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The influence of Hatha yoga as an add-on treatment in major depression on hypothalamic–pituitary–adrenal-axis activity: A randomized trial

Nina Sarubin [a,c,*], Caroline Nothdurfter [a,b], Cornelius Schüle [c], Martin Lieb [a], Manfred Uhr [b], Christoph Born [c], Ricarda Zimmermannc [c], Markus Bühner [d], Katharina Konopka [a], Rainer Rupprecht [a,b], Thomas C. Baghai [a]

[a] Department of Psychiatry and Psychotherapy, University Regensburg, Germany
[b] Max-Planck-Institute of Psychiatry, Munich, Germany
[c] Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany
[d] Department of Psychology/Statistics and Evaluation, Ludwig-Maximilian-University, Munich, Germany

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ABSTRACT

Objectives: The impact of Hatha yoga as add-on treatment to quetiapine fumarate extended release (QXR) or escitalopram (ESC) in depressed patients on hypothalamic–pituitary–adrenal (HPA) axis activity was assessed.
Methods: 60 inpatients suffering from major depressive disorder (MDD) according to DSM-IV were randomized for a 5 week treatment with Yoga or not (control group) and with either QXR (300 mg/day) or ESC (10 mg/day). Serial dexamethasone/corticotropin releasing hormone (DEX/CRH) tests were performed to assess HPA axis function. The Hamilton Depression Rating Scale (21-HAMD) was used weekly.
Results: A more pronounced down regulation of the HPA axis activity due to yoga could not be detected. The stepwise long term cortisol reduction was seen in both medication groups, irrespectively of yoga add-on treatment. In addition, cortisol improvers in week 1 of therapy (reduction in cortisol peak value within the DEX/CRH test) reached significant greater amelioration of depressive symptoms after 5 weeks.
Conclusions: Our results suggest that antidepressant agents down regulate HPA axis function to a greater extent than additional Hatha yoga treatment. Moreover, an early reduction of HPA system hyperactivity after one week of pharmacological treatment seems to raise the possibility of a favorable treatment response.

1. Introduction

Yoga combines breathing techniques, meditation, muscle relaxation and physical workout (Pilkington et al., 2005; Granath et al., 2006). The aim of the holistic yoga practice is to enhance the development of individual's self-awareness and control of the body and mind, the ultimate goal is a so called "nirvana like state" (Ross and Thomas, 2010; Patel et al., 2012; Mehta and Sharma, 2013) equivalent to deep relaxation which may be useful also as an add-on to antidepressant treatment. In our study the word yoga is used to tag Hatha yoga, which is one of the most commonly practiced types of yoga (Birdee et al., 2008). Yoga increases health-related quality of life in general while reducing perceived stress of the participants (West et al., 2004; Kjellgren et al., 2007; Vera et al., 2009; Patel et al., 2012). With respect to psychological and physiological benefits, Yoga improves a wide range of symptoms such as anxiety, stress and depressive mood, heart rate, blood pressure (Li and Goldsmith, 2012), memory performance (Ross and Thomas, 2010), insomnia (Vera et al., 2009), and reduction of emotional tension (Andrade and Pedrao, 2005). Congruent with these reports and due to a growing number of patients with mood disorders using complementary or alternative therapy interventions (Ernst, 2003), recent reviews indicate that yoga is used in clinical context as an effective therapeutic intervention in unipolar

* Corresponding author. Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich, Nussbaumstrasse 7, 80336 Munich, Germany. Tel.: +49 895160 5382; fax: +49 895160 3930.
E-mail address: nina.sarubin@med.uni-muenchen.de (N. Sarubin).

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depression (Pilkington et al., 2005; Uebelacker et al., 2010; D'Silva et al., 2012; Kinser et al., 2012; Mehta and Sharma, 2013) and bipolar disorders (Andreescu et al., 2008) regarding reduction in depressive symptoms. Practicing yoga is associated with several biochemical effects such as influence on blood pressure, heart rate, urinary catecholamines (Granath et al., 2006) and cortisol levels in healthy subjects (Vera et al., 2009; Rocha et al., 2012). The effects of yoga seem to be mediated via multiple paths such as reduction in sympathetic tone, activation of antagonistic neuromuscular systems, relaxation in the neuromuscular system and stimulation of the limbic system (Riley, 2004) which yield to the restoration of the homeostasis of the stress response systems (Streeter et al., 2012).

Due to a lack of randomized controlled trials (RCT) measuring plasma cortisol levels via DEX/CRH tests in representative study populations, the current studies report inconsistent results regarding the directions of change of potential biomarkers which are associated with depressive symptoms (Pilkington et al., 2005; Mehta and Sharma, 2013). Although the underlying mechanisms concerning neurobiological and emotional changes during yoga exercise in depressed patients are yet unknown (Kinser et al., 2012; Streeter et al., 2012), one of the discussed hypothesis are changes in stress hormone systems, which can be measured via cortisol-secretion (Vedamurthachar et al., 2006; Vadiraja et al., 2009; Ross and Thomas, 2010; Streeter et al., 2012; Woolery et al., 2004). The corticosteroid receptor hypothesis (neuroendocrinological hypothesis) is a prominent approach concerning the etiology of major depression and considers a dysregulation of the HPA axis function as a possible mechanism (Holsboer, 2000, 2001). Since depressive symptoms have been linked to HPA axis hyperactivity in a part of depressed patients, a gradual normalization of the HPA system dysregulation as measured by serial combined DEX/CRH tests precedes or coincides with the response to antidepressant treatment and is according to some authors a necessary prerequisite for clinical remission to become manifest (Ising et al., 2007). Dampening on HPA axis system results in decreased cortisol levels, this is partly mediated or moderated via restored signaling of corticosteroid-activated mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Pariante and Miller, 2001). Moreover, the HPA axis seems to be a promising target regarding new treatment strategies in depression (Schüle et al., 2009b).

To date there is no randomized controlled study investigating the effects of yoga in patients with diagnosed MDD involving a refined measurement of the HPA axis activity using cortisol levels or DEX/CRH-tests (Li and Goldsmith, 2012; Mehta and Sharma, 2013). Therefore, the impact of yoga on cortisol levels in depressed patients seems ambiguous. Only a few RCT's measuring depressive "symptoms" (major depression was not diagnosed) and cortisol levels are available (Woolery et al., 2004; Vedamurthachar et al., 2006; Vadiraja et al., 2009). These studies indicate that two weeks daily yoga sessions of 45 min (Vedamurthachar et al., 2006) and six weeks with three yoga session for one hour each week lead to a significant decrease in plasma cortisol and salivary morning cortisol (Vedamurthachar et al., 2006; Vadiraja et al., 2009) compared to brief supportive therapy (Vadiraja et al., 2009) and continued inpatient care (Vedamurthachar et al., 2006). Moreover, reductions in plasma cortisol were correlated significantly with a decreased sum score in the Beck Depression Inventory (Vedamurthachar et al., 2006; Vadiraja et al., 2009). One randomized study investigated salivary cortisol levels in the morning in young adults with mild depressive symptoms (no diagnosed MDD), which had lower BDI-scores and higher morning cortisol levels after five weeks (two 1-hour yoga classes each week) of yoga compared to wait-list group (Woolery et al., 2004). Another study (non-randomized and without control group) yielded similar results (Curtis et al., 2011): salivary cortisol levels of patients with fibromyalgia and depressive symptoms were increased after 8 weeks of yoga class (75 min twice a week). With respect to the corticosteroid receptor hypothesis, serial DEX/CRH tests are the gold standard concerning the measurement of HPA axis system in depressed patients (Schüle et al., 2009a).

Despite this clearly limited scientific research regarding HPA axis in the frame of yoga and major depression, yoga is already recommended as a second-line adjunctive treatment in mild to moderate major depression (Ravindran et al., 2009).

Given that a direct relationship between yoga, cortisol levels and declines in major depression are not yet finally supported, the purpose of this study was to determine whether yogic practices as a useful supplement to pharmacologic therapy in major depression contribute to a possible reduction of HPA axis activity. We assumed that – independent of the yoga sessions – those patients who would observe a decrease in cortisol levels within the first week (improvement) also would be more likely to show a reduction in symptoms of depression. Due to the unclear direction of possible changes in cortisol levels in DEX/CRH tests caused by yoga training, no predictions were made in this regard. The aim regarding the yoga training was exploratory and not confirmatory: we investigated whether additional yoga treatment would have both endocrine effects on cortisol levels and clinical effects on depressive symptoms regarding response and non-response in the context of conventional treatments (medication) in clinically depressed inpatients. It is widely unexplored up to now whether yoga increases or decreases the probability of a pharmacologic treatment response in depressed patients.

In the present study, the influence of 5-week treatment with the atypical antipsychotic drug with antidepressant properties quetiapine fumarate extended release (QXR) and of the selective serotonin-reuptake inhibitor (SSRI) escitalopram (ESC) in combination with yoga (60 min/week) or control group (no yoga intervention) on the time course of HPA axis activity was investigated in depressed inpatients.

- Are the endocrinological effects of yoga/no yoga treatment and QXR/ESC on HPA system related to the antidepressant efficacy of these drugs after 5 weeks of treatment?
- Is the onset of antidepressant action of QXR/ESC related to yoga?

2. Method

The intention-to-treat sample comprised 60 unrelated patients who were aged 18–65 years and suffering from a major depressive episode according to DSM-IV criteria (296.2 or 296.3). Patients were recruited from August 2009 up to February 2012. The allocation of the patients to the treatment groups was done according to the pre-defined randomization plan and occurred in a randomized order. Patients were treated for 5 weeks with either QXR (300 mg/day; group 1) or ESC (10 mg/day; group 2) and yoga therapy (Hatha yoga 60 min/week) or no yoga (control group). The yoga training group was supervised by a physical therapist and consisted of maximum 15 patients. Due to different side effect patterns of ESC and QUE as well as different administration times in clinical practice (ESC is given preferably in the morning whereas QXR is usually administered in the evening) no blinding concerning the medication was conducted. See Table 1 for details of clinical and demographical characteristics of depressed patients at admission. Details concerning the administration of QXR, ESC and the process of the DEX/CRH-test and laboratory methods see Supplemental Information.

The DEX/CRH was performed before treatment, after 1 and after 5 weeks of treatment calculating cortisol (COR) area under the

Table 1
Clinical and demographic data in 53 out of 60 depressive patients treated with yoga ($n = 22$; 60 min/week) or no yoga [control group = CG] ($n = 31$) and either QXR ($n = 25$; 300 mg/day) or ESC ($n = 28$; 10 mg/day) for 5 weeks (completer analysis). Data represent mean ± SD (standard deviation). Suppression status at baseline (week 0): S = Suppressors; NS = Non-Suppressors. Medical pre-treatment: Pre = Pre-Treatment; NPre = No Pre-Treatment. Response: R = Responders; NR = Non-Responders. Statistical parameters of Chi square tests and Fisher's exact test for qualitative variables as well as Mann–Whitney *U*-tests (non-parametric quantitative variables) and *T*-tests (parametric quantitative variables) are provided.

	All patients ($n = 53$)	Yoga ($n = 22$)	CG ($n = 31$)	Statistical evaluation		
Chi-square test (qualitative variables)				χ^2	df	*p*-value
Sex [M/F]	38/15	14/8	24/7			0.357[a]
Medical pre-treatment (Pre/NPre)	16/37	8/16	10/21	0.152	1	0.697
Suppression status (S/NS)	27/26	12/10	15/16	0.195	1	0.659
***T*-test (quantitative variables)**				***T*/*Z***	**df**	***p*-value**
21-HAMD sum score, week 0	22.04 ± 5.23	22.73 ± 6.54	21.55 ± 4.11	−0.75	32.645	0.460
Age [years]	40.25 ± 12.57	37.27 ± 11.85	42.356 ± 12.85	1.464	51	0.149
Age of onset [years]	34.91 ± 10.76	33.41 ± 8.42	35.97 ± 12.17	0.905	50.982	0.370
Number of depressive episodes	2.23 ± 1.85	2.05 ± 1.96	2.35 ± 1.78	−1.232		0.218[b]
Duration of total illness [months]	75.43 ± 116.57	58.07 ± 97.49	87.76 ± 128.53	−0.931		0.352[b]
Duration of index episode [weeks]	11.17 ± 10.76	10.59 ± 9.50	11.58 ± 11.71	−0.760		0.447[b]
Duration of wash-out period [days]	25.34 ± 14.83	26.27 ± 14.59	24.68 ± 15.21	−0.386		0.700[b]
COR AUC at baseline (week 0) [nmol/l × min]	8784.53 ± 8016.34	7280.78 ± 5697.39	9851.70 ± 9264.43	1.154	51	0.254
Weight [kg]	80.92 ± 14.99	81.22 ± 16.13	80.72 ± 14.40	−0.119	51	0.906
Height [cm]	174.87 ± 12.59	173.41 ± 17.29	175.90 ± 7.92	0.71	51	0.483

[a] Fisher's exact test (2-sided).
[b] Mann–Whitney-*U*-test (2-sided).

curve (AUC) values to assess HPA axis function. Hamilton Depression Rating Scale, 21-item version (HAMD-21) was used at day 0, 4, 7, 14, 21, 28 and 35 (Hamilton, 1960). The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki (http://www.wma.net) and had been approved both by a local ethics committee (intramural review panel of the Ludwig-Maximilian-University of Munich, Faculty of Medicine). The laboratory cortisol measurements were performed at the Max-Planck-Institute of Psychiatry, Munich, Germany.

2.1. Eligibility

The patients were diagnosed by experienced and trained psychiatrists using the Structured Clinical Interview for DSM-IV, German version (Wittchen et al., 1997). Exclusion criteria see Supplemental Information.

According to pre-protocol we present the results of 53 unipolar depressed patients (8 out of 25 QXR treated patients were in the yoga group, whereas 14 out of 28 ESC treated patients performed yoga), which completed the full study period including the completion of 3 combined DEX/CRH test (see Consort 2010 Flow Diagramm).

2.2. Outcome measures

21-HAMD sum scores and total area under the cortisol concentration time curve (COR AUC values) within the DEX/CRH tests were pre-defined as primary outcome measures. The assessment of HPA-axis activity was measured by COR AUC values between 15.00 h and 16.15 h during 3 serial DEX/CRH tests determined by the trapezoid rule (Forsythe et al., 1969).

The dexamethasone suppression status (suppression versus non-suppression) within the DEX/CRH test at admission was defined by a cortisol cut-off criterion of 5624 nmol/l (COR AUC week 0) applied to the first DEX/CRH test in week 0, which was derived from the median of COR AUC in our sample, since a generally accepted cut-off criterion defining suppression status has not been established yet for the DEX/CRH test (Schüle et al., 2009a).

HPA axis activity at the time of the second DEX/CRH test at week 1 was categorized in improver and non-improver according to the change in the peak cortisol level after CRH challenge between DEX/CRH week 0 and week 1. A cortisol peak improver was defined by a lower COR peak concentration during the second test in week 1; otherwise, a COR peak non-improver was presumed. The peak COR level was used for the categorization into HPA system improvers and non-improvers instead of the COR AUC value to be in line with previous definitions of HPA system improvement in remitted depression (Zobel et al., 1999, 2001; Ising et al., 2007).

Clinical response was defined as a reduction of more than 50% of the HAMD-21-score from day 0 (admission) within 5 weeks of treatment. Severity of depression (HAMD-21) was estimated on days − 1, 4, 7, 14, 21, 28. All raters were experienced psychiatrists or psychologists.

2.3. Statistical analysis

The software program SPSS version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used for data analysis. Analyses were performed using repeated measurement ANOVAs (rmANOVAs) for the subsamples of cortisol-suppressors vs. cortisol non-suppressors, cortisol-improvers vs. cortisol-non-improvers and clinical responder vs. non-responder. Kolmogorov–Smirnov Test (KST) was used to test about normal distribution of cortisol levels (COR). Due to significant KSTs' we computed the natural logarithm (log) of COR AUC values before ANOVAs' were performed. For details regarding the within-subjects and between-subjects factors for each analysis see Results section. A separate analysis for clinical response was carried out by Chi-Square-Tests and rmANOVAs, whereas COR AUC values (within-subject-factor) and categorization in response vs. non-response (between-subject-factor) were used to estimate differences in the complete sample as well as in the database splitted subsample of yoga and control group. The Mauchly's test of sphericity showed that sphericity cannot be assumed the Greenhouse-Geisser procedure was used to correct the degrees of freedom in the *F*-tests. For all analysis the significance level was set at $\alpha = 0.05$. Post-hoc tests were additionally performed for all rmANOVA procedures, when a significant "group" or "treatment" factor was found to compare the single time points of measurements.

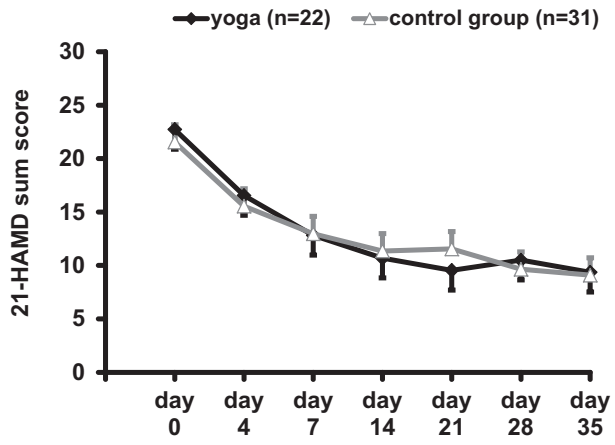

Fig. 1. 21-HAMD sum score in depressive patients treated with yoga (60 min/week) or no yoga (control group) in combination QXR (300 mg per day) or ESC (10 mg per day) for 5 weeks, respectively. SEM (standard error of mean) indicated.

3. Results

3.1. Clinical improvement

In the yoga group 13 out of 22 completers (59% of patients) were responders, whereas in the control group 18 out of 31 completers (58% of patients) showed a clinical response (21-HAMD sum score). The Chi-square test did not reveal any significant difference in the ratio of responders and non-responders between the yoga or no-yoga group ($\chi^2 = 0.030$; $df = 1$; $p = 0.862$).

When comparing the two groups (between-subject-effect: yoga vs. control group) concerning the 21-HAMD sum score (within-subject-effect: 21-HAMD sum score day 0, 4, 7, 14, 21, 28, 35) no statistical significant group effect ($F = 0.003$; $df = 1$; $p = 0.935$), but a statistical significant time effect (Greenhouse-Geisser-correction "time": $F = 75.166$; $df = 6$; $\varepsilon = 0.450$; $p = 0.000$) was detected. So, independently of the group, a statistical significant amelioration of depressive symptoms could be observed. (Fig. 1).

3.2. Assessment of HPA axis function (performance of DEX/CRH tests)

3.2.1. Comparison of patients treated with yoga and no-yoga

RmANOVA using "time" (DEX/CRH test 1–3) and "group" (yoga versus control group) as within and between subjects factors showed no significant "time" effect ($F = 2.482$; $df = 2$; $p = 0.089$), no significant "group" effect ($F = 0.316$; $df = 1$; $p = 0.577$) and no significant "time × group" interaction effect ($F = 3.095$; $df = 2$; $p = 0.054$) indicating no significant different impact of the two groups (yoga group and control group) on HPA axis function over time (Table 2, Fig. 2). The descriptive data analyses showed a partial increase in COR secretion during the DEX/CRH test after one week of therapy in patients receiving yoga treatment while there was a partial reduction after five weeks of yoga (Table 2, Fig. 2). In the control group a stepwise decrease in COR AUC values from week 0 to week 5 could be observed, which suggests that antidepressant medication without yoga therapy lead to a successively reduction in COR secretion (Table 2, Fig. 2).

To explore the influence of QXR and ESC, another rmANOVA using "time" (DEX/CRH test COR AUC week 1–3) as between and "group" (yoga versus control group) and "treatment" (ESC vs. QXR) as within subjects factors, revealed no significant "time" effect ($F = 3.057$; $df = 2$, $p = 0.525$), no significant "group" effect for yoga vs. control group ($F = 0.001$; $df = 1$; $p = 0.974$), but a significant

Table 2
COR responses to 3 DEX/CRH tests (week 0, 1, 5) in 53 out of 60 depressed patients treated with yoga or no-yoga (60 min/week) and additional QXR or ESC (completer analysis). Data are given for all patients ($n = 53$) and separately for the yoga group ($n = 22$) and control group ($n = 31$). SD (standard deviation) is indicated.

	Week 0	Week 1	Week 5
	COR_{AUC} [nmol/l × min]	COR_{AUC} [nmol/l × min]	COR_{AUC} [nmol/l × min]
All patients ($n = 53$)			
Complete sample ($n = 53$)	8784.53 ± 8016.34	8493.83 ± 11089.55	7765.70 ± 8266.47
QXR ($n = 25$)	7388.33 ± 8314.48	3410.99 ± 3430.39	5387.41 ± 7105.91
ESC ($n = 28$)	100031.13 ± 7674.45	13032.09 ± 13457.57	9889.17 ± 8764.14
Non-suppressors ($n = 26$)	14849.58 ± 7541.94	12411.07 ± 11222.03	11040.46 ± 8830.87
Suppressors ($n = 27$)	2944.11 ± 1273.88	4721.68 ± 9733.69	4612.22 ± 6374.39
Non-responders ($n = 20$)	8001.12 ± 7278.95	12546.81 ± 15056.14	7799.51 ± 7535.73
Responders ($n = 33$)	9259.32 ± 8505.90	6037.49 ± 6982.47	7745.20 ± 8793.46
Yoga ($n = 22$)			
Complete sample ($n = 22$)	7280.78 ± 5697.39	9919.13 ± 12951.36	8583.26 ± 8058.01
QXR ($n = 8$)	6282.25 ± 6467.52	3043.84 ± 2726.28	6391.63 ± 6841.64
ESC ($n = 14$)	7851.37 ± 5380.37	13847.87 ± 14874.38	9835.61 ± 8662.58
Non-suppressors ($n = 10$)	12264.93 ± 4672.94	12940.43 ± 11198.79	12328.92 ± 8225.17
Suppressors ($n = 12$)	3127.33 ± 1643.35	7401.39 ± 14226.81	6295.20 ± 7459.12
Non-responders ($n = 8$)	6600.68 ± 5555.31	16833.32 ± 18441.49	11117.05 ± 8919.34
Responders ($n = 14$)	7669.41 ± 5947.33	5968.17 ± 6450.28	7135.37 ± 7472.87
Control group ($n = 31$)			
Complete sample ($n = 31$)	9851.70 ± 9264.43	7482.33 ± 9653.94	7185.50 ± 8494.49
QXR (=17)	7908.83 ± 9192.19	3583.76 ± 3781.60	4914.83 ± 7383.82
ESC (=14)	12210.90 ± 9118.26	12216.32 ± 12388.03	9942.73 ± 9191.44
Non-suppressors ($n = 16$)	16464.98 ± 8629.17	12080.22 ± 11590.45	10860.17 ± 9433.74
Suppressors ($n = 15$)	2797.53 ± 916.54	2577.92 ± 2417.67	3265.84 ± 5232.12
Non-responders ($n = 12$)	29321.74 ± 8336.67	9689.14 ± 12363.62	5587.82 ± 5841.28
Responders ($n = 19$)	10430.83 ± 9983.11	6088.56 ± 7524.62	8194.56 ± 9830.19

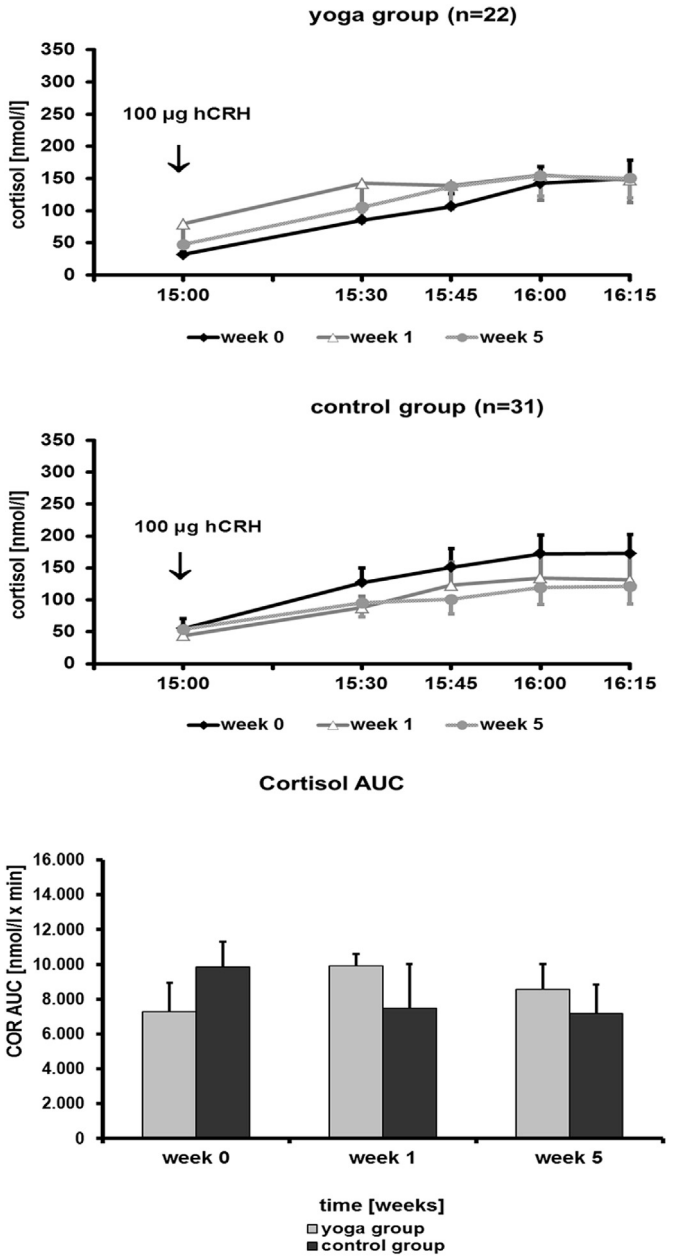

Fig. 2. Mean COR concentrations during 3 DEX/CRH tests (week 0, 1, 5) in depressed patients treated with yoga (60 min/week) or no yoga (control group) and QXR (300 mg per day) or ESC (10 mg per day) for 5 weeks. SEM (standard error of mean) indicated.

"treatment" effect for ESC vs. QXR ($F = 9.672$; $df = 1$; $p = 0.003$), and a significant "time × treatment" interaction effect ($F = 4.751$; $df = 2$; $p = 0.011$), indicating an equal impact of both, yoga vs. no yoga on HPA axis function over time, while there is a statistical significant difference on HPA axis activity due to the "treatment" medication ESC vs. QXR. So the medication seems to influence the HPA axis activity in a greater amount than yoga or no yoga therapy in our sample.

26 out of 53 depressed inpatients (49.06%) were non-suppressors (DEX/CRH test week 0) before the beginning of antidepressant therapy (Table 1). A separate analysis of the non-suppressors (baseline: week 0) demonstrated that an inhibition of HPA axis activity mainly occurred in the control group in baseline non-suppressors compared to the yoga group.

3.2.2. Separate analysis of HPA axis function in responders and non-responders

There were 33 (62.26%) treatment responders and 20 (37.74%) non-responders in the total patient sample, whereas 14 (42.42%) responders were in the yoga group while 19 (57.58%) responders were part of the control group. To detect any associations between the clinical response and COR values during DEX/CRH test, rmANOVA ("time": DEX/CRH-test 1–3; "group": responders versus non-responders) were performed and revealed a significant "time × group" interaction effect ($F = 4.002$; $df = 2$; $p = 0.024$) but not a significant "group" effect ($F = 0.465$; $df = 1$; $p = 0.498$) nor "time" effect ($F = 2.271$; $df = 2$; $p = 0.108$).

After splitting the database in yoga and control group, a separate analysis revealed that the significant "time × group" interaction effect could mainly be demonstrated in the yoga group reaching statistical significance ($F = 4.069$; $df = 2$; $p = 0.025$) whereas in the control group no significance for a "time × group" interaction effect was shown ($F = 1.415$; $df = 2$; $p = 0.251$) (Fig. 3). Nevertheless, these results suggest that an early attenuation of HPA axis activity in the control and Hatha-yoga group raises the possibility of a favorable clinical response (21-HAMD sum score).

3.2.3. Analysis of COR improvers and COR non-improvers

In our total sample of 53 patients 30 COR improvers and 23 COR non-improvers were detected (Fig. 4). RmANOVA using 21-HAMD-sum scores (day 0, 4, 7, 14, 21, 28, 35) as within-subject-factor and improvement vs. non-improvement as between-subject-factor revealed a highly significant "time" effect, i.e. decrease in 21-HAMD sum scores (Greenhouse-Geisser-correction "time": $F = 72.651$; $df = 6$; $\varepsilon = 0.470$; $p < 0.001$) and a significant "group" effect ($F = 10.078$; $df = 1$; $p = 0.003$) but no significant "time × group" interaction effect (Greenhouse-Geisser-correction "time × group": $F = 2.014$; $df = 6$; $\varepsilon = 0.470$; $p = 0.118$). In addition, post-hoc rmANOVA (comparisons of the single 21-HAMD sum score rating time points) showed a trend towards a better clinical response in improvers (in terms of a lower HAMD-21 sum score) from day 7 onwards (day 7: $F = 5.705$; $df = 1$; $p = 0.021$; day 14: $F = 8.130$; $df = 1$; $p = 0.006$; day 21: $F = 8.289$; $df = 1$; $p = 0.006$; day 28: $F = 7.379$; $df = 1$; $p = 0.009$; day 35: $F = 12.576$; $df = 1$; $p = 0.001$; see Fig. 4).

Comparing yoga and control group with respect to COR improvers and non-improvers the database was splitted in yoga and control group. Within the yoga group the clinical outcome was significant dependent of COR improvement status: a statistically significant "time" effect (21-HAMD sum scores day 0–35), a significant "group" effect (improvement vs. non-improvement) but no significant "time × group" interaction effect was demonstrated in the rmANOVA (Greenhouse-Geisser-correction "time": $F = 36.099$; $df = 6$; $\varepsilon = 0.425$; $p = 0.000$; "group": $F = 6.228$; $df = 1$; $p = 0.021$; Greenhouse-Geisser-correction "time × group": $F = 0.694$; $df = 6$; $\varepsilon = 0.425$; $p = 0.537$). In the yoga group, the possibility of a clinical response was significant higher in the improver category, suggesting that COR improvement in week 1 is a favorable condition for response after 5 weeks (Fig. 4). Nearly the same results were observed in the control group: a significant "group" effect, a significant "time" effect and a significant "time × group" interaction effect were shown indicating that COR improvement was associated with clinical response (Greenhouse-Geisser-correction; "time": $F = 26.808$; $df = 6$; $\varepsilon = 0.477$; $p = 0.000$; "group": $F = 4.816$; $df = 1$; $p = 0.036$; "time × group": $F = 2.900$; $df = 6$; $\varepsilon = 0.477$; $p = 0.042$). COR improvement in week 1 lead to a greater amelioration of depressive symptoms in week 5 independently of the membership to yoga or no yoga (Fig. 4).

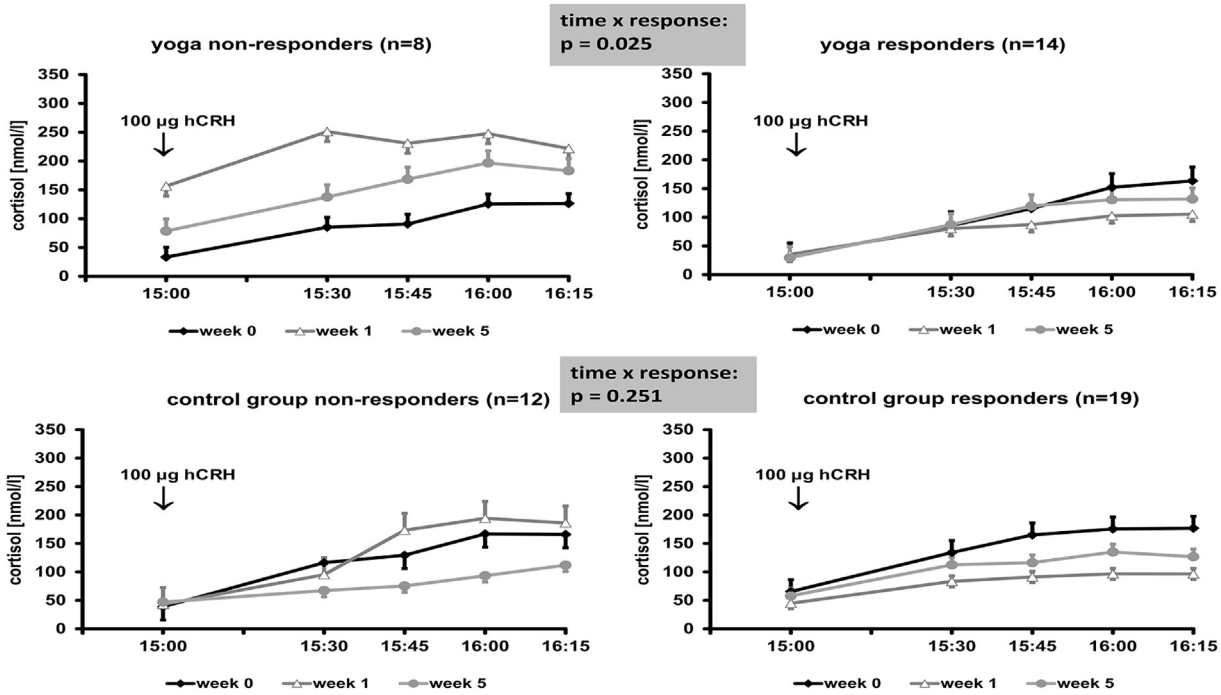

Fig. 3. Mean COR concentrations during 3 DEX/CRH tests (week 0, 1, 5) in depressed patients treated with yoga (60 min/week) or no yoga (control group) and QXR (300 mg per day) or ESC (10 mg per day) subdivided into non-responders and responders. SEM (standard error of mean) indicated.

4. Discussion

In this study we investigated the effects of ESC or QXR monotherapy with/without additional yoga on cortisol in unipolar depressed patients and analyzed if these changes are associated with depressive symptom reduction and medical response.

A statistical significant reduction in depressive symptoms (21-HAMD) after five weeks of treatment was observed in the Hatha-yoga group and in the control group (Fig. 1). One of our main results is the finding that additional yoga or no yoga therapy do not differ significantly in their long term influence on the HPA axis activity: both groups conducted a decrease of cortisol level during DEX/CRH test during week 1 to week 5, the affiliation to yoga or control-group failed to reach statistical significance (Fig. 2). However, analyzing the data descriptively, patients in the yoga group showed a different COR AUC course during DEX/CRH test from week 0 to week 5 in comparison to control group: members of the Hatha-yoga group showed an increase in COR in week 1, and a partial reduction in COR after five weeks of treatment (Fig. 2). In contrast to this, within the control group a stepwise and continuous decrease in COR AUC values during week 0 to week 5 were observed (Fig. 2). The down-regulation of the HPA axis activity may be explained to some extent by a restoration of the disturbed negative feedback control due to QXR and ESC (Nickel et al., 2003; Zobel et al., 1999). Besides that QXR and ESC influenced the HPA axis activity statistically significantly. With reference to the differential COR effects in the Hatha-yoga and control group, a possible explanation for this is the relative high number of ESC patients within the Hatha-yoga group: 8 of 22 patients in the yoga group were randomized to QXR, while 14 patients received ESC medication. In addition, taking a closer look at the control group ($n = 31$) 14 patients were treated with ESC, 17 received QXR. The unequal proportion of patients receiving QXR or ESC treatment within the yoga and control group is one of the limitations of the study, which was generated through unequal drop-out-numbers in the different subgroups (see Consort Flow Diagramm).

Regarding the COR level boost in week 1 and a partial down-regulation in week 5 in the Hatha-yoga group, these results are exactly in line with other studies reporting a temporarily COR increase due to ESC in depressed patients and in healthy subjects (Nadeem et al., 2004). With respect to the acute inhibitory effects of COR in week 1 and a partial rebound in week 5 in the control group (Fig. 2), these results are congruent with the findings of other studies investigating the effect of QXR on COR values (Cohrs et al., 2006; de Borja Goncalves Guerra et al., 2005). In this context it can be hypothesized that antidepressant medication has a significant impact on HPA axis activity, which is not exceeded by the influence of Hatha-yoga. This is the first study to date, that investigates the time course of COR values measured by serial DEX/CRH tests and states that additional yoga does not lead to a superior effect on clinical outcome and HPA axis overdrive compared to antidepressant medication alone. This illuminating result may add another jigsaw piece to the controversial discussion about changes in COR values due to yoga (Vera et al., 2009; West et al., 2004; Yoshihara et al., 2011): the influence of yoga on cortisol may be too small to be detected, especially in the context of concomitant therapy with antidepressant medication. One (non-randomized) study reports a significant drop in serum cortisol in depressed patients who received yoga or yoga in combination with antidepressant medication for three month (yoga on a daily basis of one hour), moreover those who received yoga-only showed a high correlation between reduction of serum cortisol level and antidepressant response (Thirthalli et al., 2013). Other studies report inconsistent results concerning COR level changes due to yoga: long-term yoga practice (several years) leads to an increase in blood cortisol in healthy subjects (Vera et al., 2009), while other studies found no differences in cortisol compared to control groups (Yoshihara et al., 2011). Interestingly, short-term yoga practice (several days to weeks) results in decreased cortisol levels in healthy subjects (West et al., 2004). There are only a few RCTs including major depression and cortisol levels, which are reporting significant decreases in COR, but the evidence seems to be clearly limited and should be

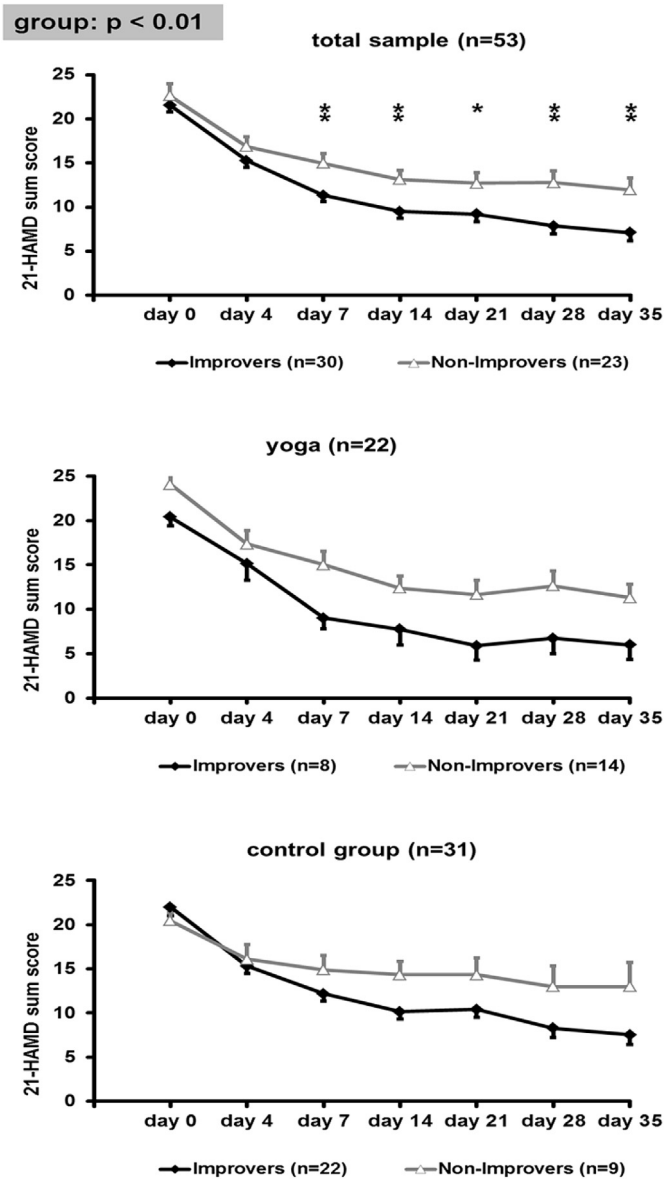

Fig. 4. Mean 21-HAMD sum scores (day 0–35) in depressed patients treated with yoga (60 min/week) or no-yoga (control group) additional with QXR (300 mg per day) or ESC (10 mg per day) subdivided into COR improvers and COR non-improvers. COR improver = patient with reduction of COR peak value in the DEX/CRH test after 1 week of treatment, as compared to baseline (week 0). SEM (standard error of mean) indicated. Significant group effects in the ANOVA for repeated measurements indicated. * = significant group differences in post-hoc tests ($p < 0.05$). **, *** = highly significant group differences in post-hoc tests ($p < 0.01$, $p < 0.001$).

viewed as very preliminary: Vadiraja and colleagues included breast cancer patients with no diagnosed major depression but "depressive symptoms" in their study (Vadiraja et al., 2009), Vedamurthachar and colleagues investigated only male patients with alcohol dependence syndrome and no diagnosed major depression according to DSM-IV (Vedamurthachar et al., 2006). Therefore, the present study provides a first attempt towards exploring neuroendocrine correlates of Hatha-yoga training in depressed patients who at least in part suffer also from HPA axis overdrive.

Regarding the predictive value of early COR improvement (reduction of the COR peak value in the DEX/CRH test after 1 week of therapy) an early down regulation of HPA system hyperactivity seems to raise highly significant the possibility of a clinical response in week 5 (Figs. 3 and 4). Moreover, the responders within the yoga and control group showed a similar significant trend during DEX/CRH-test: a rapid down-regulation of HPA axis function already after 1 week of treatment was followed by a partial re-increase of COR concentrations after 5 weeks of therapy, whereas in the non-responders (in particular within the yoga group) a more blunted response in cortisol levels in week one and a marked decrease in week 5 was observed (Fig. 3). These results are congruent with further studies reporting an association between early COR improvement and clinical response, indicating that COR is a potential biomarker for clinical response in depression (Ising et al., 2005, 2007).

To constrict these results it should be mentioned that the low frequency of Hatha-sessions (60 min/week) may not be sufficient to prove any endocrinological changes concerning COR values compared to other studies with depressed patients (Vadiraja et al., 2009; Vedamurthachar et al., 2006). In summary, patients had about 5 × 60 min of Yoga practice which definitively seems too short and too superficial to expect noteworthy endocrinological changes. Moreover, an inclusion of an ethical and spiritual component within the Yoga practice may provide additional benefits over yoga practiced as an exercise (Smith, 2011). After all, the patients' inner compliance is the basis for the efficacy of methods such as Yoga. In this study no data was collected regarding the question how yoga was received and perceived by the patients. Due to concomitant antidepressant medication it was not possible to investigate the isolated antidepressant effects of Hatha-yoga therapy alone and therefore it was not possible the replicate the finding of an immediate down-regulating effect of yoga on HPA axis activity (Ross and Thomas, 2010). A different analysis concerning the same patients but without covering the Yoga and control group subsamples and without analyzing improvement and non-improvement regarding cortisol-secretion has already been published elsewhere (Sarubin et al., 2014).

Despite several limitations, our study could not provide evidence that Hatha-yoga as augmentation to pharmacologic treatment may lead to a significant improvement in depressive symptoms. Nevertheless, in the context of growing interest about additional therapeutic strategies treating depression, Hatha-yoga seems to be a promising approach in the treatment of depression (Kinser et al., 2012; Mehta and Sharma, 2013; Pilkington et al., 2005). Further clinical studies and larger control samples are necessary to investigate the biological impact and psychological benefits of Hatha-yoga therapy as add on treatment to antidepressants in major depressed patients.

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Contributors

All authors have made substantive intellectual contributions to the submitted work in form of conception of the study, and/or acquisition of data, and/or analysis and interpretation of data, and/or drafting or revising the article. Nina Sarubin conducted the DEX/CRH tests, performed the literature search, wrote the manuscript, performed the statistical analyses and was responsible for the ratings of the patients. Cornelius Schüle designed the study, wrote the protocol and was the principal investigator of the study. Caroline Nothdurfter, Christoph Born and Martin Lieb recruited the patients for the study. Katharina Konopka participated in the literature research and statistical analyses. Markus Bühner

supervised the statistical analyses. Rainer Rupprecht and Thomas Baghai participated in the drafting of the article and revising it critically. Manfred Uhr's laboratory analyzed serum cortisol levels. All authors approved the final version of the manuscript and take public responsibility for its content.

Potential conflicts of interest

This study was supported by an unrestricted grant from AstraZeneca Germany. Rainer Rupprecht has been on AstraZeneca advisory boards. Thomas C. Baghai accepted paid speaking engagements and acted as a consultant for Astra-Zeneca, Glaxo-Smith-Kline, Janssen-Cilag, Pfizer and Servier. This study was supported by an unrestricted grant from AstraZeneca Germany. Nina Sarubin, Caroline Nothdurfter, Katharina Konopka, Manfred Uhr, Christoph Born, Martin Lieb, Markus Bühner and Cornelius Schüle reported no direct or indirect financial or personal relationships, interests, and affiliations relevant to the subject matter of the manuscript that have occurred over the last three years, or that are expected in the foreseeable future.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.02.022.

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