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Electrophysiological parameters as biomarkers for psychiatry: Intra-individual variability and influencing factors

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1. Introduction

The autonomous nervous system (ANS) and its potential imbalance play an important role in both physiological and pathological conditions (Moodithaya and Avadhany, 2011; Thayer et al., 2010; Sztajzel, 2004). Stress leads to activation of the sympathetic system and to changes in the ANS. Accordingly, resting heart rate (RHR), heart rate variability (HRV), respiration rate (RR), skin temperature (ST) and skin conductance (SC) are common clinical methods to assess stress, in which HRV is the most established parameter to assess the sympathovagal balance (Alonso et al., 2015; Lin et al., 2011; Shah et al., 2015; Kao et al., 2015; Liu et al., 2015; Klainin-Yobas et al., 2016; Vinkers et al., 2013; Barua et al., 2015; Teisala et al., 2014; Cygankiewicz and Zareba, 2013; Bootsma et al., 1994). Especially in terms of HRV, several influencing factors are discussed in the literature. These include age and gender (Li et al., 2011; Ramaekers et al., 1998; Zhang, 2007; Liu et al., 2003), obesity/body mass index (Freitas et al., 2014; Farah et al., 2013; Chintala et al., 2015; Antelmi et al., 2004), physical activity (Felber Dietrich et al., 2008; Hottenrott et al., 2006; Aeschbacher et al., 2015; Andrew et al., 2013; Cao et al., 2016; Castello et al., 2010; Galetta et al., 2013; Soares-Miranda et al., 2010), smoking, alcohol use, diet and psychosocial factors (Hemingway et al., 2005; Kluttig et al., 2010; Manzano et al., 2011; Alyan et al., 2008; Harte and Meston, 2014; Gondim et al., 2015; Dinas et al., 2011; O'Keefe et al., 2014; Karpyak et al., 2014; Randall et al., 2009; Kogan et al., 2013). There is also some evidence for the impact of pain (Terkelsen et al., 2005) and circadian rhythms (Rodriguez-Colon et al., 2014) on HRV parameters. Findings related to postprandial changes of HRV are inconsistent (Ambarish et al., 2005; Chang et al., 2010; Wijngaarden et al., 2013).

Furthermore, there is evidence for autonomic imbalance in patients with psychiatric disorders, especially in patients with psychosis (Bar et al., 2012; Clamor et al., 2015; Lincoln et al., 2015; Valkonen-Korhonen et al., 2003; Rachow et al., 2011; Olbrich et al., 2001; Sarlon et al., 2016) and depression (Lin et al., 2011; Yeragani et al., 2002; Yeragani, 2000; Won and Kim, 2016; Kemp et al., 2010; Servant et al., 2009). There are also findings indicating sympathovagal changes in patients with anxiety and phobic anxiety, social anxiety disorders and somatoform disorders (Servant et al., 2009; Alvares et al., 2013; Pollatos et al., 2011; Kawachi et al., 1995), alcohol dependence (Karpyak et al., 2014; Garland et al., 2012) or cognitive impairment (Frewen et al., 2013).

Murck et al. (2015) consider the activation of ANS as a possible objective measure to characterise patient subgroups and their response to treatment. Other findings support this hypothesis, and electrophysiological parameters have been used for assessment, treatment and treatment response evaluation (Murck et al., 2015; Wang et al., 2016; Levy, 2013; Joshi et al., 2014; Doukas et al., 2014; Thieme et al., 2015; Zullino et al., 2015; Wangelin and Tuerk, 2015).

Despite the number of studies discussing autonomic imbalance in psychiatric patients, the relationship between autonomic dysfunction and psychiatric disorders is often still unclear. Furthermore, the large inter-individual variability of autonomic responses hinders direct comparison between individuals (Johannes and Gaillard, 2014).

1.1. Aims and hypothesis

The aim of this study was to evaluate intra-individual variability and stability of ANS parameters (RHR, HRV, SC, ST, RR) in healthy subjects, and their potential capability and reliability in psychiatric research. This study also aimed to demonstrate which electrophysiological parameters of the ANS are especially robust and stable and thus suitable as objective biomarkers for psychiatric research.

The role of the main known influencing factors was also evaluated. The hypothesis is that electrophysiological parameters vary during day time and, according to the literature, could be influenced by physical activity, last meal, consumption of alcohol and nicotine, BMI or other factors. To assess the possibility of using electrophysiological parameters as biomarkers in psychiatric research, the recording of additional parameters as well as the administration of the Brief Symptom Inventory (BSI) and the visual analogue scales (VAS) of well-being, pain and anxiety were considered.

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2. Materials and methods

2.1. Participants

Altogether, 63 healthy volunteers between 18 and 65 years of age participated in the study. The subjects had a mean of 15.60 (SD = 3.12) education years; 27 were males and 36 were females, with a mean age of 35.90 (SD = 8.45) years. Exclusion criteria were a history of heart disease (myocardial infarction, heart insufficiency, and heart conduction disorders), diabetes mellitus, neurological or psychiatric disorders as well as history of cancer or other serious medical condition. Medications for existing conditions were assessed for each participant. Medications taken by eligible participants were oral contraceptives in seven cases, levothyroxine in five cases, asthma spray (that was occasionally used in six cases) and supplements such as vitamin C.

All participants were screened with BSI (Derogatis and Melisaratos, 1983, German version; 2000). BSI is a 53-item self-report inventory in which participants rate the extent to which they have been troubled (0 = “not at all” to 4 = “extremely”) in the past week by various symptoms. The BSI has nine subscales designed to assess individual symptom groups: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. If subjects scored > 63 in the global severity index (T-GSI) in two or more items, they were excluded from participation (11 candidates were excluded). Mean BMI was 23.48 (SD = 3.03). Nicotine and alcohol use, physical activity and time of the last meal were evaluated with the aid of a questionnaire.

All participants were introduced to the experimental protocols and completed a written consent form prior to participation. The experimental protocol was approved by the Ethics Committee of the Institute (Nr. 57/13).

2.2. Methods

Prior to electrophysiological measures, VAS was used to assess well-being, pain and anxiety. According to the literature, a horizontal line, 100 millimetres (mm) in length, anchored by word descriptors at each end, was used. The participants marked on the line the point most representative of their current state. The VAS score was determined by measuring in mm from the left-hand end of the line to the patient's mark.

Average and last nicotine and alcohol consumption as well as last physical activity, last meal and BMI were recorded.

Physiological data were acquired using the NeXus-10 System (NeXus-10 Mark II®, software Biotrace) and were recorded at a 1024 Hz sampling rate. NeXus-10 provides measures of the autonomic parameters within 3-channel ECG, measures of SC, ST and RR.

For ECG-measures, high quality Ag-electrodes (Ambu® BlueSensor) with electrode-gel were used. Skin was cleaned with alcohol before electrodes were placed on the apex, right and left clavicular bone. To measure SC, velcro-tape with integrated Ag/AgCl-electrodes was placed at the middle phalanx of the index and the ring finger of the left hand. The measuring unit of the SC was μSiemens. For the measurement of ST, the NeXus Temperature Sensor was placed on the middle finger of the left hand and taped to the finger at two positions to ensure stability.

To measure RR, an elastic belt with a breathing sensor was fixed around the lower thorax, at the diaphragm. According to manufacturer's instructions, one or two layers of clothes could be present between the skin and the elastic belt.

To ensure that individual data were comparable, the same procedures were used for all study participants. All measures were taken in awake subjects, sitting in a supine position. All measures were performed under comparable conditions, including room temperature, absence of noise and persons present. Electrodes were positioned according to the protocol. To reduce the impact of pre-test movements, all subjects were asked to relax for 10 min prior to placement of the electrodes.

Prior to the first measure, the participants were requested to take part in a second measurement at a separate time. To assess intra-individual variability, three groups were defined, regarding the interval between the initial 5 min baseline (test) and the second measure (5 min baseline, retest). The first group, composed of 45 participants (25 females, mean age 36.76 ± 7.12 y), was retested immediately after the first measure (after 30 min). The second group consisted of 27 participants (15 females, mean age 35.81 ± 9.49 y), who underwent measurements in the morning and afternoon, respectively. The third group (retested at the same time as the first measure, but on another day) involved 27 participants (15 females, mean age 37.96 ± 7.87 y).

Participants could select their study group. More participants were willing to participate in the first group due to the time factor (no necessity to retest on another day or at a later time), which impacted on the size of the groups. The three groups did not differ significantly in sociodemographic or influencing factors (the difference in BMI between the second and the third group, 23.32 vs. 24.89, was not significant; p = 0.079).

The mean VAS in the population (VAS, minimum = 0, maximum = 10) for pain was 0.34 (SD = 1.04), for anxiety 0.46 (SD = 0.72) and for well-being 8.08 (SD = 1.68). The median time of the last meal was 2.5 h before testing, the median time of the last alcohol consumption was 5 days. 19 participants were smokers (mean cigarettes/day 12.89, SD = 6.91, median time of the last consumption was 1 h prior to testing). 49 of 63 participants reported regular physical activity of a minimum of 20 min per week.

2.3. Data pre-processing and analysis

Regarding influencing factors, the following units were defined prior to statistical analysis: to quantify sporting activity and alcohol consumption, units per week (sport) and units per day (alcohol) were defined, whereby one unit corresponded to 20 min of sporting activity or to one bottle of beer, one glass of wine or 5 cl of high percentage alcohol. Furthermore, according to the literature, an approximation was used with a threshold of 120 min. The recording and the primary analysis of all electrophysiological parameters were performed by the software BioTrace + .

For the analysis of HRV, time and frequency domain parameters and records of 5 min length (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) with a sampling rate of 1024 Hz were used, according to the standards. The power frequency spectrum of HRV was subsequently quantified in standard frequency-domain measurements including total variance, high-frequency (HF, 0.15–0.4 Hz), low-frequency (LF, 0.04–0.15 Hz), very low-frequency (VLF, 0–0.04 Hz) and HF/LF ratio. For the time domain, principal parameters such as beat-to-beat interval (NN), square root of the beat-to-beat interval (SDNN), root mean square of successive differences (RMSSD), and number of pairs of successive RRs that differ by > 50 ms (NN50) were computed by the Software BioTrace + and presented in table form with the main statistical parameters. Additionally, the parameter coherence RR/RHR was computed as an outcome.

Prior to the analyses, all parameters were visually controlled on the 10-second window and artefacts (not physiological values or device failure in SC or ST, but artefacts due to recorded movements in RHR and HRV-parameters) were removed. Measurements with > 5% artefacts of the recorded time were excluded; this occurred in eight measures of SC, six measures of ST and seven measures of RHR and HRV parameters.

Statistical analysis was performed using SPSS software (IBM SPSS Statistics® version 22). The normality of the distribution was assessed using the Kolmogorov-Smirnov goodness of fit test.

To assess the gender differences and the differences between two measures, paired samples *t*-test (for normally distributed data) or Mann-