OXFORD

International Journal of Neuropsychopharmacology, 2023, **26**, 107–115

https://doi.org/10.1093/ijnp/pyac078
Advance access publication 6 December 2022
Regular Research Article

Regular Research Article

PARP1 and *OGG1* in Medicated Patients With Depression and the Response to ECT

Karen M. Ryan, Declan M. McLoughlin

Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland (Drs Ryan and McLoughlin); Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland (Drs Ryan and McLoughlin).

Correspondence: Declan M. McLoughlin, PhD, Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, James Street, Dublin 8, Ireland (d.mcloughlin@tcd.ie).

Abstract

Background: Oxidative stress and oxidation-induced DNA damage may contribute to the pathophysiology of depression. Two key mediators of base excision repair (BER) in response to oxidative damage of DNA are OGG1 and PARP1. Few studies have examined changes in *OGG1* or *PARP1* mRNA in patients with depression or following antidepressant treatment. We examined *PARP1* and *OGG1* mRNA levels in patients with depression at baseline/pre-electroconvulsive therapy (baseline/pre-ECT) vs in healthy controls and in patients following a course of ECT.

Methods: *PARP1* and *OGG1* were examined in whole blood samples from medicated patients with depression and controls using quantitative real-time polymerase chain reaction. Exploratory subgroup correlational analyses were performed to determine associations between *PARP1* and *OGG1* and mood (Hamilton Depression Rating Scale 24-item version) scores as well as with vitamin B3, *SIRT1*, *PGC1α*, and tumor necrosis factor alpha levels, as previously reported on in this cohort.

Results: *PARP1* levels were reduced in samples from patients with depression vs controls ($P = .03$), though no difference was noted in *OGG1*. ECT had no effect on *PARP1* or *OGG1*. Higher baseline *PARP1* weakly correlated with greater mood improvement post ECT ($P = .008$). Moreover, *PARP1* positively correlated with *SIRT1* at baseline and post ECT, and positive correlations were noted between change in *PARP1* and change in *OGG1* with change in tumor necrosis factor alpha post ECT.

Conclusions: To our knowledge, this is the first study to examine the effect of ECT on BER enzymes. A better understanding of BER enzymes and DNA repair in depression could unearth new mechanisms relevant to the pathophysiology of this condition and novel antidepressant treatments.

Keywords: PARP-1, OGG1, base excision repair, depression, ECT

Significance Statement

The exact cause of depression and how antidepressant treatments like electroconvulsive therapy work are not fully understood. This study examined changes in genes involved in the repair of DNA (*PARP1* and *OGG1*), which others have shown may be damaged in patients with depression. We compared blood samples from people with depression and healthy controls and found that one of these genes, *PARP1*, was lower in depressed patients. Patients with a higher level of *PARP1* before they received treatment with ECT showed a better improvement in their mood after treatment. Therefore, PARP1 might represent a biomarker for a person's response to ECT, though more studies are needed. The findings from this report contribute to the limited literature on this topic in depression, and further studies are needed to fully understand the role of these genes and mechanisms in depression and to determine whether they might represent new antidepressant treatment targets.

INTRODUCTION

Emerging evidence suggests that oxidative stress and oxidation-induced DNA damage may contribute to the pathophysiology of depression (Czarny et al., 2018). One of the most common consequences of reactive oxygen species interacting with DNA is the oxidation of guanine nucleotides to pre-mutagenic 8-oxo-7,-9-dihydroguanine (8-oxyG), with the presence of 8-oxyG considered an epigenetic marker of oxidative stress (Ba and Boldogh, 2018). Elevated levels of 8-oxyG have been noted in blood and urine from patients with clinical depression (Czarny et al., 2018) and in the white matter of brains from depressed patients during post-mortem analyses (Szebeni et al., 2017). Moreover,

Received for publication: July 1, 2022. **Accepted:** November 29, 2022. **Editorial decision:** November 28, 2022.

DNA damage is elevated in patients with recurrent depression, concomitant with impairments in oxidative DNA damage repair (Czarny et al., 2015a, 2017).

The two key mediators of base excision repair (BER) in response to oxidative damage of DNA are OGG1 and PARP1 (also known as ARTD1) (Szebeni et al., 2017). OGG1 is a multifunctional protein that recognizes and excises 8-oxoG from damaged DNA via the BER pathway (Ba and Boldogh, 2018). PARP1 belongs to a family of 17 poly(ADP-ribose) polymerase (PARP) enzymes that catalyze poly(ADP-ribosyl)ation (PARylation), which is an essential post-translational modification (Ke et al., 2019). PARP1 acts as a sensor of DNA damage and once activated it catalyzes the co-enzyme nicotinamide adenine dinucleotide (NAD+) into nicotinamide and ADP-ribose, which are subsequently used to form poly(ADP-riboses) (PARs) (Kauppinen, 2007) that act as signal transducers within the cell, inducing stress stimuli to promote chromatin remodeling, regulate transcription and DNA repair machinery, and mediate the interaction between transcription and DNA repair (Luo and Kraus, 2012).

Polymorphisms in *OGG1* that can modulate the risk for depression have been noted (Czarny et al., 2015b). A recent study showing that DNA oxidation is increased in the white matter of patients with major depressive disorder (MDD) compared with healthy controls also found that the gene expression levels of *PARP1* and *OGG1* were elevated in oligodendrocytes, while *PARP1* was additionally elevated in astrocytes (Szebeni et al., 2017). However, another study showed no difference in *OGG1* levels in the prefrontal cortex of medicated patients with depression compared with controls (Teyssier et al., 2011), though an additional study from the same authors showed peripheral upregulation of *OGG1* in leucocytes from medicated patients with MDD (Teyssier et al., 2012). A further study by Ahmadimanesh et al. (2019) showed that unmedicated patients with depression had increased DNA damage compared with controls and that this damage was accompanied by activation of *PARP1* in peripheral blood mononuclear cells from patients, though no difference in *OGG1* was noted between patient and control samples. Others have shown whole blood *OGG1* to be reduced in medicated patients with depression compared with controls, with levels increasing when patients attain remission and no difference noted between patients with unipolar or bipolar depression (Ceylan et al., 2020).

Few studies have examined changes in *OGG1* or *PARP1* following antidepressant treatment. One report showed that while *PARP1* and *OGG1* levels were reduced by 15 weeks of treatment with selective serotonin reuptake inhibitors (citalopram or sertraline), this change was not statistically significant (Ahmadimanesh et al., 2019). In mice, the selective serotonin reuptake inhibitor fluoxetine improved depressive-like behaviors and concurrently increased hippocampal neurogenesis and decreased markers of cell death, including PARP1 (Mendonca et al., 2022). Furthermore, in two rat models of depression, namely the Porsolt swim test and chronic exposure to psychological stress, PARP inhibitors produced antidepressant-like behavioral effects that were similar to those of fluoxetine (Ordway et al., 2017). However, in contrast to the reports described above, sertraline has been shown to dose dependently increase *PARP1* expression in vitro (Chinnapaka et al., 2020). Thus, studies of *OGG1* and *PARP1* in depression and following antidepressant administration are limited and often conflicting. Therefore, further studies in this field are required to gain a better understanding of the role of BER enzymes in the pathophysiology of depression and the response to antidepressant treatment.

We have previously reported reduced vitamin B3 levels in medicated patients with depression compared with controls (Ryan et al., 2020b). Nicotinamide, the amide form of vitamin B3, plays an important role in neuronal differentiation, survival, and function and has been indirectly implicated in neuroprotection through the inhibition of apoptosis (Fricker et al., 2018; Song et al., 2019). Once incorporated into cells, nicotinamide can be converted to NAD+ via the salvage pathway and act as a co-factor or substrate for approximately 500 cellular reactions that can enhance the production of ATP by mitochondria and activate enzymes like PARPs and histone deacetylases such as sirtuins, which are involved in metabolic homeostasis, cell survival and proliferation, stress resistance, and mitochondrial function (Klimova and Kristian, 2019; Song et al., 2019). Of note, a recent study showed that increased PARP1 depletes NAD+ and inhibits sirtuin-1 (SIRT1) activity and in turn suppresses peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) activity in neurons, and it has been suggested that the neuroprotective capacity of nicotinamide is linked to PARP1 inhibition (Lu et al., 2019). Hyperactivation of PARP1 also induces nuclear factor kappa B (NFκB)-mediated activation of pro-inflammatory cytokines and chemokines, including tumor necrosis factor alpha (TNF-α) (Krukenberg et al., 2015; Virag and Szabo, 2002). Our previous work has shown reduced mRNA levels of both *SIRT1* and its substrate *PGC-1α* in patients with depression compared with controls (McGrory et al., 2018; Ryan et al., 2018a) and that our patient cohort has a raised inflammatory tone (Ryan et al., 2020a).

Thus, in the present study we hypothesized that peripheral *OGG1* and *PARP1* mRNA levels would be increased in patients with depression compared with healthy controls and that treatment with electroconvulsive therapy (ECT) would normalize their expression levels. We also explored the relationship between *OGG1* and *PARP1* and mood both before and after ECT. In addition, we explored the association between *OGG1* and *PARP1* levels with vitamin B3, *SIRT1*, *PGC1α*, and the inflammatory mediator *TNF-α*, which we have previously reported on in this cohort (McGrory et al., 2018; Ryan et al., 2018a, 2020a, 2020b).

METHODS

Participants and Blood Sample Collection

As previously described (Semkovska et al., 2016), medicated patients with depression were recruited as part of the Enhancing the Effectiveness of ECT in Severe Depression (ISRCTN23577151) Trial, a real-world, pragmatic, patient- and rater-blinded, non-inferiority trial of patients with major depression carried out to assess the effects of twice-weekly moderate-dose bitemporal (1.5× seizure threshold) and high-dose unilateral (6× seizure threshold) ECT. Recruitment was carried out in St. Patrick's Mental Health Services (http://www.stpatricks.ie/), and the study was approved by the St Patrick's University Hospital Research Ethics Committee and performed in accordance with the Declaration of Helsinki (World Medical Association, 2013). All participants provided written informed consent. Healthy controls were recruited through advertisements in local newspapers and social media. Any participants with a chronic immune disorder or neurological disorder were excluded from molecular analyses.

Fasting blood samples were collected from patients 7:30 AM to 9:30 AM at baseline (i.e., before the first ECT treatment) and 1–3 days after the final ECT. Fasting blood samples were collected from controls between 7:30 AM and 9:30 AM on assessment days. Peripheral blood (2.5 mL) was collected into PAXgene Blood RNA tubes (PreAnalytix, Qiagen Ltd., Ireland) per the manufacturer's guidelines. Samples were stored at room temperature for 24 hours, –20°C for 24 hours, followed by long-term storage at –80°C.

Demographic and Clinical Information

Demographic data and medical/treatment history were collected for all participants. Depression severity and ECT response were assessed using the Hamilton Depression Rating Scale 24-item version (HAM-D24) (Beckham and Leber, 1985). Response was defined as a ≥60% reduction in HAM-D24 and a score ≤16 at end-of-treatment, while remission was defined as a ≥60% reduction in HAM-D24 and a score ≤10 maintained for 2 weeks.

Quantitative Real-Time Polymerase Chain Reaction

Multiplex quantitative real-time polymerase chain reaction was carried out as previously described (Ryan et al., 2019), using a StepOnePlus instrument (Applied Biosystems) with TaqMan Gene Expression Assays (*PARP1*, Hs00242302_m1; *OGG1*, Hs00213454_m1; *GAPDH*, Hs02758991_g1) and TaqMan Fast Advanced Master Mix (Applied Biosystems). The cycling conditions were as follows: 95°C for 20 seconds, 40 cycles of 95°C for 1 second, and 60°C for 20 seconds. The Thermo Fisher Connect Platform (Thermo Fisher, USA) was used to calculate relative quantification levels of each target using the comparative CT method (Livak and Schmittgen, 2001) against a calibrator sample included on each plate from a healthy volunteer not included in the study after normalization to GAPDH. After running 5 potential reference genes (*ACTB*: Hs01060665_g1; *TBP*: Hs00427620_m1; *B2M*: Hs00984230_m1; *18S*: Hs99999901_s1; *GAPDH*: Hs02758991_g1), *GAPDH* was identified as the most suitable reference gene for our study showing a NormFinder stability value of 0.012 (www.mdl.dk/publication-snormfinder.htm). Samples were plated in duplicate, and inter-plate calibrator samples were included on all plates to account for inter-run variability.

SIRT1, *PGC-1α*, and *TNF-α* levels were determined as previously described (McGrory et al., 2018; Ryan et al., 2018a, 2020a).

Vitamin B3

Plasma vitamin B3 concentrations were measured as previously described (Ryan et al., 2020b).

Statistical Analysis

All statistical analyses were performed using SPSS, version 26 (IBM Corporation, USA). All data were tested for normality using a Shapiro-Wilk test, and data were subsequently $\log_{10}$-transformed where necessary to attain normality. The baseline clinical and demographic characteristics are shown as means with SD or number (%) per group where appropriate and categorical data were analyzed using chi-square tests.

Relative quantification data were analyzed using general linear models. We adjusted for potential variance owing to age, sex, body mass index (BMI; kg/m^2), and smoking (Kendler et al., 1993; Simon et al., 2006; Chevanne et al., 2007; Zaremba et al., 2011). Smoking status was dichotomized into current vs non-smoker. We also adjusted for potential variance associated with educational attainment because this differed significantly between groups (Table 1). For pre-/post-ECT analyses, polarity, depression severity at baseline, presence of psychosis, and electrode placement were included as covariates where appropriate. Correlational analyses were carried out using either Pearson's product-moment correlation coefficient (Pearson's *r*) or Spearman's rank correlation coefficient rho (Spearman's **ρ**). Data are expressed as means with SD. Differences with a *P* value ≤.05 were deemed statistically significant.

RESULTS

Participants

Clinical and demographic data for this cohort are shown in Table 1. For this study, suitable blood samples were available from a total of 77 patients and 62 controls for the analysis of *PARP1* and a total of 74 patients and 57 controls for the analysis of *OGG1*. Correlations between PARP1 and OGG1 and age, sex, BMI, and smoking are shown in supplemental Table 1.

OGG1 and PARP1 mRNA Expression in Healthy Controls Compared With Patients With Depression

Table 2 shows the results for the comparison of *OGG1* and *PARP1* mRNA levels in peripheral blood samples from medicated patients with depression compared with healthy controls. There was a trend toward a significant reduction in *PARP1* in patients compared with controls in the unadjusted statistical model ($P=.05$) with a moderate effect size of –0.34, and this result became significant following adjustment for age, sex, BMI, smoking, and education ($P=.03$). There was no difference in *OGG1* mRNA levels between patients and controls.

Unadjusted analyses showed that *PARP1* was significantly lower in female patients with depression at baseline compared with female controls (1.89±0.66 vs 2.32±0.80; $F_{1,86}=6.75$, $P=.01$), though this did not survive adjustment for covariates ($P=.05$). There was also a significant difference in *OGG1* levels between female patients with depression compared with female controls (3.12±1.80 vs 3.64±1.49; $F_{1,81}=4.27$, $P=.04$), though this did not survive adjustment for covariates ($P=.62$). On the other hand, there was no difference in *PARP1* or *OGG1* levels between male patients with depression compared with male controls following unadjusted analyses (1.94±0.61 vs 1.85±0.76 and 2.88±1.07 vs 2.60±0.73, respectively; $F_{1,49}=0.73$, $P=.40$ and $F_{1,46}=0.54$, $P=.47$, respectively), and adjustment for covariates did not alter the results ($P>.05$).

Subgroup analyses showed no difference in *OGG1* or *PARP1* between controls and patients with unipolar depression or patients with bipolar depression, or controls and patients with psychotic or non-psychotic depression (data not shown).

OGG1 and PARP1 mRNA Levels in Patients With Depression Before and After ECT

Table 3 shows the mRNA levels of *OGG1* and *PARP1* before and after a course of ECT. There was no significant difference in the levels of *OGG1* or *PARP1* in the group of patients as a whole before or after treatment.

Subgroup analyses revealed no significant differences in *OGG1* or *PARP1* between patients with unipolar/bipolar depression, psychotic/non-psychotic depression, male/female patients, ECT responders/non-responders, or ECT remitters/non-remitters before or after treatment with ECT (data not shown).

Correlations Between OGG1 and PARP1 and Mood Scores and Duration of Illness

Table 4 shows that there was a significant negative correlation between baseline *PARP1* mRNA levels and the change in HAM-D24 score post ECT ($r=–0.251$, $P=.008$), indicating that higher *PARP1* levels at baseline are associated with a greater decrease in mood score after treatment with ECT. No other significant correlations were noted.

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Depressed (n = 77)	Controls (n = 62)	Statistical test
Age, y	55.96 (14.51)	53.53 (12.70)	$t = 1.04$, $P = .30$
Sex, No. (%)			$\chi^2 = 0.07$, $P = .79$
Male	29 (37.66)	22 (35.48)	
Female	48 (62.34)	40 (64.52)	
BMI, mean (SD)	27.01 (5.21)	24.69 (3.25)	$t = 3.20$, $P = .002$
Smokers, No. (%)	32 (41.56)	5 (8.06)	$\chi^2 = 8.97$, $P = .003$
Education, No. (%)			$\chi^2 = 34.60$, $P < .001$
Primary	14 (18.18)	3 (4.84)	
Secondary	42 (54.55)	11 (17.74)	
Tertiary/quaternary	21 (27.27)	48 (77.42)	
Bipolar depression, No. (%)	18 (23.38)		
Psychotic depression, No. (%)	19 (24.68)		
Medications, No. (%) taking			
SSRI	23 (29.87)		
SNRI	37 (48.05)		
TCA	16 (20.78)		
MAOI	1 (1.30)		
Mirtazapine	31 (40.26)		
Bupropion	2 (2.60)		
Lithium	31 (40.26)		
Agomelatine	5 (6.49)		
Trazodone	3 (3.90)		
Buspirone	1 (1.30)		
Sodium valproate/lamotrigine	27 (35.06)		
Antipsychotics	61 (79.22)		
Benzodiazepines	46 (59.74)		
Non-benzodiazepine hypnotics	38 (49.35)		
Baseline HAM-D24, mean (SD)	30.04 (5.84)	3.23 (3.02)	$U = 0.000$, $P < .001$
Post-ECT HAM-D24, mean (SD)	11.45 (8.58)		
Electrode placement, No. (%)			
Unilateral	33 (42.86)		
Bitemporal	44 (57.14)		
Previous ECT, No. (%)	26 (33.77)		
No. of ECT sessions, mean (SD)	8.30 (2.37)		
Responders, No. (%)	46 (59.74)		
Remitters, No. (%)	40 (51.95)		

Abbreviations: BMI, body mass index; ECT, electroconvulsive therapy; EEG, electroencephalogram; HAM-D24, Hamilton depression rating scale, 24-item version; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Data are presented as means with SD or number (%) per group where appropriate.

Table 2. Analysis of mRNA Levels of *OGG1* and *PARP1* in Patients With Depression Compared With Healthy Controls

mRNA targest	Depressed Pre ECT (RQ)	Control (RQ)	Cohen d	Statistics	Adjusted statistics[a]
PARP1	1.91 (0.64)	2.16 (0.82)	0.34	$F_{1,137=}4.07$, $P = .05$	$F_{1,105=}4.89$, $P = .03$
OGG1	3.03 (1.57)	3.26 (1.36)	−0.16	$F_{1,129=}1.99$, $P = .16$	$F_{1,98} = 0.10$, $P = .75$

Abbreviations: BMI, body mass index; ECT, electroconvulsive therapy; RQ, relative quantification. Data are presented as mean (SD).
$\log_{10}$RQ used for data analysis.
[a]Adjusted for age, sex, BMI, smoking, education.
PARP1: controls n = 62, depressed n = 77.
OGG1: controls n = 57, depressed n = 74.

Table 3. Analysis of mRNA Levels of *OGG1* and *PARP1* in Patients With Depression Pre and Post ECT

mRNA target	Depressed Pre ECT (RQ)	Depressed Post ECT (RQ)	Cohen d	Statistics	Adjusted statistics[a]
PARP1 (n = 77)	1.91 (0.64)	1.98 (0.61)	0.11	$F_{1,76} = 0.76$, $P = .39$	$F_{1,66} = 0.007$, $P = .93$
OGG1 (n = 74)	3.03 (1.57)	3.03 (1.47)	0	$F_{1,73} = 0.04$, $P = .85$	$F_{1,63} = 0.10$, $P = .75$

Abbreviations: BMI, body mass index; ECT, electroconvulsive therapy; RQ, relative quantification. Data are presented as mean (SD).
$\log_{10}$RQ used for data analysis.
[a]Adjusted for age, sex, BMI, smoking, education, polarity, presence of psychosis, severity of depression at baseline, electrode placement.

Table 4. Correlations Between *OGG1* and *PARP1* With HAM-D24 Scores

mRNA target	Baseline RQ and baseline HAM-D24	Baseline RQ and ΔHAM-D24	ΔRQ and ΔHAM-D24
PARP1	$\rho = -0.119$, $P = .161$	$r = -0.251$, $P = .008$	$r = -0.196$, $P = .090$
OGG1	$\rho = -0.037$, $P = .757$	$\rho = 0.107$, $P = .366$	$\rho = -0.159$, $P = .180$

Abbreviations: HAM-D24, Hamilton depression rating scale, 24-item version; *OGG1*, 8-oxoguanine DNA glycosylase; *PARP1*, poly(ADP-ribose) polymerase 1; RQ, relative quantification.

With regard to subgroup analyses, a relatively strong negative correlation was noted between the change in *OGG1* and change in mood score post ECT in patients with psychotic depression ($\rho = -0.497$, $P = .03$), indicating that larger increases in *OGG1* post ECT are associated with greater improvements in mood. However, caution is warranted as this subgroup was small and only contained 19 patients. No other correlations were noted in groups of patients with unipolar/bipolar depression, psychotic/non-psychotic depression, ECT responders/non-responders, ECT remitters/non-remitters or those treated with unilateral or bitemporal ECT (data not shown). In female patients with depression there were significant moderate negative correlations between the changes in *PARP1* and *OGG1* post ECT and the change in mood score ($r = -0.302$, $P = .04$; $\rho = -0.302$, $P = .04$, respectively). No correlations were noted in male patients with depression between *PARP1* or *OGG1* levels and mood score (data not shown).

There was no correlation between baseline *OGG1* or *PARP1* levels and the duration of illness in years (data not shown).

Correlations With Vitamin B3, SIRT1, PGC1α, or TNF-α

In the depressed group as a whole, there was a significant positive correlation between baseline *PARP1* and baseline *SIRT1* ($\rho = 0.646$, $P = 1.52 \times 10^{-9}$) and also between the change in *PARP1* and change in *SIRT1* post ECT ($\rho = 0.518$, $P = .000004$). There was a moderate positive correlation between the change in *TNF-α* and the change in *PARP1* ($r = 0.400$, $P = .002$) and between the change in *OGG1* and the change in *TNF-α* ($\rho = 0.330$, $P = .015$) post ECT. No other significant correlations were noted with vitamin B3, SIRT1, *PGC1α*, or *TNF-α*.

DISCUSSION

In contrast to our original hypothesis, we found that *PARP1* is reduced in peripheral whole blood samples from medicated patients with depression compared with healthy controls after adjustment for covariates but that ECT has no impact on *PARP1* at the time point used in this study. We noted no difference in *OGG1* mRNA levels between controls and patients with depression, and ECT did not impact *OGG1* in the overall group of depressed patients. Moreover, higher baseline expression of *PARP1* was associated with greater improvements in mood post ECT. However, in the subgroup of patients with psychotic depression, there was a moderate negative correlation between the change in *OGG1* and the change in mood score post ECT indicating that at an individual level a larger increase in *OGG1* was associated with a greater improvement in mood, though caution is warranted because the sample size of this subgroup was relatively small. *PARP1* and *OGG1* levels were lower in female patients with depression compared with female controls, though this did not survive adjustment for covariates. However, there were significant negative correlations between the change in *PARP1* and change in *OGG1* with the change in mood score post ECT in female patients with depression. These results highlight potential sex differences in the molecular mechanisms underlying depression, which requires further investigation. No other notable results were identified in subgroups of patients with depression. In the depressed group as a whole, *PARP1* levels were found to positively correlate with *SIRT1* levels both at baseline and following ECT, and there were significant positive correlations between the change in *PARP1* and the change in *OGG1* with the change in *TNF-α* post ECT.

Our results from medicated patients with depression mostly contrast with those already reported. This may be owing to the effect of chronic pharmacotherapy because the patients included in the present study were maintained on pharmacotherapy as usual throughout this study. As mentioned, Ahmadimanesh et al. (2019) showed that leukocyte-derived *PARP1* was elevated in unmedicated patients with depression compared with healthy controls. Moreover, Szebeni et al. (2017) found elevated levels of *PARP1* and *OGG1* in the BA10 white matter and amygdala of patients who had primarily died by suicide compared with controls. However, it must be noted that the patients included in that study were a mixture of individuals with a diagnosis of MDD and schizophrenia, and it is unclear if individuals were receiving treatment with psychopharmacological agents. To our knowledge, only 1 previous study examined the relationship between either *OGG1* or *PARP1* and mood and found no association between *OGG1* and HAM-D score (Teyssier et al., 2012). Our results indicate that high baseline *PARP1* may be predictive of greater improvements in mood post ECT, though replication with a larger sample size is required. Moreover, our results highlight differences in the molecular changes that occur between subgroups of patients treated with ECT because we found that a larger increase in *OGG1* was associated with a greater improvement in mood post ECT in the psychotic depression subgroup. Thus, it is important to examine

changes in relation to psychiatric diagnosis and sex when investigating molecular changes in response to ECT.

The reduction in PARP1 noted in this study could have broad implications because PARP1 is thought to account for approximately 85% of the total cellular activity of PARPs and regulate approximately 60%–70% of genes controlling cell cycle, metabolism, and transcription (Virag and Szabo, 2002; Chaitanya et al., 2010). Moreover, PARP1 has multiple functions in the maintenance of genomic stability, microtubule organization during mitosis, cell death, and neurogenesis (Virag and Szabo, 2002; Kauppinen, 2007; Martinez-Bosch et al., 2016) and can control gene expression via chromatin modulation, transcriptional regulation, and RNA regulation (Ke et al., 2019). It is also known to play a key role in initiating transcription by triggering changes in the chromatin structure through PARylation of histones, thereby opening the chromatin structure to allow access of the transcriptional machinery to DNA promoter sequences, by direct recruitment of transcription factors, and through PARylation of the methyltransferase DNMT1 to inhibit its DNA methylation activity (Eleazer and Fondufe-Mittendorf, 2021). Moreover, it is necessary for the formation of long-term memory (Goldberg et al., 2009), which is thought to be linked to the fast and transient decondensation of chromatin by PAR that might enable the transcription needed to form long-term memory without the induction of DNA strand breaks (Cohen-Armon et al., 2004). However, *PARP1* has also been implicated in a type of non-apoptotic cell death known as parthanatos, which is linked to neurodegeneration (Salech et al., 2020).

Reduced PARP1 protein enhances mitochondrial biogenesis, with a 50% increase in mitochondrial DNA copy number (mtDNAcn) noted in vitro and a 60% increase noted in vivo, with cells in which PARP1 is depleted showing higher resistance to oxidative stress (Szczesny et al., 2014). Moreover, inhibition of PARP1 has been shown to enhance the transcription of genes involved in antioxidative defense and in mitochondrial function (Czapski et al., 2018). Thus, reduced PARP1 may be protective. This may be of relevance for depression where previous studies have noted increased mtDNAcn in patient samples (Chung et al., 2019; Fernstrom et al., 2021), though mtDNAcn measurement was beyond the scope of the current study, and so further work is required to investigate if there is a link between PARP1 and mtDNAcn in our cohort. PARP1 has also been found to suppress the mitochondrial regulator PGC-1α, thereby inhibiting neuronal mitochondrial respiration (Lu et al., 2019); however, we found no association between peripheral *PARP1* and *PGC-1α* levels in the present study. Although *PARP1* levels were found to correlate positively with those of the histone deacetylase *SIRT1* both at baseline and following ECT, the direction opposes that previously reported in the literature, which suggests that there is a negative relationship between PARP1 and SIRT1 as they compete for the same pool of NAD+ for their activation (Martire et al., 2015). However, there are some reports that indicate that PARP1-induced PAR can in fact recruit SIRT1 to DNA damage sites (Chen et al., 2019). Moreover, there is also evidence to suggest that PARP1 can activate the transcription factors E2F1 and c-Myc, which in turn can induce the transcription of *SIRT1* (Luna et al., 2013). Thus, the relationship between *PARP1* and *SIRT1* is complex and requires further exploration in the context of depression and antidepressant treatments.

The neurotrophin hypothesis of depression suggests that depression occurs owing to decreased levels of neurotrophins and dysfunctional neurogenesis in brain regions important for emotion and cognition (Duman et al., 1997). PARP1 is required for normal cell proliferation and survival and differentiation of neural stem cells toward neurons (Hau et al., 2017; Hong et al., 2019). Notably, PARP1 can become activated in neurons in response to electrical stimulation, induced by inositol 1,4,5,-trisphosphate-Ca^{2+} mobilization, and, importantly, in the absence of DNA damage (Homburg et al., 2000) and under these circumstances appears to be associated with cell proliferation as opposed to DNA synthesis (Kadam et al., 2020). Mice deficient in PARP1 show defective neurogenesis due to suppression of Akt and ERK signaling and reduced brain weight, anxiety-like behaviors, and cognitive deficits (Hong et al., 2019). However, the story is complex because inhibition of PARP1 can also prevent neuronal cell death (Kauppinen, 2007). Previous studies have shown that neurotrophins such as nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 or neuroprotective glial-derived peptides such as NAP and activity-dependent neurotrophic factor-9 activate PARP1 via Ca^{2+}-dependent kinases (Visochek et al., 2005). Although we ourselves did not note changes in BDNF in this cohort of depressed patients compared with controls or following ECT at this time point (Ryan et al., 2018b), a recent systematic review indicated that BDNF levels do in fact rise after a treatment course, with some delay (Pelosof et al., 2022). Thus, there may also be a delay in changes in *OGG1* or *PARP1* post ECT, and so time-course studies are required to investigate this.

PARP1 also induces $NF_{\kappa}B$, activity of which is important for inflammatory cytokine and chemokine expression (Virag and Szabo, 2002) and appears to drive macrophage polarization toward a pro-inflammatory M1 phenotype, which produces pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Atri et al., 2018) via the interferon gamma-signal transducer and activator of transcription 1 signaling pathway (Sobczak et al., 2020). This is notable because it has previously been reported that patients with depression show alterations in circulating monocyte types (Alvarez-Mon et al., 2019), with monocytes from patients with depression found to be less reactive to an inflammatory stimulus than control cells (Lisi et al., 2013). Moreover, immune cells that are deficient in PARP1 fail to migrate to the injury site or release cytokines or inducible nitric oxide synthase (Kauppinen, 2007). PARP1-induced PAR has been suggested to act as an extracellular damage associated molecular pattern to drive inflammatory signaling and activate cytokine release in human and rodent macrophages, including TNF-α (Krukenberg et al., 2015). Notably, ECT is associated with an acute immune response (Yrondi et al., 2018), and we have previously shown that an increase in *TNF-α* is associated with improved mood post ECT (Ryan et al., 2020a). Thus, it is plausible that ECT might restore function of immune cells through increased transcription and activation of PARP1, though further work remains to assess this.

In this study we identified a significant positive correlation between the change in *TNF-α* and the change in *PARP1* and *OGG1* post ECT in peripheral whole blood. A previous report showed that TNF-α induces PARP1 activation in the absence of DNA strand breaks and that PARP1 is necessary for TNF-α-induced $NF_{\kappa}B$ activation and its pro-inflammatory effects (Vuong et al., 2015). It has also been reported that TNF-α-induced activation of PARP1 requires Ca^{2+} influx, activation of phospholipase C, and activation of the MEK1/ERK1 protein kinase cascade (Vuong et al., 2015). This is notable because reduced extracellular signal-regulated kinase (ERK) signaling has been reported in depression, with antidepressant treatment found to normalize ERK signaling and its upstream regulator BDNF along with its downstream effector CREB (Wang and Mao, 2019). OGG1 has also been

shown to bind to DNA, inducing conformational changes and pro-inflammatory gene transcription (Hao et al., 2020). Cells exposed to TNF-α show an increase in the interaction between OGG1 and the promoter regions of pro-inflammatory cytokine/chemokine genes (Hao et al., 2020), with OGG1 also shown to facilitate TNF-α-induced binding of $NF_{\kappa}B$ to DNA targets (Pan et al., 2017; Ba and Boldogh, 2018). It has previously been reported that there is a direct interaction between OGG1 and PARP1; thus, these two enzymes may cooperate in the induction of pro-inflammatory genes (Hao et al., 2020). Whether PARP1 induction occurs before the induction of TNF-α post ECT or vice versa remains to be determined.

Because PARP1 also mediates the response of microglia to inflammation and in vivo studies in mice have shown that PARP1 is necessary for TNF-α-induced proliferation and activation of microglia (Kauppinen and Swanson, 2005), these results may fit with the microglial hypothesis of depression whereby it has been suggested that either microglial suppression or activation is needed to treat depression, depending on the microglial status of the patient (Yirmiya et al., 2015). However, whether the ECT-induced changes we have observed peripherally also occur at a central level is difficult to determine.

There are several limitations to this study. First, only mRNA levels of *PARP1* and *OGG1* were measured. Thus, although peripheral blood *PARP1* mRNA levels were found to be decreased in patients with depression compared with controls, this does not tell us about the activity of PARP1. Future studies should also aim to measure activity of these enzymes. Second, the sample size included in this study was small, in particular in our subgroup analyses. Third, blood samples were collected from patients between 1 and 3 days post ECT. The optimal time point for measuring *OGG1* or *PARP1* following ECT has not yet been clarified, and time course studies are required to establish if any alterations are observed in these markers at either earlier or later time points. Fourth, all of our patients were receiving pharmacotherapy as usual while being treated with ECT. Therefore, our baseline/pre-ECT results may reflect an antidepressant effect because, as noted above, antidepressant drugs can alter *PARP1* expression. Thus, it would be helpful to conduct further studies using samples collected from drug naïve subjects. Fifth, this study only measured peripheral whole blood levels of *OGG1* and *PARP1*, and we could not assess the blood cell composition of our samples. Thus, we cannot comment on whether changes in cellular composition of the blood samples might be responsible for the changes identified here. Moreover, whole blood measures of these markers may not be reflective of the levels of these BER enzymes in the brain. Future studies should consider conducting full blood counts to determine if the changes identified are owing to changes in the blood cell composition of depressed patients. The use of cerebrospinal fluid for measuring these molecules should also be considered to gain a better understanding of their potential role in depression pathophysiology and the mechanism of action of ECT.

In conclusion, to our knowledge, this is the first study to examine the effect of ECT on BER enzymes. We identified a reduction in *PARP1* mRNA levels in depressed patients compared with healthy controls. Moreover, higher baseline *PARP1* levels were associated with a greater improvement in mood score post ECT. However, at this time point, ECT had no effect on *OGG1* or *PARP1* mRNA expression. A better understanding of BER enzymes and DNA repair in depression could unearth new mechanisms relevant to the pathophysiology of this condition and novel antidepressant treatments.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

The authors thank the patients and healthy volunteers who participated in this study.
This work was supported by awards from the Health Research Board (HRB), Ireland (TRA/2007/5 and HPF/2010/17).

Interest Statement

D.M. has received speaker's honoraria from MECTA, Otsuka, and Janssen and an honorarium from Janssen for participating in an esketamine advisory board meeting. K.R. has no competing interests to declare.

References

Ahmadimanesh M, Abbaszadegan MR, Morshedi Rad D, Moallem SA, Mohammadpour AH, Ghahremani MH, Farid Hosseini F, Behdani F, Akhondpour Manteghi A, Jowsey P, Shabani Behbahani F, Moallem SMH, Etemad L (2019) Effects of selective serotonin reuptake inhibitors on DNA damage in patients with depression. *J Psychopharmacol* **33**:1364–1376.

Alvarez-Mon MA, Gomez AM, Orozco A, Lahera G, Sosa MD, Diaz D, Auba E, Albillos A, Monserrat J, Alvarez-Mon M (2019) Abnormal distribution and function of circulating monocytes and enhanced bacterial translocation in major depressive disorder. *Front Psychiatry* **10**:812.

Atri C, Guerfali FZ, Laouini D (2018) Role of human macrophage polarization in inflammation during infectious diseases. *Int J Mol Sci* **19**:1801.

Ba X, Boldogh I (2018) 8-Oxoguanine DNA glycosylase 1: beyond repair of the oxidatively modified base lesions. *Redox Biol* **14**:669–678.

Beckham EE, Leber WR (1985) *Hamilton rating scale for depression, ECDEU version used in the treatment of depression collaborative research program*. Homewood, IL: The Dorsey Press.

Ceylan D, Yilmaz S, Tuna G, Kant M, Er A, Ildiz A, Verim B, Akis M, Akan P, Islekel H, Veldic M, Frye M, Ozerdem A (2020) Alterations in levels of 8-oxo-2'-deoxyguanosine and 8-oxoguanine DNA glycosylase 1 during a current episode and after remission in unipolar and bipolar depression. *Psychoneuroendocrinology* **114**:104600.

Chaitanya GV, Steven AJ, Babu PP (2010) PARP-1 cleavage fragments: signatures of cell-death proteases in neurodegeneration. *Cell Commun Signal* **8**:31.

Chen Y, Zhang H, Xu Z, Tang H, Geng A, Cai B, Su T, Shi J, Jiang C, Tian X, Seluanov A, Huang J, Wan X, Jiang Y, Gorbunova V, Mao Z (2019) A PARP1-BRG1-SIRT1 axis promotes HR repair by reducing nucleosome density at DNA damage sites. *Nucleic Acids Res* **47**:8563–8580.

Chevanne M, Calia C, Zampieri M, Cecchinelli B, Caldini R, Monti D, Bucci L, Franceschi C, Caiafa P (2007) Oxidative DNA damage repair and parp 1 and parp 2 expression in Epstein-Barr virus-immortalized B lymphocyte cells from young subjects, old subjects, and centenarians. *Rejuvenation Res* **10**:191–204.

Chinnapaka S, Bakthavachalam V, Munirathinam G (2020) Repurposing antidepressant sertraline as a pharmacological drug to target prostate cancer stem cells: dual activation of

apoptosis and autophagy signaling by deregulating redox balance. *Am J Cancer Res* **10**:2043–2065.

Chung JK, Lee SY, Park M, Joo EJ, Kim SA (2019) Investigation of mitochondrial DNA copy number in patients with major depressive disorder. *Psychiatry Res* **282**:112616.

Cohen-Armon M, Visochek L, Katzoff A, Levitan D, Susswein AJ, Klein R, Valbrun M, Schwartz JH (2004) Long-term memory requires polyADP-ribosylation. *Science* **304**:1820–1822.

Czapski GA, Cieslik M, Wencel PL, Wojtowicz S, Strosznajder RP, Strosznajder JB (2018) Inhibition of poly(ADP-ribose) polymerase-1 alters expression of mitochondria-related genes in PC12 cells: relevance to mitochondrial homeostasis in neurodegenerative disorders. *Biochim Biophys Acta Mol Cell Res* **1865**:281–288.

Czarny P, Kwiatkowski D, Kacperska D, Kawczynska D, Talarowska M, Orzechowska A, Bielecka-Kowalska A, Szemraj J, Galecki P, Sliwinski T (2015a) Elevated level of DNA damage and impaired repair of oxidative DNA damage in patients with recurrent depressive disorder. *Med Sci Monit* **21**:412–418.

Czarny P, Kwiatkowski D, Galecki P, Talarowska M, Orzechowska A, Bobinska K, Bielecka-Kowalska A, Szemraj J, Maes M, Su KP, Sliwinski T (2015b) Association between single nucleotide polymorphisms of MUTYH, hOGG1 and NEIL1 genes, and depression. *J Affect Disord* **184**:90–96.

Czarny P, Kwiatkowski D, Toma M, Kubiak J, Sliwinska A, Talarowska M, Szemraj J, Maes M, Galecki P, Sliwinski T (2017) Impact of single nucleotide polymorphisms of base excision repair genes on DNA damage and efficiency of DNA repair in recurrent depression disorder. *Mol Neurobiol* **54**:4150–4159.

Czarny P, Wigner P, Galecki P, Sliwinski T (2018) The interplay between inflammation, oxidative stress, DNA damage, DNA repair and mitochondrial dysfunction in depression. *Prog Neuropsychopharmacol Biol Psychiatry* **80**:309–321.

Duman RS, Heninger GR, Nestler EJ (1997) A molecular and cellular theory of depression. *Arch Gen Psychiatry* **54**:597–606.

Eleazer R, Fondufe-Mittendorf YN (2021) The multifaceted role of PARP1 in RNA biogenesis. *Wiley Interdiscip Rev RNA* **12**:e1617.

Fernstrom J, Mellon SH, McGill MA, Picard M, Reus VI, Hough CM, Lin J, Epel ES, Wolkowitz OM, Lindqvist D (2021) Blood-based mitochondrial respiratory chain function in major depression. *Transl Psychiatry* **11**:593.

Fricker RA, Green EL, Jenkins SI, Griffin SM (2018) The influence of nicotinamide on health and disease in the central nervous system. *Int J Tryptophan Res* **11**:1178646918776658.

Goldberg S, Visochek L, Giladi E, Gozes I, Cohen-Armon M (2009) PolyADP-ribosylation is required for long-term memory formation in mammals. *J Neurochem* **111**:72–79.

Hao W, Wang J, Zhang Y, Wang C, Xia L, Zhang W, Zafar M, Kang JY, Wang R, Ali Bohio A, Pan L, Zeng X, Wei M, Boldogh I, Ba X (2020) Enzymatically inactive OGG1 binds to DNA and steers base excision repair toward gene transcription. *FASEB J* **34**:7427–7441.

Hau AC, Grebbin BM, Agoston Z, Anders-Maurer M, Muller T, Gross A, Kolb J, Langer JD, Doring C, Schulte D (2017) MEIS homeodomain proteins facilitate PARP1/ARTD1-mediated eviction of histone H1. *J Cell Biol* **216**:2715–2729.

Homburg S, Visochek L, Moran N, Dantzer F, Priel E, Asculai E, Schwartz D, Rotter V, Dekel N, Cohen-Armon M (2000) A fast signal-induced activation of poly (ADP-ribose) polymerase: a novel downstream target of phospholipase c. *J Cell Biol* **150**:293–307.

Hong S, Yi JH, Lee S, Park CH, Ryu JH, Shin KS, Kang SJ (2019) Defective neurogenesis and schizophrenia-like behavior in PARP-1-deficient mice. *Cell Death Dis* **10**:943.

Kadam A, Jubin T, Roychowdhury R, Begum R (2020) Role of PARP-1 in mitochondrial homeostasis. *Biochim Biophys Acta Gen Subj* **1864**:129669.

Kauppinen TM (2007) Multiple roles for poly(ADP-ribose)polymerase-1 in neurological disease. *Neurochem Int* **50**:954–958.

Kauppinen TM, Swanson RA (2005) Poly(ADP-ribose) polymerase-1 promotes microglial activation, proliferation, and matrix metalloproteinase-9-mediated neuron death. *J Immunol* **174**:2288–2296.

Ke Y, Wang C, Zhang J, Zhong X, Wang R, Zeng X, Ba X (2019) The role of PARPs in inflammation-and metabolic-related diseases: molecular mechanisms and beyond. *Cells* **8**:1047.

Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC (1993) Smoking and major depression. A causal analysis. *Arch Gen Psychiatry* **50**:36–43.

Klimova N, Kristian T (2019) Multi-targeted effect of nicotinamide mononucleotide on brain bioenergetic metabolism. *Neurochem Res* **44**:2280–2287.

Krukenberg KA, Kim S, Tan ES, Maliga Z, Mitchison TJ (2015) Extracellular poly(ADP-ribose) is a pro-inflammatory signal for macrophages. *Chem Biol* **22**:446–452.

Lisi L, Camardese G, Treglia M, Tringali G, Carrozza C, Janiri L, Dello Russo C, Navarra P (2013) Monocytes from depressed patients display an altered pattern of response to endotoxin challenge. *PLoS One* **8**:e52585.

Livak KJ, Schmittgen TD (2001) Analysis of relative gene expression data using real-time quantitative PCR and the 2(-delta delta C(T)) method. *Methods* **25**:402–408.

Lu P, Hogan-Cann AD, Kamboj A, Roy Chowdhury SK, Aghanoori MR, Fernyhough P, Anderson CM (2019) Poly(ADP-ribose) polymerase-1 inhibits mitochondrial respiration by suppressing PGC-1alpha activity in neurons. *Neuropharmacology* **160**:107755.

Luna A, Aladjem MI, Kohn KW (2013) SIRT1/PARP1 crosstalk: connecting DNA damage and metabolism. *Genome Integr* **4**:6.

Luo X, Kraus WL (2012) On PAR with PARP: cellular stress signaling through poly(ADP-ribose) and PARP-1. *Genes Dev* **26**:417–432.

Martinez-Bosch N, Fernandez-Zapico ME, Navarro P, Yelamos J (2016) Poly(ADP-Ribose) polymerases: new players in the pathogenesis of exocrine pancreatic diseases. *Am J Pathol* **186**:234–241.

Martire S, Mosca L, d'Erme M (2015) PARP-1 involvement in neurodegeneration: a focus on Alzheimer's and Parkinson's diseases. *Mech Ageing Dev* **146–148**:53–64.

McGrory CL, Ryan KM, Kolshus E, Finnegan M, McLoughlin DM (2018) Peripheral blood SIRT1 mRNA levels in depression and treatment with electroconvulsive therapy. *Eur Neuropsychopharmacol* **28**:1015–1023.

Mendonca IP, Paiva IHR, Duarte-Silva EP, Melo MG, Silva RSD, Oliveira WH, Costa B, Peixoto CA (2022) Metformin and fluoxetine improve depressive-like behavior in a murine model of Parkinsons disease through the modulation of neuroinflammation, neurogenesis and neuroplasticity. *Int Immunopharmacol* **102**:108415.

Ordway GA, Szebeni A, Hernandez LJ, Crawford JD, Szebeni K, Chandley MJ, Burgess KC, Miller C, Bakkalbasi E, Brown RW (2017) Antidepressant-like actions of inhibitors of poly(ADP-Ribose) polymerase in rodent models. *Int J Neuropsychopharmacol* **20**:994–1004.

Pan L, Hao W, Zheng X, Zeng X, Ahmed Abbasi A, Boldogh I, Ba X (2017) OGG1-DNA interactions facilitate NF-kappaB binding to DNA targets. *Sci Rep* **7**:43297.

Pelosof R, Santos LAD, Farhat LC, Gattaz WF, Talib L, Brunoni AR (2022) BDNF blood levels after electroconvulsive therapy in patients with mood disorders: An updated systematic review and meta-analysis. *World J Biol Psychiatry* 1–10. doi: 10.1080/15622975.2022.2058083. Online ahead of print.

Ryan KM, Patterson I, McLoughlin DM (2018a) Peroxisome proliferator activated receptor gamma co-activator-1 alpha in depression and the response to electroconvulsive therapy. *Psychol Med* **49**:1859–1868.

Ryan KM, Dunne R, McLoughlin DM (2018b) BDNF plasma levels and genotype in depression and the response to electroconvulsive therapy. *Brain Stimul* **11**:1123–1131.

Ryan KM, Poelz L, McLoughlin DM (2019) Low circulating levels of GR, FKBP5, and SGK1 in medicated patients with depression are not altered by electroconvulsive therapy. *J ECT* **36**:137–143.

Ryan KM, Allers KA, McLoughlin DM, Harkin A (2020a) Tryptophan metabolite concentrations in depressed patients before and after electroconvulsive therapy. *Brain Behav Immun* **83**:153–162.

Ryan KM, Allers KA, Harkin A, McLoughlin DM (2020b) Blood plasma B vitamins in depression and the therapeutic response to electroconvulsive therapy. *Brain Behav Immun Health* **4**:100063.

Salech F, Ponce DP, Paula-Lima AC, SanMartin CD, Behrens MI (2020) Nicotinamide, a poly [ADP-Ribose] polymerase 1 (PARP-1) inhibitor, as an adjunctive therapy for the treatment of Alzheimer's disease. *Front Aging Neurosci* **12**:255.

Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, Noone M, Carton M, Lambe S, McHugh C, McLoughlin DM (2016) Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomized, non-inferiority trial. *Am J Psychiatry* **173**:408–417.

Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC (2006) Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* **63**:824–830.

Sobczak M, Zyma M, Robaszkiewicz A (2020) The role of PARP1 in monocyte and macrophage commitment and specification: future perspectives and limitations for the treatment of monocyte and macrophage relevant diseases with PARP inhibitors. *Cells* **9**:2040.

Song SB, Park JS, Chung GJ, Lee IH, Hwang ES (2019) Diverse therapeutic efficacies and more diverse mechanisms of nicotinamide. *Metabolomics* **15**:137.

Szczesny B, Brunyanszki A, Olah G, Mitra S, Szabo C (2014) Opposing roles of mitochondrial and nuclear PARP1 in the regulation of mitochondrial and nuclear DNA integrity: implications for the regulation of mitochondrial function. *Nucleic Acids Res* **42**:13161–13173.

Szebeni A, Szebeni K, DiPeri TP, Johnson LA, Stockmeier CA, Crawford JD, Chandley MJ, Hernandez LJ, Burgess KC, Brown RW, Ordway GA (2017) Elevated DNA oxidation and DNA repair enzyme expression in brain white matter in major depressive disorder. *Int J Neuropsychopharmacol* **20**:363–373.

Teyssier JR, Ragot S, Chauvet-Gelinier JC, Trojak B, Bonin B (2011) Expression of oxidative stress-response genes is not activated in the prefrontal cortex of patients with depressive disorder. *Psychiatry Res* **186**:244–247.

Teyssier JR, Chauvet-Gelinier JC, Ragot S, Bonin B (2012) Up-regulation of leucocytes genes implicated in telomere dysfunction and cellular senescence correlates with depression and anxiety severity scores. *PLoS One* **7**:e49677.

Virag L, Szabo C (2002) The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. *Pharmacol Rev* **54**:375–429.

Visochek L, Steingart RA, Vulih-Shultzman I, Klein R, Priel E, Gozes I, Cohen-Armon M (2005) PolyADP-ribosylation is involved in neurotrophic activity. *J Neurosci* **25**:7420–7428.

Vuong B, Hogan-Cann AD, Alano CC, Stevenson M, Chan WY, Anderson CM, Swanson RA, Kauppinen TM (2015) NF-kappaB transcriptional activation by TNFalpha requires phospholipase C, extracellular signal-regulated kinase 2 and poly(ADP-ribose) polymerase-1. *J Neuroinflammation* **12**:229.

Wang JQ, Mao L (2019) The ERK pathway: molecular mechanisms and treatment of depression. *Mol Neurobiol* **56**:6197–6205.

World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**:2191–2194.

Yirmiya R, Rimmerman N, Reshef R (2015) Depression as a microglial disease. *Trends Neurosci* **38**:637–658.

Yrondi A, Sporer M, Peran P, Schmitt L, Arbus C, Sauvaget A (2018) Electroconvulsive therapy, depression, the immune system and inflammation: a systematic review. *Brain Stimul* **11**:29–51.

Zaremba T, Thomas HD, Cole M, Coulthard SA, Plummer ER, Curtin NJ (2011) Poly(ADP-ribose) polymerase-1 (PARP-1) pharmacogenetics, activity and expression analysis in cancer patients and healthy volunteers. *Biochem J* **436**:671–679.