996).

Table 1
Sample characteristics.

	Relatives ($n=22$)	Controls ($n=22$)	Statistic	p
Age (years)	45 ± 14	45 ± 17	$F=0.009$	0.993
Female (%)	15 (68)	14 (64)	$\chi^2=0.101$	0.750
Body Mass Index (kg/m^2)	24 ± 2	24 ± 4	$F=-0.381$	0.705
Education (years)	11 ± 3	14 ± 3	$F=-3.603$	0.001
BDI-21 Score	9 ± 8	8 ± 9	$F=0.034$	0.973
Smokers	4 (36)	1(6)	$\chi^2=4.542$	0.033

BDI-21=21-item Beck Depression Inventory.

2.3.1. Non spectral HRV analysis

Time domain measures of HRV included mean RR interval (RR), standard deviation of all normal RR intervals (SDNN), and rMSSD (square root of the mean squared difference of successive normal RR intervals). SDNN estimates global HRV, mediated by sympathetic and parasympathetic nervous systems. rMSNN reflects short-term, beat-to-beat variations in heart rate.

2.3.2. Spectral HRV analysis

Frequency domain measures of HRV were quantified through fast Fourier transform and included low frequency power (LF, 0.03–0.15 Hz), high frequency power (HF, 0.15–0.40 Hz), and the LF/HF ratio. The high-frequency (HF) component of HRV is related to respiratory sinus arrhythmia (mediated by parasympathetic activity), and the low-frequency (LF) component is related to Mayer waves of blood pressure, which influence heart rate via the baroreceptor reflex. Thus LF depends on both sympathetic and parasympathetic influences, although in most instances (with the notable exceptions of strenuous physical exercise and heart failure) it is thought to reflect mainly sympathetic activation (Task Force, 1996; Malliani et al., 1991; Montano et al., 1994). We report absolute (ms^2) values and normalized units of each component. Normalized units are calculated in relative terms as follows: LF: LF / (Total power − very low frequency power) × 100, and HF: HF / (Total power − very low frequency power) × 100. This form of expression permits the comparison of groups of individuals with different absolute values of HRV, because when the spectral components are expressed in absolute units, the changes in total power influence LF and HF in the same direction and prevent the accurate appreciation of the fractional distribution of the energy (Task Force, 1996).

2.4. Statistical analysis

Discrete variables in relatives and controls were compared using the chi-square test, and continuous variables were compared with an independent-samples t test. Within-subject comparisons of HRV data obtained during baseline, mental stress, and recovery phases were performed with a repeated-measures ANOVA followed by a post hoc Bonferroni correction. Significance was assumed at $\alpha<0.05$, and reported results are two-tailed.

3. Results

Table 1 shows the demographic and clinical characteristics of first-degree relatives of schizophrenia probands and healthy controls. Both groups were similar in age, sex, and body mass index (BMI). Relatives of schizophrenia individuals had received fewer years of education than controls and a greater proportion were smokers. Respiratory rate fluctuated between 11 and 21 cycles per minute (0.18–0.35 Hz) in participants from both groups of the study.

3.1. Baseline heart rate variability

Fig. 1 displays the tachograms (top panels) and their corresponding power spectra (bottom panels) obtained in a healthy 24 year old male control participant (left), and a

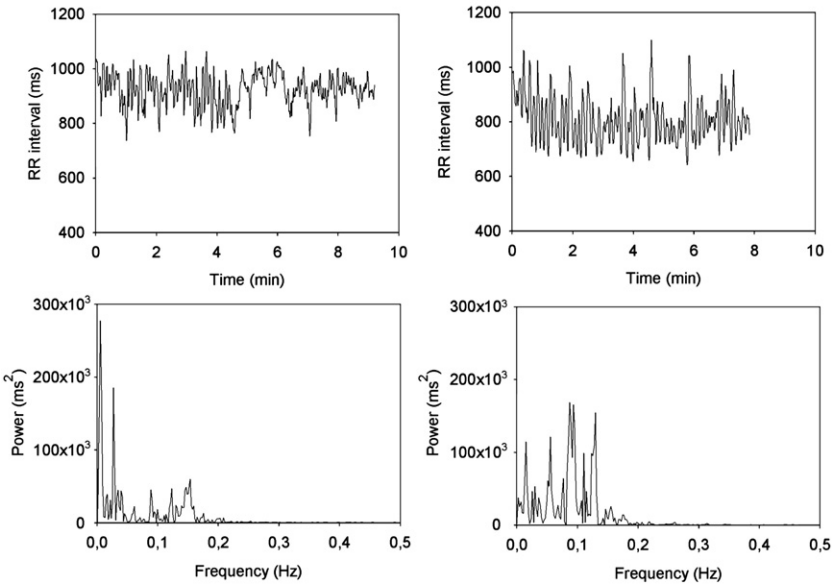

Fig. 1. Tachograms (top panels) and their power spectra (bottom panels) in a 24-year-old healthy male control (left) and a 26-year-old healthy male first-degree relative of a patient with schizophrenia obtained in baseline resting conditions. See the text for details.

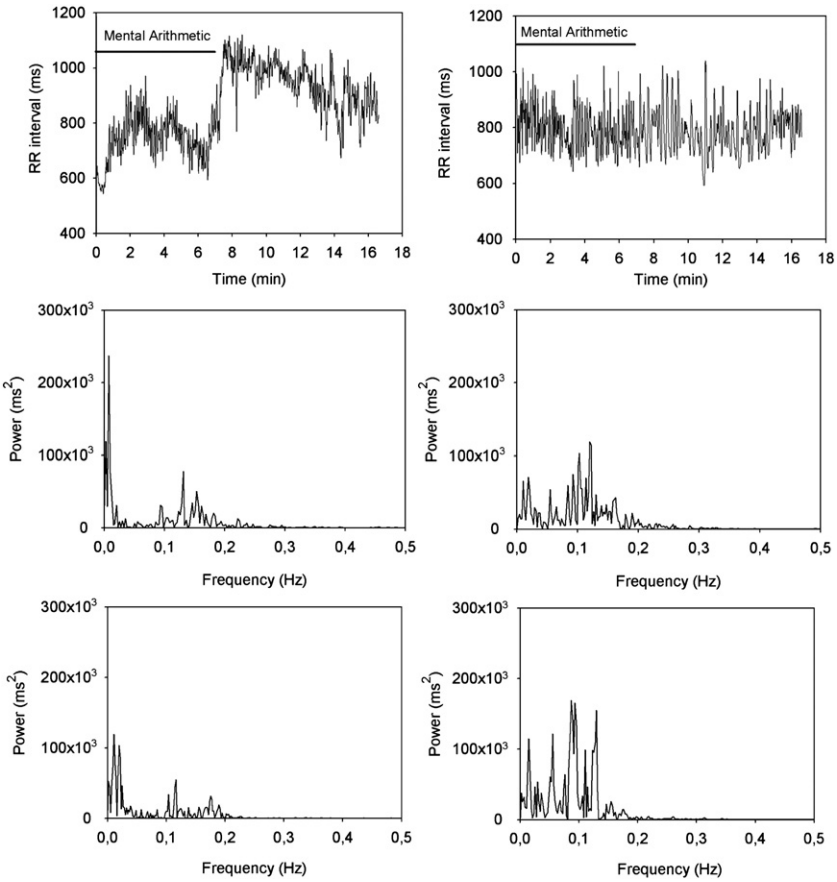

Fig. 2. Tachograms (top panels) and their power spectra in a 24-year-old healthy male control (left) and a 26-year-old healthy male first-degree relative of a patient with schizophrenia obtained during a serial 7 subtraction task (mental arithmetics) and immediately afterwards. Middle panels show the power spectra of the test portion of the tachograms, and bottom panels show the power spectra corresponding to the recovery phase. The pattern of heart rate variability in the relative is unchanged after task cessation. See the text for details.

healthy 26 year old male first-degree relative (right). Both individuals exhibit similar average heart rate and heart rate variability pattern (Fig. 1). Baseline HRV data was similar in both groups. Resting average RR interval (±SD) in relatives was 821 ± 131 ms and in healthy controls it was 823 ± 109 ms. Time-domain indicators of HRV included SDNN 30 ± 18 ms and 32 ± 17 ms, and rMSNN 25 ± 18 ms and 26 ± 19 ms, for relatives and controls respectively. Fig. 3 shows that relative contributions of LF and HF components to HRV at baseline were similar in both groups as well.

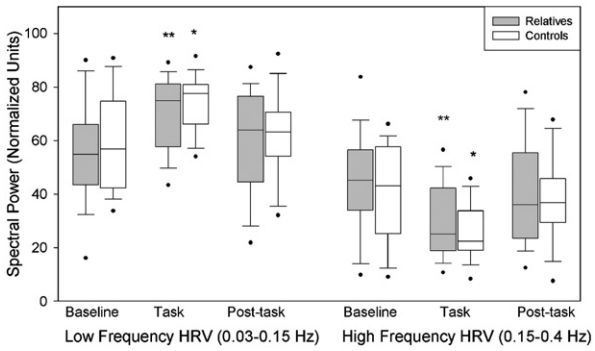

Fig. 3. Changes of heart rate variability components in response to mental arithmetic stress in unaffected first-degree relatives of schizophrenia probands and matched healthy individuals. Relatives fail to readily recover the cardiac autonomic pattern characteristic of resting conditions after a stressful task. HRV: Heart Rate Variability. *$p<0.01$ vs. baseline and post-task. **$p=0.001$ vs. baseline. See the text for details.

3.2. Mental arithmetic stress and post-task heart rate variability

Fig. 2 displays tachograms obtained during stress and immediately after its termination (top panels), and the power spectra corresponding to the task itself (middle panels) and post-task recovery phase (bottom panels) in the same participants as in Fig. 1. Mental arithmetic stress induced a shortening of average RR intervals (i.e., increased heart rate) in both groups and a reversion of this change after the task (Fig. 2, top panels). There was a significant recovery of frequency components of HRV after stress in the healthy control (Fig. 2, right middle and bottom panels). However, this recovery was not observed in the relative who maintained the same HRV pattern as observed during the task (Fig. 2, left middle and bottom panels). This is also observed as changes in HRV during mental arithmetic stress and after its termination in all participants (Fig. 3). Both groups exhibited a normal response to mental stress, characterized by significant shortening of RR intervals as compared with baseline resting state (758 ± 131 ms, $F = 12.52$, $p = 0.002$ for relatives, and 760 ± 111 ms, $F = 16.833$, $p < 0.001$ for controls). This was followed, immediately after mental stress cessation, by recovery of heart rate to baseline levels (Average RR interval 832 ± 142 ms in relatives and 829 ± 118 ms in healthy subjects). SDNN increased during mental arithmetic stress in healthy individuals (37 ± 19 ms, $F = 3.57$, $p = 0.037$) but not in relatives (32 ± 17 ms), and rMSNN did not show significant changes across testing conditions in either group. The response of each autonomic component to the mental arithmetic task was also similar in relatives of schizophrenia patients and in healthy subjects, i.e. increase in the relative contribution of LF, and decrease in the relative contribution of HF to total HRV (Fig. 3). However, after mental stress termination, the recovery of a sympathovagal pattern similar to that of baseline conditions was seen only in healthy individuals (Fig. 3), and it did not attain statistical significance among nonpsychotic relatives of schizophrenia probands (Fig. 3).

4. Discussion

This study shows that first-degree relatives of patients with schizophrenia do not readily recover the pattern of resting autonomic activity after termination of a short period of psychological stress, compared with healthy individuals without a family history of schizophrenia. Nevertheless, cardiovascular autonomic output in these individuals is normal at rest and in response to mental stress. This pattern is similar, though less intense than that observed in individuals with chronic, stable schizophrenia, whom displayed HRV abnormalities in baseline resting conditions in addition to a failure to readily recover from mental stress (Castro et al., 2008). This finding may have a pathophysiological implication as it suggests that protracted responses to stress in schizophrenia may be familial and therefore genetically heritable. Our finding of sustained autonomic reactions to psychological stress appears to be in keeping with older studies that employed galvanic skin responses as a tool to explore peripheral autonomic function (Salzman and Klein, 1978; Prentky et al., 1981). These earlier studies suggested that first-degree relatives of individuals with schizophrenia display an impaired habituation of autonomic nervous system activity (Salzman and Klein, 1978; Prentky et al., 1981; Erlenmeyer-Kimling et al., 1985; Hollister et al., 1994). Heart rate variability analysis as employed in the present study has allowed us to confirm the protracted sympathetic activation in response to mental stress in first degree relatives of schizophrenia patients, and extend the observation to an effect on the parasympathetic division of the autonomic nervous system.

Existing structural and functional studies of the brain in schizophrenia may help to explain the present findings. Structural abnormalities specific to schizophrenia include abnormalities of prefrontal cortex and volume reduction in the temporal lobe and medial temporal structures (hippocampus, parahippocampal gyrus, and amygdala) (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Harrison, 1999; Wright et al., 2000; McDonald et al., 2004). These structures are involved in the hierarchical control of peripheral autonomic responses and, when altered, can impede the appropriate temporal focusing of autonomic responses to stress (Williams et al., 2004b; Zahn et al., 1981; Williams et al., 2004a; Zahn and Pickar, 2005). As previously suggested by our group and others, an abnormal prolongation of autonomic responses to stress might have a bearing on the production of positive and negative symptoms of schizophrenia (Castro et al., 2008; Williams et al., 2004b). Some authors have proposed that a functional disconnection in autonomic and central systems for processing threat-related signals (i.e. a reduction in amygdala/medial prefrontal activity) can produce an exacerbation and persistence of alertness leading to an hypervigilance state. In this light, paranoid cognition may reflect an internally generated cycle of misattribution regarding incoming fear signals due to a breakdown in the regulation of these systems (Williams et al., 2004b).

Abnormal autonomic responses to stress as described in the present study constitute a phenotype that appears to have a familial aggregation. We previously characterized similar but more intense abnormalities in the schizophrenia probands of these families. Protracted autonomic responses to psychological stress are relatively easy to measure and comply with the usual definition of endophenotype (Gottesman and Gould, 2003), so this construct might be of help in identifying genetic abnormalities ultimately contributing to schizophrenia. In recent years, several functional variables have complied with the definition of endophenotype and their genetic basis is being probed. Some of these variables include abnormalities of sensory-motor gating (Cadenhead et al., 2000), smooth pursuit eye movements (Hong et al., 2006), early visual sensory deficits (Yeap et al., 2006), and working memory abnormalities (Saperstein et al., 2006). An important heuristic difficulty with some of these variables (most notably those referred to visual function) is that they are difficult to incorporate into a model of schizophrenia symptom formation. In theory, they could simply aggregate with the syndrome because structures that govern their development are located in the vicinity of those relevant to production of symptoms of schizophrenia (e.g. altered frontal eye fields as part of more widespread prefrontal abnormalities involved in working memory problems). As mentioned above, the “vulnerability-stress model”, is an established construct of schizophrenia symptom formation (Nuechterlein and Dawson, 1984). The demonstration of exaggerated autonomic nervous system responses to mental stress might

therefore help to bridge the gap between psychosocial and biological culprits of schizophrenia development. For example, Myin-Germeys et al. (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005) have demonstrated that schizophrenia patients and their first-degree relatives show a similarly exaggerated subjective reactivity to daily stress compared with healthy individuals. Their study showed that the subjective appraisal of events was associated with mood, and in this context, our demonstration of protracted stress-related autonomic profiles might represent a bodily correlate of such appraisal. With this hypothesis in mind, it would be of interest to determine whether the autonomic alterations described in our study are a generic phenomenon accompanying all forms of stress, or restricted to a standard stress inducing task initially developed to bring about strong sympathetic activation and parasympathetic withdrawal. Neurocognitive models of social cognition (Baron-Cohen et al., 2001; Stone et al., 1998) may provide further insight into the characteristics of physiological phenomena feeding back into cognition and decision-making (Damasio et al., 1991), which are known to be altered in schizophrenia.

The present study had methodological limitations that should be taken into account when interpreting the results. First, major depressive disorders are associated to changes in the sympathovagal balance onto the cardiovascular system in a variety of patient populations (Vigo et al., 2004; Guinjoan et al., 1995; Carney et al., 2007), and the fact that two of the participants had depression might have contributed to the observed results. Second, some relatives were exposed to antidepressants and benzodiazepines. HRV effects of either type of agent are unclear as different studies have offered conflicting results (Winn et al., 2005; Kitajima et al., 2004; van Zyl et al., 2008), so their influence on the observed results cannot be ruled out. Third, a "dose–response" relationship between clinical status and HRV pattern could not be established, because all relatives were nonpsychotic and had a first-degree relationship with a schizophrenia proband. Further studies assessing the relationship between genetic risk and autonomic response to stress are thus warranted to clearly establish the correlation between genetic risk of schizophrenia and HRV responses to mental stress.

The precise heritability of the psychophysiological abnormalities described remains unknown. Their relationship to schizophrenia liability and their usefulness as markers of genetic abnormalities are questions that necessitate further investigation.

Role of Funding Source

MNC was a medical student research fellow from the University of Buenos Aires upon completion of this study (Project M084) and is now a PGY-I Psychiatry Resident at the Hospital de Clínicas, UBA. DEV is a fellow from the Argentine National Council on Scientific and Technological Research, CONICET. This study was supported in part by FLENI Foundation, UBACyT (Project M084, SMG), and CONICET (SMG, DPC). These funding sources had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Contributors

SMG and MNC designed the study and wrote the protocol. SMG, MNC, HW, and EC managed the literature searches and analyses. SMG, MNC, HW, RDF, MN, DA, and RCL collected experimental data. DEV, SMG, MNC, DPC, and HW undertook the statistical analysis, and MNC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

None.

Acknowledgements

MNC was a medical student research fellow from the University of Buenos Aires (UBA) upon completion of this study (Project M084) and is now a PGY-I Psychiatry Resident at the Hospital de Clínicas, UBA. DEV is a fellow from the Argentine National Council on Scientific and Technological Research, CONICET.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Press, Washington DC.
Andreasen, N.C., 2000. Schizophrenia: the fundamental questions. Brain Res. Brain Res. Rev. 31 (2–3), 106–112.
Andreasen, N.C., Nopoulos, P., O'Leary, D.S., Miller, D.D., Wassink, T., Flaum, M., 1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol. Psychiatry. 46 (7), 908–920.
Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger Syndrome or high-functioning autism. J. Child Psychol. Psychiatry Allied Discipl. 42, 241–251.
Burian, R.M., 2004. Molecular epigenesis, molecular pleiotropy, and molecular gene definitions. Hist. Philos. Life Sci. 26, 59–80.
Cadenhead, K.S., Light, G.A., Geyer, M.A., Braff, D.L., 2000. Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder. Am. J. Psychiatry 157 (1), 55–59.
Carney, R.M., Freedland, K.E., Stein, P.K., Miller, G.E., Steinmeyer, B., Rich, M.W., Duntley, S.P., 2007. Heart rate variability and markers of inflammation and coagulation in depressed patients with coronary heart disease. J. Psychosom. Res. 62, 463–467.
Castro, M.N., Vigo, D.E., Weidema, H., Fahrer, R.D., Chu, E.M., de Achával, D., et al., 2008. Heart rate variability response to mental arithmetic stress in patients with schizophrenia. Schizophr. Res. 99, 294–303.
Chakravarti, A., 2002. A compelling genetic hypothesis for a complex disease: PRODH2/DGCR6 variation leads to schizophrenia susceptibility. Proc. Natl. Acad. Sci. U. S. A;. 99 (8), 4755–4756.
Cloninger, C.R., 2002. The discovery of susceptibility genes for mental disorders. Proc. Natl. Acad. Sci. U. S. A. 99 (21)), 13365–13367.
Cowan, W.M., Kopnisky, K.L., Hyman, S.E., 2002. The human genome project and its impact on psychiatry. Annu. Rev. Neurosci. 25, 1–50.
Crow, T.J., 1995a. A continuum of psychosis, one human gene, and not much else – the case for homogeneity. Schizophr. Res. 17 (2), 135–145.
Damasio, A.R., Tranel, D., Damasio, H.C., 1991. Frontal Lobe Function and Dysfunction. Oxford University Press, Oxford, pp. 217–229.
Erlenmeyer-Kimling, L., Friedman, D., Cornblatt, B., Jacobsen, R., 1985. Electrodermal recovery data on children of schizophrenic parents. Psychiatry Res. 14 (2), 149–161.
Ewing, D.J., 1992. Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System, third ed. Oxford Medical Publications, Oxford, pp. 326–327.
Flint, J., 2003. Analysis of quantitative trait loci that influence animal behavior. J. Neurobiol. 54, 46–77.
Gottesman, I.I., Moldin, S.O., 1997. Schizophrenia genetics at the millennium: cautious optimism. Clin. Genet. 52 (5), 404–407.
Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160 (4), 636–645.
Guinjoan, S.M., Bernabó, J.L., Cardinali, D.P., 1995. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J. Neurol. Neurosurg. Psychiatry 59, 299–302.
Guinjoan, S.M., de Guevara, M.S., Correa, C., Schauffele, S.I., Nicola-Siri, L., Fahrer, R.D., et al., 2004. Cardiac parasympathetic dysfunction related to depression in older adults with acute coronary syndromes. J. Psychosom. Res. 56, 83–88.
Harrison, P.J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122 (Pt 4), 593–624.
Hollister, J.M., Mednick, S.A., Brennan, P., Cannon, T.D., 1994. Impaired autonomic nervous system habituation in those at genetic risk for schizophrenia. Arch. Gen. Psychiatry 51, 552–558.
Hong, L.E., Mitchell, B.D., Avila, M.T., Adami, H., McMahon, R.P., Thaker, G.K., 2006. Familial aggregation of eye-tracking endophenotypes in families of schizophrenic patients. Arch. Gen. Psychiatry 63 (3), 259–264.
Kendler, K.S., 2006. Reflections on the relationship between psychiatric genetics and psychiatric nosology. Am. J. Psychiatry 163, 1138–1146.
Kendler, K.S., Greenspan, R.J., 2006. The nature of genetic influences on behavior: lessons from "simpler" organisms. Am. J. Psychiatry 163 (10), 1683–1694.

Kendler, K.S., Gruenberg, A.M., Kinney, D.K., 1994. Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. Arch. Gen. Psychiatry 51, 456–468.
Kitajima, T., Kanbayashi, T., Saito, Y., Takahashi, Y., Ogawa, Y., Sugiyama, T., et al., 2004. Diazepam reduces both arterial blood pressure and muscle sympathetic nerve activity in human. Neurosci. Lett. 355, 77–80.
Kraepelin, E., 1899. Psychiatrie. Ein Lehrbuch fur Studirende und Aertze, Psychiatry. A Textbook for Students and Physicians, 1991 edn. Watson Publishing International, Canton, MA, pp. 110–111.
Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., et al., 2001. International human genome sequencing consortium. Initial sequencing and analysis of the human genome. Nature 409 (6822), 860–921.
Lawrie, S.M., Abukmeil, S.S., 1998. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br. J. Psychiatry 172, 110–120.
Malliani, A., Pagani, M., Lombardi, F., Cerutti, S., 1991. Cardiovascular neural regulation explored in the frequency domain. Circulation 84 (2), 482–492.
McDonald, C., Murray, R.M., 2000. Early and late environmental risk factors for schizophrenia. Brain Res. Brain Res. Rev. 31, 130–137.
McDonald, C., Bullmore, E.T., Sham, P.C., Chitnis, X., Wickham, H., Bramon, E., Murray, R.M., 2004. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch. Gen. Psychiatry 61 (10), 974–984.
Montano, N., Ruscone, T.G., Porta, A., Lombardi, F., Pagani, M., Malliani, A., 1994. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 90 (4), 1826–1831.
Myin-Germeys, I., van Os, J., Schwartz, J.E., Stone, A.A., Delespaul, P., 2001. Emotional reactivity to daily life stress in psychosis. Arch. Gen. Psychiatry 58, 1137–1144.
Myin-Germeys, I., Delespaul, P., van Os, J., 2005. Behavioural sensitization to daily life stress in psychosis. Psicol. Med. 35, 733–741.
Nelson, M.D., Saykin, A.J., Flashman, L.A., Riordan, H.J., 1998. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch. Gen. Psychiatry 55 (5), 433–440.
Nuechterlein, K.H., Dawson, M.E., 1984. A heuristic vulnerability/stress model of schizophrenic episodes. Schizophr. Bull. 10, 300–312.
Prentky, R.A., Salzman, L.F., Klein, R.H., 1981. Habituation and conditioning of skin conductance responses in children at high risk. Schizophr. Bull. 7, 281–291.
Salzman, L.F., Klein, R.H., 1978. Habituation and conditioning of electrodermal responses in high risk children. Schizophr. Bull. 4 (2), 210–222.
Saperstein, A.M., Fuller, R.L., Avila, M.T., Adami, H., McMahon, R.P., Thaker, G.K., Gold, J.M., 2006. Spatial working memory as a cognitive endophenotype of schizophrenia: assessing risk for pathophysiological dysfunction. Schizophr. Bull. 32 (3), 498–506.
Sklar, P., 2002. Linkage analysis in psychiatric disorders: the emerging picture. Annu. Rev. Genomics Hum. Genet. 3, 371–413.
Stone, V.E., Baron-Cohen, S., Young, A.W., Calder, A.J., Keane, J., 1998. Impairments in social cognition following orbitofrontal or amygdala damage. Soc. Neurosci. Abstr. 24, 1176.
Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry 60 (12), 1187–1192.
Task Force, 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur. Heart J. 17 (3), 354–381.
van Zyl, L.T., Hasegawa, T., Nagata, K., 2008. Effects of antidepressant treatment on heart rate variability in major depression: a quantitative review. Biopsychosoc. Med. 2, 12.
Venter, J.C., Adams, M.D., Myers, E.W., Li, P.W., Mural, R.J., Sutton, G.G., et al., 2001. The sequence of the human genome. Science 291 (5507), 1304–1351.
Vigo, D.E., Nicola, S.L., Ladron De Guevara, M.S., Martinez-Martinez, J.A., Fahrer, R.D., Cardinali, D.P., et al., 2004. Relation of depression to heart rate nonlinear dynamics in patients > or =60 years of age with recent unstable angina pectoris or acute myocardial infarction. Am. J. Cardiol. 93, 756–760.
Williams, L.M., Brown, K.J., Das, P., Boucsein, W., Sokolov, E.N., Brammer, M.J., et al., 2004a. The dynamics of cortico-amygdala and autonomic activity over the experimental time course of fear perception. Brain Res. Cogn. Brain Res. 21 (1), 114–123.
Williams, L.M., Das, P., Harris, A.W., Liddell, B.B., Brammer, M.J., Olivieri, G., et al., 2004b. Dysregulation of arousal and amygdale — prefrontal systems in paranoid schizophrenia. Am. J. Psychiatry 161, 480–489.
Winn, N.N., Fukayama, H., Kohase, H., Umino, M., 2005. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. Anesth. Analg. 101, 97–102.
Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W., David, A.S., Murray, R.M., Bullmore, E.T., 2000. Meta-analysis of regional brain volumes in schizophrenia. Am. J. Psychiatry 157 (1), 16–25.
Yeap, S., Kelly, S.P., Sehatpour, P., Magno, E., Javitt, D.C., Garavan, H., et al., 2006. Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. Arch. Gen. Psychiatry 63 (11), 1180–1188.
Zahn, T.P., Pickar, D., 2005. Autonomic activity in relation to symptom ratings and reaction time in unmedicated patients with schizophrenia. Schizophr. Res. 79 (2–3), 257–270.
Zahn, T.P., Carpenter, W.T., McGlashan, T.H., 1981. Autonomic nervous system activity in acute schizophrenia, I: method and comparison with normal controls. Arch. Gen. Psychiatry 38, 251–258.