Gut Microbiome alterations in Major Depressive Disorder: Relevance to Pathophysiology

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Coláiste na hOllscoile Corcaigh

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Introduction

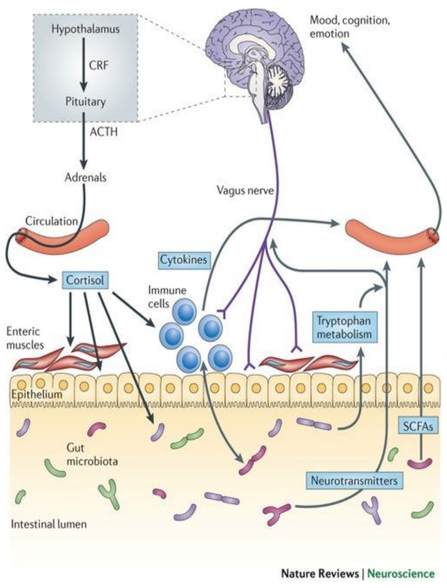

Figure 1: Signaling pathways involved in The Brain Gut Microbiota Axis. Cryan & Dinan, Nat Rev Neuroscience, 2012

- The biological mechanisms underlying the pathophysiology of MDD involve immune [1], endocrine [2] and neurotransmitter dysregulation.
- Pre-clinical findings suggest that the gut microbiota can modulate brain development, function and behaviour by recruiting the same neuroimmune, neuroendocrine and neural pathways of the brain-gut-axis which are dysfunctional in MDD [3].
- However, the extent to which these pre-clinical findings translate to clinical populations is currently unknown.

Aim

Determine the composition of the gut microbiota in patients with MDD compared to healthy control participants and its relationship to:

- Short Chain Fatty acids (SCFAs)
- Immune activity (plasma cytokines)
- Hypothalamic-Pituitary-Adrenal axis (HPA-axis) function and
- Tryptophan metabolism

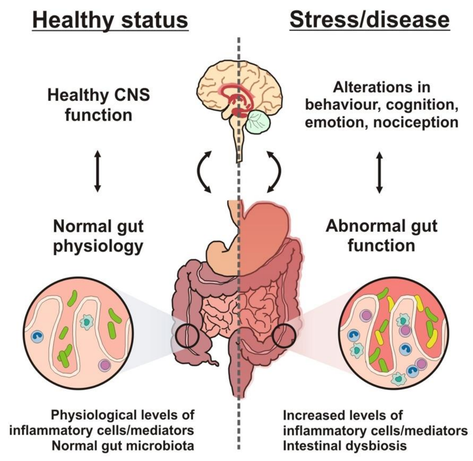

Figure 2: Brain Gut Microbiota Communication in Health & Disease. Grenham & Clarke et al., Frontiers in Physiology, 2011

Methods

Study Population:
34 patients with DSM IV MDD
(MINI International Neuropsychiatric Interview)

33 healthy subjects matched for gender, age & ethnicity (see **Table 1** for demographics & clinical characteristics)

Measures:

Gut Microbiota Structure & Diversity
16s rRNA gene sequencing

Hypothalamic-Pituitary-Adrenal (HPA) Axis
Salivary Cortisol (ELISA)

Inflammatory
Plasma Cytokines & C-Reactive Protein/CRP (Meso Scale Discovery)

Tryptophan Metabolites
Plasma tryptophan & kynurenine (HPLC)

Subjective Mood & Stress
Hamilton Depression rating scale (HAMD 17)
Beck Depression & Anxiety scales (BDI & BAI)
Perceived Stress scale (PSS)
Pittsburgh Sleep Quality Index (PSQI)

Diet & Exercise
Food Frequency Questionnaire (FFQ)
International Physical Activity Questionnaire (IPAQ)

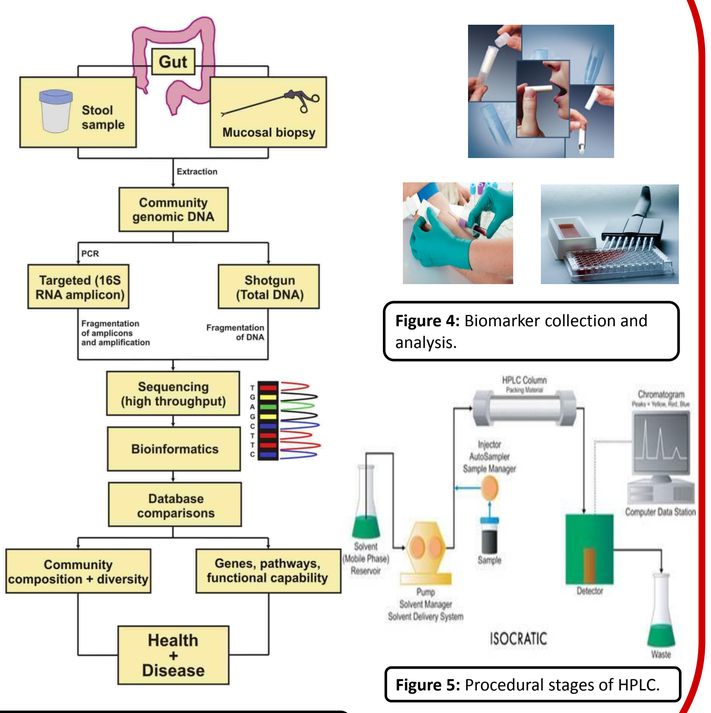

Figure 3: Procedural stages of gut microbiota sampling & sequencing.

Figure 4: Biomarker collection and analysis.

Figure 5: Procedural stages of HPLC.

Sample Characteristics

Demographics & Health Measures	Healthy Controls (n=33)	Depression (n=34)	p-value
Age mean (s.d.)	45.8 (11.9)	45.8 (11.5)	0.98
Sex Male (%)	19 (57.6)	21 (61.8)	0.73
BMI mean (s.d.)	24.58 (2.7)	26.2 (4.5)	0.07
Education, degree level (%)	26 (78.8)	8 (23.5)	<0.001***
Relationship status (% yes)	26 (78.8)	8 (23.5)	<0.001***
Employed (% yes)	31 (93.9)	16 (47.1)	<0.001***
Smoker (% current)	3 (9.1)	13 (38.2)	0.003
Dyslipidaemia (%)	4 (12.1)	7 (20.6)	0.51
Hypertension (%)	3 (9.1)	3 (8.8)	0.97
IPAQ Low (%)	7 (21.2)	13 (39.4)	0.18
IPAQ Moderate (%)	16 (48.5)	14 (42.4)	0.62
IPAQ High (%)	10 (30.3)	6 (18.2)	0.26
Metabolic Equivalent Task Units (MET) median, range	1386 (7287)	693 (7722)	0.10
HAMD 17 median (range)	NA	19.5 (14)	NA
Beck Depression mean, (s.d)	NA	32.4 (9.92)	NA
Beck Anxiety median, (range)	NA	25.5 (45)	NA
Duration of Depressive sx (months) median, (range)	NA	3.0 (72)	NA
Number of Depressive episodes median (range)	NA	1.0 (8)	NA
Depression in 1st degree relative (%)	2 (6.1)	21 (61.8)	<0.001***
Perceived Stress Scale (PSS) mean, (s.d)	7.5 (4.9)	27.7 (6.0)	<0.001***
Pittsburgh Sleep Quality Index (PSQI) mean, (s.d)	2.8 (1.8)	11.7 (4.3)	<0 .001***

Table 1: Comparisons between MDD patients & Healthy controls on demographics and clinical characteristics. Study participants were matched on the basis of age, BMI and ethnicity.

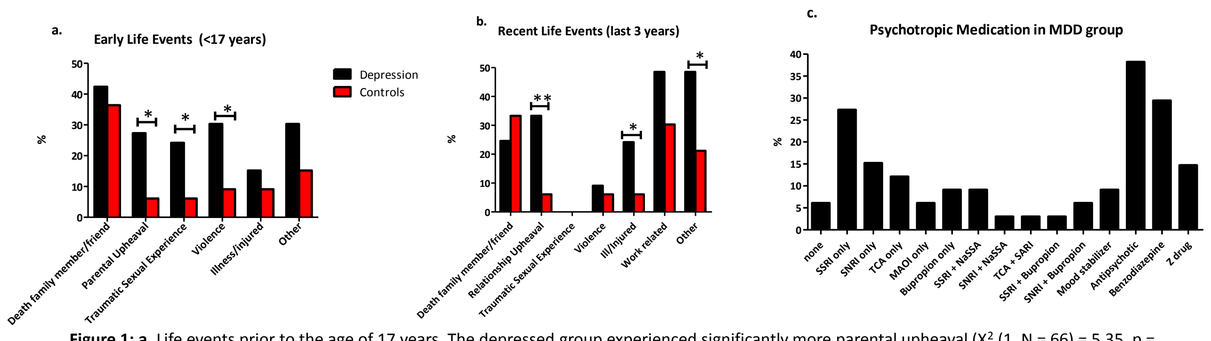

Figure 1: a. Life events prior to the age of 17 years. The depressed group experienced significantly more parental upheaval (X^2 (1, N = 66) = 5.35, p = 0.02), traumatic sexual experiences X^2 (1, N = 66) = 4.24, p = 0.04, and violence X^2 (1, N = 66) = 4.70, p = 0.03 compared to the controls. **b.** Life events within the last 3 years. The depressed group experienced significantly more relationship upheaval X^2 (1, N = 66) = 7.76, p = 0.01, illness/injury X^2 (1, N = 66) = 4.24, p = 0.04. **c.** Psychotropic medication in the depressed group.

Results

Altered Gut Microbiota Composition, Diversity & Richness in MDD compared to Controls

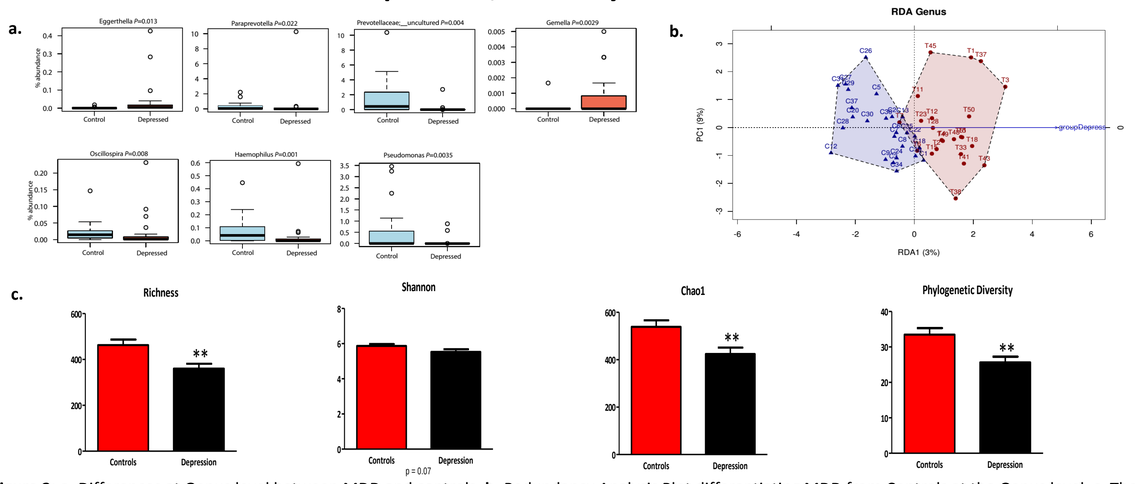

Figure 2: a. Differences at Genus level between MDD and controls. **b.** Redundancy Analysis Plot differentiating MDD from Controls at the Genus level. **c.** The MDD group had significantly reduced richness p = 0.002, Chao1, p = 0.004 and Phylogenetic Diversity, p = 0.002. There was a trend reduction in the Shannon Index in the MDD group, p = 0.07.

Fibre, Short Chain Fatty Acids (SCFAs) & Intestinal Permeability in MDD compared to Controls

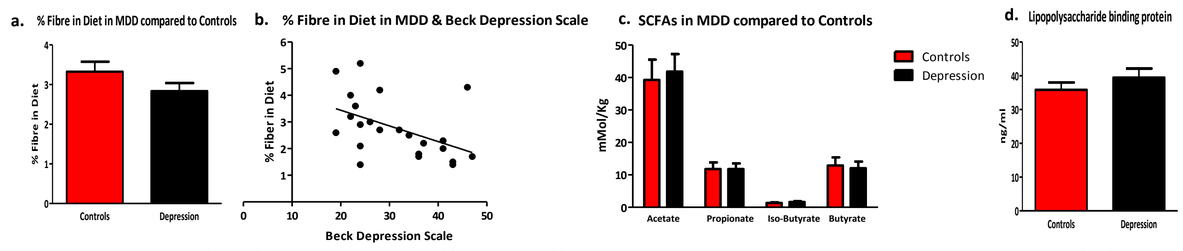

Figure 3: a. There no significant differences in percentage fibre consumed between the groups as measured by a Food Frequency Questionnaire. **b.** There was a negative correlation between % Fibre consumed in diet and Beck Depression Scale in the MDD group. r = -0.43, p = 0.01. **c.** There were no significant differences in fecal SCFAs; acetate, propionate, iso-butyrate or butyrate between the groups. **d.** There were no significant differences in intestinal permeability as measured by Lipopolysaccharide binding protein.

Altered Stress Response in MDD compared to Controls

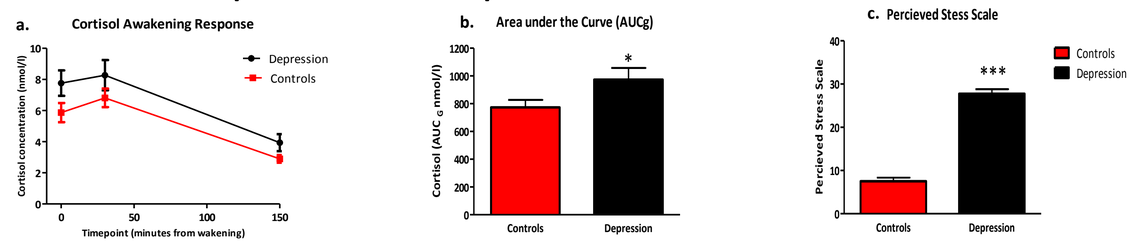

Figure 4: a. Salivary Cortisol Awakening Response. Repeated measures ANOVA across all sample collection time points revealed a significant main effect of group F (1,50) = 5.30, p=0.03). **b**. There was a significant increase in salivary cortisol as measured by Area under the Curve with respect to ground (AUCg) in the MDD group. p = 0.05**. c.** The MDD group had significantly higher PSS scores compared to the Control group. p = <0.001.

Inflammatory Profile in MDD compared to Controls

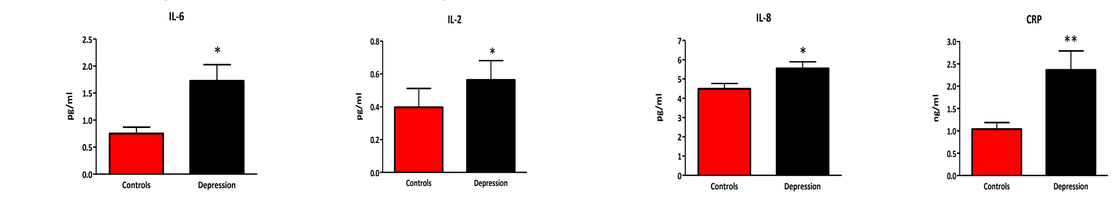

Figure 5: a. The MDD had significantly higher levels of IL-6, p = 0.02, IL-2, p = 0.02, IL-8, p = 0.02 and CRP, p = 0.01 in the MDD group compared to the Control group.

Tryptophan Metabolite Profile in MDD compared to Controls

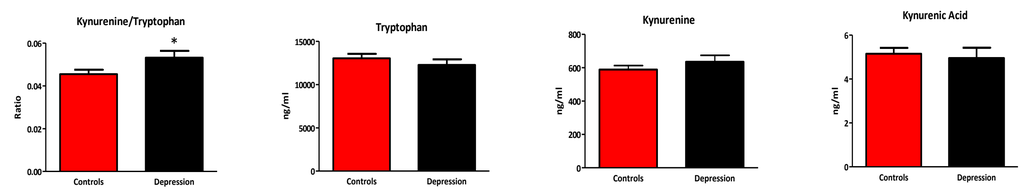

Figure 6: There was a significant difference in the tryptophan: Kynurenine ratio, p = 0.05. There were no significant differences in Tryptophan, p = 0.36, Kynurenine, p = 0.32 or Kynurenic Acid levels p = 0.70 between the groups.

Conclusions

- Alterations in the gut microbiota in patients with MDD are pronounced and may drive the prominent pathophysiological features of this disorder. The mechanisms underpinning these effects require further investigation. Ultimately, these findings may pave the way for therapeutic targeting of the gut microbiome as a viable strategy for novel antidepressant development.

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