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Cortisol is not associated with pre-treatment medial temporal lobe volume or volume changes after electroconvulsive therapy in patients with late-life depression

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ABSTRACT

Accumulating evidence suggests that late-life depression is associated with reduced hippocampal volume and that cortisol might be related to this volumetric reduction. We explored whether cortisol awaking response (CAR), which is the increase in cortisol after awakening, was associated with volumetric changes in the medial temporal lobe (MTL) after electroconvulsive therapy (ECT) in 41 patients (age ≥ 55) treated for major depressive disorder (MDD) with ECT. Cortisol was measured before the start of the ECT treatment and was related to MTL volumes derived from structural T1-weighted images. The study assessed associations between CAR and pre-treatment MTL volumes, and CAR and ECT-induced MTL volumetric changes. There were no significant correlations found between CAR, operationalized as Area Under the Curve with respect to ground (AUCg) and Area Under the Curve with respect to increase (AUCi), and pre-treatment MTL volumes. Neither was there an association between AUCg or AUCi and the ECT-induced changes in MTL volumes after correction for multiple comparisons. Finally, neither AUCg or AUCi were able to predict ECT-induced volumetric changes in the MTL. Hence, we conclude that CAR is unrelated to pre-treatment hippocampus and amygdala volumes, and to the volumetric changes in the aforementioned areas following ECT.

1. Introduction

A consistent finding in patients with major depressive disorder (MDD) is the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Belvederi et al., 2014; Fischer et al., 2017; Frodl and O'Keane, 2013; Stetler and Miller, 2011). Two recent meta-analyses confirmed that MDD is associated with hyperactivity of the HPA axis, in both depressed adults and elderly (Belvederi et al., 2014; Stetler and Miller, 2011). Furthermore, it has also been suggested that the suppression of corticotrophin-releasing hormone (CRH) is impaired in depressed individuals (Frodl and O'Keane, 2013). However, studies which used the cortisol awakening response (CAR), (the increase in cortisol levels occurring within the first hour after awakening) as an indicator of HPA axis dysfunction have yielded inconsistent results in MDD (Belvederi et al., 2014; Dedovic and Ngiam, 2015; Stetler and Miller, 2011; Vreeburg et al., 2009).

1.1. Cortisol and the medial temporal lobe in depression

HPA axis dysfunction (Belvederi et al., 2014; Fischer et al., 2017; Frodl and O'Keane, 2013; Knorr et al., 2010; Mckay and Zakzanis, 2010; Stetler and Miller, 2011) has been linked to structural brain changes (Arnone et al., 2012; Campbell et al., 2004; Geerlings and Gerritsen, 2017; Gerritsen et al., 2011; McKinnon et al., 2009; Schmaal et al.,

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2016; Sexton et al., 2013) in depressed individuals. These findings provide evidence for the so-called "neurotoxicity hypothesis", which proposes that chronic stress leads to chronic hypercortisolemia which in turn leads to neural atrophy due to the toxic effects of prolonged glucocorticoid dysregulation (Geerlings and Gerritsen, 2017; Lupien et al., 2007; O'Brien et al., 2004). This hypothesis is supported by evidence of chronic stress leading to dendritic atrophy and inhibition of the development of new neurons in the hippocampus of rats (McEwen, 2000). Further, there is evidence that cortisol secretion is negatively correlated with hippocampal volume in healthy humans (Frodl and O'Keane, 2013). Moreover, a meta-analysis confirmed that the inverse relationship between cortisol secretion and hippocampal volume was also present in patients with late-life depression (LLD) (Geerlings and Gerritsen, 2017).

Another region in the medial temporal lobe, the amygdala, has also been investigated with respect to cortisol and MDD. This region is known to activate the HPA axis under stress and has been a target for glucocorticoids (Herman et al., 2005). Furthermore, evidence from individuals exposed to trauma suggests a relationship between stress exposure and volumetric alterations of the amygdala (Cacciaglia et al., 2017). Specifically, individuals exposed to severe levels of stress had increased left amygdala volume, which in turn was associated with suppressed morning salivary cortisol (Cacciaglia et al., 2017). However, multiple studies investigating amygdala volumes in MDD patients found inconclusive evidence. In some studies, amygdala volume was decreased in patients with MDD (Kronenberg et al., 2009; Lorenzetti et al., 2009; Sacher et al., 2012; Schuhmacher et al., 2012), whereas other studies found an increase in amygdala volume in MDD patients (Lorenzetti et al., 2009; Schuhmacher et al., 2012). It has been argued that these inconclusive results are the outcome of a dynamic process of amygdala volumetric change in relation to depression (Lorenzetti et al., 2009). For example, one study found that amygdala volume was decreased in MDD patients in their first depressive episode, whereas it was increased in MDD with recurrent episodes (Schuhmacher et al., 2012).

1.2. Cortisol and electroconvulsive therapy-induced medial temporal lobe volume changes

Considering neuronal loss following aberrant cortisol secretion in MDD, treatment of MDD should be accompanied by an increase in neuronal growth, which is confirmed by the literature (Brunoni et al., 2008). Neuronal growth and volumetric increases are especially evident following electroconvulsive therapy (ECT) (Madsen et al., 2000), which is a highly effective and safe treatment for MDD (Geduldig and Kellner, 2016). Notably, the volumetric increase in hippocampal volume associated with ECT contrasts with the volumetric decrease associated with the toxic effects of cortisol (Bouckaert et al., 2016a; Gbyl and Videbech, 2018; Takamiya et al., 2018) suggesting ECT may (partially) normalise hypercortisolemia-induced atrophy. Volumetric increases in the amygdala region have also been observed after ECT treatment (Joshi et al., 2016; Takamiya et al., 2018; Tendolkar et al., 2013). However, the origin of these ECT-induced volumetric changes, which are transient (Bouckaert et al., 2016b; Jorgensen et al., 2016; Nordanskog et al., 2014) and unrelated to the clinical outcome (Oltedal et al., 2018; Wilkinson et al., 2017), are still undetermined. Considering the relation between cortisol and neural atrophy, it is relevant to investigate whether cortisol secretion is associated with the volumetric changes following ECT. Two meta-analyses concluded that during ECT, an initial rise in plasma cortisol levels is observed, which subsequently appears to be reduced after the termination of ECT (Mckay and Zakzanis, 2010; Yrondi et al., 2018). This initial rise in plasma cortisol levels could be explained by an acute stress reaction during ECT (Yrondi et al., 2018). The changes in cortisol levels following ECT treatment appear to be unrelated to the clinical outcome (Mckay and Zakzanis, 2010).

It should be noted that the methodology used to measure hippocampal and amygdalae structures may also influence study findings. Given there is no universal standard for delineation of MTL structures, hippocampal and amygdala volumes may be obtained using different methods. Automatic methods are efficient and highly reproducible, whereas manual approaches are considered to be more accurate (Frisoni et al., 2015; Zandifar et al., 2017). Indeed manual delineation is considered the gold-standard approach for hippocampal measurement, but it is labour intensive and time-consuming (Frisoni et al., 2015; Zandifar et al., 2017). Both their approaches have their merits and are widely applied in morphometry studies, yet rarely in the same analysis. Therefore, confirming findings using both approaches improves confidence in the study outcomes.

In this study, we investigated the relationship between cortisol secretion, measured as CAR, and the pre-treatment volumes of the hippocampus and amygdala. We hypothesized that elevated CAR levels would be associated with reduced hippocampal and altered amygdala volumes in accordance with the literature. Further, we explored the association between CAR and volumetric changes in the MTL (including hippocampus and amygdala) following ECT. With respect to the role of cortisol in neuroplasticity and atrophy, we hypothesized that higher values of CAR are related to smaller ECT-induced volumetric changes.

2. Methods

2.1. Study sample

Patients were included from the Mood Disorders in Elderly treated with ECT (MODECT) study (Dols et al., 2017), which included depressed in-patients ($n = 110$) from two centers; GGZinGeest Amsterdam, the Netherlands and the University Psychiatric Center KU Leuven, Belgium. Patients were older than 55 years, were hospitalized, had a diagnosis of MDD according to DSM-IV criteria as assessed by the Mini International Neuropsychiatric Interview (MINI), and consented with ECT treatment (Dols et al., 2017). Exclusion criteria included: comorbid major psychiatric illness (based on the MINI), alcohol or drug dependence, major neurological illness (including Parkinson disease, stroke, and dementia), metal implants precluding MRI, and the use of corticosteroids. The study was approved by both center's ethical committees and was conducted according to the declaration of Helsinki (Dols et al., 2017).

2.2. ECT procedure

As described previously by Dols et al. (2017), patients received right unilateral (RUL) brief-pulse ECT (0.5 – 1.0 ms) twice a week in agreement with the Dutch standards (van den Broek et al., 2010). If the patient did not respond to the treatment after six sessions of RUL ECT, they were switched to bilateral (BL) stimulation. ECT treatments were conducted with the Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA) (maximum energy 200%, 1,008 C). Empirical dose titration was used to determine stimulus intensity at the first treatment. The stimulus intensity for RUL ECT was six times the initial seizure threshold and 1.5 times the seizure threshold for BL ECT. If a motor seizure lasted less than 20 s the dose was subsequently raised according to Dutch guidelines (van den Broek et al., 2010).

2.3. Measurements

2.3.1. Salivary cortisol and CAR

The procedure to collect salivary cortisol has been thoroughly described in Suijk et al. (2018). Salivary cortisol was collected before the start of the ECT treatment ($n = 102$). Salivettes were used to take saliva samples at time of awakening (Timepoint 1) and, 30 (Timepoint 2), 45 (Timepoint 3), and 60 min (Timepoint 4) after awakening. Patients received clear instructions concerning saliva sampling (e.g. eating, drinking, etc.). Salivettes were placed in tubes labelled with time and

date. The tubes were centrifuged (using Eppendorf Centrifuge 5702 R) at 3000 rotations a minute for 10 min. Samples were stored at −21 °C. An automated immunoassay (ECLIA) was used to determine the salivary cortisol concentration in each time sample.

As described in Suijk et al. (2018), the area under the curve to the ground (AUCg) and to the increase (AUCi) were calculated from the samples (Timepoint 1 to 4) using Pruessners formula (Pruessner et al., 2003). AUCg estimates the total cortisol secretion within the first hour after awakening, and AUCi is a measure of the dynamics of the cortisol awakening response related to the sensitivity of the system (Pruessner et al., 2003; van Santen et al., 2011). A complete set of samples (Timepoint 1 to 4) was available for 18 patients. For patients with one or two missing values ($n = 42$), the missing value was imputed using linear regression analysis including information on the 2 or 3 available cortisol values (Rhebergen et al., 2015). Hence, the cortisol awakening response was calculated for a total of 60 patients.

2.3.2. MRI acquisition and volumetric measurements

Structural MRI was performed 1 week before the start of ECT (Pretreatment, $n = 74$), and one week after the last ECT session (Posttreatment, $n = 68$). As described by Bouckaert et al. (2016a), high-resolution 3D T1-weighted images were acquired using an eight-channel head-coil with a 3D turbo field echo sequence on a 3T Philips Intera scanner in Leuven and on a 3T GE Signa HDxt scanner in Amsterdam under the following parameters: repetition time 9.6 ms, echo time 4.6 ms, flip angle 8°, slice thickness 1.2 mm, in-plane voxel size $0.98 \times 0.98 \times 1.2$ mm^3, 182 slices, acquisition time 383 s.

Automatic segmentation of the hippocampus and the amygdala was performed using Freesurfer 6.0.0 with default settings (http://surfer.nmr.mgh.harvard.edu). Before automatic delineation, T1 images were pre-processed with bias correction using N4ITK (Tustison et al., 2010). In a small number of cases, voxels containing dura mater were included in the white matter mask. These were removed by masking out voxels within 3mm of the brain boundary using binary erosion of the brain mask. For subjects with multiple time points, the standard longitudinal pipeline (Reuter et al., 2012) was applied to perform refinement of cross-sectional results. Amygdala and hippocampal volumes were taken from whole-brain segmentation images. Manual segmentation of the hippocampus was performed by a single-trained rater blinded to time point using ITK-SNAP version 2.4 (http://www.itksnap.org/pmwiki/pmwiki.php) in accordance with the HarP guidelines (Frisoni et al., 2015) as part of prior analysis on this dataset (Bouckaert et al., 2016a). No manual segmentation data was available for the amygdala. All hippocampal and amygdala volumes were normalized using total intracranial volume obtained from an automated segmentation of grey matter, white matter, and cerebrospinal fluid (Jain et al., 2015) according to Jack et al. (1989).

2.4. Statistical analysis

Subjects were excluded from analysis when structural imaging was incomplete, the delineation process was inadequate, when three or more salivary cortisol measurements were absent, or when cortisol values differed by more than two standard deviations from the average. We conducted separate analysis of variance (ANOVA) calculations to assess effects of gender, site (Amsterdam vs. Leuven), presence of psychotic features, level of alcohol use, level of smoking and early vs. late-onset depression on CAR in our sample. To test whether hippocampal and amygdala volumes changed significantly over time, change in hippocampal and amygdala volumes were analysed using a paired-samples *t*-test (Bonferroni correction). Pearson correlations were used to analyse associations between CAR and hippocampal and amygdala volumes at different time points and were corrected for multiple comparisons (Bonferroni correction). Multiple linear regression was used to examine whether change in hippocampal or amygdala volume could be predicted by CAR. The dependent variable, volumetric change, was calculated as the percentage change in volume from pre-treatment to posttreatment. To examine the relation between ECT-induced volumetric changes in the medial temporal lobe and CAR, separate regression models were used for each distinct subfield (and delineation method) with AUCg and AUCi as main predictors. The manually delineated and the automatically delineated hippocampal volumes were analysed in parallel. The analyses were controlled for age and number of previous depressive episodes. The assumption of normality was assessed via visual inspection of the Q-Q plots and a Kolmogorov-Smirnov test on the residuals. Assessment of the assumption of equal variance was performed by visual inspection of the residuals (vs. fitted values) plots, and the linearity assumption was checked via visual inspection of the residuals (vs. predictor) plots.

3. Results

3.1. Clinical and demographical characteristics

Of the 110 patients included in the MODECT study, 60 patients had CAR data and 65 patients had complete structural MRI data. A total of 41 patients (63% female, 56% Leuven) had both adequate CAR and structural MRI data and met the criteria to be included in the analysis. The average age of our sample was 70.8 years (range 55 – 87, SD = 8.11). Twenty patients (49%) had late-onset depression, 19 patients (46%) presented psychotic features, and the average number of depressive episodes was 3.5 (range 1 −15, SD = 3.56) including the present one. Fourteen patients (34%) had a first-time depressive episode. Twenty-three patients (57%) reported that they did not drink alcohol, 7 (17%) and 10 (25%) patients reported that they drank alcohol on a monthly or weekly basis respectively. Twenty-two patients (54%) stated that they had never smoked, three patients (7%) reported to have smoked in the past, 8 patients (19%) were still smoking during the study, and 8 patients (20%) failed to report their smoking habits.

3.2. Cortisol awakening response

The average AUCg of CAR was 6.83 ($n = 41$, SD = 3.10, range 1.65 – 12.44) and the average AUCi of CAR was 6.02 ($n = 41$, SD = 2.95, range 1.15 – 11.44). The individual trajectories of morning salivary cortisol levels from which AUCg and AUCi are derived are depicted in Fig. 2. The correlation between both CAR parameters is high ($r(39) = .99$, $p < .001$). Hence, for further analyses, only AUCg was used due to multicollinearity, and AUCg and AUCi are not discussed separately. In our sample, CAR was not correlated with age ($r(39) = -.12$, $p = .436$) nor with number of previous depressive episodes ($r(39) = .19$, $p = .227$). Further, a one-way analysis of variance (ANOVA) revealed no effect of early vs. late-onset depression ($F(1,39) = 0.06$, $p = .805$), presence of psychotic features ($F(1,39) = 3.41$, $p = .072$), gender ($F(1,39) = 0.04$, $p = .847$), study centre ($F(1,39) = 0.57$, $p = .455$), alcohol consumption ($F(4,35) = 1.70$, $p = .171$) or smoking habit ($F(2,30) = 0.34$, $p = .715$) on CAR.

3.3. Hippocampal volume

Manual delineation revealed an average normalized left and right hippocampal pre-treatment volume of respectively 3393.87 (SD = 394.38) mm^3 and 3437.21 (SD = 439.08) mm^3. The average normalized left and right hippocampal volume one week after ECT was respectively 3497.33 (SD = 416.18) mm^3 and 3593.77 (SD = 482.90) mm^3. Paired t-tests revealed a significant increase in both left ($t(40) = -4.41$, $p < .0001$) and right ($t(40) = -5.13$, $p < .0001$) hippocampal volume after ECT (Fig. 1), which remained significant after correction for multiple comparisons (Bonferroni method). The average increase in left and right hippocampal volume was 3.11% and 4.64% respectively.

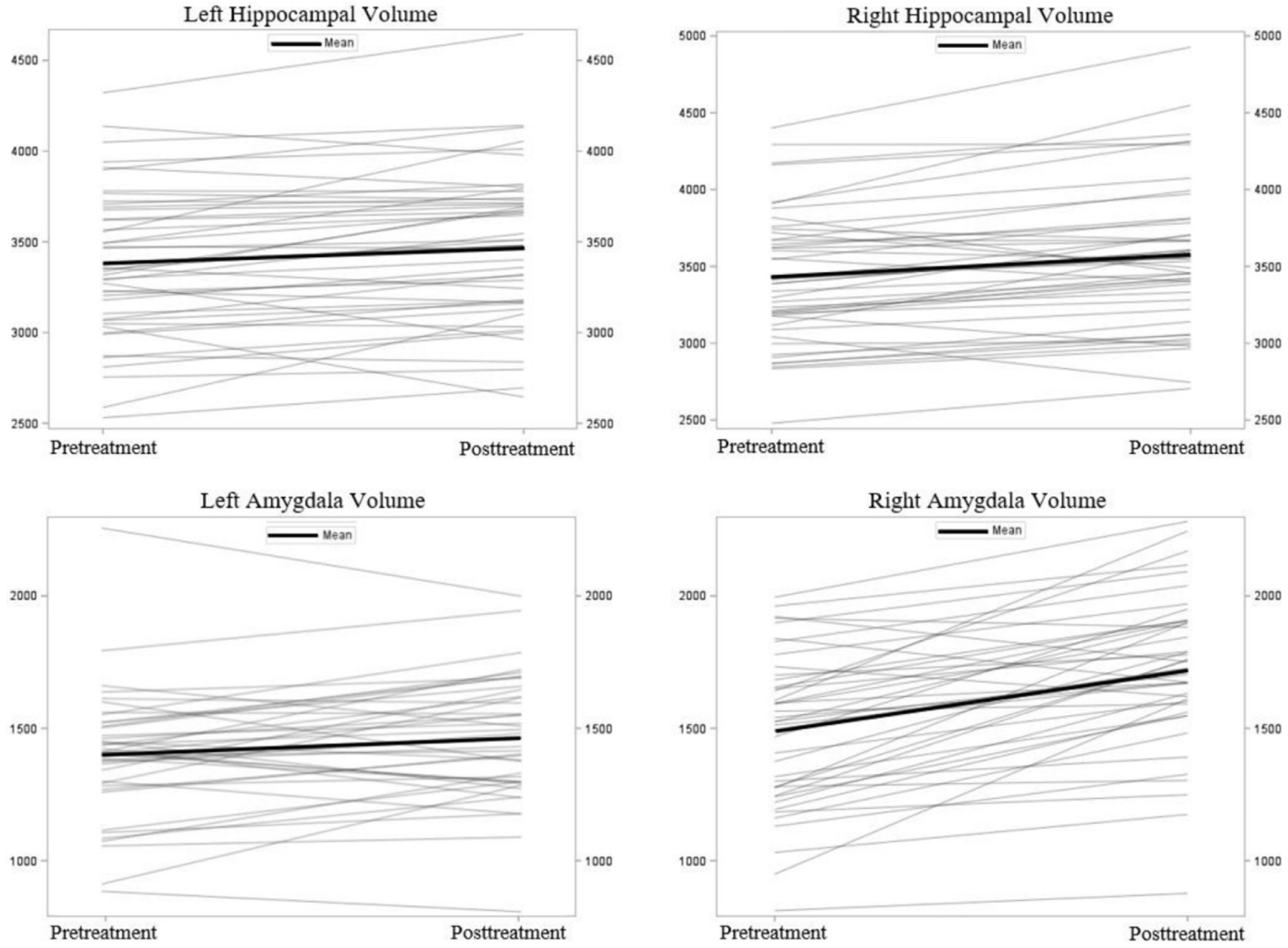

Fig. 1. Paired profiles for volumetric changes in hippocampus and amygdala from pretreatment to posttreatment.

Automatic delineation indicated an average normalized left and right pre-treatment volume of respectively 3427.63 (SD = 392.72) mm^3 and 3478.07 (SD = 417.15) mm^3. The average normalized left and right hippocampal volume one week after ECT was respectively 3554.16 (SD = 402.29) mm^3 and 3665.78 (SD = 426.68) mm^3. Paired t-tests revealed a significant increase in both left ($t(40) = -6.72$ $p <$ .0001) and right ($t(40) = -8.98$, $p < .0001$) hippocampal volume after ECT, and remained significant after correction for multiple comparisons (Bonferroni method). The average increase in left and right hippocampal volume was 3.71% and 5.49% respectively.

3.4. Amygdala volume

Automatic delineation revealed that the average normalized left and right amygdala pre-treatment volume were respectively 1313.60 (SD = 199.32) mm^3 and 1583.93 (SD = 214.55) mm^3. The average normalized left and right amygdala volume one week after ECT was respectively 1378.52 (SD = 188.83) mm^3 and 1733.51 (SD = 230.41) mm^3. Paired t-tests revealed a significant increase in both left ($t(40) = -5.20$, $p = < .0001$) and right ($t(40) = -9.66$, $p < .0001$) amygdala volume after ECT (Fig. 1), and remained significant after correction for multiple comparisons (Bonferroni method). The average increase in left and right amygdala volume was 5.28% and 9.61% respectively.

3.5. Association between cortisol awakening response and pre-treatment hippocampal or amygdala volume

There were no significant correlations between CAR (defined as AUCg) and either left ($r(39) = .003$, $p = .983$) or right ($r(39) = .13$, $p = .434$) manually delineated hippocampal pre-treatment volume or left ($r(39) = -.03$, $p = .872$) or right ($r(39) = .02$, $p = .892$) automatically delineated hippocampal pre-treatment volume. The same is true for left ($r(39) = .05$, $p = .736$) and right ($r(39) = .08$, $p = .632$) amygdala pre-treatment volume.

3.6. Association between cortisol awakening response and increase in hippocampal or amygdala volume

There were no significant correlations between CAR (defined as AUCg) and either left ($r(39) = .21$, $p = .170$) or right ($r(39) = -.07$, $r = .707$) hippocampal volume change (defined as percentage change) following ECT as measured by manual delineation. These results were consistent with the automatic delineation method. Neither left or right hippocampal volume change correlated with CAR (left: $r(39) = -.21$, $p = .180$; right: $r(39) = -.14$, $p = .39$). Further, both left ($r(39) = -.05$, $p = .775$) and right ($r(39) = -.01$, $p = .952$) amygdala volume change were uncorrelated to CAR.

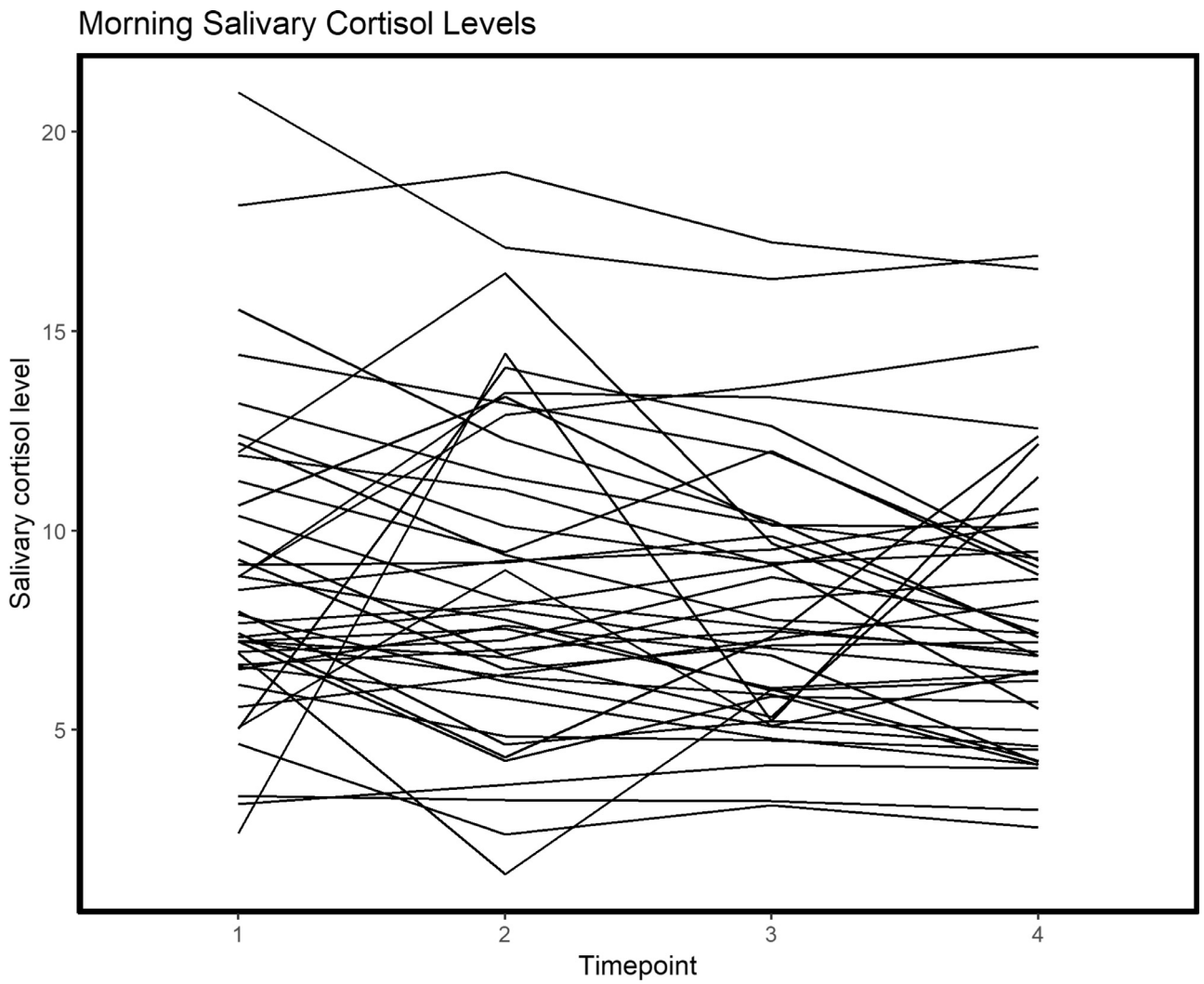

Fig. 2. Spaghetti plot showing the individual trajectories of the measured morning salivary cortisol levels from awakening (timepoint 1) to 60 min later (timepoint 4).

3.7. Prediction of ECT-induced medial temporal volume increase by cortisol awakening response

Separate multiple linear regression models were used to determine whether CAR (defined as AUCg) could predict ECT-volumetric changes in the hippocampus and amygdala. Table 1 summarizes the associations between CAR (defined as AUCg) and hippocampal and amygdala volume changes independently for each hemisphere and delineation method. The assumptions of normality, linearity and equal variance were met in all separate regression models. No significant effects of CAR on the volumetric changes in the MTL were found in our sample. This finding remains after adjusting the linear regression models for age and number of depressive episodes (Table 2). The overall conclusion is that CAR was not associated with ECT-induced volumetric changes in the medial temporal lobe in our sample.

Table 1
Associations between salivary cortisol and percentage volumetric change following ECT treatment. Linear prediction of volumetric change (%) by CAR expressed as AUCg.

		Manual delineation Hippocampus change left	change right	Automatic delineation Hippocampus change left	change right	Amygdala change left	change right
Model	$F_{1, 39}$	1.95(.170)	0.14 (.707)	1.86 (.180)	0.74 (.393)	0.08 (.775)	0.00 (.952)
Predictor variables							
Intercept	β	0.99	3.91	5.49	6.71	5.91	9.76
	p	(.555)	(.070)	(< .001)	(< .001)	(.018)	(< .001)
AUCg	β	0.31	1.11	−0.26	−0.18	−0.09	−0.02
	p	(.170)	(.707)	(.180)	(.394)	(.775)	(.952)

AUCg: Area under the curve with respect to the ground Change expressed in% *$p < 0.05$.

Table 2
Associations between salivary cortisol and percentage volumetric change following ECT treatment, adjusting for age and number of depressive episodes. Linear prediction of volumetric change (%) by CAR expressed as AUCg.

		Manual delineation Hippocampus		Automatic delineation Hippocampus		Amygdala	
		change left	change right	change left	change right	change left	change right
Model	$F_{1, 37}$	3.09*	2.01	0.15	0.24	0.23	1.17
		(.039)	(.130)	(.929)	(.865)	(.873)	(.341)
Predictor variables							
Intercept	β	−9.30	−3.95	5.52	6.53	−3.25	−10.95
	p	(.138)	(.617)	(.367)	(.284)	(.798)	(.39)
AUCg	β	0.26	0.01	−0.02	0.07	−0.01	0.26
	p	(.232)	(.960)	(.929)	(.718)	(.976)	(.571)
Age	β	0.13	0.09	−0.03	−0.02	0.13	0.27
	p	(.130)	(.400)	(.658)	(.833)	(.418)	(.107)
Number of depressive episodes	B	0.47*	0.63	0.08	−0.16	0.08	−0.22
	p	(.033)	(.027)	(.682)	(.434)	(.839)	(.620)

AUCg: Area under the curve with respect to the ground Change expressed in%.
* $p < 0.05$.

4. Discussion

This study examined the association between CAR and pre-treatment hippocampal and amygdala volume and, ECT-induced hippocampal and amygdala volume change in patients with late-life depression treated with ECT. None of the analyses revealed an association between CAR and pre-treatment MTL volumes, or CAR and ECT-induced volumetric changes in the MTL.

In our study population, CAR was not correlated with age. This is somewhat unexpected since two meta-analyses demonstrated that increasing age was associated with increased cortisol levels in depressed adults (Belvederi et al., 2014; Stetler and Miller, 2011). In both of these studies, the effect of depression on cortisol levels was found to be smallest in the morning (Belvederi et al., 2014; Stetler and Miller, 2011), which is when cortisol levels were measured in our study. This could partially explain why our study using CAR as an indicator for HPA axis function was unable to demonstrate a relationship with age. Another possible explanation for the absence of a relation of CAR with age could be the limited age range in our sample. Furthermore, in our sample, we did not detect any effects of early vs. late-onset depression, presence of psychotic features, gender, site, alcohol consumption or smoking habit on cortisol levels.

Our study did not find an association between CAR and pre-treatment hippocampal or amygdala volume. This is in contrast to a meta-analysis in patients with late-life depression which did report a negative correlation between cortisol levels and hippocampal volume (Geerlings and Gerritsen, 2017). However, both cortisol levels and hippocampal volume have been shown to be age-dependent in depressed individuals, so it could be possible that the previously mentioned meta-analysis measured an indirect relationship between both parameters (Geerlings and Gerritsen, 2017), however, this mediation by age is not supported by our data. Two smaller studies in elderly depressed patients that adjusted for age did not find a relation between cortisol levels and hippocampal volume (Gerritsen et al., 2011; O'Brien et al., 2004). Our negative findings relating to CAR and pre-treatment amygdala volume are in line with the findings of a more recent study in which no association was found between amygdala volume and HPA reactivity (Barry et al., 2017). Furthermore, reviews on the relation between amygdala volume, cortisol and depression revealed inconclusive results (Lorenzetti et al., 2009; Sacher et al., 2012).

To our knowledge, no previous studies have assessed the relationship between HPA axis function and hippocampal or amygdala volume change following ECT treatment in depressed individuals. In our sample, CAR was not related to either hippocampal volume or amygdala volume increase following ECT. However, it should be kept in mind that neither changes in cortisol levels, nor changes in hippocampal or amygdala volume have previously been shown to be related to clinical outcome after ECT treatment (Bouckaert et al., 2016b; Mckay and Zakzanis, 2010; Suijk et al., 2018; Wilkinson et al., 2017). Specifically, within the larger MODECT study from which these data are taken, neither pre-ECT cortisol levels (Suijk et al., 2018) or MTL volume changes (Bouckaert et al., 2016b) were related to the clinical outcome of ECT in our sample. Furthermore, the mechanism underlying the volumetric increase seen after ECT in humans has yet to be determined. It is therefore not yet known if and to what extent neuroplastic changes or a non-neurobiological process like oedema contribute to the observed volume changes (Mander et al., 1987). Hence, the increase in volume could be unrelated to neurobiological processes like cortisol reactivity. The notion that the increase in volume is related to solely neurobiological processes is less evident when we consider the size of MTL-volume changes related to depression in comparison to the size of changes observed after ECT. The ENIGMA consortium compared hippocampal volume data from 1728 MDD patients to 7199 controls and identified a robust, but a small decrease of 1.24% in MTL-volumes in MDD patients compared with controls (Schmaal et al., 2016). In contrast, the average changes in MTL-volumes following ECT in our sample ranged between 3 and 9%. However, our relatively small sample needs to be kept in mind when comparing it with the ENIGMA study (Schmaal et al., 2016). In comparison, the GEMRIC mega-analysis (Oltedal et al., 2018) on MTL-volume changes following ECT in a younger population ($n = 281$) reported a 0.28% increase in right hippocampal volume per ECT session (mean no. ECT per patient = 12), which translates to roughly 3.3% increase on average after an acute treatment of ECT. Disentangling the mechanisms underlying the origin of grey matter changes following ECT is an active area of research which will prove useful for the future interpretation of clinical neuroimaging studies. There are a number of methodological limitations that require consideration when interpreting the findings of this study. Firstly, we used a non-invasive procedure to measure HPA function. Salivary sampling was the preferred method to assess cortisol levels in our depressed sample. However, it is known that the effect of depression on cortisol levels is smaller when salivary samples are used (Knorr et al., 2010; Stetler and Miller, 2011). Secondly, cortisol levels were only measured on one day, yet CAR fluctuates considerably from day to day (Almeida et al., 2009), and is sensitive to environmental factors and lifestyle characteristics (Dedovic and Ngiam, 2015). Even though our analyses were adjusted for confounders, controlling for intrapersonal variability would have been more successful if CAR was measured on two or more separate occasions. Furthermore, as this study was part of the larger MODECT study (Dols et al., 2017) as a secondary objective, a power analysis had not been conducted with regard to cortisol. Consequently, the absence of such an analysis could

have led to low statistical power to detect meaningful relations between cortisol and MTL-volume changes.

Further, it is important to note the observed discrepancy between the two different delineation methods used to measure hippocampal volume in our study. Manual delineation by appropriately trained researchers is believed to be more anatomically accurate than automated procedures (Frisoni et al., 2015). This could be the reason why in our sample the automatic delineated hippocampal volumes showed a larger variability than the manually delineated volumes. Hence, due caution is required when interpreting findings based on automated delineation methods in small populations. However, manual delineation requires extensive training and may be prohibitively time-consuming for larger studies. State-of-the-art, well-validated methods such as the Freesurfer 6.0.0 longitudinal pipeline that we used in this study, represent a suitable and reproducible alternative. As manual delineation of the amygdala was not available, we opted to include automatic delineation for this region in our analysis and to include the automatically delineated hippocampal volumes as well for methodological consistency.

In our study, CAR, a measure of HPA axis functionality, was found to be unrelated to pre-treatment hippocampal and amygdala volume and ECT-induced hippocampal and amygdala volume changes in patients with late-life depression treated with ECT. These findings provide no support for the hypothesis that cortisol has a role in hippocampal volume and amygdala changes in patients with late-life depression, nor in the ECT-induced increase of hippocampal and amygdala volume.

CRediT authorship contribution statement

Maarten Laroy: Formal analysis, Writing - original draft, Writing - review & editing. **Justien Weydts:** Formal analysis, Writing - review & editing. **Kristof Vansteelandt:** Formal analysis, Writing - review & editing. **Louise Emsell:** Data curation, Writing - review & editing. **Christopher Adamson:** Formal analysis, Writing - review & editing, Software. **Pascal Sienaert:** Data curation, Writing - review & editing. **Annemiek Dols:** Conceptualization, Data curation, Writing - review & editing. **Didi Rhebergen:** Data curation, Writing - review & editing. **Max Stek:** Data curation, Writing - review & editing. **Mathieu Vandenbulcke:** Data curation, Writing - review & editing. **Filip Bouckaert:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.07.006.

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