Nordic Journal of Psychiatry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipsc20

Intercorrelation of physiological seizure parameters and hormonal changes in electroconvulsive therapy

Elin Thörnblom, Malin Gingnell, Janet L. Cunningham, Mikael Landén & Robert Bodén

To cite this article: Elin Thörnblom, Malin Gingnell, Janet L. Cunningham, Mikael Landén & Robert Bodén (2023) Intercorrelation of physiological seizure parameters and hormonal changes in electroconvulsive therapy, Nordic Journal of Psychiatry, 77:3, 312-318, DOI: 10.1080/08039488.2022.2107237

To link to this article: https://doi.org/10.1080/08039488.2022.2107237

Published online: 15 Aug 2022.

NORDIC JOURNAL OF PSYCHIATRY
2023, VOL. 77, NO. 3, 312–318
https://doi.org/10.1080/08039488.2022.2107237

Taylor & Francis
Taylor & Francis Group

ARTICLE

Intercorrelation of physiological seizure parameters and hormonal changes in electroconvulsive therapy

Elin Thörnblom[a], Malin Gingnell[a], Janet L. Cunningham[a], Mikael Landén[b,c] and Robert Bodén[a]

[a]Department of Medical Sciences, Psychiatry, Uppsala University, Uppsala, Sweden; [b]Institute of Neuroscience and Physiology, Sahlgrenska academy at University of Gothenburg, Gothenburg, Sweden; [c]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

ABSTRACT

Objective: Physiological parameters that predict electroconvulsive therapy (ECT) effectiveness may reflect propagation of the induced epileptic seizure. As an indication of seizure propagation to the diencephalon, we here examined the correlation between prolactin increase after ECT and clinical seizure evaluation parameters, focusing on peak heart rate. As a proxy for peripheral endocrine stress response, we examined the correlation to postictal cortisol increase.

Methods: Participants were consecutively recruited from clinical ECT patients ($n = 131$, age 18–85 years). The first ECT session in a series was examined. For each participant, blood serum concentrations of prolactin and cortisol were measured immediately before and within 30 min after the seizure. Physiological parameters were extracted from clinical records: peak heart rate (HR) during seizure, electroencephalography (EEG) seizure duration, and motor seizure duration. Correlations were calculated using non-parametric tests.

Results: Serum prolactin increased after ECT and correlated with peak HR, EEG seizure duration, and motor seizure duration. Peak HR during seizure also correlated positively with both EEG seizure duration and motor seizure duration. Correlations were unaffected by age, sex, baseline prolactin levels, antipsychotics, or beta-blocking agents. Serum cortisol increased after ECT but did not correlate with the seizure evaluation parameters, nor with prolactin concentrations.

Conclusions: Our findings of a positive correlation between peak HR and prolactin that was independent from the peripheral endocrine stress response might be in line with the idea that tachycardia during ECT seizures reflects seizure propagation to the diencephalon. This supports the practice of monitoring cardiovascular response for ECT seizure evaluation.

ARTICLE HISTORY
Received 17 March 2022
Revised 15 June 2022
Accepted 11 July 2022

KEYWORDS
Electroconvulsive therapy; epileptic seizure; heart rate; prolactin; cortisol

Introduction

Electroconvulsive therapy (ECT) response usually takes several treatments repeated over weeks, making it difficult to ascertain directly how each treatment session affects the targeted illness [1]. However, seizure propagation beyond the stimulated area seems necessary to achieve treatment effect [2]. Thus, the potential efficacy of each seizure is clinically evaluated by parameters believed to be markers of seizure propagation, such as cardiovascular response, epileptic activity on an electroencephalogram (EEG), and observations of motor seizure manifestations [3–5].

Among commonly used parameters to evaluate seizures, peak heart rate (HR) during seizure [6,7] and postictal EEG suppression have been found to correlate with treatment effectiveness [8–10]. While the duration of epileptic activity on EEG has not shown a linear association with treatment outcome [9,11], it can be assumed that some minimal duration is required, which is grounds for the widespread use of EEG seizure duration as a treatment evaluation parameter [5]. Regarding duration of motor seizures, professional consensus deem very short motor seizure duration to be a negative predictor of treatment effect [5].

Among the seizure evaluation parameters mentioned above, peak HR relates well to ECT treatment effect, and may thus offer an opportunity to understand the underlying therapeutic mechanism. ECT-induced tachycardia could reflect a central nervous sympathetic reaction due to propagation of epileptic activity to insular cortex, hypothalamus, or brain stem nuclei [12–15]. However, tachycardia might also be elicited as an indirect effect of the ECT procedure, with peripheral stress response including adrenal gland activation causing catecholamine release [16]. Common EEG monitoring in ECT only reflects superficial cortical activity [17], and motor seizures seems to reflect an even smaller aspect of elicited seizures [18].

A marker of seizure propagation to the diencephalon is postictal increase of serum prolactin, which has been observed in both epilepsy [19,20] and ECT [21,22]. A

CONTACT Elin Thörnblom elin.thornblom@neuro.uu.se Department of Medical Sciences, Psychiatry, Uppsala University Hospital, Brain Stimulation Unit, Uppsala SE-751 85, Sweden

prolactin increase has been suggested to reflect postictal increase of gamma-aminobutyric acid (GABA) signaling in the diencephalon, which in turn suppresses tonic dopaminergic inhibition of prolactin release from hypothalamic-pituitary neurons [23]. If tachycardia in ECT reflects propagation of the epileptic seizure to subcortical brain areas [12–15], peak HR in the ECT seizure should correlate with elevation of serum prolactin after ECT. Also, postictal EEG suppression, which at least partially seems to be GABA-dependent [24], should correlate with elevation of serum prolactin after ECT.

The alternative model is that ECT tachycardia is caused by a peripheral stress response from the adrenal gland as an indirect seizure effect. A cortisol increase could be a possible marker with similar pattern as described above. A postictal increase of serum cortisol has been observed in ECT [25,26]. To our knowledge, no study has hitherto examined the correlations between cortisol and peak HR or EEG suppression.

The aim of this study was thus to evaluate clinical seizure evaluation parameters focusing on peak HR as a proxy marker for subcortical seizure propagation in ECT. To this end, we explored how peak HR during ECT seizures correlates to other clinical seizure evaluation parameters as well as to prolactin increase as a marker of postictal inhibition in the diencephalon, and to cortisol increase as a possible marker of peripheral endocrine stress activation.

Materials and methods

Study design

Observational cohort study.

Setting

This study is a subsample of the Predictors for ECT (PREFECT) multicentre study [27,28], including participants from one study site, Uppsala University Hospital.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (registration numbers: 2012/1969-31/1 and 2018/869-32). All procedures were performed according to the ethical standards of relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Inclusion for the PREFECT study ran from 2014 through 2016. All clinical patients referred for ECT were invited to participate with inclusion criteria: age $\geq$ 18 years, the capacity to give informed consent, and a planned ECT series of at least six treatments.

At the Uppsala University Hospital study site, 133 participants were included.

ECT procedure

ECT was performed with a Thymatron® System IV (Somatics LLC, Lake Bluff, IL, USA). Initial stimulus dose was decided by the local ECT practitioner based on age and sex in accordance with the manufacturer's instruction manual [29]. Only right unilateral (RUL) electrode placement was used. Pulse width was almost exclusively 0.5 ms. Median (Q1, Q3) stimulus charge was 252 (152, 350) milliCoulomb. Information on anesthetic agent and dose was available in 106 of 131 participants. In these, thiopental was used in all treatments except one, where propofol (2.46 mg/kg) was used instead. Median (Q1, Q3) thiopental dose was 4.43 (3.91, 4.90) mg/kg. Suxamethonium was routinely used for muscle relaxation. No adjunctive medications apart from anesthetics and muscle relaxants were used as part of the routine anesthetic procedure for the first ECT treatment.

Variables

The planned two main outcomes were peak HR during seizure (beats per minute, bpm) and occurrence of postictal EEG suppression (yes or no). Correlations were planned between these main outcomes and the following four parameters: (1) EEG seizure duration (s), (2) duration of motor seizures (s), and changes in serum concentrations of (3) prolactin (measured in Normalized Protein Expression (NPX), further described under 'measurements' below), and (4) serum cortisol, (ng/ml). Information on type and dose of anesthetic agents and concurrent use of any antipsychotic or oral beta-blocking agents was collected from the medical charts.

Measurements

Seizure evaluation parameters (peak HR, postictal EEG suppression, EEG seizure duration, and motor seizure duration) were extracted by a retrospective chart review. All measurements had been recorded by clinical staff (physician, nurses, nurse's assistant) as per the clinical routine at the site during the study period. Baseline HR and Peak HR during seizure was observed on continuous electrocardiography. Postictal EEG suppression was assessed visually and recorded as confirmation or negation of occurrence of suppression (yes or no). EEG seizure duration was measured by a two-channel-EEG recording (one channel over each temporal lobe). The endpoint of epileptic activity was determined visually. Motor seizure duration was assessed by visual inspection, with muscle relaxant effect (neither any cuffing method nor electromyography were used).

Blood samples were collected before the first ECT treatment and within 30 min after seizure termination. Blood was drawn in 10 ml serum tubes, left 30–60 min at room temperature, then centrifuged for 15 min at 2000xg. After centrifugation, blood serum aliquots were stored at $-20\,^{\circ}C$ for a maximum of 30 days, transferred to biobank, and then stored at $-70\,^{\circ}C$ until analysis.

Serum concentrations of prolactin were analysed as part of a larger protein assay in the PREFECT study, using the commercially available Proximity Extension Assay (PEA) technique (Olink Proseek® Multiplex ONC Lv2 panel, OLink Bioscience, Uppsala, Sweden) [30]. PEA results are given as NPX, a relative unit which can be used to compare changes

in protein concentrations within one assay, but not for comparison of separate analyses [30].

From the PREFECT study biobank, 0.25 ml of serum blood was analysed for cortisol using ultra-performance supercritical fluid chromatography-tandem mass spectrometry (UPSFC-MS/MS) [31].

Statistical methods

Statistical analyses were performed with SPSS Statistics 25 (IBM Corporation and others).

Peak HR and baseline HR were the only parameters with a normal distribution, as confirmed with Shapiro–Wilks normality test, and are presented as mean value with standard deviation. The other continuous variables, which were not normally distributed, are presented as median values with the first and third quartile presented.

Significance in changes of prolactin and cortisol concentrations following the first ECT seizure was assessed using the sign test.

Data on postictal suppression were excluded from further analysis due to few available data ($n = 62$).

Correlations between peak HR and EEG seizure duration, motor seizure duration, and changes in prolactin and cortisol concentrations were calculated with Spearman's rank test. Mann–Whitney *U* was used for comparing subjects when grouped by use of antipsychotics or not.

To enable controlling for potential confounders, regression analyses using generalized linear models were applied. Peak HR was entered as dependent variable, and each variable with a significant correlation ($p < 0.05$) in the Spearman test above was entered as independent variable along with potential confounders (age, sex, baseline HR, baseline prolactin, antipsychotic medication, and beta-blocking medication) in separate multiple regression analyses. Three regression models (linear, gamma distribution, and negative binominal log link distribution) were tested for best fit with the data, and the model with the lowest AIC (Aikaike's Information Criterion) was selected, which yielded a linear model for all three regressions.

Results

Participants

Of the initial 133 participants with samples collected from the PREFECT biobank, 131 participants had available medical chart data at the Uppsala site. Two participants had blocked access to their medical charts after study inclusion and were thus excluded from this study as no retrospective chart review was possible.

Descriptive data

The study population consisted of more women ($n = 80$, 61%) than men. Median (Q1, Q3) age in the population was 45 (30, 59) years. There was no significant age difference between sexes. Sixty-six participants were on antipsychotics. Baseline prolactin concentrations were higher in subjects using antipsychotics compared with those that did not ($p < 0.01$). There were no significant differences between subjects with and without antipsychotic medications regarding age (mean 46 years with antipsychotics, 45 years without, $p = 0.77$) or sex (number of women vs. men 40/26 with antipsychotics, 40/25 without, $p = 0.91$). Further, there was no difference between the groups regarding prolactin change, baseline HR, or peak HR (all $p \geq 0.16$).

Main results

Seizure evaluation parameters and changes in prolactin and cortisol are shown in Table 1. Heart rate increased from mean (SD) 78 (15) bpm at baseline, to 120 (23) bpm peak HR during the ECT seizure. Both prolactin and cortisol concentrations increased after ECT, as listed in Table 1.

Individual postictal changes in prolactin and cortisol are shown in Figures 1 and 2, respectively.

When grouped by use of antipsychotics, a significant prolactin increase was seen in both groups ($p < 0.001$ both groups).

There was a positive correlation between peak HR on the one hand, and EEG seizure duration ($r = 0.56$, $p < 0.001$), motor seizure duration ($r = 0.63$, $p < 0.001$), and prolactin increase ($r = 0.24$, $p = 0.03$) on the other. Peak HR did not correlate with cortisol increase ($r = 0.03$, $p = 0.78$). A scatter plot of postictal hormone concentration changes vs. peak HR is shown in Figure 3.

The correlations between peak HR on the one hand, and EEG seizure duration, motor seizure duration, and postictal prolactin increase on the other hand, remained significant ($p < 0.001$) when each parameter with a statistically significant ($p < 0.05$) correlation to peak HR was entered into regression analyses along with potential confounders (Table 2).

Discussion

In this study of the first seizure in 133 patients receiving ECT, we explored how peak HR correlates to other clinical seizure evaluation parameters and changes in serum concentrations of prolactin and cortisol. We can for the first time report that

Table 1. Seizure evaluation parameters and serum hormone concentrations.

Seizure evaluation parameters	
Baseline heart rate, bpm, mean (SD)[a]	78 (15)
Peak heart rate, bpm, mean (SD)[a]	120 (23)
Seizure duration EEG, s, median (Q1, Q3)	40 (25, 54)
Motor seizure duration, s, median (Q1, Q3)[a]	23 (13, 36)
Serum hormone concentrations	
Prolactin before seizure, NPX, median (Q1, Q3)[a]	38 (25, 60)
Prolactin after seizure, NPX, median (Q1, Q3)[a]	95 (52, 172)
Prolactin change, NPX, median (Q1, Q3)[a]	45 (14, 93)[b]
Cortisol before seizure, ng/ml, median (Q1, Q3)	183 (142, 238)
Cortisol after seizure, ng/ml, median (Q1, Q3)	221 (182, 257)
Cortisol change, ng/ml, median (Q1, Q3)	49 (−20, 93)[b]

[a]Missing data: baseline heart rate $n = 14$, peak HR $n = 7$, motor seizure $n = 1$, prolactin before $n = 40$, prolactin after $n = 41$, prolactin change $n = 43$.
[b]Change before/after seizure is significant at the 0.01 level with the sign test.
bpm: beats per minute; SD: standard deviation; EEG: electroencephalogram; Q1: first quartile; Q3: third quartile; NPX: normalized protein expression.

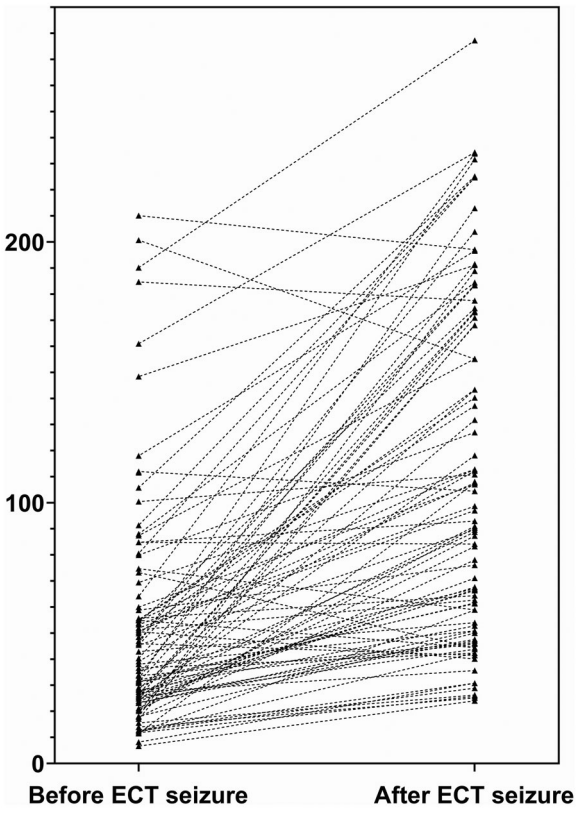

Figure 1. Serum prolactin concentration before and after ECT, normalised protein expression. Grouped scatter plots with individual changes indicated by connecting lines.

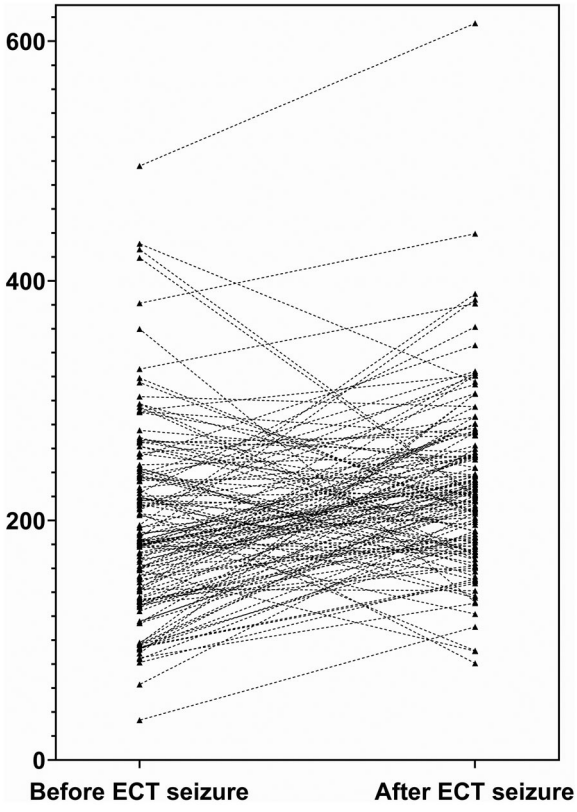

Figure 2. Serum cortisol before and after ECT, ng/mL. Grouped scatter plots with individual changes indicated by connecting lines.

tachycardia during ECT seizures correlate with postictal prolactin increase (albeit the correlation coefficient of 0.24 warrants some caution in interpretation) but not to postictal cortisol increase. The positive correlation between peak HR and prolactin increase, in conjunction with the lack of correlation between peak HR and cortisol increase, strengthens the suggestion that peak HR reflects propagation of the epileptic activity to the diencephalon. Both tachycardia during ECT seizure [7,32] and postictal prolactin increase [33] have previously been reported to correlate with ECT treatment effect, but to our knowledge a possible correlation between these markers has not previously been examined.

The exclusive use of RUL electrode placement in this material should be considered, as in threshold stimulations, bitemporal electrode placement has been found to require a higher stimulus charge to reach the EEG duration threshold, but also produce a larger prolactin release [34]. Possibly reflecting similar phenomena with other measures, a more recent study on differences in seizure propagation as measured with single photon emission computed tomography reported that generalized seizures elicited with bitemporal electrode placement resulted in a more bilateral engagement of subcortical structures than RUL placement—however, suprathreshold stimulus charges were used and serum changes in prolactin were not measured [35]. With these previous findings taken into account, an investigation on peak HR relating to postictal prolactin increase in a setting with bitemporal electrode placement would be valuable, and might show a stronger correlation between the two parameters.

We found no correlation between cortisol increase and peak HR or postictal EEG suppression, which to our knowledge has not been examined in previous studies.

There are previous reports on prolactin elevation [21,22,33] and on cardiovascular activation in effective ECT seizures [6,7]. Our findings of a correlation between the two strengthens the notion of peak HR as a feasible marker for seizure propagation in clinical practice, especially as both peak HR [6,7] and postictal prolactin increase [33] have previously been proposed as markers of clinical ECT effectiveness.

Due to a lack of available data, postictal suppression was excluded as outcome variable in this study, but considering the previous connection to treatment outcome, the relation of postictal EEG suppression and other clinical seizure parameters and hormonal effects in ECT remains an interesting topic for future explorations.

There are several limitations to this study. Data from clinical routines may suffer from inherent quality issues, as they are recorded in a less standardized and reliable manner than in a controlled study setting. Several of the issues raised below stem from this fact. On the other hand, this increases the generalizability of results, as the situation for data collection is highly similar to daily clinical work. Exact time points of blood sampling with relation to the ECT treatment were not recorded, which lower the temporal precision. As only one sample was taken after seizure termination, it is also possible that the peak in prolactin and cortisol concentrations was not captured, particularly in regards to prolactin

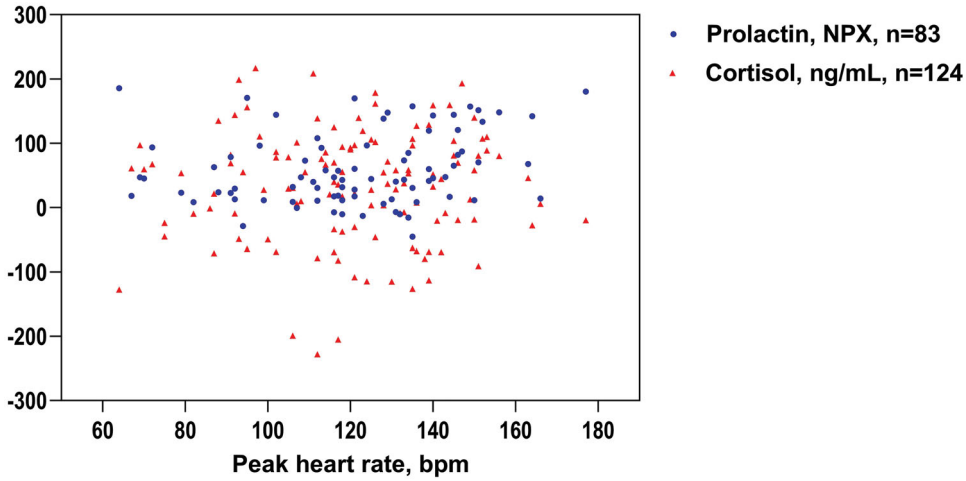

Figure 3. Scatter plot of postictal hormone change vs. peak heart rate during the ECT seizure.

Table 2. Association between peak heart rate and postictal prolactin increase, EEG seizure duration, and motor seizure duration investigated in separate linear multiple regression analyses with potential confounders added as independent variables.

	Peak heart rate ($n = 78$)	
	B (SE)	*p*
Postictal prolactin increase	0.05 (0.04)	<0.001
Baseline prolactin	0.11 (0.05)	0.029
Baseline heart rate	0.58 (0.15)	<0.001
Age	0.24 (0.14)	0.101
Male sex	7.69 (4.77)	0.107
Antipsychotic medication	10.73 (4.58)	0.019
Beta-blocking medication	23.09 (8.36)	0.006
	Peak heart rate ($n = 115$)	
	B (SE)	*p*
Seizure duration on EEG	0.59 (0.09)	<0.001
Baseline heart rate	0.38 (0.11)	<0.001
Age	−0.25 (0.09)	0.008
Male sex	−0.28 (3.24)	0.932
Antipsychotic medication	6.23 (3.21)	0.052
Beta-blocking medication	14.51 (5.46)	0.008
	Peak heart rate ($n = 114$)	
	B (SE)	*p*
Motor seizure duration	0.82 (0.10)	<0.001
Baseline heart rate	0.37 (0.11)	<0.001
Age	−0.23 (0.09)	0.011
Male sex	−2.61 (3.11)	0.401
Antipsychotic medication	4.88 (3.04)	0.109
Beta-blocking medication	8.86 (5.21)	0.089

EEG: electroencephalogram.

which seems to have a faster decline of postictal concentration increase than cortisol, with peak levels of postictal prolactin repeatedly recorded at ∼10–15 min after an ECT seizure [25,36–38]. Peak concentrations of postictal cortisol have been reported to remain 15–30 min after an ECT seizure [36,37], although one study reported this duration of the postictal cortisol peak only with a stimulus charge three times seizure threshold, as compared with threshold stimulus intensity (threshold defined as the lowest stimulus intensity producing a motor seizure ≥25 s) [25]. Assuming postictal changes of prolactin and cortisol from these previous studies apply to our study setting, this might result in an underestimation of the postictal hormone concentration change in the material, and in consequence increase the risk of type 2 errors.

Intravenous anticholinergic or beta-blocking drugs, which may influence peak HR, are sometimes used as part of the ECT anesthesia routine and were not controlled for in this study. However, since such drugs were not used routinely for the anesthetic procedure at the study site, especially in the first ECT treatment, we believe it unlikely that this would introduce any systematic error into the data. Further, in this study we could not control for all medications, indications for ECT, body mass index, menstrual cycle, substance use, or concomitant medical conditions which might influence seizure parameters, prolactin release, or autonomic nervous regulation. Antipsychotics increase baseline prolactin, and although subjects with and without antipsychotics did not differ in median prolactin concentration change in this study there is a possibility that patients taking antipsychotic drugs may have decreased headroom above baseline, which may have influenced the range of prolactin elevation. However, we consider it unlikely that any such factor would introduce a systematic error in a way to produce the observed correlations. Rather, the relatively small data set increases the risk for type-II errors. The calculations were not corrected for multiple comparisons and we have therefore not corrected for the risk of random significance in the findings.

Another aspect of this study data is that only the first seizure of the full ECT series was observed. Previous studies have reported a decrease in EEG seizure duration [39] and postictal prolactin increase [26,37], with an increasing number of treatments in a series of ECT. A possible explanation for these observations is the anticonvulsant effect of ECT seizures [40], and this aspect of study design can be important to consider when comparing different studies of ECT seizure quality, which might include different parts of a treatment series.

We conclude that peak HR during the ECT seizure, as well as other ECT evaluation parameters, correlate with prolactin increase after ECT, but not with cortisol increase. This supports the notion of tachycardia in ECT seizures as centrally elicited, rather than primarily caused by an indirect stress response from secondary treatment effects. As peak HR is

easy to measure, reflects epileptic activity in diencephalon, and predicts ECT effect, it seems to be a feasible parameter for seizure evaluation in ECT. Going forwards, such measurements should be further tested in prospective studies including bilateral and bifrontal electrode placements.

Acknowledgements

The authors wish to thank Hans Arinell for statistic support.

Disclosure statement

J.L.C. has received lecturing fees from Otsuka Pharma Scandinavia, Janssen-Cilag AB and H. Lundbeck AB. None of the other authors have any conflicts of interest to disclose.

Funding

The study was supported by grants from the Swedish Research Council under grant 2018-02653; the Swedish foundation for Strategic Research under grant KF10-0039; the Bror Gadelius memory fund; and from the Fredrik and Ingrid Thurings trust under grant 2015-00148. R.B. was supported by a Swedish Research Council Grant under grant 2016-02362. J.L.C. and M.G. have Gullstrand Fellowships at Uppsala University Hospital.

Notes on contributors

Elin Thörnblom, MD is a psychiatrist at Uppsala University Hospital and PhD student at the Department of Medical Sciences, Uppsala University, Sweden.

Malin Gingnell, MD, PhD is a resident in psychiatry at Uppsala University Hospital, Associate Professor at the Department of Psychology, and Department of Medical Sciences, Uppsala University, Sweden.

Janet L. Cunningham, MD, PhD is a psychiatrist at Uppsala University Hospital and Associate Professor of psychiatry at the Department of Medical Sciences, Uppsala University, Sweden.

Mikael Landén, MD, PhD is a psychiatrist at Sahlgrenska University Hospital, Gothenburg, and Professor of psychiatry at the Institute of Neuroscience and Physiology, University of Gothenburg, Sweden and a researcher at Department of Medical Epidemiology and Biostatistics at Karolinska Institutet, Stockholm, Sweden.

Robert Bodén, MD, PhD is a psychiatrist at Uppsala University Hospital and Professor of psychiatry at the Department of Medical Sciences, Uppsala University, Sweden.

ORCID

Elin Thörnblom http://orcid.org/0000-0002-4908-0983
Mikael Landén http://orcid.org/0000-0002-4496-6451
Robert Bodén http://orcid.org/0000-0002-2198-8842

References

[1] Husain MM, Rush AJ, Fink M, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a consortium for research in ECT (CORE) report. J Clin Psychiatry. 2004;65(4):485–491.

[2] Kalinowsky LB, Barrera SE, Horwitz WA. The "Petit mal" response in electric shock therapy. Asian J Pharm. 1942;98(5):708–711.

[3] Minelli A, Abate M, Zampieri E, et al. Seizure adequacy markers and the prediction of electroconvulsive therapy response. J Ect. 2016;32(2):88–92.

[4] Brunner I, Grözinger M. Brief vs. ultrabrief pulse ECT: focus on seizure quality. Eur Arch Psychiatry Clin Neurosci. 2018;268(8):831–838.

[5] American Psychiatric Association, Weiner RD, editor. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association. 2nd ed. Washington, DC: American Psychiatric Association; 2001.

[6] Azuma H, Fujita A, Sato K, et al. Postictal cardiovascular response predicts therapeutic efficacy of electroconvulsive therapy for depression. Psychiatry Clin Neurosci. 2007;61(3):290–294.

[7] Swartz CM. Physiological response to ECT stimulus dose. Psychiatry Res. 2000;97(2-3):229–235.

[8] Krystal AD, Weiner RD. EEG correlates of the response to ECT: a possible antidepressant role of brain-derived neurotrophic factor. J Ect. 1999;15(1):27–38.

[9] Mayur P. Ictal electroencephalographic characteristics during electroconvulsive therapy: a review of determination and clinical relevance. J Ect. 2006;22(3):213–217.

[10] Azuma H, Fujita A, Sato K, et al. Postictal suppression correlates with therapeutic efficacy for depression in bilateral sine and pulse wave electroconvulsive therapy. Psychiatry Clin Neurosci. 2007;61(2):168–173.

[11] Folkerts H. The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy. Eur Arch Psychiatry Clin Neurosci. 1996;246(3):155–164.

[12] Chouchou F, Mauguière F, Vallayer O, et al. How the insula speaks to the heart: cardiac responses to insular stimulation in humans. Hum Brain Mapp. 2019;40(9):2611–2622.

[13] Chouchou F, Bouet R, Pichot V, et al. The neural bases of ictal tachycardia in temporal lobe seizures. Clin Neurophysiol. 2017;128(9):1810–1819.

[14] Swanson LW, Sawchenko PE. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annu Rev Neurosci. 1983;6:269–324.

[15] Jansen AS, Nguyen XV, Karpitskiy V, et al. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. Science 1995;270(5236):644–646.

[16] Kvetnansky R, Lu X, Ziegler MG. Stress-triggered changes in peripheral catecholaminergic systems. Adv Pharmacol. 2013;68:359–397.

[17] Ramantani G, Maillard L, Koessler L. Correlation of invasive EEG and scalp EEG. Seizure 2016;41:196–200.

[18] Mayur PM, Gangadhar BN, Janakiramaiah N, et al. Motor seizure monitoring during electroconvulsive therapy. Br J Psychiatry. 1999;174(3):270–272.

[19] Chen DK, So YT, Fisher RS, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Use of serum prolactin in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65(5):668–675.

[20] Bilo L, Meo R, Striano S. Serum prolactin evaluation after "minor" generalised seizures monitored by EEG. J Neurol Neurosurg Psychiatry. 1988;51(2):308–309.

[21] Schoretsanitis G, Cicek M, Mathur N, et al. Prolactin changes during electroconvulsive therapy: a systematic review and Meta-analysis. J Psychiatr Res. 2020;128:25–32.

[22] Ohman R, Balldin J, Walinder J, et al. Prolactin response to electroconvulsive therapy. Lancet Lond Engl. 1976;308(7992):936–937.

[23] McCann SM, Vijayan E, Negro-Vilar A, et al. Gamma aminobutyric acid (GABA), a modulator of anterior pituitary hormone secretion by hypothalamic and pituitary action. Psychoneuroendocrinology 1984;9(2):97–106.

[24] de Curtis M, Avoli M. Initiation, propagation, and termination of partial (focal) seizures. Cold Spring Harb Perspect Med. 2015;5(7):a022368.

[25] Zis AP, Yatham LN, Lam RW, et al. Effect of stimulus intensity on prolactin and cortisol release induced by unilateral electroconvulsive therapy. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 1996;15(3):263–270.
[26] Deakin JF, Ferrier IN, Crow TJ, et al. Effects of ECT on pituitary hormone release: relationship to seizure, clinical variables and outcome. Br J Psychiatry. 1983;143:618–624.
[27] Clements CC, Karlsson R, Lu Y, et al. Genome-wide association study of patients with a severe major depressive episode treated with electroconvulsive therapy. Mol Psychiatry. 2021;26(6):2429–2439. Published online January 22
[28] Sigström R, Nordenskjöld A, Juréus A, et al. Long-term subjective memory after electroconvulsive therapy. BJPsych Open. 2020;6(2):e26.
[29] Swartz CM, Abrams R. ECT instruction manual. 5th ed. New York, NY, USA: Somatics Incorporated; 1994.
[30] Assarsson E, Lundberg M, Holmquist G, et al. Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. PLoS One. 2014;9(4):e95192.
[31] de Kock N, Acharya SR, Ubhayasekera SJKA, et al. A novel targeted analysis of peripheral steroids by ultra-performance supercritical fluid chromatography hyphenated to tandem mass spectrometry. Sci Rep. 2018;8(1):16993.
[32] Swartz CM, Shen WW. ECT generalized seizure drives heart rate above treadmill stress test maximum. J Ect. 2007;23(2):71–74.
[33] Swartz CM. Prolactin response to electroconvulsive therapy. Biol Psychiatry. 1999;45(3):378–381.
[34] McCall WV, Weiner RD, Carroll BJ, et al. Serum prolactin, electrode placement, and the convulsive threshold during ECT. Convuls Ther. 1996;12(2):81–85.
[35] Blumenfeld H, Westerveld M, Ostroff RB, et al. Selective frontal, parietal, and temporal networks in generalized seizures. NeuroImage 2003;19(4):1556–1566.
[36] Kronfol Z, Hamdan-Allen G, Goel K, et al. Effects of single and repeated electroconvulsive therapy sessions on plasma ACTH, prolactin, growth hormone and cortisol concentrations. Psychoneuroendocrinology 1991;16(4):345–352.
[37] Whalley LJ, Eagles JM, Bowler GM, et al. Selective effects of ECT on hypothalamic-pituitary activity. Psychol Med. 1987;17(2):319–328.
[38] Swartz CM. Time course of post-electroconvulsive therapy prolactin levels. Convuls Ther. 1985;1(2):81–88.
[39] Luccarelli J, McCoy TH, Seiner SJ, et al. Changes in seizure duration during acute course electroconvulsive therapy. Brain Stimul. 2021;14(4):941–946.
[40] Coffey CE, Lucke J, Weiner RD, et al. Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. Biol Psychiatry. 1995;37(11):777–788.