European Neuropsychopharmacology 79 (2024) 38–48

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Effect of erythropoietin on cognitive side-effects of electroconvulsive therapy in depression: A randomized, double-blind, placebo-controlled trial

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ARTICLE INFO

Keywords:
ECT
Cognition
Erythropoietin
Treatment
Randomized controlled trial

ABSTRACT

Electroconvulsive therapy (ECT) is one of the most effective and rapid-acting treatment for severe depression but is associated with cognitive side-effects. Identification of add-on treatments that counteract these side-effects would be very helpful. This randomized, double-blinded, placebo-controlled, parallel-group study investigated the effects of four add-on erythropoietin (EPO; 40,000 IU/ml) or saline (placebo) infusions over 2.5 weeks of ECT (eight ECT sessions) in severely depressed patients with unipolar or bipolar depression. Neuropsychological assessments were conducted pre-ECT, three days after the eighth ECT (week 4), and at a 3-month follow-up. Further, functional magnetic resonance imaging (fMRI) was conducted after the eighth ECT. The primary outcome was change from pre- to post-ECT in a 'speed of complex cognitive processing' composite. Secondary outcomes were verbal and autobiographical memory. Of sixty randomized patients, one dropped out before baseline. Data were thus analysed for 59 patients (EPO, $n = 33$; saline, $n = 26$), of whom 28 had fMRI data. No ECT-related decline occurred in the primary global cognition measure ($ps \geq 0.1$), and no effect of EPO versus saline was observed on this outcome ($ps \geq 0.3$). However post-ECT, EPO-treated patients exhibited faster autobiographical memory recall than saline-treated patients ($p = 0.02$), which was accompanied by lower memory-related parietal cortex activity. The absence of global cognition changes with ECT and EPO, coupled with the specific impact of EPO on autobiographical memory recall speed and memory-related parietal cortex activity, suggests that assessing autobiographical memory may provide increased sensitivity in evaluating and potentially preventing cognitive side-effects of ECT.
Trial registrations: ClinicalTrials.gov: NCT03339596, EudraCT no.: 2016-002326-36.

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https://doi.org/10.1016/j.euroneuro.2023.12.004
Received 6 July 2023; Received in revised form 11 December 2023; Accepted 14 December 2023
Available online 20 December 2023

1. Introduction

Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depression, with response and remission rates of around 70 % and 50 %, respectively, in severely ill and treatment-resistant patients (van den Broek et al., 2004; van Diermen et al., 2018a, b). However, ECT is often a treatment of last resort because of its cognitive side-effects that may persist for weeks (Fernie et al., 2014; Landry et al., 2021; Semkovska and McLoughlin, 2010; Sienaert et al., 2010). Side-effects have been observed across several domains, including episodic memory and executive functions (Landry et al., 2021; Semkovska and McLoughlin, 2010). However, they occur with considerable inter-individual variability that may render them undetectable at a group level (Obbels et al., 2018). Memory impairments are the most frequently reported side effect of ECT (Chakrabarti et al., 2010), with around half of ECT-treated patients exhibiting subjective memory difficulties, which they attribute to ECT (Rose et al., 2003; Sigstrom et al., 2020). This is in keeping with meta-analytic evidence for particular side-effects within verbal memory and autobiographical memory (Landry et al., 2021). Despite memory complaints after the treatment, there is no long-term increased incidence of dementia (Hjerrild et al., 2021; Osler et al., 2018).

Autobiographical memory gaps are of primary concern to patients and their relatives because of the importance of personal memories for patients' identity and sense of a coherent self (Conway and Pleydell-Pearce, 2000; Wilson and Ross, 2003). However, the persistency and severity of autobiographical memory decline with ECT is controversial (Lomas et al., 2021) because of methodological challenges. While most studies have used the Columbia University Autobiographical Memory Interview or its short form (AMI-SF) (McElhiney et al., 2001), the validity and reliability of this interview has been questioned (Semkovska and McLoughlin, 2013, 2014). An alternative is the Autobiographical Memory Test (AMT) (Williams and Broadbent, 1986), which is a performance-based neuropsychological measure of autobiographical memory that is clinically relevant for predicting the course of major depressive disorder (MDD) (Summer et al., 2010), has good psychometric properties (Griffith et al., 2012). The AMT has been adapted for functional magnetic resonance imaging (fMRI) (Papadatou-Pastou et al., 2012) but has not yet been used in ECT studies.

Investigation of medications to reduce the cognitive side-effects of ECT has gained increasing interest over the past few years. A recent systematic review of these studies found preliminary evidence for effects of memantine, an antagonist of the NMDA (N-Methyl-D-Aspartate)-receptor subtype of the glutamate receptor that is used to treat Alzheimer's disease, and of liothyronine, a thyroid hormone replacement for treatment of hypothyroidism (Verdijk et al., 2022). However, the overall quality of the evidence was low because of small sample sizes and high risk of bias in the studies. This highlights the need to investigate the potential of new add-on treatments to diminish the cognitive side-effects of ECT.

Erythropoietin (EPO) is a promising add-on treatment to ECT because of its potential to improve cognition in mood disorders (Kellner et al., 2015; Miskowiak et al., 2014a, b). In addition to the synthesis of EPO in the kidney, EPO is produced in the brain, where it plays key roles in neuroprotection and development, attenuation of oxidative stress and inflammation (Fond et al., 2012) and cognition (Kastner et al., 2012; Siren et al., 2009). Systemically administered EPO crosses the blood-brain barrier and aids neuroplasticity and cognition when given in high doses (≥500 IU/kg body weight) (Miskowiak et al., 2012; Sargin et al., 2010). We found in a series of randomized controlled trials that eight to twelve weeks of high-dose EPO improved speed of complex cognitive processing across attention, memory, and executive function, in patients with MDD (Miskowiak et al., 2014b), bipolar disorder (BD) (Miskowiak et al., 2014a) (although with no effects on the primary depression and verbal memory outcome measures, respectively), multiple sclerosis (Ehrenreich et al., 2007a), or schizophrenia (Ehrenreich et al., 2007c). These effects were accompanied by and correlated with increased fronto-parietal activity during memory encoding and working memory, as evidenced by functional magnetic resonance imaging (fMRI) (Miskowiak et al., 2014a, 2014b, 2016). Importantly, the EPO-related changes in cognition and neural activity were independent of mood symptoms and lasted beyond red blood cell normalization. It is therefore possible that they are mediated by direct neurobiological actions, potentially including activation of anti-inflammatory, anti-apoptotic, and antioxidant signalling pathways (Brines et al., 2000; Miljus et al., 2014; Sargin et al., 2010), growth of dendrites, and maturation of neural progenitor cells (Almaguer-Melian et al., 2016; Byts and Sirén, 2009).

The present randomized, double-blind, placebo-controlled study aimed to investigate (i) whether add-on EPO treatment over three weeks could counteract cognitive side-effects of ECT, and (ii) the neuronal underpinnings of potential cognitive benefits (for details, see the study protocol (Schmidt et al., 2018a)). We hypothesized that EPO would reduce ECT-related decline in: (I) a broad cognition measure that showed sensitivity to EPO (Miskowiak et al., 2014a) (primary outcome), and (II) autobiographical memory and verbal memory, given their particular sensitivity to side-effects of ECT (Landry et al., 2021) (secondary outcomes), and that this would be accompanied by differences in memory-related activity in fronto-parietal regions in an fMRI adapted version of the AMT.

2. Experimental procedures

2.1. Study design and procedures

This trial has a randomized, double-blinded, placebo-controlled, parallel group design. The study investigated the effects of EPO vs. placebo (saline) on reducing cognitive side effects of ECT. The first infusion was given within 24 h prior to the first ECT session, while the following three infusions were given immediately after ECT at weekly intervals (i.e., after the first, fourth, and seventh ECT session, respectively) (Schmidt et al., 2018b). Neuropsychological assessments and treatment sessions were conducted at psychiatric centres in the Capital Region of Denmark. Neuropsychological assessments were conducted before ECT initiation (pre-ECT/baseline), week 4 (i.e., after the last EPO/saline infusion and three days after the 8th ECT session), and at a 3-month follow-up visit.

Prior to inclusion, patients were screened with Mini International Neuropsychiatric Interview (MINI) to verify an International Classification of Diseases 10th edition (ICD-10) diagnosis of depression as part of a unipolar disorder (UD) or BD (Lecrubier et al., 1997) with current moderate to severe depressive episode symptoms, a Hamilton Depression Rating Scale 17-items version (HDRS-17) total score≥17 (Hamilton, 1960), fluency in Danish language, and were able to provide informed consent. Eligible patients were randomized to receive four intravenous infusions of high-dose recombinant human EPO (Epoetin alpha; Eprex; 40.000 IU/ml) or saline (1 ml sodium chloride (NaCl) 0.9 %); placebo) diluted with 100 ml saline (0.9 % NaCl) during a 2.5-week add-on treatment period (see (Schmidt et al., 2018b) for details on EPO storage and administration procedures). The EPO dosage administered was equal to the amount found to be effective for modulating cognition with short-term administration (Miskowiak et al., 2007) and for enhancing cognitive function with long-term treatment across neuropsychiatric conditions in other trials (Ehrenreich et al., 2004, 2007b, c; Miskowiak et al., 2014a, b).

The sample size and statistical power have been calculated by Pharma Consulting Group AB using PROC POWER and the SAS code in SAS version 3. We used block randomization with stratification for sex and age (<40/ =>40 years) with varying block sizes, as described in the published study protocol (Schmidt et al., 2018a). See the published study protocol for descriptions of power calculation and blinding procedures (Schmidt et al., 2018a).

2.2. ECT procedures

ECT was administered with the Thymatron System IV device (Somatics, LLC, USA) according to the standard protocol of the Mental Health Services of the Capital Region of Denmark. Treatments were given three times per week. Patients were anaesthetized with thiopental, and succinylcholine was administered for muscle relaxation. Bitemporal electrode placement with energy dosage 1.5 times above seizure threshold was the standard treatment but could be changed to right unilateral (RUL) treatment in the case of severe cognitive side-effects. A dosing strategy with the initial dose based on the patient's age was used (charge [per cent of 500 millicoulomb] = 50 % of the age). In subsequent treatments, a titration based on seizure quality (configuration and length of the EEG seizure, which should exceed 25 s) was applied.

2.3. Participants

We recruited in-patients from the Mental Health Services, Capital Region of Denmark. Eligible participants were 18–70 years of age, had a diagnosis of UD or BD with current moderate to severe depressive episode symptoms, as reflected by a HDRS-17 total score≥17. Key exclusion criteria were involuntary ECT, previous ECT within the last three months, other neuropsychiatric conditions (schizophrenia or schizoaffective disorder), current alcohol or substance use disorder, or acute significant suicide risk. Candidates with contraindications to EPO were also excluded.

2.4. Study approvals

The study was approved by the Danish Research Ethics Committee for the Capital Region of Denmark (H-16038506; BIO protocol no.: H-7-2014-007) and The Danish Data Protection Agency Capital Region of Denmark (RHP-2017-023; BIO protocol no.: RHP-2015-023). Written informed consent following oral and written study information was collected from all participants prior to inclusion. The trial was performed in accordance with the Declaration of Helsinki. Trial registrations: ClinicalTrials.gov: NCT03339596 and EudraCT: 2016-002326-36.

2.5. Outcome measures

2.5.1. Neuropsychological test measures

The *primary outcome* was change from pre- to post-ECT (week 4) in 'speed of complex cognitive processing', a broad cognitive composite score assessing attention, verbal learning and memory, and executive functions. This composite was selected based on (a) previously detected improvement on this as secondary/tertiary outcome measure following eight weeks of EPO vs. saline treatment in BD (Miskowiak et al., 2014a) and (b) the ISBD Targeting Cognition Task Force recommendations to generally include a broad cognitive composite score as the primary outcome measure in pro-cognitive treatment trials (Miskowiak et al., 2017). Specific measures included in this composite score were: Rey Auditory Verbal Learning Test (RAVLT) List I-V total recall (Miskowiak et al., 2008; Schmidt, 1996), The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding (Randolph et al., 1998), Verbal Fluency (letter "D") (Borkowski et al., 1967), Wechsler Adult Intelligence Scale (WAIS)-III Letter-Number Sequencing (Wechsler, 1997), Trail Making Test Part B (TMT-B) (Battery), and Rapid Visual Information Processing (RVP) Mean Latency from Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd.).

The *originally planned secondary outcomes* were: (i) retrograde autobiographical memory, measured with the Columbia University Autobiographical Memory Interview – Short Form (AMI-SF) (Lisanby et al., 2000; McElhiney et al., 1995) and (ii) verbal learning and memory assessed with RAVLT (the List I-V total recall score) (Miskowiak et al., 2008; Schmidt, 1996). However, it turned out that these often severely depressed patients were mostly unable to complete the AMI-SF interview after their neuropsychological assessment. Therefore, we decided early in the project to *omit the AMI-SF* and instead assess autobiographical memory with the fMRI-adapted AMT (details below).

The *tertiary cognitive outcomes* (Table S3) included single measures of RAVLT (Immediate recall, Delayed recall, and Recognition), TMT-B, WAIS-III LNS, RBANS Coding, Verbal Fluency "D", and RVP A' and Mean Latency (CANTAB), respectively. Further tertiary outcomes comprised depression severity as rated with HDRS-17 and the Beck Depression Inventory 21 items-version (BDI-21) (Beck et al., 1961), respectively, and subjectively-reported cognitive difficulties on the Cognitive Complaints in Bipolar Disorder Rating Assessment scale (COBRA) (Rosa et al., 2013).

2.5.2. The Autobiographical Memory Test fMRI paradigm

Using ePrime version 2.0 (Psychology Software Tools, Pittsburgh, U. S.), a modified block-design, button-click version of the Autobiographical Memory Test (AMT) (Papadatou-Pastou et al., 2012) for fMRI was translated and adapted to Danish. Hence, AMT data was only collected post-ECT as part of the fMRI assessment. Participants were presented with a cue word on a monitor, such as 'ginger', and were instructed to retrieve a memory at a specific time and place with the word 'ginger', such as "last month, when I went to the restaurant with my friends and had a spicy Asian soup with ginger". This task was practiced prior to scanning. During scanning, participants were presented with 24 stimulus blocks interleaved with fixation crosses in a fixed order. They were instructed to retrieve a specific memory from their lives in response to each cue word and to press a button immediately upon successful retrieval of their memory. They were then asked to continue to dwell on this memory until the cue word was replaced by the fixation cross. As a control task, participants were instructed to count the letters of nonsense words and press the same button once they had finished. In total, 12 cue words and 12 nonsense words were presented on a black screen for 20 s each, each trial separated by a 1000 ms fixation cross. Stimuli were intermixed in the order of cue, nonsense, cue, etc. Stimulus onset times and times between onset and button-presses were logged by ePrime to be used in the statistical analyses. After the session, the recalled memories were verified by the rater.

Average search time (ST) between cue word onset and button presses for successful autobiographical memory retrieval was calculated for each participant by adding together the STs of each trial and dividing the sum by the number of trials. Only participants with complete behavioural logs available were included in the analysis.

2.6. MRI data acquisition protocol

Functional MRI data were collected using a SIEMENS Prisma scanner and a 64-channel head-neck coil at the University Hospital of Copenhagen, Denmark. Functional blood-oxygen-level-dependent (BOLD) T2*-weighted images were acquired using an echo-planar imaging two-dimensional (EP2D) sequence employing the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, matrix size = 64×64, slices per volume = 63, slice thickness = 3 mm with 25 % gaps in-between, total volumes per scan = 254, field of view (FOV) = 230×230 mm. Structural T1-weighted images used for registration were acquired employing a standard Magnetization Prepared Rapid Gradient Echo (MPRAGE) pulse sequence (TR = 1900 ms; TE = 2.58 ms; flip angle = 9°; distance factor = 50 %; FOV = 230×230 mm; slice thickness = 0.9 mm). To account for B0 inhomogeneities, fieldmap data were acquired using a gradient echo sequence (TR = 400 ms; TE1 = 4.92 ms; TE2 = 7.38 ms; flip angle = 60°). Using the FMRIB Software Library (FSL) version 6.0.5.2, a fieldmap was calculated using the phase difference between the two echoes to be used in the image reconstruction process to correct for geometric distortions.

2.7. Statistical analyses of the demographic and clinical data

We conducted statistical analyses using the IBM Statistical Packages for the Social Sciences (SPSS) v28.0.1.0 with significance α-level $p<0.05$ (two-tailed). Group comparisons for demographic and clinical data were performed with independent samples *t*-tests (normally distributed data), Mann-Whitney *U* (non-parametric data), and Pearson's Chi-square (χ^2). Data normality was established applying Shapiro-Wilk's test (Shapiro and Wilk, 1965) along visual inspection of histograms and Q-Q-plots. We *z*-transformed patients' cognitive test performance raw scores to standardize these scores onto the same standard normal deviate scale, necessary to calculate our primary cognitive outcome score ('speed of complex cognitive processing') as well as individual cognitive domain composite scores. To *z*-transform patients' cognitive test performance scores, we extracted and used neuropsychological test score data from an age-, sex-, and educational years-matched healthy control (HC) group from our Bipolar Illness Onset (BIO) study (Kessing et al., 2017) ($N = 36$). These HC had no personal or first-degree relative history of psychiatric disorder, neurological illness (including dementia), nor current alcohol or substance use disorder (Kessing et al., 2017).

Firstly, the possible cognitive side effects of ECT on the primary and secondary cognition measures were investigated using within-group paired samples *t*-tests for saline treated patients alone. This within-group analysis was essential to determine whether EPO treatment could be expected to mitigate cognitive side effects of ECT, i.e., mitigate any overall performance decline observed in placebo-treated patients from pre- to post-ECT. Secondly, to investigate effects of EPO vs. saline, the pre-defined primary, secondary, and tertiary outcomes were analysed with linear mixed-effects models. Model factors were time, stratum (classifying age and sex), and treatment (with placebo treatment as the reference category to ensure baseline correction). Fixed effects were time, stratum, time*stratum, and time*treatment in accordance with the approach in our recent cognitive intervention trial. For autobiographical memory, which was assessed only post-ECT, an independent samples *t*-test was conducted to investigate potential differences in AMT performance between treatment groups. We applied Benjamini-Hochberg method (Benjamini and Hochberg, 1995) to adjust any significant group differences for multiple comparisons and control for false discovery rate (FDR; i.e., the expected rate of type I error) for secondary and tertiary outcomes, respectively. The FDR was set to 5 %/0.05, while adjusted *p*-values below the calculated critical value (Benjamini and Hochberg, 1995) were considered significant. We applied this correction procedure to reduce the FDR based on the large number of comparisons conducted in the present analyses. Indeed, this approach is less stringent and conservative, thereby leading to higher power, than e.g. the commonly used family-wise error rate (FER) (e.g., applying Bonferroni correction procedures) (Benjamini and Hochberg, 1995).

2.8. fMRI data pre-processing and analysis

The FEAT (Woolrich et al., 2001) tool from FSL version 6.0.5.2 was used to process all 37 available functional volumes. As a means of assuring data quality, visual assessment of functional and structural volumes was conducted using fsleyes within FSL. Pre-processing steps included brain extraction, rigid-body motion correction, linear registration to the individual T1-weighted image, non-linear registration to the standard-space MNI152 at 2 mm isotropic voxel size, and spatial smoothing using a 5 mm FWHM gaussian kernel. Geometric distortions were corrected for inhomogeneities of the B0 field using the acquired field map.

For first-level subject analysis, a general linear model (GLM) was implemented with three explanatory variables (EVs): Fixation, Cue, and Nonsense, corresponding to the interstimulus fixation cross, mnemonic cue words, and nonsense words, respectively. EVs were convolved using a double-gamma hemodynamic response function (HRF) and slice-timing corrected through temporal derivatives. Six subject-level movement regressors (translations and rotations in 3D) were added as confounding variables. To further ensure data integrity, we inspected the outcome of the subject-level analysis including the extraction of motion outputs as calculated by the MCFLIRT tool within FSL. Movement outliers exceeding 0.25 mm in relative mean displacement (RMD) were excluded, while those with RMD > 0.20 but below exclusion threshold were visually inspected and kept or discarded according to the severity of their displacement plots. The contrast of interest was the difference between the mean activation during the mnemonic cue condition and the mean activation during the nonsense word condition (cue vs. nonsense).

Whole-brain group-level analyses of the contrast of interest were carried out using FMRIB's Local Analysis of Mixed Effects stage 1 (FLAME 1) within FSL's FEAT tool (Woolrich et al., 2004). First, we confirmed task-related activations (cue vs. nonsense) across all participants using a one sample *t*-test. Then, to investigate potential effects of treatment, we employed a two-sample unpaired *t*-test, with treatment (EPO/saline) as the grouping variable. Cluster significance was assessed at corrected $p = 0.05$ based on a cluster forming threshold of $Z = 2.57$ (Worsley, 2001). Significant clusters were reported with peak z cluster coordinates in standard MNI152 space.

3. Results

3.1. Participant flow

Fig. 1 displays the CONSORT flowchart diagram. A total of 60 patients were enrolled and randomized (EPO: $n = 34$; saline: $n = 26$) from June 2017 to September 2022 with the last post-ECT assessment conducted in October 2022. Prior to the baseline assessment, one EPO-randomized patient withdrew consent from study participation and was excluded. Five patients (i.e., 8 %) did not complete the week 4 post-ECT neuropsychological assessment (EPO: $n = 3$; saline: $n = 2$), while 20 (34 %) were lost to the 3-month post-ECT follow-up (EPO: $n = 12$; saline: $n = 8$). One EPO-treated patient received three infusions, i.e., more than half of the intended infusions, which was the criterion for being followed up with neuropsychological assessment post-ECT. However, two EPO-treated patients were not assessed post-ECT, because they only received two infusions at baseline. Data from all patients were included in the intention-to-treat (ITT) analyses in the linear mixed models as described in the trial protocol (Petersen et al., 2018; Schmidt et al., 2018b). Hence, we analysed data for a total of $N = 59$ patients (EPO: $n = 33$; saline, $n = 26$) (see CONSORT flowchart diagram in Fig. 1).

The MRI scanner was not available after March 2021, and we were therefore unable to scan the three last participants included between March 2021 and September 2022 (see Fig. 1 for CONSORT Flowchart). Additionally, 12 participants (EPO, $n = 5$; saline, $n = 7$) did not undergo fMRI due to either symptom exacerbation, claustrophobia, metal implants in the body, or technical issues with the MRI response pad at the day of assessment. Consequently, fMRI was conducted for a total of 37 participants (EPO, $n = 21$; saline, $n = 16$), of whom seven exhibited excessive movement during the scan (EPO, $n = 3$; saline, $n = 4$), one (EPO) misunderstood the task, and one (EPO) had missing behavioural data (no button presses upon recall of autobiographical memories). Thus, AMT fMRI data was available and analysed for 28 patients (EPO, $n = 16$; saline, $n = 12$).

3.2. Group characteristics

3.2.1. Comparisons of patients vs. healthy controls

The entire patient cohort ($N = 59$) and the HC group ($N = 36$), from which data were used for neuropsychological test performance *z*-score transformations, were matched on age ($p = 0.2$), sex ($p = 0.4$), and years of education ($p = 0.5$) (Table S1).

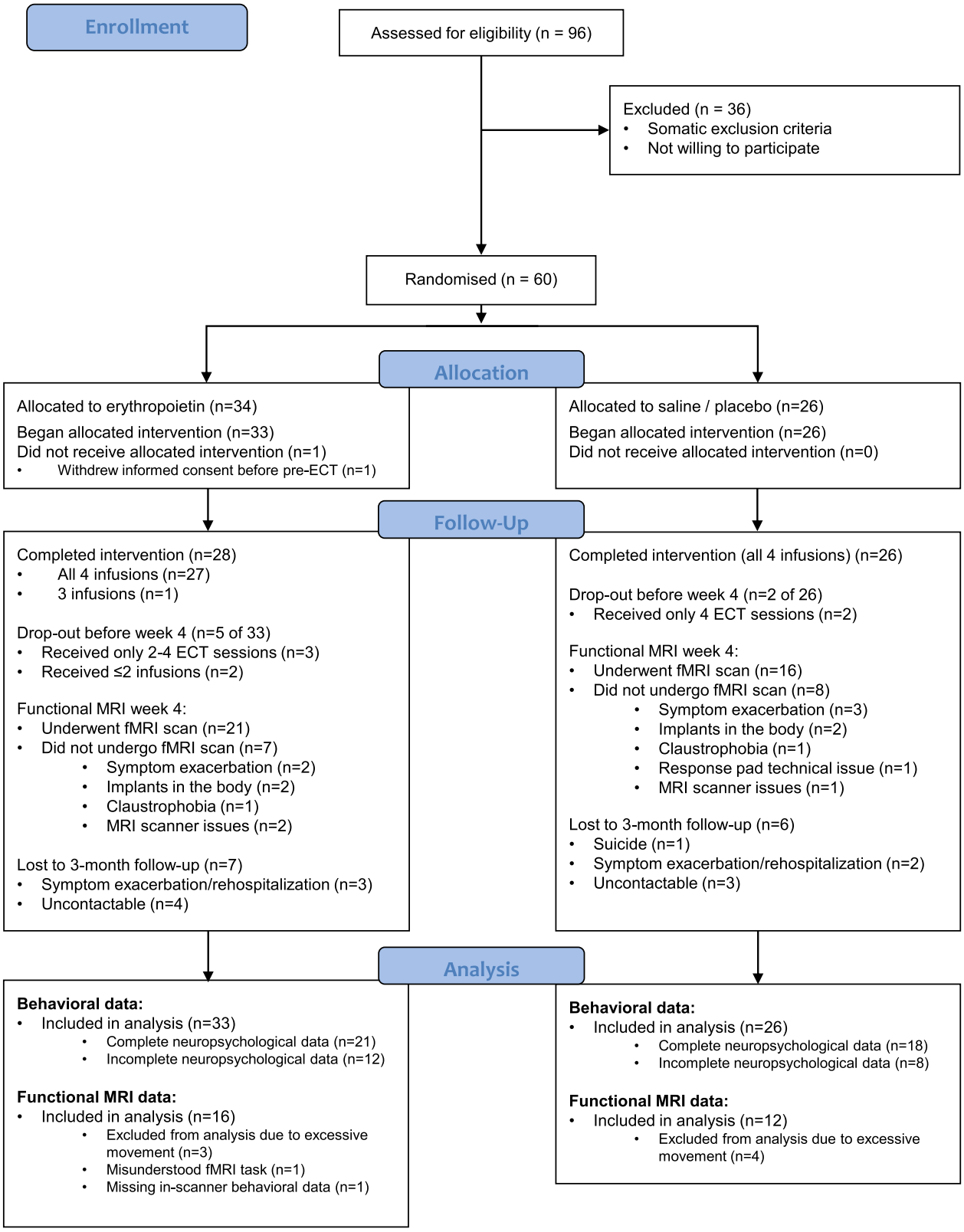

Fig. 1. CONSORT Flow Diagram. Diagram of the patient flow chart in accordance with CONSORT 2010 statement. Of the $N = 60$ patients included in the study, $n = 34$ were randomized to 40.000 IU recombinant human EPO, and 26 patients were randomized to saline (placebo) treatment. Data from $N = 59$ patients ($n = 33$ EPO-treated patients and $n = 26$ saline-treated patients) were included in the final mixed model analysis with intention-to-treat approach.

3.2.2. Comparisons of EPO and saline treatment groups

Pre-ECT demographic and clinical comparisons of EPO-treated (n = 33) and saline-treated (n = 26) patients are presented in Table 1. Groups were balanced in terms of demographic and clinical characteristics, including age, sex, years of education, body mass index (BMI), diagnosis distribution (unipolar vs. bipolar depression), pre-ECT depression symptom severity (i.e., HDRS-17 total score at time of inclusion), as well as year of illness onset, duration of illness, and number of previous psychiatric hospitalizations ($ps \geq 0.2$). Moreover, groups were matched in terms of medication status ($ps \geq 0.5$) (see Table 1). Twenty-two patients (EPO, n = 16; saline, n = 6) had current/previous comorbid psychiatric disorders, including attention-deficit-hyperactivity disorder (ADHD) (n = 2), anxiety disorder (n = 2), personality disorder (n = 10), post-traumatic stress disorder (PTSD) (n = 4), autism (Asperger's syndrome, n = 1), and previous anorexia nervosa (n = 1), and/or previous alcohol use disorder (n = 2). For the 28 patients with available fMRI data, EPO and saline groups were balanced in terms of demographic and clinical characteristics (Table S2).

3.3. Primary and secondary outcomes

Regarding the investigation of potential cognitive side-effects of ECT, within-group paired samples t-tests conducted within the saline group alone revealed no ECT-associated decline in the *primary outcome,* the 'speed of complex cognitive processing' composite from pre- to post-ECT (week 4) in saline-treated patients (p = 0.1; Table S4). In contrast, for the *secondary outcome*, verbal memory measured with the RAVLT Total Recall (list I-V), there was a substantial decline from pre- to post-ECT (change, mean±SD = −0.63±0.97, p = 0.004), with no improvement from pre-ECT to the 3-month follow-up in saline-treated patients (change, mean±SD =0.03±0.69, p = 0.9; Table S4).

Table 2 displays linear mixed models results for primary and secondary outcomes comparing the EPO and saline treatment groups across assessments. No significant effect was found of EPO over saline on the primary speed of complex cognitive processing composite from pre- to post-ECT or 3-month follow-up ($ps \geq 0.3$). There was also no significant effect of EPO on the secondary outcome, RAVLT Total Recall ($p \geq 0.1$; Table 2). Regarding the co-secondary outcome, autobiographical memory assessed post-ECT, EPO-treated patients were faster to recall personal memories than those given saline, with a large effect size (recall time in seconds, mean±SD: EPO, 7 ± 2; saline, 10±4; $t(26) = -2.41$, p = 0.02, d = −0.92; Fig. 2). This effect survived Benjamini-Hochberg p-value correction (calculated critical $p \leq 0.025$). Since we observed no effects of EPO over saline treatment on our primary and secondary cognitive outcomes nor on the degree of mood symptom reduction from pre- to post-ECT and 3 months follow-up (Section 3.4), these primary and secondary analyses were not controlled for mood symptoms.

Table 1
Group comparison of EPO- and saline-treated patients (N = 59).

	EPO (n = 33)	Saline (n = 26)	p-value
Demographics			
Age in years, M (SD)	40 (14)	38 (12)	0.7
Sex, female/male (%)	73/27	69/31	0.8
BMI, M (SD)	23 (4)	23 (3)	0.4
Years of education, M (SD)	16 (3)	15 (3)	0.7
Clinical characteristics			
Diagnosis, UD/BD (%)	79/21	69/31	0.6
HDRS-17 pre-ECT, M (SD)	28 (6)	27 (6)	0.6
Illness onset (years), Mdn (IQR)	22 (19)	21 (13)	0.4
Illness duration (years), Mdn (IQR)	13 (14)	14 (19)	0.3
No. of hospitalizations, Mdn (IQR)	2 (2)	1 (2)	0.2
No. of ECT treatment sessions, M (SD)	11 (4)	11 (4)	0.7
Psychotropic medication, n (%)			
Antidepressants	23 (70 %)	16 (62 %)	0.6
Antipsychotics	21 (64 %)	18 (69 %)	0.8
Anticonvulsants	6 (18 %)	7 (27 %)	0.5
Lithium	8 (24 %)	8 (31 %)	0.8
Other psychotropic medication	20 (61 %)	16 (61 %)	0.9
No. of psychotropic medication classes, n (%)			0.5
1	18 %	12 %	
2	36 %	23 %	
3	36 %	54 %	
4	9 %	8 %	

Abbreviations: EPO=erythropoietin; M=mean; SD=standard deviation; Mdn=Median; IQR=Interquartile range; BMI=body mass index; UD=unipolar disorder; BD=Bipolar depression; HDRS-17=Hamilton Depression Rating Scale 17-items. Independent samples t-tests for normally distributed data (mean (SD)), Mann-Whitney U test for non-parametric data (median (IQR)), chi-square for categorical variables.
Missing data: n = 13 patients on years of education (7=EPO, 6=saline); n = 2 patients on HDRS-17 pre-ECT (1=EPO; 1=saline); n = 2 on no. of hospitalizations (EPO=2).

Table 2
Primary and secondary cognitive outcomes: effects of erythropoietin (EPO) vs. saline estimated with linear mixed-effects models. Assessments were conducted at baseline, in week 4 and 3 months post electroconvulsive therapy in EPO- and saline-treated patients with unipolar or bipolar depression (N = 59).

	Baseline	Week 4		3 months post-ECT	
		EPO/saline Treatment effect [95 % CI]	p-value	EPO/saline Treatment effect [95 % CI]	p-value
Primary cognitive outcome					
Speed of complex cognitive processing		0.1 [−0.53, 0.72]	p = 0.8	0.16 [−0.17, 0.49]	p = 0.3
EPO, z-score M (SD)	−1.30 (1.12)	−1.40 (1.23)		−0.70 (0.83)	
Saline, z-score M (SD)	−1.04 (1.22)	−1.32 (1.46)		−0.65 (0.98)	
Secondary cognitive outcomes					
RAVLT List I-V total recall		1.08 [−3.94, 6.10]	p = 0.7	3.50 [−1.07, 8.06]	p = 0.1
EPO, z-score M (SD)	−1.02 (1.27)	−1.38 (1.36)		−0.46 (1.15)	
Saline, z-score M (SD)	−0.57 (1.37)	−1.06 (1.50)		−0.42 (1.55)	
Autobiographical memory recall, speed		–	–	–	–
EPO, seconds M (SD)	-	7 (2)	***p* = *0.02****[a]	–	–
Saline, seconds M (SD)	–	10 (4)		–	–

Abbreviations: EPO=erythropoietin; M=mean; SD=standard deviations; CI=confidence interval; RAVLT=Rey Auditory Verbal Learning Test; fMRI=functional magnetic resonance imaging. Missing data: **Speed of complex cognitive processing** (week 4: EPO=5, saline=2; 3-months post-ECT: EPO=12, saline=8), **RAVLT List I-V total recall** (week 4: EPO=5, saline=2; 3-months post-ECT: EPO=12, saline=8). Autobiographical memory was assessed post-ECT based on data from n = 28 patients (EPO. N = 16; saline, n = 12). [a] Independent samples t-test comparison analysis.

3.4. Tertiary outcomes

Mean and standard deviation (SD) data and linear mixed models results for treatment groups on tertiary outcome measures across assessments are presented in Tables 3 and S4. No significant effects of EPO over saline were detected within any tertiary cognitive outcomes ($ps \geq 0.09$) or self-reported subjective cognitive difficulties at any time point (COBRA; $ps \geq 0.4$) (Tables 3 and S3). Using paired samples t-tests, we observed a significant reduction in observer-rated and self-reported

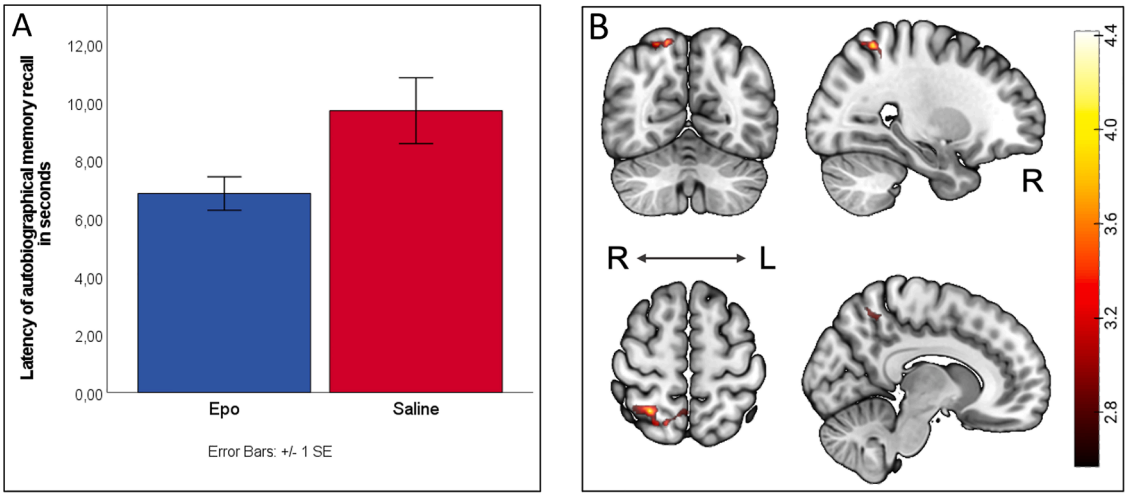

Fig. 2. A. Plot of mean time in seconds to retrieve autobiographical memories by treatment group (EPO vs. saline) in EPO- and saline-treated patients with unipolar or bipolar depression ($N = 28$). Error bars represent standard deviations. B. Brain regions showing lower Autobiographical Memory Recall (cue – nonsense words) in EPO vs. placebo group (corrected cluster $p < 0.05$). Statistical maps thresholded at $z = 2.57$.

mood symptom severity (HDRS-17 total score and BDI-21 total score, respectively) within both the EPO- and saline-treated groups from pre-ECT to post-ECT and 3 months follow-up, respectively ($ps<0.001$). However, no significant effects of EPO over saline were detected on observer-rated or self-rated depression severity over time (HDRS-17 or BDI-21 total scores; $ps\geq0.3$) (Tables 3 and S3).

3.5. fMRI results

Across the entire patient sample, a distributed task-relevant network was found to be activated during autobiographical memory recall (cue vs nonsense). The network demarcated spans the bilateral hippocampi, the posterior and anterior divisions of the cingulate gyri, and the precuneus. In addition, several left-lateralized areas were also found to be involved in this contrast, including the superior, middle, and inferior frontal gyri, as well as the insular cortex, the middle temporal gyrus, and the angular gyrus (Table 4 for peak cluster activations).

Comparing activity specific to autobiographical memory recall (cue vs. nonsense) between EPO and saline groups, we identified a significant region in the right superior parietal lobe and precuneus, showing lower activation in EPO vs saline groups (Table 4 for peak cluster activations). Because no significant differences in HDRS-17-scores were found between the groups at the time of scanning ($t(26) = 1.96$, $p>0.05$), no covarying for symptom severity was done.

3.6. Posthoc exploratory analyses of cognition outcomes

Posthoc exploratory analysis of the *within-group change* from Pre-ECT to Post-ECT in RAVLT Total Recall (secondary outcome) showed that the ECT-related verbal memory decline seen in the saline group (change, mean±SD: −0.63±0.97, $p = 0.004$) was absent in the EPO-treated group (change, mean±SD: −0.28±1.12, $p = 0.2$; Table S4). Also, in contrast with the saline group, the EPO-treated patients showed a verbal memory improvement from pre-ECT to the 3-month post-ECT follow-up (change, mean±SD: 0.64±0.94, $p = 0.003$; Table S4). The selective within-group stability of verbal memory (secondary outcome) during ECT and subsequent improvement in the EPO group provides *hypothesis-generating evidence* for possible memory benefits of EPO. However, these preliminary findings should be interpreted with caution because the effects did not emerge in the a priori planned linear mixed models analyses.

3.7. Safety outcomes

The safety outcomes in Supplementary Appendix I detail incidents and adverse events reported by participants, encompassing symptoms like headache, dizziness, malaise, and abnormalities in blood parameters such as haemoglobin and erythrocyte levels. Notably, while suicide and suicidal behaviour occurred in individual cases (unrelated to the intervention), no serious adverse events were observed. EPO-treated patients exhibited normalization of haemoglobin and erythrocyte levels at the 3-month follow-up compared to the saline-treated group (Table S5).

4. Discussion

In this RCT of the effects of add-on EPO ($n = 33$) vs. saline ($n = 26$) in depressed patients with MDD or BD undergoing ECT, we found no effects of EPO on the primary cognition outcome, a broad 'speed of complex cognitive processing' measure. This broad cognition measure was, unexpectedly, also unaffected by ECT. There was no effect of EPO on verbal memory, one of the two secondary outcomes. In contrast, the other secondary outcome, autobiographical memory, revealed significantly faster recall performance in the EPO vs saline groups, and the effect survived correction for multiple testing. This effect of EPO on autobiographical memory was accompanied by reduced activity in parietal cortex activity during autobiographical memory retrieval in EPO vs. saline treated patients. These effects of EPO occurred in the absence of differences between EPO and saline groups in depression severity or subjective cognitive function.

The absence of ECT-associated decline in the primary broad 'speed of complex cognitive processing' outcome was unexpected, although recent meta-analytic evidence indicates side-effects specifically within verbal and autobiographical memory (Landry et al., 2021). In line with this meta-analytic finding, we found in the exploratory analysis that ECT produced only a specific decline in verbal memory. This is noteworthy, given evidence for greater cognitive side-effects of bilateral than unilateral ECT (Sackeim et al., 2000). Hence, it is possible that the absence of 'preventive effects' of EPO in speed of complex cognitive processing reflected suboptimal a priori selection of the primary outcome measure, despite previous EPO effects on this as a secondary outcome measure (Miskowiak et al., 2014a). In retrospect, autobiographic memory, verbal memory –or alternatively spatial memory (Fernie et al., 2014)- would have been more optimal choices as primary outcomes for trials investigating cognitive side-effects of ECT. In keeping with this, we found in

Table 3
Linear mixed-effects models results for tertiary outcomes in EPO- and saline-treated patients with unipolar or bipolar depression ($N = 59$).

	Post-ECT (week 4, after 8 ECT sessions)		3-month follow-up	
	Treatment effect [95 % CI]	***p*-value**	**Treatment effect [95 % CI]**	***p*-value**
Cognition				
Verbal learning and memory				
RAVLT Immediate recall	0.44 [−1.50, 2.38]	$p = 0.7$	0.22 [−1.37, 1.81]	$p = 0.8$
RAVLT Delayed recall	0.82 [−0.69, 2.33]	$p = 0.3$	1.18 [−0.18, 2.53]	$p = 0.09$
RAVLT Recognition	0.65 [−1.28, 2.57]	$p = 0.5$	0.25 [−0.82, 1.32]	$p = 0.6$
Working memory and executive functions				
TMT-B	−14.88 [−48.72, 18.96]	$p = 0.4$	−2.56 [−16.50, 11.39]	$p = 0.7$
WAIS-III LNS	0.26 [−1.14, 1.66]	$p = 0.7$	0.45 [−0.94, 1.84]	$p = 0.5$
Verbal fluency "d"	−0.18 [−1.99, 1.63]	$p = 0.8$	−0.04 [−2.09, 1.99]	$p = 0.9$
Sustained attention and psychomotor speed				
RBANS Coding	1.54 [−3.16, 6.25]	$p = 0.5$	2.80 [−1.55, 7.15]	$p = 0.2$
CANTAB RVP A'	0.003 [−0.03, 0.04]	$p = 0.9$	−0.01 [−0.05, 0.03]	$p = 0.5$
CANTAB RVP Mean Latency	16.36 [−63.06, 95.78]	$p = 0.7$	−4.42 [−68.39, 59.55]	$p = 0.9$
Subjective cognitive complaints				
COBRA total score	0.54 [−2.91, 3.99]	$p = 0.8$	−2.03 [−6.45, 2.39]	$p = 0.4$
Depression symptom severity				
HDRS-17 total score (observer-rated)	2.71 [−2.83, 8.24]	$p = 0.3$	−0.20 [−5.34, 4.95]	$p = 0.9$
BDI total score (self-rated)	3.12 [−4.41, 10.65]	$p = 0.4$	−3.56 [−11.06, 3.94]	$p = 0.3$

Abbreviations: EPO=erythropoietin; ECT=electroconvulsive treatment; CI=confidence interval; RAVLT=Rey Auditory Verbal Learning Test; TMT-B=Trail Making Test B; WAIS-III LNS=Wechsler Adult Intelligence Scale Version III Letter–Number Sequencing; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; CANTAB=Cambridge Neuropsychological Test Automated Battery; RVP=Rapid Visual Information Processing; COBRA=Cognitive Complaints in Bipolar Disorder Rating Assessment; HDRS-17=Hamilton Depression Rating Scale, 17-items version; BDI=Beck Depression Inventory.

post hoc exploratory within-group analyses that EPO-treated patients displayed an *absence of* decline of verbal memory. This provides preliminary hypothesis-generating support for subtle protective effects of EPO in this aspect of cognition, although the finding should be interpreted with caution.

The differences between EPO and saline groups post-ECT in the secondary behavioural and neuronal measures of autobiographical memory were interesting. Recent research (Landry et al., 2021; Lomas et al., 2021) emphasizes the importance of autobiographical memory as a sensitive indicator of cognitive side effects of ECT. This type of memory is particularly relevant to patients as it shapes their sense of identity and coherence (Conway and Pleydell-Pearce, 2000; Wilson and Ross, 2003). While we had originally planned to include the AMI-SF for measuring autobiographical memory, this interview-based instrument turned out to be too exhausting for patients and we had to omit this measure early in the trial. Instead, we used the AMT, which provides a brief, performance-based and less biased insight into autobiographical memory function and may thus be preferrable in future studies of ECT side-effects on cognition. In support of its validity, our fMRI adapted AMT activated brain regions previously implied in autobiographical memory, including the inferior and middle frontal gyri, PCC, insula, temporo-parietal regions, and the hippocampus across all participants (Ino et al., 2011; Maguire, 2001; Papadatou-Pastou et al., 2012; Young et al., 2012). The EPO-related *reduction* in parietal response during autobiographical memory retrieval is noteworthy because this region is a hub of the central executive and dorsal attention networks (Yeo et al., 2011), in which activity increases with an increasing load on attentional resources during memory performance (Magen et al., 2009). The reduced parietal activity in EPO-treated patients may therefore reflect a reduced need for recruiting neuronal resources to retrieve autobiographical memories (i.e., more efficient neural processing), in line with their faster autobiographical memory recall. While it would be premature to move away from the AMI-SF as an autobiographical memory measure in ECT trials, the clinical relevance of AMT (Summer et al., 2010) and present indication of sensitivity to ECT highlight AMT as promising test that deserves further investigation in ECT studies. To ensure fMRI compatibility, our adapted AMT paradigm used a limited set of key words ($n = 12$), leading to ceiling effects on memory recall. Future research should explore parallel, extended out-of-scanner AMT versions administered pre- and post-ECT to investigate autobiographical memory specificity (number and detail of memories).

Despite the encouraging preliminary effects of EPO on behavioural and neuronal measures of autobiographical memory, the effects on other aspects of cognition were overall relatively weak. One potential reason is that ECT is not associated with brain damage (Gbyl and Videbech, 2018) and therefore cannot be compared with traumatic, ischemic, hypoxic insults for which EPO has shown neuroprotective effects in preclinical studies (Siren et al., 2009) or with cognitive decline due to illness-related disruption of neuroplasticity or neurodegeneration (Ehrenreich et al., 2007a, c; Miskowiak et al., 2014a, b; Siren et al., 2009). In fact, ECT stimulates neurotrophic mechanisms (Perera et al., 2007; Schloesser et al., 2015; Wennstrom et al., 2004) and increases hippocampal volume, similar to EPO (Argyelan et al., 2021; Gbyl and Videbech, 2018; Miskowiak et al., 2015). However, paradoxically, this hippocampal effect of ECT was found to correlate with ECT-related cognitive decline (Argyelan et al., 2021; Gbyl et al., 2021). This may be due to a delay of functional integration of new neurons (Aimone et al., 2006), or because ECT is not a physiological stimulus (like running or learning) and may therefore result in excessive hippocampal neuroplasticity or other neurobiological effects that temporary disturb hippocampal function. Overlapping neuroplastic effects of EPO and ECT

Table 4
Cluster maxima for network of brain regions activated during Autobiographical Memory Recall (cue – nonsense words) across all participants and differences between treatment groups (EPO vs. saline) in EPO- and saline-treated patients with unipolar or bipolar depression ($N = 28$).

Contrast and region	Brodmann area	*x*	*y*	*z*	*z* statistics	*p*-value	Voxels
Task activations across all participants							
Left frontal medial cortex	10	−8	50	−10	6.10	> 0.001	13.413
Left precuneus cortex	30	−4	−54	14	6.83	> 0.001	10.596
Right lateral occipital cortex	0	58	−70	28	4.74	> 0.001	420
EPO < Saline							
Right superior parietal lobule	7	28	−54	60	4.33	.005	457

Abbreviations: EPO=erythropoietin. *Note.* Significant clusters (corrected $p < 0.05$) are identified by peak coordinate *x, y, z* in Montreal Neurological Institute (MNI) space.

may be an explanation for the generally limited effects of EPO in this ECT-treated cohort if the cognitive side-effects of ECT do indeed originate from this increase in neuroplasticity. Finally, four EPO infusions over 2.5 weeks may be suboptimal to produce robust and more broad cognitive gains in this group of severely depressed patients undergoing ECT. Indeed, previous studies used 8–12 weeks of treatment with EPO and the cognitive side effects of ECT increase with more ECT sessions. Nevertheless, the effect of EPO on neuronal and behavioural measures of autobiographical memory is noteworthy and in line with the evidence for this aspect of cognition being most sensitive to ECT (Landry et al., 2021).

Strengths were the randomized, double-blind, placebo-controlled design as well as high treatment completion rates and complete data for all neuropsychological assessments. However, the study has several limitations. First, the planned measurement of the secondary outcome, autobiographical memory, using AMI-SF was not feasible due to patients' symptom severity and attrition. Instead, AMT was employed post-treatment. The effect of EPO vs saline on AMT recall speed should therefore be interpreted with caution. Further, it is difficult to separate depression- and ECT-related impairments in autobiographical memory observed after ECT because of the cross-sectional design of the autobiographical memory assessment during fMRI. Indeed, depression itself is robustly associated with impairments in autobiographical memory (Brittlebank et al., 1993). Longitudinal studies with a before and after design are therefore needed to separate effects of depression and ECT, although such studies are difficult in practice because ECT is prescribed for critically ill patients who need urgent treatment and often cannot postpone treatment to accommodate a pre-ECT fMRI scan. It was a limitation that the fMRI assessment included only 28 participants (i.e., around half of the sample). However, this was mainly because of technical issues (including the scanner being closed, MRI response pad problems or patients having metal implants), but also illness related factors (claustrophobia, symptom exacerbation and excessive movement). This could have led to inclusion of only the least ill patients in the fMRI assessments. However, we found no such demographic and clinical differences between patients with and without fMRI. In line with precision psychiatry (Fusar-Poli et al., 2022), we recognize the need to consider patient and disorder characteristics influencing treatment outcomes. A limitation was therefore the inability to conduct posthoc analyses of baseline factors associated with treatment efficacy due to the lack of robust cognitive benefits of EPO. Finally, the exclusion of patients with psychotic depression, owing to challenges in obtaining informed consent and conducting cognitive assessments, introduces a potential selection bias that can limit the generalizability of our findings to the broader spectrum of patients undergoing ECT.

In conclusion, this RCT showed no significant benefit of add-on EPO vs. saline treatment over 2.5 weeks to patients undergoing ECT in speed of complex cognitive processing (the primary outcome), a broad cognition measure that was also unaffected by ETC, or in the secondary verbal memory measure. However, EPO treatment was associated with a specific improvement in autobiographical memory measured with the AMT, as reflected by faster recall and reduced recruitment of parietal cortex resources during memory retrieval. The findings provide preliminary evidence for a beneficial effect of EPO on autobiographical memory, an aspect of cognition that, together with verbal and spatial memory, seems particularly sensitive to side-effects of ECT. The findings warrant further exploration autobiographical memory side-effects of ECT, assessed with the AMT, and their potential mitigation with pro-cognitive interventions.

Author contributions

Conceptualization and methodology: MBJ and KWM with input from IH, LVK, MV, HE. Funding acquisition: MBJ. Project leadership KWM, MBJ (sponsor/investigator). Data curation and analysis: JZP, JM, ATYN, KWM. Interpretation of data: All authors. Writing – original draft: KWM, JZP. Writing – reviewing critically and editing: All authors. Final approval: All authors.

Declaration of Competing Interest

KWM has received consultancy fees from Lundbeck, Janssen, Angelini Pharma and Gedeon Richter in the past three years. JZP has within the last three years received honoraria from Lundbeck Pharma A/S. MV has within the last three years received consultancy fees from Janssen Cilag and Lundbeck. LVK has within recent three years been a consultant for Lundbeck and Teva. CHK receives honoraria from Cambridge University Press, and fees from UpToDate and Northwell Health. JMAC, KC, IAL, ATYN, MBM, HE, IH, PV, KG, LGH, JLJ, and MBJ report no conflicts of interest.

Funding

This study was supported by: Mental Health Service Foundation in the Capital Region of Denmark, the Augustinus Foundation, Ivan Nielsens Fonden for Personer med Specielle Sindslidelser, the Lundbeck Foundation and Læge Gerhard Linds Legat. The foundations had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgements

We wish to thank all participants, who participated in this clinical trial. We thank psychiatric centers in the Capital Region of Copenhagen for referring patients to study participation. Further, we thank Good Clinical Practice (GCP) monitor Jeanette Blom for her thorough guidance in ensuring that the trial was conducted in accordance with the GCP as well as conducting the inspections. Finally, we wish to thank all the research assistants (psychology and medical students) in the NEAD Centre (www.nead.dk) for their assistance with participant inclusions, neuropsychological testing and fMRI.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.12.004.

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