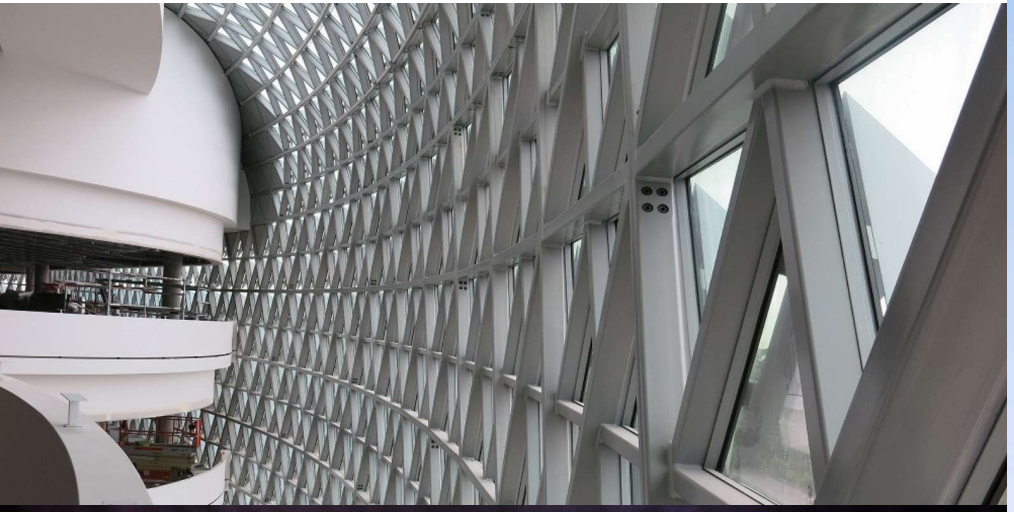
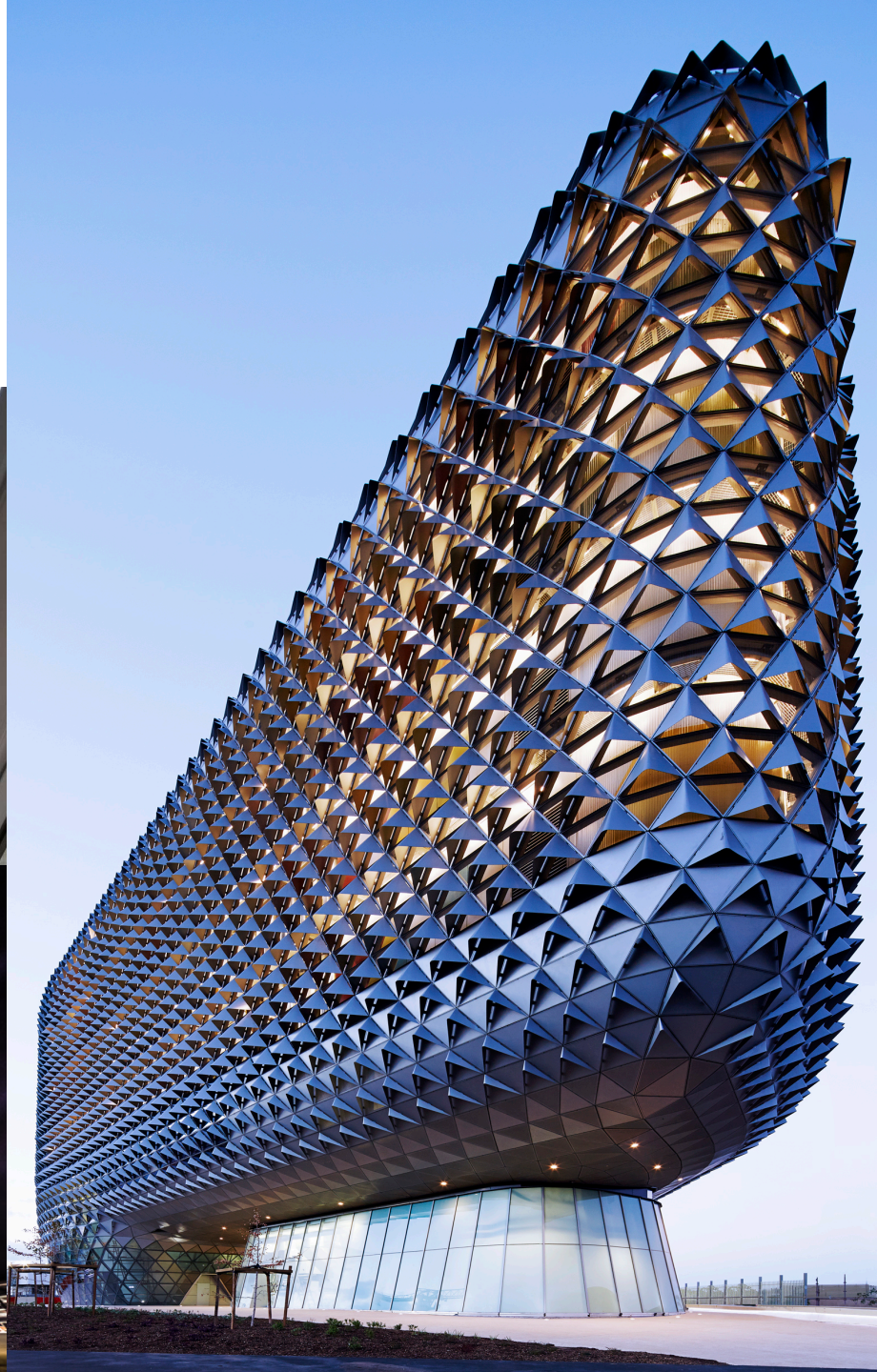
Neuroscience and mental health – challenges and opportunities

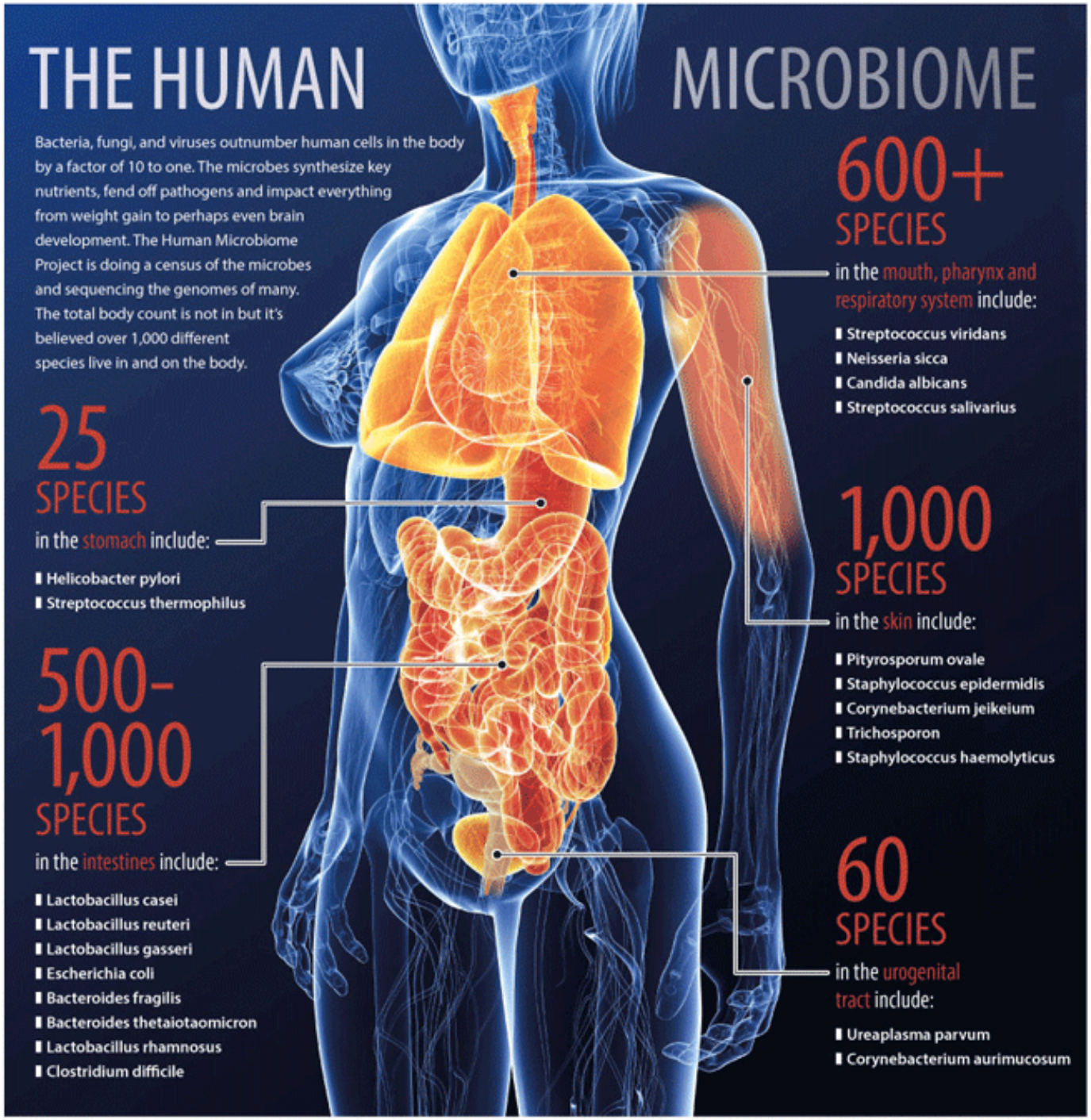
Searching for new mechanisms and pathways

Julio Licinio, MD, FRANZCP






1
Your body is
mostly microbes



- If you are not really you, but instead you are your bugs,
- Maybe your depression is not really within you, but it may be in your bugs.
- If that is true, if we treat your bugs, your depression will go away.
- A wild fantasy?
- Remember, the decades of therapy and surgery for ulcers, caused by "stress"?
- It was a bug all along: Marshall & Warren, Nobel Prize, 2005.

Molecular Psychiatry (2016) 21, 738–748
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OPEN

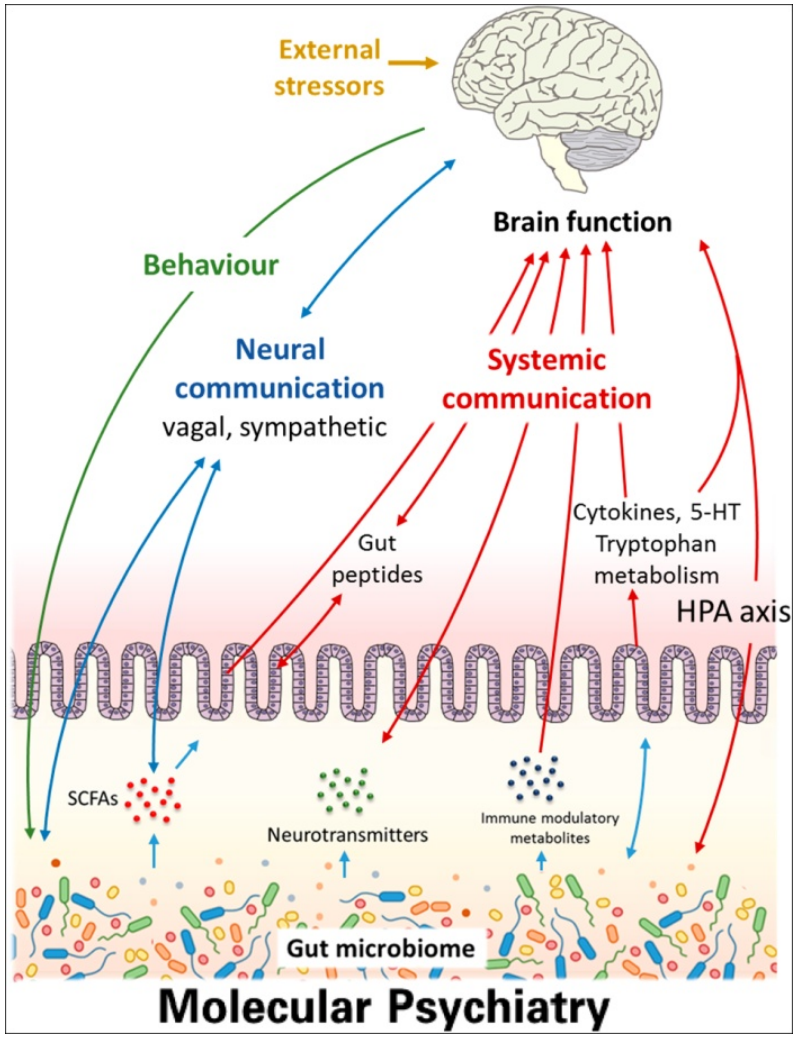
EXPERT REVIEW

From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways

GB Rogers[1], DJ Keating[2], RL Young[3], M-L Wong[4], J Licinio[4] and S Wesselingh[1]

The human body hosts an enormous abundance and diversity of microbes, which perform a range of essential and beneficial functions. Our appreciation of the importance of these microbial communities to many aspects of human physiology has grown dramatically in recent years. We know, for example, that animals raised in a germ-free environment exhibit substantially altered immune and metabolic function, while the disruption of commensal microbiota in humans is associated with the development of a growing number of diseases. Evidence is now emerging that, through interactions with the gut–brain axis, the bidirectional communication system between the central nervous system and the gastrointestinal tract, the gut microbiome can also influence neural development, cognition and behaviour, with recent evidence that changes in behaviour alter gut microbiota composition, while modifications of the microbiome can induce depressive-like behaviours. Although an association between enteropathy and certain psychiatric conditions has long been recognized, it now appears that gut microbes represent direct mediators of psychopathology. Here, we examine roles of gut microbiome in shaping brain development and neurological function, and the mechanisms by which it can contribute to mental illness. Further, we discuss how the insight provided by this new and exciting field of research can inform care and provide a basis for the design of novel, microbiota-targeted, therapies.

Molecular Psychiatry (2016) **21,** 738–748; doi:10.1038/mp.2016.50; published online 19 April 2016



Molecular Psychiatry (2016) **21**, 738-748;
doi:10.1038/mp.2016.50

Molecular Psychiatry (2016) 21, 786–796

www.nature.com/mp

ORIGINAL ARTICLE

Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism

P Zheng[1,2,3,8], B Zeng[4,8], C Zhou[1,2,3,8], M Liu[1,2,3], Z Fang[1,2,3], X Xu[1,2,3], L Zeng[1,2,3], J Chen[1,2,3], S Fan[1,2,3], X Du[1,2,3], X Zhang[1,2,3], D Yang[5], Y Yang[1,2,3], H Meng[6], W Li[4], ND Melgiri[1,2,3], J Licinio[7,9], H Wei[4,9] and P Xie[1,2,3,9]

Major depressive disorder (MDD) is the result of complex gene–environment interactions. According to the World Health Organization, MDD is the leading cause of disability worldwide, and it is a major contributor to the overall global burden of disease. However, the definitive environmental mechanisms underlying the pathophysiology of MDD remain elusive. The gut microbiome is an increasingly recognized environmental factor that can shape the brain through the microbiota-gut-brain axis. We show here that the absence of gut microbiota in germ-free (GF) mice resulted in decreased immobility time in the forced swimming test relative to conventionally raised healthy control mice. Moreover, from clinical sampling, the gut microbiotic compositions of MDD patients and healthy controls were significantly different with MDD patients characterized by significant changes in the relative abundance of Firmicutes, Actinobacteria and Bacteroidetes. Fecal microbiota transplantation of GF mice with 'depression microbiota' derived from MDD patients resulted in depression-like behaviors compared with colonization with 'healthy microbiota' derived from healthy control individuals. Mice harboring 'depression microbiota' primarily exhibited disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism. This study demonstrates that dysbiosis of the gut microbiome may have a causal role in the development of depressive-like behaviors, in a pathway that is mediated through the host's metabolism.

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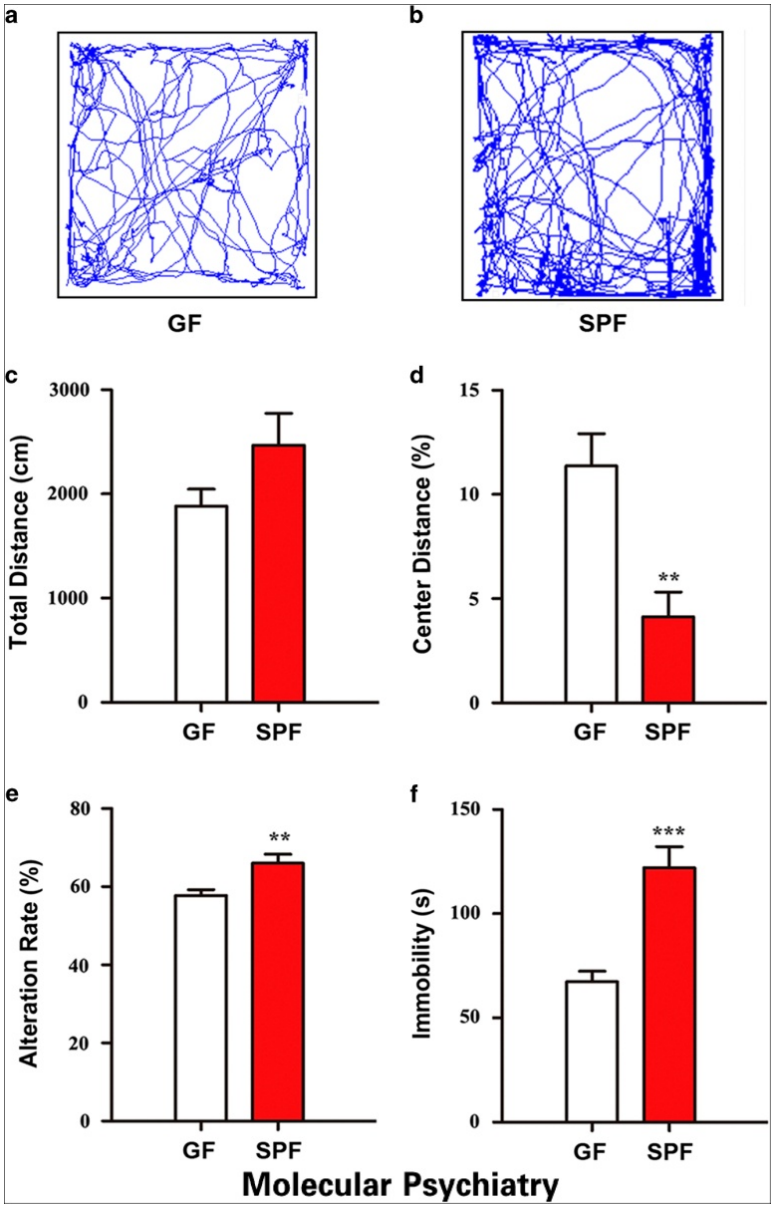
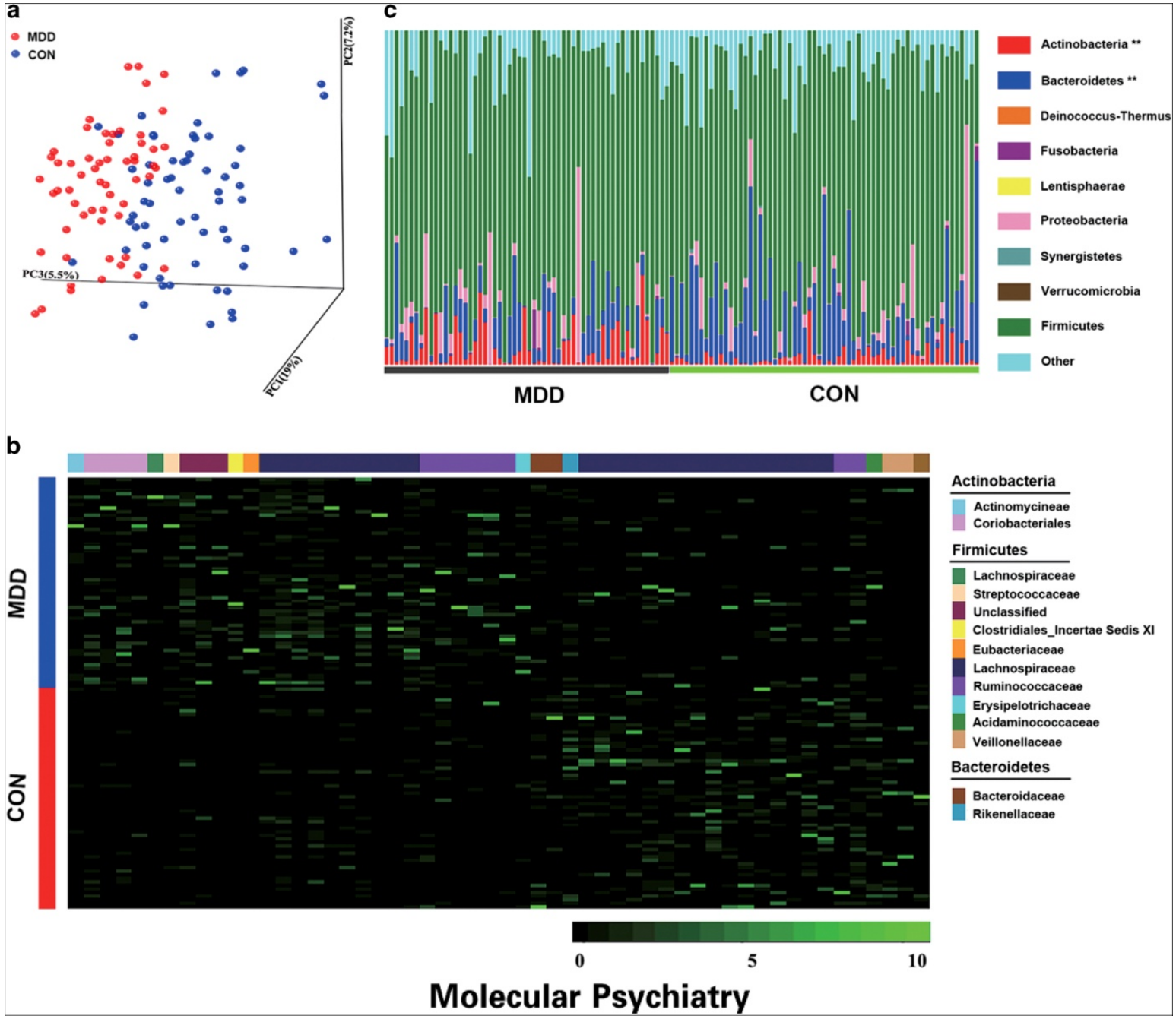
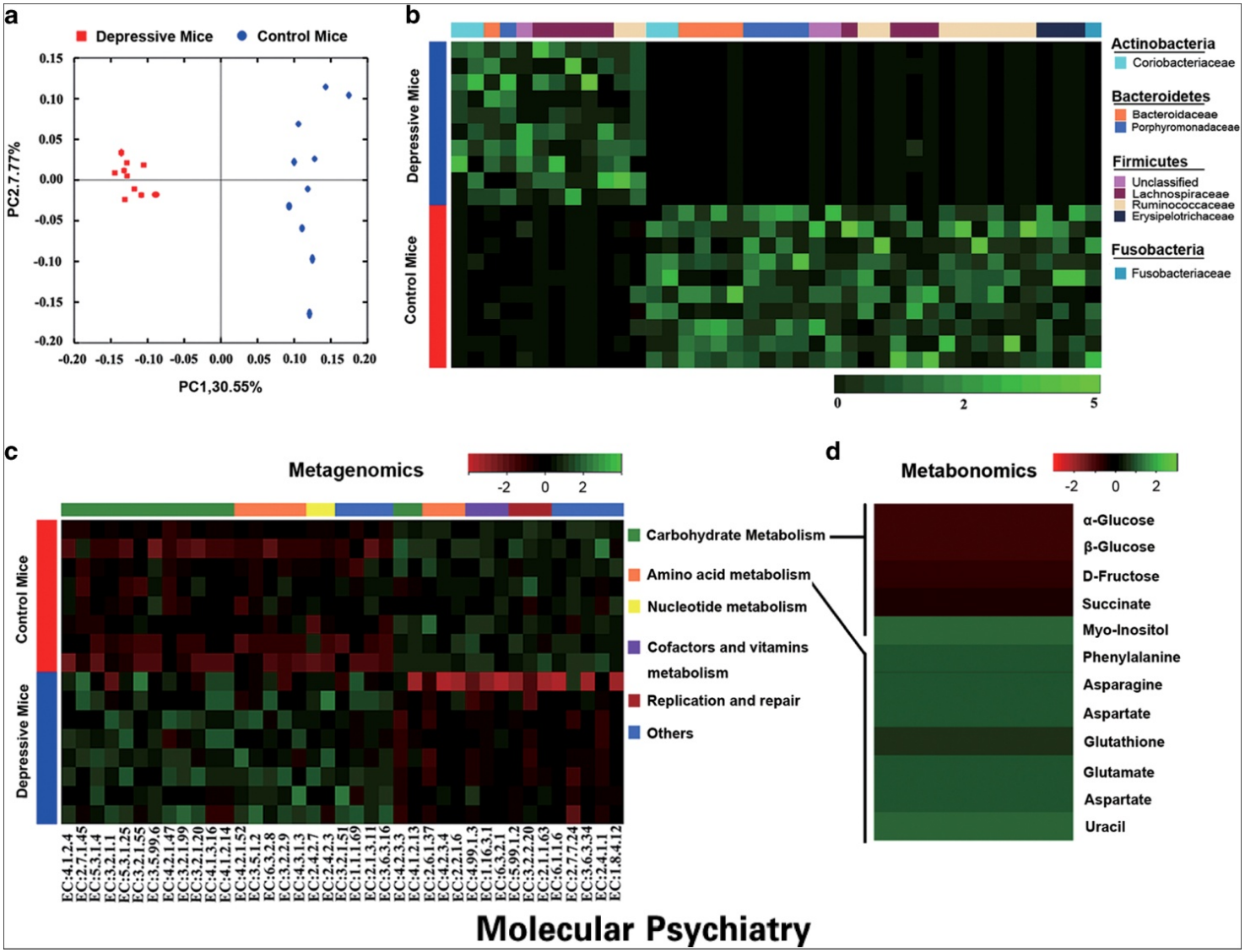
Findings

- Germ-free (GF) mice have less depressive-like behaviors than SPF mice.
- Fecal transplantation from depressed humans (compared to healthy controls) into GF mice results in more depressive-like behaviors.




a
MDD
CON
PC2(7.2%)
PC3(5.5%)
PC1(19%)
c
Actinobacteria **
Bacteroidetes **
Deinococcus-Thermus
Fusobacteria
Lentisphaerae
Proteobacteria
Synergistetes
Verrucomicrobia
Firmicutes
Other
MDD
CON
b
MDD
CON
Actinobacteria
Actinomycineae
Coriobacteriales
Firmicutes
Lachnospiraceae
Streptococcaceae
Unclassified
Clostridiales_Incertae Sedis XI
Eubacteriaceae
Lachnospiraceae
Ruminococcaceae
Erysipelotrichaceae
Acidaminococcaceae
Veillonellaceae
Bacteroidetes
Bacteroidaceae
Rikenellaceae
0
5
10
Molecular Psychiatry

Microbiota is different in GF mice receiving transplant from depressed humans (compared to healthy controls). Behavioral outcomes possibly mediated by the metabolome.



OPEN

Molecular Psychiatry (2016) 21, 797–805

www.nature.com/mp

ORIGINAL ARTICLE

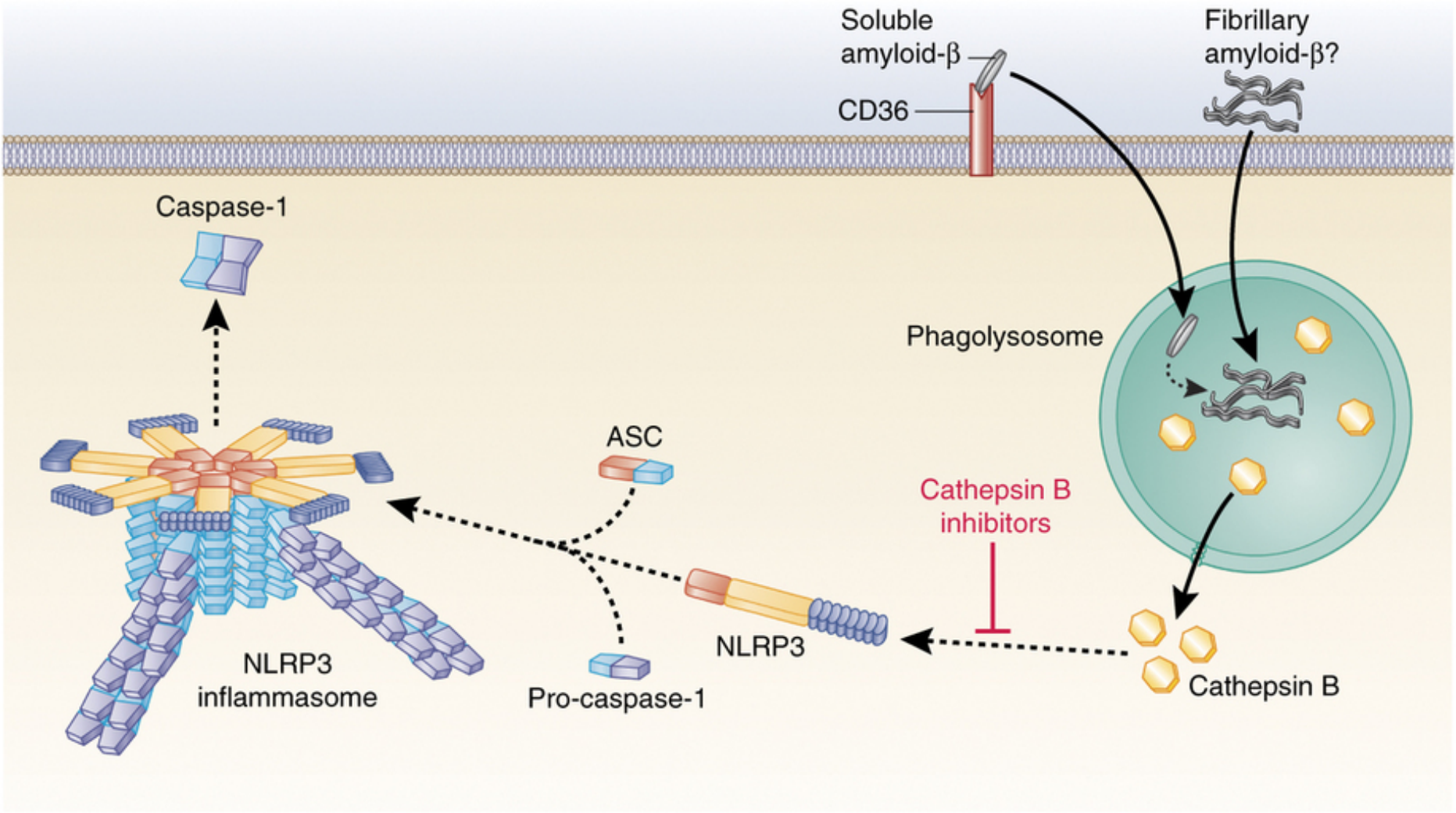
Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition

M-L Wong[1,2,9,10], A Inserra[1,2,9], MD Lewis[1,2], CA Mastronardi[3], L Leong[4,5], J Choo[4,5], S Kentish[6], P Xie[7,10], M Morrison[8], SL Wesselingh[4,5], GB Rogers[4,5,10] and J Licinio[1,2,10]

The inflammasome is hypothesized to be a key mediator of the response to physiological and psychological stressors, and its dysregulation may be implicated in major depressive disorder. Inflammasome activation causes the maturation of caspase-1 and activation of interleukin (IL)-1β and IL-18, two proinflammatory cytokines involved in neuroimmunomodulation, neuroinflammation and neurodegeneration. In this study, C57BL/6 mice with genetic deficiency or pharmacological inhibition of caspase-1 were screened for anxiety- and depressive-like behaviors, and locomotion at baseline and after chronic stress. We found that genetic deficiency of caspase-1 decreased depressive- and anxiety-like behaviors, and conversely increased locomotor activity and skills. Caspase-1 deficiency also prevented the exacerbation of depressive-like behaviors following chronic stress. Furthermore, pharmacological caspase-1 antagonism with minocycline ameliorated stress-induced depressive-like behavior in wild-type mice. Interestingly, chronic stress or pharmacological inhibition of caspase-1 *per se* altered the fecal microbiome in a very similar manner. When stressed mice were treated with minocycline, the observed gut microbiota changes included increase in relative abundance of *Akkermansia* spp. and *Blautia* spp., which are compatible with beneficial effects of attenuated inflammation and rebalance of gut microbiota, respectively, and the increment in Lachnospiracea abundance was consistent with microbiota changes of caspase-1 deficiency. Our results suggest that the protective effect of caspase-1 inhibition involves the modulation of the relationship between stress and gut microbiota composition, and establishes the basis for a gut microbiota–inflammasome–brain axis, whereby the gut microbiota via inflammasome signaling modulate pathways that will alter brain function, and affect depressive- and anxiety-like behaviors. Our data also suggest that further elucidation of the gut microbiota–inflammasome–brain axis may offer novel therapeutic targets for psychiatric disorders.

Molecular Psychiatry (2016) **21,** 797–805; doi:10.1038/mp.2016.46; published online 19 April 2016

Inflammasome in Alzheimer's disease

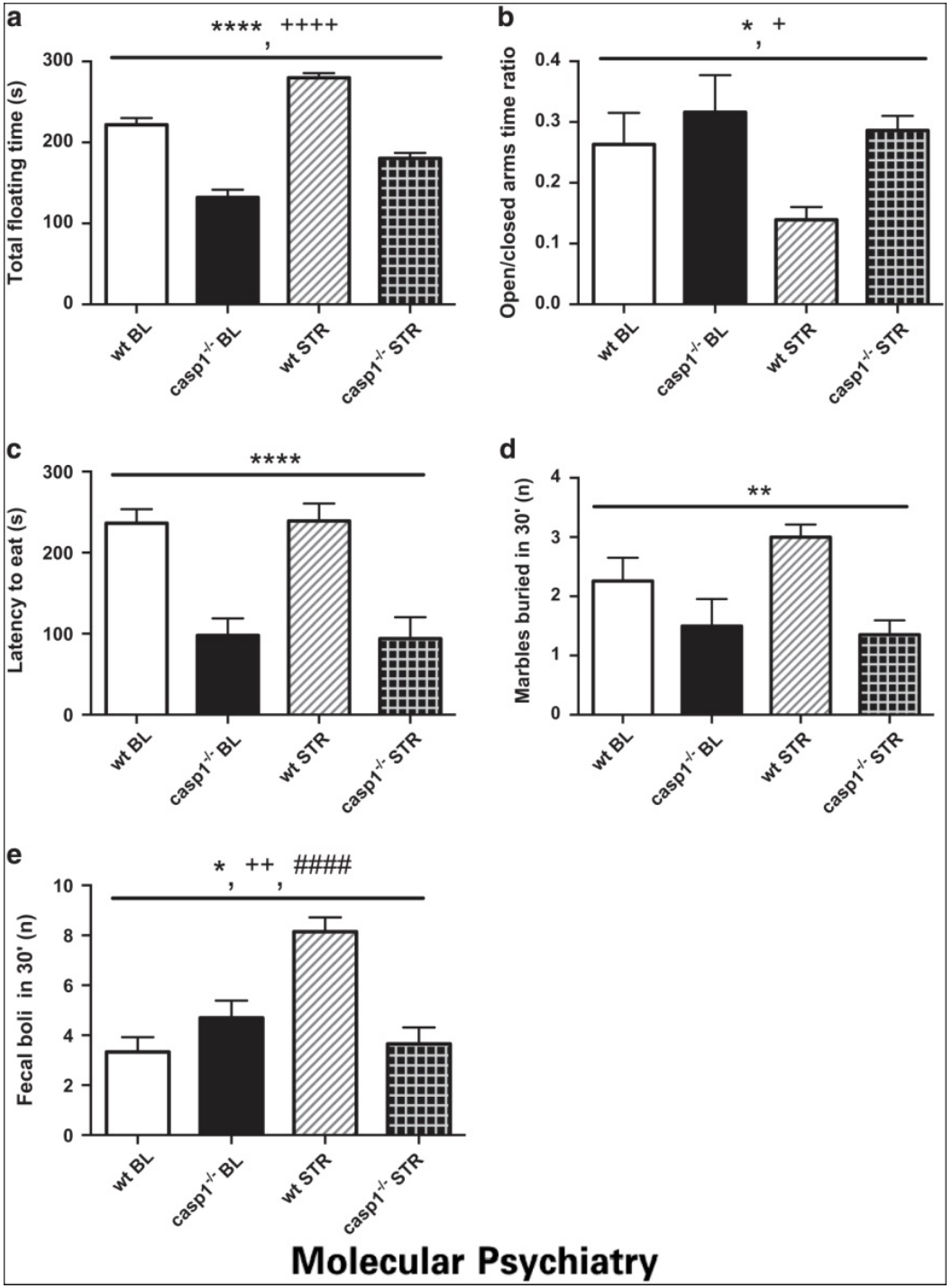


Debbie Maizels/Nature Publishing Group

- Caspase 1 activation: mature IL-1ß and IL-18
- Induces potent inflammatory response

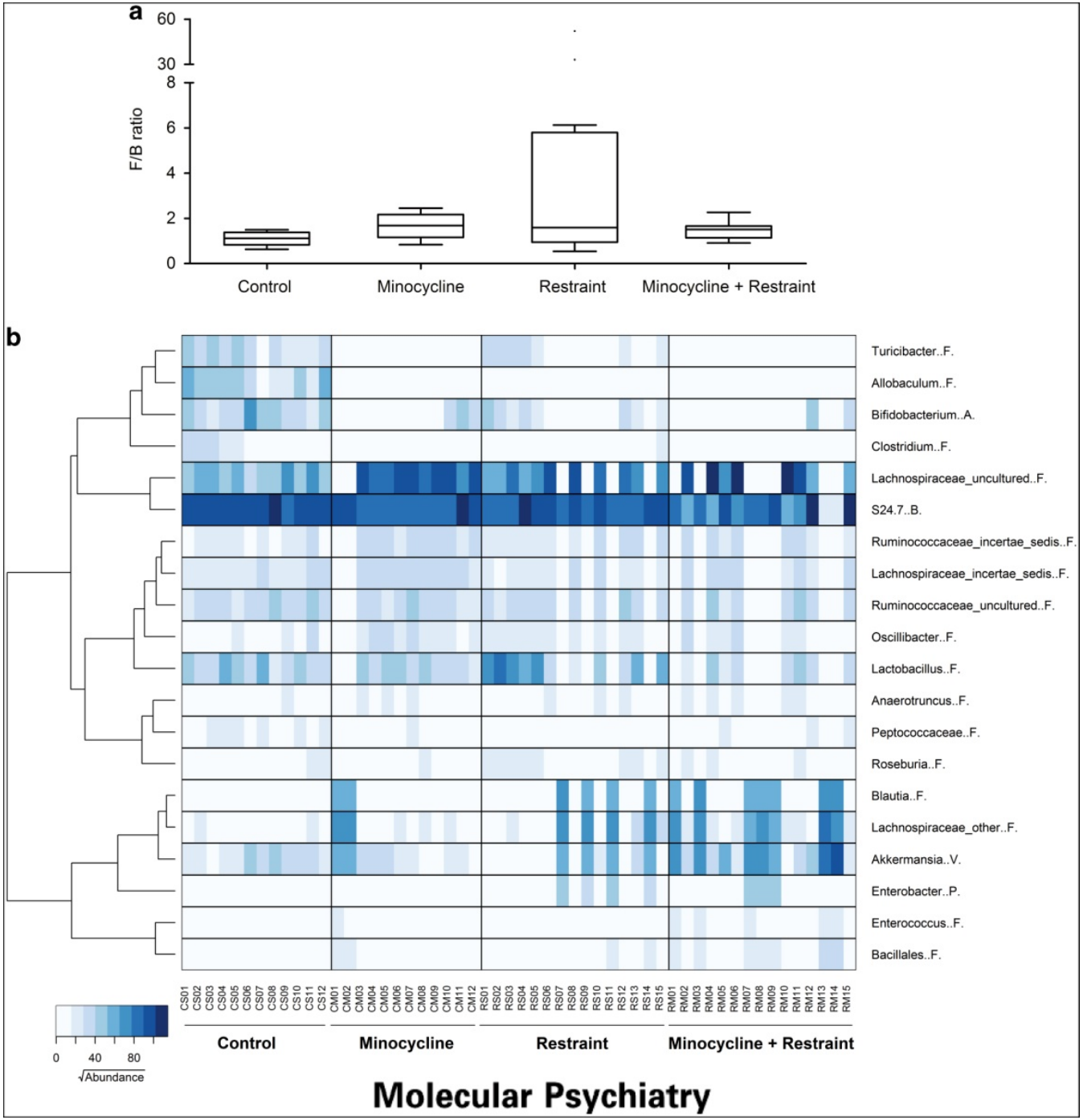
Findings

- Caspase 1 knockout has antidepressant-like effects.
- Reaction to chronic stress is substantially blunted in the absence of caspase 1 bioactivity.



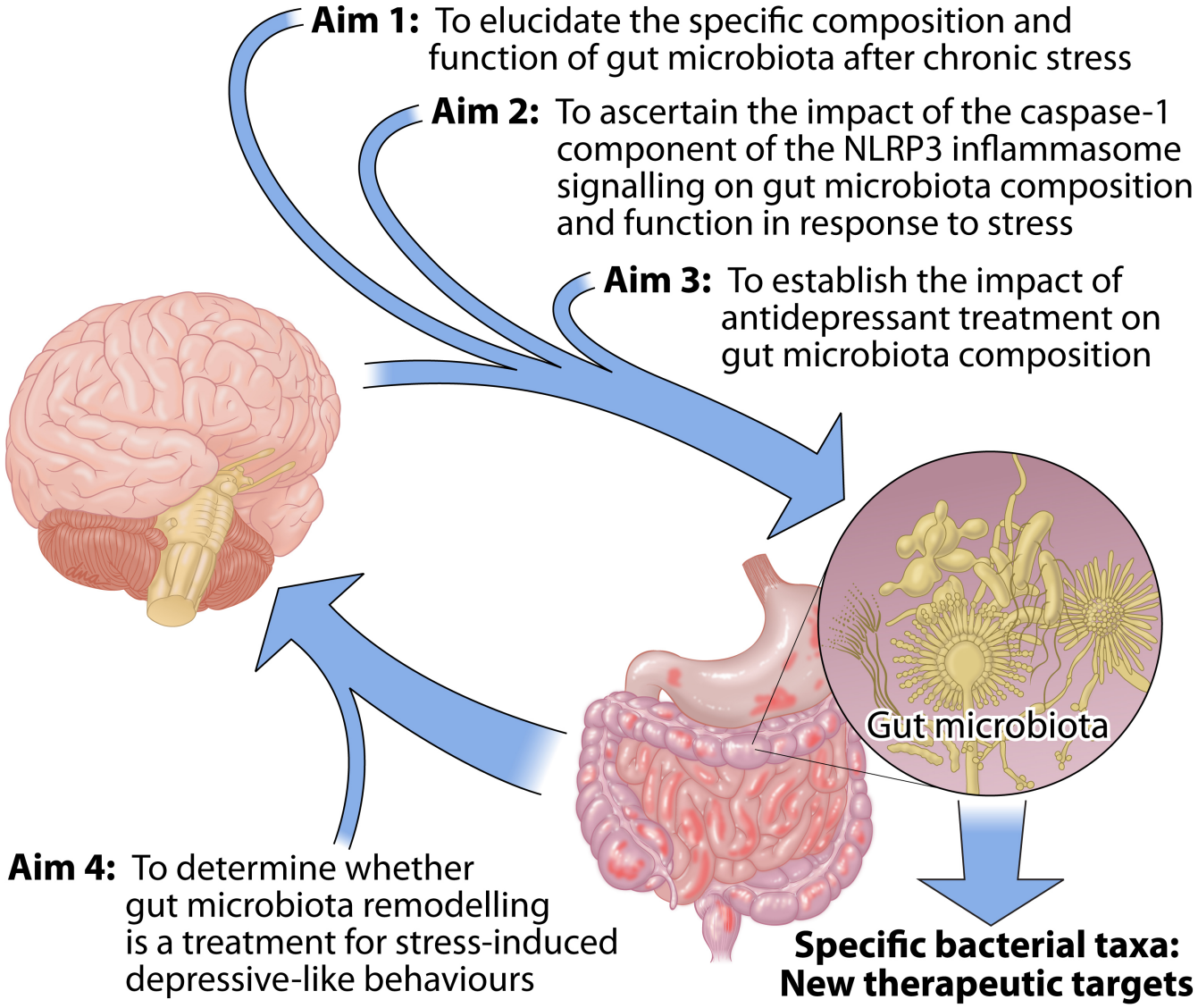
Findings

- Pharmacological inhibition of caspase 1 results in changes in the microbiota.
- Could such changes mediate the effects of caspase 1 on behavior?



Conclusions

- Germ-free mice: decreased immobility time in forced swimming relative to conventionally raised healthy control mice.
- Gut microbiotic compositions of healthy controls: significantly different from those of MDD patients.
- Fecal microbiota transplantation of GF mice with 'depression microbiota' derived from MDD patients resulted in depression-like behaviors compared with colonization with 'healthy microbiota.'
- Mice with 'depression microbiota' exhibited disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism, indicating that depressive-like behaviors are mediated through the host's metabolism.
- Changes in behavior brought about by chronic stress, genetic manipulation or pharmacological intervention result in changes in the gut microbiota. Possible mediation by the inflammasome.
- **We propose that the microbiota–gut–brain (MGB) axis is fully bidirectional, functioning in a manner through which changes in microbiota affect behavior and alterations in behavior result in changes in the gut microbiota.**
- **The MGB axis may represent a novel target for antidepressant tx.**



The microbiota-gut-brain axis (MGB) axis provides a conceptual framework for the four Aims of our ongoing research program on the microbiome and depression.

Molecular Psychiatry TOP TEN

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01

From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways OPEN

G B Rogers, D J Keating, R L Young, M-L Wong, J Licinio & S Wesselingh

doi:10.1038/mp.2016.50

Abstract | Full Text | PDF

02

Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition OPEN

M-L Wong, A Inserra, M D Lewis, C A Mastronardi, L Leong, J Choo, S Kentish, P Xie, M Morrison, S L Wesselingh, G B Rogers & J Licinio

doi:10.1038/mp.2016.46

Abstract | Full Text | PDF

03

Genetics and intelligence differences: five special findings OPEN

R Plomin & I J Deary

doi:10.1038/mp.2014.105

Abstract | Full Text | PDF

04

Genome-wide association study of cognitive functions and educational attainment in UK Biobank (*N*=112 151) OPEN

G Davies, R E Marioni, D C Liewald, W D Hill, S P Hagenaars, S E Harris, S J Ritchie, M Luciano, C Fawns-Ritchie, D Lyall, B Cullen, S R Cox, C Hayward, D J Porteous, J Evans, A M McIntosh, J Gallacher, N Craddock, J P Pell, D J Smith, C R Gale & I J Deary

doi:10.1038/mp.2016.45

Abstract | Full Text | PDF

05

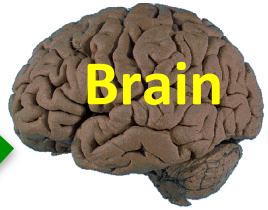
Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group OPEN

L Schmaal, D J Veltman, T G M van Erp, P G Sämann, T Frodl, N Jahanshad, E Loehrer, H Tiemeier, A Hofman, W J Niessen, M W Vernooij, M A Ikram, K Wittfeld, H J Grabe, A Block, K Hegenscheid, H Völzke, D Hoehn, M Czisch, J Lagopoulos, S N Hatton, I B Hickie, R Goya-Maldonado, B Krämer, O Gruber, B Couvy-Duchesne, M E Rentería, L T Strike, N T Mills, G I de Zubicaray, K L McMahon, S E Medland, N G Martin, N A Gillespie, M J Wright, G B Hall, G M MacQueen, E M Frey, A Carballedo, L S van Velzen, M J van Tol, N J van der Wee, I M Veer, H Walter, K Schnell, E Schramm, C Normann, D Schoepf, C Konrad, B Zurowski, T Nickson, A M McIntosh, M Papmeyer, H C Whalley, J E Sussmann, B R Godlewska, P J Cowen, F H Fischer, M Rose, B W J H Penninx, P M Thompson & D P Hibar

doi:10.1038/mp.2015.69

Abstract | Full Text | PDF

A Conceptual Framework for Psychiatry



Defined/functional changes

To be discovered/confirmed microstructural or functional changes

Alterations in key functions

- Mood
- Memory
- Cognition
- Food intake, etc.

Licinio J & Wong M-L
Molecular Psychiatry
(July, 2013) 18, 846–848

MIND & BRAIN
Translational Research

Vertical and horizontal integration

Vertical integration

Cells
↓
Animal models
↓
First in human studies
↓
Clinical trials
↓
New treatments
↓
Improved outcomes

Major depression | **Bipolar disorder** | **Schizophrenia, …**

Shared biological processes

e.g., inflammation, microbiome, neuroendocrine

Technical approaches

e.g., imaging, genetics

Horizontal integration