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Grey Matter changes in treatment-resistant depression during electroconvulsive therapy  
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## Introduction

20–30% of depressed patients experience Treatment Resistant Depression (TRD).

Electroconvulsive Therapy (ECT) remains the treatment of choice for TRD. However, the exact mechanism of ECT remains unclear. We aim to assess grey matter changes in patients with TRD undergoing bilateral ECT treatment at different points during and after treatment.

## Methods

Patients are recruited at the University Hospital of Toulouse. Eligibility criteria include a diagnosis of TRD and an age between 50 and 70 years old. Patients received clinical assessments (Hamilton Depression Rating Scale) and structural scans (MRI) at three points: baseline (within 48 h before the first ECT); V2 (after the first ECT considered effective); and V3 (within 1 week of completing ECT).

## Results

At baseline, controls had significantly higher cortical thickness than patients in the fusiform gyrus, the inferior, middle and superior temporal gyrus, the parahippocampal gyrus and the transverse temporal gyrus (respectively:  $t(35)=2.7$ ,  $p=.02$ ;  $t(35)=2.89$ ,  $p=.017$ ;  $t(35)=3.1$ ,  $p=.015$ ;  $t(35)=3.6$ ,  $p=.009$ ;  $t(35)=2.37$ ,  $p=.031$ ;  $t(35)=2.46$ ,  $p=.03$ ). This difference was no longer significant after ECT. We showed an increase in cortical thickness in superior temporal gyrus between (i) baseline and V3 ( $t(62)=-3.43$   $p=.009$ ) and (ii) V2 and V3 ( $t(62)=-3.42$   $p=.009$ ). We showed an increase in hippocampal volume between (i) baseline and V3 ( $t(62)=-5.23$   $p<.001$ ) and (ii) V2 and V3 ( $t(62)=-5.3$   $p<.001$ ).

Conclusion: We highlight that there are grey matter changes during ECT treatment in a population with TRD compared to a healthy control population. These changes seem to occur after several rounds of ECT.

Keywords: Treatment Resistant Depression; Electroconvulsive therapy; MRI; Cortical

thickness; Hippocampus; Amygdala.

## 1. Introduction

With more than 300 million people affected and a high lifetime prevalence of between 16–17% in the general population (Kessler et al., 2005), major depressive disorder (MDD) is an increasingly widespread illness and a leading cause of disability worldwide (“WHO | Depression,” n.d.). Beyond its social costs and economic burden (Mrazek et al., 2014), MDD induces both psychological and physical suffering through a broad range of health consequences (Lépine and Briley, 2011) (i.e. increased risks of suicidal behaviour or cardiovascular death). Treatment-resistant depression (TRD) has been estimated to represent half of the overall treatment costs for major depression (Greden, 2001; Olsen et al., 2004). It can be assumed that approximately between 20-30% of depressed patients experience TRD (Rush et al., 2006), and up to one-half of patients only respond to treatment partially (Fava and Davidson, 1996). TRD is currently defined as the failure of at least two sequential courses of antidepressant treatments, administered at an appropriate dose and for the corresponding duration (Berlim and Turecki, 2007; Fava and Davidson, 1996). TRD is known to have a heterogeneous aetiology. Some sources of variability include different environmental risk factors (e.g., childhood adversities), multiple genetic determinants (related to numerous genetic loci), and various epigenetic contributors (e.g., hypothalamic–pituitary–adrenal axis, immune function, monoamines, neurotrophic factors, etc. (El-Hage et al., 2013; Fava and Davidson, 1996; Greden, 2001; Malhi et al., 2005; Olsen et al., 2004)). Moreover, our clinical approach to TRD may be suboptimal. Despite these sources of variability, Electroconvulsive Therapy (ECT) continues to be the treatment of choice for severe TRD (Fink and Taylor, 2007).

However, the exact mechanism of ECT remains unclear. There are many hypotheses that can explain its efficacy, albeit only in part: involvement of (i) monoamine pathway (for details, see (Rudorfer et al., 2003)), (ii) immune inflammation (for details, see (Yroni et al., 2017))

(iii) neuroplastic changes (for details, see (Andrade, 2014a, 2014b; Taylor, 2008)) and brain functional connectivity changes (Mulders et al., 2016). Currently, most structural neuroimaging studies focus on changes in hippocampal and amygdala volume after ECT (Gbyl and Videbech, 2018; Oltedal et al., 2018). Furthermore, most of these studies focus on changes in the volume of these structures between baseline and the end of treatment. Only Joshi et al. (Joshi et al., 2015) included an MRI after 2 sessions of ECT. In addition, only one study focused on Treatment Resistant Depression (TRD) (Gryglewski et al., 2018). There are a total of only 4 studies that focus on cortical thickness (Gryglewski et al., 2018; Pirnia et al., 2016; Sartorius et al., 2016; van Eijndhoven et al., 2016). Only one study focused on Treatment Resistant Depression (TRD), but without including comparisons to a control group (Gryglewski et al., 2018). One single study assessed cortical thickness during ECT (after 2 sessions of ECT), even though ECT (with both right unilateral-RUL and bilateral-BL ECT) and diagnosis (21 unipolar disorders/5 bipolar disorders) are heterogeneous (Pirnia et al., 2016). Two other studies only assessed cortical thickness after the treatment (Sartorius et al., 2016; van Eijndhoven et al., 2016).

In light of these disparate results in the literature, we aim to assess grey matter changes at different time points during and after ECT BL treatment in patients with TRD (unipolar disorder).

## 2. Methods

### 2.1. Participants

Patients scheduled to begin ECT at the University Hospital of Toulouse were recruited into the study if they had been diagnosed with TRD (Thase and Rush  $\geq 2$  (Thase and Rush, 1997)) and were between 50 and 70 years of age. Patient diagnoses were established by clinical consultation using the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM

5) (APA, 2013) criteria with Structured Clinical Interview (SCID-5) (First et al., 2016).

Patients with independently diagnosed comorbid psychiatric disorders including schizophrenia, schizoaffective disorders, bipolar disorder, post-traumatic stress disorder, attention hyper- active deficit disorder, dissociative disorders, and patients independently diagnosed with anxiety disorders were excluded from the study. Other exclusion criteria included comorbidity of dementia, Traumatic Brain Injury (TBI), depression related to a medical condition, ECT or other neuromodulation therapies in the previous 6 months, or ECT and anaesthesia contraindications.

Demographically similar healthy controls were recruited from the Toulouse area and screened with the M.I.N.I. to exclude a history of depression, other psychiatric illness, and antidepressant use. Additional exclusion criteria for our patients included a history of alcohol or substance abuse within 6 months and/or dependence within 12 months of participation, neurological disorders, or conditions contraindicated for magnetic resonance imaging (MRI). The antidepressant treatment was not modified once a patient was included in the study.

Of a total of 17 patients were enrolled in the study. We were able to collect data for all three time points for 15 of these patients (6 females and 9 males) (Table 1). Of the 2 patients who were lost to the study, one continued ECT without MRI assessment and the other discontinued ECT early.

All participants provided written informed consent as required by the CPP Sud Ouest Outre Mer 4 (CPP15-053) (i.e. the 4th ethics research committee of south western France and French overseas territories)

## 2.2 Data acquisition

Patients were assessed clinically and by structural scans (MRI) at three time points: V1 (baseline) completed within 48 hrs prior to the first ECT; V2 completed within the first ECT

that was considered effective; and V3 completed within 1 week of completing ECT.

### 2.2.1. Clinical assessment

The 17-item Hamilton depression rating scale (HAM-D) was administered at each visit to assess symptoms and treatment responses.

### 2.2.2. ECT<sub>SEP</sub>

ECT (5000Q MECTA, Tualatin, OR, USA) was administered twice a week, using a standard protocol for anaesthesia (propofol) and paralysis (succinylcholine). ECT followed the seizure threshold (ST) titration method, where following establishment of the ST, treatments were delivered at 1.5 to 2× ST for BL (using brief pulse width). The length of ECT is determined on an individual clinical basis. Patients received a mean of 12.07 ECTs (Table 1).

### 2.2.3. MRI acquisition and analysis

High-resolution T1-weighted structural scans were acquired using a Philips 3 Tesla (Intera Achieva, Philips, Best, The Netherlands) (170 sagittal slices; scan mode: 3D; multishot; contrast T1; voxel resolution (mm<sup>3</sup>): 1.00 x 1.00 x 1.00)

Structural images were processed using the FreeSurfer's image analysis pipeline (version 5.3.0). To extract reliable volume and thickness estimates, images were automatically processed with the longitudinal pipeline in FreeSurfer (Reuter et al., 2012). Specifically, a template space and intra-topic image (Reuter and Fischl, 2011) are created using robust coregistration (Reuter et al., 2010). Several processing steps, such as skull extraction, Talairach transformations, atlas recording, as well as surface maps and parcellations were



then initialised with common information from the internal model, thereby significantly increasing reliability and statistical power (Reuter et al., 2012). The automated volumetric segmentation of the grey matter and various structures, including the hippocampus and amygdala, was performed in this manner (Fischl et al., 2004, 2002). Segmentations of the various structures were visually reviewed by two independent evaluators (AY and PP). The thicknesses in each region of the FreeSurfer atlas were obtained from FreeSurfer's \*.aparcs.stats files. The FreeSurfer cortical thickness algorithm calculates the average distance between the vertices of a corrected and triangulated estimated GM/WM surface and the GM/CSF (pial) surface (Fischl and Dale, 2000).

### 2.3. Statistical analysis

Analyses of demographic data and associations between clinical and anatomical data were performed using SPSS (IBM SPSS Statistics for Mac OS, Version 20.0, Armonk, NY, USA). The Chi2 test was used to compare categorical variables (gender) and the t-test was used to compare continuous variables (age) between groups. A linear regression analysis was used to assess associations between independent variables (delta HAM-D between V1 and V3) and dependent variables (hippocampus and amygdala volume changes). Repeated measures ANOVA was used to compare HAM-D throughout the time series.

Analyses of cortical thickness and subcortical nuclei volumes were performed using R (R Core Team, 2017) and the “nlme” and “lsmeans” packages (Pinheiro et al., 2017).

Cross-sectional data at visit 1 and visit 3 were analysed using mixed-effect linear models. The fixed effect part included cortical thickness or subcortical nuclei volume (normalised for total intracranial volume) as dependent variables and as a group, and regions and their interaction

as independent variables. The model also included age and sex in order to correct for any possible effects of these variables on cortical thickness and subcortical nuclei volumes. The random effect included a random intercept for each subject.

$$CT/Normalised\ Volume - Baseline/V_{3ij} = \beta_0 + \beta_1 Group + \beta_2 Frontal\ Regions/Temporal\ Regions/Subcortical\ Nuclei + \beta_3 Group \times Frontal\ Regions/Temporal\ Regions/Subcortical\ Nuclei + \beta_4 Age + \beta_5 Sex + u_{0i} + \epsilon_{ij}$$

For all significant effects identified, we performed post-hoc comparisons using false discovery rate (FDR) corrections. If the interaction between region and group was significant, we followed up with planned comparisons: by comparing the two groups within each region/nucleus with FDR correction.

Longitudinal data was analysed using mixed-effect linear models. The fixed-effect part included cortical thickness of subcortical nuclei volume (normalised for total intracranial volume) as a dependent variable and visit, group, and their interaction as independent variables. The model also included age and sex in order to correct for any possible confounding effects introduced by these variables.

$$CT/Normalised\ Volume_{ij} = \beta_0 + \beta_1 Group + \beta_2 Visit + \beta_3 Group \times Visit + \beta_4 Age + \beta_5 Sex + u_{0i} + \epsilon_{ij}$$

In order to reduce the number of comparisons, we analysed the longitudinal data (1) averaged

over the sub regions in the frontal and temporal lobe and (2) focused on those regions or subcortical nuclei that differed between patients and controls at baseline. In cases where significant effects were observed, we performed post-hoc comparisons using false discovery rate (FDR) corrections. If the interaction between region and group was significant, we followed up with planned comparisons: by comparing the two groups within each region/nucleus with FDR corrections.

The sub regions included in the frontal and temporal lobes are listed in the supplementary materials.

The threshold for statistical significance was set to 0.05 FDR corrected.

### 3. Results

#### 3.1. Demographic and clinical data

We analysed 15 patients and 24 healthy controls. Only 18 healthy controls were assessed at all three time points. 6 of these healthy controls only had baseline assessments (MRI). There were no differences between the two populations in terms of age (patients: 59.2 years old (Standard Deviation (SD): 7.1); healthy controls: 61.9 years old (SD :6.9);  $p=0.921$ ), gender (patients: 6 females/ 9 males; healthy controls: 10 females/ 14 males;  $p=0.918$ ), and the level of education (patients: 11.57 years (SD :3.27); healthy controls: 12.58 years (SD: 3.94) ;  $p=0.423$ ).

#### 3.2. Clinical data

Using a threshold of a 50% improvement in symptoms at the end of the treatment index, 100% (n=15) of patients were categorised as responsive to treatment. And using a threshold

of HAM-D  $\leq 7$ , 93.3% (14 patients) went into remission.

There was an improvement in depressive symptoms after treatment (repeated measures ANOVA for HAM-D(V1)=22.8 (SD=3.05); HAM-D(V2)=20.8 (SD=2.91); HAM-D(V3)=4 (SD=2.65);  $p < 0.001$ ).

### 3.3. MRI data

#### 3.3.1. Baseline analyses

##### *Frontal lobe sub regions*

We detected a significant effect of the group ( $F[1,35]=13.17$ ,  $p < 0.001$ ), while the effect of the region ( $F[11,407]=0.58$ ,  $p=0.84$ ) and the interaction between group and region ( $F[11,407]=1.52$ ,  $p=0.12$ ) were not significant. Both age and sex were not significant ( $F[1,35]=2.4$ ,  $p=0.14$ ;  $F[1,35]=0.25$ ,  $p=0.62$ ). A post-hoc analysis revealed that, at baseline, controls had a greater cortical thickness than patients ( $t(37)=4.02$ ,  $p < 0.001$ ) (Table 1).

##### *Temporal Lobe sub regions*

The effect of the group was not significant ( $F[1,35]=1.56$ ,  $p=0.22$ ), neither was the effect of the region ( $F[7,259]=1.44$ ,  $p=0.19$ ). However, the interaction between group and region was found to be significant ( $F[7,259]=3.74$ ,  $p < 0.001$ ). Age was also found to be significant ( $F[1,35]=10.48$ ,  $p=0.002$ ), while sex was not significant ( $F[1,35]=0.09$ ,  $p=0.76$ ). A post-hoc analysis revealed that, at baseline, controls had a greater cortical thickness than patients in the fusiform gyrus, the inferior, middle and superior, the parahippocampal gyrus and the transverse temporal gyrus (respectively:  $t(35)=2.7$ ,  $p=0.02$ ;  $t(35)=2.89$ ,  $p=0.017$ ;  $t(35)=3.1$ ,  $p=0.015$ ;  $t(35)=3.6$ ,  $p=0.009$ ;  $t(35)=2.37$ ,  $p=0.031$ ;  $t(35)=2.46$ ,  $p=0.03$ , FDR corrected), while there were no significant differences in the entorhinal cortex and the temporal pole (all  $p$  values  $> 0.48$  FDR corrected). (Table 1.)

##### *Subcortical nuclei*

The region played a significant role in the left hemisphere ( $F[3,111]=454.56, p<0.001$ ), while the effect of the group was not significant ( $F[1,34]=0.40, p=0.53$ ). The interaction between group and region however, was found to be significant ( $F[3,111]=4.68, p=0.004$ ). The effect of total grey matter volume was also found to be significant ( $F[1,34]=42.96, p<0.001$ ), while the effects of age and sex were not significant ( $F[1,34]=1.9, p=0.18$ ;  $F[1,34]=1.2, p=0.28$ ). None of the planned interaction comparisons (i.e., between groups, within regions) were found to be significant (all p values > 0.32).

The region played a significant role in the right hemisphere ( $F[3,111]=398.62, p<0.001$ ), while the effect of the group was not significant ( $F[1,34]=0.0, p=0.94$ ). The interaction between group and region was also not significant ( $F[3,111]=2.55, p=0.059$ ). The effect of total grey matter volume was significant ( $F[1,34]=69.9, p<0.001$ ), while the effects of age and sex were not found to be significant ( $F[1,34]=3.35, p=0.076, F[1,34]=3.75, p=0.06$ ).

### 3.3.2. Visit 3 Analyses

#### *Frontal Lobe sub regions*

The effect of the group was not significant and the region was also not found to be significant (respectively  $F[1,29]=1.7, p=0.2$  and  $F[11,341]=0.27, p=0.99$ ), their interaction was also not significant ( $F[11,341]=0.59, p=0.83$ ).

#### *Temporal Lobe sub regions*

The effect of the group was not significant ( $F[1,29]=2.32, p=0.14$ ), while the effect of region was found to be significant ( $F[7,217]=2.54, p=0.016$ ), their interactions were also found to be significant ( $F[7,217]=5.59, p<0.001$ ). None of the planned interaction comparisons (i.e., between groups, within regions) were found to be significant (all p values > 0.14). (Table 1.)

#### *Subcortical Nuclei*

The region played a significant role in the left hemisphere ( $F[3,93]=357.7$ ,  $p<0.001$ ), while the effect of the group was not significant ( $F[1,28]=0.0$ ,  $p=0.95$ ). The interaction between group and region was not significant ( $F[3,93]=1.33$ ,  $p=0.27$ ). The effect of total grey matter volume was significant ( $F[1,28]=36.5$ ,  $p<0.001$ ), while age and sex were not significant ( $F[1,28]=0.96$ ,  $p=0.23$ ;  $F[1,28]=1.8$ ,  $p=0.19$ ).

The region played a significant role in the right hemisphere ( $F[3,93]=270.23$ ,  $p<0.001$ ), while the effect of the group was not significant ( $F[1,28]=0.03$ ,  $p=0.86$ ). The interaction between group and region was not significant ( $F[3,93]=0.90$ ,  $p=0.44$ ). The effect of total grey matter volume was also found to be significant ( $F[1,28]=47.23$ ,  $p<0.001$ ) while age and sex were not significant ( $F[1,28]=2.4$ ,  $p=0.13$ ;  $F[1,28]=3.74$ ,  $p=0.06$ ).

### 3.3.3. Longitudinal Analyses

#### *Frontal Lobe*

The effect of the group was significant ( $F[1,29]=6.49$ ,  $p=0.016$ ), while the effect of the visit and their interaction were not significant (respectively  $F[2,62]=0.78$ ,  $p=0.46$ ;  $F[2,62]=1.78$ ,  $p=0.18$ ). A post-hoc analysis revealed that, at baseline, the controls had a greater cortical thickness than patients ( $t(29)=2.64$ ,  $p=0.12$ ).

#### *Temporal Lobe*

The effect of the group was significant ( $F[1,29]=4.7$ ,  $p=0.038$ ) while the visit was not significant ( $F[2,62]=0.91$ ,  $p=0.40$ ). The interaction between group and visit was found to be significant ( $F[2,62]=4.99$ ,  $p=0.01$ ). A post-hoc analysis revealed that patients' cortical thickness in the temporal lobe increased between baseline and V3 ( $t(62)=-2.78$ ,  $p=0.054$  FDR corrected), between V3 and V2 ( $t(62)=-3.19$ ,  $p=0.034$  FDR corrected) but did not increase

between baseline and V2 ( $t(62)=-1.63$ ,  $p=0.4$  FDR corrected). Conversely, the different visits had no effect on the controls (all  $p$  values  $> 0.4$ ). Patients were marginally different from controls at baseline ( $t(29) = 2.2$ ,  $p=0.065$ ) and significantly different at V2 ( $t(29) = 2.86$ ,  $p=0.04$ ), but were not significantly different at V3 ( $t(29) = 1$ ,  $p=0.36$ )

### *Regions/nuclei differing at V1*

#### **-Fusiform Gyrus**

The effect of the group was significant ( $F[1,29]=7.26$ ,  $p=0.01$ ), while the effect of the visit was not significant ( $F[2,62]=0.35$ ,  $p=0.7$ ). The interaction between group and visit was not found to be significant ( $F[2,62]=1.38$ ,  $p=0.26$ ).

#### **-Superior Temporal**

The effect of the group was significant ( $F[1,29]=5.74$ ,  $p=0.02$ ), while the effect of the visit was not significant ( $F[1,62]=2.2$ ,  $p=0.12$ ). The interaction between group and visit was found to be significant ( $F[2,62]=6.82$ ,  $p=0.002$ ). Post-hoc analysis of the group factor revealed that, on average, controls had a greater cortical thickness than patients, at baseline ( $t(29)=2.18$ ,  $p=0.037$ ). Pairwise comparison of the interaction revealed that, cortical thickness in the superior temporal gyrus in the patient group did not significantly increase between baseline and V2 ( $t(62)=-0.02$ ,  $p=0.99$ ), but it *did* significantly increase between V1 and V3 ( $t(62)=-3.43$ ,  $p=0.009$ ) and between V2 and V3 ( $t(62)=-3.42$ ,  $p=0.009$ ). In contrast, cortical thickness did not increase in the controls (all  $p$  values  $> 0.2$ ). The difference in cortical thickness between controls and patients was significant at baseline and V2 (respectively  $t(29)=2.40$ ,  $p=0.054$ ;  $t(29)=3.7$ ,  $p=0.004$ ), but was not significant at V3 ( $t(29)=2$ ,  $p=0.068$ ) (Figure 1A).

#### **-Middle Temporal**

The effect of the group was significant ( $F[1,29]=4.4$ ,  $p=0.045$ ), but the effect of the visit was not significant ( $F[1,29]=1.59$ ,  $p=0.21$ ). The interaction between group and visit was also not found to be significant ( $F[2,62]=3$ ,  $p=0.057$ ).

#### -Parahippocampal gyrus

The effects of the group and the visit were not significant (respectively  $F[1,29]=0.2$ ,  $p=0.17$ ;  $F[2,62]=0.1$ ,  $p=0.9$ ), and their interaction was also not significant ( $F[2,62]=2.75$ ,  $p=0.071$ ).

#### -Transverse occipital gyrus

The effect of the group was significant ( $F[1,29]=5.92$ ,  $p=0.021$ ), while the visit was not significant ( $F[2,62]=1.87$ ,  $p=0.16$ ). The interaction between group and visit was also not found to be significant ( $F[2,62]=0.35$ ,  $p=0.70$ ).

#### -Hippocampus

The effects of the group and the visit were not significant (respectively  $F[1,31]=0.19$ ,  $p=0.66$ ;  $F[2,61]=1.47$ ,  $p=0.24$ ). However, the interaction between group and visit was significant ( $F[2,62]=15.3$ ,  $p<0.001$ ). A post-hoc analysis revealed that in the patient group, cortical thickness in the hippocampus did not increase between baseline and 2 ( $t(62)=-0.44$ ,  $p=0.63$ ), but it *did* significantly increase between V1 and V3 ( $t(62)=-5.23$ ,  $p<0.001$ ) and between V2 and V3 ( $t(62)=-5.3$ ,  $p<0.001$ ). In contrast, cortical thickness did not increase in the controls (all  $p$  values  $> 0.65$ ). A significant difference between patients and controls was detected at all the time points examined (all  $p$  values  $> 0.65$ ). (Figure 1B)

#### -Amygdala

The effects of the group, the visit, and their interaction were not significant (respectively  $F[1,29]=0.2$ ,  $p=0.64$ ;  $F[2,61]=0.96$ ,  $p=0.39$ ;  $F[2,61]=2.71$ ,  $p=0.074$ ). The effect of total grey matter volume was significant ( $F[1,61]=33.46$ ,  $p<0.001$ ).

#### -Caudate

The effects of the group, the visit, and their interaction were not significant (respectively  $F[1,29]=2.3$ ,  $p=0.14$ ;  $F[2,61]=0.06$ ,  $p=0.93$ ;  $F[2,61]=0.5$ ,  $p=0.61$ ). The effect of total grey matter volume was significant ( $F[1,61]=17$ ,  $p<0.001$ ).



## -Putamen

The effects of the group, the visit, and their interaction were not significant (respectively  $F[1,29]=1.37$ ,  $p=0.25$ ;  $F[2,61]=0.4$ ,  $p=0.67$ ;  $F[2,61]=0.46$ ,  $p=0.63$ ). The effect of total grey matter volume was significant ( $F[1,61]=31.3$ ,  $p< 0.001$ ).

### 3.4. Effect of clinical response

There was no significant association between structural MRI changes and clinical improvement (Delta HAM-D between V1 and V3): (i) Hippocampus ( $\beta=0.245$ ;  $p=0.38$ ) and (ii) Amygdala ( $\beta=-0.256$ ;  $p=0.357$ )

## 4. Discussion

A baseline comparison of a population of patients with TRD and healthy controls detected a significantly greater cortical thickness in the controls in the fusiform gyrus, in the parahippocampal gyrus, and in the transverse, middle and superior temporal gyrus. These differences were no longer significant after the whole sessions of ECTs. Moreover, we detected a significant increase in cortical thickness in the superior temporal gyrus in the patient group between (i) baseline and V3 and (ii) V2 and V3, but not between baseline and V2. This suggests that grey matter changes only occur after multiple ECT sessions.

In addition to changes in cortical thickness, we observed an increase in hippocampal volume between (i) baseline and V3 and (ii) V2 and V3 in our patient group. These results parallel those found for cortical thickness, suggesting that grey matter volume only increases after multiple sessions of ECT. We did not detect any changes in the amygdala, caudate, or putamen.

As suggested by Pirnia et al. (Pirnia et al., 2016) and Gryglewski et al. (Gryglewski et al., 2018), we showed an increase in cortical thickness in the superior temporal gyrus in patients

with TRD treated using ECT (and not in controls). Our results are in agreement with the current literature (Gbyl and Videbeck, 2018; Oltedal et al., 2018; Yroni et al., 2016), as we detected an increase in hippocampal volume. Our results nevertheless suggest that these changes only occur after several effective sessions of ECT. Indeed, we did not find any differences between baseline and the first assessment in hippocampal nor cortical thickness. It seemed that we cannot discount a cumulative effect of ECT on these brain structures, since we were unable to detect effects of a single ECT session, perhaps because this effect may have been too weak to be detected in our sample.

To our knowledge, this is the first study to monitor differences in grey matter (cortical thickness and subcortical region) at 3 distinct time points in a population of patients with TRD treated with ECT BL, compared to a healthy control population. As it is likely that the majority of patients treated with ECT for MDD probably have TRD, our results can therefore be compared to many other studies focusing on MDD, but which did not specifically examine treatment resistant depression. The consortium Global ECT-MRI Research Collaboration (GEMRIC ) find that volume enlargement is not significantly related to treatment outcome. This is consistent with our results specifically in our TRD population. Indeed, we did not find any significant association between structural MRI changes and clinical improvement. However, contrary to our results, Oltedal et al. (GEMRIC) (Oltedal et al., 2017) show an inverse relationship between hippocampal volume and the improvement of symptoms.

In addition to the Gbyl's meta-analysis (Gbyl and Videbeck, 2018), recent studies seem to confirm this increase of hippocampal and amygdala volume in MDD populations. In the largest study (N=92) examining the effect of ECT on the brain structure of an MDD population (not specifically resistant), Sartorius et al. (Sartorius et al., 2019) show an increase in temporo-mesial regions mainly in the hippocampus and amygdala. When examining

subfields of hippocampus, Nuninga et al. (Nuninga et al., 2019) report a large and significant increase in Dentate Gyrus volume (MRI 7 tesla) after ten bilateral ECT sessions. Moreover, Bouckaert et al. (Bouckaert et al., 2016) also detected an increase in hippocampal volume after ECT in specific populations (N=88) with late life depression (>55 years old). The age of this population is comparable to our population and, even though this was not a specific TRD population, these results are consistent with ours.

In light of the results reported in the literature, the strengths of our study are (i) an MRI scan very early (after the first ECT session that was considered effective) which suggests that there is a cumulative effect of ECT on brain structure; (ii) a population limited to patients ranging from 50 to 70 years of age (to select a more homogeneous population in terms of aging brain structures) with only unipolar TRD (to limit the heterogeneity of our sample) and (iii) exclusion criteria including anxiety disorder and PTSD (to limit the heterogeneity of our sample).

However, although this is a population with severe TRD according to the thresholds recommended in the APA's Handbook of Psychiatric Measures (Rush et al., 2008) to define grades of severity on the HAM-D: mild to moderate: 8-18; severe: 19- 22; very severe  $\geq 23$  (ranging from 19 to 29 in our sample) and according to the thresholds recommended in Thase and Rush scale to define different grades of resistance:  $\geq 2$  (Thase and Rush, 1997) (ranging from 2 to 4 in our sample), the severity and the resistance could be considered as relatively low with, in addition to this, 2 attempted suicides and 2 lifetime hospitalisations for depressive disorders. Moreover, the patients are rather old (50-70 years), which is a prognostic response factor (van Diermen et al., 2018). In addition to this, patients do not have any psychiatric comorbidity. Finally, patients received a large number of ECTs [12.1 (5.26)]. These data could explain the very high response and remission rates in our sample. All these issues should be taken into account when extrapolating from our results.

## Limitations

Our study does have some limitations. Firstly, we included only a small number of patients (15), which precluded the analyses of different MDD clusters (Drysdale et al., 2017). Thus, this increases the risk of a heterogeneous population. Moreover, we decided to maintain the antidepressant treatment during ECT (as we do in daily care in our unit). This can affect grey matter changes if we take the effects of antidepressants into consideration. But to limit this effect, we did not alter antidepressant treatment after inclusion of patients into the study. Moreover, our last visit was close to the end of the course of ECT. However, some studies report a decrease in the volume of brain structures such as the hippocampus throughout the time following the treatment without a relapse in depressive symptoms (Bouckaert et al., 2016; Nordanskog et al., 2014). These data should be taken into account when interpreting our results.

## Perspectives

Future studies with larger sample sizes and/or consortium initiatives such as the GEMRIC (Oltedal et al., 2017) seem to be necessary to better understand the mechanisms underlying ECT effects. Moreover, assessment of mean diffusivity and fractional anisotropy (in Diffusion Tensor Imaging) of hippocampus in addition to volume could be of interest to understand these mechanisms and potentially assess a link between volumetric increases and treatment effects and side effects.

## 5. Conclusion

We report grey matter changes during ECT in a population with TRD when compared to a healthy control population. These changes seem to occur after multiple ECT sessions. This

may contribute to a better understanding of the ECT mechanism.

#### Conflicts of interest disclosure

The authors declare no competing financial interests.

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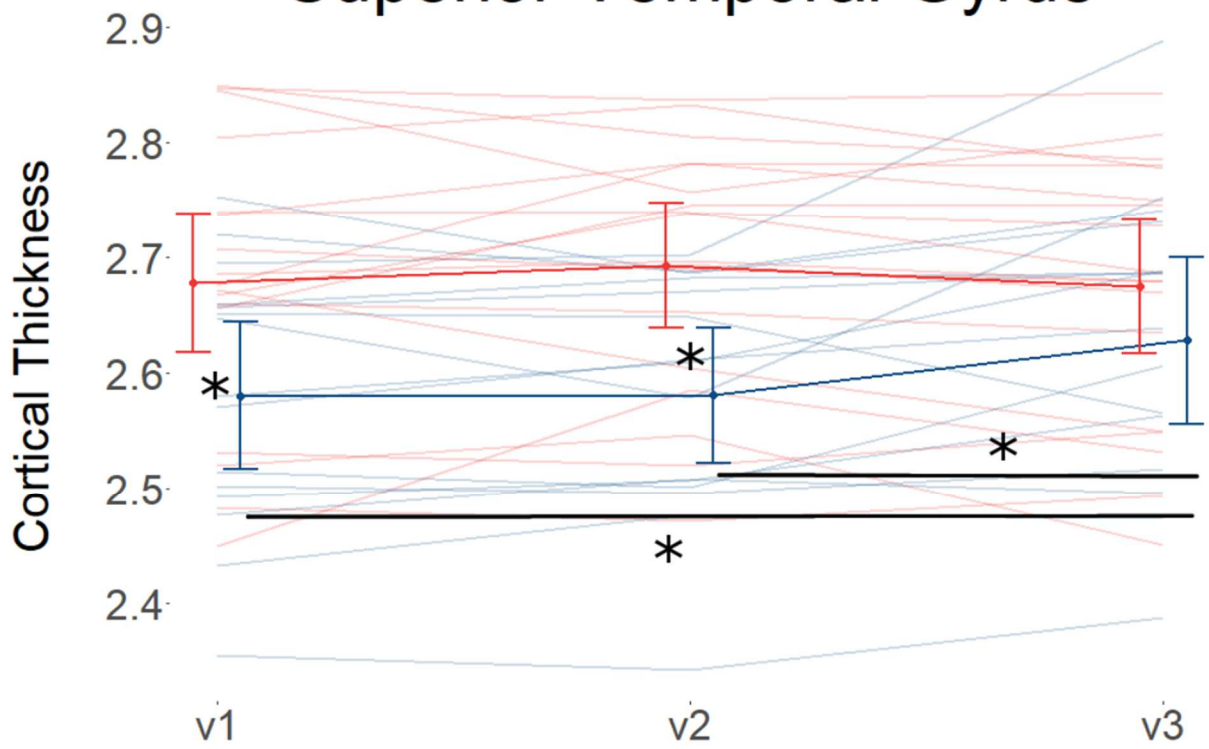
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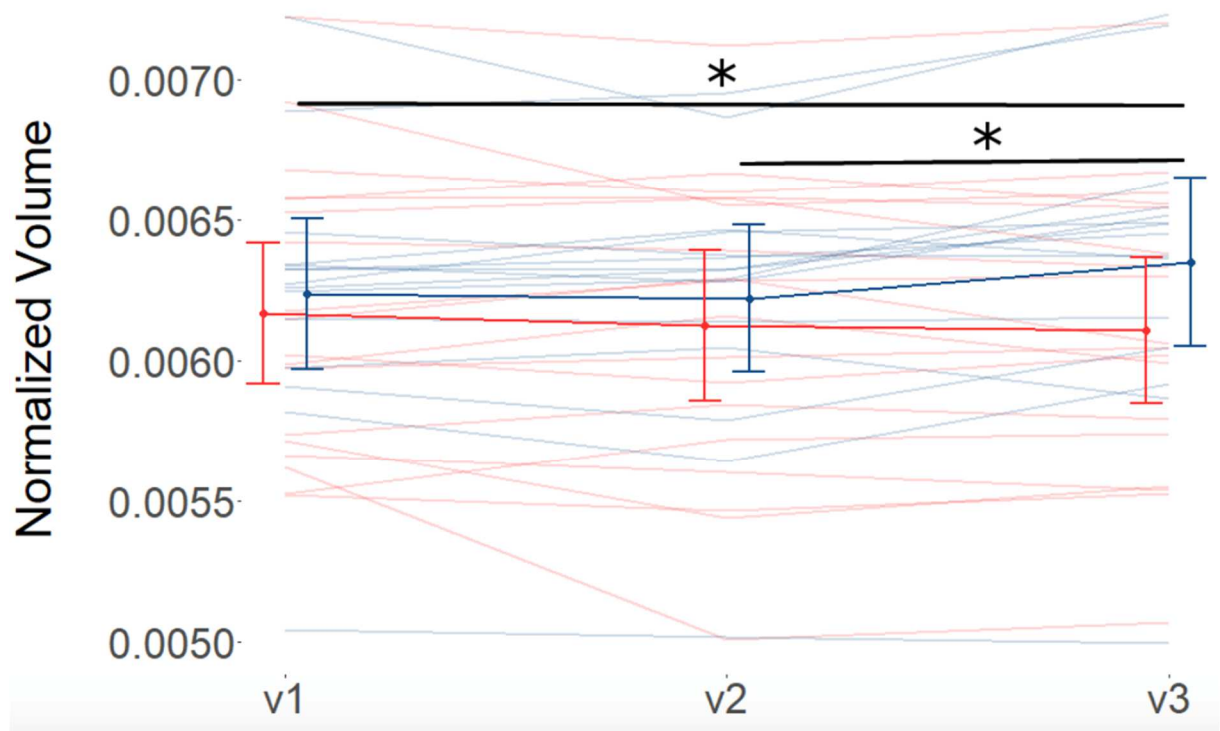


# Superior Temporal Gyrus



A

# Hippocampus



B

\*:  $p < .05$

Figure 1. Longitudinal change in superior temporal gyrus (A) and Hippocampus (B) over time

	DF	F/t <sup>1</sup>	p <sup>2</sup>
<b>Main Effects. Interactions. post-hoc</b>			
<i>Frontal Lobe – V1</i>			
Group	1.35	5.67	> 0.001
Region	11.407	0.59	0.840
Group x Region	11.407	1.52	0.12
<u>HC vs PT</u>	35	4.3	0.001
<i>Temporal Lobe – V1</i>			
Group	1.35	1.56	0.22
Region	7.259	1.44	0.189
Group x Region	7.259	3.7	0.007
<u>HC.entorhinal - PT.entorhinal</u>	35	-1.25	0.25
<u>HC.fusiform - PT.fusiform</u>	35	2.72	0.02
<u>HC.inferior temporal - PT.inferior temporal</u>	35	2.89	0.017
<u>HC.middle temporal - PT.middle temporal</u>	35	3.1	0.015
<u>HC.parahippocampal - PT.parahippocampal</u>	35	2.37	0.031
<u>HC.superior temporal - PT.superior temporal</u>	35	3.55	0.009
<u>HC.temporal pole - PT.temporal pole</u>	35	0.72	0.48
<u>HC.transverse temporal - PT.transverse temporal</u>	35	2.46	0.031
<i>Left Subcortical Nuclei – V1</i>			
Group	1.34	0.54	0.54
Region	3.111	454.95	< 0.001
Group x Region	3.111	4.68	0.004
<u>HC.Amygdala - PT.Amygdala</u>	34	0.63	0.99
<u>HC.Caudate - PT.Caudate</u>	34	-2.18	0.39
<u>HC.Hippocampus - PT.Hippocampus</u>	34	1.36	0.86
<u>HC.Putamen - PT.Putamen</u>	34	-2.29	0.37
<i>Right Subcortical Nuclei – V1</i>			
Group	1.34	0	.94
Region	3.111	398.63	< 0.001
Group x Region	3.111	2.56	0.059
<i>Frontal Lobe – V3</i>			
Group	1.29	1.7	0.2
Region	11.341	0.27	0.99
Group x Region	11.341	0.6	0.83
<i>Temporal Lobe – V3</i>			
Group	1.29	2.32	0.14
Region	7.217	2.54	0.016
Group x Region	7.217	5.59	<0.001
<u>HC.entorhinal - PT.entorhinal</u>	29	-1.52	0.16
<u>HC.fusiform - PT.fusiform</u>	29	2.46	0.053

<u>HC.inferior temporal - PT.inferior temporal</u>	29	2.6	0.053
<u>HC.middle temporal - PT.middle temporal</u>	29	1.62	0.15
<u>HC.parahippocampal - PT.parahippocampal</u>	29	1.44	0.16
<u>HC.superior temporal - PT.superior temporal</u>	29	1.76	0.15
<u>HC.temporal pole - PT.temporal pole</u>	29	-1.72	0.15
<u>HC.transverse temporal - PT.transverse temporal</u>	29	3.041	0.053
<i>Left Subcortical Nuclei – V3</i>			
Group	1.28	0	0.95
Region	3.93	357.7	< 0.001
Group x Region	3.93	1.33	0.27
<i>Right Subcortical Nuclei – V1</i>			
Group	1.28	0.3	0.86
Region	3.93	270.22	< 0.001
Group x Region	3.93	0.91	0.44
<i>Frontal Lobe - Longitudinal</i>			
Group	1.29	6.5	0.016
Visit	2.62	0.78	0.46
Group x Visit	2.62	1.78	0.18
<u>HC vs PT</u>	29	2.55	0.016
<i>Temporal Lobe - Longitudinal</i>			
Group	1.29	4.7	0.038
Visit	2.62	0.91	0.40
Group x Visit	2.62	4.99	0.01
<u>HC.v1 - PT.v1</u>	29	2.22	0.065
<u>HC.v2 - PT.v2</u>	29	2.86	0.039
<u>HC.v3 - PT.v3</u>	29	1.07	0.035
<u>HC.v1 - HC.v2</u>	62	-1.21	0.65
<u>HC.v1 - HC.v3</u>	62	-0.01	0.94
<u>HC.v2- HC.v3</u>	62	1.13	0.36
<u>PT.v1 - PT.v2</u>	62	0.41	0.73
<u>PT.v1 - PT.v3</u>	62	-2.78	0.039
<u>PT.v2- PT.v3</u>	62	-3.19	0.034
<i>Fusiform – Longitudinal</i>			
Group	1.29	7.6	0.01
Visit	2.62	0.35	0.7
Group x Visit	2.62	1.38	0.26
<u>HC vs PT</u>	29	3.4	0.002
<i>Inferior Temporal – Longitudinal</i>			
Group	1.29	7.68	0.009
Visit	2.62	0.56	0.58

Group x Visit	2.62	0.71	0.49
<u>HC vs PT</u>	29	2.77	0.009
<i>Superior Temporal – Longitudinal</i>			
Group	1.29	5.74	0.023
Visit	2.62	2.26	0.12
Group x Visit	2.62	6.82	0.002
<u>HC.v1 - PT.v1</u>	29	3.36	0.005
<u>HC.v2 - PT.v2</u>	29	3.73	0.004
<u>HC.v3 - PT.v3</u>	29	2.05	0.068
<u>HC.v1 - HC.v2</u>	62	-1.17	0.28
<u>HC.v1 - HC.v3</u>	62	0.3	0.81
<u>HC.v2- HC.v3</u>	62	1.47	0.18
<u>PT.v1 - PT.v2</u>	62	-0.01	0.99
<u>PT.v1 - PT.v3</u>	62	-3.43	0.004
<u>PT.v2- PT.v3</u>	62	-3.42	0.004
<i>Middle Temporal – Longitudinal</i>			
Group	1.29	4.4	0.045
Visit	2.62	1.59	0.21
Group x Visit	2.62	3	0.057
<u>HC vs PT</u>	29	3.1	0.005
<i>Parahippocampal– Longitudinal</i>			
Group	1.29	1.98	0.17
Visit	2.62	0.1	0.9
Group x Visit	2.62	2.75	0.071
<i>Transverse Temporal– Longitudinal</i>			
Group	1.29	5.92	0.021
Visit	2.62	1.87	0.16
Group x Visit	2.62	0.35	0.71
<u>HC vs PT</u>	29	2.51	.018
<i>Caudate – Longitudinal</i>			
Group	1.29	2.31	0.14
Visit	2.61	0.07	0.94
Group x Visit	2.61	0.5	0.61
<i>Putamen – Longitudinal</i>			
Group	1.29	1.37	0.25
Visit	2.61	0.4	.68
Group x Visit	2.61	0.46	0.63
<i>Hippocampus – Longitudinal</i>			
Group	1.29	0.19	0.66

Visit	2.61	1.47	0.24
Group x Visit	2.61	15.29	< 0.001
<u>HC.v1 - PT.v1</u>	29	-0.44	0.71
<u>HC.v2 - PT.v2</u>	29	-0.54	0.71
<u>HC.v3 - PT.v3</u>	29	1.35	0.65
<u>HC.v1 - HC.v2</u>	62	0.86	0.71
<u>HC.v1 - HC.v3</u>	62	1.71	0.46
<u>HC.v2- HC.v3</u>	62	0.85	0.71
<u>PT.v1 - PT.v2</u>	62	0	0.99
<u>PT.v1 - PT.v3</u>	62	-5.23	<0.001
<u>PT.v2- PT.v3</u>	62	-5.29	<0.001

Table 1. Degrees of Freedom (DF). statistics and significance of the cross-sectional and longitudinal statistical analyses. Main effect and interactions are in plain text. post-hoc analyses are underlined. HC = Healthy Controls. PT = Patients. <sup>1</sup>F statistic is reported for main effects and interactions while t statistic is reported for post-hoc comparisons. <sup>2</sup>Uncorrected p values are reported for main effects and interactions. FDR corrected p values are reported for post-hoc comparisons