Serum brain-derived neurotrophic factor levels and symptom improvements following ketamine and ECT treatment in treatment-resistant depression

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

EMAIL: andrewallen@ucc.ie

Poster No. P001

Allen, A.P.[1,2], Naughton, M.[1], Dowling, J.[3], Walsh, A.[3], Ismail, F.[1], Shorten, G.[3], Scott, L.[1], McLaughlin, D.[4], Cryan, J.F.[2,5], Dinan, T.G.[1,2], Clarke, G.[1,2]

1. Department of Psychiatry, University College Cork; 2. Alimentary Pharmabiotic Centre, University College Cork; 3. Department of Anaesthesia and Intensive Care Medicine, University College Cork; 4. Department of Psychiatry and Trinity College Institute of Neuroscience, Trinity College Dublin; 5. Department of Anatomy & Neuroscience, University College Cork

Alimentary Pharmabiotic Centre

1. Introduction

Ketamine is associated with fast antidepressant efficacy [**1**], but research is needed to describe the biological mechanism that mediates this effect [**2**; see **Figure 1**]. Brain derived neurotrophic factor (BDNF), a neurotrophin associated with hippocampal neurogenesis, is a potential circulating biomarker of the ketamine response; it is reduced in depression and can be normalised following successful treatment. In patients with treatment-resistant depression (TRD), a reduction in depressive symptoms by ketamine was associated with heightened plasma BDNF four hours post-infusion [**3**]. However, given that the clinical response to ketamine can last for over a week, there is a paucity of research on whether BDNF increases persist over this time frame. Furthermore, although ketamine has occasionally been given repeatedly to TRD patients in off-licence protocols, it is unknown if multiple infusions lead to sustained effects on BDNF levels. There is also a need to compare ketamine to electroconvulsive therapy (ECT). This is the gold standard for treatment-resistant depression, and has similarly been shown to enhance BDNF [**4**].

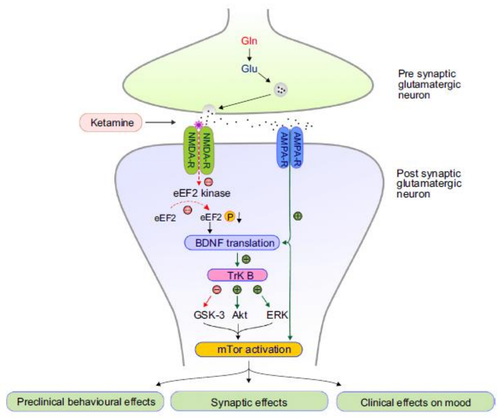

Figure 1 [Adapted from **2**]: Blockade of the NMDA receptor by the glutamatergic drug ketamine reduces activation of eukaryotic elongation factor 2 (eEF2), which results in the reversal of BDNF gene transcription silencing [**5**]. This in turn impacts upon mood via TrK B and mTor activation.

2. Aims & Hypothesis

Aim: Investigate the effect of multiple ketamine infusions and ECT sessions on the relationship between serum BDNF and severity of depression. Hypothesis: Ketamine induces a rapid increase in serum BDNF that accompanies symptom improvement in treatment-resistant depression, comparable to that in ECT. This increase in serum BDNF by ketamine persists for up to one week.

3. Methods

Participants

Age- and gender-matched patients with TRD (N = 35) and healthy controls (N = 20) were recruited. Exclusion criteria: >10% above ideal body weight, endocrine, immune or metabolic disorder. Severity of depression was assessed using the Hamilton Depression Rating Scale (HDRS). 74.3% of the TRD cohort had a diagnosis of major depressive episode- recurrent with melancholia, 14.3% had a diagnosis of major depressive episode with melancholia and 11.4% had a diagnosis of major depressive episode- recurrent using the MINI-Neuropsychiatric interview. Patients who showed a 50% or greater HDRS reduction were classified as responders.

Table 1: Participant characteristics

	Healthy Controls	TRD
Males:Females	10:10	15:20
Mean age	42.85 (SD = 9.9)	49.09 (SD = 15.38)
Baseline HDRS	-	20.86 (SD = 5.06)

Procedure

Blood samples were collected at baseline in all participants, including healthy controls.

Ketamine: 1-3 infusions (0.5mg/kg) were administered at visits one week apart. Post-infusion blood samples were collected at 24 hours following the first infusion and at 2 hours and 1 week following each infusion (see **Figure 2**).

ECT: Twice-weekly brief-pulse bitemporal ECT was administered using a Mecta 5000M device, with methohexitone (0·75–1·0 mg/kg) for anaesthesia and suxamethonium (0·5–1·0 mg/kg) for muscle relaxation. Participants completed up to 12 sessions of ECT. Post-treatment blood was collected on completion of the final ECT session.

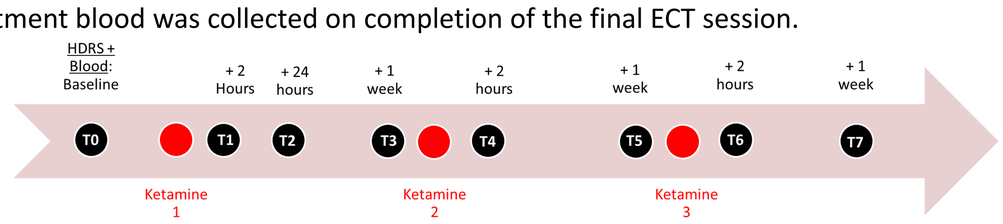

Figure 2: Ketamine study timeline

BDNF levels were assessed in serum using MesoScale Discovery custom assays according to manufacturer's instructions. Lower limit of detection = 0.035 pg/ml. For each sampling time, to assess the effect of treatment on BDNF, post-treatment BDNF data were compared to corresponding baseline data for patients who responded symptomatically.

4. Results

Clinical effects of treatment

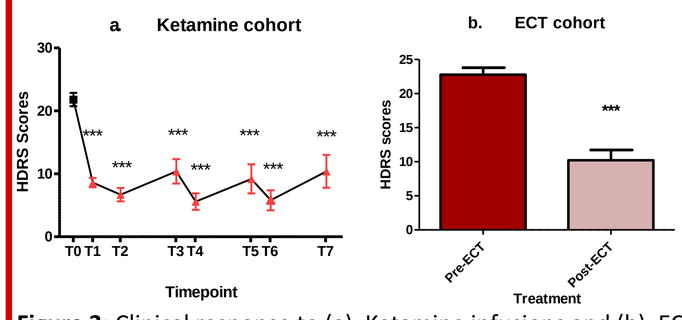

Figure 3: Clinical response to (a). Ketamine infusions and (b). ECT.

Ketamine was associated with a significant reduction in depressive symptoms, $F(2.3, 20.7) = 22.56$, $p < .001$, partial eta squared = .72 (see **Figure 3a**). ECT also significantly reduced HDRS compared to pre-ECT baseline, $t(18) = 4.15$, $p = .001$, Cohen's d = 0.98 (see **Figure 3b**).

Treatment effects on serum BDNF

Baseline

Pre-treatment, the treatment-resistant depression group had significantly lower serum BDNF compared to the healthy controls, $t(50) = -3.07$, $p = .003$, Cohen's d = 0.86 (see **Figure 4**).

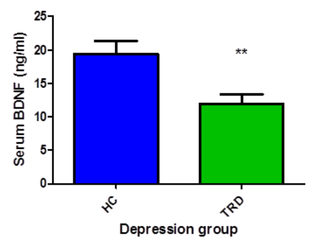

Figure 4: Baseline differences in serum BDNF.

ECT

ECT did not significantly alter BDNF levels in those who responded to ECT, $t(6) = 1.3$, $p > .05$, Cohen's d = 0.48 (see **Figure 5a**), nor did it affect BDNF in non-responders (see **Figure 5b**).

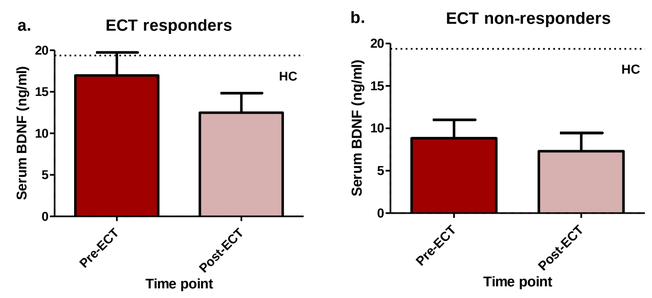

Figure 5: Serum BDNF pre- and post-treatment in (a). ECT responders and (b). ECT non-responders.

Ketamine

Patients who exhibited a sustained clinical response to ketamine at T3 showed enhanced BDNF at this time compared to baseline, $t(6) = -2.85$, p = .03, Cohen's d = 1.08 (see **Figure 6a**), but non-responders did not (see **Figure 6b**). Ketamine was not associated with a significant change in serum BDNF for the patients who completed all 3 infusions (see **Figure 6c**), nor was it associated with clinical response at any time other than T3.

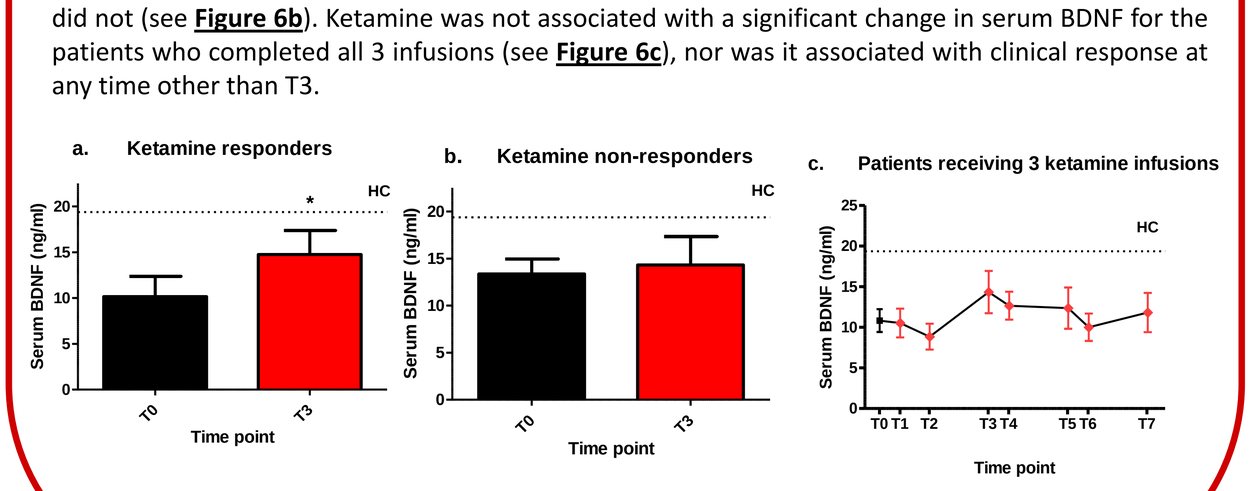

Figure 6: Serum BDNF (a) at T0 and T3 in responders (b) at T0 and T3 in non-responders and (c) at all timepoints for all those who completed all 3 infusions.

5. Discussion & conclusions

- Ketamine and ECT were both associated with a significant reduction in depressive symptoms in a majority of patients.
- Treatment-resistant depression was associated with lower serum BDNF at baseline compared to healthy controls.
- At one week after the first infusion, those patients who responded symptomatically to ketamine also had heightened serum BDNF. However, this was not the case at other timepoints, nor did ECT significantly alter serum BDNF.
- Future research is required to further clarify the potential importance of the delayed BDNF response to the initial ketamine infusion.

6. Acknowledgements & Disclosure

The Alimentary Pharmabiotic Centre is a research centre funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan. The authors and their work are supported by SFI (grant numbers SFI/12/RC/2273, 02/CE/B124 and 07/CE/B1368), by the Health Research Board (HRB) through Health Research Awards (grants no HRA_POR/2011/23; TGD, JFC and GC,HRA_POR/2012/32; JFC, TGD, and HRA_POR-2014-647; GC, TGD) and through EU GRANT 613979 (MYNEWGUT FP7-KBBE-2013-7). The Centre has conducted studies in collaboration with several companies including GSK, Pfizer, Wyeth and Mead Johnson. GC is supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Grant Number 20771).
The authors declare no conflict of interest.

7. References

[1] Berman, R.M., et al., 2000. *Biological Psychiatry* 47, 351-354.
[2] Naughton, M., et al., 2014. *Journal of Affective Disorders* 156, 24-35.
[3] Haile, C.N., et al., 2013. *International Journal of Neuropsychopharmacology* 17, 331-336.
[4] Brunoni, A.R., et al., *The World Journal of Biological Psychiatry*, 15, 411-418.
[5] Autry, A.E., et al., *Nature*, 475, e95.

Fondúireacht Eolaíochta Éireann Science Foundation Ireland
HRB Health Research Board
BRAIN & BEHAVIOR RESEARCH FOUNDATION Awarding NARSAD Grants