Peripheral blood *SIRT1* mRNA levels in depression and treatment with electroconvulsive therapy

Claire L. McGrory[a,b], Karen M. Ryan[a,b], Erik Kolshus[a,b], Declan M. McLoughlin[a,b]

[a]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland
[b]Dept. of Psychiatry, Trinity College Dublin, St Patrick's University Hospital, Dublin 8, Ireland

P.045

Introduction

The sirtuins are a group of seven (SIRT1-7) nicotinamide (NAD+)-dependent deacetylases[1]. SIRT1 has been linked to depression through genetic, gene expression and animal studies, with lower levels of *SIRT1* mRNA being linked to depression[2-3]. However, to our knowledge no studies have assessed the effects of acute treatment on blood *SIRT1* mRNA levels in depression, or if *SIRT1* levels are associated with clinical outcomes.

Electroconvulsive therapy (ECT) is the most effective treatment for severe depression but its mechanism is not fully understood. A recent study showed that a single ECS increases *Sirt1* mRNA levels in mouse hippocampus and hypothalamus[4]. Finally, we recently identified two microRNAs (miR-126-3p and miR-106a-5p) that were elevated in psychotic depressed patients and that returned to control levels following ECT[5]. Of note, SIRT1 is a shared target of these two microRNAs.

Aim

Our primary aim was to examine *SIRT1* mRNA levels in patients with depression and controls, and characterise the effects of ECT on peripheral blood *SIRT1* mRNA. As a secondary aim we explored differences in depression subtypes and associations between *SIRT1* mRNA levels and clinical outcomes. Depressed patients were recruited as part of the EFFECT-Dep Trial (ISRCTN:23577151)[6].

Methods

Whole blood samples collected using the PaxGene system

↓

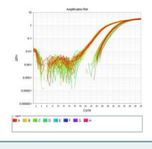
mRNA extraction using the PaxGene Blood RNA Kit

↓

cDNA synthesis using a High Capacity cDNA Reverse Transcription Kit

↓

quantitative real-time polymerase chain reaction (qRT-PCR) with TaqMan® gene expression assays and TaqMan Fast Advanced Master Mix



↓

Data analysis using SPSS version 21.0

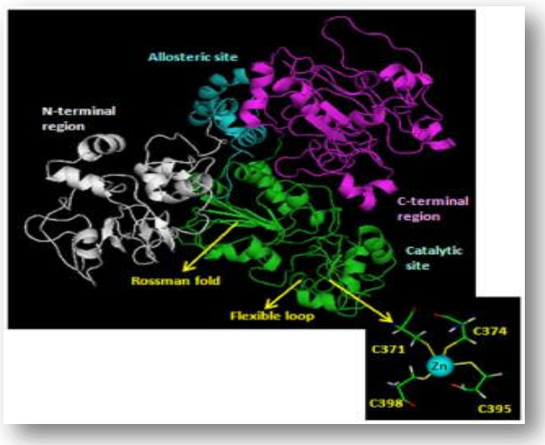
Results

Table 1 Demographic and clinical details of patients and controls

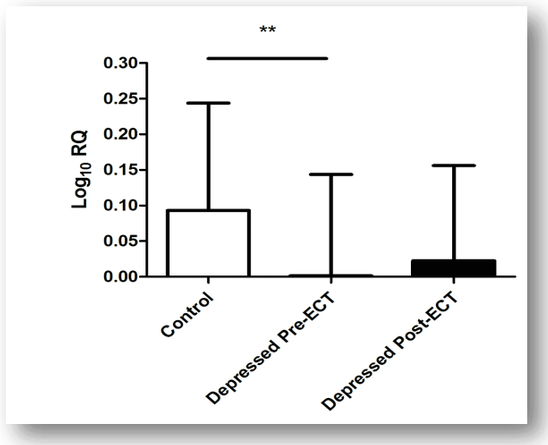
Variable	Patient (*n*=91)	Control (*n*=85)	Statistical Test
Age	56.8 (13.5)	54.7 (10.7)	p=0.27
Sex, female n (%)	59 (64.8)	53 (62.4)	χ^2= 0.12, p=0.76
Smoker, yes n (%)	38 (41.8)	19 (22.4)	χ^2=7.56, p<0.01**
BMI	27.02 (5.1)	25.14 (4.0)	U=2922.0, p<0.01**
HAM-D24 Baseline	30.27 (6.4)	3.29 (2.5)	U<0.001, p<0.001***
HAM-D24 EOT	10.94 (8.2)		
Bipolar Depression, n (%)	19 (20.9)		
Psychosis Subtype, n (%)	22 (24.2)		
Responder, n (%)	56 (61.5)		
Remitter, n (%)	47 (51.6)		

Abbreviations: BMI, body mass index; HAM-D24, Hamilton Depression Rating Scale, 24-item version; EOT, end of treatment; ECT, electroconvulsive therapy; U, standardised Mann-Whitney test. Data are presented as means (SD) or *n* (%).

1



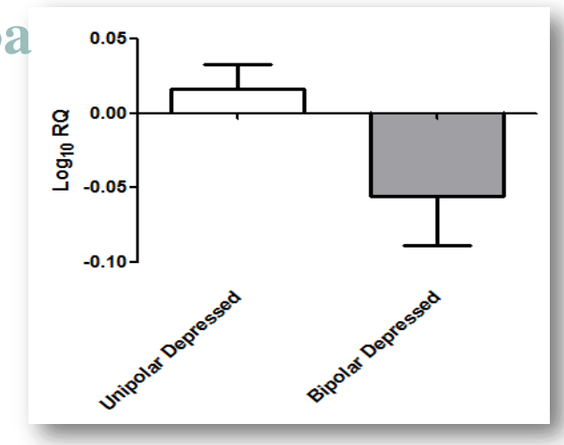
2



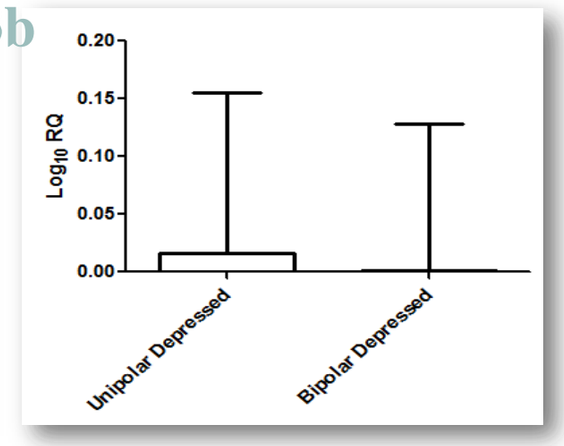
1. Model of human SIRT1, Autiero et al, 2009

***2. SIRT1* mRNA levels.** Log transformed RQ values of *SIRT1* mRNA in controls (*n*=85) and pre-ECT in depressed patients, and after a course of ECT in patients (*n*=91). Data are presented as unadjusted mean ± SD. ** p=0.005 healthy controls versus depressed pre-ECT.

3a

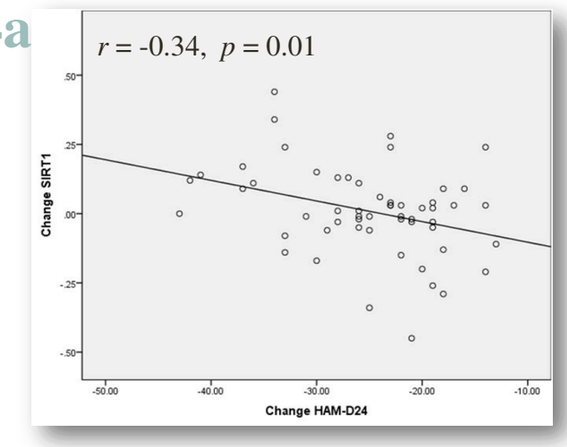


3b

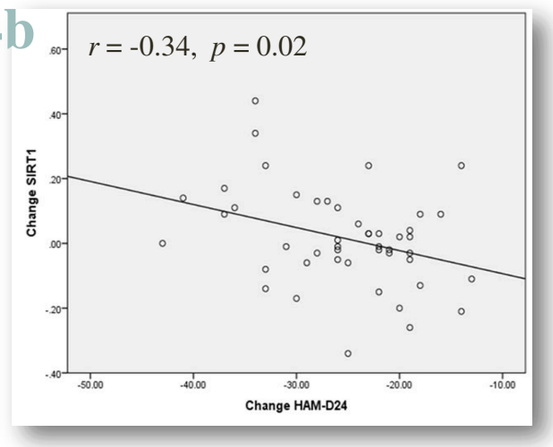


***3. SIRT1* mRNA levels and polarity of depression (a) pre-ECT and (b) post-ECT.** An unadjusted GLM found a significant difference between the two groups (p=0.049). However, after adjusting for covariates this significance was no longer seen (p=0.13). (b) There was also a trend for a polarity × time interaction (p=0.08) but this effect was lost after correction (p=0.23). Data are presented as unadjusted mean ± SD.

4a



4b



4. Relationship between a change in *SIRT1* mRNA levels and a change in HAMD-24 scores in (a) responders and (b) remitters. There was a trend for a negative correlation between the change in *SIRT1* levels and change in HAM-D24 score in patients who (a) responded to ECT (*n*=56), and also in those who (b) attained remission (*n*=47).

Discussion & Conclusion

Lower levels of *SIRT1* mRNA in depressed patients in comparison to healthy controls is in line with previous studies however we found no effect of treatment with ECT on *SIRT1* mRNA levels.

SIRT1 levels were lower in bipolar patients but this was not significant. Our sample size was small, therefore this needs to be replicated with a larger sample size.

There was a negative association between a change in *SIRT1* levels and a change in HAM-D24 scores in ECT responders /remitters. This could implicate *SIRT1* in ECT response and could provide a marker for monitoring response to ECT. However, these correlations were exploratory and therefore need to be replicated in a larger group of responders/remitters before the findings can be interpreted accurately.

Overall, the results of this study indicate that reduced peripheral blood *SIRT1* mRNA could be a trait marker of depression.

References

[1] Buler, M., et al. 2016. Who watches the watchmen? Regulation of the expression and activity of sirtuins. FASEB J 30, 3942-3960.
[2] CONVERGE Consortium., 2015. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 523, 588–591.
[3] Abe, N., et al.., 2011. Altered sirtuin deacetylase gene expression in patients with a mood disorder. J Psychiatr Res 45, 1106-1112.
[4] Chung, S., et al., 2013. Electroconvulsive Shock Increases SIRT1 Immunoreactivity in the Mouse Hippocampus and Hypothalamus. J Ect 29, 93-100.
[5] Kolshus, E., et al., 2017. Peripheral blood microRNA and VEGFA mRNA changes following electroconvulsive therapy: implications for psychotic depression. Acta Psychiatr Scand 136, 594-606
[6]Semkovska, M., et al.,, 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.

TRINITY COLLEGE Institute of Neuroscience

HRB Health Research Board

Disclosure of Interest
Declan McLoughlin has received a speaker's honorarium from Mecta. The other authors report no conflict of interest.