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Altered autonomic arousal in psychosis: An analysis of vulnerability and specificity

Annika Clamor [a,*], Maike M. Hartmann [a], Ulf Köther [b], Christian Otte [c], Steffen Moritz [b], Tania M. Lincoln [a]

[a] Department of Clinical Psychology and Psychotherapy, University of Hamburg, Germany
[b] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Germany
[c] Department of Psychiatry and Psychotherapy, Charité University Medical Center, Berlin, Germany

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ABSTRACT

Vulnerability–stress models implicate that alterations of the autonomous nervous system contribute to the development of psychosis. Previous research has found autonomic arousal alterations in psychotic disorders and at-risk individuals that are not explained by medication alone. To test whether these alterations are associated with the extent of an individual's vulnerability and whether they are specific to psychosis, we compared participants with psychosis ($n = 23$), first-degree relatives of individuals with psychosis ($n = 21$), and healthy participants with attenuated positive symptoms ($n = 23$) to participants with depression ($n = 24$) and healthy controls ($n = 24$). At rest, skin conductance level was assessed and photoplethysmography was applied to measure time- and frequency-domain heart rate variability (HRV). Univariate and multivariate analyses of covariance with perceived stress and psychophysiological values as dependent variables showed significant between-group differences for perceived stress ($p = .010$), heart rate ($p = .022$), time-domain HRV indices (all $ps \leq .027$), and vagal activity ($p = .017$). Group differences in sympathetic activity were nonsignificant ($p = .069$). In an additional analysis with medication as a second between-group factor, the physiological between-group differences remained significant or trend significant (all $ps \leq .060$). With the exception of sympathetic activity, participants with psychosis exhibited more extreme arousal than the control groups. First-degree relatives and participants with attenuated symptoms showed comparable autonomic activity to healthy controls. Thus, the hypothesized association of an alteration of arousal and vulnerability to psychosis was not confirmed. However, particularly low time-domain HRV was found for psychosis, with significant differences to healthy controls (all $ps \leq .007$) and to depression (all $ps \leq .004$), with the latter indicating a specificity to psychosis.

1. Introduction

Alterations of the autonomous nervous system imply adaptation difficulties and are therefore considered to be important in the pathogenesis of psychotic symptoms (Nuechterlein and Dawson, 1984). An autonomic parameter with great importance for adaptability (Thayer et al., 2012) is the heart rate variability (HRV). It is produced by regulatory fluctuations of the heart rate, where frequency ranges reflect vagal or sympathetic efferent input (Berntson et al., 1997). Furthermore, the skin conductance level (SCL) serves as a prominent sympathetic index (Dawson et al., 2007).

Previous research in unmedicated patients with psychotic disorders found significantly increased heart rate, decreased time-domain HRV (Bär et al., 2005; Voss et al., 2010; Bär et al., 2012), decreased vagal activity (Bär et al., 2005, 2012), and increased sympathetic activity (Voss et al., 2010) at rest compared to healthy controls. Similar findings were observed for medicated patients (Castro et al., 2008; Kim et al., 2011) and for healthy first-degree relatives (Voss et al., 2010; Bär et al., 2012). Furthermore, participants with prodromal symptoms exhibited lower time-domain HRV and vagal activity than healthy controls (Valkonen-Korhonen et al., 2003).

Additionally, higher SCL was associated with more severe symptomatology (Zahn and Pickar, 2005) and lower functioning (Schell et al., 2005) in psychosis. Furthermore, SCL was found to be increased at rest during prodromal states (Hazlett et al., 1997; Dawson et al., 2010). Overall, these findings indicate a characteristic autonomic response pattern for psychosis that is not explained by medication alone. However, the variety of parameters has rarely been regarded systematically or directly related to patients' perceived stress (see Kimhy et al., 2010).

In the vulnerability–stress model advocated by Nuechterlein and Dawson (1984), autonomic alterations are described as transient

* Corresponding author at: University of Hamburg, Department of Clinical Psychology and Psychotherapy, Von-Melle-Park 5, 20146 Hamburg, Germany. Tel.: +49 40 42838 5372; fax: +49 40 42838 6170.
E-mail addresses: annika.clamor@uni-hamburg.de (A. Clamor), maike.hartmann@uni-hamburg.de (M.M. Hartmann), ukoether@uke.de (U. Köther), christian.otte@charite.de (C. Otte), moritz@uke.de (S. Moritz), tania.lincoln@uni-hamburg.de (T.M. Lincoln).

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intermediate states that occur prior to psychotic symptoms but also as enduring vulnerability characteristics. To test the assumption that autonomic alterations are an enduring vulnerability marker, it is of interest to compare autonomic response patterns in groups with differing levels of vulnerability, such as genetic or symptomatic vulnerability (Keshavan et al., 2011). Moreover, the specificity of autonomic alterations to psychosis as compared to depression is unclear as low time-domain HRV, low vagal activity, and high sympathetic activity have also been shown in depression (Kemp et al., 2010).

In the present study, we compared autonomic and subjective stress between patients with psychotic disorders, first-degree relatives, healthy participants with attenuated positive symptoms, participants with depression and healthy controls. We expected higher vulnerability to be associated with (a) increased perceived stress, (b) increased heart rate, (c) decreased time-domain HRV, (d) decreased vagal activity, and (e) increased sympathetic activity. Specifically, we hypothesized that participants with psychosis would show more stress than healthy controls, first-degree relatives, and participants with attenuated positive symptoms (i.e., more perceived stress, higher heart rate, lower HRV, lower vagal activity, and higher sympathetic activity). Furthermore, first-degree relatives and participants with attenuated positive symptoms were expected to show more stress than healthy controls. If this pattern is specific for psychosis, we expected it to be evident in a more pronounced alteration in participants with psychosis when compared to participants with depression.

2. Methods

2.1. Participants

The study was conducted in Hamburg and Marburg (Germany). In total, 151 participants with psychotic disorders (PSY), first-degree relatives of individuals with psychosis (REL), participants with attenuated positive symptoms (AS), control participants with depression (DEP), and healthy controls (HC) were included. Recruitment occurred in inpatient and outpatient treatment settings (PSY, DEP), in outpatient family intervention services (REL), via leaflets, advertisements in local newspapers, and the Internet (AS, HC, REL). Inclusion criteria were age ≥18 years and sufficient language abilities, which was made explicit along with the diagnostic criteria in the information leaflet and in a short telephone contact and brief screening. Furthermore, the ability to provide informed consent and absence of neurological impairment were ensured at the assessment date (prior to participation). No participant had to be excluded due to non-fulfillment of inclusion criteria in this phase.

For the reported psychophysiological analyses, exclusion criteria were (a) nonsufficient quality or absence of five-minute baseline blood volume pulse data ($n = 14$), (b) current intake of cardiac medication (e.g., beta-blocking, angiotensin converting enzyme inhibitors; $n = 16$), (c) cardiac illness ($n = 3$), or (d) smoking within 30 min prior to testing ($n = 2$). Moreover, one participant was excluded because of participating in a blinded medication trial.

Diagnostic criteria were verified with the structured Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). For PSY, an acute or remitted psychotic disorder without extreme current arousal/tension (scores <6 in items P4 and G4 in the Positive and Negative Syndrome Scale; Kay et al., 1987) was required. The other groups were matched to PSY regarding sex, age, and education. Attenuated positive symptoms in AS were quantified by an online prescreening with the Community Assessment of Psychic Experiences (CAPE, Stefanis et al., 2002) requiring a positive subscale score >1.45 ($M + 1SD$ of two healthy samples from previous studies; Lincoln et al., 2009, 2010). To achieve a sample with high scorers, at least 50% were ensured to score above 1.75 ($M + 2SD$). Present or past psychotic disorders were exclusion criteria for AS. REL had to be first-degree relatives of individuals with psychosis with no present/past psychotic or present affective disorders. One participant who volunteered as a relative was assigned PSY group status after the diagnostic assessment, as criteria for a psychotic episode were met. DEP had to have a present/past affective disorder and no psychotic symptoms. Finally, exclusion criteria for HC were any clinically relevant present Axis I disorder (tolerating substance misuse or specific phobias), any mental disorder that had required treatment, the intake of psychotropic medication, a first-degree relative with psychosis, and a CAPE positive subscale score >1.45.

In total, 115 participants were analyzed. PSY included 23 participants ($n = 19$ schizophrenia; $n = 4$ schizoaffective disorder), either acute ($n = 14$) or remitted ($n = 9$). REL comprised 21 participants who had a sibling ($n = 8$), a parent ($n = 7$) or a child ($n = 6$) with psychosis. The 23 AS participants had a CAPE positive subscale mean of 1.84 ($SD = 0.18$). Bonferroni post-hoc tests showed significant differences to REL, DEP, and HC (all $ps < .001$) but not to PSY ($p > .999$). Within the 24 DEP participants, the diagnoses were reoccurring depressive disorders ($n = 17$), present major ($n = 4$), past major ($n = 1$) or present minor ($n = 2$) depressive disorders. DEP showed significantly higher depression scores than REL, AS, and HC (Bonferroni post-hoc test $p < .001$). Finally, HC comprised 24 participants. For sample characteristics see Table 1.

2.2. Procedure

Prior to the experiment, participants gave written informed consent. Local ethics committees approved the study's design. Autonomic arousal was recorded with "ProComp 2™ BioGraph Infiniti™" by Thought Technology Ltd. within a larger experiment. It included a baseline assessment for diagnostics and three experimental sessions with randomized stressors (noise, social stressor, non-stress; Lincoln et al., submitted for publication). All participants were tested between 2 pm and 8 pm, after a minimum abstinence from alcohol for 12 h, from food, coffee, and tea for 1 h, and from smoking for 30 min. The analyzed parameters refer to a baseline initiating the first session. After connecting the participant to the psychophysiology system, the experimenter demonstrated at the computer screen how participants' movements produce artifacts and then gave instructions to sit still and relax for 10 min (0 s to 600 s). A five-minute period (200 s to 500 s) from the medium phase of this baseline was selected in order to minimize any potential disturbance effects.

Psychophysiological data of all participants were visually inspected for any abnormalities. Due to movement artifacts, we analyzed an earlier five-minute baseline period in six cases (2 = PSY, 1 = REL, 2 = AS, 1 = HC), with a minimum of 30 second relaxation beforehand (30s–180s to 330 s–480 s). In three cases (1 = REL, 2 = HC) SCL data were excluded due to unreliability of measurement, which was manifested in no SCL change during the whole session.

2.3. Outcome parameters

2.3.1. Perceived stress

After 10 min of relaxation (see Section 2.2), we assessed perceived stress by applying a visual analog scale (based on Gaab et al., 2003). Participants marked the item "I feel stressed by the situation" on a 10 cm line (0 = "not at all" to 10 = "very intensely").

2.3.2. HRV

Heart rate and HRV were assessed using photoplethysmography to detect the blood volume pulse from the thumb of the non-dominant hand with a sampling rate of 256/s. Compared to electrocardiography, the inconvenience of this method is minimal. Also, HRV estimates derived from blood volume pulse are reliable if measurement is conducted carefully (Lu et al., 2008; Selvaraj et al., 2008, 2009) and if movement is prevented (Gil et al., 2010). The interval length of 5 min was chosen according to the recommendations of the Task Force of the European