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Research paper

The basal ganglia: A central hub for the psychomotor effects of electroconvulsive therapy

Jan-Baptist Belge[a,b,*], Linda Van Diermen[a,b], Didier Schrijvers[a,b], Bernard Sabbe[a,b], Eric Constant[c], Philippe de Timary[c], Sven De Keyzer[d], Paul Parizel[d], Kristof Vansteelandt[e], Pascal Sienaert[f], Philip van Eijndhoven[g]

[a] Department of Psychiatry, University Psychiatric Center Duffel, Duffel, Belgium
[b] Department of Psychiatry, Collaborative Antwerp Psychiatric Research Institute (CAPRI), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[c] Adult Psychiatry Department and Institute of Neuroscience, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Woluwe-Saint-Lambert, Belgium
[d] Department of Radiology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
[e] Department of Statistics, University Psychiatric Center, KU Leuven, Leuven, Belgium
[f] Department of Mood Disorders and Electroconvulsive Therapy, University Psychiatric Center, KU Leuven, Leuven, Belgium
[g] Department of Psychiatry, Radboud University, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is the most effective biological treatment for depression. Aside the well-known therapeutic effect on mood symptoms, it has also a unique positive impact on psychomotor agitation and retardation, which are core symptoms of depression. The neurobiology behind these effects, however, remains unclear. The basal ganglia are proposed to be important regions in the pathogenesis of psychomotor symptoms in depression. Since ECT can trigger neuroplasticity in these subcortical nuclei, we speculate that ECT-induced volumetric changes of the basal ganglia will positively influence psychomotor symptoms.

Methods: Psychomotor symptoms were analyzed in 17 patients with severe depression before and after an acute ECT course using a CORE assessment of the retardation, agitation, and non-interaction domains. The volumes of the caudate, putamen, pallidum, and accumbens regions were determined using magnetic resonance imaging one week before and after ECT.

Results: Psychomotor functions had improved significantly after ECT and significant volume increases were found for the accumbens region, the putamen, and pallidum. The volume increase of the nucleus accumbens correlated with an improvement of psychomotor retardation, while the volume increase of the pallidum correlated negatively with an improvement of the agitation subscore.

Conclusion: Our findings support the notion of an association between the impact of ECT on depression-related psychomotor symptoms and volume increases of the accumbens region and pallidum, pointing to the importance of the basal ganglia in the therapeutic effect of ECT on psychomotor functioning.

1. Introduction

Clinical Trial registration number: NCT02562846 https://clinicaltrials.gov/ct2/show/NCT02562846

Electroconvulsive therapy (ECT) is a very effective treatment for severe depression (Kho et al., 2003; UK ECT Review Group, 2003), generating a fast and positive effect not only on mood, but also on psychomotor functioning (Hickie et al., 1996; van Diermen et al., 2018), which is important because psychomotor disturbances, such as retardation and agitation, are key aspects of depression (Buyukdura et al., 2011) and their response to other antidepressant therapies is far more limited (Buyukdura et al., 2011). ECT therefore addresses an unmet therapeutic need in the field of depression, possibly by a specific and unique neurobiological mechanism that yet remains unexplained (Buyukdura et al., 2011).

A recent study by Bouckaert et al. (2016) was the first to shed some light on potential underlying pathways (Bouckaert et al., 2016). Investigating gray matter volume (GMV) changes following ECT in a

* Corresponding author: Department of Psychiatry, Collaborative Antwerp Psychiatric Research Institute (CAPRI) University of Antwerp Stationstraat 22, Duffel 2570, Belgium.
E-mail address: jan-baptist.belge@uantwerpen.be (J.-B. Belge).

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group of patients with severe late-life depression together with changes in psychomotor functions, they observed that a GMV increase in the bilateral caudate nucleus, an important subcortical nucleus of the basal-ganglia complex, correlated significantly with an improvement of psychomotor functioning, as assessed by the CORE rating scale (Bouckaert et al., 2016). This finding corroborates the idea that in depression psychomotor symptoms are related to the dysfunction of the basal ganglia, a system facilitating the performance of voluntary movement through complex interactions with cortex, thalamus, and brainstem (Schrijvers et al., 2008; Sobin and Sackeim, 1997; Hickie et al., 1999; Martinot et al., 2001; Herrero et al., 2002). Functionally, the different structures of the basal ganglia generate direct and indirect motor loops that tune the activity levels of the ventrolateral and ventroanterior nuclei of the thalamus, a higher-level subcortical nucleus, which, in its turn, stimulates the motor cortex, allowing movement (Herrero et al., 2002). Moreover, the possibility that in depression alterations of the basal ganglia could be responsible for the observed psychomotor disorders, supposes a bottom-up effect, where the abnormal function of lower-level subcortical structures induces the dysfunctions of higher-level relay nuclei like the thalamus and, ultimately, the motor cortex. This idea was recently supported by Loo et al. (2008), who demonstrated that psychomotor retardation in depressed participants involves an impaired ability to drive or activate the motor cortex (Loo et al., 2008).

With these findings in mind, we propose that ECT might have an impact on psychomotor symptoms in depression by a neuroplastic effect on the basal ganglia. In an attempt to confirm this assumption, we conducted a longitudinal, structural neuroimaging study in a cohort of adult patients diagnosed with depression and explored the correlation between GMV changes and psychomotor functioning before and after patient-tailored ECT. We used the subcortical segmentation technique as implemented in Freesurfer to specifically investigate the effects of ECT on the basal ganglia. More precisely, we scrutinized those subcortical structures that are mainly included in the motor loops (caudate, putamen, and pallidum), as well as the nucleus accumbens, which is part of the limbic pathway of the basal ganglia and thought to be the functional interface between the limbic and motor systems (Salgado and Kaplitt, 2015), controlling the biological drives and motivation for action (Mogenson et al., 1980). All these structures are known to be altered in depression and implicated in past research investigating the neurobiology of psychomotor symptoms in depression (Buyukdura et al., 2011).

2. Methods and materials

2.1. Participants

Participants were recruited from among patients being seen at the University Psychiatric Center in Duffel, Belgium. All were examined by a psychiatrist specialized in ECT and eligible participants were asked for their written informed consent before they were included in the study protocol. In case of incapacity, a close relative was asked to give informed consent. Participants had to satisfy the following inclusion criteria: age over 40 years (to thus limit age-dependent volumetric differences and create a more homogeneous group. Our earlier, stricter inclusion criteria read ‘age over 50 years’, as age-dependent differences also occur between the ages of 40 and 50 years. However, because of a lack of volunteers, we had to extend the age range.) and scheduled for ECT because of major depressive disorder (MDD) or a major depressive episode (MDE) in bipolar disorder (according to DSM-5 criteria (American Psychiatric Association, 2013)), a score of ≥ 17 on the Hamilton Depression Rating Scale–17 items (HDRS-17) (Trajkovic et al., 2011), and being medically stable as established by physical examination and vital signs verified during the pre-ECT screening procedure. The exclusion criteria were: drug or alcohol dependence as established with the MINI interview conducted as part of the baseline screening procedure (<6 months before ECT), a primary psychotic disorder according to DSM-5 criteria (<6 months before ECT), being currently enrolled in a study involving a trial drug, and metal implants precluding magnetic resonance imaging (MRI). Moreover, suicidality, severe anxiety and agitation were additional exclusion criteria to prevent any adverse events during the patients’ transfer to the University Hospital Antwerp where the MRI scanner was located. All participants could refuse MRI. Due to the more stringent exclusion criteria only 17 patients of an initial sample of 73 patients were selected (a description of this cohort can be found in van Diermen et al., 2019 (van Diermen et al., 2019)). Eleven patients refused to undergo MRI, 13 patients were excluded because of technical reasons, 12 patients could not participate because of logistic issues, 11 patients were under 40 years, 6 patients were agitated, 1 patient was excluded because of severe anxiety during the procedure, 1 patient had an intracranial electrode, 1 patient had brain damage due to alcohol abuse. The central ethical committee of the University Hospital Antwerp approved the study, which was conducted according to the latest version of the declaration of Helsinki.

2.2. ECT procedure

ECT was administered twice weekly using a brief-pulse (0.5 ms), constant-current Thymatron IV system (Somatics LLC, Lake Bluff, IL, USA). We used a right unilateral (RUL) electrode position and a bitemporal (BT) positioning when a fast antidepressant effect was needed. Following international recommendations, patients were switched to BT ECT if response was inadequate after six treatments (National Institute for Clinical Excellence (NICE) 2003). We defined inadequate response as a decrease of less than 25% improvement on the HDRS17 score, in addition to the clinical assessment of response by a trained psychiatrist. Stimulus doses were determined by means of the age method for RUL-electrode placement and the half-age estimation method for bilateral electrode positions. Anesthesia was achieved with intravenous administration of etomidate (0.15 mg/kg), with propofol (1 mg/kg) or ketamine (1–2 mg/kg) being used when etomidate was not (well) tolerated or in case of a lack of clinical response after the first 12 sessions. As a muscle relaxant, succinylcholine (0.5 mg/kg) was used. For each patient, the endpoint of the ECT course was based on the weekly clinician ratings of mood (HDRS17) and treatment-related side effects. The ECT regimen was continued until the moment that a patient was either in remission (HDRS-17 ≤ 7), showed no further improvement during the last three sessions, or reported intolerable side effects. All patients continued their treatment during their ECT course. Benzodiazepines and lithium were withheld at least 12 h before each session given the negative influence of benzodiazepines on seizure duration and to prevent cognitive disturbances following ECT due to lithium. All medications were permitted none were discontinued.

2.3. MRI acquisition and processing

A structural, whole-brain MRI scan was acquired of all patients in the week before the first ECT session and within one week after completion of the acute course by means of a Siemens Magnetom Prisma Fit 3T scanner (Siemens, Erlangen, Germany) using a three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) with the following acquisition parameters: TI 900 [ms], TR 2300 [ms], TE 2.98 [ms], flip angle 9 [deg], voxel-size 1.0 × 1.0 × 1.0 [mm]. To extract reliable volume and thickness estimates, images were automatically processed with the longitudinal stream in FreeSurfer (version 5.3) (Reuter et al., 2012). Specifically, an unbiased within-subject template space and image (Reuter and Fischl, 2011) is created using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information

from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). We manually corrected the cases where the dura was included in the gray matter. The FS application allows automatic labeling of subcortical structures using a probabilistic algorithm. Initially, each image is a rigid-body registration that is mapped onto a probabilistic atlas based on the manually-labeled image. Thereafter, the image is morphed to the atlas by non-linear transformation using a Bayesian segmentation procedure. Each voxel in the MRI volume is automatically assigned to a neuro-anatomical label based on probabilistic information estimated from a manually-labeled training set. The labeling procedure is not biased by anatomical variability. The segmentation procedure is based on three types of probabilities to disambiguate labels: 1) the likelihood that a given structure occurs at a specific atlas location; 2) the likelihood of the image intensity given that tissue class; and 3) the probability that a voxel belongs to a given tissue class based on the likelihood of the spatial configuration of labels. This automated segmentation and labeling procedure has been shown to be of equal accuracy to manual-tracing methods and relatively insensitive to changes in acquisition parameters (Fischl et al., 2004). Quality control of the segmentations was based on visual inspection. No manual editing was done for the subcortical volumes. See Fig. 2 for an illustration of a single subject Freesurfer based segmentation of the analyzed subcortical nuclei.

2.4. Clinical instruments

2.4.1. Mood

Depressive symptoms were assessed one week before and after the ECT course using the Hamilton Rating Scale for Depression–17 items (HDRS17), one of the most widely used instruments for assessing depression severity (Trajkovic et al., 2011). A reduction of 50% or more on the HDRS17 was defined as a treatment response.

2.4.2. Psychomotor symptoms

Psychomotor functioning was assessed as part of a larger test battery including the assessment of mood and cognitive functioning. The patients had therefore been observed for about 1 h before psychomotor functioning was assessed by the main researcher, a Doctor of Medicine trained in psychiatry. The CORE is a clinician rating scale. It is used to measure observable psychomotor functioning impairments. It was developed as a diagnostic tool with the aim of classifying melancholic and non-melancholic subtypes of depression (Hickie et al., 1996). During assessment, 18 observable clinical features related to psychomotor functioning are scored on a 4-point scale based on severity, ranging from 0 (absence of the symptom) to 3 (severe). The CORE generates scores in three psychomotor categories: retardation, agitation, and non-interaction. A decrease of the CORE scores implies an improvement of the assessed psychomotor symptoms. The validity of the Dutch version of the CORE as a measure of psychomotor symptoms has been confirmed, and a high inter-rater reliability has been demonstrated (Rhebergen et al., 2012). Moreover, previous studies used successfully this method to determine the predictive value of improvements in psychomotor symptoms on ECT response (Hickie et al., 1996; van Diermen et al., 2018). We used the CORE scores as our primary outcome measure, where scores of ≤ 7 represent the absence of clinically relevant psychomotor dysfunction. Based on recent research, we consider that psychomotor disturbances (agitation, retardation) and other depressive dimensions are independent and that their assessment captures different symptoms (Vares et al., 2015).

2.5. Data analysis

We calculated descriptive statistics (means, standard deviation, range) for basic demographic and clinical variables. Both the percentage change in GMV of the caudate, putamen, pallidum, accumbens region and absolute difference scores between baseline and follow-up data for the behavioral measures (HDRS and CORE scores) were computed to assess changes over time while controlling for age and gender. The difference scores and percentage changes were computed as followed: CORE difference scores; CORE before ECT - CORE after ECT, HDRS17 difference scores; HDRS17 before ECT- HDRS17 after ECT. Brain volume percentage changes: ((brain volume after ECT-brain volume before ECT)/brain volume after ECT) x100. Paired t-tests were used to evaluate the significance of the observed changes. To assess the possible influence of the demographic and clinical variables on the observed changes in GMV and the behavioral measures, we carried out an analysis of variance (ANCOVA), with the absolute difference scores/percentage change as the dependent variables and age, gender, diagnosis, duration of the current episode, number of ECT sessions and electrode position as independent variables. We computed Pearson correlations to study the associations between significant changes in the psychomotor measures and GMV changes in the regions of interest. Considering this study exploratory, we fixed the p value at 0.05. All statistical analyses were performed using JMP SAS version 14-PRO.

3. Results

Table 1 summarizes patient demographic details, clinical characteristics and ECT treatment information. Table 2 summarizes the individual ECT parameters.

3.1. Mood and psychomotor functioning before and after ECT

Table 3 summarizes mood and psychomotor functioning before and after ECT. All participants were severely depressed at study entry and after ECT showed both a significant improvement of their mood, as assessed with the HDRS17, and psychomotor functions, as indicated by a significant reduction of their CORE total scores, which was based on reductions in agitation and retardation but not on non-interaction.

3.2. Gray matter volumes before and after ECT

Table 4 summarizes the gray matter volumes before and after ECT. Of the four regions of interest, the total accumbens and left accumbens, the total putamen, and total pallidum showed significant volume increases. Changes in the caudate nucleus were not significant.

3.3. Comparison with the original sample

The original sample and the sample of the actual study were similar in terms of age ($p = 0.73$) and gender, ($p = 0.18$). They did not differ for the improvement in mood ($p = 0.15$), psychomotor agitation ($p = 0.32$) and retardation ($p < 0.12$) (van Diermen et al., 2019).

Table 1
Patient demographics, clinical characteristics and ECT treatment information.

Variable	$n = 17$
Demographic Information	
Age, mean years (SD)	58.9 (12.1)
Gender (M/F)	3/14
Clinical Information	
Current episode duration, mean months (SD)	13.8 (19.4)
Unipolar/bipolar depression	14/3
ECT treatment information	
Unilateral/bilateral lead placement	13/4
Number of ECT index sessions, mean (SD)	9.35 (5.3)
Number of ECT index sessions, range	4–25
Responders[a], n (%)	15 (88%)

[a] Response was defined as a 50% or larger reduction in HDRS score from baseline to end-of-treatment.

Abbreviations: ECT = electroconvulsive therapy. *F* = female. *M* = male. SD = standard deviation.

Table 2
Individual ECT parameters.

Patient	% Energy (means)	Pulse Width (milliseconds)	Duration (seconds)	Frequency (hertz)	Millicoulombs
P1	60%	0.5	6.71	50	296
P2	40%	0.5	7.45	30	202
P3	60%	0.5	6.71	50	296
P4	60%	0.5	6.71	50	296
P5	65%	0.5	7.27	50	329
P6	65%	0.5	7.27	50	329
P7	45%	0.5	7.45	30	227
P8	60%	0.5	6.71	50	296
P9	45%	0.5	7.45	30	227
P10	60%	0.5	6.71	50	296
P11	55%	0.5	6.15	50	279
P12	55%	0.5	6.15	50	279
P13	60%	0.5	6.71	50	296
P14	65%	0.5	7.27	50	329
P15	35%	0.5	6.52	30	176
P16	60%	0.5	6.71	50	296
P17	65%	0.5	7.27	50	329

Individual ECT parameters: (pulse width, duration, frequency, millicoulombs), are calculated based on the mean energy (mean% energy) dial settings of the, Thymatron apparatus.

3.4. Correlational results

Correlational results are described in Table 5 and Fig. 1. A volume increase of the total accumbens and the left accumbens regions correlated significantly with an improvement in the scores on the CORE retardation subscale. Although most patients showed improvement of their agitation scores and an increase in pallidum volume, this volume increase correlated negatively with the psychomotor improvement. Significant correlations between the volume increase in subcortical structures and an improvement in the HDRS17 scores were not observed. Results of the ANCOVA revealed that neither behavioral nor volumetric changes were significantly influenced by age, gender, number of ECT sessions, electrode position, depression duration, or treatment outcome.

4. Discussion

To our knowledge, ours is the second study, after Bouckaert et al. (Bouckaert et al., 2016), to investigate the neurobiology of the psychomotor effects of ECT in depression by exploring the relationship between longitudinal brain-volume changes in specific subcortical nuclei and psychomotor symptoms. Considering global subcortical volumes, we observed significant post-ECT gray-matter volume (GMV) increases of the accumbens region, the putamen, and the pallidum. Furthermore, the volume increase of the accumbens region correlated significantly with an improvement on the CORE subscale assessing retardation. The noted GMV increase of the total pallidum, however, correlated negatively with reductions in the patients' CORE agitation subscale scores. It is important to notice that all the observed results are exploratory and should therefore be considered with caution and confirmed in a larger sample.

4.1. Gray matter volume changes

Our data corroborate recent findings of increased nucleus accumbens, pallidum, and putamen (Wade et al., 2016; Bouckaert et al., 2014) volumes post-ECT.

Indeed, most of the research about ECT-induced volumetric changes and the treatment's positive effect on depression has focused on the hippocampus (Bouckaert et al., 2014). The hippocampus is an important structure in depression (Vares et al., 2015) and treatment of depression with ECT seems to increase its volume (Liu et al., 2017; Abbott et al., 2014; Joshi et al., 2016), which change is proposed to depend on a complex neuroplastic effect of ECT on the region (Malberg et al., 2000). However, the relationship between this hippocampal volume increase and clinical response remains ambiguous (32).

Inta et al. demonstrated that electroconvulsive seizures in rats can induce neurogenesis of specific GABAergic interneurons in the striatum (Inta et al., 2013). Moreover, in humans, neurogenesis in striatal structures seems to be much more extensive than it is in the hippocampal dentate gyrus (Inta et al., 2013). This could mean that the antidepressant effects of ECT and, more specifically, the effects on psychomotor functioning, not only depend on the induction of neurogenesis in the hippocampus but also on new neurons being formed in striatal structures (Inta et al., 2013).

Interestingly, the implication of the striatum and pallidum in the pathogenesis of depression is highlighted by current theories describing depression as a brain-network disorder implicating functional and structural alterations of a complex limbic-cortical-striatal-pallidal-thalamic circuit (Schmaal et al., 2016; Lorenzetti et al., 2009; Drevets et al., 2008). Specific mood symptoms of depression have indeed been linked to functional disturbances in the ventral and dorsal striatum, in the pallidum (Drevets et al., 2008; Kuhn et al., 2014; Ochsner et al., 2012; Disner et al., 2011), and to disturbances in frontostriatal connectivity (Furman and Hamilton, 2011). Moreover, Leaver et al. recently demonstrated that ECT can normalize the functional desynchronization between dorsal and ventral corticolimbic neural circuits in major depression by modulating striatal activity (Leaver et al., 2016). Another line of argument supporting this idea, is the positive effect ECT exerts on the motor symptoms of Parkinson's disease (Popeo and Kellner, 2009). Centrally, the importance of the basal ganglia, and, principally, the striatum and pallidum, in the neurobiology of depression is compelling. These structures, first and foremost the subcortical components of the motor system, could to be crucial in the pathophysiology of depression and in the antidepressant effect of ECT. Future research should therefore try to unravel the role of the motor system in the pathogenesis and treatment of a complex mood disorder where higher functions such as emotion processing and other more complex cognitive processes are altered. This would also illustrate the recent views in developmental neuroscience that basic motor functions could be the foundation of higher cognitive functions (Haggard, 1993).

Table 3
Mood and psychomotor functioning before and after ECT.

n = 17	Before ECT Mean ± SD	After ECT Mean ± SD	Difference scores[a] Mean ± SD	t value	p value[b]
HDRS17	24.4 ± 6,17	7.53 ± 5.15	16.9 ± 9.02	- 7.72	< **0.001**
CORE total	8.24 ± 8.2	1.24 ± 1.48	7 ± 7.73	−3.73	< **0.01**
CORE retardation	4.53 ± 5.1	0.24 ± 0.44	4.29 ± 5.01	- 3.53	< **0.01**
CORE agitation	1.94 ± 2.08	0.06 ± 0.24	1.88 ± 2.06	- 3.77	< **0.01**
CORE non-interaction	1.76 ± 3.19	0.94 ± 1.34	0.82 ± 3.11	- 1.09	0.29

[a] Difference scores were computed: HDRS before ECT - HDRS after ECT, CORE before ECT - CORE after ECT.
[b] Abbreviations: M = Mean. SD = standard deviation. HDRS = Hamilton Depression Rating Scale.

Table 4
Gray matter volumes before and after ECT.

n = 17	Before ECT Mean ± SD	After ECT Mean ± SD	% Changes[a] Mean ± SD	t value	p value[b,c]	95% CI
Total Accumbens, mm^3	1008.4 ± 276.41	1088.7 ± 312.62	6.46% ± 11.35%	2.4	**0.03**	9.09 - 151.67
Total Pallidum, mm^3	2752.6 ± 417.52	2865.8 ± 441.58	3.58% ± 8.36%	1.78	**0.04**	−17.98 - 210.13
Total Putamen, mm^3	9765.7 ± 1386.6	10,028 ± 1395.3	2.56% ± 4.9%	2.24	**0.03**	13.83 - 511.57
Total Caudate, mm^3	7112.2 ± 960.38	7166.4 ± 894.57	0.81% ± 4.29%	0.726	0.48	−104.09 - 212
Left Accumbens, mm^3	447.13 ± 126.31	493.53 ± 139.55	7.39% ± 17.7%	2.31	**0.03**	−88.91 - 3.89
Left Pallidum, mm^3	1332.1 ± 225.85	1428.1 ± 299.79	5.05% ± 13.6%	1.79	0.09	−17.98 - 210.13
Left Putamen, mm^3	5001.3 ± 740.07	5116 ± 742.36	2.15% ± 5.73%	1.6	0.13	- 266.76 - 37.34
Left Caudate, mm^3	3502.8 ± 515.07	3509.1 ± 461.13	0.26% ± 5.4%	0.13	0.89	−92.25 - 104.79
Right Accumbens, mm^3	561.24 ± 156.93	595.22 ± 188.22	7.52% ± 8.18%	1.56	0.14	−80.22 - 12.25
Right Pallidum, mm^3	1420.5 ± 216.81	1437.7 ± 218.49	0.65% ± 10.76%	0.46	0.65	−61.87 - 95.52
Right Putamen, mm^3	4764.3 ± 676.39	4912.4 ± 689.86	2.89% ± 5.86%	2,06	0.06	4.13 - 300.33
Right Caudate, mm^3	3609.3 ± 461.76	3657.3 ± 450.37	1.3% ± 4.17%	1.3	0.21	−30.07 - 126

[a] % changes were computed for subcortical volumes: ((subcortical volume after ECT – subcortical volume before ECT) / subcortical volume after ECT) x 100.
[b,c] Paired t-test, p-values below significance threshold 0.05 are marked in bold.

4.2. Clinical correlates of GMV increases

4.2.1. The accumbens region and retardation

The significant correlation we found between the percentage of GMV increase in total accumbens and the left accumbens region and improvement on the CORE retardation subscale is interesting considering the accumulating evidence that the nucleus accumbens plays an important role in the pathophysiology of depression (Russo and Nestler, 2013). Indeed, as part of the dopaminergic reward system, the nucleus accumbens is linked to anhedonia, an important feature of depression (Nestler and Carlezon, 2006; Koob and Le Moal, 2008; Wise, 2008). However, this region has also an output to the motor nuclei of the basal ganglia and is even cytochemically similar (Salgado and Kaplitt, 2015). The accumbens has therefore been proposed to be the functional interface between the limbic and motor systems (Salgado and Kaplitt, 2015), controlling the biological drives for action and decision making (Mogenson et al., 1980). This important role in behavioral activation has led others to already assume its implication in psychomotor slowing, fatigue, or anergia in depression (Salamone et al., 2007; Salamone et al., 2009). The fact that we observe a lateralization towards the left accumbens is interesting given the motor system is highly lateralized. It may then be the right-handedness of the majority (14) of the patients that explains this phenomenon as the left hemisphere may be recruited more during development and during motor activities, which would contribute to the maintenance of the neural circuits (Corballis, 2014).

Our study is the first to demonstrate a positive correlation between a volumetric increase of the accumbens region and an improvement of psychomotor retardation. Compellingly, the 2016 study by Bouckaert et al. (Bouckaert et al., 2016) demonstrated a positive correlation between a volumetric increase of the caudate nucleus and this specific psychomotor symptom. Although the caudate nucleus is part of the dorsal striatum and also implicated in psychomotor speed, we found no such correlation. A possible explanation could be the older age of the patients in Bouckaert's study. It has indeed been documented that the volume reduction of the caudate and its increase after ECT is much more manifest in elderly depressed patients (Bouckaert et al., 2016). The question if there could be two phenotypes of psychomotor retardation in depression, one linked to the ventral striatum (accumbens) in younger individuals and one to the dorsal striatum (caudate) in older patients hence merits further investigation. As a matter of fact, research indicates that the relevance of the ventral striatum in motivated behavior increases after mid-adulthood and that in younger individuals the region contributes more to the motivational motor drive (Porter et al., 2015). Lastly, it is important to note that the accumbens nucleus is an effective target for deep-brain stimulation for resistant depression (Bewernick et al., 2012).

4.2.2. The pallidum and agitation

Notably, we observed that a volumetric increase of the pallidum correlated negatively with an improvement of the CORE agitation subscale. To our knowledge, we are the first to detect such an effect. As the general agitation levels of our participants were very low, the fact that we did only find a medium correlation between the increase in pallidum size and improvement in agitation scores could result from our study being underpowered to detect smaller effects. Therefore, this finding should be considered with caution and confirmed in a more agitated or larger sample.

The pallidum, and mainly the globus pallidus internus and externus, are important components of the basal ganglia motor system (Herrero et al., 2002). This system is functionally divided into a direct and an indirect pathway that crucially tune the activity of the ventrolateral thalamic nucleus, a structure that activates the motor cortex (Herrero et al., 2002). An optimal motor performance hence depends on the tight balance between the activity of these two pathways. Hyperactivity as characterized by agitation and repetitive movements can occur when a dis balance between these two pathways arises (Jankovic, 2009). Overactivity of a direct pathway combined with

Table 5
Correlations between clinical and gray matter volume changes.

N = 17	Total accumbens, mm^3 % change[a]	Left accumbens, mm3 % change[a]	Total putamen, mm3 % change[a]	Total pallidum, mm^3 % change[a]	Total caudate, mm3 % change[a]
HDRS17 Difference scores[b]	p = 0.91	p = 0.84	p = 0.19	p = 0.17	p = 0.38
	r = 0.03	r = 0.05	r = −0.33	r = −0.34	r = 0.23
CORE retardation Difference scores[b]	p = **0.04**	p = **0.01**	p = 0.8	p = 0.68	p = 0.63
	r = 0.49	r = 0.59	r = 0.07	r = −0.11	r = 0.12
CORE agitation Difference scores[b]	p = 0.45	p = 0.95	p = 0.12	p = **0.03**	p = 0.59
	r = 0.2	r = −0.02	r = −0.38	r = −0.5	r = −0.28

[a] % changes were computed for subcortical volumes: ((subcortical volume after ECT – subcortical volume before ECT) / subcortical volume after ECT) x 100.
[b] Abbreviations: M = Mean. SD = standard deviation. mm^3 = Cubic millimeter. HDRS = Hamilton Depression Rating scale.

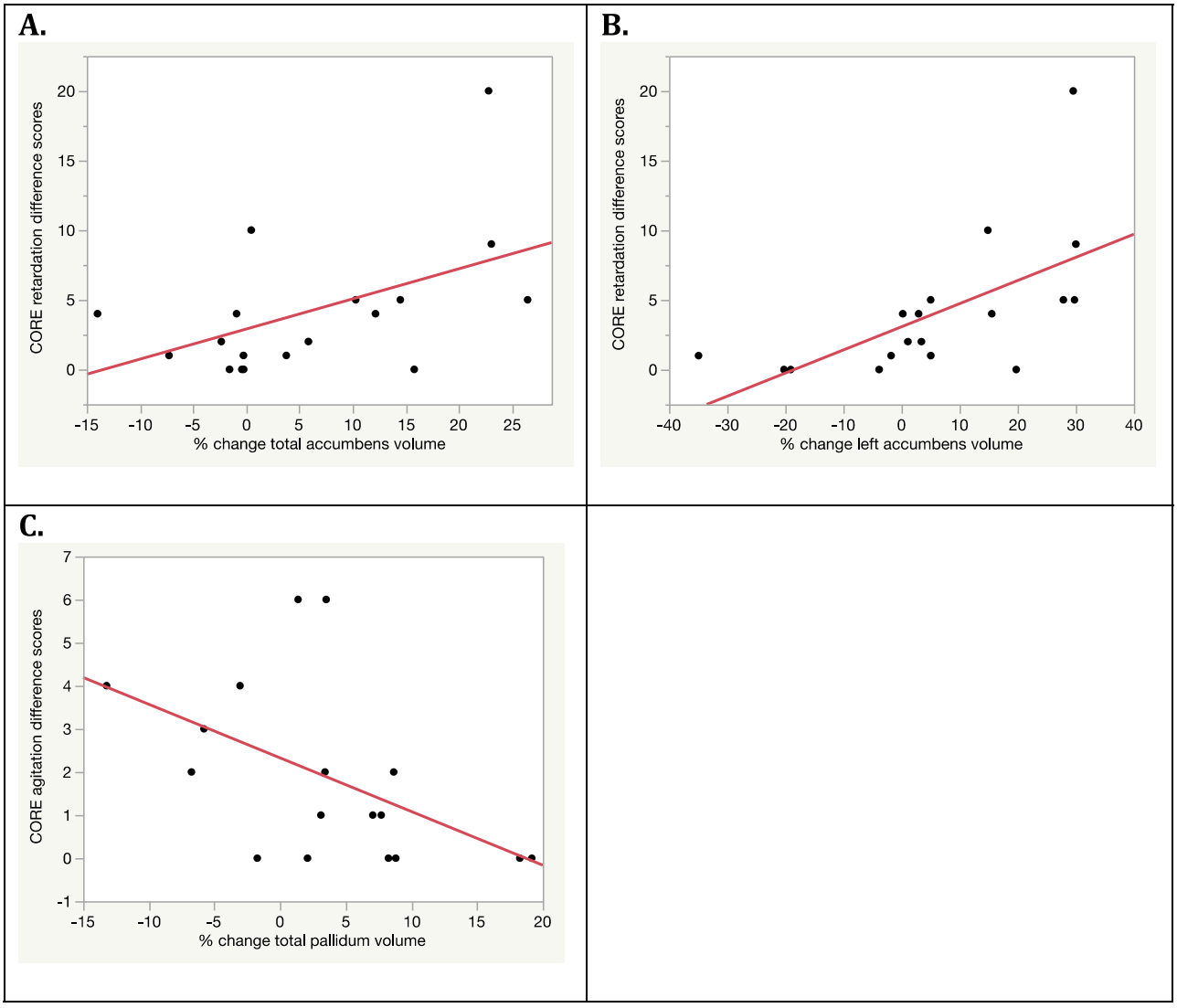

Fig. 1. Correlations between% changes in the gray matter volume of the total (A) and left (B) accumbens and difference scores of the CORE retardation subscale, and the correlation between% changes in the gray matter volume of the total pallidum (C) and difference scores of the CORE agitation subscale.

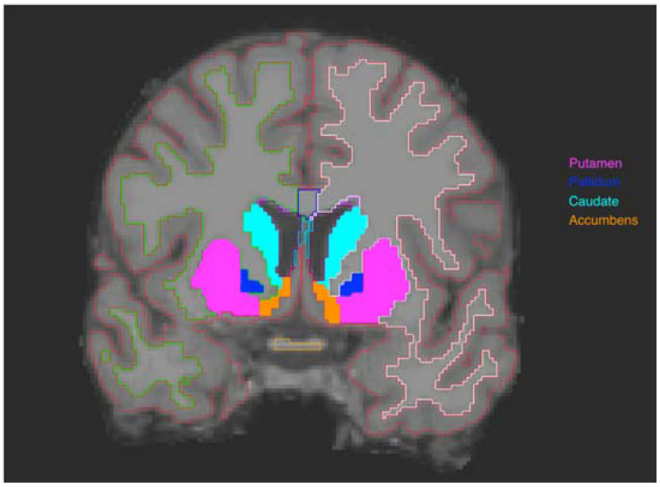

Fig. 2. Illustration of the regions of interest. Freesurfer based subcortical segmentation of selected nuclei (putamen, pallidum, caudate and accumbens) on a single subject.

decreased activity of an indirect pathway then leads to the activation of thalamic neurons and excitation of cortical neurons, resulting in increased motor output (Sanger et al., 2010). It is therefore tempting to suggest that the effect of ECT on the pallidum could limit the reduction of agitation by creating a dis balance in this tightly controlled system. A certain disbalance in favor of motor activation has been suggested by a recent study reporting an increase of blood flow in the thalamus and motor cortex after ECT (Yrondi et al., 2018). Future studies using functional imaging techniques should clarify this issue.

Finally, it is important to note that changes in psychomotor symptoms did correlate specifically with important nuclei of the basal ganglia system. Indeed, to test the specificity of these relationships, we explored the correlations between psychomotor symptom changes and changes in hippocampus volume, a subcortical structure known to increase following ECT (Liu et al., 2017; Abbott et al., 2014; Joshi et al., 2016). Whilst we observed a significant volume increase of the hippocampus ($p < 0.001$, $t = 4.61$) we failed to observe significant correlations for both the core retardation ($p = 0.6$, $r = 0.11$) and agitation scores ($p = 0.72$, $r = 0.09$). This provides supplementary evidence of the specific link between the post-ECT changes of psychomotor symptoms and the basal ganglia.

4.3. Limitations

Our results should be interpreted with caution for several reasons. Firstly, as this study was exploratory, we chose not to correct for multiple comparisons to prevent type II statistical errors already increased by our small sample size ($n = 17$), but by doing this we run the risk of type I error. Secondly, as we studied patients older than 40 years only, the observed results exclusively apply to adults in the age range investigated and cannot be generalized to all adults. A strength of our study was the use of the CORE assessment of psychomotor functioning, which qualitative rating scale affords an accurate assessment of these depression-related symptoms. However, the CORE rating scale relies on the subjective judgment of the investigator. More objective methods have been developed to assess psychomotor functioning. These objective measurements focus on the domains of gross (movements of the entire body) and fine motor activity (writing, drawing) which are assessed using respectively wrist actimetry and drawing tasks. Future studies should investigate the neurobiological underpinnings of ECT's psychomotor effect by using these more precise methods.

5. Conclusion

Our findings demonstrate that ECT is associated with a significant increase in gray matter volume of the accumbens nucleus, pallidum and putamen. Moreover, the positive correlation between increased accumbens volume and retardation on the one hand, and the negative correlation between increased pallidum volume and agitation on the other hand, suggest that the basal ganglia are indeed important structures in the psychomotor effect of ECT. Therefore, future research should not only investigate volumetric changes but also functional changes in subcortical/cortical motor pathways after ECT and link them to specific psychomotor symptoms in depression.

Disclosures

None of the authors report any biomedical or financial interests, nor any conflicts of interest.

CRediT authorship contribution statement

Jan-Baptist Belge: Formal analysis, Writing - original draft. **Linda Van Diermen:** Data curation, Writing - review & editing. **Didier Schrijvers:** Writing - review & editing. **Bernard Sabbe:** Writing - review & editing. **Eric Constant:** Writing - review & editing. **Philippe de Timary:** . **Sven De Keyzer:** Data curation. **Paul Parizel:** Data curation. **Kristof Vansteelandt:** Formal analysis. **Pascal Sienaert:** Writing - review & editing. **Philip van Eijndhoven:** Software, Writing - review & editing.

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References

Abbott, C.C., Jones, T., Lemke, N.T., et al., 2014. Hippocampal structural and functional changes associated with electroconvulsive therapy response. Transl. Psychiatr. 4, e483.
American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders: diagnostic and statistical manual of mental disorders, 5th Edition. American Psychiatric Association, Arlington, VA.
Bewernick, B.H., Kayser, S., Sturm, V., et al., 2012. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. Neuropsychopharmacology 37, 1975–1985.
Bouckaert, F., De Winter, F.L., Emsell, L., et al., 2016. Grey matter volume increase following electroconvulsive therapy in patients with late life depression: a longitudinal MRI study. J. Psychiatr. Neurosci. 41, 105–114.
Bouckaert, F., Sienaert, P., Obbels, J., et al., 2014. ECT: its brain enabling effects: a review of electroconvulsive therapy-induced structural brain plasticity. J ect 30, 143–151.
Buyukdura, J.S., McClintock, S.M., Croarkin, P.E., 2011. Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. Prog. Neuropsychopharmacol. Biol. Psychiatr. 35, 395–409.
Corballis, M.C., 2014. Left brain, right brain: facts and fantasies. PLoS Biol. 12, e1001767.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Disner, S.G., Beevers, C.G., Haigh, E.A., et al., 2011. Neural mechanisms of the cognitive model of depression. Nat. Rev. Neurosci. 12, 467–477.
Fischl, B., Salat, D.H., van der Kouwe, A.J., et al., 2004. Sequence-independent segmentation of magnetic resonance images. Neuroimage 23 (Suppl 1), S69–S84.
Furman, D.J., Hamilton, J.P., et al., 2011. Frontostriatal functional connectivity in major depressive disorder. Biol. Mood Anxiety Disord. 1, 11.
Haggard, P., 1993. Sensorimotor basis of higher cognition. Oxford University Press.
Herrero, M.T., Barcia, C., Navarro, J.M., 2002. Functional anatomy of thalamus and basal ganglia. Childs Nerv. Syst. 18, 386–404.
Hickie, I., Mason, C., Parker, G., et al., 1996. Prediction of ect response: validation of a refined sign-based (CORE) system for defining melancholia. Br. J. Psychiatr. 169, 68–74.
Hickie, I., Ward, P., Scott, E., et al., 1999. neo-striatal rCBF correlates of psychomotor slowing in patients with major depression. Psychiatr. Res. 92, 75–81.
Inta, D., Lima-Ojeda, J.M., Lau, T., et al., 2013. Electroconvulsive therapy induces neurogenesis in frontal rat brain areas. PLoS One 8, e69869.
Jankovic, J., 2009. Treatment of hyperkinetic movement disorders. Lancet Neurol. 8, 844–856.
Joshi, S.H., Espinoza, R.T., Pirnia, T., et al., 2016. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. Biol. Psychiatr. 79, 282–292.
Kho, K.H., van Vreeswijk, M.F., Simpson, S., et al., 2003. A meta-analysis of electroconvulsive therapy efficacy in depression. J ect 19, 139–147.
Koob, G.F., Le Moal, M., 2008. Addiction and the brain antireward system. Annu. Rev. Psychol. 59, 29–53.
Kuhn, S., Vanderhasselt, M.A., De Raedt, R., et al., 2014. The neural basis of unwanted thoughts during resting state. Soc. Cogn. Affect Neurosci. 9, 1320–1324.
Leaver, A.M., Espinoza, R., Joshi, S.H., et al., 2016. Desynchronization and plasticity of striato-frontal connectivity in major depressive disorder. Cereb. Cortex 26, 4337–4346.
Liu, W., Ge, T., Leng, Y., et al., 2017. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural. Plast. 2017, 6871089.
Loo, C.K., Sachdev, P., Mitchell, P.B., et al., 2008. A study using transcranial magnetic stimulation to investigate motor mechanisms in psychomotor retardation in depression. Int. J. Neuropsychopharmacol. 11, 935–946.
Lorenzetti, V., Allen, N.B., Fornito, A., et al., 2009. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J. Affect Disord. 117, 1–17.
Martinot, M., Bragulat, V., Artiges, E., et al., 2001. Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. Am. J. Psychiatr. 158, 314–316.
Malberg, J.E., Eisch, A.J., Nestler, E.J., et al., 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J. Neurosci. 20, 9104–9110.
Mogenson, G.J., Jones, D.L., Yim, C.Y., 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. 14, 69–97.
National Institute for Clinical Excellence (NICE), 2003. Guidance on the use of electroconvulsive therapy. National Inst. Clin. Excellence.
Nestler, E.J., Carlezon Jr., W.A., 2006. The mesolimbic dopamine reward circuit in depression. Biol. Psychiatr. 59, 1151–1159.
Ochsner, K.N., Silvers, J.A., Buhle, J.T., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann. N Y Acad Sci. 1251, E1–24.
Popeo, D., Kellner, C.H., 2009. ECT for Parkinson's disease. Med. Hypotheses 73, 468–469.
Porter, J.N., Roy, A.K., Benson, B., et al., 2015. Age-related changes in the intrinsic functional connectivity of the human ventral vs. dorsal striatum from childhood to middle age. Dev. Cogn. Neurosci. 11, 83–95.
Reuter, M., Schmansky, N.J., Rosas, H.D., et al., 2012. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61, 1402–1418.
Reuter, M., Fischl, B., 2011. Avoiding asymmetry-induced bias in longitudinal image processing. Neuroimage 57, 19–21.
Reuter, M., Rosas, H.D., Fischl, B., 2010. Highly accurate inverse consistent registration: a robust approach. Neuroimage 53, 1181–1196.
Russo, S.J., Nestler, E.J., 2013. The brain reward circuitry in mood disorders. Nat. Rev. Neurosci. 14, 609–625.
Rhebergen, D., Arts, D.L., Comijs, H., et al., 2012. Psychometric properties of the dutch version of the core measure of melancholia. J Affect. Disord. 142, 343–346.
Salamone, J.D., Correa, M., Farrar, A., et al., 2007. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl) 191, 461–482.
Salamone, J.D., Correa, M., Farrar, A.M., et al., 2009. Dopamine, behavioral economics, and effort. Front Behav. Neurosci. 3, 13.
Salgado, S., Kaplitt, M.G., 2015. The nucleus accumbens: a comprehensive review. Stereotact. Funct. Neurosurg. 93, 75–93.
Sanger, T.D., Chen, D., Fehlings, D.L., et al., 2010. Definition and classification of hyperkinetic movements in childhood. Mov. Disord. 25, 1538–1549.
Schmaal, L., Veltman, D.J., van Erp, T.G., et al., 2016. Subcortical brain alterations in

major depressive disorder: findings from the enigma major depressive disorder working group. Mol Psychiatry 21, 806–812.
Schrijvers, D., Hulstijn, W., Sabbe, B.G., 2008. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. J. Affect Disord. 109, 1–20.
Sobin, C., Sackeim, H.A., 1997. Psychomotor symptoms of depression. Am. J. Psychiatr. 154, 4–17.
Trajkovic, G., Starcevic, V., Latas, M., et al., 2011. Reliability of the Hamilton Rating Scale for depression: a meta-analysis over a period of 49 years. Psychiatry Res. 189 (1), 1–9.
UK ECT Review Group, 2003. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 361, 799–808.
van Diermen, L., van den Ameele, S., Kamperman, A.M., et al., 2018. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. Br. J. Psychiatr. 212, 71–80.
van Diermen, L., Vanmarcke, S., Walther, S., et al., 2019. Can psychomotor disturbance predict ect outcome in depression? J Psychiatr. Res. 117, 122–128.
Vares, E.A., Salum, G.A., Spanemberg, L., et al., 2015. Depression dimensions: integrating clinical signs and symptoms from the perspectives of clinicians and patients. PLoS One 10, e0136037.
Wade, B.S., Joshi, S.H., Njau, S., et al., 2016. effect of electroconvulsive therapy on striatal morphometry in major depressive disorder. Neuropsychopharmacology 41, 2481–2491.
Wise, R.A., 2008. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox. Res. 14, 169–183.
Yrondi, A., Peran, P., Sauvaget, A., et al., 2018. Structural-functional brain changes in depressed patients during and after electroconvulsive therapy. Acta Neuropsychiatr. 30, 17–28.