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Sleep-EEG in patients with primary aldosteronism in comparison to healthy controls and patients with depression

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ABSTRACT

The mineralocorticoid receptor (MR)/glucocorticoid receptor balance plays an important role in the pathophysiology of anxiety and depression. Aldosterone, a primary MR ligand, seems to be related to the pathophysiology of anxiety and depressive symptoms. The objective of this study was to investigate effects of aldosterone excess on sleep EEG, as sleep EEG is a tool to gain insight into psychoneuroendocrine function. Here, 19 untreated patients (9 males, 10 females) suffering from primary aldosteronism were investigated using sleep EEG and several rating scales for anxiety, depression, quality of life and sleep before starting specific treatment. Parameters were compared to age and sex matched healthy controls and patients with depression and correlated with laboratory findings and blood pressure. Patients had higher values for anxiety and depression compared to the general population, although a psychiatric disorder in their history was ruled out. Although sleep disturbances were reported in the Pittsburgh sleep quality index, sleep EEG did not show significant changes between patients and healthy controls. No depression specific pattern in sleep EEG was found. But in contrast to females, several sleep-EEG parameters of male PA patients differed significantly from patients with depression. There was a significant correlation between blood pressure and the severity of depression and anxiety in females. Correlation analysis between blood pressure and rating scales indicate a relationship between blood pressure and anxiety in women. In conclusion, these data suggest gender related effects of aldosterone excess in males and females.

1. Introduction

Aldosterone, a primary physiological ligand of the mineralocorticoid receptor (MR), may be involved in the pathogenesis of depressive disorders and anxiety. MR are differentiated in hippocampal MR, which are primarily occupied by cortisol/corticosterone, due to the absence of the enzyme 11 beta HSD, and MR in brain areas, including the nucleus of the solitary tract (NTS), which appear to contain this enzyme, and are therefore specific to aldosterone (Funder, 2017; Geerling et al., 2006).

Elevated aldosterone levels have been reported in patients with depression (Murck et al., 2003); (Emanuele et al., 2005). Holsboer described reduced aldosterone response to corticotropin-releasing hormone stimulation (Holsboer, 1987). Furthermore, polymorphisms in the angiotensin converting enzyme gene appear to be associated with unipolar depression and hypercortisolism (Baghai et al., 2006).

An involvement of aldosterone via the MR in the pathophysiology of anxiety and depression is also supported by animal studies (Hlavacova et al., 2010; Hlavacova and Jezova, 2008a; Hlavacova et al., 2012). Hlavacova and colleagues reported that stimulation of MR results in anxiogenic behavior and blockade of MR in anxiolytic effects (Hlavacova et al., 2012). Data for the role of MR in depression are not consistent, but there are indications that the MR is involved in the response to antidepressive treatment. Several animal studies describe an upregulation of central MR in response to antidepressive treatment (Seckl and Fink, 1992; Yau et al., 2002). Clinical data presented by Hinkelmann et al., (2016) (Hinkelmann et al., 2016) point out the important role of the MR in the pathophysiology of depression. They suggest a disturbed MR signaling to be associated with depression. These findings suggest the MR to be important for the mediation of antidepressive drug effects. De Kloet underlined the importance of the MR/glucocorticoid balance (de Kloet, 2014). Chronic stress and depression are characterized by an imbalance of these two receptors.

A study of Buttner et al., 2015) (Buttner et al., 2015) gives support

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to this hypothesis. These authors report a poorer clinical outcome in patients with depression that show a higher aldosterone/cortisol ratio. In males, additional parameters like increased slow wave sleep (SWS), reduced salt taste sensitivity, increased salt preference and decreased respiratory sinus arrhythmia were able to predict a worse outcome. They also discuss parameters of reduced peripheral MR activity to be associated with higher anxiety levels (Buttner et al., 2015). Segeda et al., (2017) (Segeda et al., 2017) found salivatory aldosterone to be associated with severity, duration and outcome of a depressive episode. Additionally higher aldosterone concentrations were found in females. Furthermore Murck et al., 2019 (Murck et al., 2019) tested several biomarkers as slow wave sleep, morning salivary cortisol and aldosterone, systolic blood pressure, salt taste intensity (STI), salt pleasantness (SP), and plasma electrolytes in patients with depression. They report early changes in central MR to be associated with outcome of standard antidepressant treatment. A “natural model” for aldosterone excess is provided by patients suffering from primary aldosteronism (PA), a special form of arterial hypertension. It is characterized by high levels of circulating aldosterone, arterial hypertension and an often occurring hypokalemia. Psychiatric comorbidities have been described in these patients.

Sonino et al. (Sonino et al., 2006; Sonino et al., 2011) found a higher prevalence of anxiety disorders in patients with essential hypertension. These findings were supported by a cross-sectional study by Apostolopoulou et al. (2014) who reported significantly higher values for depressive symptoms and anxiety in patients with PA compared to the general population and additionally reported gender differences with females being more affected than males by affective symptoms. In a previous study, a lower quality of life in patients with PA with specific gender differences was found (Kunzel et al., 2012).

Sleep EEG is a valid instrument that can help to understand the role of various receptors and transmitters in depression. A specific sleep architecture pattern has been described for depression, like rapid eye movement (REM) disinhibition and disturbance of sleep continuity (Steiger and Kimura, 2010). The role of MR in sleep regulation is not clear. Born et al. (Born et al., 1991) reported a corticosteroid mediated effect on SWS. In contrast, Steiger et al. (1993) found that MR-inhibition had no effect on sleep-EEG.

Despite these findings in animals and human studies, the role of the MR in the pathogenesis of depression and anxiety is not fully understood yet. The aim of our study was to provide a deeper insight into the role of aldosterone excess on psychoneuroendocrine regulations assessed by sleep EEG. Therefore, we analyzed sleep EEG in patients with PA in comparison to healthy controls and patients with depression.

2. Methods

2.1. Sample

2.1.1. Patients

19 patients (9 males, 10 females) with a mean age of 47.11 years (range 18–66 years) with first diagnosed Conn's syndrome (Primary Aldosteronism = PA) were enrolled in this study. Patients were prospectively recruited from the German Conn Registry. All patients gave their written informed consent. All patients were already treated with standardized antihypertensive medication according to the Conn Registry protocol (a combination of Verapamil, Doxazosin and/or Urapidil), thus not affecting the renin-aldosterone-angiotensin system (RAAS) (Schirpenbach et al., 2009). An extensive examination, including basic clinical and laboratory data, several psychiatric scales and sleep EEG was performed at time point of firstly diagnosing PA. Exclusion criteria included shift work, jetlag, treatment with spironolactone, any psychoactive drugs or hormonal therapy. Patients abusing drugs or alcohol were excluded as were those with other hormonal disturbances or known sleeping disorders.

The study was performed in accordance with the Declaration of Helsinki and with the "Note for Guidance on Good Clinical Practice for Studies on Medical Products in the European Community, July 11, 1990". The study was approved by the ethical committee of the University of Munich.

Investigations and psychiatric assessments were performed by physicians and specially trained stuff.

2.1.2. Control group

Sleep-EEG data were obtained from 19 age- and sex-matched healthy volunteers with mean age of 46.89 years ranging from 20 to 66 years. Controls met the following exclusion criteria: Existing psychiatric or somatic diseases, ingestion of any medication within the last four weeks, participation in any other clinical trial within the last three months, shiftwork or transmeridian flights. All subjects gave their written informed consent.

2.1.3. Depressed group

Sleep-EEG data of 19 age- and sex-matched depressed patients with mean age of 47.47 years ranging from 20 to 67 years were collected by review of the medical chart. All patients suffered from a first or recurrent depressive episode according to the diagnostic criteria of ICD-10 respectively DSM-IV. Further clinical and hormonal data including serum cortisol, BMI and psychiatric scales was collected at the time of the presentation in the sleep laboratory (see Table 2).

2.2. Data acquisition, clinical assessment

Normal laboratory routine parameters in patients with PA were collected in a standardized way together with the hormones cortisol and aldosterone in the morning after resting for at least 10 min.

Blood samples for cortisol in patients with depression were collected in the morning after 30 min of resting.

2.2.1. PA- hormone assays

Plasma aldosterone concentrations of the PA patients were measured using a commercial radioimmunoassay (DiaSorin Liasion CLIA Aldosterone ng/l). Plasma renin concentrations were determined using a chemiluminescence immunoassay (Renin Diasorin Liaison Act. 4.4–64uU/ml, Italy). Cortisol was measured with a chemiluminescence immunoassay (Liaison Diasorin REF 313261).

2.2.2. Depressed group

The serum cortisol level of the depressed group was collected in the morning after recording of sleep-EEG after resting for 30 min in the bed.

2.2.3. Psychiatric scales in patients with PA and depression

Several psychiatric scales were applied within the PA group.

To evaluate quality of life, we used the SF-12 questionnaire, a validated, multipurpose measure that can discriminate between mental and physical impairment of quality of life (Jenkinson and Layte, 1997a). Reference values were set by the normal sample of the German population (1994) (SF-12 Manual).

To assess depression and anxiety, we performed the Beck Inventory of Depression (BDI) as well as the Hamilton Rating Scale for Depression (HAM-D), the generalized anxiety disorder questionnaire (GAD-7) and the Hamilton Anxiety Rating Scale (HAM-A). The BDI and the HAM-D are validated scales widely used for characterising the severity of depression (Bech, 2009; Beck et al., 1988; Gräfe et al., 2004). The HAM-A and GAD-7 are used to identify and quantify the extent of anxiety (Bech, 2009; Spitzer et al., 2006).

Reference data for the BDI was provided by Beck et al. (1988). No depression was present with scores of < 10, a mild depressive syndrome from 10 to 19, a moderate syndrome from 20 to 29 and a severe syndrome score ≥ 30 (S3-Guideline).

Concerning the HAM-D, reference data was provided by Zimmerman et al. A score of ≤ 8 indicated no depression, a mild syndrome was set by 9–16 points, a moderate syndrome 17–24 points and a severe syndrome ≥25 points (S3-Guideline).

Concerning the GAD-7, normative data of the German population was set by Lowe et al. (2008). According to the cut-offs set by Spitzer et al. (2006), scores of 5, 10 and 15 represent mild, moderate and severe anxiety, respectively.

A HAM-A gradation for severity was laid out by Hamilton et al. (Hamilton, 1959). Range for a mild severity level was set from 14 to 17 points, a moderate severity ranged from 18 to 24 points; a moderate to severe severity ranged from 25 to 30 points.

Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI): The PSQI is able to evaluate retrospectively the quality and patterns of sleep over a one month time interval by observing seven different components which can create one global score (Buysse et al., 1989). Additionally we performed three sum scores to improve the assessment:

1. ”Sleep Efficiency Sum Score” which contained the components ”Sleep Duration” and ”Sleep Efficiency”
2. ”Perceived Sleep Quality Sum Score” which contained the components ”Subjective Sleep Quality”, ”Sleep Latency” and ”Use of Sleeping Medication”
3. ”Daily Disturbances Sum Score” which contained the components ”Sleep Disturbances” and ”Daytime Dysfunction”

PSQI reference values concerning the sleep quality of the Austrian population were obtained from the study of Zeitlhofer et al. (2000).

Daily fatigue was assessed by Epworth Sleepiness Scale (ESS) (Johns, 1991). Normative values of the German Epworth Sleepiness Scale were set by Sauter et al. (2007).

Quality of life was evaluated with SF-12 questionnaire, a validated short form of the SF-36. This questionnaire is able to discriminate between physical and mental impairment in quality of life (Jenkinson et al., 1997)

Questionnaires that were incomplete or had missing values were excluded from further analysis. The psychological testing was performed by professionally trained staff.

Patients with depression were characterized by using the HAM-D. Additionally, the PSQI was performed to evaluate sleep quality.

Table 1

Clinical data of the primary aldosteronism (PA) patient group (parameters are presented as mean (min) ± standard deviation).

Parameter	Whole Group	PA Men	PA Women	f value	p-value
Number N (%)	**19**	**9** (47.37%)	**10** (52.63%)	-	-
Age (y)	**47.11** (12.52)	**48.44** (10.88)	**45.90** (14.32)	-	-
Mean 24 h systolic BP (mm mercury)	**148.28** (14.54)	**153.89** (17.71)	**142.67** (8.05)	-	0.124
Mean 24 h diastolic BP in (mm mercury)	**95.61** (8.90)	**100.00** (7.97)	**91.22** (7.84)	$F_{1,15} = 6.445$	**0.023**
Mean systolic BP at daytime (mm mercury)	**149.79** (15.97)	**154.89** (19.55)	**145.20** (11.00)	-	0.217
Mean diastolic BP at daytime (mm mercury)	**96.72** (9.85)	**101.00** (9.79)	**92.44** (8.32)	-	0.114
Mean systolic BP at night (mm mercury)	**140.50** (13.79	**149.78** (13.31)	**131.22** (5.76)	$F_{1,15} = 13.569$	**0.002**
Mean diastolic BP at night (mm mercury)	**88.67** (10.39)	**96.22** (4.79)	**81.11** (8.82)	$F_{1,14} = 23.888$	**< 0.001**
Waist-To-Hip Ratio	**0.92** (0.09)	**0.99** (0.07)	**0.87** (0.07)	$F_{1,16} = 15.712$	**0.001**
Body mass index (kg/m2)	**27.20** (3.93)	**28.83** (3.58)	**25.73** (3.80)	-	0.104
Serum sodium (135 – 150 mmol/l)	**140.58** (2.63)	**140.89** (2.67)	**140.30** (2.71)	-	0.765
Serum potassium (3.5 – 5.0 mmol/l)	**3.51** (0.48)	**3.40** (0.37)	**3.60** (0.56)	-	0.317
Serum cortisol (1.8 – 24.0 µg/dl)	**12.87** (3.84)	**13.58** (4.10)	**12.24** (3.69)	-	0.508
Serum aldosterone (40 – 310 ng/l)	**230.55** (184.15)	**200.44** (138.27)	**257.65** (221.61)	-	0.534
Plasma renin concentration (8 – 99 µU/ml)	**4.36** (3.76)	**4.60** (4.95)	**4.14** (2.53)	-	0.702
Aldosterone/renin ratio (< 20 ng/l/mU/l)	**79.78** (75.85)	**84.15** (95.85)	**75.84** (57.46)	-	0.889
HAM-D	**5.83** (5.50)	**3.22** (2.73)	**8.44** (6.44)	$F_{1,16} = 6.077$	**0.025**
Reference value (RV) (cut-off ≤8)	*3.2 (3.2)*	*3.3 (3.3)*	*3.1 (3.2)*		-
BDI	**4.24** (6.21)	**2.11** (3.44)	**6.63** (7.89)	-	0.118
RV (cut-off < 10)	*10.9 (8.1)*	-	-		-
GAD-7	**5.59** (5.58)	**3.56** (3.54)	**7.88** (6.75)	-	0.076
RV (cut-off < 5)	*2.95 (3.41)*	*2.66 (3.24)*	*3.20 (3.52)*		-
HAM-A (cut-off < 14)	**7.44** (7.07)	**4.78** (4.89)	**10.11** (8.13)	-	0.153
SF-12; PCS	**45.30** (12.12)	**46.82** (11.74)	**43.03** (13.43)	-	0.416
RV		*50.2 (8.68)*	*47.9 (9.74)*		-
SF-12; MCS	**50.83** (9.10)	**51.01** (7.52)	**50.55** (11.89)	-	0.936
RV		*53.25 (7.57)*	*51.30 (8.41)*		-
ESS	**8.12** (4.65)	**8.78** (4.63)	**7.38** (4.87)	-	0.427
RV	*6.6 (3.5)*	*6.9 (3.3)*	*6.2 (3.7)*		-
PSQI- Global Score	**6.38** (4.12)	**6.11** (4.65)	**6.71** (3.82)	-	0.675
RV	*4.55 (3.71)*	-	-		-
PSQI- Subjective Sleep Quality	**1.44** (0.73)	**1.33** (0.71)	**1.57** (0.79)	-	0.462
RV	*0.75 (0.78)*				
PSQI- Sleep Latency	**1.25** (1.00)	**1.00** (1.00)	**1.57** (0.98)	-	0.141
RV	*0.88 (0.85)*				
PSQI- Sleep Duration	**0.94** (0.99)	**1.00** (1.00)	**0.86** (1.07)	-	0.907
RV	*0.74 (0.71)*				
PSQI- Habitual Sleep Efficiency	**0.50** (0.89)	**0.33** (1.00)	**0.71** (0.76)	-	0.411
RV	*0.31 (0.71)*				
PSQI- Sleep Disturbances	**1.25** (0.68)	**1.22** (0.67)	**1.29** (0.76)	-	0.714
RV	*0.83 (0.99)*				
PSQI- Use of Sleeping Medication	**0.00** (0.00)	**0.00** (0.00)	**0.00** (0.00)	-	-
RV	*0.23 (0.68)*				
PSQI- Daytime Dysfunction	**1.00** (0.97)	**1.22** (1.20)	**0.71** (0.49)	-	0.359
RV	*0.82 (0.76)*				
PSQI- Sleep Efficiency Sum Score	**1.44** (1.71)	**1.33** (1.87)	**1.57** (1.62)	-	0.719
PSQI- Perceived Sleep Quality Sum Score	**2.69** (1.54)	**2.33** (1.50)	**3.14** (1.57)	-	0.194
PSQI- Daily Disturbances Sum Score	**2.25** (1.48)	**2.44** (1.74)	**2.00** (1.16)	-	0.668

2.2.4. Sleep data acquisition

After confirmation of PA, sleep-EEG acquisition of the PA group was carried out. Participants' sleep EEG was recorded during two consecutive nights. The first night served as an adaptation to the laboratory setting, in the second night sleep data were recorded.

On both nights, lights were switched off at 23.00 and patients were woken up at 07.00 the following morning. The equipment of the sleep laboratory was in consensus with the standards of American Academy of Sleep Medicine, electrodes were positioned according to the international "10–20 System".

Two EEGs (C3-A2, C4-A1; time constant 0.3 s, low-pass filtering 70 Hz), vertical and horizontal electrooculograms (EOG), an electromyogram (EMG) and an electrocardiogram were used for polysomnography EEG. EOG, EMG and EEG signals were filtered and transmitted by an optical fiber system to polygraph (Nihon Kohden).

Manual scoring of the sleep EEG was done in accordance to the scoring system described by Rechtschaffen and Kales (1968) and to the AASM classification (Iber, 2007).

2.3. Statistical analysis

Whenever significant global factor effects emerged, univariate F-tests with age as a covariate followed to identify the variables on which the factor effects are significant.

In order to avoid co-linearities, variables concerning clinical data and sleep EEG characteristics were partitioned in subsets of possible no linear dependent variables before applying variance analyses.

Calculations for better characterization of the reference group (PA group) in a gender-related manner were performed in Table 1. Clinical data provided by the PA patients and depressed patients was compared in Table 2. Sleep EEG data comparison between the reference group, the healthy control group and the depressed group were worked out in Table 3.

To observe possible associations, correlation analysis with Pearson's coefficient was performed when dealing with interval-scaled variables. According to Cohen et al. (Cohen, J. 1988) the correlation coefficient r of 0.1 is classified small, $r = 0.3$ is classified medium and $r = 0.5$ is classified large. Due to the sample sizes and to improve expressiveness, only significant correlations with a correlation coefficient $r > 0.700$ were taken into account. Correlations within night halves and night thirds were not taken into consideration.

For all statistical tests an $\alpha = 0.05$ was accepted as nominal level of significance (type I error). No correction for multiple testing was performed due to the explorative character of this work.

3. Results

3.1. Basic internistic and laboratory data

The male PA group had higher blood pressure (BP) levels in comparison to the female group in all measurements. Both BMI and waist-to-hip ratio were significantly higher in the male group. No significance difference between the sexes was observed on laboratory data (see Table 1).

Age was not significantly different between the three different groups was found. Cortisol levels between the depressed and the PA group were significantly lower in the PA group both when observing the whole group as well as when comparing male and female patients (for values see Table 2).

3.2. Psychiatric scales

Results of the psychiatric assessment are presented in Table 1. Female PA PA patients scored higher mean values in all evaluated psychiatric scales in comparison to the males. Concerning the HAM-D this difference was significant.

Table 2
Comparison of data between depressed patients and PA patients (parameters are presented as mean (min) ± standard deviation).

Parameter	Whole Group		Men		Women		f value (referring to "whole group")	p-value (referring to "whole group")
Number N (%)	19		9 (47.37%)		10 (52.63%)			
Group	PA	Depressed	PA	Depressed	PA	Depressed		
Age (y)	**47.11** (12.52)	**47.47** (12.42)	**48.44** (10.88)	**48.67** (11.00)	**45.90** (14.32)	**46.40** (14.08)	-	p = 0.928
Body mass index (kg/m2)	**27.20** (3.93)	**25.69** (4.97)	**28.83** (3.58)	**25.95** (2.36)	**25.73** (3.80)	**25.38** (7.24)	-	p = 0.631
Serum Cortisol *(1.8 – 24.0 µg/dl)*	**12.87** (3.84)	**16.32** (9.51)	**13.58** (4.10)	**18.05** (6.75)	**12.24** (3.69)	**14.58** (11.98)	$F_{1,30} = 43.859$	**p < 0.001**
HAM-D	**5.83** (5.50)	**21.88** (5.17)	**3.22** (2.73)	**20.89** (5.49)	**8.44** (6.44)	**23.00** (4.89)	$F_{1,32} = 79.279$	**p < 0.001**
PSQI- Global Score	**6.38** (4.12)	**11.57** (2.98)	**6.11** (4.65)	**11.43** (2.94)	**6.71** (3.82)	**11.71** (3.25)	$F_{1,27} = 15.662$	**p < 0.001**

Table 3
Sleep EEG characteristics (presented as mean (min) ± standard deviation).

	PA	PA Men	PA Women	Healthy	Healthy Men	Healthy Women	Depressed	Depressed Men	Depressed Women
Sleep stage (min)									
Time In Bed (TIB)	**481.24** (1.39)	481.11 (0.78)	481.35 (1.81)	**480.47** (4.04)	480.61 (1.02)	480.35 (5.63)	**482.21** (4.85)	482.44 (6.31)	482.00 (3.39)
Total Sleep Time (TST)[a]	**404.16** (43.13)	402.22 (54.53)	405.90 (32.72)	**402.39** (57.96)	410.78 (43.36)	394.85 (70.09)	**383.84** (60.33)	364.56 (64.81)	401.20 (53.28)
Sleep Period Time (SPT)	**451.97** (29.70)	458.83 (22.24)	445.80 (35.14)	**460.11** (21.88)	467.06 (9.93)	453.85 (27.88)	**449.50** (45.47)	434.72 (61.54)	462.80 (18.79)
Sleep Efficiency Index (SEI) (=TST/TIB)[b,c]	**83.99** (8.94)	83.62 (11.34)	84.32 (6.73)	**83.70** (11.77)	85.46 (9.03)	82.12 (14.11)	**79.62** (12.54)	75.58 (13.52)	83.25 (10.99)
N2 Latency[d,e]	**4.58** (5.38)	3.61 (4.47)	5.45 (6.19)	**5.16** (6.74)	5.06 (6.38)	5.25 (7.39)	**26.03** (42.02)	39.89 (56.65)	12.17 (10.51)
N3 Latency[f]	**26.32** (24.54)	30.28 (33.88)	22.75 (12.42)	**28.17** (36.88)	35.81 (51.83)	22.05 (19.66)	**59.50** (60.01)	83.44 (74.59)	38.22 (35.37)
REM Latency[g]	**81.24** (32.03)	85.78 (33.88)	77.15 (31.50)	**80.11** (37.19)	76.11 (52.97)	83.70 (15.57)	**80.31** (48.27)	55.83 (30.53)	104.78 (51.68)
Slow Wave Sleep Latency	**26.32** (24.54)	30.28 (33.88)	22.75 (12.42)	**28.17** (36.88)	35.81 (51.83)	22.05 (19.66)	**59.50** (60.01)	83.44 (74.59)	38.22 (35.37)
N1 Sleep Stage	**57.53** (33.40)	64.17 (38.74)	51.55 (28.52)	**48.79** (31.00)	66.61 (36.88)	32.75 (10.48)	**66.63** (35.11)	81.56 (30.28)	53.20 (35.04)
N2 Sleep Stage[h,i]	**197.32** (30.79)	201.17 (31.96)	193.85 (30.98)	**218.55** (39.53)	228.00 (36.45)	210.05 (42.12)	**188.63** (46.05)	167.06 (39.25)	208.05 (44.58)
N3 Sleep Stage	**72.18** (38.69)	59.78 (29.86)	83.35 (43.69)	**58.63** (43.94)	36.72 (29.75)	78.35 (46.49)	**55.53** (35.25)	44.00 (40.73)	65.90 (27.54)
REM Sleep Stage	**76.63** (21.47)	76.44 (28.79)	76.80 (13.60)	**74.68** (21.48)	77.61 (23.44)	72.05 (20.45)	**72.55** (22.07)	72.00 (23.50)	73.05 (21.97)
NREM Sleep Stages	**327.03** (36.96)	325.11 (44.58)	328.75 (30.97)	**325.97** (45.67)	331.33 (30.12)	321.15 (57.54)	**310.79** (57.62)	292.61 (62.78)	327.15 (50.09)
Light Sleep Stages (= N1 + N2)	**254.84** (43.37)	265.33 (38.71)	245.40 (47.12)	**267.34** (48.55)	294.61 (35.04)	242.80 (47.01)	**255.26** (56.26)	248.61 (63.48)	261.25 (51.62)
Slow Wave Sleep Stages (= N3)[j,k]	**72.18** (38.69)	59.78 (29.86)	83.35 (43.69)	**58.63** (43.94)	36.72 (29.75)	78.35 (46.49)	**55.52** (35.25)	44.00 (40.73)	65.90 (27.54)
Wake stages[l,m]	**73.68** (40.74)	74.17 (51.58)	73.25 (30.90)	**76.82** (54.39)	68.67 (41.97)	84.15 (65.01)	**97.71** (60.43)	117.94 (64.88)	79.50 (52.76)

[a] PA Men vs. Depressed Men: $F_{1,15} = 7.021$, $p = 0.018$.
[b] PA Men vs. Depressed Men: $F_{1,15} = 7.520$, $p = 0.015$.
[c] Healthy Men vs. Depressed Men: $F_{1,15} = 4.679$, $p = 0.047$.
[d] PA Group vs. Depressed Group: $F_{1,34} = 4.736$, $p = 0.037$.
[e] Healthy Group vs. Depressed Group: $F_{1,34} = 4.449$, $p = 0.042$.
[f] PA Group vs. Depressed Group: $F_{1,33} = 5.727$, $p = 0.023$.
[g] PA Men vs. Depressed Men: $F_{1,15} = 4.998$, $p = 0.041$.
[h] Healthy Group vs. Depressed Group: $F_{1,35} = 4.473$, $p = 0.042$.
[i] Healthy Men vs. Depressed Men: $F_{1,15} = 11.467$, $p = 0.004$.
[j] PA Group vs. Healthy Group: $F_{1,35} = 1.124$, $p = 0.296$.
[k] PA Group vs. Depressed Group: $F_{1,35} = 2.196$, $p = 0.147$.
[l] PA Men vs. Depressed Men: $F_{1,15} = 9.959$, $p = 0.007$.
[m] Healthy Men vs. Depressed Men: $F_{1,15} = 5.263$, $p = 0.037$.

Referring to the depression-related scales (HAM-D, BDI), the cut-off indicating depressive symptoms was not reached. But the PA group had higher HAM-D scores in comparison to the reference values obtained by Zimmerman et al. (Zimmerman et al., 2004) whereas the control group showed lower mean values. Compared with depressed patients the PA group showed significantly lower scores (see Table 2).

In anxiety-related scales, the PA group had higher GAD-7 means compared to the reference data by Lowe et al. (2008) (5.59 ± 5.58 vs. 2.95 ± 3.41) (see Table 1). Female patients score indicated a mild anxiety disorder, male one's stayed below the cutoff. The cut-off of HAM-A was not reached.

3.3. Sleep questionnaires: ESS and PSQI

No significant differences for sleep questionnaires were found when comparing male and female patients with PA (for results see Table 1).

Patients with PA showed worse sleep quality measured by PSQI and daily fatigue assessed by ESS than the general population.

In comparison to patients with depression PA patients show significantly lower score, except for the "Use of sleeping medication subscale".

3.4. Quality of life

In both the physical (PCS) and the mental (MCS) SF-12 subscales, female PA patients scored lower mean values without coming to statistical significance (see Table 1). In comparison to the German reference data, our PA group scored lower mean values on both subscales.

3.5. Sleep EEG characteristics 3.4.1 PA patients

No significant gender-related sleep EEG difference within the PA group could be observed (see Table 2).

3.5.1. PA patients – controls

No significant group- and/or gender-related sleep EEG difference was detected between PA patients and healthy controls.

3.5.2. PA patients – depressed

When comparing the PA and the depressed group, PA patients showed a significant shorter N2 and N3 latency. Male PA patients had a significantly longer Total Sleep Time (TST) and a better sleep efficiency compared to the depressed patients.

REM latency of the male PA patients was longer, "Wake time" was significantly shorter in the PA group.

No significant gender-related group differences were displayed on the side of the female patients (See Table 3).

3.6. Correlation analysis

Significant correlations concerning the PA group are listed in Table 4.

Male PA patients expressed several significant associations especially in the light sleep stages (=N1+N2). So, a negative connection to serum aldosterone levels ($r = -0.872$) and the Aldosterone/renin ratio ($r = -0.818$) and a positive one to plasma renin levels ($r = +0.761$) was noted. In the female PA group, also the deeper sleep stages showed significant correlations with hormonal parameters (serum cortisol: $r = +0.747$, plasma renin: $r = +0.021$).

Several correlations between psychiatric scales and blood pressure values especially in the nighttime measurements appeared in the female group. GAD-7 ($r = +0.754$, $r = 0.752$), the BDI ($r = +0.824$) and the ESS ($r = +0.718$) correlated positively. The MCS of the SF-12 correlated negatively ($r = -0.969$, $r = -0.917$).

No significant correlation coefficient $r > 0.700$ was displayed when taking the whole group into account.

4. Discussion

The aim of the study was to get a better insight into the effects of aldosterone on psychoneuroendocrine regulations by investigating sleep EEG of a sample of patients with chronically high levels of aldosterone in comparison with healthy controls and patients with depression. Psychopathological data from a former study in a large sample were confirmed in this sample. Although psychiatric diagnosis was an exclusion criterion, PA patients were more affected by depressive symptoms and anxiety compared to the general population. Similar to a previous study this was particularly evident in female patients (Apostolopoulou et al., 2014). Additionally, male and female patients showed a markedly impaired physical quality of life in SF-12 compared to the German reference values (Kunzel et al., 2012).

The first main finding in this study was that patients with PA showed no significant differences in sleep-EEG pattern to healthy controls. Analyzing the subjective perception of sleep in the PSQI, again no significant differences compared to the general population were found. However, males and females had significantly worse sleep compared to the normative sample.

Sleep-EEG pattern of patients with PA was not found to be similar to patients with depression. Comparing the sleep-EEG of PA patients with sleep-EEG of patients with depression we found significant lower N2-latency and N3-latency in the PA group, indicating better sleep in patients with PA compared to depressed patients. When analyzing gender differences, only male PA patients differed significantly from patients with depression. They were found to have significantly better SEI, longer TST and REM latency and shorter wake time compared to depressed men. For females, no significant differences compared to depressive females were found. These finding resembles the psychometric data which indicate females with PA to be more affected with anxiety and depressive symptoms than males.

The overall lack of characteristic sleep -EEG changes seems to be in line with other studies modulating the MR without significant effects (Demiralay et al., 2015; Demiralay et al., 2014), although we had expected more effects of chronically high levels of aldosterone as aldosterone excess causes different changes for example a high blood pressure. Anxiety disorders do not relate to changes in sleep-architecture as reported for major depressive disorder (Baglioni et al., 2016; Benca, 1996). Nevertheless our results provide some support for the view that PA contributes to clinically accentuated anxiety as sleep-EEG parameters in males and females mainly correlate with anxiety.

Going deeper into gender specific correlation analysis our data from appear to provide similarities to findings from patients with depression (Buttner et al., 2015). These authors report prolonged slow wave sleep (SWS) in male patients with depression as a marker for poorer outcome to anti-depressive treatment. Although this did not reach significant difference, our patients – males and females – show more SWS than controls and patients with depression. According to Buttner et al., 2015) (Buttner et al., 2015) they suppose this effect to be associated to an increased central MR-activity. We could not find a significant correlation between sleep parameters and depression. However, a correlation with anxiety was found as NREM sleep correlated positively with HAM-A score and N2 showed a significant positive correlation with GAD-7 score. This is also reflected by a poorer outcome in the MCS of the SF-12. In females only sleep onset (N2) latency correlated positively with depressive symptoms measured by PHQ9.

Gender differences were also reflected by humoral factors. In males LS was negatively correlated to aldosterone, whereas LS and SWS in females seem to be associated to serum cortisol. Again these data might indicate a sexually dimorphic regulation of the MR.

Renin correlated positively with SWS in females and with sleep onset (N2) latency in males. This is in line with other studies. Brandenberger et al., (1990) (Brandenberger et al., 1990) reported plasma renin activity (PRA) to be associated with non-REM sleep in the REM/non-REM cycle. Schussler et al., 2010 (Schussler et al., 2010)

Table 4
Significant Correlations within the PA group.

Group	Parameters			Correlation Coefficient	Sig.
Whole group	-	-	-	-	-
PA men	Sleep EEG – Laboratory data	N2 latency	Plasma renin	+0.761	0.017
		LS stages (= N1+N2)	Serum aldosterone	−0.872	0.002
			Aldosterone/renin ratio	−0.818	0.007
	Sleep EEG -RR values	-	-	-	-
	Sleep EEG -Psychiatric/Sleep scales	REM latency	SF-12; PCS	−0.730	0.026
		N2 sleep stage	GAD-7	+0.745	0.021
		N2 sleep stage	SF-12; MCS	−0.744	0.021
		NREM sleep stages	HAM-A	+0.792	0.011
		NREM sleep stages	ESS	+0.735	0.024
	Psychiatric scales - Laboratory data	-	-	-	-
	Psychiatric scales – RR values	-	-	-	-
PA Women	Sleep EEG - Laboratory data	N2 sleep stage	Serum cortisol	−0.808	0.005
		LS stages (=N1+N2)	Serum cortisol	−0.815	0.004
		SWS stages (= N3)	Serum cortisol	+0.747	0.013
		SWS stages (=N3)	Plasma renin	+0.711	0.021
	Sleep EEG - RR values	N2 sleep stage	Mean systolic RR	+0.800	0.010
	Sleep EEG - Psychiatric/Sleep scales	Time in Bed (= TIB)	GAD-7	−0.744	0.034
		Time in Bed (= TIB)	PSQI - Global Score	−0.816	0.025
		N2 latency	PHQ9	+0.788	0.020
	Psychiatric scales - Laboratory data	-	-	-	-
	Psychiatric scales - RR values	GAD-7	Mean systolic RR	+0.754	0.031
		GAD-7	Mean systolic RR at night	+0.752	0.031
		BDI	Mean diastolic RR at night	+0.824	0.023
		SF-12; MCS	Mean systolic RR at night	−0.969	0.001
		SF-12; MCS	Mean diastolic RR at night	−0.917	0.010
		ESS	Mean diastolic RR	+0.718	0.045

found a positive correlation between renin concentrations and NREM sleep and the sleep efficiency index in healthy volunteers, but independent from gender.

More meaningful in females are significant associations between BP and anxiety and depressive symptoms with a negative effect on mental quality of life. Additionally, a positive correlation between systolic BP and sleep stage 2 was found. This leads to the assumption that women are more affected by high BP although they had significantly lower values than males. A relationship between hypertension and panic attacks was described in the literature, but there was no investigation of gender effects (Davies et al., 1997, 1999). Again, an association between anxiety and increased risk for hypertension has been described (Pan et al., 2015). So, high BP and anxiety could both be a consequence of higher MR activation.

However, a direct correlation between hormone values on symptoms of depression and anxiety was not found. This may be due to the one-point estimate of hormone concentration, when in reality hormone concentrations fluctuate in the course of the day.

For the suggested role of MR in SWS regulation by Born et al., (1991) (Born et al., 1991) our study could not show significant effects on SWS, although SWS seems to be prolonged in patients with PA. But in general aldosterone and the MR might not have a strong influence on sleep-EEG pattern as reported by Steiger et al. (1993), who could not observe a significant effect on sleep EEG by modulation with MR agonist and MR antagonist.

The worsened sleep quality in PA patients, found using the PSQI, may be associated additionally to the high BP as Javaheri et al. reported a relationship between poor sleep-quality and pre-hypertension (Javaheri et al., 2008).

With this study we could contribute to the assumption that aldosterone and the MR are involved in the pathophysiology of depression and especially anxiety with regard to gender aspects. Our findings correspond to the study of Segeda et al., 2017 (Segeda et al., 2017) reporting an association between aldosterone and severity and outcome in depression in a gender dependent manner. In our small sample we could not find an association between aldosterone and symptoms of anxiety as reported in animal data by Hlavacova et al. (Hlavacova et al., 2010, 2012; Hlavacova and Jezova, 2008a; Hlavacova and Jezova, 2008b). But former studies in a bigger sample gave indirect support to animal data, as higher aldosterone levels were associated with poorer mental Quol in female patients, who also showed higher levels of anxiety (Apostolopoulou et al., 2014; Kunzel et al., 2012). We propose, however, the MR activity and not aldosterone concentration directly to be the main regulatory element for symptoms of anxiety. An animal study by Rozeboom et. indicated the importance of MR in the control of stress and anxiety, and that a MR/glucocorticoid receptor imbalance may disturb the control of emotional reactivity (Rozeboom et al., 2007).

Due to these results aldosterone excess might have different effects in males and females. We only can speculate that these findings are caused by a sexually dimorphic function of the MR. As described by Büttner et al. (Buttner et al., 2015) central MR might be in males associated to depression and anxiety. Sex differences were also described in animal data by Ter Horst et al. (Ter Horst, Carobrez, van der Mark, de Kloet and Oitzl, 2012) who proposed the MR to be involved in female stress and anxiety related disorders by additional modification by female sex hormones. Support comes from Deuter et al., (2017) who report sex differences in decision making after stimulation of the MR (Deuter et al., 2017).

These results support the relevance of gender specific studies and treatment strategies in depression and anxiety. Clinical relevance is especially provided for patients with PA. They should be screened and if necessary be treated for psychiatric symptoms.

Strength and limitations

Limitation of this study is the small sample size of patients. Also, aldosterone was not measured in patients with depression. But to our knowledge, this is the first study to characterise patients with PA with sleep-EEG and psychiatric assessments.

Conflicts of interest

The authors have no conflict of interest to declare/none.

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Disclosure

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