Effects of high-frequency prefrontal rTMS on heart frequency rates and blood pressure in schizophrenia

Mattia Campana [a,*,1], Elias Wagner [a,1], Thomas Wobrock [b,c], Berthold Langguth [d], Michael Landgrebe [d,e], Peter Eichhammer [d], Elmar Frank [d], Joachim Cordes [f], Wolfgang Wölwer [f], Georg Winterer [g], Wolfgang Gaebel [f], Göran Hajak [h], Christian Ohmann [i], Pablo E. Verde [j], Marcella Rietschel [k], Berend Malchow [b], Raees Ahmed [l], Wolfgang Strube [m], Jan Häckert [m], Thomas Schneider-Axmann [a], Peter Falkai [a], Alkomiet Hasan [m]

[a] *Department of Psychiatry and Psychotherapy, Klinikum der Universität München, Ludwig-Maximilians-University, München, Germany*
[b] *Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany*
[c] *County Hospitals Darmstadt-Dieburg, Groß-Umstadt, Germany*
[d] *Department of Psychiatry and Psychotherapy, University of Regensburg, Germany*
[e] *Department of Psychiatry, Psychosomatics and Psychotherapy, Kbo-Lech-Mangfall-Klinik Agatharied, Germany*
[f] *Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany*
[g] *Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité– Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany*
[h] *Department of Psychiatry, Psychosomatics and Psychotherapy, Sozialstiftung Bamberg, Bamberg, Germany*
[i] *European Clinical Research Network (ECRIN), Düsseldorf, Germany*
[j] *Coordination Centre for Clinical Trials, Heinrich-Heine University, Düsseldorf, Germany*
[k] *Department of Genetic Epidemiology in Psychiatry, Institute of Central Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany*
[l] *University Medical Center, Goettingen, Germany*
[m] *Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, BKH, Augsburg, Germany*

* Corresponding author. Department of Psychiatry and Psychotherapy, LMU Munich, Nussbaumstraße 7, D- 80336, Munich, Germany.
E-mail address: mattia.campana@med.uni-muenchen.de (M. Campana).
[1] both authors contributed equally.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that is applied to the scalp using rapidly changing magnetic fields to induce local and remote changes in neuronal excitability and plasticity. In the last years, a magnitude of clinical trials using high-frequency, low-frequency or patterned rTMS has been conducted in the fields of neurology and psychiatry targeting various difficult-to-treat diseases, such as Parkinson's disease, dementia, depression or schizophrenia (Lefaucheur et al., 2020). In general, rTMS is a safe neuromodulation technique that is now widely used for the treatment of various neuropsychiatric disorders.

The most severe adverse reactions to rTMS are seizures that occur very rarely in participants receiving rTMS. Estimations rate the risk for seizures within the range of a standardized risk of 67/100,000 sessions to 1/100.000 sessions dependent on the individual risk profile (Rossi et al., 2021). More frequent and thus clinically relevant adverse reactions include headache or hearing problems due to transient acoustic artefacts of the rTMS pulse. Moreover, in clinical practice, some participants report dizziness or vertigo and autonomic dysfunction (Makovac et al., 2017). Interestingly, the latter was not included in the recent rTMS safety consensus statements (Rossi et al., 2021) and the effect of rTMS applied to the cortex on autonomic functions such as heart rate or blood pressure has not been studied systematically in large patient cohorts. As many patients who receive rTMS may have disease-associated impairments in autonomic regulation (e.g. patients with schizophrenia or Parkinson's disease (Bar, 2015; Ziemssen and Reichmann, 2010)) and as those patients may receive medication that may pronounce autonomic dysfunction (e.g. antipsychotics) more evidence about the effects of rTMS on the brain-heart-circulation circle is needed. To date, potential effects of rTMS on autonomic functions have been primarily investigated in healthy subjects. A recent meta-analysis showed that non-invasive brain stimulation (NIBS), especially rTMS, is effective in reducing heart rate (Hedges' $g = 0.17$) and enhancing heart rate variability (HRV) ($g = 0.30$) with marginal effect on blood pressure ($g = 0.21$) (Makovac et al., 2017). It must be noted that in this meta-analysis, healthy subjects, and subjects with highly heterogeneous disorders (with major depressive disorder, autism, migraine, bulimia nervosa, stroke, or spinal cord injury) were included. From the view of therapeutic rTMS it must be noted that the medial PFC, which represents the main target region for rTMS, is presumed to be one cortical key region in the regulation of autonomic functions (Thayer et al., 2012). The most common tests to assess autonomic dysfunction are heart rate, heart rate variability, blood pressure levels, microneurography, functional sweating tests, pupil size, and respiration rate evaluations (Schestatsky et al., 2013). These variables were mainly investigated in open-label studies with a small number of healthy subjects following a single-pulse rTMS design and none of the studies contained long-term follow-up data significantly beyond the end of stimulation (Schestatsky et al., 2013). Thus, there is a need to investigate the effects of rTMS in conditions where autonomic or cardiovascular systems are affected (Makovac et al., 2017), since knowledge about potential beneficial or harmful effects of rTMS on autonomic functions in patient cohorts might have both therapeutic and safety implications. Therefore, we undertook secondary analyses of the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial (Wobrock et al., 2015), the largest available rTMS trial on the treatment of negative symptoms in schizophrenia to date. In this trial vital parameters related to autonomic nerve function were systematically assessed as safety parameters. Schizophrenia is a severe mental illness that has been associated with a potential life loss of more than ten years compared to the general population (Hjorthoj et al., 2017) with cardiovascular diseases (CVD) contributing considerably to this increased mortality risk (Castagnini et al., 2013). In addition, autonomic functions are often hampered in schizophrenia patients (Alvares et al., 2016; Clamor et al., 2016; Quintana et al., 2016) possibly related to an imbalance of vagal and sympathetic control mechanisms (Bar et al., 2005, 2007; Chang et al., 2009). Even though the role of autonomic dysfunction for the higher mortality risk among schizophrenia patients remains overall unclear, it was previously suggested that decreased parasympathetic activity could be associated with an increased mortality in older patients with schizophrenia (Hattori et al., 2018). Here, we present the first analyses of long-term rTMS effects on heart rate and blood pressure based on the safety data of a large sham-controlled randomized and multicentric trial.

2. Methods

This is a secondary analysis of the RESIS trial. The design of the RESIS trial has been described and published elsewhere and the primary outcome was published in 2015 (Cordes et al., 2009; Wobrock et al., 2015). In brief, 197 patients with schizophrenia and predominant negative syndrome as defined elsewhere (Cordes et al., 2009; Wobrock et al., 2015) were screened and 175 patients were enrolled and randomly assigned to either active or sham rTMS in this multicenter randomized controlled trial. 157 patients received either active ($n = 76$) or sham ($n = 81$) rTMS treatment and at least one PANSS assessment prior to the intervention. rTMS was delivered at all centers by a MagPro X100 stimulator (Medtronic A/S, Copenhagen, Denmark) with a passively cooled figure-of-eight coil (Medtronic A/S) (Hansbauer et al., 2018; Wobrock et al., 2015). The stimulated target region for active rTMS was determined with the EEG International 10–20 system (F3 electrode, left DLPFC) (Herwig et al., 2001, 2003; Homan et al., 1987).

The active rTMS intervention was defined with the following parameters: 10 Hz, five treatment sessions/week for a 3-week treatment period (from day 0 to day 21) with an intensity of 110% of the individual resting motor threshold and 1000 stimuli (20 trains with 50 stimuli per train, 30-sec intertrain interval) (Hansbauer et al., 2018; Wobrock et al., 2015). Sham rTMS was defined with the same parameters, but the stimulation coil was tilted over one wing at an angle of 45° (Hansbauer et al., 2018; Lisanby et al., 2001; Wobrock et al., 2015). Please see other RESIS publications for the complete study description (including details of blinding, randomization procedures, detailed inclusion and exclusion criteria, primary endpoint analyses and a complete list of all outcome parameters) (Cordes et al., 2009; Hansbauer et al., 2018; Wobrock et al., 2015). Prior to the inclusion of the first patient, the trial was registered at http://clinicaltrials.gov/with the number: NCT00783120.

2.1. Outcome measures

For this secondary analysis, we evaluated the following parameters that serve as a proxy for autonomous nerve function: (1) blood pressure (diastolic and systolic) in the reclining posture (BP_{rec}); (2) blood pressure (diastolic and systolic) in standing posture (BP_{sta}); (3) heart rate in the reclining posture (HR_{rec}); (4) heart rate in the standing posture (HR_{sta}). According to the clinical trial protocol, the measures in standing posture were taken after 1 min of standing up. Moreover, we analyzed whether the criteria for tachycardia (yes/no; defined as heart rate > 100/min) were met in both positions. All these parameters were initially taken as safety parameters (vital signs) as part of the regular study visits. We evaluated these parameters at six time points: screening, treat 0 (before intervention), treat 21 (directly after intervention), FU 28 (day 28), FU 45 (day 45) and FU 105 (day 105) with no defined timing related to the rTMS session during the intervention phase. We first analyzed the contrast screening vs. treat 21 and then the complete time course with all available data points. Several other variables, including body mass index, smoking status, handedness or pharmacological treatment (e.g. antipsychotic dose) were added where necessary. Main demographic and clinical variables, such as the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) score for severity, the Global Assessment of Functioning (GAF), the Calgary Depression Scale for Schizophrenia (CDSS) or the Montgomery Asberg Depression Rating Scale (MADRS) were used to describe the sample characteristics.

2.2. Statistical analyses

All analyses were carried out in SPSS25 (IBM Inc.) with a significance level of $\alpha = 0.05$. The normality of all outcome variables was examined with Kolmogorov-Smirnov tests and Levene's test was used to check variance homogeneity. Baseline between-group differences were analyzed with one-way ANOVAs and χ^2-tests. As the concerning data were not normally distributed, baseline CGI scores were compared using Mann-Whitney *U* test. For the intention-to-treat population (defined as all patients randomized to a treatment group who started at least one treatment session (Wobrock et al., 2015)), all continuous outcome parameters (BP_{rec} diastolic and systolic, BP_{sta} diastolic and systolic, HR_{rec}, HR_{sta}) were analyzed with general linear mixed model analysis, non-restrictively assuming an unstructured covariance matrix (Krueger and Tian, 2004) in accordance to foregoing publications (Wobrock et al., 2015). Group (active rTMS vs. sham rTMS) was the between-subject factor and time (pre rTMS vs. post rTMS) was the within-subject factor. Analyses were adjusted for age, sex, center and were appropriate for the body mass index (BMI). As detailed above, we first analyzed the contrast screening vs. day 21 and then conducted consecutive analyses including all time points from the screening phase to day 105 (end of the extension phase). Next, we analyzed the impact of response status, defined as an improvement of ≥20% on the PANSS negative symptom scale (ΔPANSS-NS%= (PANSS-NS_{T1}− PANSS-NS_{T0}) × 100/(PANSSNS$_{T0}$− 7)) (Wobrock et al., 2015). χ^2-tests were used to test for different distributions of tachycardia (yes/no) between groups. Breslow-Day tests were applied to test for significant inhomogeneities of the odds ratios. The significance level of $\alpha = 0.05$ was not adjusted for the different outcome variables (m = 6), since such an adjustment would have increased the probability of false-negative findings in case of existing mean differences between active and sham rTMS in the total population. Therefore, our results must be interpreted with caution. For the blood pressure and pulse variables presented here, post hoc power analyses using actual sample sizes and observed variances were calculated. A sufficient power of $1 - ß > 0.8$ was achieved simulating the following assumed mean differences θ = *active rTMS (μday21 – μscreening) - sham rTMS (μday21 – μscreening)*: $\theta = 9$ (BP_{rec} systolic), $\theta = 10$ (BP_{sta} systolic), $\theta = 7$ (BP_{rec} and BP_{sta} diastolic, and $\theta = 8$ (HR_{rec}, HR_{sta}).

3. Results

3.1. Study subjects

Apart from a significant higher proportion of females in the sham group and a trend towards higher PANSS positive and total symptoms (in accordance with the clinical data publication (Wobrock et al., 2015)) no significant group differences were observed as detailed in Table 1.

Table 1
Baseline characteristics.

Variable	Active rTMS (N = 62)		Sham rTMS (N = 70)		Active vs. Sham		
					LR χ^2	df	p
Gender (male: female)	52 : 10		48 : 22		4.2	1	0.041[a]
Employment (employed: not employed)	10 : 52		9 : 61		0.3	1	0.59[a]
Center (Duesseldorf: Goettingen: Regensburg)	14 : 10: 28		19 : 23: 28		0.5	2	0.78[a]
Hand preference (right: not right)	52 : 8		55 : 10		0.0	1	0.74[a]
Antidepressant use (yes: no)	25 : 36		25 : 44		0.3	1	0.58[a]
	Mean	SD	Mean	SD	F	df	p
Age, yr	35.7	10.4	35.2	8.8	0.1	1, 130	0.76[b]
Education, yr	11.3	1.9	11.4	2.0	0.0	1, 126	0.91[b]
Left resting motor threshold	46.5	8.5	46.0	12.0	0.1	1, 116	0.78[b]
Severity of illness and treatment							
PANSS negative symptoms	25.8	4.3	25.2	3.8	0.7	1, 128	0.40[b]
PANSS positive symptoms	14.1	4.4	12.9	3.5	3.1	1, 125	0.08[b]
PANSS total score	80.2	15.5	75.6	12.8	3.4	1, 125	0.07[b]
Clinical Global Impression score for severity[e]	4.6	0.9	4.7	0.9	Z = −0.6	1	0.58[c]
Global Assessment of Functioning[g]	51.9	11.9	52.7	11.4	0.1	1, 118	0.72[b]
Antipsychotic dose (chlorpromazine equivalents), mg/day	574	421	580	548	0.0	1, 125	0.82[d]
Depression related							
Calgary Depression Scale for Schizophrenia[i]	5.1	3.6	5.1	4.0	0.0	1, 123	0.91[b]
Montgomery Asberg Depression Rating Scale[j]	14.7	6.0	13.3	6.2	1.6	1, 127	0.21[b]

Legend: Abbreviations: LR χ^2, likelihood ratio chi square statistic; df, degrees of freedom; SD, standard deviation; F, F statistic; Z, Z statistic; yr, years; mg, milligram; PANSS, Positive and Negative Syndrome Scale. [a] Comparison by likelihood ratio test; [b] Comparison by analysis of variance; [c] Comparison by Mann-Whitney *U* test; [d] comparison on logarithmic transformed variable by analysis of variance.

3.2. Continuous outcomes screening to treat 21

LMM analyses adjusted for age, gender, center and BMI showed no significant time × group interactions for diastolic ($p = 0.123$) and systolic ($p = 0.982$) BP_{rec} or diastolic ($p = 0.732$) and systolic ($p = 0.782$) BP_{sta} and no time effect for any of the variables (all $p > 0.343$). For HR_{rec}, LMM adjusted for age, gender and center showed a trend towards a time × group interaction ($p = 0.056$) that could not be observed for HR_{sta} ($p = 0.515$). Again, no time effects were observed (all $p > 0.203$). These findings indicate neither an impact of active nor of sham rTMS on autonomic functions during the period of the daily active stimulation. Please see Table 2 for all test statistics and Fig. 1A – F for the course of the effects.

3.3. Continuous outcomes screening to treat 105

LMM analyses adjusted for age, gender, center and BMI showed in principle the same pattern as the analyses until treat 21, but with some significant effects as detailed hereafter. We were not able to observe a significant time × group interaction for diastolic ($p = 0.141$) and systolic ($p = 0.672$) BP_{rec} or systolic ($p = 0.496$) BP_{sta}. However, for diastolic ($p = 0.017$) BP_{sta} a significant time × group interaction was shown. The time analyses of diastolic ($p = 0.003$) BP_{rec} and diastolic ($p = 0.036$) BP_{sta} showed a significant effect while all others remained non-significant (all $p > 0.377$). The pattern of these results indicates an unspecific increase in diastolic blood pressure in both groups over time. For both HR measures, LMM adjusted for age, gender and center showed no significant time × group interaction (HR_{rec}: $p = 0.188$; HR_{sta}: $p = 0.853$), but for both analyses significant time effects interactions could be observed (HR_{rec}: $p = 0.030$; HR_{sta}: $p = 0.025$). This indicates an increase for HR_{sta}, but despite the significant time effect no clear pattern for HR_{rec}. Please see Table 2 for all test statistics and Fig. 1 A – F for the course of the effects.

Table 2
Results of LMM analyses.

	Time			Time x Group		
Variable	F	df	p	F	df	p
Screening to treat21						
BP_{rec} diastolic	0.525	1, 94.434	0.470	2.416	1, 93.383	0.123[a]
BP_{rec} systolic	0.904	1, 97.505	0.344	0.001	1, 96.485	0.982[a]
BP_{sta} diastolic	0.812	1, 102.945	0.370	0.118	1, 102.466	0.732[a]
BP_{sta} systolic	0.687	1, 100.425	0.409	0.077	1, 99.898	0.782[a]
HR_{rec}	1.635	1, 99.702	0.204	3.748	1, 99.423	0.056[b]
HR_{sta}	0.396	1, 104.388	0.531	0.427	1, 104.541	0.515[b]
All time points						
BP_{rec} diastolic	4.074	5, 66.552	0.003	1.726	5, 66.541	0.141[a]
BP_{rec} systolic	1.081	5, 75.028	0.378	0.637	5, 74.353	0.672[a]
BP_{sta} diastolic	2.542	5, 70.619	0.036	2.965	5, 71.231	0.017[a]
BP_{sta} systolic	1.054	5, 71.482	0.393	0.885	5, 71.622	0.496[a]
HR_{rec}	2.647	5, 69.770	0.030	1.541	5, 69.611	0.188[b]
HR_{sta}	2.755	5, 73.544	0.025	0.392	5, 73.660	0.853[b]

Legend: Abbreviations: BP = blood pressure, df: degrees of freedom, HR = heart rate, F: F statistic, p: p-value, rec = reclining, sta = standing; [a]LMM adjusted for sex, age, center and BMI; [b]LMM adjusted for sex, age and center.

3.4. Impact of response status

Adding the fixed-factor "response" (yes/no) to the analyses resulted in no change in the aforementioned findings of all outcome variables until treat 21 (response status directly after the end of intervention) and during the complete course of follow-up (response until day 105) (see Table 3).

Frequency of tachycardia at screening, treat 0 and treat 21.

The frequency of tachycardia in reclining position did not differ across groups when assessed at screening (active: n = 8, 12.1%, sham: n = 14, 18.7%, Chi^2 (1) = 1.1, p = 0.28), treat 0 (active: n = 6, 12.8%, sham: n = 7, 14.3%, Chi^2 (1) = 0.05, p = 0.83) and treat21 (active: n = 8, 16.7%, sham: n = 9, 16.7%, Chi^2 (1) = 0.0, p = 1.00). The same pattern was observed for the frequency of tachycardia in the standing position: screening (active: n = 22, 34.4%, sham: n = 29, 38.7%, Chi^2 (1) = 0.3, p = 0.60), treat 0 (active: n = 13, 28.3%, sham: n = 19, 37.3%, Chi^2 (1) = 0.9, p = 0.35) and Treat21 (active: n = 16, 33.3%, sham: n = 23, 40.4%, Chi^2 (1) = 0.5, p = 0.46). For all of the investigated time points, no significant inhomogeneities for the odds ratios between active and sham rTMS was observed (treat 21 vs. screening: Breslow-Day Test for HR_{rec}: Chi^2 (1) = 0.5, p = 0.48; HR_{sta} Chi^2 (1) = 0.05, p = 0.83; treat21 vs. treat0: Breslow-Day Test: HR_{rec}: Chi^2 (1) = 0.03, p = 0.87, HR_{sta}: Chi^2 (1) = 0.035, p = 0.86). These findings indicate no significant impact on the frequency of tachycardia during active rTMS compared to sham rTMS.

4. Discussion

This is the first large-scale randomized controlled trial investigating the impact of prefrontal rTMS on autonomic function assessed with systolic and diastolic blood pressure and heart rate in two different positions in patients with schizophrenia. To the best of our knowledge, no study investigated the effect of high-frequency rTMS applied to the left DLPFC on the autonomic functions among schizophrenia patients yet. Our results did not find a specific effect of active rTMS compared to sham rTMS on autonomic functions, neither during the intervention period nor during the follow-up period. Response status did in general not affect the course of the here evaluated outcome variables. Although no significant effects between active rTMS and placebo on autonomic function were found, it was possible to detect some numerical effects in the data. Above all, it is worth mentioning the increase between baseline and FU 28 of both HR_{STA} and HR_{REC} in patients receiving active rTMS, which was not observed in patients receiving sham rTMS. This could point towards an effect of prefrontal rTMS on autonomic functions which deserves further investigation. With this being a secondary analysis, more studies are needed to replicate the data and investigate the possible biological underpinning of the reported trend. Since non-invasive brain stimulation such as rTMS is frequently applied in treatment-refractory populations which might represent an even more vulnerable subgroup regarding autonomic dysfunction due to disease course and prolonged antipsychotic treatment, controlling for effects of rTMS on the cardiovascular system is crucial. Especially since the long-term effects of prefrontal rTMS on autonomic function are unknown, our analyses contribute to a better understanding of safety aspects of rTMS in schizophrenia. Of note, none of the studies included in published meta-analysis on the impact of NIBS on autonomic dysfunction were conducted in patients with schizophrenia (Makovac et al., 2017), making our randomized controlled trial an important contributor to the discussion around safety and rTMS-related changes in autonomic functions in schizophrenia. Moreover, this study adds further high-quality evidence regarding safety aspects of high-frequency rTMS through its sham-controlled design.

As mentioned above, the results presented here stem from a secondary analysis of the RESIS trial and as such entail some limitations. Although LMM analyses controlled for age, gender, center and BMI, a more thorough adjustment for variables such as comorbidities, cardiovascular health or concomitant medications could not be undertaken. Moreover, a lack of a healthy control group prevents comparisons between schizophrenia patients and healthy volunteers. Furthermore, it is important to mention that this trial was not designed to assess changes in autonomic function in real-time during rTMS treatment. This should be taken into consideration when discussing safety aspects of rTMS and should be evaluated in future studies. Finally, while HR and BP were assessed as part of the regular study visits, we are not able to determine the concrete timing of these assessments in relation of the rTMS intervention during the 3-week intervention phase. Nevertheless, the results reported here show that even in a population with presumably multiple vulnerabilities regarding autonomic dysfunction the application of therapeutic rTMS appears safe.

Overall, the effects of rTMS on parameters modulated by the autonomic nervous system such as HR, HRV or BP appear to be an important and yet under investigated topic in non-invasive neuromodulation treatments. As explored in recent research on major depressive disorder (Iseger et al., 2020a, 2020b), prefrontal brain structures like the DLPFC appear to be strongly interconnected with central autonomic nervous system regulating regions making the investigation of autonomic nervous system parameters important both in the discussion around safety and efficacy. Moreover, from another perspective (efficacy rather than safety) rTMS effects on heart rate might represent a potential for individualizing rTMS treatments (Iseger et al., 2017; Kaur et al., 2020). However, being aware that our trial was not designed to answer this question comprehensively, we were neither able to detect a beneficial or a harmful relationship between response status and changes in autonomic outcome parameters. Future studies should assess, possibly in real-time, correlates of autonomic (dis-)function such as but not limited to HR, HRV and BP when investigating prefrontal NIBS treatments in psychiatric populations to foster the evidence about potentially harmful NIBS-related effects.

5. Conclusions

In this first large-scale randomized controlled trial investigating the impact of prefrontal rTMS on autonomic function in patients with schizophrenia no significant effect of active rTMS compared to sham rTMS on autonomic functions was found, neither during the intervention period nor during the follow-up period. These secondary analyses presented here contribute to a better understanding of safety aspects of rTMS in schizophrenia.

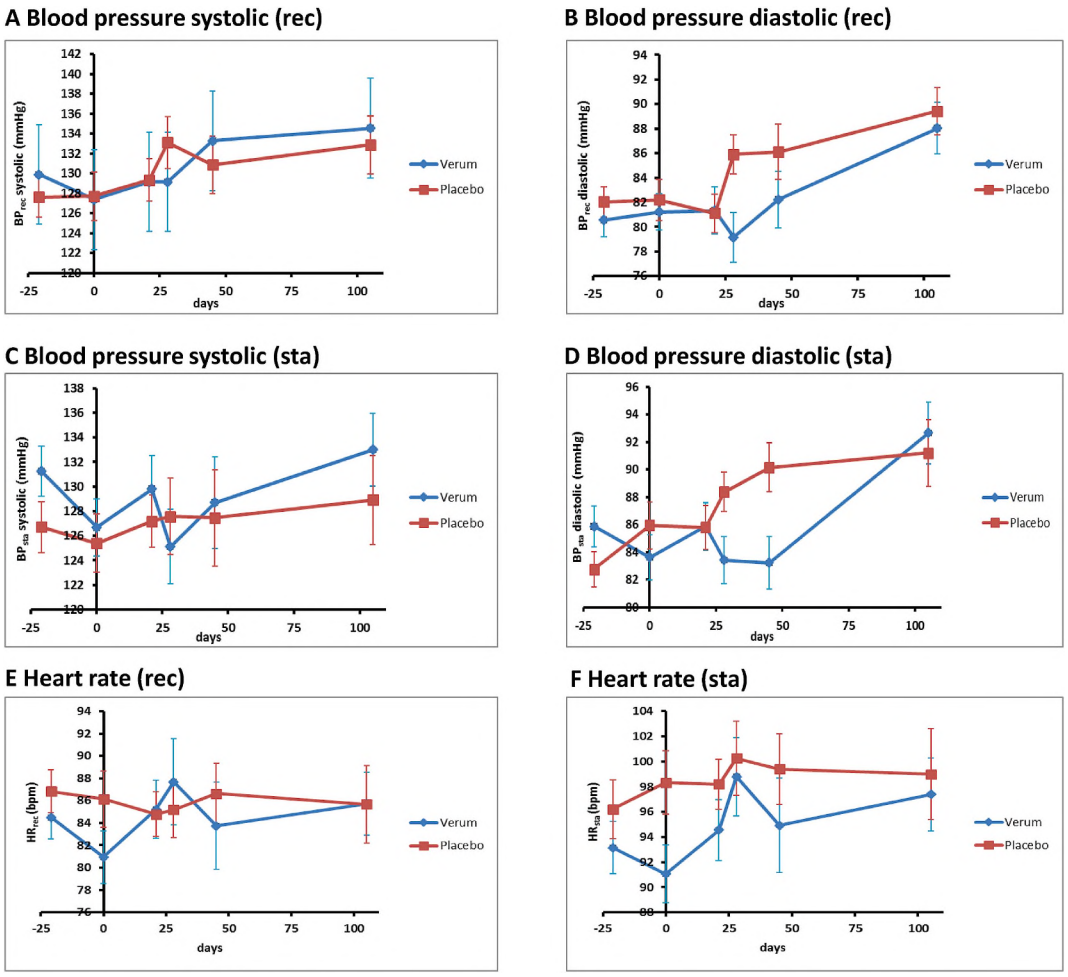

Fig. 1. A-F: The course of blood pressure (BP) systolic and diastolic (in mmHg) and heart rate (HR) (in bpm) in reclining (rec) and standing (sta) position from screening to day 105 (FU105) in the LMM-analysis. The figure represents the data for the six variables. For BP_{rec} systolic **(A)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 62, Baseline: N = 62, Treat 0: N = 48, Treat 21: N = 48, FU 28: N = 25, FU45: N = 26, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 49, Treat 21: N = 55, FU 28: N = 36, FU45: N = 29, FU105: N = 24.
For BP_{rec} diastolic **(B)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 62, Baseline: N = 62, Treat 0: N = 48, Treat 21: N = 48, FU 28: N = 25, FU45: N = 26, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 49, Treat 21: N = 55, FU 28: N = 36, FU45: N = 29, FU105: N = 24. For BP_{sta} systolic **(C)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 60, Baseline: N = 60, Treat 0: N = 46, Treat 21: N = 48, FU 28: N = 26, FU45: N = 27, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 51, Treat 21: N = 57, FU 28: N = 35, FU45: N = 28, FU105: N = 25. For BP_{sta} diastolic **(D)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 60, Baseline: N = 60, Treat 0: N = 46, Treat 21: N = 48, FU 28: N = 26, FU45: N = 27, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 51, Treat 21: N = 57, FU 28: N = 35, FU45: N = 28, FU105: N = 25. For HR_{rec} **(E)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 61, Baseline: N = 61, Treat 0: N = 47, Treat 21: N = 48, FU 28: N = 25, FU45: N = 26, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 49, Treat 21: N = 54, FU 28: N = 36, FU45: N = 29, FU105: N = 24. For HR_{sta} **(F)** the following group sizes (N) were used for the analyses: **Verum:** Screening: N = 60, Baseline: N = 60, Treat 0: N = 46, Treat 21: N = 48, FU 28: N = 26, FU45: N = 27, FU105: N = 29; **Placebo**: Screening: N = 70, Baseline: N = 70, Treat 0: N = 51, Treat 21: N = 57, FU 28: N = 35, FU45: N = 28, FU105: N = 25.
Abbreviations: BP = blood pressure, bpm = beats per minute, HR = heart rate, rec = reclining, sta = standing. Error bars represent standard errors of the mean.

Declaration of competing interest

M. Campana reports no conflicts of interest. E. Wagner reports no conflicts of interest. T. Wobrock has received paid speakerships from Alpine Biomed, AstraZeneca, Bristol Myers Squibb, Eli Lilly, I3G, Janssen Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis, Otsuka and Pfizer. He was an advisory board member of Janssen Cilag and Otsuka/Lundbeck and has received restricted research grants from AstraZeneca, Cerbomed, I3G and AOK (health insurance company) as well as the German Research Foundation and the German Bundesministerium für Bildung und Forschung. J. Cordes was a member of an advisory board of Roche, accepted travel or hospitality not related to a speaking engagement from Servier, support for symposia from Inomed, Localite, Magventure, Roche, Mag & More, NeuroConn, Syneika, FBI Medizintechnik, Spitzer Arzneimittel and Diamedic, research and study participation funded by the German Research Foundation and the German Bundesministerium für Bildung und Forschung, Foundation European Group for Research In Schizophrenia, ACADIA Pharmaceuticals Inc., Boehringer Ingelheim Pharma GmbH & Co. KG, Otsuka Pharmaceutical Europe Ltd. and EnVivo Pharmaceuticals. W. Wölwer has received paid speakerships from Bristol-Myers Squibb, Essex Pharma, Janssen-Cilag, Lilly Deutschland, and Pfizer Neuroscience. He is a member of the Neuroscience Academy of Roche Pharma. G. Winterer is Chief Executive Officer of Pharmaimage Biomarker Solutions GmbH Berlin Germany and President of Pharmaimage Biomarker Solutions Inc. Boston USA. W. Gaebel has received symposia support from Janssen-Cilag GmbH, Neuss, Lilly Deutschland GmbH, Bad Homburg and Servier, Munich. He is a member of the Faculty of the Lundbeck International Neuroscience Foundation (LINF), Denmark. B. Langguth is an advisory board member of Neuromod and Desyncra, received honoraria and speakers' fees from

Table 3
Results of LMM analyses with regard to the response status.

Variable	Time x Group x Response		
	F	df	p
At treat21			
BP_{rec} diastolic	0.155	2, 96.610	0.857[a]
BP_{rec} systolic	0.416	2, 100.085	0.661[a]
BP_{sta} diastolic	0.119	2, 99.899	0.888[a]
BP_{sta} systolic	0.528	2, 98.581	0.591[a]
HR_{rec}	0.383	2, 107.532	0.683[b]
HR_{sta}	0.719	2, 109.329	0.490[b]
At all time points			
BP_{rec} diastolic	0.550	6, 67.518	0.768[a]
BP_{rec} systolic	0.546	6, 75.786	0.772[a]
BP_{sta} diastolic	0.836	6, 68.055	0.547[a]
BP_{sta} systolic	0.819	6, 78.788	0.558[a]
HR_{rec}	1.236	6, 68.052	0.299[b]
HR_{sta}	1.608	6, 71.520	0.157[b]

Legend: Abbreviations: BP = blood pressure, df: degrees of freedom, HR = heart rate, F: F statistic, p: p-value, rec = reclining, sta = standing; [a]LMM adjusted for response, sex, age, center and BMI; [b]LMM adjusted for response, sex, age and center.

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